Impact of augmented renal clearance in critically ill patients

population pharmacokinetics of levetiracetam and dosing evaluation

Idoia Bilbao Meseguer

Vitoria-Gasteiz 2022

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Universidad del País Vasco

Euskal Herriko Unibertsitatea

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Idoia Bilbao Meseguer

Grupo Farmacocinética, Nanotecnología y Terapia génica (PharmaNanoGene)

Laboratorio de Farmacia y Tecnología Farmacéutica

Universidad del País Vasco/Euskal Herriko Unibertsitatea

Facultad de Farmacia

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RESUMEN:

Impacto del Aclaramiento Renal Aumentado en Pacientes Críticos: Farmacocinética Poblacional de Levetiracetam y Evaluación de la Dosificación

INTRODUCCIÓN

Las alteraciones fisiopatológicas que se producen en los pacientes críticos pueden tener un gran impacto en los parámetros farmacocinéticos de los fármacos. El concepto de aclaramiento renal aumentado (ARC) es relativamente nuevo, pero se ha descrito con frecuencia en pacientes ingresados en unidades de cuidados intensivos (UCI).

En pacientes críticos con ARC, el aclaramiento (CL) plasmático de los fármacos que se eliminan por vía renal es significativamente mayor. Esto se asocia a un mayor riesgo de fracaso terapéutico con las dosis y/o pautas de administración habituales. En este sentido, varios estudios, principalmente enfocados en antimicrobianos, muestran el alto riesgo de infradosificación en pacientes con ARC. Sin embargo, el ARC tiene el potencial de influir en el perfil farmacocinético de cualquier fármaco que se elimine por vía renal y que tenga una correlación directa entre su CL renal y el aclaramiento de creatinina (ClCr), como es el caso del levetiracetam.

Actualmente, el rango de referencia para las concentraciones valle de levetiracetam, recomendado por la Liga Internacional contra la Epilepsia (ILAE), es de 12 a 46 mg/L. Su farmacocinética favorable, junto con la ausencia de interacciones farmacológicas importantes y la amplia ventana terapéutica, hacen que la monitorización rutinaria de sus niveles plasmáticos sea innecesaria. Sin embargo, podría estar indicada en ciertas circunstancias, en las que el comportamiento farmacocinético de levetiracetam se encuentre alterado de manera relevante. Este podría ser el caso de los pacientes críticos.

La aplicación del modelado farmacocinético poblacional y las simulaciones de Monte Carlo han demostrado ser una herramienta útil para optimizar las dosis en pacientes críticos. Existe una amplia experiencia con estas técnicas en la terapia antimicrobiana, donde el uso del análisis PK/PD aumenta la probabilidad de éxito del tratamiento, minimiza la aparición de resistencias y

reduce los efectos adversos. Estas técnicas también podrían ser aplicadas para la propuesta de pautas posológicas que aseguren una correcta exposición de levetiracetam en pacientes críticos.

OBJETIVOS

El objetivo principal de esta tesis doctoral es el desarrollo de un modelo farmacocinético poblacional de levetiracetam en pacientes críticos, incluidos pacientes con ARC, y evaluar la efectividad de diferentes regímenes de dosificación mediante simulaciones de Monte Carlo.

Para ello, se llevaron a cabo los siguientes pasos:

1. Revisión sistemática sobre el fenómeno del ARC en pacientes críticos; su definición, mecanismo, epidemiología, diagnóstico e impacto tanto en la farmacocinética como en los resultados clínicos del fármaco (Anexo I).

2. Desarrollo de un modelo farmacocinético poblacional de levetiracetam en pacientes críticos sin insuficiencia renal, identificando aquellos factores fisiológicos y patológicos que influyen significativamente en la farmacocinética del fármaco y, por tanto, en su exposición (Anexo II).

3. Evaluación de la capacidad de las pautas posológicas habituales de levetiracetam para alcanzar niveles valle entre 12 y 46 mg/L en pacientes críticos (Anexo II).

4. Evaluación de esquemas de dosificación alternativos para levetiracetam, mediante el uso de infusión extendida o continua y/o la administración de dosis superiores, capaces de alcanzar concentraciones objetivo en pacientes críticos con ARC (Anexo III).

5. Evaluación de la viabilidad de las pautas posológicas propuestas para levetiracetam desde un punto de vista clínico, considerando su potencial eficacia y toxicidad, así como la estabilidad del fármaco (Anexo III).

METODOLOGÍA

1. Revisión sistemática sobre el fenómeno del ARC en pacientes críticos (Anexo I)

Se llevó a cabo una revisión sistemática, publicada según las recomendaciones de la declaración PRISMA, en las bases de datos MEDLINE, EMBASE e International Pharmaceutical Abstracts, desde su creación hasta mayo de 2017.

El objetivo fue incluir todos los estudios que proporcionaran información sobre ARC en pacientes críticos. Para ello se empleó la siguiente estrategia de búsqueda: (augmented renal clearance OR hyperfiltration) AND (critic* OR intensive). La búsqueda se limitó a artículos en inglés y se permitió la inclusión de referencias secundarias provenientes de los artículos incluidos.

Se incluyeron todos los trabajos que proporcionaran información sobre el mecanismo, la epidemiología, el diagnóstico o el impacto del ARC en pacientes críticos. Los artículos que incluían pacientes pediátricos o que fueran casos clínicos, revisiones, cartas o editoriales fueron excluidos.

2. Desarrollo de un modelo farmacocinético poblacional de levetiracetam en pacientes críticos sin insuficiencia renal (Anexo II)

Estudio observacional

Se llevó a cabo un estudio prospectivo, abierto y multicéntrico en pacientes críticos ingresados en las UCI del Hospital Universitario Araba (Vitoria-Gasteiz, España) y del Hospital Doce de Octubre (Madrid, España).

El protocolo de estudio fue aprobado por el Comité de Ética de la Investigación con medicamentos de Euskadi (EPA2018019 (SP)) y el estudio se llevó a cabo según las normas de buena práctica clínica.

Se incluyeron pacientes ingresados en UCI que estaban en tratamiento con levetiracetam, cuyo ClCr medido en orina era >50mL/min y que otorgaron su consentimiento informado. Los pacientes menores de 18 años, las embarazas y los pacientes con hipersensibilidad al fármaco o a cualquiera de sus excipientes fueron excluidos.

Administración del medicamento, procedimiento de muestreo y método analítico

Cada paciente recibió, como parte de su tratamiento médico, una dosis de 500, 1000 o 1500 mg de levetiracetam cada 12 h, en infusión intravenosa de 30 min.

Para cada paciente, se tomaron muestras de sangre (3 ml) a las 0 h (antes de la dosis), al final de la infusión (0,5 h) y al final del intervalo de dosificación (12 h). Además, se tomó muestra en los intervalos de 1 a 2 h, 3 a 5 h y 6 a 8 h después de la administración del fármaco. El plasma obtenido tras la centrifugación de las muestras se almacenó a -80ºC hasta su análisis mediante cromatografía líquida de alta resolución con detector ultravioleta (HPLC-UV).

Modelo farmacocinético poblacional

El modelo farmacocinético se desarrolló con el programa NONMEM (v.7.4). Los datos se ajustaron a modelos mono y bi-compartimentales. La variabilidad inter-individual (IIV) se modeló exponencialmente y para el error residual se exploraron modelos de error proporcional, aditivo o combinado.

Las covariables estudiadas fueron: sexo, edad, peso, talla, área de superficie corporal (ASC), ClCr (medido en orina), glucosa, albúmina, bilirrubina total, hemoglobina, leucocitos, APACHE II y diagnóstico. Tras la selección de covariables, el modelo farmacocinético final se evaluó mediante gráficos de bondad de ajuste, análisis Bootstrap y mediante gráficos de tipo prediction corrected visual predictive check (pcVPC).

3. Evaluación de las pautas posológicas habituales de levetiracetam en pacientes críticos (Anexo II)

Con el modelo final, se realizaron simulaciones de Monte Carlo (NONMEM® v.7.4) para predecir las concentraciones valle de levetiracetam en 1000 sujetos virtuales con valores de ClCr entre 80 y 240 ml/min. Se ensayaron regímenes de dosificación entre 500 mg y 2000 mg administrados cada 12 u 8 h en infusión intravenosa de 30 min.

Las concentraciones valle objetivo fueron de 12 a 46 mg/L, según lo recomendado por la ILAE, y la probabilidad de alcanzar el objetivo (PTA) se calculó en R (v.4.0.2).

4. Evaluación de esquemas de dosificación alternativos para levetiracetam en pacientes críticos con ARC (Anexo III)

Con el modelo final, se realizaron simulaciones de Monte Carlo (NONMEM® v.7.4) para predecir las concentraciones valle de levetiracetam en 1000 sujetos virtuales con ClCr entre 160 y 240mL/min. Se ensayaron varios regímenes de dosificación (de 3000 mg a 6000 mg diarios) y el uso de infusiones prolongadas (4 o 6 h) o continuas.

Las concentraciones valle objetivo fueron de 12 a 46 mg/L, según lo recomendado por la ILAE, y la PTA se calculó en R (v.4.0.2).

5. Evaluación de la viabilidad de las pautas posológicas propuestas para levetiracetam desde un punto de vista clínico (Anexo III)

La evaluación de la viabilidad de las pautas propuestas se realizó analizando tres factores: la eficacia/toxicidad de la administración en infusión continua o extendida, la eficacia/toxicidad de las dosis elevadas y la estabilidad del fármaco diluido a temperatura ambiente.

Para llevar a cabo esta evaluación se analizaron las bases de datos terciarias UpToDate® y Micromedex® y las fichas técnicas de levetiracetam autorizadas por la EMA y la FDA. También se realizó una búsqueda bibliográfica para ampliar la información sobre las infusiones continuas o extendidas de levetiracetam empleando la siguiente estrategia de búsqueda: ("levetiracetam" OR "keppra") AND ("extended" OR "continuous") AND "infusion". Por último, se consultaron las bases de datos King Guide to Parenteral Admixtures®, Trissel's 2 Clinical Pharmaceutics Database® y Stabilis® para obtener información sobre la estabilidad de levetiracetam diluido.

RESULTADOS Y DISCUSIÓN

1. Revisión sistemática sobre el fenómeno del ARC en pacientes críticos (Anexo I)

La revisión sistemática incluyó 48 referencias, 35 artículos originales y 13 comunicaciones científicas presentadas en congresos.

Definición

El ARC se define como un incremento en la depuración de solutos del plasma respecto a un nivel basal, un proceso que implica cambios en la filtración glomerular y en la función tubular renal. Actualmente existe un amplio consenso en considerar 130 mL/min/1,73m^2 como el límite de ClCr a partir del cual se diagnostica ARC.

Mecanismo

El mecanismo fisiológico responsable del ARC no está bien establecido, aunque existen diferentes teorías. Por un lado, se ha postulado que el síndrome de respuesta inflamatoria sistémica (SRIS), caracterizado por una activación inespecífica y generalizada del sistema inmune, podría estar implicado. La liberación de citocinas y mediadores proinflamatorios conduciría a una disminución de la resistencia vascular y a un aumento del gasto cardíaco, lo que, junto con la fluidoterapia intensiva y los fármacos inotrópicos comúnmente utilizados en pacientes críticos, podrían aumentar el flujo sanguíneo renal y la tasa de filtración glomerular. Sin embargo, los ensayos no han podido establecer una relación estadística y clínicamente significativa entre el índice cardíaco, el balance hídrico o el uso de vasopresores y el ARC. Otras teorías sugieren que la reserva funcional renal puede desempeñar un papel en el ARC. El concepto de reserva funcional renal hace referencia a la capacidad del riñón para aumentar su función en respuesta a determinados estímulos fisiológicos o patológicos. Sin embargo, es la combinación de ambos mecanismos la hipótesis que actualmente tiene una mayor aceptación.

Epidemiología y diagnóstico

El ARC está presente entre un 20 y un 65% de pacientes críticos. Existen ciertas condiciones clínicas como el traumatismo craneoencefálico (85%), hemorragia subaracnoidea (100%) o grandes quemados (65%) donde está especialmente presente. Adicionalmente, la edad más joven, el politraumatismo y la enfermedad de menor gravedad se han identificado como factores de riesgo para ARC.

El ARC es una situación dinámica y transitoria, que se ha de monitorizar diariamente mediante la medición del ClCr medido en orina. Esto es debido a que las ecuaciones de estimación de la función renal tienden a subestimar el valor de ClCr en pacientes críticos con ARC.

Impacto del ARC en la farmacocinética de los medicamentos y en el resultado clínico

El impacto del ARC ha sido principalmente estudiado en la farmacocinética de los antimicrobianos. Se ha demostrado que la presencia de ARC está relacionada con niveles plasmáticos menores y niveles subterapéuticos de vancomicina y β-lactámicos.

Sin embargo, la influencia del ARC sobre el resultado clínico no está bien establecida ya que existen pocos estudios publicados y con resultados dispares. Es difícil establecer una relación entre ARC y resultados clínicos negativos debido a que, a pesar de que su influencia sobre la farmacocinética de los antimicrobianos es clara, la aparición de este fenómeno también se ha considerado un marcador de buen pronóstico al predecir una mejor capacidad del paciente para adaptarse y resistir una infección grave.

2. Desarrollo de un modelo farmacocinético poblacional de levetiracetam en pacientes críticos sin insuficiencia renal (Anexo II)

Se incluyeron en el estudio un total de 27 pacientes, de los que se obtuvieron 157 muestras de plasma. La mayoría de los pacientes (18 de 27), fueron tratados con levetiracetam 500mg/12h.

El modelo farmacocinético que mejor describía la evolución de las concentraciones plasmáticas fue un modelo bicompartimental. La IIV se modeló de manera exponencial y el error residual de manera proporcional. El shrinkage fue inferior al 25%.

El ClCr fue la única covariable que mostró una influencia significativa en el aclaramiento de levetiracetam. No se identificó ninguna covariable con influencia significativa sobre el resto de parámetros farmacocinéticos. Los valores de los parámetros estimados se recogen en la tabla 1.

Tabla 1. Parámetros estimados del modelo farmacocinético poblacional final

Parameter	Final model estimate (RSE (%))
CL (L/h) = θnr + (CrCl/120)$^{\theta r}$	-
θnr	3.5 (9)
θr	2.5 (17)
V1 (L)	20.7 (18)
Q (L/h)	31.9 (22)
V2 (L)	33.5 (13)
IIV_CL (%)	32.7 (21)
IIV_V1 (%)	56.1 (29)
RE_proportional (%)	22.3 (15)

CL, clearance; CrCl, creatinine clearance; V1, central volume of distribution; Q, intercompartmental clearance; V2, peripheral volume of distribution; IIV, inter-individual variability; RE, Residual error; RSE, Relative standard errors.

El análisis Bootstrap demostró una buena precisión en las estimaciones de los parámetros y el pcVPC evidenció que el modelo caracteriza la evolución temporal de las concentraciones plasmáticas de levetiracetam de forma adecuada.

3. Evaluación de la eficacia de las pautas posológicas habituales de levetiracetam en pacientes críticos (Anexo II)

La simulación de Monte Carlo mostró que con las pautas de dosificación cada 12 horas, en infusión de 30 minutos, sólo se alcanza una PTA (probabilidad de que la concentración valle >12

mg/L) mayor al 80% en pacientes sin ARC. Concretamente son necesarias dosificaciones de 1.500 mg y 2.000 mg cada 12 h para pacientes con ClCr de 80 y 120 ml/min, respectivamente.

Las pautas de dosificación cada 8 horas permiten alcanzar una PTA mayor al 80% en pacientes con ClCr de 160mL/min y 200mL/min, siendo necesarias dosis de 1500mg y 2000mg cada 8 horas respectivamente. Sin embargo, en el caso de pacientes con ClCr de 240mL/min no se pudieron alcanzar niveles valle objetivo, con una probabilidad mayor al 80%, incluso con la pauta de 2000mg cada 8 horas.

En todas las pautas propuestas la probabilidad de concentraciones valle superiores a 46mg/L fue inferior al 5%.

Por lo tanto, para pacientes críticos sin ARC la pauta de 500mg/12h, frecuentemente empleada en este entorno, es insuficiente para alcanzar niveles valle objetivo. Además, en el caso de pacientes críticos con ARC son necesarias dosis superiores y/o intervalos de administración inferiores a las autorizadas en la ficha técnica de levetiracetam.

4. Evaluación de esquemas de dosificación alternativos para levetiracetam en pacientes críticos con ARC (Anexo III)

La simulación de Monte Carlo mostró que para pacientes con ClCr de 160 ml/min, sería posible lograr una PTA de al menos 80 % con una dosis de 1000 mg cada 8 horas administrada mediante perfusión extendida (4 horas) o con 1500 mg cada 8 horas en perfusión corta (30 minutos). Para pacientes con ClCr de 200 mL/min, sería necesario administrar 3000 mg en infusión continua, 1500 mg durante 4 horas cada 8 horas o 2000 mg durante 30 minutos cada 8 horas. Por último, en pacientes con ClCr de 240 mL/min, sería necesario administrar 4500 mg en infusión continua o 2000 mg durante 4 horas cada 8 horas.

En todas las pautas propuestas la probabilidad de concentraciones valle superiores a 46mg/L fue inferior al 5%.

Por lo tanto, el empleo de infusiones continuas o extendidas de levetiracetam podrían ser una opción para alcanzar niveles valle objetivo de levetiracetam sin necesidad de administrar dosis superiores a las autorizadas en pacientes críticos con ARC y ClCr inferior a 240mL/min.

5. Evaluación de la viabilidad de las pautas posológicas propuestas para levetiracetam desde un punto de vista clínico (Anexo III)

Respecto al modo de administración, existe evidencia publicada sobre el empleo de levetiracetam en infusión continua tanto por vía intravenosa como por vía subcutánea en el entorno de cuidados paliativos.

Respecto al empleo de dosis elevadas, también existen trabajos en los que levetiracetam se administra a dosis elevadas con un buen perfil de seguridad.

Por último, respecto a la estabilidad de levetiracetam diluido a temperatura ambiente, aunque existe disparidad de información en las fichas técnicas autorizadas por la FDA y por la EMA, se puede asumir que levetiracetam tiene una estabilidad de 24 horas a temperatura ambiente tal y como se recoge en la ficha técnica de la EMA.

CONCLUSIONES

1. La revisión sistemática realizada sobre el aclaramiento renal aumentado (ARC), definido como un aclaramiento de creatinina (ClCr) >130 mL/min/1,73m^2, señaló que este fenómeno está presente en 20 a 65% de los pacientes críticos siendo más frecuente en ciertas condiciones como traumatismo craneoencefálico (85%), hemorragia subaracnoidea (100%) y grandes quemados (65%). Además, la edad más joven, el politraumatismo y la enfermedad de menor gravedad se identificaron como factores de riesgo para ARC.

2. La evidencia recolectada mostró que el ARC es una condición dinámica y temporal que influye en el aclaramiento de los fármacos eliminados por excreción renal. En consecuencia, sería necesario ajustar la dosis de acuerdo con las variaciones diarias del aclaramiento renal de los pacientes. Las ecuaciones de estimación de la función renal tienden a subestimar el valor de ClCr en pacientes críticos con ARC, por lo que en estos pacientes se recomienda determinar el ClCr medido en orina.

3. Se ha desarrollado un modelo farmacocinético poblacional para levetiracetam en pacientes críticos con función renal normal o aumentada. El modelo bicompartimental fue el que mejor describió la farmacocinética del fármaco, y el ClCr fue la única covariable significativa del aclaramiento de levetiracetam.

4. El análisis farmacocinético de levetiracetam en pacientes críticos con ARC demostró que las pautas de dosificación convencionales (500-1500 mg dos veces al día en infusión de 30 minutos) no permiten obtener concentraciones valle objetivo, entre 12 y 46 mg/L. Por

tanto, son necesarias recomendaciones específicas para el ajuste de dosis de levetiracetam en esta subpoblación.

5. Las simulaciones de Monte Carlo mostraron que en pacientes críticos con ARC y ClCr entre 160 y 200 mL/min levetiracetam debería administrarse en infusiones prolongadas o continuas en lugar de infusiones cortas para alcanzar las concentraciones plasmáticas objetivo. Para pacientes con valores de ClCr de 240 mL/min o superiores serían necesarias dosis mayores a las autorizadas en ficha técnica. Los pacientes críticos con función renal normal requerirían infusiones cortas de al menos 1000 mg cada 8 h o 1500 mg cada 12 h para alcanzar las concentraciones objetivo.

6. Las pautas posológicas propuestas para implementar en pacientes críticos con ARC cumplen los criterios de seguridad y eficacia que permiten trasladarlas al medio clínico, no obstante; se necesitarían más estudios clínicos para confirmar estos resultados.

GLOSSARY

APACHE: acute physiology and chronic health evaluation

ARC: augmented renal clearance

ARCTIC: Augmented Renal Clearance in Trauma Intensive Care

BSA: Body surface area

CG: Cockcroft-Gault

CI: confidence interval

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

CL: clearance

Cmin: minimum drug concentrations

Cr: creatinine

CrCl: creatinine clearance

CV: coefficient of variation

CWRES: conditional weighted residual errors

DV: observed drug concentrations

EBE: empirical Bayes estimates

FDA: United States Food & Drug Administration

FME: Full Model Estimation

FO: first order

FOCE: first-order conditional estimation

FOCE+I: first-order conditional estimation with interaction

GAM: Generalized Additive Model

GFR: Glomerular filtration rate

GOF: goodness of fit

HPLC: high-performance liquid chromatography

ICU: intensive care unit

IIV: interindividual variability

ILAE: international league against epilepsy

IOV: inter-occasion variability

IPRED: individual predictions

IWRES: individual weighted residuals

LLOQ: lower limit of quantification

MAP: maximum a posteriori probability

MCS: Monte Carlo simulation

MDRD: Modification of Diet in Renal Disease

NLME: non-linear mixed-effects

NONMEM: non-linear mixed-effects modelling

NPC: Numerical predictive check

OBS: observed drug concentrations

OFV: objective function value

pcVPC: Prediction-corrected visual Predictive Check

PI: prediction interval

PK: pharmacokinetics

PPK: Population pharmacokinetic

PRED: Population predictions

PsN: Perl speaks NONMEM

PTA: probability of target attainment

Q: intercompartmental clearance

RE: residual error

RES: population residuals

RSE: Relative standard errors

SAPS: Simplified Acute Physiologic Score

SCM: Stepwise Covariate Model

SOFA: Sequential Organ Failure Assessment

SPC: summary of product characteristics

TAD: time after dose

TDM: therapeutic drug monitoring

Tmax: time to reach the peak concentration

V1: central volume of distribution

V2: peripheral volume of distribution

Vd: volume of distribution

VPC: visual predictive check

WRES: Population weighted residuals

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SECTION 1:

INTRODUCTION

1. STATE OF THE ART

The pharmacologic effect of drugs depends on complex interactions between their physicochemical properties in the administration form and the body's biological systems. Dosing regimens have to be established considering those interactions to maximize the desired pharmacological effect and minimize the risk of adverse effects. However, a drug dosage regimen is generally established through the results obtained from studies conducted on healthy volunteers and non-critically ill patients. Results from these trials are usually extrapolated, assuming similar drug pharmacokinetics (PK), which is hardly presumable. As the PK of plenty of drugs is usually altered in critically ill patients, expected drug concentrations are not always achieved.

Augmented renal clearance (ARC) is a phenomenon that has been recently identified in critically ill patients. Subjects with ARC could be at risk of sub-optimal drug exposure when conventional dosage regimens are used. The ARC is a relatively new concept, and the evidence available to date concerning this state is scarce and diverse.

This thesis emerges from a need in intensive care units (ICU) to gather all the evidence on ARC in critically ill patients, including the underlying mechanisms, epidemiology, diagnosis, and impact on drug pharmacokinetics and clinical outcomes to facilitate the dose individualization. The effect of ARC on drug concentrations has been specially investigated in antimicrobials. However, other drugs with high renal clearance and commonly used in ICU, such as the antiepileptic levetiracetam, could also be primarily affected by ARC.

1.1. Pharmacokinetic alterations in critically ill patients

During critical illness, physiological changes and therapeutic interventions can alter some PK parameters in comparison to healthy subjects: volume of distribution (Vd), protein binding and total body clearance (CL) (Figure 1).

Inflammatory response and aggressive fluid loading result in capillary leak and oedema, leading to fluid third-spacing into the interstitial compartment. Increased Vd has been demonstrated for hydrophilic antimicrobial drugs such as aminoglycosides, β-lactams, daptomycin, linezolid and glycopeptides. In contrast, lipophilic agents such as fluoroquinolones, distributed intracellularly or into adipose tissue, are not significantly influenced (1-3).

Hypoalbuminaemia, also frequently found in this population, might change the unbound drug fraction in blood, likely influencing the pharmacokinetics of highly protein-bound drugs. Hypoalbuminaemia is likely to lead to a high free fraction. Subsequently, more unbound drugs will be available for distribution and excretion, leading to lower drug concentrations in the blood (1-4).

Further, ARC has also been frequently identified in ICU patients (5). Although the mechanism is not fully understood, renal drug CL can be increased in these patients compared with non-ARC patients. This recently described phenomenon may be significant for drugs eliminated by the kidney and is known to have a direct correlation between their renal CL and creatinine clearance (CrCl) which would be the case for some antibacterial agents, such as vancomycin or beta-lactams, and other drugs, such as enoxaparin or levetiracetam.

With some intensive care procedures, such as continuous renal replacement therapies or extracorporeal membrane oxygenation, all these alterations could lower the plasma levels of drugs (1-4).

In contrast, kidney or liver impairment can result in an accumulation of the drugs in plasma. A decline in kidney perfusion or the administration of nephrotoxic drugs can lead to acute kidney injury (AKI) and reduced CL of renally-eliminated drugs. AKI is identified by elevated serum creatinine (Cr) concentrations or reduced urine output. The impact of kidney disease on the excretion of eliminated drugs is well established, and the requirement for drug dosage adjustment in impaired kidney function patients. Hepatic dysfunction may also cause a decrease in drug metabolism and CL (1-4).

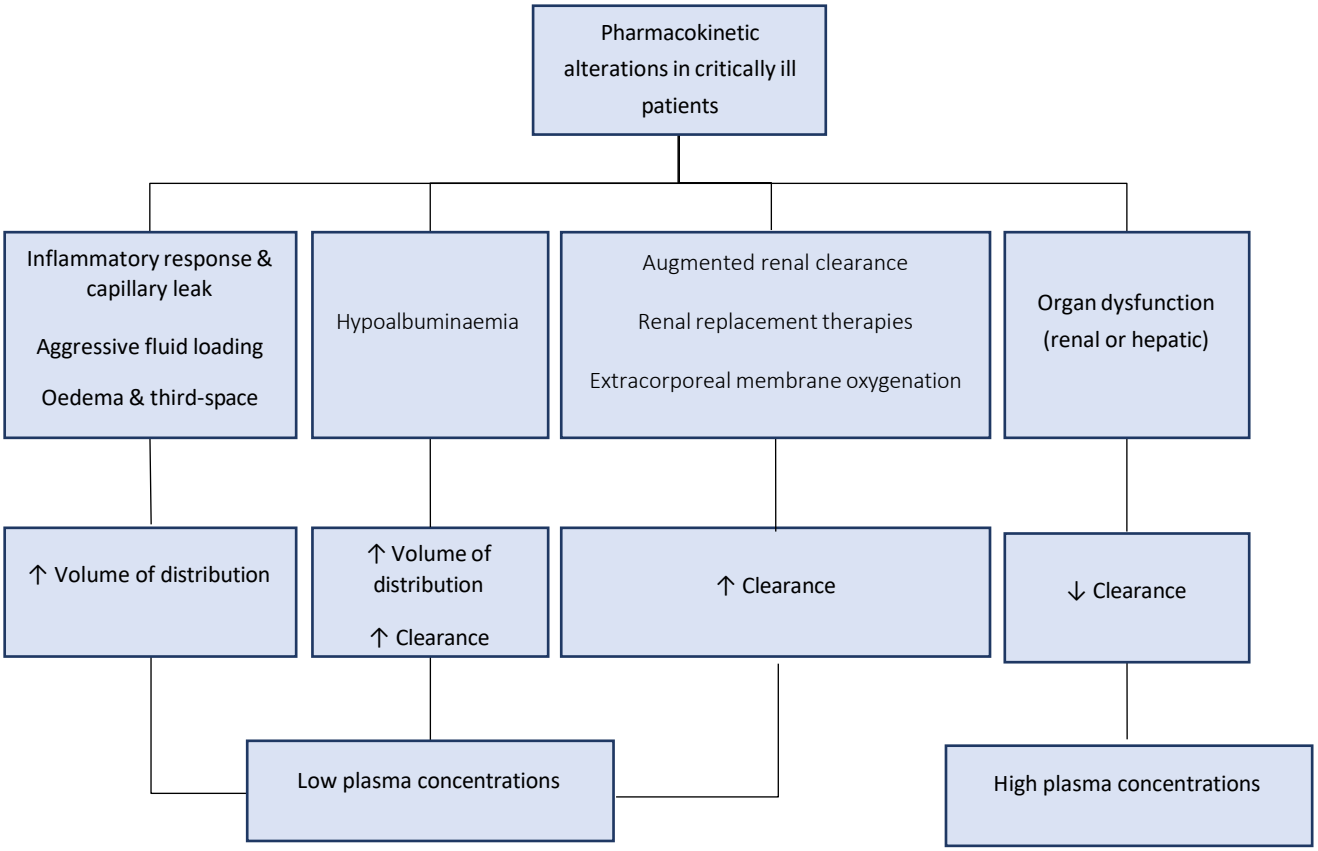

Figure 1. Pathophysiological changes in the critically ill patient and induced pharmacokinetic modifications.

1.2. Population pharmacokinetic modelling to optimize dosage in critically ill patients

Population pharmacokinetics (PPK) studies variability in drug concentrations between individuals. It comprises the assessment of variability within the population and accounts for the variability in patient characteristics such as age, renal function or disease state (6).

PPK models have their most important uses in drug development and direct patient care. Today, PPK modelling is widely used in the field of clinical pharmacology. It is used, for example, to provide the best possible initial dosage regimens in situations where no individual concentrations have been measured. Some drugs may measure concentration, but the sampling is often sparse. The population model is a pivotal element in this case, as it provides the Bayesian priors for individualized Bayesian adaptative control (7, 8).

1.2.1. PPK estimation methods

A variety of methods have been proposed to characterize the PPK of drugs during the last years. A brief description of the main methods is provided in this section.

Naive pooled data analysis

In this method, all data for all individuals are considered as arising for one unique individual, characterized by a set of parameters (Φ). With least-squares fitting, Φ will be the parameter vector minimizing the global objective function. The usefulness of this method in clinical practice is minimal since the adjustment is made without taking into account the physiological and clinical changes that may occur in an individual, and interindividual variability cannot be estimated (9).

Standard two-stage approach

This method estimates individual parameters in the first stage by separately fitting each subject's data using classical methods (i.e. weighted non-linear least-squares regression). Then, in a second stage, these individual estimates provide input data for obtaining population parameter estimates (i.e. if normally distributed, population parameter estimates are described with the mean, variance and covariance of individual parameter estimates)(9). This method allows a reasonable estimation of the parameters if done with a large number of individuals and rich data.

Iterative two-stage Bayesian estimation

The first stage of this method requires an initial estimate of mean PK parameter values (Bayesian priors). These priors are then used to obtain individual maximum a posteriori probability (MAP) Bayesian parameter values. The second stage calculates population means and individual posterior parameter values variances. These new population values can then be used as MAP Bayesian priors to obtain each individual's MAP Bayesian posterior values until convergence is reached (7).

Non-linear mixed-effects modelling (NLME).

NLME method is a single-stage approach that considers the population rather than the individual as the unit of analysis for estimating the distribution of PK parameters and their relationship with covariates within the population. Thus, this approach estimates mean and variability parameters simultaneously, but it can differentiate between inter-individual and intra-individual variability. In other words, it describes the median tendency of the studied population and quantifies the variability found among individuals responsible for the different profiles among subjects (7, 9).

This method overcomes the disadvantages of the previous ones and is most often referred to as the PPK approach, as it accommodates an imbalanced or sparsely sampled dataset.

The term "mixed" refers to the fact that fixed effects (structural parameters) and random effects (variability) are modelled simultaneously (8):

- Fixed effects: are the average population values of PK parameters (CL, V1, V2, Q…) that may, in turn, be a function of demographic or pathophysiological characteristics of the patients (gender, age, CrCl…). These characteristics are called covariates and explain variability among subjects.
- Random effects: quantify the amount of PK variability that is not explained by the fixed effects. Thus, they account for the interindividual variability (IIV), the inter-occasion variability (IOV) and the residual error (RE).
    - The IIV defines the discrepancies between the population's typical value for a parameter and the individual values.
    - The IOV defines the variability when a drug is administered to the same subject on two or more occasions and individual PK parameters change. The source of variability can sometimes be identified, such as changing patient status or compliance. To include IOV in the population model, more than one sample or measurement per occasion is required; otherwise, it would be indistinguishable from RE.
    - The RE accounts for the discrepancy between the predicted and the observed concentration once the parameter for each subject is established.

In summary, the PPK model for the observed y dependent variable (e.g., plasma level at time points t_{ij}) for the ith subject can be expressed as follows(8):

$$y_{ij} = f_{ij}(\Phi_i, t_{ij}) + \varepsilon_{ij} \qquad \text{Eq.1}$$

where f is the function representing the structural model, Φ_i represents the model parameters for the ith subject, and ε_{ij} is the residual error.

It is assumed that the residual variability follows a normal distribution with mean zero and variance σ^2:

$$\varepsilon = N(0, \sigma^2) \quad \text{Eq.2}$$

As previously said, structural parameters (Φ_i) will exhibit interindividual variability (IIV).

$$\Phi_i = \Phi + \eta \quad \text{Eq.3}$$

The interindividual error (η) represents the variability in the parameter values within a population between the different subjects. It is assumed to follow a normal distribution with a mean of zero and a variance of ω^2.

$$\eta = (0, \omega^2) \quad \text{Eq.4}$$

Most of the NLME methods estimate the parameters by the maximum likelihood approach. The probability of the data under the model is written as a function of the model parameters. Parameter estimates are chosen to maximize this probability and amount to asserting that the best parameter estimates render the observed data more probable than they would be under any other set of parameters (9).

It is difficult to calculate the likelihood of the data for most PK models because of the non-linear dependence of the observations on the random parameters η_i (intersubject variability) and possibly ε_{ij} (residual variability). As a solution, several approximate methods have been proposed and are available in different pieces of software (9).

NONMEM® (NON-linear Mixed Effects Modelling) is the most extensively-used program among pharmacometricians. In this program, linearization of the model in the random effects can be done using the first order (FO), FO conditional estimation (FOCE) or FOCE with interaction (FOCE+I) methods. The FO method is based on the first-order Taylor series approximation to the

model. The model linearized near the mean of the random parameters (at the expected value of η, which is 0, i.e. at the typical value). The prediction corresponds to the population prediction for residual error models with dependency on model predictions (heteroscedastic models). In the FOCE method, the model is linearized by the individual conditional estimates of η (at the empirical Bayes estimates of η, i.e. at the individual value). For heteroscedastic models, the prediction corresponds to the population prediction. FOCE+I method is as FOCE but for heteroscedastic models, the prediction corresponds to the individual prediction, i.e. the interaction between inter-individual variability and residual error is taken into account(6, 9).

1.2.2. Development of a PPK model in NONMEM

The development of a PPK model in NONMEM has two stages:

Development of the base model (10)

The development includes the selection of the PK model (one-, two-, three-compartment), the structural part (average values of the PK parameters) and the statistical model (IIV and RE).

IIV modelling

The interaction between IIV (η) and the typical value of the parameter can be modelled in different ways:

- **Additive model**: η is added to the typical population value of the parameter. In this case, parameter variance is constant along with the independent variable range.

$$\Phi_{ji} = \Phi_{jpop} + \eta_{ji} \qquad \text{Eq.5}$$

where Φ_{ji} is the jth PK parameter for the ith subject, Φ_{1pop} is the population typical value for the jth parameter, η_{ji} is a random variable for the i-th individual on the j-th parameter

- **Proportional model**: η is multiplied by the typical population value of the parameter. In this case, parameter variance increases with the increase of the parameter value. It can be modelled as equation 1.6 (normal distribution) or 1.7 (log-normal distribution).

$$\Phi_{ji} = \Phi_{jpop} \times (1 + \eta_{ji}) \quad \text{Eq.6}$$

$$\Phi_{ji} = \Phi_{jpop} \times e^{\eta_{ji}} \quad \text{Eq.7}$$

As previously said, η follows a normal distribution with a mean of zero and a variance of $\omega 2$. The variance-covariance matrix Ω includes variances $\omega^2{}_{1\ldots n}$ (n is the number of estimated PK parameters) and possible covariance that characterizes IIV of the PK parameters.

RE modelling

The interaction between RE (ε) and the typical value of the parameter can be modelled in three different ways:

- **Additive model**: ε is added to the function that describes the individual PK profile. In this case, parameter variance is constant along with the independent variable range.

$$y_{ij} = f_{ij}(\Phi_i, D_{i,} t_{ij}) + \varepsilon_{ij} \quad \text{Eq.8}$$

where y_{ij} is the observed concentration of the drug in the ith subject at time j, f is the function that represents the structural model, Φ_i represents the model parameters estimated for the ith, D_i is the dose administered to the ith subject, t_{ij} is the independent variable time, and ε_{ij} is the residual error.

- **Proportional model**: ε is multiplied by the function that describes the individual PK profile. The residual error increases with the increase of the parameter value.

$$y_{ij} = f_{ij}(\Phi_i, D_{i,} t_{ij}) \times (1 + \varepsilon_{ij}) \quad \text{Eq.9}$$

- Combined model: is the combination of the additive and the proportional model.

$$y_{ij} = f_{ij}(\Phi_i, D_i, t_{ij}) \times (1 + \varepsilon_{ij}) + \varepsilon_{2ij} \quad \text{Eq.10}$$

As previously said, ε is assumed to follow a normal distribution with a mean of zero and a variance of σ^2. The variance-covariance matrix Σ includes variances $\sigma^2{}_{1\ldots n}$ (n is the number of estimated PK parameters) and possible covariance that characterizes the RE of the PK parameters.

Development of the final model

Includes the base model plus the covariates. A covariate is any variable specific to an individual and may explain PK variability. Thus, a helpful covariate is expected to explain some of the overall variability and should lead to a decrease in unpredictable (random effects) variability. Covariates can be classified in different ways:

- Classification I: according to the type of information they provide
    - Demographic factors: gender, age, ethnicity, height, bodyweight…
    - Laboratory findings: albumin, bilirubin, Cr…
    - Pathology status: co-medication, dialysis, health scores…
    - Habits: smoking, alcohol, diet.
    - Time: season, circadian time, meal, treatment.
- Classification II: according to the type of the covariate
    - Continuous: body weight, age, haemoglobin, CrCl.
    - Categorical
        - Binary: gender, fasted status.
        - Non-ordered categorical: ethnicity, centre.
        - Ordered categorical: health scores.

The second classification is more relevant for using covariates with NONMEM® since the covariates will be introduced in the PPK model following different mathematical expressions depending on the covariate analyzed.

The relationship between a PPK parameter and a continuous covariate is usually expressed by linear (Eq.11-13), power (Eq.14) or exponential (Eq.15) correlations.

$$TVP = \theta_1 + \theta_2 \times COV \quad \text{Eq.11}$$

$$TVP = \theta_1 + \theta_2 \times \left(\frac{COV}{COV_{ref}} \right) \quad \text{Eq.12}$$

$$TVP = \theta_1 \times (1 + \theta_2 \times COV) \quad \text{Eq.13}$$

$$TVP = \theta_1 \times \left(\frac{COV}{COV_{ref}} \right)^{\theta_2} \quad \text{Eq.14}$$

$$TVP = \theta_1 \times e^{(\theta_2 \times COV / COV_{ref})} \quad \text{Eq.15}$$

where TVP is the typical value of a model parameter, θ_1 describes the typical parameter value for an individual with covariate values equal to the reference values, θ_2 is the parameter quantifying the magnitude of the covariate parameter relationship, COV is the value of the covariate in an individual and COV_{ref} usually refers to the median or mean value of the covariate across the studied population.

As we can see, it is common to standardize the covariate value by the mean or median of the population.

In the case of binary variables, such as gender, which divides the population into two groups, a parameter θ_{cov}, which takes 0 and 1, is included (Eq.16). In this way, the covariate's influence is only manifested for one of the two groups, leaving the other as a reference.

$$TVP = \theta_1 \times \theta_2^{\theta_{cov}} \quad \text{Eq.16}$$

In the case of non-binary categorical covariates, they can be entered into the model using various equations depending on the number of options that the covariate has (Eq. 17-19)

$$TVP = \theta_1; \text{ if COV=1 (most common situation)} \quad \text{Eq.17}$$

$$TVP = \theta_1 + \theta_2; \text{ if COV=2} \quad \text{Eq.18}$$

$$TVP = \theta_1 + \theta_3; \text{ if COV=3} \quad \text{Eq.19}$$

The decision to incorporate a covariate in the model must take into account:

- Biological plausibility
- Statistical significance: The covariate, once incorporated in the model, should improve significantly the fit (reduction in the value of objective function value (OFV), improves model performance and goodness of fit (GOF) plots, reduces de IIV)
- Clinical relevance

It is recommended that systematic procedures be incorporated for covariate model building to improve consistency and harmonization across analyses. It is essential to be aware that each systematic covariate selection procedure has limitations.

- Generalized Additive Model (GAM) analysis

The GAM is like a stepwise multiple linear regression but is not restricted to linear model shapes. The stepwise search is carried out according to a defined hierarchy (one for each covariate) of possible functional relationships, which by default is: the covariate is not included in the model, the covariate is included in a linear fashion, and the covariate is included in a non-linear fashion according to a natural cubic spline function with one internal break-point. Model discrimination is performed by comparing the Akaike information criterium (AIC) (11).

- Stepwise Covariate Model (SCM)

The SCM procedure is commonly used for covariate model building. This method includes a forward selection (resulting in a full covariate model) and a backward elimination process (resulting in a final model). Model discrimination is carried out according to the magnitude of OFV. During the forward selection, covariates are included for a defined level of statistical significance, usually a decrease of the OFV ≥ 3.84 units (equivalent to $p < 0.05$ for one degree of freedom), until reaching a model that does not accept any additional covariate, called the full model. It then carries out a backward elimination process by eliminating covariates one by one according to a more restrictive statistical criterion, usually increasing the OFV ≤ 6.63 (equivalent to $p > 0.01$ for one degree of freedom) until reaching the final model. Its main limitations are its sensitivity to the effects of collinearity when it occurs between two or more covariates. It does not guarantee the selection of the feasible model since the possibility that some covariate combination with a strong influence will not be considered during the procedure (12, 13).

- Full Model Estimation (FME)

The FME procedure directly assesses all covariate relations of interest without relying on data-driven model selection criteria. The FME procedure can also be conducted quickly as only a single run is needed, and the output is easy to interpret. On the other hand, correct inferences drawn from the output using the FME procedure assume that the covariate relationships have been captured correctly and that no critical covariates have been omitted (13).

1.2.3. PPK model selection and validation

There are different methods for model selection and evaluation, and a combination of different ones should be used.

a) The likelihood ratio test

The likelihood ratio test is based on the difference in minimum OFV between models with and without the covariate relationship.

The OFV output by NONMEM® is approximately proportional to minus two times the logarithm of the likelihood of the data, and the difference in OFV (i.e., likelihood ratio, ΔOFV) between two nested models is approximately χ^2 -distributed (degrees of freedom equal to the number of different parameters).

The improvement in fit caused by including a covariate relationship in a model can hence be assigned a significance level based on the likelihood ratio. Differences in OFV of 3.84, 6.63, and 10.83 correspond to nominal significance levels of <0.05, <0.01, and <0.001, respectively (for 1 degree of freedom) (14).

b) Relative standard errors (RSE)

Expressed as the coefficient of variation (CV) indicates the precision with which the parameters have been estimated. The uncertainty of model parameters must be small; that is, the per cent relative standard error for mean and random-effects parameters should not exceed 25% and 50%, respectively. Parameter precision might be affected by several factors: experimental design, quality of data, and model misspecification or over-parametrization (15).

c) Prediction based graphical methods (16)

Prediction based graphical methods can be based on population or individual predictions and residuals.

Population predictions

Population predictions (PRED) are the expectation of the model. The observations (OBS) can be plotted versus PRED, and the line of identity and a local regression line is added to the graph. Even if the model is correctly specified, the data points are not necessarily scattered around the line of identity, but the regression line will be more or less close to the identity line (Fig.2A). A systematic departure of the data points or the trend line from the identity line could indicate misspecification of the structural model (Fig.2B). On the other hand, misspecification in the residual error model is challenging to detect using these graphs because the residual error model is not considered in the computation of PRED (Fig.2C and 2D).

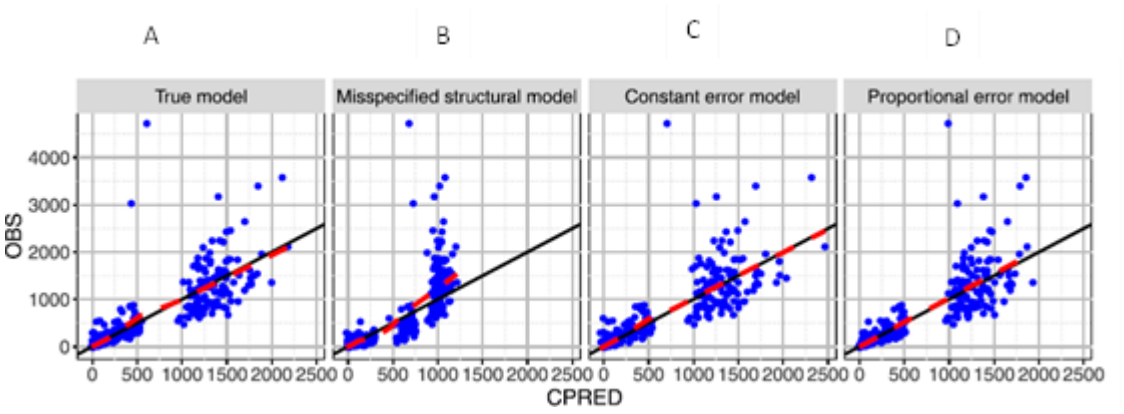

Figure 2. Goodness of fit (GOF) plots to represent observation (OBS) *vs* conditional population predictions (CPRED) for true model (A), misspecified structural model (B), misspecified constant error model (C), and misspecified proportional error model (D). Identity and local regression lines are presented in black and red, respectively. Adapted from Nguyen, 2016 (16).

Population residuals

The population residuals (RES) are defined as the difference between the observations and population predictions ($RES_i = y_i - PRED_i$). The residuals are correlated within each individual, and their magnitude may depend on that of observations if the residual error model is not homogeneous (i.e. additive error model), which is called heteroscedastic.

Population weighted residuals (WRES) standardize and decorrelate the population residuals using the model-predicted variance-covariance matrix of observations, Var(yi):

$$WRES_i = Var(y)_i^{-\frac{1}{2}} \times (y_i - PRED_i) \quad \text{Eq.20}$$

Various graphs based on WRES have been proposed to evaluate NLME, such as the scatterplots of WRES *vs* time (Fig.3) or PRED (Fig.4). If the model is true, the WRES should be randomly scattered around the horizontal zero-line (Fig.3A and Fig. 4A). A systematic bias from the zero-line may imply deficiencies in the structural model (Fig.3B and Fig. 4B). A misclassified error model can be identified from the amplitude of the residual distribution along the x-axis (e.g., a cone-shaped pattern of residuals would suggest a heteroscedastic error model; Fig.3C and Fig.4D).

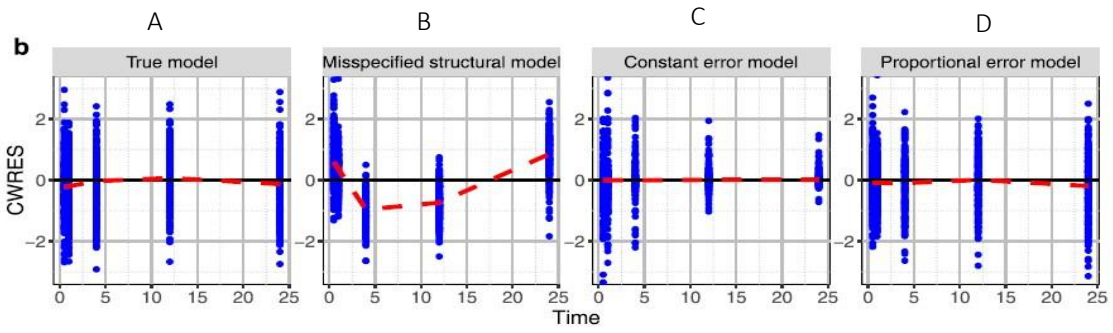

Figure 3. Goodness of fit (GOF) plots for conditional weighted residuals (CWRES) *vs* time plots for true model (A), misspecified structural model (B), misspecified constant error model (C) and misspecified proportional error model (D). Adapted from Nguyen, 2016 (16).

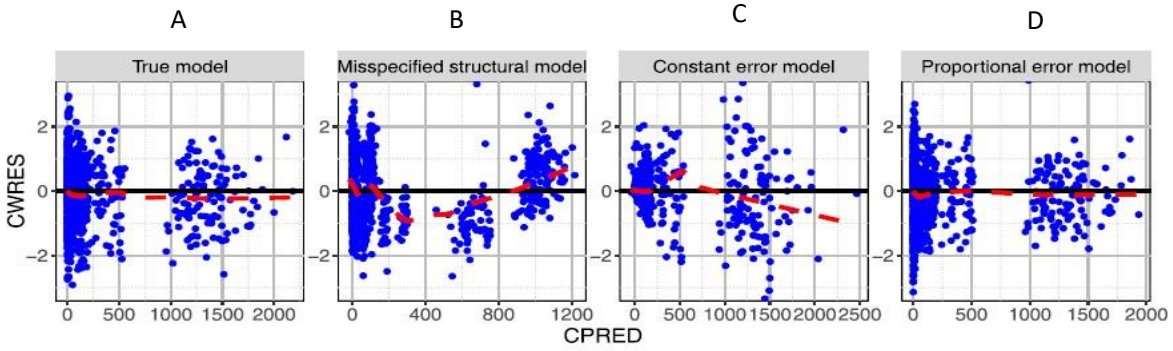

Figure 4. Goodness of fit (GOF) plots for conditional weighted residuals (CWRES) *vs* conditional population predictions (cPRED) plots for true model (A), misspecified structural model (B), misspecified constant error model (C) and misspecified proportional error model (D). Adapted from Nguyen, 2016 (16).

Individual predictions and individual residuals

Individual estimated vector of random effect (η_i) can be used to calculate individual-based evaluation metrics, such as individual predictions (IPRED) and individual weighted residuals (IWRES). Several graphs based on these individual metrics can be used for model evaluation.

- OBS *vs* IPRED: offers a global assessment of the individual fit of all patients, mainly to identify misspecification in the structural model. The considerations provided for OBS *vs* PRED are also applicable here.
- IWRES *vs* TIME or IPRED: to detect structural and residual error models.

The graphs based on IPREDs or residuals are similar to those based on population predictions but less variability because IIV was considered in their computation. Therefore, model misspecification can be detected more easily with individual-based metrics in some cases. However, unlike population-based metrics, IPRED and IWRES do not allow for the evaluation of covariate models as the variability that results from any existing covariate that is not taken into account will be considered part of IIV and, therefore, is included in the estimated individual random effect, η_i.

Evaluation based on empirical Bayes estimates (EBE)

The EBEs can be used to evaluate IIV. For each component of the vector of EBEs (or of the vector individual parameters estimates), graphs, such as a histogram or a boxplot, could be drawn and compared to their estimated predicted population distribution. A substantial discordance between an EBE distribution and a population distribution may imply misspecification of the random effect models. EBE-based evaluation graphs can also be used to detect deficiencies in the structural model and evaluate a covariate model.

Influence of shrinkage on individual-based evaluation tools

The estimation of IPREDs and EBE is susceptible to a phenomenon called shrinkage that occurs when the individual data are not sufficiently informative concerning one or more parameters. Under these conditions, the individual parameter estimates would shrink close to the population mean. The η-shrinkage and the ε-shrinkage can quantify this phenomenon. The individual-based evaluation tools become less informative with high shrinkage and do not allow for a correct model evaluation. In order to be able to rely on individual plots, shrinkage values of 20-30% (if calculated from standard deviation) have been suggested as a threshold.

d) Simulation-based graphical methods (16, 17)

Simulation-based evaluation relies on the concept of the posterior predictive check, whose principle is that if a model correctly describes a dataset, the data simulated under that model would be similar to the observations. Predictive checks select a statistical that a good model should be able to simulate (i.e. area under de curve or maximum drug concentration) and that can be derived from de data without using the model. To evaluate a model with these methods, one needs to simulate a large number (K) of Monte Carlo samples under the tested model.

Simulation-based diagnostics include different types of graphs, being the most common ones:

- Visual Predictive Check (VPC): The observed data's percentile (5^{th}, 50^{th} and 95^{th}, for example) are represented. The area defined by the lowest and the highest percentile is usually called the prediction interval (PI) of the data (for example, the 5^{th} and 95^{th} percentiles define a 90% PI). By calculating the percentiles of interest for each simulated replicates of the original dataset design, a nonparametric confidence interval (CI) can be generated for the predicted percentiles. The size of the CI acts as a reference to better judge what is likely to be a true deviation between observations and model predictions, and this is thought to make the interpretation of VPCs less subjective.

- **Prediction-corrected VPC (pcVPC)**: When there is heterogeneity in design, such as differing doses, dosing regimen or route of administration, the VPC becomes uninformative. pcVPC offers a solution to these problems. In a pcVPC, the variability is removed by normalizing the observed and simulated dependent variables based on the population predictions (Figure 5).

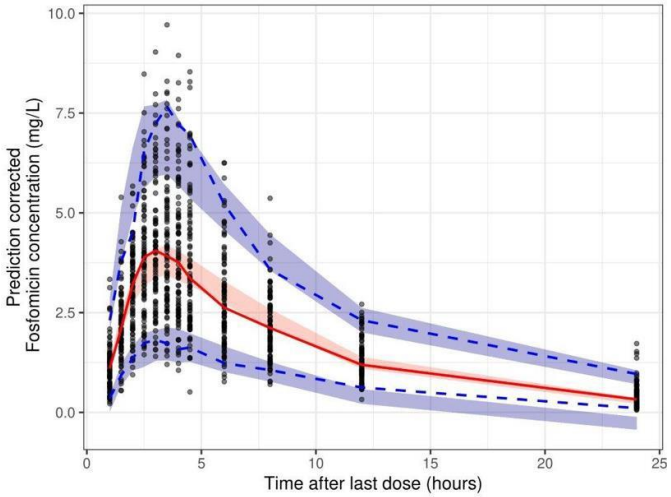

Figure 5. Prediction-corrected visual predictive check. The dots represent the observed prediction–corrected concentrations (mg/L). The continuous red line represents the 50th observed percentiles, and the dashed blue lines represent the 10th, and 90th observed percentiles. Simulation-based 95% confidence intervals for the median and 10th and 90th percentiles are displayed by red and blue shading, respectively.

- **Numerical predictive check (NPC)**: The NPC calculates the percentage of outliers for different selected PI (for example the 20, 40, 50, 60, 80, 90 and 95% PIs). By providing the same calculation for each of the K simulated datasets, we can obtain a CI for the percentage of outliers. The observed percentage can be compared with the empirical CI using a coverage plot.

Trends in these plots would indicate misspecification of structural, IIV or RE models.

e) Bootstrap methods

These are resampling techniques. In brief, bootstrapping involves generating a replicate dataset where individuals are randomly drawn for the original database. Thus, they can be drawn multiple times in each replicate or might not be selected at all. Once the replicates have been performed, the median value and 5^{th} and 95^{th} percentiles calculated for each parameter can be compared with values obtained in the final model (17).

f) External validation

External validation involves the application of the developed model to the validation of a dataset obtained from a different study to evaluate differences between observed values and model predictions. It is considered one of the most stringent approaches for model testing.

1.3. Monte Carlo simulations

Once a PPK model is developed, Monte Carlo simulation (MCS) can be performed. Monte Carlo or stochastic simulation allows expanding the sample size considering the PK parameters' variability to predict the likely result of different therapeutic approaches or the achievement of therapeutic targets (4, 18).

To perform MCS, a validated PPK model is needed, including the structural model (providing PPK parameters), a variability model (providing inter-individual variability) and a covariate model (studying the influence of patient characteristics on the PK parameters). This method simulates thousands of different subjects, considering the equations of the PPK model and taking into account the variability between patients. Then, the probability of target attainment (PTA) can be calculated. PTA is defined as the probability that a specific value of the PK index associated with the efficacy of the drug (i.e. Cmin, Cmax…) is achieved. In other words, it corresponds to the

percentage of simulated patients with an estimated PK index equal to or higher than the value related to the efficacy (i.e. Cmin>12mg/L for levetiracetam) (4, 18).

In conclusion, MCS can describe the proportion of patients that will achieve a pre-specified PK target considering different patient characteristics (covariates of the model). Such analyses can then inform dosing requirements to a high likelihood of achieving these PK targets. It is a valuable technique to guide clinical practice where robust descriptive PK data exist.

1.4. Levetiracetam

Levetiracetam (Figure 6) is a broad-spectrum antiepileptic drug with proven efficacy in treating multiple seizure types in both adult and paediatric populations. It is available as tablets, an oral solution, and a concentrate made up into a solution for intravenous infusion.

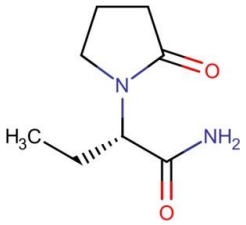

Figure 6. Levetiracetam molecular structure

Its primary mechanism of action modulates neurotransmitter release via binding to the synaptic vesicle protein 2A, thus, inhibiting calcium release from intracellular stores. Other mechanisms of action include opposition of the negative modulation of gamma butyric acid (GABA) and glycine-gated currents, inhibition of the neuronal synchronization, and the N-type calcium channels (19, 20).

Levetiracetam pharmacokinetic profile

Levetiracetam has a linear PK profile. Its main PK characteristics are summarized in Table 1. It is rapidly and almost completely absorbed when administered orally, with a time to reach the peak

concentration (Tmax) of 1–2 h and high bioavailability (>95%). Its apparent Vd is 0.5–0.7 L/kg with non-significant plasma protein binding (<3%). Renal CL represents the main elimination mechanism, with 66% of the dose excreted unchanged in the urine. Additionally, a fraction of the dose (24%) is eliminated by metabolism through enzymatic hydrolysis of the acetamide group, carried out by a type B esterase, mainly in blood. Clinically relevant interactions are not expected, as this metabolic pathway is only responsible for the metabolism of a small part of the administered dose. Additionally, levetiracetam does not induce or inhibit cytochrome P450 enzymes resulting in minimal drug-drug interactions. The metabolites have no known pharmacological activity and are renally excreted. The renal CL of levetiracetam occurs at a rate of 0.6mL/min/kg, and the elimination half-life in healthy young volunteers is 6-8 hours (19, 21, 22).

Table 1. Pharmacokinetic characteristics of levetiracetam in healthy adults

Levetiracetam PK characteristics	
Bioavailability	>95%
Tmax	1-2 hours
Volume of distribution	0.5–0.7 L/kg
Protein binding	<3%
Time to steady-state	24-48 hours
Metabolism (enzymatic hydrolysis)	34% (24%)
Renal elimination (unchanged/metabolized)	93% (66%/27%)
Half-life	6-8 hours
Total clearance	0.96 mL/min/kg
Renal clearance	0.6 mL/min/kg

Indications and use in intensive care setting

Currently, levetiracetam therapeutic indications are (19):

- As monotherapy, in treating partial-onset seizures with or without secondary generalization in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

- As adjunctive therapy
    - In the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, children and infants from 1 month of age with epilepsy.
    - In the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
    - In the treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalized Epilepsy.

Because of its improved safety profile and ease of use compared to other conventional antiepileptic drugs is frequently used "off-label" to treat status epilepticus and seizure prophylaxis after a neurologic injury. For example, prophylactic use is frequent to prevent stroke-related seizures, post-traumatic seizures, seizures following subarachnoid or intracerebral haemorrhage and tumour-related seizures (19, 20, 23, 24).

Levetiracetam therapeutic drug monitoring

There is no clear correlation between levetiracetam serum concentration and efficacy or tolerability. The current reference range for trough concentrations is 12–46 mg/L (25). The favourable PK profile and the absence of significant drug interactions and broad therapeutic window make routine therapeutic drug monitoring (TDM) unnecessary. However, TDM, as a way to ensure effective and safe exposures, may be indicated in certain circumstances, such as in patients with altered levetiracetam CL, for example, in the case of elderly patients, children, pregnant women, patients with renal insufficiency or critically ill patients (26, 27). The PK behaviour of levetiracetam has been poorly studied in critically ill patients with ARC.

2. METHODOLOGY

The main methods used throughout the thesis are briefly explained in this section, and any other methodology is accurately explained in their respective Appendixes.

2.1. Systematic research on the ARC phenomenon in critically ill patients (Appendix I)

A systematic review was carried out on the ARC in critically ill patients and reported following the applicable criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines (28).

The MEDLINE, EMBASE and International Pharmaceutical Abstracts databases were systematically searched, from inception until May 2017, for all studies that reported information on ARC in critically ill patients. The following terms were used: (augmented renal clearance OR hyperfiltration) AND (critic* OR intensive). The search was additionally limited to English-language articles, and secondary literature was identified using the references included in the first search.

All references that reported information on underlying mechanisms, epidemiology, diagnosis, or impact of ARC in critically ill patients were included. Articles were excluded if they assessed paediatric patients or were clinical cases, reviews, letters or editorials.

For each record, the following data regarding ARC, when reported, were extracted: definition of ARC, the proposed mechanism(s), frequency, course, related factors, method of diagnosis, and impact on both drug pharmacokinetics and clinical outcome.

2.2. Development of a PPK for levetiracetam in critically ill patients (Appendix II)

Clinical study

A multicentric open-label prospective study was conducted on critically ill patients admitted to the ICUs of Araba University Hospital (Vitoria-Gasteiz, Spain) and Doce de Octubre Hospital (Madrid, Spain).

The study protocol was approved by the Basque Clinical Research Ethics Committee (EPA2018019 (SP)) and was carried out under ICH Guidelines for Good Clinical Practice. The Basque Biobank (www.biobancovasco.org) provided samples and data from patients who were processed following standard operation procedures with appropriate ethical approval.

All de participants need to meet the following eligibility criteria:

- Inclusion criteria:
  - ICU patients treated with levetiracetam
  - CrCl > 50 mL/min measured in urine
  - Provided informed consent
- Exclusion criteria:
  - Age less than 18 years
  - Pregnancy
  - Hypersensitivity to the active substance or any of the excipients.

Drug Administration, Sampling Procedure and Analytical Method

As part of their medical treatment, each patient received a dose of 500, 1000 or 1500 mg of levetiracetam every 12 hours as a 30-min intravenous infusion.

For each patient, blood samples (3 mL) were taken at 0 h (pre-dose), at the end of the infusion (0.5 h) and the end of the dosing interval (12 h). Moreover, one sample was taken within 1–2 h, 3–5 h and 6–8 h intervals after drug administration.

Each sample was immediately centrifuged at 3000 rpm for 10 min to collect the plasma, which was immediately frozen at −20 ◦C. Within the following week, samples were stored at −80 ◦C until analysis.

- Analytical method

Plasma concentrations of levetiracetam were quantified with a high-performance liquid chromatography (HPLC) assay with ultraviolet detection at a wavelength of 205 nm. Separation was performed on a Symmetry® C18 (4.6 mm × 150 mm × 5 µm) column (Waters, Milford, Massachusetts, United States) eluted with ammonium phosphate and acetonitrile (95:5, v:v) mobile phase, and it was delivered at 1.2 mL/min. Sample preparation consisted of protein precipitation with acetonitrile and centrifugation for 10 min at 15,000× g. The supernatants were then injected into the HPLC system.

The assay was linear over the concentration range from 2 to 100 mg/L. Specificity was assessed using six blank standards and lower limit of quantification (LLOQ) level samples. The chromatograms were checked for interference, with no interference peaks detected at the retention time of levetiracetam. Intra–batch and inter–batch accuracy and precision were evaluated in six replicates at four different concentration levels (LLOQ and low, middle, and high-quality control). The intraday and inter-day CV and bias were never above 15%.

Stock solution stability, the stability of levetiracetam in storage conditions (at −20◦C for one month and −80 ◦C for one year), freeze-thaw stability of the analyte in the matrix from freezer storage conditions to room temperature, and auto-sampler rack stability were also evaluated and confirmed. Levetiracetam substance for standards and quality controls was a reference standard, United States Pharmacopoeia, USP.

Pharmacometric Modelling

A population PK model was built using the first-order conditional estimation method with interaction (FOCE-I) utilizing NONMEM® (v.7.4),

One- and two-compartment models were considered to describe the levetiracetam concentration-time data. The IIV associated with the structural PK parameters was modelled exponentially, and the RE was tested as either a proportional, additive or combined error model.

- Structural model selection

The model selection was based on the following aspects:

1. Biological plausibility
2. Significant reduction in the OFV
3. The precision of the parameter estimation is expressed as the relative standard error (RSE [%]) and calculated as the ratio between the standard error and the parameter estimate
4. Visual inspection of the GOF plots, including the observed versus individual and population, predicted concentration, and residual plots.

- Covariate model

The covariates studied were: sex, age, weight, height, body surface area (BSA), CrCl (measured in urine), glucose, albumin, total bilirubin, haemoglobin, leukocytes, acute physiology and chronic health evaluation (APACHE II) and diagnosis.

Random effects associated with parameters of interest were plotted versus covariates to explore potential relationships, and the SCM building tool of Perl speaks NONMEM (PsN) (v.4.8) was performed as a preliminary selection of covariates.

Categorical covariates were modelled as a shift in the typical value for the least common categories:

For dichotomous covariates:

TVP=THETA(X)*THETA(Y)**COV

For non-dichotomous covariates:

TVCL=THETA(1)

IF(DIAG.EQ.1)TVCL= THETA(1) (most common situation)

IF(DIAG.EQ.2)TVCL= THETA(1) +THETA(7)

IF(DIAG.EQ.3)TVCL= THETA(1) +THETA(8)

Continuous covariates were modelled using linear, exponential or power functions after centring on the median.

$TVP=THETA(X)*(COV/COV_{ref})**THETA(Y)$

$TVP=THETA(X)+(COV/COV_{ref})*THETA(Y)$

$TVP=THETA(X)+(COV/COV_{ref})**THETA(Y)$

Covariates were retained in the model if their inclusion significantly decreased the OFV ≥ 3.84 units (equivalent to $p < 0.05$ for one degree of freedom) compared to the previous model without the covariate. This forward inclusion approach was followed by its reverse (backward elimination), removing those covariates whose elimination did not produce a significant increase of the OFV ≤ 6.63 (equivalent to $p > 0.01$ for one degree of freedom). Therefore, when all the statistically significant covariates were added to the model, they were individually removed. If removing a covariate was found insignificant, it was dropped, favouring the simpler model.

Final model evaluation

- GOF plots: GOF plots were used as the first indicator of fittingness, including the plotting of model-based IPRED and population predictions (PRED) versus the observed concentrations (DV), conditional weighted residual errors (CWRES) vs time after dose (TAD) and the CWRES *vs* PRED.
- Bootstrap analysis: The parameter precision was evaluated by running a 2000 sample bootstrap (PsN v.4.8).
- Prediction-corrected Visual Predictive Check (pcVPC): a pcVPC was constructed by replicating 1000 studies with the same design as the original clinical study (PsN v.4.8) and representing the 10^{th}, 50^{th}, and 90^{th} percentiles of the observed data and the 95% CI for the mentioned percentiles, based on the simulated data sets (R v.4.0.2).

2.3. Evaluation of the effectiveness of levetiracetam dosages in achieving therapeutic levels in critically ill patients (Appendix II)

Stochastic simulations with the final model were performed in NONMEM® (v.7.4) to predict levetiracetam plasma minimum concentrations (Cmin). One thousand virtual subjects were simulated with CrCl values ranging from 80 to 240 mL/min. Various dosing regimens (from 500 mg to 2000 mg given at either 12- or 8-h intervals) were given as a 30-min intravenous infusion was tested.

The target Cmin concentrations were 12 to 46 mg/L at a steady state, as recommended by the International League Against Epilepsy (ILAE). The PTA was calculated in R (v.4.0.2).

2.4. Evaluation of alternative dosage regimens able to achieve target concentrations for levetiracetam in critically ill patients with ARC (Appendix III)

Stochastic simulations with the final model were performed in NONMEM® (v.7.4) in 1000 virtual subjects with CrCl values ranging from 160 to 240 mL/min to predict levetiracetam Cmin.

Various dosing regimens (from 3000 mg to 6000 mg daily) and the use of extended (4 or 6 h) or continuous infusions were tested. The PTA for a target Cmin concentrations of 12 to 46 mg/L at a steady-state was calculated in R (v.4.0.2).

2.5. Evaluation of the feasibility of the proposed dosing regimens for levetiracetam from a clinical point of view (Appendix III)

To assess the clinical feasibility of proposed dosages of levetiracetam, we evaluated the following aspects:

- Evidence of toxicity or efficacy of extended or continuous administration mode
- Evidence of toxicity or efficacy of high doses
- Stability issues.

UpToDate®(29), Micromedex® (30), the manufacturer's online labelling (19, 31) and other references considered to be relevant were consulted to gather information on stability issues.

A bibliographic search was also carried out in MEDLINE, from inception until October 2021, to evaluate the extended or continuous infusion mode. The following terms were used: ("levetiracetam" OR "Keppra") AND ("extended" OR "continuous") AND "infusion".

Finally, three electronic drug compatibility references (King Guide to Parenteral Admixtures® (32), Trissel's 2 Clinical Pharmaceutics Database® (33) and Stabilis® database (34)) were consulted for stability evaluation.

3. HYPOTHESIS AND OBJECTIVES

3.1. Hypothesis

The altered pathophysiology in critically ill patients can significantly impact the PK parameters of drugs. The concept of ARC is relatively new, but it has been frequently observed in patients admitted to ICU. However, the published information at the time of starting this thesis was scarce and consisted of isolated articles that studied ARC from an epidemiological, diagnostic, or therapeutic approach.

In critically ill patients with ARC, the plasma CL of drugs predominantly eliminated by the kidneys is significantly higher than those observed in other patients and is associated with a higher risk of therapeutic failure with the usual doses or administration methods. Several studies, mainly focused on antimicrobials, show the high risk of underdosing drugs in patients with ARC. However, ARC has the potential to influence the PK profile of any drug that is renally cleared and known to have a direct correlation between renal CL and CrCl, such as levetiracetam.

The reference range for levetiracetam trough concentrations is currently 12–46 mg/L at a steady state, as recommended by the ILAE. The favourable PK profile and the absence of significant drug interactions and broad therapeutic window make routine TDM unnecessary. However, TDM, as a way to ensure effective and safe exposures, may be indicated in certain circumstances, such as in patients with altered levetiracetam CL. An example could be the case of critically ill patients.

PPK modelling and MCS have been valuable tools for performing dose optimization in critically ill patients. There is extensive experience with these techniques in antimicrobial therapy, where the use of PK/PD analysis increases the probability of treatment success, minimizes the emergence of resistance and reduces adverse effects. We could also apply

them to the proposal of dosage regimens that ensure a correct exposure of levetiracetam in critically ill patients.

3.2. Objectives

This thesis's main objective is to develop a PPK model of levetiracetam in critically ill patients, including patients with ARC, and evaluate the adequacy of different dosage regimens by MCS.

To achieve this aim, the following steps were carried out:

1. Systematic research on the ARC phenomenon in critically ill patients, including its definition, underlying mechanisms, epidemiology, diagnosis and impact on drug pharmacokinetics and clinical outcomes (Appendix I).
2. Development of a PPK for levetiracetam in critically ill patients to identify the physiological and pathological factors that significantly influence drug pharmacokinetics and, therefore, the exposure in these patients. In this regard, causes of PK variability will be identified and quantified (Appendix II).
3. Evaluation of the effectiveness of levetiracetam dosages in achieving therapeutic levels in critically ill patients (Appendix II).
4. Evaluation of alternative dosage regimens for levetiracetam, with continuous or extended infusion time or the administration of increasing doses, able to achieve target concentrations in critically ill patients with ARC (Appendix III).
5. Evaluation of the feasibility of the proposed dosing regimens for levetiracetam from a clinical point of view considering the potential toxicity and efficacy of the doses and mode of administration evaluated and the stability of the pharmaceutical preparation (Appendix III).

4. RESULTS AND DISCUSSION

The results obtained in the different stages of this work are summarized and discussed in the following sections.

4.1. Systematic research on the ARC phenomenon in critically ill patients (Appendix I)

Study selection process

The study selection process is described in Figure 7. 48 references were selected, including 35 original articles and 13 conference abstracts.

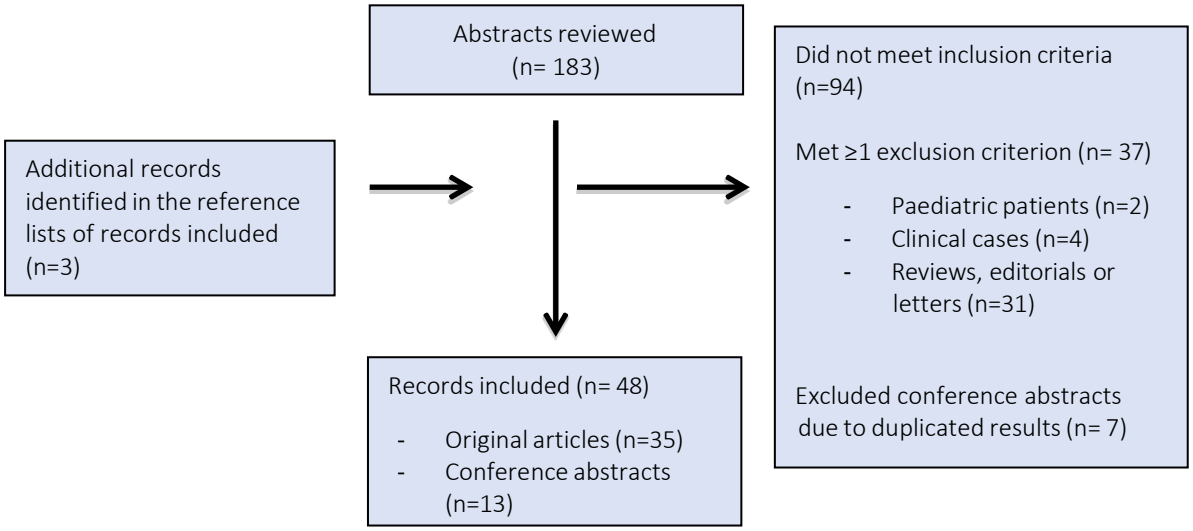

Figure 7. Study flow diagram. Adapted from Bilbao-Meseguer et al. (35).

Definition of ARC

ARC refers to the enhanced elimination of solutes compared with an expected baseline, which involves glomerular filtration and renal tubular function changes. There is currently a broad consensus in considering 130 mL/min/1.73m^2 as the lower limit of CrCl for the diagnosis of ARC, since there are studies linking CrCl>130 mL/min/1.73m^2 with subtherapeutic antimicrobial concentration (36-42).

In critically ill patients, measured CrCl in urine is generally preferred over equations that estimate glomerular filtration rate (GFR). These equations are inappropriate in this population, but a good correlation between measured GFR using inulin or radioactive iothalamate and urine CrCl in critically ill patients (43-45).

In summary, ARC is defined as a CrCl>130 mL/min/1.73m^2, preferably calculated by measuring CrCl in urine.

Mechanism of ARC in critically ill patients

The physiological mechanism responsible for ARC in critically ill patients is not well-defined, and the propositions put forward to date need to be studied further.

It has been postulated that systemic inflammatory response syndrome (SIRS), a clinical syndrome resulting from the general and nonspecific activation of the immune system, could be associated with ARC (46). The release of cytokines and pro-inflammatory mediators leads to decreased vascular resistance and increased cardiac output, which, together with intensive fluid therapy and inotropic drugs commonly used in critically ill patients, may increase renal blood flow and GFR (40, 41, 47). Nevertheless, trials have not established a statistically and clinically significant relationship between cardiac index, fluid balance, vasopressors use and ARC. Although a weak correlation has been noted between cardiac index and CrCl, it is of little use in identifying patients at risk of ARC (48).

Other theories suggest that renal functional reserve may play a role in ARC. The concept of renal functional reserve refers to the capacity of the kidney to increase GFR in response to specific physiological or pathological stimuli (49). In clinical conditions in which ARC is present (pregnant

women, kidney donors, or critically ill patients), the renal functional reserve may be used to achieve normal or supranormal renal function. The renal functional reserve can be assessed after a protein load and seems significantly lower in the elderly than in young, healthy individuals. This would explain some of the demographic characteristics that have most consistently been linked to the presence of ARC in critically ill patients, such as young age and diagnosis of polytrauma (48).

The combination of systemic inflammation coupled with a greater physiological reserve, rather than any single mechanism, has been accepted by several authors as a possible mechanism for ARC (5, 50). ARC has even been considered a marker of a good prognosis as it may predict a host's increased ability to adapt to and withstand severe infection (36, 51).

Some studies try to explain the high incidence of ARC in neurocritical patients. The usual management of these patients with vasopressors and hypertonic solutions or the presence of neuroendocrine factors, such as atrial natriuretic peptide, have been suggested as possible mechanisms (52). Indeed, a relationship between brain autoregulation impairment and estimated kidney GFR has been documented (53).

Epidemiology of ARC in critically ill patients

Frequency and course

ARC is present in 20–65% of critically ill patients (5, 36-39, 41, 46-48, 50, 51, 54-69), and it seems to be more common in certain conditions, such as traumatic brain injury (85%) (52, 53, 70), subarachnoid haemorrhage (100%) (71) and burns (65%) (44).

ARC must be considered a dynamic situation. Therefore, daily monitoring of urinary CrCl is recommended. It has been shown to be permanently present in 23-59% of patients and transient (lasting one day) in 35% of patients with one CrCl value higher than 130 mL/min/1.73m^2 (59, 62).

Between 55.4 and 74% of patients with CrCl higher than 130 mL/min/1.73m^2 in one measurement have values higher than this level in more than 50% of measurements done during ICU stay (5, 61). The relative duration of ARC per patient is five days (66), and the highest prevalence of ARC is observed on day five after admission (5, 47).

Traditionally, the main focus of assessing kidney function has been to adjust drug dosing in renal impairment. However, ARC should be recognized as a frequent alteration in critically ill patients that can lead to accelerated drug elimination and suboptimal drug levels. Thus, renal function evaluation should be routinely assessed also in patients with serum Cr within the average values.

Risk factors related to ARC

ARC has been associated with a wide range of factors such as younger age, trauma diagnosis or illness severity (Figure 8).

- Younger age: Younger age is the factor that has been most consistently related to a high risk of ARC (5, 36, 39, 41, 44, 47, 48, 50, 51, 55-59, 61, 62, 66, 69, 72). Most studies show a difference of 10–20 years between patients with and without ARC, and the mean or median age of patients with ARC is between 34 and 50 years in most studies, while in the case of patients without ARC, it is consistently over 50 years, and, in most studies, over 60 years. Just two studies have not found significant age differences, probably because the majority of participants were young (mean age<40 years) (54, 60).
- Trauma: Diagnosis of trauma has been described as a risk factor for developing ARC in several studies (5, 36, 41, 48, 50, 56, 58, 69). Publications that provide information on demographic characteristics by reason for admission (5, 48, 69) indicate that patients admitted for trauma are significantly younger. However, trauma admission has been identified as a significant risk factor in multivariate analysis when also considering age (48, 58, 69), and hence its biological influence remains uncertain.

- Illness severity: Some studies have found a significant relationship between lower severity and ARC (36, 41, 47, 48, 51, 69). This relationship has not been observed in other studies (5, 61, 62) or has only been observed using the Simplified Acute Physiologic Score (SAPS II) and APACHE II score, but not the Sequential Organ Failure Assessment (SOFA) score (50, 56, 58). It should be considered that the SAPS II and APACHE II scores are influenced by age.
- Other factors: There are other factors for which associations with ARC have been found in univariate analysis but not subsequently confirmed. This is the case of male sex (5, 48, 51, 55, 61, 69), mechanical ventilation (5, 39), high diastolic blood pressure (47), elevated cardiac index (48), high (39, 70) or low (59) vasopressor use, low use of furosemide (5, 50), high diuretic volumes (47, 50, 69) and a less-positive fluid balance (47, 50).

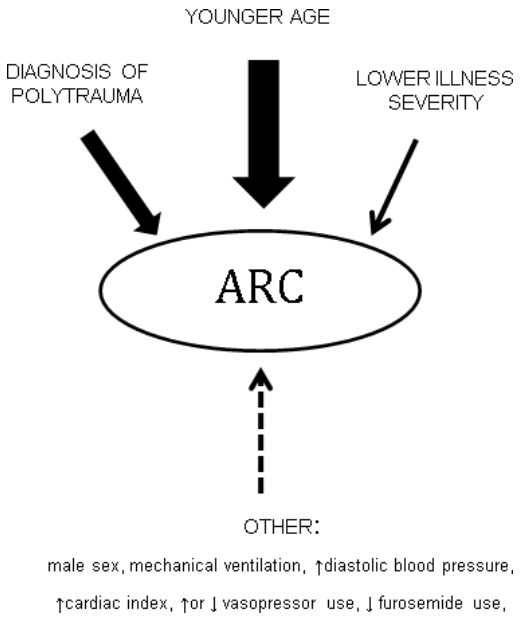

Figure 8. Risk factors associated with augmented renal clearance (ARC). Image from Bilbao-Meseguer et al. (35).

Identification of ARC in critically ill patients

Estimated versus measured CrCl

Over recent years, several observational studies have been conducted to establish the usefulness of GFR estimating equations in diagnosing critically ill patients with ARC.

- Serum creatinine-based equations: Similar results have been obtained in the vast majority of the studies, namely weak correlations and significant bias and imprecision, in critically ill patients with ARC or serum Cr concentration within the normal range for Cockcroft-Gault (CG) (46, 57, 58, 60, 61, 64, 71, 73), modified CG (64), Modification of Diet in Renal Disease (MDRD)-4 (64), MDRD-4-IDMS (46, 57, 58, 61), MDRD-6 (64) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (46, 57, 58, 61, 74). In all cases, equations underestimated CrCl, compared with measured urinary CrCl, when ARC was. In contrast, a single study (63) concluded that GFR estimating equations (CG and MDRD-4-IDMS) predicted higher CrCl than the measured values. This was attributed to differences in the population (older, with lower body weight, and more severely ill), which could lead to falsely high renal function when estimated.
- Serum cystatin C- based equations: Studies with equations based on cystatin C have also been carried out. Both, Hoek (74, 75) and Larson's (75) equations are inaccurate in detecting critically ill patients with ARC.
- Exogenous markers: two studies have been identified in which an exogenous marker is used to assess GFR in patients at risk of ARC (44, 76). A close correlation between 125I-iothalamate, inulin and sinistrin CL concerning urinary CrCl was found in these studies.

A detailed overview of the studies identified is provided in Appendix I, and all the equations mentioned are given in Table 2 of the same appendix.

Given the current evidence, measuring urinary CrCl should be considered the method of choice for identifying critically ill patients with ARC.

ARC diagnostic scores

The limited usefulness of CrCl estimating equations has motivated the creation of three scales with greater sensitivity and specificity for identifying patients at risk of ARC.

- Baptista et al. (77) proposed the use of the combination of urinary Cr <45 mg/mL and age>65 years to identify patients with ARC, with a specificity of 0.88 but low sensitivity (0.60).
- Udy et al. (48) created a scoring system to identify ARC patients, in which a modified SOFA score≤ 4 was given 1 point, admission post-trauma was given 3 points and age≤ 50 years was given 6 points. Scores were then summed, and patients were grouped into categories of low (0–3), medium (4–6) or high (7–10) risk of ARC. Higher scores were strongly associated with a greater prevalence of ARC.
- Barletta et al. (55) developed the Augmented Renal Clearance in Trauma Intensive Care (ARCTIC) scoring system to predict ARC in trauma patients. The risk factors included in the final ARCTIC score were age below 56 years (4 points), age between 56 and 75 years (3 points), serum Cr<0.7 mg/dL (3 points) and male sex (2 points). An ARCTIC score of 6 or higher had a sensitivity of 0.84 and a specificity of 0.68.

We must bear in mind that all these studies select patients with serum Cr within the normal range. Therefore, the application of ARC scores makes little sense in patients with serum Cr higher than 1.3 mg/dL, despite Cr levels not being included in the scores. Scores to detect patients at risk of ARC are valuable and easy to apply in ICUs. They can help identify patients at risk of ARC and indicate the need to measure urinary CrCl to obtain a definitive diagnosis based on the level of risk.

Impact of ARC on antimicrobial treatment

The presence of ARC in critically ill patients may have a negative impact on the attainment of therapeutic levels of many drugs. For example, enoxaparin activity is shorter in patients with ARC

(54); however, almost all of the scarce references published about this subject are focused on antimicrobial therapy, where ARC is critical because it could condition the drug efficacy also the emergence of resistance.

ARC can influence the PK profile of antimicrobial drugs that are renally cleared and have a direct correlation between their renal CL and CrCl, such as β-lactams, vancomycin or aminoglycosides.

- Impact of ARC on vancomycin pharmacokinetics: Several studies have been conducted to determine the influence of ARC on the plasma concentration of vancomycin (37, 39, 41, 42, 50, 78). The main conclusions of these studies are that patients with ARC reach lower vancomycin levels and that these levels are also more likely to be subtherapeutic.
- Impact of ARC on β-lactam pharmacokinetics: Studies investigating the influence of ARC on treatment with β-lactam antimicrobials also have been carried out. ARC patients often need higher doses of β-lactams, and there is a strong relationship between ARC and subtherapeutic levels of these antimicrobials, as observed in several studies (36, 38, 40, 79-82). In this context, the individualization of dosage regimens, such as administering antimicrobials in the extended infusion, can be useful (83). Extended infusions were found to maximize the likelihood of achieving target blood concentrations, especially in patients with ARC or obesity and with infections caused by organisms with borderline susceptibility.
- Impact of ARC on clinical outcomes in patients treated with antimicrobials: Studies investigating the relationship between ARC and clinical outcomes in patients treated with antimicrobial drugs are scarce and with different conclusions. One study (62) found that the rate of treatment failure was higher in patients who had ARC than in those who did not have ARC. On the contrary, there was no link between ARC and clinical outcome in the other two studies (36, 51).

Appendix I contains a detailed description of all these studies in the results section. In summary, ARC has been significantly and consistently related to subtherapeutic concentrations of β-lactams and vancomycin. It is expected that the influence of this phenomenon is not restricted to these specific antimicrobials but will also affect others, such as aminoglycosides, fluoroquinolones or daptomycin, and other types of drugs, such as anticoagulants or antiepileptics. On the other hand, the existing evidence on the influence of ARC on the clinical outcome is, however, scarce and diverse. It should be noted that it is difficult to establish a relationship between ARC and clinical outcomes in critically ill patients due to the complexity and variability of this population. Indeed, although ARC can increase antimicrobial elimination, increasing the risk of therapeutic failure, it has also been considered a marker of a good prognosis as it may predict a host's increased ability to adapt to and withstand severe infection. Thereby, even if ARC itself may not be a factor in poor prognosis in the critical patient, its influence on drug pharmacokinetics is evident. We also know that the success of pharmacologic treatment in ICU depends on using a suitable dosage regimen. So, in the same way, that we use reduced doses in patients with impaired renal function, the appearance of the phenomenon of ARC in critically ill patients could raise the need to establish dose recommendations based on increasing GFR.

4.2. Development of a PPK for levetiracetam in critically ill patients (Appendix II)

Twenty-seven critically ill patients were included in the study. One hundred fifty-eight plasma samples were analyzed, with a median of six and a minimum of five plasma samples per patient. Most of the patients (18 out of 27) were treated with levetiracetam 500 mg/12 h. Subjects' characteristics are described in Table 2, and the concentration versus time profile of levetiracetam in all the patients is represented in Figure 9.

Table 2. Characteristics of the population included in the study.

Covariate	N (%)	Median (range)
Sex		
Male	18 (67)	-
Female	9 (33)	-
ARC (CrCl >130 mL/min)		
Yes	10 (37)	
No	17 (63)	
Diagnostic		
Haemorrhagic strokes	10 (37)	-
Trauma	8 (30)	-
Others	9 (33)	-
Age (years)	-	60 (23–81)
Weight (kg)	-	80 (58–115)
Height (cm)	-	168 (148–189)
BSA (m^2)[1]	-	1.9 (1.59–2.33)
APACHE II	-	18 (5–35)
CrCl (mL/min)[2]	-	117 (54–239)
Glucose (mg/dL)	-	142 (91–337)
Albumin (g/dL)	-	3.4 (2.1–3.9)
Total bilirubin (mg/dL)	-	0.6 (0.2–2.1)
Hemoglobin (g/dL)	-	11.6 (6.7–14.5)
Leukocytes (10^9/L)	-	10.4 (3–24.6)

APACHE: acute physiology and chronic health evaluation; ARC: Augmented renal clearance; BSA: Body Surface Area; CrCl: creatinine clearance. [1]Body surface area (Du Bois method)= 0.007184 × Height $^{0.725}$ × Weight $^{0.425}$. [2] Creatinine clearance= [Urine creatinine (mg/dL) × Volume of urine per minute (mL/min)]/Creatinine plasma level (mg/dL). Adapted from Bilbao-Meseguer et al. (84).

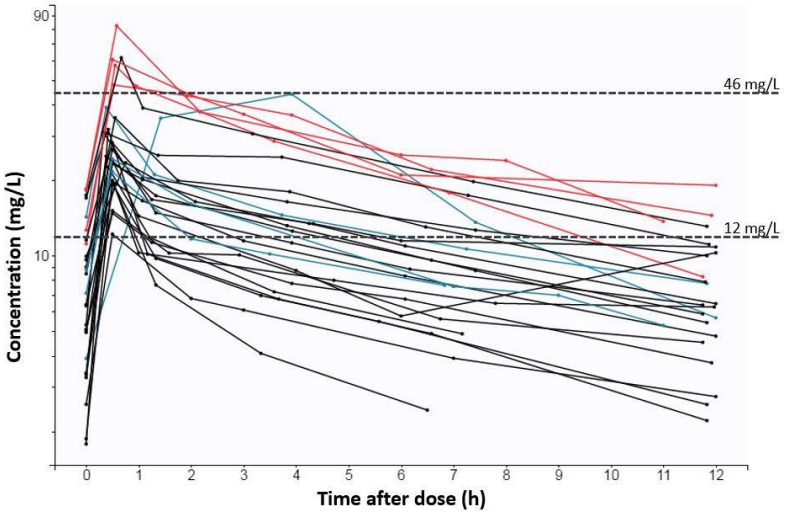

Figure 9. Spaghetti plots for plasma levetiracetam concentration-time profiles, according to the dose received by each subject. Black lines, 500 mg; blue lines, 1000 mg; red lines, 1500 mg. Dashed lines represent the target concentration values (12 mg/L- 46 mg/L). Adapted from Bilbao-Meseguer et al. (84).

Base Model

Plasma concentrations were best described by a two-compartment linear model (Table 3), characterized by drug total body CL, central volume of distribution (V1), the peripheral volume of distribution (V2) and intercompartmental clearance (Q). IIV was exponentially included for CL and V1, and no correlation was detected between the random effects associated with the PK parameters. Residual variability was proportionally modelled, and the shrinkage was low (<25%). The goodness of fit of the selected base model is depicted in Figure 10.

Table 3. Population pharmacokinetic parameters of levetiracetam estimated with one and two-compartment models.

	One- compartment (OFV=656.306) Estimate (RSE(%);shr [%])	Two- compartment (OFV=584.338) Estimate (RSE(%);shr [%])
CL (L/h)	4.37 (7)	4.6 (8)
V1 (L)	39.3 (8)	20.8 (18)
Q (L/h)	-	31.4 (21)
V2 (L)	-	34.1 (14)
IIV_CL (%)	32.3 (17) [4]	38.3 (19) [1]
IIV_V1 (%)	33.3 (20) [22]	54.4 (29) [23]
RE_proportional (%)	29.1 (9) [11]	22.3 (15) [12]

CL, clearance; V1, central volume of distribution; Q, intercompartmental clearance; V2, peripheral volume of distribution; IIV, inter-individual variability; RE, Residual error; RSE, Relative standard errors; shr, shrinkage. Adapted from Bilbao-Meseguer et al. (84).

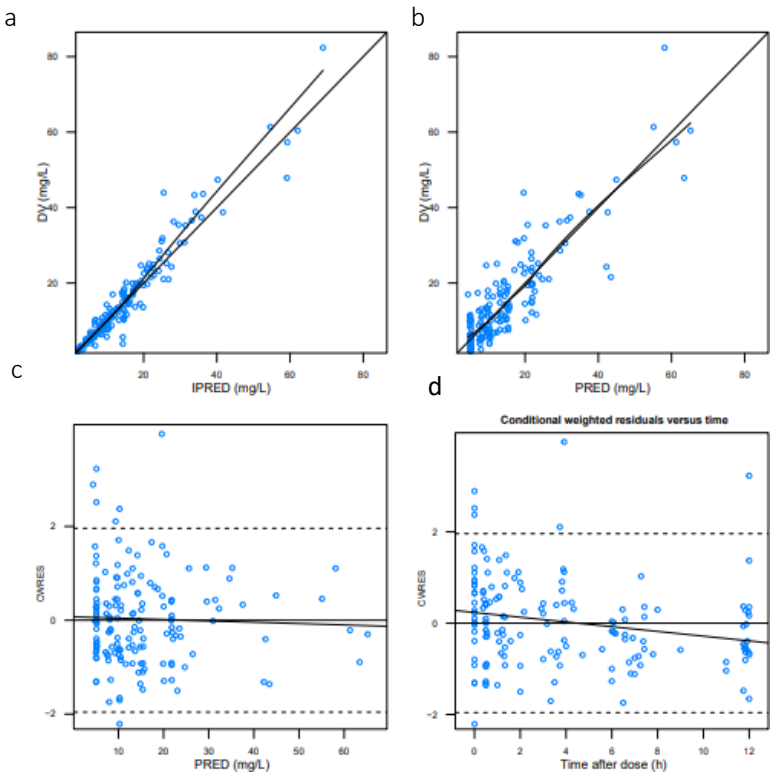

Figure 10. The goodness of fit plots of (a) individual predicted (IPRED) versus the observed (DV) levetiracetam concentrations, (b) population predicted (PRED) versus DV levetiracetam concentrations, (c) conditional weighted residuals (CWRES) versus PRED and (d) CWRES versus time after dose of the two-compartment base model. Image from Bilbao-Meseguer et al. (84).

Final model

- Covariate selection

Both the CrCl, as a continuous variable, and the ARC, as a categorical covariate, showed significant influence over CL. CrCl was selected for the final model since the reduction in IIV was greater than with the categorical variable (5.6% *vs* 3.9%). Trauma *vs* non-trauma diagnosis and APACHE II also showed influence over V1. However, they were eventually excluded from the final model since their individual deletion did not significantly increase the OFV. Therefore, the final model only considered the CrCl as a covariate of the total CL.

The final model equations were:

$$CL(L/h) = (3.5 + (\frac{CrCl}{120})^{2.5}) \times e^{\eta 1} \quad \text{Eq.21}$$

$$V1(L) = 20.7 \times e^{\eta 2} \quad \text{Eq.22}$$

where CL is clearance, CrCl is urinary creatinine clearance, V1 is central volume of distribution, η1 and η2 represent the IIV for CL and V1, respectively, followed normal distributions with a mean of 0.

Inclusion of the CrCl on the CL decreased the unexplained IIV of CL from 38.3% in the base model to 32.7% in the final model, and a statistically significant drop in the OFV was obtained with respect to the base model (ΔOFV > 6.63). Base and final PPK models' estimates are shown in Table 4.

Table 4. Base and final population pharmacokinetic models' estimates.

Parameter	Base Model (OFV= 584.338) Estimate (RSE(%);shr [%])	Final Model (OFV= 576.875) Estimate (RSE(%);shr [%])
CL (L/h) = θnr + (CrCl/120)$^{\theta r}$	4.6 (8)	-
θnr	-	3.5 (9)
θr		2.5 (17)
V1 (L)	20.8 (18)	20.7 (18)
Q (L/h)	31.4 (21)	31.9 (22)
V2 (L)	34.1 (14)	33.5 (13)
IIV_CL (%)	38.3 (19) [1]	32.7 (21) [2]
IIV_V1 (%)	54.4 (29) [23]	56.1 (29) [23]
RE_proportional (%)	22.3 (15) [12]	22.3 (15) [12]

CL, clearance; CrCl, creatinine clearance; V1, central volume of distribution; Q, intercompartmental clearance; V2, peripheral volume of distribution; IIV, inter-individual variability; RE, Residual error; RSE, Relative standard errors; shr, shrinkage. Adapted from Bilbao-Meseguer et al. (84).

- Model validation

The final PPK model and the results of the bootstrap analysis are shown in Table 5. The residual standard errors revealed that all parameters were precisely estimated. Moreover, the estimates of the parameters were very similar to the median values obtained from the bootstrap analysis.

Figure 11 displays the GOF plots for the final model. GOF plots showed no relevant trend in CWRES along with TAD or PRED, and they displayed a good correlation between population or individual prediction against the dependent variable.

Finally, the pcVPC, provided in Figure 12, confirmed that the model appropriately predicts the observed concentrations' central tendency and variability.

Table 5. Final population pharmacokinetic model estimates and bootstrap results.

Parameter	Final model estimate (RSE (%))	Bootstrap Median (95th percentile)
CL (L/h) = θnr + (CrCl/120)$^{\theta r}$	-	
θnr	3.5 (9)	3.5 (2.8–4.1)
θr	2.5 (17)	2.5 (0.9–3.9)
V1 (L)	20.7 (18)	20.8 (13.4–27.7)
Q (L/h)	31.9 (22)	30.9 (22.5–47.8)
V2 (L)	33.5 (13)	34.2 (19.9–45.4)
IIV_CL (%)	32.7 (21)	30.7 (20.2–48.3)
IIV_V1 (%)	56.1 (29)	58.0 (22.6–114.0)
RE_proportional (%)	22.3 (15)	21.5 (15.7–27.7)

CL, clearance; CrCl, creatinine clearance; V1, central volume of distribution; Q, intercompartmental clearance; V2, peripheral volume of distribution; IIV, inter-individual variability; RE, Residual error; RSE, Relative standard errors. Adapted from Bilbao-Meseguer et al. (84).

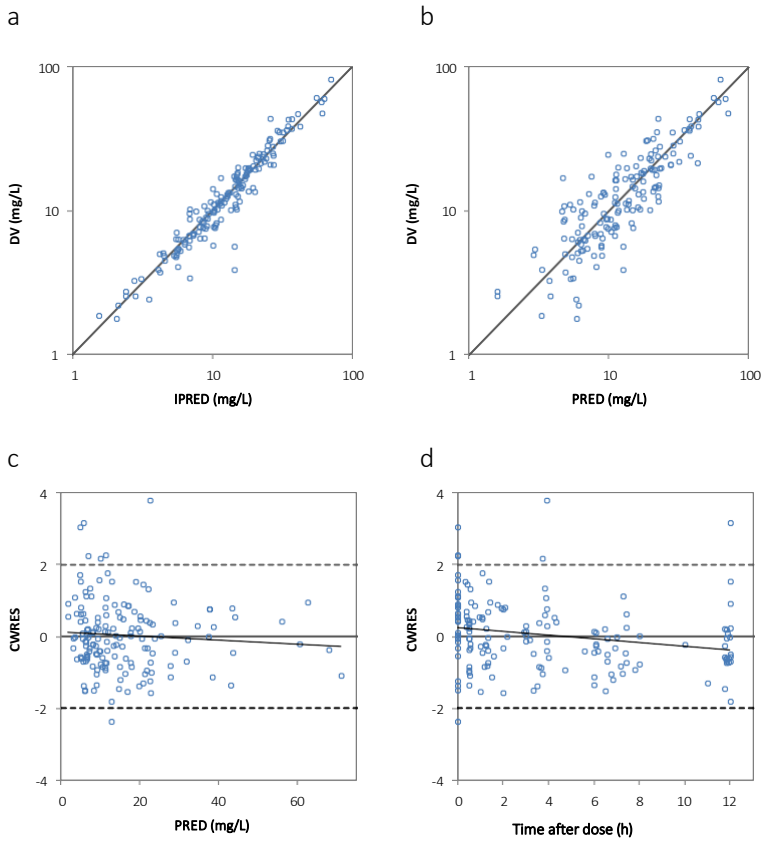

Figure 11. The goodness of fit plots of (a) individual predicted (IPRED) versus the observed (DV) levetiracetam concentrations, (b) population predicted (PRED) versus DV levetiracetam concentrations, (c) conditional weighted residuals (CWRES) versus PRED and (d) CWRES versus time after dose of the final model. Image from Bilbao-Meseguer et al. (84).

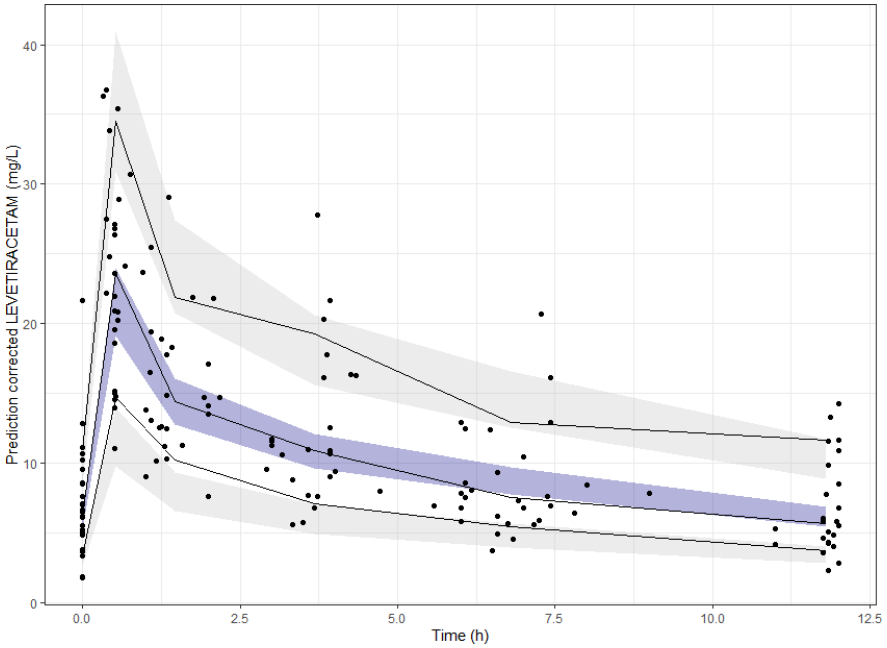

Figure 12. Prediction-corrected visual predictive check of the final model. The dots represent the prediction–corrected concentrations (mg/L). The continuous line represents the 10th, 50th and 90th observed percentiles. Simulation-based 95% confidence intervals for the median and 10th and 90th percentiles are displayed by dark and light grey shading, respectively. Image from Bilbao-Meseguer et al. (84).

4.3. Evaluation of the effectiveness of levetiracetam dosages in achieving therapeutic levels in critically ill patients (Appendix II).

Table 6 summarizes the PTA for simulated patients with different CrCl, calculated as the percentage of virtual subjects with levetiracetam trough concentrations above 12 mg/L and below 46 mg/L.

- Twice daily dosing: PTA >80% was only obtained in patients without ARC. More specifically, doses of 1500 mg and 2000 mg every 12 h would be needed for patients with CrCl of 80 and 120 mL/min, respectively.
- Three times daily dosing: In patients with CrCl of 160 and 200 mL/min, doses of 1500 and 2000 mg, respectively, given every 8 hours, would be needed. Notably, in patients with CrCl of 240 mL/min, the targeted minimum concentration of 12 mg/L was not reached even with doses of 2000 mg every eight hours.

With those dosing regimens, the probability of Cmin exceeding the value of 46 mg/L is low (<5%) in the respective group of patients.

The results of our study are in line with other PPK studies carried out on critically ill patients (85-87). According to these PPK models, the dosage regimen of 500mg every 12 hours is insufficient to achieve a PTA of at least 80% in ICU patients with normal renal function. However, this is a widely used dosage in clinical practice, especially in the prophylactic context, where between 34% and 100% of patients receive this dosage. Furthermore, the maximum dosage approved for levetiracetam, 3000mg daily in short infusion, also resulted in subtherapeutic levels in patients with ARC. Considering this evidence, it is worth wondering whether we are using levetiracetam adequately in critically ill patients and highlights the need to establish new dosing guidelines for levetiracetam in critically ill patients with ARC.

Table 6. Probability of target attainment based on Monte Carlo simulations of the final population model

CrCl (mL/min)	Dose (mg)	Perfusion duration (min)	Daily Dose (mg)	Probability of Cmin (%) > 12 mg/L	> 46 mg/L
Twice daily (Tau = 12 h)					
80	500	30	1000	12	0
	1000	30	2000	60	0
	1500	30	3000	**85**	3
	2000	30	4000	**94**	14
120	500	30	1000	6	0
	1000	30	2000	43	0
	1500	30	3000	72	2
	2000	30	4000	**85**	6
160	500	30	1000	1	0
	1000	30	2000	22	0
	1500	30	3000	51	0
	2000	30	4000	69	2
200	1000	30	2000	6	0
	1500	30	3000	25	0
	2000	30	4000	42	0
240	1500	30	3000	7	0
	2000	30	4000	15	0
Three times daily (Tau = 8 h)					
80	500	30	1500	51	0
	1000	30	3000	**93**	5
	1500	30	4500	**99**	31
120	500	30	1500	33	0
	1000	30	3000	**84**	2
	1500	30	4500	**96**	17
160	500	30	1500	12	0
	1000	30	3000	65	0
	1500	30	4500	**89**	5
	2000	30	6000	**97**	17
200	500	30	1500	4	0
	1000	30	3000	39	0
	1500	30	4500	69	1
	2000	30	6000	**84**	5
240	1000	30	3000	15	0
	1500	30	4500	38	0
	2000	30	6000	59	1

Cmin: Minimum levetiracetam concentration; CrCl, creatinine clearance; Tau, dosing interval. In bold, probability of Cmin>80%. Adapted from Bilbao-Meseguer et al. (84).

4.4. Evaluation of alternative dosage regimens able to achieve target concentrations for levetiracetam in critically ill patients with ARC (Appendix III).

Table 7 summarizes the PTA for simulated ARC patients with different CrCl, calculated as the percentage of virtual subjects with levetiracetam trough concentrations above 12 mg/L and below 46 mg/L.

- For patients with CrCl of 160 mL/min: it would be possible to achieve a PTA of at least 80% with 1000mg infused over 4 hours every 8 hours or with 1500 mg over 30 minutes every 8 hours.
- For patients with CrCl of 200 mL/min: it would be necessary to administer 3000mg in a continuous infusion, 1500mg over 4 hours every 8 hours or 2000mg over 30 minutes every 8 hours.
- For patients with CrCl of 240 mL/min: it would be necessary to administer 4500mg in continuous infusion or 2000mg over 4 hours every 8 hours.

With those dosing regimens, the probability of Cmin exceeding the value of 46 mg/L is <5%.

In summary, according to our results, the target plasma levels would only be reached in ARC patients with the administration of at least 3000mg in a 4-hours infusion (in patients with CrCl of 160mL/min) or continuous infusion (in patients with CrCl of 200mL/min). Although extended and continuous infusions are not included in the summary of product characteristics (SPC) of levetiracetam, they may be an alternative that avoids the use of doses higher than 3000mg. However, in patients with CrCl of 240 mL/min, it is not possible to reach the target plasma levels with the maximum authorized dose regardless of the mode of administration, and higher doses are compulsory. Our results indicate that it is necessary to optimize the dosage regimen in terms of increasing the dose and/or infusion time to reach the target plasma concentrations in critically ill patients with ARC.

Table 7. Probability of target attainment based on Monte Carlo simulations.

CrCl (mL/min)	Total daily dose (mg)	Dose (mg)	Dosing interval (hours)	Perfusion duration (hours)	Probability of Cmin (%) >12mg/L	>46mg/mL
160	3000	1500	12	0.5	51	0
				4	62	<0.5
				6	70	<0.5
		1000	8	0.5	65	0
				4	**81**	<0.5
				6	**88**	1
		3000	24	24	**98**	1
	4500	1500	8	0.5	**89**	5
200	3000	1000	8	6	69	<0.5
		3000	24	24	**89**	<0.5
	4500	1500	8	4	**84**	1
				6	**92**	2
	6000	2000	8	0.5	**84**	5
240	3000	3000	24	24	68	<0.5
	4500	1500	8	4	61	<0.5
				6	74	<0.5
		4500	24	24	**96**	1
	6000	2000	8	4	**80**	2
				6	**89**	3
		6000	24	24	**99**	7

Cmin: Minimum levetiracetam concentration; CrCl, creatinine clearance. In bold, PTA (probability of Cmin higher than 12 mg/L) >80%. Adapted from Bilbao-Meseguer et al. (88).

4.5. Evaluation of the feasibility of the proposed dosing regimens for levetiracetam from a clinical point of view (Appendix III)

Mode of administration: extended or continuous infusion

Currently, there is the experience of using levetiracetam in a continuous infusion, both intravenously and subcutaneously. Although more studies would be necessary, levetiracetam given as a continuous infusion appears to be effective and well-tolerated.

Our search identified two publications that include patients receiving intravenous levetiracetam in continuous infusion. In both studies no safety issues regarding the administration of

levetiracetam in continuous infusion was described (89, 90). However, one of these studies was carried out in patients diagnosed with status epilepticus, and continuous infusion without bolus was less effective than bolus administration of levetiracetam. Although the study aimed not to investigate the differential efficacy of both administration methods, the authors hypothesized that in the context of status epilepticus, peak levels after rapid levetiracetam infusions might be responsible for higher effectiveness bolus (89).

There are also case reports assessing the administration of levetiracetam in continuous subcutaneous infusion in palliative care. In this setting, levetiracetam subcutaneous infusion seems an efficacious option for seizure control with an excellent adverse effect profile (91- 94). However, randomized controlled trials are needed to establish the efficacy and tolerability of subcutaneous levetiracetam administration.

Micromedex® (30) includes the study of Burakgazi et al. (90) in its information, while UpToDate® (29) does not refer to this administration method in its monograph of levetiracetam.

The use of high doses

The information contained in the SPC establishes a maximum dose of 3000mg per day (19, 31) based on phase III trials with fixed-dose regimens. Even though evaluating a dose-effect relationship was not the primary objective of these trials, the results indicate a dose-effect relationship in this dose range (95-97).

However, higher doses (up to 4000 mg) did not increase efficacy but increased the rate of side effects (98, 99). This is based on studies that compared differing levetiracetam fixed doses to a group comparison. A more recent retrospective study (100) analyzed the individual response to a levetiracetam dose increment. It concluded that

dose-escalation improved treatment outcomes without additional safety hazards. The final daily doses ranged from 1000mg to 6000mg.

In tertiary databases (29, 30), the maximum dose recommended in treating focal and generalized onset seizures or prophylactically is also 3000 mg per day.

Stability of levetiracetam infusion solutions

According to the European SPC of Keppra® (19), intravenous levetiracetam is physically compatible and chemically stable for at least 24 hours at room temperature. While the SPC, authorized by the United States Food & Drug Administration (FDA), pointed out that the diluted solution should not be stored for more than 4 hours at controlled room temperature. However, other FDA-approved levetiracetam medications maintain 24-hour stability, and there are also pre-diluted alternatives (101).

The information regarding the stability of levetiracetam solutions found in the consulted electronic databases is scarce and differs between them:

- King Guide to Parenteral Admixtures® (32): a 24-hour at room temperature
- Trissel's 2 Clinical Pharmaceutics Database® (33): 4 hours at room temperature
- Stabilis® database (34): does not provide information on stability at room temperature.

In summary, the proposed new dosage recommendations for critically ill patients with ARC meet feasibility criteria that allow them to be transferred to the clinical environment with safety and efficacy.

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SECTION 2:

CONCLUSIONS

1. The systematic review conducted on augmented renal clearance (ARC), defined as a creatinine clearance (CrCl) >130 mL/min/1.73 m^2, pointed out that this phenomenon is a prevalent condition in critically ill patients, being present in 20 to 65% of the patients. The highest prevalence has been observed in certain conditions such as traumatic brain injury (85%), subarachnoid haemorrhage (100%) and burns (65%). In addition, younger age, polytrauma and lower severity illness were identified as risk factors for ARC.

2. The collected evidence showed that ARC is a dynamic and temporary condition that influences the clearance of drugs primarily eliminated by renal excretion. Consequently, it would be necessary to modulate the dose according to the patients' daily variations in renal clearance. The use of glomerular filtration rate estimating equations tends to underestimate the value of CrCl in critically ill patients, leading to the underdiagnosis of ARC in the intensive care setting. Therefore, urinary CrCl measurement in these patients is recommended.

3. A population pharmacokinetic model has been developed for levetiracetam in critically ill patients with normal renal function or ARC. A two-compartment model best described the drug's pharmacokinetics, and only CrCl was found to be a significant covariate of levetiracetam clearance.

4. The pharmacokinetic analysis of levetiracetam in critically ill patients with ARC demonstrated that the conventional dosage regimens (500-1500 mg twice daily in a short infusion) do not allow to obtain through plasma concentrations in the defined target, between 12 and 46mg/L. Therefore, specific recommendations for dosing adjustment of levetiracetam in this subpopulation are needed, and this should be extended to other drugs whose pharmacokinetics are affected by this clinical situation.

5. Monte Carlo simulations showed that levetiracetam in critically ill patients with ARC should be administered in extended or continuous infusions rather than short infusions to achieve target plasma concentrations. Higher doses than those stated in the summary of product characteristics would be necessary for patients with ARC and CrCl values of 200 mL/min or greater. Critically ill patients with normal renal function would require short infusions of at least 1000 mg every eight hours or 1500 mg every 12 h to attain target concentrations.

6. The proposed dosage regimens to be implemented in critically ill patients with ARC consider biopharmaceutical and pharmacokinetic aspects that condition the probability of treatment success, such as the controversial stability of the drug in solution or the duration of perfusion. Consequently, the new dosage recommendations meet feasibility criteria that allow them to be transferred to the clinical environment with safety and efficacy; nevertheless, further clinical studies are needed to confirm these results.

SECTION 3:

APPENDIXES

APPENDIX I:

Augmented Renal Clearance in Critically Ill Patients: A Systematic Review

Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís MÁ.

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SYSTEMATIC REVIEW

Augmented Renal Clearance in Critically Ill Patients: A Systematic Review

Idoia Bilbao-Meseguer[1] · Alicia Rodríguez-Gascón[2] · Helena Barrasa[3] · Arantxazu Isla[2] · María Ángeles Solinís[2]

Abstract

Background Traditionally, renal function in critically ill patients has been assessed to identify renal dysfunction, and dose adjustment is generally accepted in such a context. Nevertheless, augmented renal clearance (ARC) is a less well-studied phenomenon that could lead to faster elimination of drugs, resulting in subtherapeutic concentrations and poorer clinical outcomes when standard dosage guidelines are followed.

Objective The aim of this systematic review was to gather and summarise all the available evidence on ARC in critically ill patients, including its definition, underlying mechanisms, epidemiology, diagnosis and impact on both drug pharmacokinetics and clinical outcomes.

Method A systematic review was conducted to include all the original studies that provided information on ARC in critically ill patients, and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results Augmented renal clearance, defined as a creatinine clearance (CrCl) > 130 mL/min/1.73 m^2, preferably measured in urine, is present in 20–65% of critically ill patients. Younger age, polytrauma and lower severity illness have been identified as risk factors. An influence of ARC on antimicrobial pharmacokinetics has been observed, with ARC consistently being associated with subtherapeutic antibiotic plasma concentrations.

Conclusion ARC is a prevalent condition in critically ill patients, especially in young people, with urinary CrCl being the best diagnostic method because mathematical estimates tend to underestimate CrCl. ARC increases renal drug elimination and has a clear influence on certain antimicrobial plasma levels, but is yet to define its impact on clinical outcomes and on pharmacokinetics of other types of drugs. Research on the need to stage ARC and establish specific dosing guidelines is warranted.

Key Points

Augmented renal clearance (ARC), defined as a creatinine clearance (CrCl) > 130 mL/min/1.73 m^2, is present in 20–65% of critically ill patients. The best diagnostic method for the identification of critically ill patients with ARC is measured urinary CrCl.

Younger age, polytrauma and lower severity illness have been identified as risk factors for ARC.

ARC has been consistently associated with subtherapeutic antimicrobial plasma concentrations.

✉ Arantxazu Isla
arantxa.isla@ehu.eus

✉ María Ángeles Solinís
marian.solinis@ehu.eus

[1] Department of Pharmacy, Cruces University Hospital, Plaza de Cruces 12, 48903 Barakaldo, Bizkaia, Spain

[2] Pharmacokinetic, Nanotechnology and Gene Therapy Group (PharmaNanoGene), Faculty of Pharmacy, Lascaray Research Center, University of the Basque Country UPV/EHU, Paseo de la Universidad, 7, 01006 Vitoria-Gasteiz, Spain

[3] Intensive Care Unit, University Hospital of Alava, c/ Olaguibel no 29, Vitoria-Gasteiz, Spain

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1 Introduction

Antimicrobial treatment in critically ill patients remains challenging. During critical illness, physiological changes and therapeutic interventions can alter drug pharmacokinetics, making the standard dosage guidelines unsuitable. Drugs in critically ill patients usually have a greater volume of distribution (Vd) due to capillary leak, inflammatory response and aggressive fluid loading. Increased Vd has been demonstrated for hydrophilic antimicrobials such as aminoglycosides, β-lactams, daptomycin, linezolid and glycopeptides [1, 2]. Hypoalbuminaemia, also frequently found in this population, might change the unbound drug fraction in blood, which in turn would be likely to influence the pharmacokinetics of antimicrobials that are highly protein bound (>90%) and have high extraction rates. For a drug that is highly protein bound, hypoalbuminaemia is likely to lead to a high free fraction of antimicrobial in the early stage of the dosing interval, which might result in advantageously high unbound concentrations. On the other hand, changes in Vd and protein binding can lead to low unbound concentrations later in the dosing interval, which could reduce the effectiveness of time-dependent antimicrobials [1–3]. These alterations, together with some intensive care procedures such as continuous renal replacement therapies, could lead to lower plasma levels of antimicrobials [1–3]. In contrast, kidney or liver impairment can result in an accumulation of the drugs in plasma and therefore higher plasma concentrations [1–3].

Traditionally, renal function in critically ill patients has been routinely assessed with the objective of detecting renal impairment and adjusting drug doses. Nevertheless, augmented renal clearance (ARC) has also been identified in intensive care unit (ICU) patients. As a result, renal drug clearance can be increased in these patients compared with noncritically ill patients. This may be particularly important for antibacterial agents that are eliminated by the kidney and whose activity is time-dependent, such as β-lactams. Patients with ARC could be at risk of suboptimal antimicrobial exposure when conventional dosage regimens are used.

Changes in antimicrobial pharmacokinetics that take place in the critically ill can lead to clinical failure or an increased risk of adverse effects. In this context, individualised antimicrobial dosing and the application of pharmacokinetic/pharmacodynamic (PK/PD) principles are recommended [1–3]. The use of PK/PD analysis increases the probability of treatment success, minimises the emergence of resistance and reduces adverse effects [3]. The combination of the PK/PD analysis with Monte Carlo simulation can guide antimicrobial prescribing, considering the individual characteristics of patients and adjusting the antimicrobial therapy to their clinical status, which is especially relevant in certain subpopulations such as critically ill patients with ARC. Monte Carlo simulation is a statistical modelling tool that allows expanding the sample size, considering the variability of the PK and PD parameters in the estimation of the PK/PD indices [3]. It allows individualisation of antimicrobial therapy and simulation of different scenarios (higher doses, extended or continuous infusions, etc.) to support decision making and thereby improve clinical outcome. One of the principal requirements to perform Monte Carlo simulations is a validated population PK model including PK parameters, their variability and a covariate model [3]. For these reasons, it is important to investigate the pharmacokinetic alterations that take place in the intensive care setting and their influence on antimicrobial treatment.

In line with the fact that ARC is a relatively new concept, and the difficulty of conducting research in the intensive care setting, the evidence available to date regarding ARC is scarce and diverse. The aim of this review was to gather and summarise all the evidence on ARC in critically ill patients, including its definition, underlying mechanisms, epidemiology, diagnosis, and impact on drug pharmacokinetics and clinical outcomes.

2 Methods

2.1 Adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines

This systematic review is reported following the applicable criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines [4].

2.2 Search Strategy

The MEDLINE, EMBASE and International Pharmaceutical Abstracts (IPA) databases were systematically searched, from inception until May 2017, for all studies that reported information on ARC in critically ill patients. The following terms were used: (augmented renal clearance OR hyperfiltration) AND (critic* OR intensive). The search was additionally limited to English-language articles. Secondary literature was identified using the references included from the first search.

2.3 Eligibility Criteria

All references that reported information on underlying mechanisms, epidemiology, diagnosis, or impact of ARC

in critically ill patients were included. Articles were excluded if they assessed paediatric patients or were clinical cases, reviews, letters or editorials.

2.4 Study Selection

Records obtained from the MEDLINE, EMBASE and IPA databases were compared and duplicates were eliminated. Abstracts of all records were screened to identify relevant publications according to the selection criteria. If there was insufficient information in the abstract, the full text was retrieved and assessed.

2.5 Data Collection Process and Analysis

For each record, the following data regarding ARC, when reported, were extracted: definition of ARC, proposed mechanism(s), frequency, course, related factors, method of diagnosis, and impact on both drug pharmacokinetics and clinical outcome. Given the nature of the topic studied, that ARC is a fairly new concept and that randomised trials were not expected, we conducted a descriptive critical analysis of the records included.

3 Results

3.1 Study Selection

As described in Fig. 1, we reviewed the abstracts of the 183 records obtained. Of these, 131 were not included as they did not meet the selection criteria. Additionally, seven conference abstracts were excluded because they were based on the same study and gave the same results as an original article published subsequently and included in this review. Of the 45 records included, 32 were original articles [5–36] and 13 were conference abstracts [37–49]. An additional three original articles were identified from the reference lists of selected papers [50–52].

3.2 Definition of Augmented Renal Clearance (ARC)

ARC refers to enhanced elimination of solutes compared with an expected baseline, a process that involves changes in glomerular filtration and renal tubular function. Glomerular filtration rate (GFR) is generally accepted as the best overall index of kidney function, and ARC has been associated with elevated urinary creatinine clearance (CrCl); hence, this parameter is used to define ARC [21, 53].

The normal GFR in young adults is approximately 125 mL/min/1.73 m^2 [53]. ARC is a fairly new concept and does not have a standard definition. Nevertheless, there is currently a broad consensus in considering 130 mL/min/1.73 m^2 as the lower limit of CrCl for the diagnosis of ARC, since there are studies linking CrCl > 130 mL/min/1.73 m^2 with subtherapeutic antimicrobial concentration [15, 18, 24, 26, 31, 32, 48].

Assessing the presence of ARC in critically ill patients is still challenging. GFR measured as the clearance of an exogenous filtration marker is the best overall index of kidney function. The 'gold standard' method is the urinary clearance of inulin during a continuous intravenous infusion. However, this is an invasive and expensive method, and, to simplify the procedure, alternative endogenous filtration markers are used in clinical practice, mainly creatinine and cystatin C. In the general population, GFR estimating equations to derive GFR from serum creatinine are preferred over relying on serum creatinine concentration alone. These equations have been developed from large epidemiological studies with the aim of diagnosing and monitoring patients with chronic kidney disease and stable renal function. As they all assume that endogenous serum markers are in steady state and this cannot be assumed in critically ill patients, the use of measured CrCl in urine is generally preferred in this setting. A good correlation has been observed between measured GFR using inulin or radioactive iothalamate and urine CrCl in critically ill patients [16, 51]. In summary, ARC is defined as a

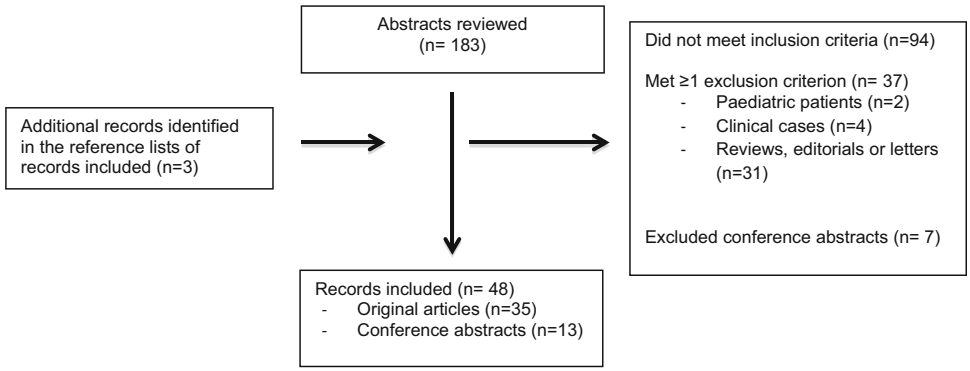

Fig. 1 Study selection process

CrCl > 130 mL/min/1.73 m^2, preferably calculated by measuring CrCl in urine (urinary CrCl).

3.3 Mechanism of ARC in Critically Ill Patients

No articles were found whose main objective was to establish the mechanism(s) underlying ARC. The physiological mechanism responsible for ARC in critically ill patients is not well-defined and the propositions put forward to date need to be studied further. It has been postulated that systemic inflammatory response syndrome (SIRS), a clinical syndrome resulting from the general and nonspecific activation of the immune system, could be associated with ARC [25]. SIRS may occur in several conditions that may or may not be related to infection, including sepsis, severe trauma, major surgery and burns. The release of cytokines and pro-inflammatory mediators leads to decreased vascular resistance and increased cardiac output, which, together with intensive fluid therapy and inotropic drugs commonly used in critically ill patients, may increase renal blood flow and GFR [31, 32, 34].

Nevertheless, trials have been unable to establish a statistically and clinically significant relationship between cardiac index, fluid balance or use of vasopressors and ARC. Although a weak correlation has been noted between cardiac index and CrCl, it has been shown to be of little use in identifying patients at risk of ARC [28].

Other theories suggest that renal functional reserve may play a role in ARC. The concept of renal functional reserve refers to the capacity of the kidney to increase GFR in response to certain physiological or pathological stimuli [54]. In clinical conditions in which ARC is present (pregnant women, kidney donors or critically ill patients), renal functional reserve may be used to achieve normal or supranormal renal function. Renal functional reserve can be assessed after a protein load and seems to be significantly lower in the elderly than in young healthy individuals. This would explain some of the demographic characteristics that have most consistently been linked to the presence of ARC in critically ill patients, such as young age and diagnosis of polytrauma [28].

The combination of systemic inflammation coupled with a greater physiological reserve, rather than any single mechanism, has been accepted by several authors as a possible mechanism for ARC [19, 23]. ARC has even been considered a marker of a good prognosis as it may predict a host's increased ability to adapt to and withstand severe infection [5, 15].

In critically ill patients with severe traumatic brain injury, Dias et al. [10] documented a relationship between brain autoregulation impairment and estimated kidney GFR. Autoregulation of blood flow is the inherent capacity of the vascular bed to maintain constant perfusion despite variations in arterial blood pressure (ABP) and intracranial pressure (ICP), and is an important mechanism for maintaining cerebral and kidney blood flow constant. In the aforementioned study, CrCl was found to be negatively correlated with the cerebrovascular pressure reactivity index (PRx), which expresses the correlation between ABP and ICP. For each 10 mL/min increase in estimated CrCl, a mean decrease in PRx of 0.01 was expected, i.e. the higher the CrCl, the better the cerebrovascular reactivity. Furthermore, the mean PRx value for a fatal outcome was significantly greater than the mean PRx for a nonfatal outcome. Udy et al. [36] have also recently explored the potential mechanisms of ARC in patients with traumatic brain injury and found significantly elevated atrial natriuretic peptide (ANP) levels compared with those reported in healthy volunteers. ARC is a common finding in neurocritic patients and some theories to explain this relationship have also been postulated. The usual management of these patients with vasopressors and hypertonic solutions or the presence of neuroendocrine factors, such as ANP, is suggested to explain the high incidence of ARC in this population. These studies open a new line of research on the mechanism of ARC in patients with traumatic brain injury, and further studies are needed to understand the pathophysiological mechanism between brain and kidney autoregulation and the practical implications of this relationship.

3.4 Epidemiology of ARC in Critically Ill Patients

3.4.1 Frequency and Course

Observational studies show that ARC is present in 20–65% of critically ill patients [5–9, 11, 12, 15, 17–19, 22–28, 30, 32–34, 37, 44, 45, 49, 52], and that it seems to be more common in certain conditions, such as traumatic brain injury (85%) [10, 36, 50], subarachnoid haemorrhage (100%) [35] and burns (65%) [51].

Most studies define patients with ARC as those in which a single measurement of urinary CrCl is greater than a given limit (120–130 mL/min/1.73 m^2). In some studies, patients have been considered to have ARC if more than 50% of the CrCl measurements during admission had been higher than 130 mL/min/1.73 m^2. These studies have shown that between 55.4 and 74% [22, 23] of patients who have CrCl higher than 130 mL/min/1.73 m^2 in one measurement are found to have values higher than this level in more than 50% of measurements. De Waele et al. [12] found that 59% of patients found to have CrCl higher than 130 mL/min/1.73 m^2 once, had ARC throughout their ICU stay. Another study showed that ARC was permanently present in 23% of patients and was transient (lasting 1 day)

in 35% of patients with one CrCl value higher than 130 mL/min/1.73 m^2 [27], while Grootaert et al. [44] found that 40% of patients who had one CrCl value higher than 120 mL/min/1.73 m^2 had episodes of CrCl higher than this level for at least 5 days, and that 5 days was also the relative duration of ARC per patient. In addition, we have identified two studies that describe ARC prevalence over time in patients admitted to the ICU. In both studies, the highest prevalence of ARC is observed on day 5 after admission [23, 34].

3.4.2 Related Factors

ARC has been associated with a wide range of factors (Fig. 2). One that has most consistently been linked to a high risk of ARC, in both univariate and multivariate analysis, is younger age [5, 7–9, 11, 12, 15, 19, 22, 23, 26–28, 32, 34, 38, 44, 51, 52]. Most studies show a difference of 10–20 years between patients with and without ARC. The mean or median age of patients with ARC is between 34 and 50 years in most studies, while in the case of patients without ARC, it is always over 50 years, and, in most studies, over 60 years. Just two studies have not found significant differences in age, probably because the majority of participants were young (mean age < 40 years) [6, 17].

Trauma has also been described as a risk factor for developing ARC in several studies [8, 11, 15, 19, 23, 28, 32, 52]. Publications that provide information on demographic characteristics by reason for admission [23, 28, 52] indicate that patients admitted for trauma are significantly younger. On the other hand, trauma admission has been identified as a significant risk factor in multivariate analysis, when also considering age [11, 28, 52], and hence its biological influence remains uncertain.

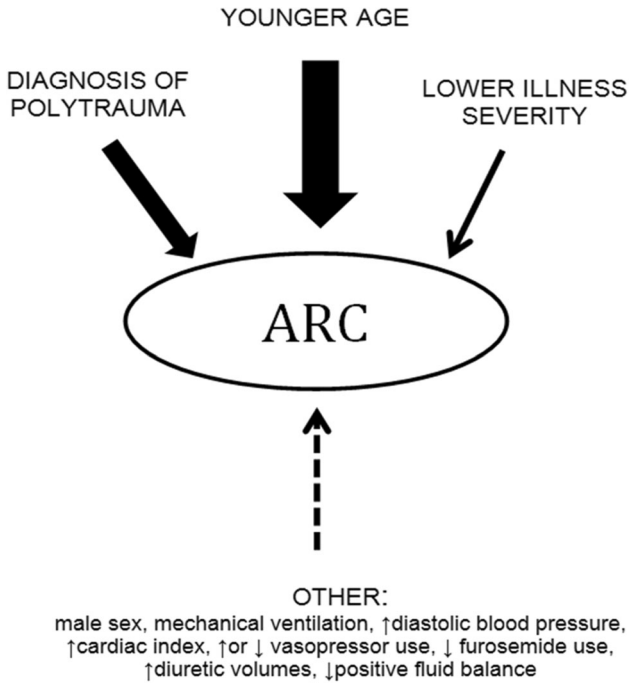

Fig. 2 Risk factors associated with ARC. *ARC* augmented renal clearance

Research has also focused on the relationship of ARC with illness severity, assessed by the Acute Physiology And Chronic Health Evaluation II (APACHE II) score, Simplified Acute Physiology Score (SAPS II) and/or Sequential Organ Failure Assessment (SOFA) score. Some studies have found a significant relationship between lower severity and ARC [5, 15, 28, 32, 34, 52]. This relationship has not been observed in other studies [22, 23, 27] or has only been observed using the SAPS II and APACHE II score, but not the SOFA score [8, 11, 19]. It should be considered that the SAPS II and APACHE II scores are influenced by age.

Other factors for which associations with ARC have been found in univariate analysis, but not subsequently confirmed, include male sex [5, 7, 22, 23, 28, 52], mechanical ventilation [23, 26], high diastolic blood pressure [34], elevated cardiac index [28], high [26, 50] or low [12] vasopressor use, low use of furosemide [19, 23], high diuretic volumes [19, 34, 52] and a less-positive fluid balance [19, 34].

3.5 Identification of ARC in Critically Ill Patients

3.5.1 Estimated Versus Measured Creatinine Clearance

Over recent years, several observational studies have been conducted to establish the usefulness of GFR estimating equations in the diagnosis of critically ill patients with ARC. A detailed overview of the studies identified is provided in Table 1. The conclusions should be interpreted with caution because the comparator used is CrCl measured in urine, which, despite being a pragmatic alternative, is not the 'gold standard'. All the equations mentioned are given in Table 2.

Baptista et al. [33] were the first to characterise the accuracy of four commonly used estimating equations—Cockcroft–Gault (CG), Modified CG, 4-variable Modification of Diet in Renal Disease (MDRD-4) and 6-variable Modification of Diet in Renal Disease (MDRD-6). In 86 critically ill patients with ARC (CrCl > 130 mL/min/1.73 m^2), all the equations, except MDRD-6, yielded values that were statistically significantly but weakly correlated with measured urinary CrCl ($r^2 < 0.3$, $p < 0.05$). They all significantly underestimated the measured value of CrCl, with a bias of between 39 mL/min/1.73 m^2 (for CG) and 84 mL/min/1.73 m^2 (for modified CG), and a precision of ± 70–75 mL/min/1.73 m^2, which is clinically unacceptable. Grootaert et al. [30] conducted a similar study, retrospectively comparing the validity of two

Table 1 Overview of studies included in this review that analysed the accuracy of methods for diagnosing ARC in critically ill patients

Study	Reference test and definition of ARC	Method assessed	ARC samples [*n*]	Spearman coefficient[a] [r_S]	Bias ± precision[b] [mL/min/1.73 m^2 or mL/min]	Detection of ARC patients [specificity/sensitivity]	Other information provided
Barletta et al. [9]	CrCl measured in urine > 130 mL/min	mCG CKD-EPI MDRD-4-IDMS	45	NA	mCG: − 52 ± 58 CKD-EPI: NA MDRD-4-IDMS: NA	NA	Underestimation of ARC Inaccurate CrCl estimates became evident when measured CrCl > 160 mL/min
Ruiz et al. [11]	CrCl measured in urine > 130 mL/min/1.73 m^2	CG mCG MDRD-4 CKD-EPI	120	NA	CG: − 35.7 ± 47 mCG: − 78.6 ± 78.6 MDRD-4: − 40.9 ± 51.9 CKD-EPI: − 57.9 ± 58.3	CG: 0.63/0.83 mCG: 0.71/0.67 MDRD-4: 0.61/0.77 CKD-EPI: 0.74/0.75	Underestimation of ARC
Steinke et al. [14]	CrCl measured in urine > 130 mL/min/1.73 m^2	CG CKD-EPI Hoek	16	NA	NA	CG: 0.81/0.69 CKD-EPI: 0.96/0.25 Hoek: 0.96/0.38	Underestimation of ARC
Adnan et al. [17]	CrCl measured in urine > 130 mL/min	CG	19	CG: − 0.04 (NS)	CG: − 57 ± 54	NA	Underestimation of ARC
Baptista et al. [22]	CrCl measured in urine > 130 mL/min/1.73 m^2 in ≥ 50% of measurements	CG CKD-EPI MDRD-4-IDMS	30	NA	NA	NA	Progressive underestimation of CrCl > 120 mL/min/m^2 and overestimation of CrCl < 120 mL/min/m^2
Udy et al. [25]	*Group A:* CrCl measured in urine between 120 and 149 mL/min/1.73 m^2 *Group B:* CrCl measured in urine ≥150 mL/min/1.73 m^2	CG CKD-EPI MDRD-4-IDMS	53	*Group A:* CG: 0.369 (NS) CKD-EPI: 0.347 (NS) MDRD-4-IDMS: 0.047 (NS) *Group B:* CG: 0.399 (p = 0.009) CKD-EPI: 0.46 (p = 0.005) MDRD-4-IDMS: 0.427 (p = 0.009)	*Group A:* CG: − 6.62 ± 23.9 CKD-EPI: − 29.2 ± 10.8 MDRD-4-IDMS: − 22.7 ± 26.1 *Group B:* CG: − 27.8 ± 27.2 CKD-EPI: − 55 ± 20.9 MDRD-4-IDMS: − 36.1 ± 31.3	NA	Underestimation of ARC
Grootaert et al. [30]	CrCl measured in urine > 120 mL/min/1.73 m^2	CG MDRD-4-IDMS	1679	CG: 0.343 (p < 0.001) MDRD-4-IDMS: 0.29 (p < 0.001)	CG: 11.2 ± 61.5 MDRD-4-IDMS: 19.9 ± 76.8	NA	Overestimation of ARC

Table 1 continued

Study	Reference test and definition of ARC	Method assessed	ARC samples [*n*]	Spearman coefficient[a] [r_S]	Bias ± precision[b] [mL/min/1.73 m^2 or mL/min]	Detection of ARC patients [specificity/sensitivity]	Other information provided
Baptista et al. [33]	CrCl measured in urine > 130 mL/min/1.73 m^2	CG mCG MDRD-4 MDRD-6	86	CG: 0.26 (p = 0.017) mCG: 0.22 (p = 0.044) MDRD-4: 0.22 (p = 0.047) MDRD-6: 0.18 (NS)	CG: − 39 ± 75 mCG: − 84 ± 70 MDRD-4: − 48 ± 76 MDRD-6: − 68 ± 76	CG: ND/0.62 mCG: ND/0.62 MDRD-4: ND/0.47 MDRD-6: ND/0.29	Underestimation of ARC
May et al. [35]	*Females:* CrCl measured in urine > 120 mL/min/1.73 m^2 *Males:* CrCl measured in urine > 130 mL/min/173 m^2	CG	20	NA	NA	NA	Underestimation of ARC
Neves et al. [43]	CrCl measured in urine > 130 mL/min/1.73 m^2	CG	319	NA	NA	NA	Progressive underestimation of CrCl > 120 mL/min/m^2 and overestimation of CrCl < 120 mL/min/m^2
Baptista et al. [46]	CrCl measured in urine > 130 mL/min/1.73 m^2	Hoek Larson	29	NA	NA	Hoek: NA/0.08 Larson: NA/0.22	NA

ARC augmented renal clearance, *CrCl* creatinine clearance, *GC* Cockcroft–Gault, *mCG* modified Cockcroft–Gault, *MDRD-4* 4-variable Modification of Diet in Renal Disease, *MDRD-4-IDMS* updated MDRD-4 equation with standardised serum creatinine values, *MDRD-6* 6-variable Modification of Diet in Renal Disease, *CKD-EPI* Chronic Kidney Disease Epidemiology Collaboration, *NA* not available, *NS* nonsignificant

[a]Only in ARC samples

[b]Precision expressed as standard deviation

estimating equations—the CG and the updated MDRD-4 (MDRD-4-IDMS)—in 1679 samples from 390 critically ill adults with a measured CrCl of 120 mL/min/1.73 m^2 or more. Estimates showed poor agreement with measured CrCl values, with a bias between 11.2 mL/min (for CG) and 19.9 mL/min/1.73 m^2 (for MDRD-4-IDMS), and a precision of ± 61 mL/min and ± 77 mL/min/1.73 m^2, respectively. In contrast to Baptista et al., estimates predicted higher CrCl than the measured values, which was attributed to differences in the population (older, with lower body weight, and more severely ill), which could lead to falsely high renal function when estimated.

Udy et al. [25] assessed the performance of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), CG and MDRD-4-IDMS equations in a prospective, observational study in which they included 110 critically ill patients with plasma creatinine concentration within the normal range. In the subgroup analysis, the Udy et al. observed that for CrCl < 120 mL/min/1.73 m^2, the equations tend to overestimate the CrCl, while the opposite occurred for CrCl ≥ 120 mL/min/1.73 m^2. Although a moderate correlation was found for CKD-EPI (r^2 = 0.46, p = 0.005), CG (r^2 = 0.399, p = 0.009) and MDRD-4-IDMS (r^2 = 0.427, p = 0.009) in patients with measured CrCl ≥ 150 mL/min/1.73 m^2, there was no significant correlation in patients with measured CrCl between 120 and 149 mL/min/1.73 m^2. All of the equations underestimated the measured value of CrCl with significant bias and imprecision (29.2 ± 10.8 mL/min/1.73 m^2 for CKD-EPI, 6.62 ± 23.9 mL/min/1.73 m^2 for CG and 22.7 ± 26.1 mL/min/1.73 m^2 for MDRD-4-IDMS) in patients with measured CrCl between 120 and 149 mL/min/1.73 m^2. Bias and imprecision were even higher for patients with measured CrCl ≥ 150 mL/min/1.73 m^2.

Table 2 Equations used in the studies for the estimation of the glomerular filtration rate in adults

Name	Units	Equation
Cockcroft-Gault (CG)		
[11, 14, 22, 25, 33, 35, 42]	mL/min/1.73 m^2	$\frac{(140-Age)\times Wt\times 1.73}{Scr\times 72\times BSA} \times 0.85$ *if female*
[17, 30]	mL/min	$\frac{(140-Age)\times Wt}{Scr\times 72} \times 0.85$ *if female*
Modified Cockcroft-Gault (mCG)		
[9]	mL/min	IBW (if TBW > 130% of IBW, use ABW) and not BSA-adjusted
[11]	mL/min/1.73 m^2	If sCr < 1 mg/dL, use 1 mg/dL and IBW
[33]	mL/min/1.73 m^2	If sCr < 1 mg/dL, use 1 mg/dL
4-variable Modification of Diet in Renal Disease (MDRD-4)		
[11, 33]	mL/min/1.73 m^2	$186 \times Scr^{-1.154} \times Age^{-0.203} \times 1.21$ *if black* $\times 0.742$ *if female*
Updated MDRD-4 equation with standardised sCr values (MDRD-4-IDMS)		
[9, 22, 25, 30]	mL/min/1.73 m^2	$175 \times Scr^{-1.154} \times Age^{-0.203} \times 1.21$ *if black* $\times 0.742$ *if female*
6-variable Modification of Diet in Renal Disease (MDRD-6)		
[33]	mL/min/1.73 m^2	$170 \times Scr^{-0.999} \times BUN^{-0.17} \times S_{Alb}^{0.318} \times Age^{-0.176} \times 1.18$ *if black* $\times 0.762$ *if female*
Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)		
[9, 11, 14, 22, 25]	mL/min/1.73 m^2	Females sCr ≤ 0.7
		$144 \times \left(\frac{Scr}{0.7}\right)^{-0.329} \times 0.993^{Age}$
		Females sCr ≥ 0.7
		$144 \times \left(\frac{Scr}{0.7}\right)^{-1.209} \times 0.993^{Age}$
		Males sCr ≤ 0.9
		$141 \times \left(\frac{Scr}{0.9}\right)^{-0.411} \times 0.993^{Age}$
		Males sCr ≥ 0.9
		$141 \times \left(\frac{Scr}{0.9}\right)^{-1.209} \times 0.993^{Age}$
Hoek		
[14, 45]	mL/min/1.73 m^2	$\frac{80.35}{S_{cys}} - 4.32$
Larson		
[45]	mL/min/1.73 m^2	$77.239 \times S_{cys}^{-1.262328}$

Age = years

Wt weight (kg), *sCr* serum creatinine concentration (mg/dL), *BSA* body surface area (m^2), *IBW* ideal body weight, *TBW* total body weight, *ABW* adjusted body weight, *BUN* blood urea nitrogen (mg/dL), S_{Alb} serum albumin concentration (g/dL), S_{cys} serum cystatin C (mg/L)

Similar results have been obtained in other studies, namely weak correlations and significant bias and imprecision, in critically ill patients with serum creatinine concentration within the normal range for CG [9, 11, 17, 22, 35, 43], MDRD-4-IDMS [9, 11, 22] and CKD-EPI [9, 11, 22]. In all cases, equations tended to underestimate CrCl, compared with measured urinary CrCl, when there was ARC.

Steinke et al. [14] compared the agreement of the estimated CrCl using equations based on plasma creatinine (CG and CKD-EPI) or cystatin C (Hoek) with measured urinary CrCl. This retrospective analysis included 100 critically ill patients from two pharmacokinetic studies, 16 of whom had ARC (urinary CrCl > 130 mL/min/1.73 m^2). Both the Hoek and CKD-EPI equations significantly underestimated CrCl in patients with ARC. The specificity to detect patients with ARC was 0.81 (95% confidence interval [CI] 0.71–0.89), 0.96 (95% CI 0.90–0.99) and 0.96 (95% CI 0.90–0.99) for the CG, CKD-EPI and Hoek equations, respectively, but sensitivity was only 0.69 (95% CI 0.41–0.89), 0.25 (95% CI 0.07–0.52) and 0.38 (95% CI 0.15–0.65), respectively. Similar results were obtained by Baptista et al. [46] regarding the inaccuracy of the Hoek and Larson cystatin C-derived equations when applied to ICU patients with ARC.

Only two studies have been identified in which an exogenous marker is used to assess GFR in patients at risk of ARC. The first, conducted by Loirat et al. [51], found a close correlation between ^{125}I-iothalamate clearance and CrCl ($r^2 = 0.93$, $p < 0.001$) and between inulin clearance and CrCl ($r^2 = 0.74$, $p < 0.001$) in 20 burn patients, 13 of whom had ARC. More recently, Udy et al. [21] used

sinistrin clearance as a marker of GFR and compared it with measured urinary CrCl and the CKD-EPI equation. They found that sinistrin clearance was highly correlated with measured CrCl ($r^2 = 0.7$, $p < 0.01$). Both measured CrCl and the CKD-EPI-estimated value tended to underestimate sinistrin clearance, although the bias was smaller in the measured value.

Given the current evidence, measuring urinary CrCl should be considered the method of choice for identifying critically ill patients with ARC. Nevertheless, in most ICUs, renal function is still determined based on estimating equations or serum creatinine values. In England, for instance, nearly 60% of ICUs use serum creatinine [40].

3.5.2 ARC Diagnostic Scores

The limited usefulness of CrCl estimating equations has motivated the creation of scales with greater sensitivity and specificity for identifying patients at risk of ARC. As reported in an abstract at the 2014 Congress of the European Society of Intensive Care Medicine, Baptista et al. [41] presented a retrospective analysis of urine samples of patients admitted to the ICU of a tertiary university hospital in 2012. They excluded urine samples with contemporaneous serum creatinine ≥ 1.2 mg/dL and grouped patients according to their measured urinary CrCl (< 60 mL/min/1.73 m^2, 60–130 mL/min/1.73 m^2 and > 130 mL/min/1.73 m^2). Overall, they analysed 4271 urine samples from 477 patients, 33% of whom had ARC and 20% had renal dysfunction. The best diagnostic value for ARC was obtained using the combination of urinary creatinine > 45 mg/mL and age < 65 years, with a specificity of 0.88 but low sensitivity (0.60).

Udy et al. [28] conducted a study that included 71 critically ill patients with trauma ($n = 28$) or sepsis ($n = 43$), enrolled in a wider pharmacokinetic study on antimicrobials, who had serum creatinine within the normal range (< 1.3 mg/dL). ARC (urinary CrCl > 130 mL/min/1.73 m^2) was present in 58% of the patients. Based on the results of the multivariate analysis, they created a scoring system to identify ARC patients, in which modified SOFA score ≤ 4 was given 1 point, admission post-trauma was given 3 points and age ≤ 50 years was given 6 points. Scores were then summed and patients grouped into categories of low (0–3), medium (4–6) or high (7–10) risk of ARC. Higher scores were strongly associated with a greater prevalence of ARC, with an area under the receiver operating characteristic curve (AUC_{ROC}) of 0.89 ($p < 0.001$).

Recently, Barletta et al. [7] developed the Augmented Renal Clearance in Trauma Intensive Care (ARCTIC) scoring system to predict ARC in trauma patients. They included 133 trauma patients with serum creatinine within the normal range (< 1.3 mg/dL) and performed a multivariate analysis to identify independent predictors of ARC. The risk factors included in the final ARCTIC score were age below 56 years (4 points), age between 56 and 75 years (3 points), serum creatinine < 0.7 mg/dL (3 points) and male sex (2 points). The score had an AUC_{ROC} of 0.813 ($p < 0.001$) and an ARCTIC score of 6 or higher had a sensitivity of 0.84 and a specificity of 0.68.

We must bear in mind that all these studies select patients with serum creatinine within the normal range. Therefore, the application of ARC scores makes little sense in patients with serum creatinine higher than 1.3 mg/dL, despite creatinine levels not being included in the scores. Scores to detect patients at risk of ARC are useful and easy to apply in ICUs. They can help identify patients at the highest risk of ARC, and, based on the level of risk, indicate the need to measure urinary CrCl to obtain a definitive diagnosis.

3.6 Impact of ARC on Antimicrobial Treatment

The presence of ARC in critically ill patients may have a negative impact on the attainment of therapeutic levels of many drugs. For example, the activity of enoxaparin has been shown to be shorter in patients with ARC [6]; however, almost all of the scarce references published about this subject are focused on antimicrobial therapy, where ARC is very important because it could condition not only the drug efficacy but also the emergence of resistance.

ARC can influence the pharmacokinetic profile of antimicrobial drugs that are renally cleared and known to have a direct correlation between their renal clearance and CrCl, such as β-lactams, vancomycin or aminoglycosides. According to their activity pattern, antimicrobial drugs can be classified into three groups: concentration-dependent killing along with prolonged effects (aminoglycosides, fluoroquinolones, polymyxins, daptomycin or metronidazole), time-dependent activity with no or very short persistent effects (β-lactams) and concentration-independent killing with prolonged persistent effects (tetracyclines, tigecycline, macrolides, azithromycin, clindamycin, linezolid, chloramphenicol, trimethoprim, sulphonamides and vancomycin). For the first and the third groups, the PK/PD indexes that best correlated with efficacy are the maximum serum concentration (C_{max})/minimum inhibitory concentration (MIC) ratio or the area under the concentration-time curve (AUC)/MIC ratio, because the prolonged persistent effects protect against regrowth when the active drug concentration falls below the MIC. For the second group, time-dependent activity, the PK/PD index that best correlated with efficacy is the duration of time that free antimicrobial concentrations exceeded the MIC.

Enhanced drug clearance will lead to a shorter half-life, lower C_{max} and smaller AUC of renally cleared drugs

compromising their effectiveness [2, 3]. Some research has been conducted attempting to assess the influence of ARC on antimicrobial pharmacokinetics and clinical outcomes in critically ill patients, and the main findings are outlined below.

3.6.1 Impact of ARC on Vancomycin Pharmacokinetics

Vancomycin is a glycopeptide that is primarily eliminated by the kidneys (90%) and whose clearance is directly related to CrCl. It is bactericidal and exhibits concentration-independent bacterial killing. Clinically, an AUC/MIC ratio > 400 has been linked to efficacy of this drug [3]. Several studies have been conducted to determine the influence of ARC on the plasma concentration of vancomycin [13, 18, 19, 26, 32, 48]. Baptista et al. [32] evaluated the effect of ARC (urinary CrCl > 130 mL/min/1.73 m^2) in 93 critically ill septic patients who started empirical or directed treatment that included vancomycin by continuous infusion. Patients with ARC (40% of the study population, $n = 37$) reached between 25 and 30% lower vancomycin levels ($p < 0.05$), and ARC was strongly associated with subtherapeutic serum concentrations of vancomycin on the first 3 days of treatment. In a subsequent study [18], these same authors developed a nomogram for dosing vancomycin administered by continuous infusion during the first 24 h of treatment. First, they retrospectively analysed 79 patients, of whom 36% ($n = 29$) had ARC, treated with the standard hospital protocol; only 28% ($n = 8$) of the patients with ARC reached the target level of 20–30 mg/L, compared with 64% ($n = 32$) of those who did not have ARC ($p = 0.092$). Then, using these data, they developed a predictive equation for vancomycin clearance and a dosing nomogram based on 8-h urine collections to measure urinary CrCl, and tested it in 25 patients. Applying the nomogram, 84% of patients, including all those with ARC, reached the target level.

Campassi et al. [19] conducted a prospective study to determine the effect of ARC on vancomycin concentrations. Of the 44 patients treated with vancomycin, 12 had ARC (urinary CrCl > 120 mL/min/1.73 m^2). None of the patients with ARC reached the target level by 24 h after starting treatment, and they had lower vancomycin plasma concentrations during the first 48 h after the start of the treatment ($p < 0.05$). Furthermore, they needed higher doses of the drug to finally reach the target level than non-ARC patients ($p < 0.05$). Another study, conducted by Spadaro et al. [13], aimed to estimate the efficacy of a vancomycin dosing protocol in critically ill patients with and without kidney dysfunction. It was found that 50, 66 and 80% of patients with subtherapeutic levels of vancomycin had ARC (urinary CrCl > 130 mL/min/1.73 m^2) at the first (day 2), second (day 4) and third (day 6) monitoring tests, respectively. Similar findings were obtained by Minkute et al. [26], who concluded that the risk of subtherapeutic vancomycin levels is doubled in patients with ARC (estimated CrCl > 130 mL/min, $p = 0.011$).

3.6.2 Impact of ARC on β-Lactam Pharmacokinetics

β-lactam antibacterials are primarily eliminated by the kidneys and have time-dependent antibacterial activity. Their efficacy is best predicted by the duration of time for which the free drug plasma concentration remains above the MIC ($fT > MIC$). Traditionally, an $fT > MIC$ of between 40 and 70% (depending on the agent) of the dosing interval has been accepted as a PK/PD target, although it has also been suggested that greater drug exposure, up to four times the MIC for the entire dosing interval, could improve clinical outcomes in critically ill patients [3, 55].

Udy et al. [31] retrospectively analysed 52 trough concentrations of β-lactam obtained in 48 critically ill patients. Only 58 and 31% of patients had trough concentrations above the MIC and four times above the MIC, respectively. Patients having ARC (urinary CrCl > 130 mL/min/1.73 m^2) was associated with trough concentrations lower than the MIC or lower than four times the MIC in 82 and 72% of cases, respectively ($p < 0.01$). The multivariate analysis confirmed that CrCl contributed significantly to the likelihood of obtaining subtherapeutic levels of β-lactams, and a 25 mL/min/1.73 m^2 increase in the measured CrCl was associated with a mean 60% reduction in the probability of achieving a trough concentration greater than or equal to four times the MIC.

Carlier et al. [24] assessed the influence of ARC (urinary CrCl > 130 mL/min/1.73 m^2) on PK/PD target attainment in critically ill patients receiving meropenem or piperacillin/tazobactam administered as an extended infusion. Overall, only 33 of 60 patients reached the PK/PD target of 100% $fT > MIC$. ARC patients less often reached the PK/PD targets of 100% $fT > MIC$ (24 vs. 84%, $p < 0.001$) and 50% $fT > MIC$ (63 vs. 94%, $p < 0.01$). Furthermore, the mean percentage of $fT > MIC$ in ARC patients was lower (61 vs. 94%, $p < 0.001$). Multivariate analysis demonstrated that CrCl was an independent predictor of not achieving the PK/PD target.

Akers et al. [20] studied ARC as a predictor of subtherapeutic levels of piperacillin and tazobactam. They included 13 critically ill patients treated with piperacillin/tazobactam and with an estimated CrCl of > 90 mL/min/1.73 m^2 according to the MDRD-4-IDMS equation. Patients were classified as low risk (0–6 points) or high risk (> 6 points) based on the ARC score proposed by Udy et al. [28]. The score had a sensitivity of 1 (95% CI 0.52–1) and a specificity of 0.71 (95% CI 0.30–0.95) for

detecting increased clearance, increased Vd and decreased AUC. The ARC score also had a sensitivity of 1 (95% CI 0.52–1) for predicting subtherapeutic levels of piperacillin/tazobactam (considering as PK/PD target, free piperacillin concentrations greater than the MIC for at least 50% of the dose interval) at an MIC of 16 μg/mL.

ARC patients often need higher doses of β-lactams and there is a strong relationship between ARC and subtherapeutic levels of these antimicrobials, as has been observed in several studies [15, 39, 42, 47]. In this context, the individualisation of dosage regimens, for example, by the administration of antimicrobials in extended infusion can be useful, as demonstrated by Roberts and Lipman [29]. They describe the population pharmacokinetics of doripenem in critically ill patients with nosocomial pneumonia and found that doripenem clearance was correlated with CrCl and peripheral Vd was correlated with patient body weight. Then they performed Monte Carlo dosing simulations to optimise dosing schedules. Extended infusions were found to maximise the likelihood of achieving target blood concentrations, especially in patients with ARC or obesity and with infections caused by organisms with borderline susceptibility.

3.6.3 Impact of ARC on Clinical Outcomes in Patients Treated with Antimicrobials

Studies investigating the relationship between ARC and clinical outcome in patients treated with antimicrobial drugs are scarce. Claus et al. [27] conducted an observational prospective study in which they investigated the impact of ARC on clinical outcome in critically ill patients treated with antimicrobial agents. Of the 128 patients included, 51.6% (n = 66) had ARC, with this being permanently present, throughout the antimicrobial treatment, in 23% (n = 15) of patients, and transient, lasting just one day, in 35% (n = 23) of patients. The rate of treatment failure was higher in patients who had ARC than those who did not have ARC (27.3 vs. 12.9%, p = 0.04), and also tends to be higher in those with permanent rather than transient ARC (33.3 vs. 17.4%, p = 0.436), although the difference was not significant, probably due to the small number of patients in this subgroup.

In another observational prospective study, Huttner et al. [15] investigated the relationship between ARC, plasma concentrations of β-lactam antibacterials and clinical outcome in critically ill patients. They recruited 100 critically ill patients with suspected or documented severe bacterial infection for which treatment with intravenous imipenem/cilastatin, meropenem, piperacillin/tazobactam or cefepime was initiated. Overall, 64% (n = 64) of the patients had ARC. Despite ARC strongly predicting undetectable trough concentrations (odds ratio [OR] 3.3, 95% CI 1.11–9.94], no link was observed between ARC and clinical failure.

Recently, Udy et al. [5] performed a substudy of the BLING-II trial seeking to explore the relationship between ARC and clinical outcomes in 254 critically ill patients with severe sepsis, among whom 45 (17.7%) had ARC (urinary CrCl > 130 mL/min/1.73 m^2). They found no differences in ICU-free days at day 28 or in 90-day mortality. On the contrary, they found that the clinical cure rate at 14 days after ceasing antimicrobial administration was significantly higher in patients with ARC (73.3 vs. 55%, p = 0.024). Nevertheless, this association was lost in the multivariate analysis adjusted for age, modified SOFA and dosing strategy. They also found no difference between ARC status and clinical outcomes according to the dosing strategy employed (continuous infusion vs. intermittent infusion).

4 Discussion

Critically ill patients undergo physiological changes that can alter drug pharmacokinetics. Traditionally, the main focus of assessing kidney function has been to adjust antimicrobial dosing in renal impairment. However, ARC has recently begun to be recognised as an alteration that can lead to accelerated drug elimination and suboptimal drug levels. Although there is no standardised definition of ARC, there is a broad consensus among authors to consider it as a CrCl higher than 130 mL/min/1.73 m^2. Even if changes in renal tubular function are also expected [21], this definition seems reasonable considering that GFR is recognised as the best overall index of renal function, that the normal GFR values in young adult patients are approximately 125 mL/min/1.73 m^2 [53], and the emerging evidence linking CrCl higher than 130 mL/min/1.73 m^2 with subtherapeutic antimicrobial concentrations [15, 18, 24, 26, 31, 32, 48]. Current evidence indicates that, in critically ill patients, renal function should be evaluated by measuring urinary CrCl. Several diagnostic scores [7, 28, 41] have been published that may help to identify critically ill patients at increased risk of developing ARC, but they are unable to establish a definitive diagnosis.

The phenomenon of ARC is not negligible in the intensive care setting, being present in 20–65% of patients [5–9, 11, 12, 15, 17–19, 22–28, 30, 32–34, 37, 44, 45, 49, 52], and significantly more common in young patients [5, 7–9, 11, 12, 15, 19, 22, 23, 26–28, 32, 34, 38, 44, 51, 52]. ARC has been significantly and consistently related to subtherapeutic β-lactam [15, 20, 24, 29, 31, 39, 42, 47] and vancomycin [13, 18, 19, 26, 32, 48] levels, which could potentially lead to the appearance of resistances and therapeutic failure [56, 57]. Despite the fact that the evidence is

scarce, it is expected that the influence of this phenomenon is not restricted to β-lactams and vancomycin, but will also affect other antimicrobials such as aminoglycosides, fluoroquinolones or daptomycin [38, 51, 58–60], and other types of drugs, such as anticoagulants [6] or antiepileptics.

We found only three studies evaluating the effect of ARC on clinical outcomes, and the results are discordant. Claus et al. [27] found a higher rate of treatment failure in patients with ARC (23.7 vs. 8%, $p = 0.04$), whereas Huttner et al. [15] and Udy et al. [5] found no relationship between ARC and clinical outcomes. Huttner et al. are the only authors who performed plasma monitoring of antimicrobials. On the other hand, they did not provide information on the MIC of isolated microorganisms and they use EUCAST's nonspecies-related thresholds to establish subtherapeutic concentrations. Furthermore, they found no relationship between undetectable trough levels and clinical outcomes. As stated by the authors, this apparent lack of relationship might reflect their low-resistance setting, where some pathogens may have such low MICs that they lie beneath the limit of plasma antimicrobial detection, and thus even patients with seemingly undetectable plasma concentrations may be attaining the PK/PD target of 100% $fT > MIC$.

It is difficult to establish a relationship between ARC and clinical outcomes in critically ill patients due to the complexity and variability of this population. The physiological mechanism responsible for ARC in critically ill patients is still not well-defined, but a possible mechanism, accepted by several authors, is the combination of systemic inflammation together with a greater physiological renal reserve. In this sense, it should be noted that although ARC can increase antimicrobial elimination, increasing the risk of therapeutic failure, it has also been considered a marker of a good prognosis as it may predict a host's increased ability to adapt to and withstand severe infection [5, 15].

Overall, when ARC is present in critically ill patients, two scenarios should be considered for future research. On the one hand is the possibility that critically ill patients with ARC could be less likely to develop certain organ dysfunction such as acute kidney injury (AKI). Patients with both sepsis and AKI are widely recognised as having an unacceptably high mortality rate [61, 62] and the same occurs with trauma patients [63, 64]. The development of AKI is a marker of bad prognosis [65–68], while the development of ARC could reflect the opposite situation. On the other hand, although the ARC itself may not be a factor of poor prognosis in the critical patient, its influence on drug pharmacokinetics is clear. The success of antimicrobial treatment in ICU depends on early initiation, correct drug selection and the use of a suitable dosage regimen to attain the PK/PD target [69]. Currently, there is great evidence on the importance of therapeutic drug monitoring and the application of PK/PD criteria in the antimicrobial treatment of ICU patients [55, 70–72]. An increase in antimicrobial clearance can have negative consequences but could be overcome with alternative dosing strategies that optimise drug exposure, such as higher daily doses, continuous/extended infusions or loading doses [73–78]. Recently, several guidelines and consensus documents, such as the Surviving Sepsis Campaign [69], the AGORA project for intra-abdominal infections [79], or Infectious Diseases Society of America (IDSA) guidelines for the management of adults with hospital-acquired and ventilator-associated pneumonia [80], have made specific mention to ARC and include recommendations on the use of dosing strategies based on the PK/PD principles.

Renal impairment is successfully staged in chronic kidney disease according to GFR, defining a normal GFR as ≥ 90 mL/min/1.73 m^2 [53]. The use of reduced doses in patients with impaired renal function is widely accepted, however the appearance of the phenomenon of ARC in critically ill patients could raise the need to establish dose recommendations based on increasing GFR. In 2012, the European Medicines Agency published a press release recommending to double the dose of Doribax® (doripenem) for the treatment of nosocomial pneumonia in patients with ARC and/or with infections caused by non-fermenting gram-negative pathogens [81]. The reason was the preliminary results from a clinical trial in which patients treated with Doribax® were less likely to recover than patients in the control group. The Agency's Committee for Medicinal Products for Human Use considered that factors such as ARC and infections involving specific types of bacteria might influence the effectiveness of treatment with Doribax®. However, the influence of ARC is not limited to antimicrobials, and, similarly, recently marketed drugs such as edoxaban [82, 83] already include in their summary of product characteristics (SmPC) specific recommendations or warnings about reduced efficacy in nonvalvular atrial fibrillation patients with increased CrCl.

Given the high frequency of ARC in the intensive care setting, further studies in this subgroup of critically ill patients are warranted in order to explore the need to stage the ARC and make dosage recommendations. Similar to AKI, ARC could be a dynamic and temporary situation in critically ill patients, therefore a continuous evaluation of the renal function would be necessary.

4.1 Limitations

All the included studies are observational, with relatively few patients and mostly from single centres. They also present a great deal of variability in terms of patient type, selection criteria and definition of the study variables. In

addition, not all the studies define ARC in the same way or detect it with the same diagnostic techniques. For these reasons, only a descriptive analysis has been performed and a synthesis of the results has not been considered appropriate. Nevertheless, we consider that this descriptive study has allowed us to focus on the main features of ARC and that this global vision of the problem will be very useful for designing future clinical studies. Finally, another limitation in our search strategy was the English-language restriction, and hence information may have been overlooked if it was published in other languages.

5 Conclusions

ARC is a prevalent condition in critically ill patients, especially in young people. The use of GFR estimating equations leads to the underdiagnosis of ARC in the intensive care setting, therefore urinary CrCl measurement is recommended. The presence of ARC has a clear influence on antimicrobial plasma levels but further research is needed to define its impact on clinical outcomes in patients treated with antimicrobials or other types of drugs.

As happens with acute renal failure, ARC is a dynamic condition and modulation of dosing according to the daily variations in renal clearance would be necessary. More trials with greater statistical power need to be undertaken to develop a validated pharmacokinetic population model and drug dosing guidelines for critically ill patients with ARC. PK/PD analysis and Monte Carlo simulation can be applied in this setting to simulate different antimicrobial dosage regimens (e.g. higher doses and extended or continuous infusions) and establish the optimal approach to enhance clinical outcomes.

The concept of ARC is becoming increasingly relevant and is even included in the SmPC of some new drugs. In the near future, patients with ARC could be considered as a special subpopulation with specific dosage adjustments in the SmPC.

Compliance with ethical standards

Conflicts of interest Idoia Bilbao-Meseguer, Alicia Rodríguez-Gascón, Helena Barrasa, Arantxazu Isla and María Ángeles Solinís have no conflicts of interest that are relevant to the content of this review.

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APPENDIX II:

Population Pharmacokinetics of Levetiracetam and Dosing Evaluation in Critically Ill Patients with Normal or Augmented Renal Function

Bilbao-Meseguer I, Barrasa H, Asín-Prieto E, Alarcia-Lacalle A, Rodríguez-Gascón A, Maynar J, Sánchez-Izquierdo JÁ, Balziskueta G, Griffith MS, Quilez Trasobares N, Solinís MÁ, Isla A.

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Population Pharmacokinetics of Levetiracetam and Dosing Evaluation in Critically Ill Patients with Normal or Augmented Renal Function

Idoia Bilbao-Meseguer [1,2], Helena Barrasa [3,4], Eduardo Asín-Prieto [5,†], Ana Alarcia-Lacalle [2,6], Alicia Rodríguez-Gascón [2,6], Javier Maynar [3,4], José Ángel Sánchez-Izquierdo [7], Goiatz Balziskueta [3,4], María Sánchez-Bayton Griffith [7], Nerea Quilez Trasobares [7], María Ángeles Solinís [2,6,*] and Arantxa Isla [2,6,*]

1 Department of Pharmacy, Cruces University Hospital, Plaza de Cruces 12, 48903 Barakaldo, Spain; idoia.bilbaomeseguer@osakidetza.eus
2 Pharmacokinetic, Nanotechnology and Gene Therapy Group (PharmaNanoGene), Faculty of Pharmacy, Centro de Investigación Lascaray Ikergunea, University of the Basque Country UPV/EHU, Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain; ana.alarcia@ehu.eus (A.A.-L.); alicia.rodriguez@ehu.eus (A.R.-G.)
3 Instituto de Investigación Sanitaria Bioaraba, 01009 Vitoria-Gasteiz, Spain; helena.barrasagonzalez@osakidetza.eus (H.B.); FRANCISCOJAVIER.MAYNARMOLINER@osakidetza.eus (J.M.); goiatz.baltziskuetaflorez@osakidetza.eus (G.B.)
4 Intensive Care Unit, Araba University Hospital, Osakidetza Basque Health Service, 01009 Vitoria-Gasteiz, Spain
5 Inserm U1070: Pharmacologie des Anti-Infectieux, Pôle Biologie Santé, Université de Poitiers, Bâtiment B36, 1 Rue Georges Bonnet, 86022 Poitiers, France; eduardo.asin.prieto@gmail.com
6 Instituto de Investigación Sanitaria Bioaraba, Microbiology, Infectious Disease, Antimicrobial Agents, and Gene Therapy, 01006 Vitoria-Gasteiz, Spain
7 Intensive Care Unit, Doce de Octubre Hospital, Avda de Córdoba, s/n, 28041 Madrid, Spain; jasiruci@gmail.com (J.Á.S.-I.); mariabayton@hotmail.com (M.S.-B.G.); nerida.mia@gmail.com (N.Q.T.)
* Correspondence: marian.solinis@ehu.eus (M.Á.S.); arantxa.isla@ehu.eus (A.I.)
† Present address: Pharma Mar S.A., Avda. de los Reyes, 1, Pol. Ind. La Mina, 28770 Colmenar Viejo, Spain.

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Abstract: Levetiracetam is a broad-spectrum antiepileptic drug commonly used in intensive care units (ICUs). The objective of this study is to evaluate the adequacy of levetiracetam dosing in patients with normal or augmented renal clearance (ARC) admitted to the ICU by population modelling and simulation. A multicentre prospective study including twenty-seven critically ill patients with urinary creatinine clearance (CrCl) > 50 mL/min and treated with levetiracetam was developed. Levetiracetam plasma concentrations were best described by a two-compartment model. The parameter estimates and relative standard errors (%) were clearance (CL) 3.5 L/h (9%), central volume of distribution (V1) 20.7 L (18%), intercompartmental clearance 31.9 L/h (22%), and peripheral volume of distribution 33.5 L (13%). Interindividual variability estimates were, for the CL, 32.7% (21%) and, for V1, 56.1% (29%). The CrCl showed significant influence over CL. Simulations showed that the administration of at least 500 mg every 8 h or 1000 mg every 12 h are needed in patients with normal renal function. Higher doses (1500 or 2000 mg, every 8 h) are needed in patients with ARC. Critically ill patients with normal or ARC treated with levetiracetam could be at high risk of being underdosed.

Keywords: levetiracetam; augmented renal clearance; intensive care; critically ill patients; population pharmacokinetic; modelling; Monte Carlo simulations; seizure

1. Introduction

Levetiracetam is a broad-spectrum antiepileptic drug with proven efficacy in treating multiple seizure types, in both the adult and paediatric population. Because of its improved

safety profile and ease of use compared to other conventional antiepileptic drugs such as phenytoin, it is frequently used in the treatment of status epilepticus and in seizure prophylaxis after a neurologic injury, being a commonly used treatment in intensive care units (ICUs) [1–3].

Levetiracetam has a linear pharmacokinetic profile. It is rapidly and almost completely absorbed when administered orally, with a time to reach the peak concentration (Tmax) of 1–2 h and a high bioavailability (>95%). Its apparent volume of distribution is 0.5–0.7 L/kg with non-significant plasma protein binding (<3%). Renal clearance represents the main elimination mechanism with a 66% of the dose excreted unchanged in urine, which leads to a good correlation between levetiracetam clearance and a patient's creatinine clearance (CrCl). Additionally, a fraction of the dose (24%) is eliminated by metabolism through enzymatic hydrolysis of the acetamide group, carried out by a type B esterase, mainly in blood. Clinically relevant interactions are not expected, as this metabolic pathway is only responsible for the metabolism of a small part of the administered dose. Additionally, levetiracetam does not induce or inhibit CYP enzymes resulting in minimal drug-drug interactions. The metabolites have no known pharmacological activity and are renally excreted [1,4,5].

There is no clear correlation between levetiracetam serum concentration and efficacy or tolerability. The current reference range for trough concentrations is 12–46 mg/L [6], although some authors have proposed a more modest target range of 6–20 mg/L [7]. The favourable pharmacokinetic profile together with the absence of major drug interactions and broad therapeutic window makes routine therapeutic drug monitoring (TDM) unnecessary. However, TDM, as a way to ensure effective and safe exposures, may be indicated in certain circumstances, such as in patients with altered levetiracetam clearance. This is the case of elderly patients, children, pregnant women, patients with renal insufficiency or critically ill patients [8,9].

In fact, the pharmacokinetic behaviour of levetiracetam has been poorly studied in critically ill patients with augmented renal clearance (ARC). The ARC, defined as a CrCl > 130 mL/min/1.73 m^2, is present in 20–65% of critically ill patients, being more common in certain conditions, such as traumatic brain injury (TBI) (85%) or subarachnoid haemorrhage (SAH) (100%). Although the physiological mechanism responsible for ARC in critically ill patients is not well-defined, the combination of systemic inflammation coupled with a greater renal functional reserve and together with intensive fluid therapy and the administration of inotropic and vasopressor drugs could explain this phenomenon. The presence of ARC could lead to faster elimination of renally excreted drugs, such as levetiracetam, potentially resulting in subtherapeutic concentrations and poorer clinical outcomes [10–13].

In this regard, the aim of this study is to evaluate the adequacy of levetiracetam dosing for the achievement of therapeutic levels in patients with normal or high renal clearance admitted to the ICU by the characterization of the levetiracetam pharmacokinetics by population modelling and simulation.

2. Materials and Methods

2.1. Study Design and Patient Population

A multicentric open-label prospective study was conducted in critically ill patients admitted to the ICUs of Araba University Hospital (Vitoria-Gasteiz, Spain) and Doce de Octubre Hospital (Madrid, Spain). Patients were recruited during 2019 and 2020 following a protocol previously approved by the Basque Clinical Research Ethics Committee (EPA2018019 (SP)). The study was carried out in accordance with ICH Guidelines for Good Clinical Practice. Samples and data from patients were provided by the Basque Biobank (www.biobancovasco.org) and were processed following standard operation procedures with appropriate ethical approval. ICU patients were eligible if they were treated with levetiracetam and had a CrCl > 50 mL/min measured in urine. The exclusion criteria were

age less than 18 years, pregnancy or hypersensitivity to the active substance or to any of the excipients.

2.2. Drug Administration, Sampling Procedure and Analytical Method

Each patient received a dose of 500, 1000 or 1500 mg of levetiracetam every 12 h, as a 30-min intravenous infusion. For each patient, blood samples (3 mL) were taken at 0 h (pre-dose), at the end of the infusion (0.5 h) and at the end of the dosing interval (12 h). Moreover, one sample was taken within the intervals of 1–2 h, 3–5 h and 6–8 h after drug administration. Each sample was immediately centrifuged at 3000 rpm for 10 min to collect the plasma, which was immediately frozen at −20 °C. Within the following week, samples were stored at −80 °C until analysis.

Plasma concentrations of levetiracetam were quantified with a high-performance liquid chromatography (HPLC) assay with ultraviolet detection at a wavelength of 205 nm. The method was validated following the US Food and Drug Administration (FDA) (2018) and the European Medicines Agency (EMA) (2012) guidelines. Separation was performed on a Symmetry® C18 (4.6 mm × 150 mm × 5 µm) column (Waters, Milford, Massachusetts, United States) eluted with ammonium phosphate and acetonitrile (95:5, v:v) mobile phase and it was delivered at 1.2 mL/min. Sample preparation consisted of protein precipitation with acetonitrile and centrifugation for 10 min at 15,000× *g*. The supernatants were then injected into the HPLC system.

The assay was linear over the concentration range from 2 to 100 mg/L. Specificity was assessed using six blank standards and lower limit of quantification (LLOQ) level samples. The chromatograms were checked for interference, with no interference peaks detected at the retention time of levetiracetam. Intra–batch and inter–batch accuracy and precision were evaluated at four different concentration levels (LLOQ and low, middle, and high-quality control) in six replicates. The intra–day and inter–day coefficients of variation (CV) and bias were never above 15%. Stock solution stability, the stability of levetiracetam in storage conditions (at −20 °C for one month and at −80 °C for one year), freeze–thaw stability of the analyte in the matrix from freezer storage conditions to room temperature, and auto-sampler rack stability were also evaluated and confirmed. Levetiracetam substance for standards and quality controls was a reference standard, United States Pharmacopoeia, USP.

2.3. Noncompartmental Analysis

PK parameters for levetiracetam were initially explored by noncompartmental analysis using Phoenix 64 (Build 8.3.0.5005, Certara, Princeton, NJ, USA). The following PK parameters were provided for levetiracetam: the area under the concentration-time curve within the dosing interval (AUC_{12}), peak plasma concentration (Cmax), apparent systemic clearance (CL), elimination half-life ($t_{1/2}$) and apparent volume of distribution (Vz). Area under the concentration-time curve was calculated using the linear-log trapezoidal rule. Afterwards, the correlation between clearance and CrCl at an individual level was explored.

Statistical analysis was performed with IBM® SPSS® Statistics for Windows, Version 26. Student t tests were used to compare the pharmacokinetic parameters of levetiracetam between patients in different groups. Statistical significance was assessed at $p < 0.05$.

2.4. Pharmacometric Modelling

Nonlinear mixed-effects modelling was implemented in NONMEM (v.7.4), using first-order conditional estimation method with interaction (FOCE+I). On the basis of visual exploration of the data and a review of the literature, one- and two-compartment models were considered to describe the levetiracetam concentration-time data. Regarding the variability model, interindividual variability (IIV) associated with the structural pharmacokinetic parameters was modelled exponentially, whereas the residual variability was tested as either proportional, additive or combined error model. The significance of the off-diagonal elements of the Ω variance–covariance matrix was also explored.

Selection between models was based on the following criteria. First, biological plausibility. Second, a significant reduction in the objective function value (OFV = $-2 \times$ log-likelihood). Third, the precision of the parameter estimation expressed as the relative standard error (RSE [%]) and calculated as the ratio between the standard error and the parameter estimate. Fourth, visual inspection of the goodness-of-fit (GOF) plots, including the observed versus individual and population predicted concentration and the residuals plots.

The covariates assessed at baseline evaluated in the analysis included demographic factors (sex, age, height and serum albumin), CrCl (measured in urine), blood chemistry (glucose, albumin, total bilirubin, haemoglobin and leukocytes), acute physiology and chronic health evaluation (APACHE II) and diagnosis. Random effects associated with parameters of interest were plotted versus covariates to explore potential relationships and the Stepwise Covariate Model building tool of Perl speaks NONMEM (v.4.8) was performed as a preliminary selection of covariates. Categorical covariates were modelled as a shift in the typical value for the least common categories, whereas continuous covariates were modelled using linear, exponential or power functions after centring on the median. CrCl was explored as a continuous covariate, but it was also dichotomized into two groups, CrCl < 130mL/min or CrCl $\geq$ 130 mL/min. Covariates were retained in the model if their inclusion produced a significant decrease of the OFV $\geq$ 3.84 units (equivalent to $p < 0.05$ for one degree of freedom) in comparison with the previous model without the covariate. This forward inclusion approach was followed by its reverse (backward elimination) removing those covariates, whose elimination did not produce a significant increase of the OFV $\leq$ 6.63 (equivalent to $p > 0.01$ for one degree of freedom). Therefore, when all the statistically significant covariates were added to the model, each of them was individually removed. If the removal of a covariate was found not to be significant it was dropped in favour of the simpler model.

2.5. Final Model Evaluation

GOF plots were used as the first indicator of goodness-of-fit, including the plotting of model-based individual predictions (IPRED) and population predictions (PRED) versus the observed concentrations (DV), conditional weighted residual errors (CWRES) vs time after dose (TAD) and the CWRES vs PRED. The parameter precision was evaluated by running a 2000 sample bootstrap (PsN v.4.8). Finally, a simulation-based model diagnostic to study the performance of the final model, a prediction-corrected Visual Predictive Check (pcVPC), was constructed by replicating 1000 studies with the same design as the original clinical study and representing the 10th, 50th, and 90th percentiles of the observed data and the 95% confidence intervals for the mentioned predicted percentiles, based on the simulated data sets.

2.6. Dosing Simulations

Using the same dosing regimens administered to patients, 1000 subjects with different CrCl were simulated (80, 120, 160, 200 and 240 mL/min) to evaluate the impact of the covariate on the levetiracetam clearance. Moreover, stochastic simulations were performed to predict levetiracetam plasma minimum concentrations (Cmin) under various dosing regimens (doses from 500 mg to 2000 mg given at either 12- or 8-h intervals, as a 30-min intravenous infusion) and to estimate the probability of target attainment. The target trough concentrations were 12 to 46 mg/L at steady state as recommended by the International League Against Epilepsy (ILAE). A lower target trough range (>6 mg/L) was also investigated. Simulations with the final model were performed with 1000 virtual subjects with CrCl values within the range from 80 to 240 mL/min. CrCl cut-off values were selected based on the observed distribution of CrCl values of the population included in the study and on the summary of product characteristics of levetiracetam, where dosage adjustments are recommended for CrCl below 80 mL/min, but not above this threshold [1].

Simulations extending infusion time to 2 h were performed in those situations in which target attainment with a minimum probability of 80% was not reached.

3. Results

3.1. Patient Demographics

Twenty-seven critically ill patients were included in the study. The main diagnoses were haemorrhagic strokes (n = 10), trauma (n = 8) or other diagnostics such as meningitis, space occupying lesions, convulsive crisis, encephalopathy, arteriovenous malformations or low level of consciousness. Subject characteristics are described in Table 1. A total of 158 plasma samples were analysed, with a median of six, and a minimum of five, plasma samples per patient. Most of the patients (18 out of 27) were treated with 500 mg/12 h of levetiracetam and 10 presented ARC. Levetiracetam was well tolerated, as no evidence of adverse events was recorded, even with the highest dose. Concentration versus time profile of levetiracetam in all the patients is represented in Figure 1.

Table 1. Characteristics of the population included in the study.

Covariate	N (%)	Median (Range)
Sex:		
• Male	18 (67)	-
• Female	9 (33)	-
ARC (CrCl > 130 mL/min):		
• Yes	10 (37)	
• No	17 (63)	
Diagnostic:		
• Haemorrhagic strokes	10 (37)	-
• Trauma	8 (30)	-
• Others	9 (33)	-
Age (years)	-	60 (23–81)
Weight (kg)	-	80 (58–115)
Height (cm)	-	168 (148–189)
BSA (m^2) [1]	-	1.9 (1.59–2.33)
APACHE II	-	18 (5–35)
CrCl (mL/min) [2]	-	117 (54–239)
Glucose (mg/dL)	-	142 (91–337)
Albumin (g/dL)	-	3.4 (2.1–3.9)
Total bilirubin (mg/dL)	-	0.6 (0.2–2.1)
Hemoglobin (g/dL)	-	11.6 (6.7–14.5)
Leukocytes (10^9/L)	-	10.4 (3–24.6)

APACHE: acute physiology and chronic health evaluation; ARC: Augmented renal clearance; BSA: Body Surface Area; CrCl: creatinine clearance. [1] Body surface area (Du Bois method) = $0.007184 \times \text{Height}^{0.725} \times \text{Weight}^{0.425}$. [2] Creatinine clearance= [Urine creatinine (mg/dL) × Volume of urine per minute (mL/min)]/Creatinine plasma level (mg/dL).

3.2. Noncompartmental Analysis

Pharmacokinetic parameters obtained with noncompartmental analysis are summarized in Table 2. The dose-normalized Cmax and CL were significantly higher in patients with ARC than in those with normal CrCl ($p > 0.05$). Figure 2 shows the correlation between CrCl and levetiracetam clearance calculated by noncompartmental analysis.

3.3. Population Pharmacokinetic Modelling

Plasma concentrations were best described by a two-compartment linear model, characterized by drug total body clearance (CL), central volume of distribution (V1), peripheral volume of distribution (V2) and intercompartmental clearance (Q). IIV was exponentially included for CL and V1, and no correlation was detected between the random effects associated with the pharmacokinetic parameters. Residual variability was proportionally modelled. The goodness of fit of the base model was verified by GOF plots.

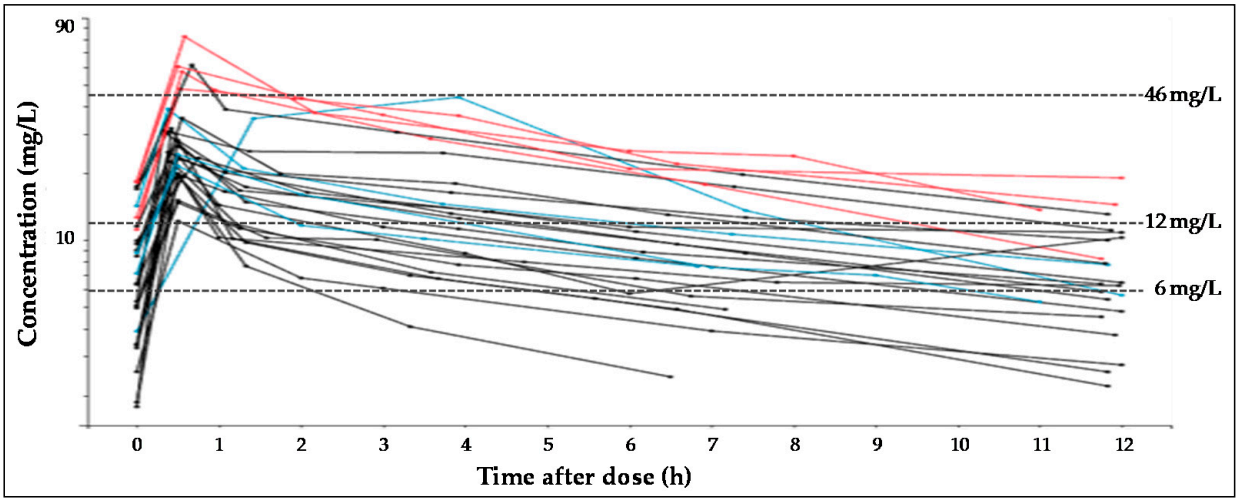

Figure 1. Spaghetti plots for plasma levetiracetam concentration-time profiles, according to dose received by each subject. In black, lines represent profiles after dose of 500 mg, blue lines, 1000 mg and red lines, 1500 mg. Dashed lines represent the target concentration values (6 mg/L, 12 mg/L or 46 mg/L).

Table 2. Levetiracetam pharmacokinetic parameters (mean and standard deviation) at steady state following intravenous administration of 500–1500 mg every 12 h to critically ill patients.

	Cmax (mg/L)	Cmax/D (L^{-1})	AUC_{12} (mg·h/L)	AUC_{12}/D (h/L)	$t_{1/2}$(h)	CL (L/h)	Vz (L)
No ARC	36.36 (17.93)	0.053 (0.032)	186.49 (97.79)	0.267 (0.118)	8.86 (6.13)	4.28 (1.40)	54.41 (42.79)
ARC	24.25 (12.41)	0.036 (0.011) *	121.05 (66.08)	0.182 (0.081)	7.25 (4.11)	6.51 (2.65) *	61.09 (25.07)

ARC: Augmented renal clearance; Cmax: peak plasma concentration; D: dose; AUC_{12}: area under the concentration-time curve within the dosing interval, $t_{1/2}$: elimination half-life; CL: apparent systemic clearance; Vz: apparent volume of distribution; * statistically significant differences between patient with or without ARC ($p < 0.05$).

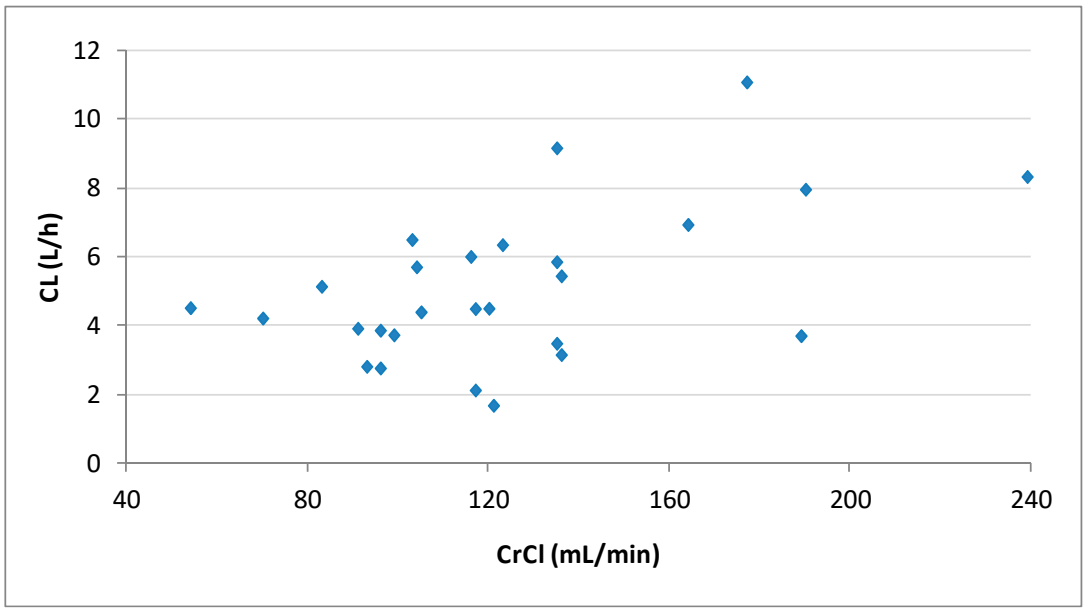

Figure 2. Plot of the individual levetiracetam clearances (CL) calculated by noncompartmental analysis vs. creatinine clearances (CrCl) for the 27 patients.

Both the CrCl, as a continuous variable, and the ARC, as a categorical covariate showed significant influence over CL. CrCl was selected for the final model since the reduction in IIV was greater than with the categorical variable (5.6% vs 3.9%). trauma vs non-trauma diagnosis and APACHE II also showed influence over V1. However, they were eventually excluded from the final model since their individual deletion did not significantly increase the OFV. Therefore, the final model only considered the CrCl as a covariate of the total clearance.

The final model equations were:

$$\mathrm{CL(L/h)} = \left(3.5 + \left(\frac{\mathrm{CrCl}}{120}\right)^{2.5}\right) \times e^{\eta 1}$$

$$\mathrm{V1(L)} = 20.7 \times e^{\eta 2}$$

where CL is clearance, CrCl is urinary creatinine clearance, V1 is central volume of distribution, η1 and η2 represent the interindividual variability for CL, and V1, respectively, which followed normal distributions with a mean of 0.

Inclusion of the CrCl on the CL decreased the unexplained IIV of CL from 38.3% in the base model to 32.7% in the final model and a statistically significant drop of the OFV was obtained with respect to the base model (ΔOFV > 6.63). The population PK model and the results of the bootstrap analysis are shown in Table 3. The residual standard errors revealed that all parameters were precisely estimated. Moreover, the estimates of the parameters were very similar to the median values obtained from the bootstrap analysis. Figure 3 displays the GOF plots for the final model. Figure 4 shows the correlation found between CrCl and levetiracetam clearance. The pcVPC, provided in Figure 5, confirmed that the model appropriately predicts both central tendency and variability of the observed concentrations.

Table 3. Base and final population pharmacokinetic models estimates, shrinkage [a] values and bootstrap results.

Parameter	Base Model Estimate (RSE (%))	Final Model Estimate (RSE (%))	Bootstrap Median (95% CI)
CL (L/h) = θnr + (CrCl/120)$^{\theta r}$	4.6 (8)	-	
θnr	-	3.5 (9)	3.5 (2.8–4.1)
θr		2.5 (17)	2.5 (0.9–3.9)
V1 (L)	20.8 (18)	20.7 (18)	20.8 (13.4–27.7)
Q (L/h)	31.4 (21)	31.9 (22)	30.9 (22.5–47.8)
V2 (L)	34.1 (14)	33.5 (13)	34.2 (19.9–45.4)
IIV_CL (%)	38.3 (19)	32.7 (21)	30.7 (20.2–48.3)
IIV_V1 (%)	54.4 (29)	56.1 (29)	58.0 (22.6–114.0)
RE_proportional (%)	22.3 (15)	22.3 (15)	21.5 (15.7–27.7)

CL, clearance; CrCl, creatinine clearance; V1, central volume of distribution; Q, intercompartmental clearance; V2, peripheral volume of distribution; IIV, inter-individual variability; RE, Residual error; RSE, Relative standard errors; CI, Confidence interval. [a] CL ηsh = 2%; V1 ηsh = 23%; εsh = 12%.

3.4. Dosing Simulations

Tables 4 and 5 show the probability of target attainment for simulated patients with different CrCl, calculated as the percentage of virtual subjects (n = 1000) who had levetiracetam trough concentrations above the previously defined values. Considering the target of trough concentrations higher than 12 mg/L, with the twice daily dosing regimen, probabilities higher than 80% were only obtained in patients with no ARC and with the highest doses. More specifically, doses of 1500 mg and 2000 mg every 12 h would be needed for patients with CrCl of 80 and 120 mL/min, respectively. In patients with CrCl of 160 and 200 mL/min, dosing schedules with 8-h interval would be needed (doses of 1500 and 2000 mg, respectively). With those dosing regimens, the probability of Cmin to

exceed the value of 46 mg/L is low (<5%) in the respective group of patients. Notably, in patients with CrCl of 240 mL/min the targeted minimum concentration of 12 mg/L was not reached even with doses of 2000 mg every 8 h. Extending the infusion time of the 2000 mg dose to 2 h in this group, did not increase enough the probability of reaching the targeted minimum concentration of 12 mg/L (from 59% to 67%).

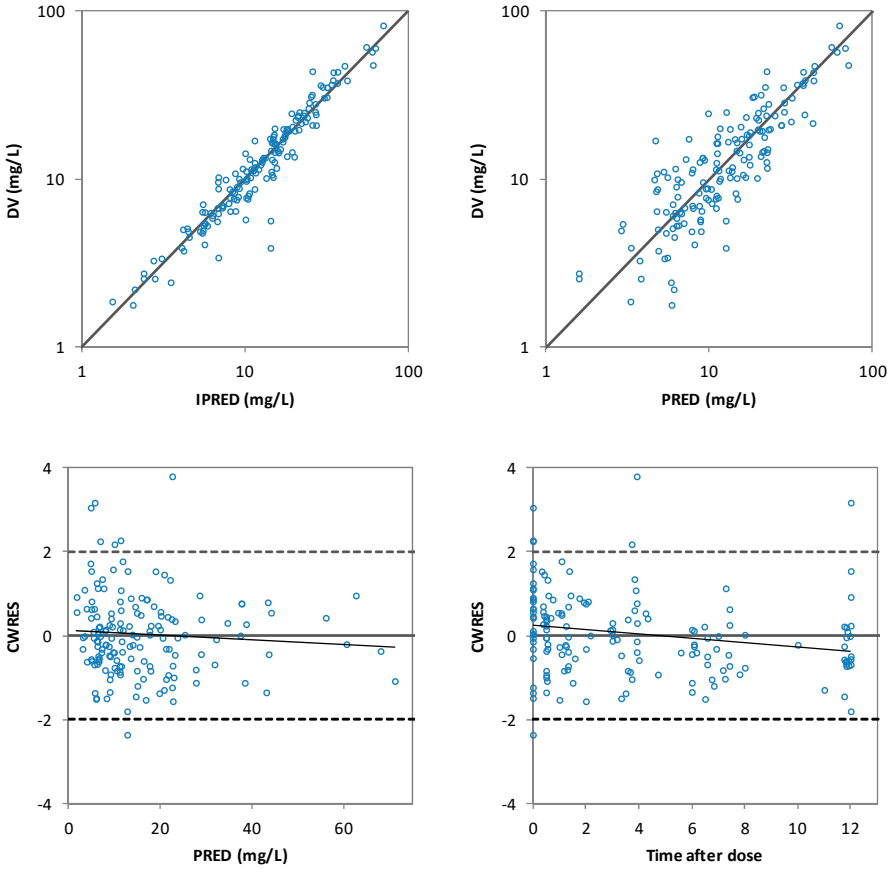

Figure 3. The goodness of fit plots of individual predicted (IPRED) versus the observed (DV) levetiracetam concentrations (**top-left**), population predicted (PRED) versus DV levetiracetam concentrations (**top-right**), conditional weighted residuals (CWRES) versus PRED (**bottom-left**) and CWRES versus time after dose (**bottom-right**) of the final model.

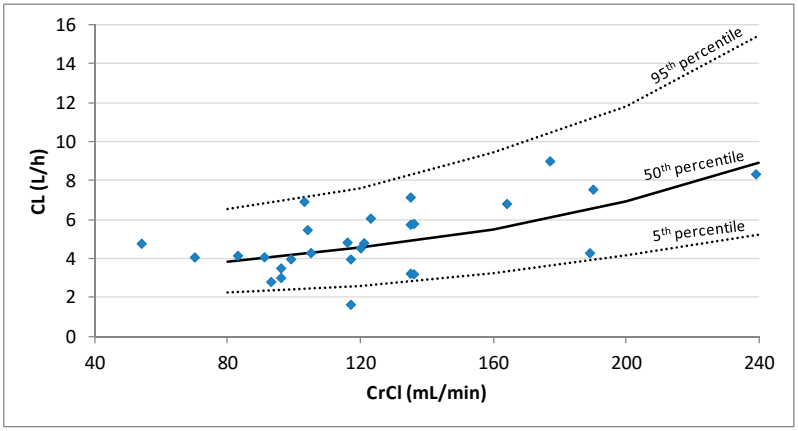

Figure 4. Plot of the individual predicted levetiracetam clearances (CL) estimated by population PK analysis vs. creatinine clearance (CrCl) for the 27 patients. Lines represent the 5th, 50th, and 95th percentiles of 1000 simulations performed at CrCl values of 80, 160, 200, and 240 mL/min.

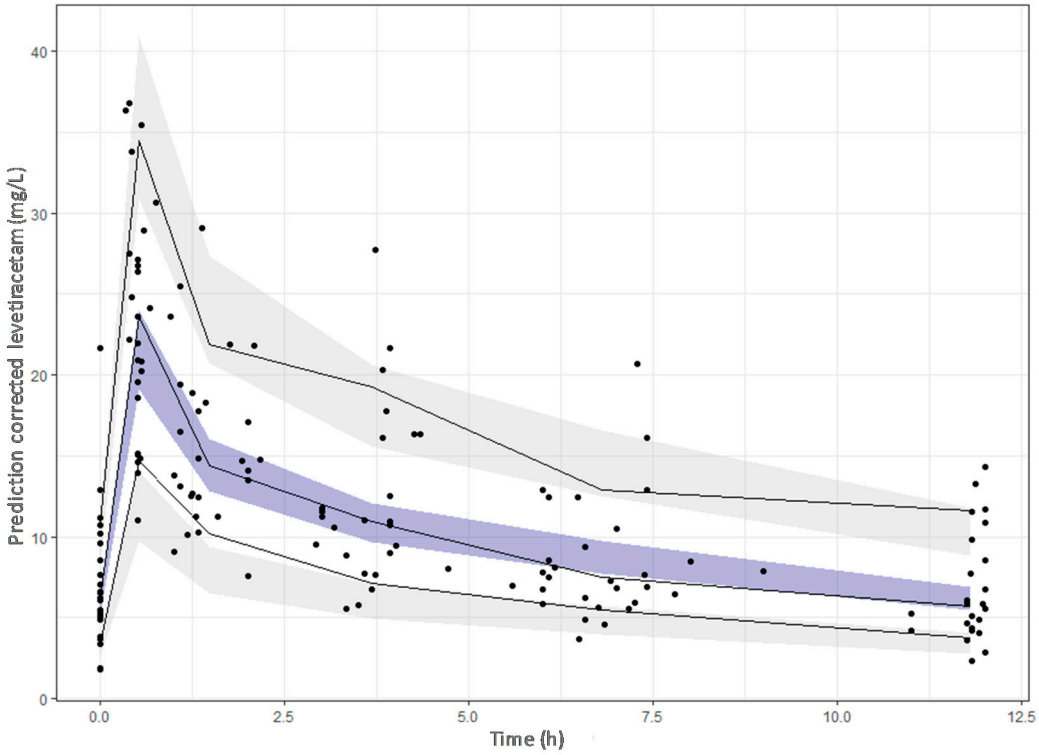

Figure 5. Prediction-corrected visual predictive check of the final model. The dots represent the prediction–corrected concentrations (mg/L). The continuous line represents the 10th, 50th and 90th observed percentiles. Simulation-based 95% confidence intervals for the median and the 10th and 90th percentiles are displayed by dark and light grey shading, respectively.

Table 4. Probability of target attainment based on simulations of the final population model with different doses administered every 12 h. In bold are represented those probabilities ≥80%.

CrCl (mL/min)	Dose (mg)	Perfusion Duration (min)	Daily Dose (mg)	Probability of Cmin (%)		
				>6 mg/L	>12 mg/L	>46 mg/L
Twice Daily (Tau = 12 h)						
80	500	30	1000	62	12	0
	1000	30	2000	**93**	60	0
	1500	30	3000	**99**	**85**	3
	2000	30	4000	**100**	**94**	14
120	500	30	1000	43	6	0
	1000	30	2000	**86**	43	0
	1500	30	3000	**95**	72	2
	2000	30	4000	**98**	**85**	6
160	500	30	1000	22	1	0
	1000	30	2000	67	22	0
	1500	30	3000	**87**	51	0
	2000	30	4000	**94**	69	2
200	1000	30	2000	39	6	0
	1500	30	3000	68	25	0
	2000	30	4000	**80**	42	0
240	1500	30	3000	37	7	0
	2000	30	4000	55	15	0

Cmin, Minimum levetiracetam concentration; CrCl, creatinine clearance; Tau, dosing interval.

Table 5. Probability of target attainment based on simulations of the final population model with different doses administered every 8 h. In bold are represented those probabilities ≥80%.

CrCl (mL/min)	Dose (mg)	Perfusion Duration (min)	Daily Dose (mg)	Probability of Cmin (%)		
				>6 mg/L	>12 mg/L	>46 mg/L
Three Times Daily (Tau = 8 h)						
80	500	30	1500	**94**	51	0
	1000	30	3000	**100**	**93**	5
	1500	30	4500	**100**	**99**	31
120	500	30	1500	**84**	33	0
	1000	30	3000	**99**	**84**	2
	1500	30	4500	**100**	**96**	17
160	500	30	1500	65	12	0
	1000	30	3000	**94**	65	0
	1500	30	4500	**99**	**89**	5
	2000	30	6000	**100**	**97**	17
200	500	30	1500	38	4	0
	1000	30	3000	**83**	39	0
	1500	30	4500	**95**	69	1
	2000	30	6000	**98**	**84**	5
240	1000	30	3000	61	15	0
	1500	30	4500	**80**	38	0
	2000	30	6000	**89**	59	1
	2000	120	6000	**94**	67	1

Cmin, Minimum levetiracetam concentration; CrCl, creatinine clearance; Tau, dosing interval.

When considering the lower target trough concentrations of >6 mg/L twice daily dosing regimens were able to reach the therapeutic interval with a probability greater than 80%, except in patients with CrCl of 240 mL/min, in which dosing every 8 h seemed mandatory. In detail, 1000 mg every 12 h would be suitable for patients with normal renal function, 1500 mg every 12 h for patients with CrCl of 160 mL/min, 2000 mg every 12 h for patients with CrCl of 200 mL/min and 1500 mg every 8 h for patients with CrCl of 240 mL/min.

4. Discussion

In this study, a population pharmacokinetic model of levetiracetam in critically ill patients was developed, for a better selection or optimization of the dose regimen, with special focus on ARC condition. ICU patients commonly show altered pharmacokinetics due to their intrinsic heterogeneity and the disease status that can lead to suboptimal drug concentrations. In fact, the high variability observed in levetiracetam concentrations, partially explained by patients' renal function, suggested the need for dosing optimization in patients with ARC and Monte Carlo simulations revealed the need of high doses to attain the target concentrations.

The ARC condition has recently drawn attention due to its prevalence (present in 20–65% of the patients [10,14] in the intensive care setting), and its potential impact on the elimination of the drugs, especially those primarily eliminated by renal excretion. Pharmacokinetics of renally excreted antimicrobials, such as vancomycin, β-lactams or linezolid, have demonstrated to be significantly modified in patients with ARC [15–19], leading to sub-therapeutic concentrations. In this regard, clinicians should routinely assess the renal function of critically ill patients, by measuring urinary CrCl, not only with the aim of detecting renal impairment, but also, to detect ARC, in order to adjust drug doses.

Levetiracetam is a widely used drug in ICUs, both in treatment and in prophylaxis of seizures, and is mainly excreted unchanged in urine (66%) making it vulnerable to suffer from increased elimination in patients who display ARC. Nevertheless, the effect of ARC on levetiracetam serum concentrations has been poorly investigated. In a case

report, Cook et al. described a 22-year-old girl with severe TBI who displayed ARC. The patient presented a higher than usual systemic clearance of levetiracetam and required significantly higher dose [20].

In a study published by Spencer et al. [21], in 12 neurocritical care patients requiring seizure prophylaxis who received 500 mg twice daily, they found a higher levetiracetam clearance and a shorter half-life, compared with previously published results in healthy volunteers. ARC was not present in their population, but there was a statistically significant relationship between the systemic clearance of levetiracetam and estimated CrCl. Just one patient with renal impairment (CrCl 42 mL/min), achieved a steady-state trough concentration greater than 6 mg/L. Recently, two population pharmacokinetic models of levetiracetam in neurocritical patients have been published [22,23]. Sime et al. [22] developed a population pharmacokinetics model in 30 critically ill patients with TBI or SAH without renal disfunction. ARC (urinary CrCl > 130 mL/min/1.73 m^2) was present in 70% of the patients. Urinary CrCl was found as a covariate that significantly influences levetiracetam clearance, whereas body surface area (BSA) was found to influence levetiracetam clearance, volume of distribution and the absorption rate constant. For every 40 mL/min/1.73 m^2 increase in urinary CrCl, levetiracetam clearance increased by 50% and the median trough concentrations were reduced by 50%. They performed dosing simulations with dosages ranging from 1000 mg every 12 h to 2000 mg every 8 h and concluded that for urinary CrCl greater than 120 mL/min/1.73 m^2, none of the simulated regimens had a probability of 80% or above of achieving trough concentrations higher than 12 mg/L. Similarly, Ong et al. [23] have recently developed a population pharmacokinetics model in 20 neurosurgical patients with TBI, SAH or brain tumour resection. ARC (estimated CrCl > 150 mL/min/1.73 m^2) was present in 30% of the patients. In this study, no covariates were found to significantly influenced levetiracetam pharmacokinetic parameters. They also performed Monte Carlo simulations showing a low probability of reaching trough concentrations > 6 mg/L with the 500 mg twice daily dosing regimen. A dose of 1000 mg twice daily was required to achieve a probability of 80%.

In our study, the pharmacokinetics of levetiracetam were best described by a two-compartment model, agreeing with that reported by Sime et al. [22] and Ong et al. [23]. None of the variables analysed had a significant influence on V1. Trauma diagnosis showed statistical significance at a level of $p < 0.05$, but not at the level of $p < 0.01$, probably because of the scarce number of patients presenting this diagnosis ($n = 10$), and thereby; was not retained in the final model. Other authors have found significant influence of BSA [22,24] or body weight [25] in levetiracetam V1 and/or CL. In a systematic review about levetiracetam pharmacokinetics [25] in paediatric population, healthy subjects or non-critically ill adults, great differences in the volume of distribution, with values from 33 L to 69.9 L (calculated for a 75 kg subject), were reported. In our study, the total volume of distribution was 54.9 L, in the range of most studies, although higher than that observed by Sime et al. (32 L) and Ong et al. (37.2 L) [22,23].

In our model, the levetiracetam CL was only dependent on CrCl, which had a great influence on patients with ARC (mean levetiracetam CL increased from 4.5 L/h to 9.2 L/h in patients with CrCl from 120 to 240 mL/min). Sime et al. [22] also included CrCl as a covariate for CL. However, for similar values of CrCl, their model estimates higher levetiracetam clearance. The discrepancies observed between both models could, in part, be due to the differences among the recruited subjects; Sime et al. [22] included only TBI and SAH patients, whereas our population was more heterogeneous according to diagnosis, and also, to age, body weight and CrCl. Ong et al. [23] found similar levetiracetam clearance to that found in our study (3.6 vs. 4.1 L/h for a mean CrCl of 100 mL/min), however, they could not include CrCl as a covariate. This may be, in part, because the subjects included in their study had a narrower range of CrCl than our patients. Moreover, it has to be considered that their patients' renal function was estimated according to equations, instead of being based on CrCl measured in urine.

Despite the differences in the in the PK parameters, all studies bring out the risk of not achieving the target concentrations in ARC patients. Currently, the most accepted target is to achieve trough concentrations between 12 and 46 mg/L, proposed by ILAE [6], although other authors have proposed lower values. This is the case of the Norwegian Association of Clinical Pharmacology, which recommends target trough concentrations of 5 to 41 mg/L [26]. While ILAE recommendations are based on a retrospective database study that only included the highest doses used by each patient [3], the latter also considered other studies (globally 45% of all samples were below 12 mg/L, and 80% of all samples were between 5 and 25 mg/L) [26]. Moreover, other authors also propose a target trough range of 6–20 mg/L based on typical concentrations values reached with doses ranging from 500 to 1500 mg every 12 h [7].

In our study, a dose of 500 mg every 12 h has shown to be insufficient in critical patients with normal or augmented renal function. In fact, 100% and 67% of these patients had at least one sub-therapeutic level considering the threshold of 12 mg/L or 6 mg/L, respectively. Our results corroborate the need for dose optimization, as the risk for under dosing is highly variable and dependent on the dosing regimen and the renal function of the patients.

Monte Carlo simulations showed that the maximum dose approved in the summary of product characteristics (1500 mg every 12 h) only guarantees to achieve trough concentration of 12 mg/L in critically ill patients with CrCl $\leq$ 80 mL/min. In fact, the probability to achieve target trough concentrations higher than 12 mg/L is very low in ARC patients receiving levetiracetam in a twice daily dosing. Doses of 1500 mg and 2000 mg every 8 h are needed to achieve probabilities >80% for individuals with CrCl $\geq$ 160 and 200 mL/min, respectively, while in patients with CrCl of 240 mL/min, or higher this objective was not reached, even with 2000 mg every 8 h. Several studies have proposed prolonged or continuous infusion to ensure therapeutic concentrations of drugs in patients with ARC [19,27]. We evaluated in patients with CrCl $\geq$ 240 mL/min if the probability of achieving Cmin target would improve by prolonging the infusion time to 2 h. Monte Carlo simulation showed only a mild improvement. Longer infusions were not studied due to concerns about the stability of levetiracetam solutions at room temperature beyond 4 h [28]. When considering the target trough concentrations of 6 mg/L, probabilities greater than 80% were obtained with 1500 mg every 12 h only for patients with CrCl up to 160 mL/min. Sime et al. [22] reported worse results in their population, as they concluded that even with doses as high as 6 g of levetiracetam per day, trough concentrations within the currently accepted target range were not guaranteed. Therefore, further studies are needed in order to better elucidate the optimal dosing regimen in this population. Moreover, although the role of TDM of levetiracetam has not yet been established, its use in ascertaining compliance and managing patients that are at risk of being over- or under-dosed, such as critically ill patients, would be surely helpful. In addition, it is important to bear in mind that ARC is a dynamic a temporary situation [10], and accordingly, the renal function of the patients should be daily evaluated in order to adjust dosing regimens if needed.

This study has several limitations. Firstly, this study enrolled a relatively small number of patients, leading to a lack of external validation of the population PK model and limited statistical power. Previous studies were also carried out with a similar number of patients (20–30 patients) [22,23], but a larger sample could allow including any other covariates able to explain some of the remaining variability. In any case, accurate and precise estimates of all parameters were obtained, since a rich sampling strategy was followed in our study. Finally, the lack of consensus about the trough concentration target is a point to address. It would be advisable to determine a well-defined and universally accepted therapeutic range, although it is difficult to establish a correlation between drug concentration and clinical efficacy when levetiracetam is administered prophylactically to prevent seizures.

5. Conclusions

A population pharmacokinetic model has been developed for levetiracetam in critically ill patients with normal or ARC. The pharmacokinetics of the drug were best described by a two-compartment model and CrCl was found to have a significant effect on levetiracetam clearance, which can lead to a high risk of under-exposure, especially in patients with ARC. According to our results, the administration of 500 mg every 12 h could not be enough to achieve the target plasma concentration in the studied population. At least 500 mg every 8 h or 1000 mg every 12 h could be needed in patients with normal renal function. Even the maximum dose approved in the summary of product characteristics (1500 mg every 12 h) could be insufficient in the presence of ARC. However, further studies with a greater number of patients are necessary to determine effective and safety dose regimens in ARC patients.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and ICH Guidelines for Good Clinical Practice, and approved by the Basque Clinical Research Ethics Committee (protocol code EPA2018019 and date of approval 15 May 2018).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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APPENDIX III:

Optimization of levetiracetam dosing regimen in critically ill patients with augmented renal clearance: a Monte Carlo simulation study.

Bilbao-Meseguer I, Barrasa H, Rodríguez-Gascón A, Asín-Prieto E, Maynar J, Sánchez-Izquierdo JÁ, Solinís MÁ, Isla A.

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RESEARCH

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Optimization of levetiracetam dosing regimen in critically ill patients with augmented renal clearance: a Monte Carlo simulation study

Idoia Bilbao-Meseguer[1,3], Helena Barrasa[4,5], Alicia Rodríguez-Gascón[1,2], Eduardo Asín-Prieto[6,8], Javier Maynar[4,5], José Ángel Sánchez-Izquierdo[7], María Ángeles Solinís[1,2*] and Arantxazu Isla[1,2*]

Abstract

Background: Levetiracetam pharmacokinetics is extensively altered in critically ill patients with augmented renal clearance (ARC). Consequently, the dosage regimens commonly used in clinical practice may not be sufficient to achieve target plasma concentrations. The aim of this study is to propose alternative dosage regimens able to achieve target concentrations in this population. Furthermore, the feasibility of the proposed dosing regimens will be discussed from a clinical point of view.

Methods: Different dosage regimens for levetiracetam were evaluated in critically ill patients with ARC. Monte Carlo simulations were conducted with extended or continuous infusions and/or high drug doses using a previously developed population pharmacokinetic model. To assess the clinical feasibility of the proposed dosages, we carried out a literature search to evaluate the information on toxicity and efficacy of continuous administration or high doses, as well as the post-dilution stability of levetiracetam.

Results: According to the simulations, target concentrations in patients with CrCl of 160 or 200 mL/min can be achieved with the 3000 mg daily dose by prolonging the infusion time of levetiracetam. For patients with CrCl of 240 mL/min, it would be necessary to administer doses higher than the maximum recommended. Available evidence suggests that levetiracetam administration in continuous infusion or at higher doses than those approved seems to be safe. It would be desirable to re-examinate the current recommendations about drug stability and to achieve a consensus in this issue.

Conclusions: Conventional dosage regimens of levetiracetam (500–1500 mg twice daily in a short infusion) do not allow obtaining drug plasma concentrations among the defined target in critically ill patients with ARC. Therefore, new dosing guidelines with specific recommendations for patients in this subpopulation are needed. This study proposes new dosages for levetiracetam, including extended (4 or 6 h) infusions, continuous infusions or the administration of doses higher than the recommended in the summary of product characteristics (> 3000 mg). These new dosage recommendations take into account biopharmaceutical and pharmacokinetic aspects and meet feasibility criteria, which allow them to be transferred to the clinical environment with safety and efficacy. Nevertheless, further clinical studies are needed to confirm these results.

*Correspondence: marian.solinis@ehu.eus; arantxa.isla@ehu.eus
[1] Pharmacokinetic, Nanotechnology and Gene Therapy Group (PharmaNanoGene), Faculty of Pharmacy, Centro de Investigación Lascaray Ikergunea, University of the Basque Country UPV/EHU, Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain
Full list of author information is available at the end of the article

Keywords: Levetiracetam, Dosing, Pharmacokinetics, Pharmacodynamics, Monte Carlo simulation, Augmented renal clearance, Critically ill patient, Neurocritical care

Background

Since levetiracetam was introduced in Europe, it has become a very frequently used antiseizure medication in the intensive care units (ICUs). It is used both in the treatment of focal and generalized onset seizures, and in the second line treatment of status epilepticus. Moreover, despite the lack of a robust recommendation, levetiracetam has been increasingly used in the ICUs in many clinical scenarios (after craniotomy, subarachnoid hemorrhage (SAH) or traumatic brain injury (TBI)) due to its relative ease of use, efficacy, and low side effects profile [1]. There is no clear differentiation between prophylactic and therapeutic doses. Thus, in general, it is recommended to start with 500 mg twice daily and increase the dose until the therapeutic effect is achieved up to a maximum of 1500 mg twice daily. This could justify that the most frequently used dose in prophylaxis is 500 mg/12 h [2].

The altered pathophysiology in critically ill patients can have a major impact on the pharmacokinetic parameters of drugs [3–5]. One of the phenomena in this population that is gaining relevance is augmented renal clearance (ARC). ARC is defined as a creatinine clearance (CrCl) > 130 mL/min/1.73 m^2. It is present in 20–65% of critically ill patients with younger age, polytrauma and lower severity illness being identified as risk factors [6]. Furthermore, it seems to be more common in certain situations, such as TBI and SAH, clinical conditions that usually justify the use of anticonvulsants either prophylactically or therapeutically [7–10]. The presence of ARC in critically ill patients has been consistently associated with subtherapeutic antimicrobial plasma concentrations and it may have a negative impact on the attainment of therapeutic levels of many drugs [11–15]. Although its influence has been studied mainly in the context of antimicrobial therapy, ARC has the potential to influence the pharmacokinetic profile of any drug that is renally cleared and known to have a direct correlation between their renal clearance (CL) and CrCl, such as levetiracetam.

The reference range for levetiracetam trough concentrations is 12–46 mg/L at steady state, as recommended by the International League Against Epilepsy (ILAE) [16]. To date, several studies on levetiracetam in critically ill patients indicate that the dosages regimens commonly used are not sufficient to achieve plasma concentrations within this range, specifically in critically ill patients with ARC [17–20].

These results are in line with a recently published systematic review and meta-analysis (30 studies, $n = 7609$ patients), which assesses the use of levetiracetam compared with no antiseizure medication or with a different antiseizure medication for the prevention of first seizure across neurocritical patients [2]. They could not demonstrate significant reductions in seizure incidence and, neither support nor refute the use of levetiracetam prophylaxis in TBI, SAH, intracerebral hemorrhage or supratentorial neurosurgery. However, their data suggested that levetiracetam might be superior to other seizure medications following supratentorial neurosurgery. They hypothesized that the use of low-dosage levetiracetam, with 500 mg twice daily being the most common dosage used across the studies, might not generate therapeutic levels. These results suggested the need to establish new dosage guidelines that allow reaching the therapeutic objective in this population.

Therefore, the aim of this study is to put forward alternative dosage regimens, using stochastic simulations, able to achieve target concentrations in critically ill patients with ARC receiving levetiracetam. Furthermore, the feasibility of the proposed dosing regimens will be discussed from a clinical point of view considering the potential toxicity and efficacy of the doses and mode of administration evaluated, as well as the stability of the pharmaceutical preparation.

Methods

Optimized dosage regimen proposals for critically ill patients with ARC in treatment with levetiracetam

New dosage regimens for levetiracetam were simulated in critically ill patients with ARC (CrCL of 160, 200 and 240 mL/min). Dosing proposals include the use of continuous infusion, extended infusion times (4 or 6 h) and/or the administration of increasing doses (from 3000 mg up to 6000 mg daily). Stochastic dosing simulations were performed by a population pharmacokinetic model (PPK) recently published by our group [17]. This PPK model was developed from a multicentric open-label prospective study conducted in 27 critically ill patients treated with levetiracetam and with a CrCl > 50 mL/min (range 54–239 mL/min) measured in urine. The model is described in Table 1.

Monte Carlo simulations were performed in NONMEN® (v.7.4) to generate the concentration–time profiles in 1000 virtual subjects. The percentiles of steady-state trough concentrations by the simulated

Table 1 Population pharmacokinetic model used in the simulations

Parameter	Model estimate (RSE (%))
CL (L/h) = θnr + (CrCl/120)$^{\theta r}$	–
θnr	3.5 (9)
θr	2.5 (17)
V1 (L)	20.7 (18)
Q (L/h)	31.9 (22)
V2 (L)	33.5 (13)
IIV_CL (%)	32.7 (21)
IIV_V1 (%)	56.1 (29)
RE_proportional (%)	22.3 (15)

CL clearance, *CrCl* creatinine clearance, *V1* central volume of distribution, *Q* intercompartmental clearance, *V2* peripheral volume of distribution, *IIV* inter-individual variability, *RE* residual error, *RSE* relative standard errors

dosing regimens were subsequently determined in R (v.4.0.2). The probabilities of achieving target trough concentrations were estimated for the reference range of 12–46 mg/L.

Evaluation of dosage regimens feasibility

To assess the clinical feasibility of proposed dosages of levetiracetam, we carried out an evaluation of the following aspects: (1) evidence of toxicity or efficacy of extended or continuous administration mode, (2) evidence of toxicity or efficacy of high doses and (3) stability issues.

To gather information on these aspects, two tertiary databases, UpToDate® [21] and Micromedex® [22] were consulted. In addition, to evaluate the extended or continuous infusion mode, a bibliographic search was carried out in MEDLINE, from inception until October 2021. The following terms were used: ("levetiracetam" OR "keppra") AND ("extended" OR "continuous") AND "infusion". For stability evaluation three electronic drug compatibility references (King Guide® to Parenteral Admixtures® [23], Trissel's 2 Clinical Pharmaceutics Database® [24] and Stabilis® database [25]) and manufacturers' online labeling were also consulted [26–28]. Finally, other references considered to be relevant were identified in a non-systematic literature search.

Results

Optimized dosage regimen proposals for critically ill patients with ARC in treatment with levetiracetam

Table 2 summarizes the probabilities of target attainment (PTA), that is, the percentage of virtual patients that maintained trough drug concentrations at steady state above 12 mg/L and below 46 mg/L.

Based on our simulations, for patients with CrCl of 160 mL/min, it would be possible to achieve a PTA of at least 80% with 1000 mg infused over 4 h every 8 h or with 1500 mg over 30 min every 8 h. For patients with CrCl of 200 mL/min, it would be necessary to administer 3000 mg in continuous infusion, 1500 mg over 4 h every 8 h or 2000 mg over 30 min every 8 h. For patients with CrCl of 240 mL/min, it would be necessary to administer 4500 mg in continuous infusion or 2000 mg over 4 h every 8 h. With those dosing regimens, the probability of Cmin to exceed the value of 46 mg/L is < 5%.

Evaluation of dosing regimens feasibility

Mode of administration: extended or continuous infusion

Currently, there is experience on the use of levetiracetam in continuous infusion, both intravenously and subcutaneously. Overall, although more studies would be necessary, levetiracetam given as a continuous infusion appears to be effective and well tolerated.

Our search identified two publications that include patients receiving intravenous levetiracetam in continuous infusion. Moodle et al. [29], made a retrospective study of 36 patients with diagnosis of status epilepticus and who had been treated with intravenous levetiracetam. Thirty patients received levetiracetam as bolus infusions and 6 as continuous infusion. Efficacy was higher if a bolus was administered compared with continuous infusions without initial loading bolus ($p = 0.002$). The aim of the study was not to investigate the differential efficacy of both methods of administration and plasma levels were not measured. Nevertheless, authors hypothesized that in the context of status epilepticus peak levels after rapid levetiracetam infusions might be responsible for higher effectiveness of bolus compared with continuous pump infusions. No severe adverse effects related to levetiracetam infusion were described and treatment was overall well tolerated. Burakgazi et al. [30] published a retrospective study with 33 patients who received intravenous levetiracetam (16 as bolus and 17 as continuous infusion) for treatment or prevention of seizures with the aim of discussing its safety and tolerability. They concluded that intravenous levetiracetam, regardless of the method of administration, was not associated with any adverse events in hospitalized patients.

There are also case reports assessing the administration of levetiracetam in subcutaneous continuous infusion in the context of palliative care. In this setting, levetiracetam subcutaneous infusion seems to be an effective option for seizure control with good adverse effect profile [31–34]. However, randomized controlled trials are needed to establish the efficacy and tolerability of subcutaneous levetiracetam administration.

Table 2 Probability of target attainment based on Monte Carlo simulations

CrCl (mL/min)	Total daily dose (mg)	Dose (mg)	Dosing interval (h)	Perfusion duration (h)	Probability of Cmin (%)	
					> 12 mg/L	> 46 mg/mL
160	3000	1500	12	0.5	51	0
				4	62	< 0.5
				6	70	< 0.5
		1000	8	0.5	65	0
				4	**81**	< 0.5
				6	**88**	1
		3000	24	24	**98**	1
	4500	1500	8	0.5	**89**	5
200	3000	1000	8	6	69	< 0.5
		3000	24	24	**89**	< 0.5
	4500	1500	8	4	**84**	1
				6	**92**	2
	6000	2000	8	0.5	**84**	5
240	3000	3000	24	24	68	< 0.5
	4500	1500	8	4	61	< 0.5
				6	74	< 0.5
		4500	24	24	**96**	1
	6000	2000	8	4	**80**	2
				6	**89**	3
		6000	24	24	**99**	7

Cmin minimum levetiracetam concentration, *CrCl* creatinine clearance. In bold, PTA (probability of Cmin higher than 12 mg/L) > 80%

Micromedex® [22] includes the study of Burakgazi et al. [30] in its information, while UpToDate® [21] does not make references to this method of administration in its monograph of levetiracetam.

The use of high doses

The information contained in the summary of product characteristics (SPC) establishes a maximum dose of 3000 mg per day [26, 27], based on phase III trials with fixed dose regimens. Even that the evaluation of a dose–effect relationship was not the primary objective of these trials, the results give an indication of a dose–effect relationship in this dose range [35–37].

However, for higher doses (up to 4000 mg) it has been considered that they did not increase efficacy but increased the rate of side effects [38, 39]. This is based on studies that compared differing levetiracetam fixed doses according to a group comparison. A more recent retrospective study [40], which included 61 patients treated with levetiracetam, analyzed individual response to a levetiracetam dose increment. It concluded that dose escalation improved treatment outcomes without additional safety hazards. The final daily doses ranged from 1000 to 6000 mg.

In tertiary databases [21, 22], the maximum dose recommended in the treatment of focal and generalized onset seizures or prophylactically it is also 3000 mg per day.

Stability of levetiracetam infusion solutions

According to the European SPC of Keppra® [26], intravenous levetiracetam is physically compatible and chemically stable for at least 24 h at room temperature. In the case of the SPC authorized by FDA [27], the information was the same until 2016, when it was modified. Currently it states that the diluted solution should not be stored for more than 4 h at controlled room temperature. However, there are other FDA-approved levetiracetam medications that maintain 24-h stability and there are also pre-diluted alternatives [28].

The information regarding stability of levetiracetam solutions found in the consulted electronic databases is scarce and differs between them. While in King Guide to Parenteral Admixtures® [23], a 24 h at room temperature stability is granted, Trissel's 2 Clinical Pharmaceutics Database® [24] only gives a stability of 4 h at room temperature based on the SPC of Keppra® authorized by FDA. Stabilis® database [25] does not provide information on stability at room temperature.

Discussion

This study is, to the best of our knowledge, the first to propose alternative dosing regimens for levetiracetam in critically ill patients with ARC. Dosing simulations suggest the need to administer up to 6000 mg of levetiracetam daily to reach the target plasma level. Our results indicate that it is necessary to optimize the dosage regimen in terms of increasing the dose and/or infusion time to reach the target plasma concentrations in this group of patients. Considering this evidence, it is worth wondering whether we are using levetiracetam adequately in critically ill patients, especially in those with ARC. This should be an issue to be taken into account in daily clinical practice, because ARC has been identified in 20–65% of ICU patients and in up to 85% of neurocritical patients [6–10].

Currently, the reference range for levetiracetam trough concentrations has been stablished by the ILAE in 12–46 mg/L [16]. However, studies carried out in critically ill patients have shown that these plasma concentrations are not achieved with the authorized adult dosing regimen. To date, four PPK studies of levetiracetam have been identified in neurocritical care patients. Spencer et al. [19] included 12 adult patients who received levetiracetam. They estimated a higher levetiracetam CL and a shorter half-life compared with previously published results in healthy volunteers. Just one patient, with renal impairment (CrCl 42 mL/min), achieved a steady-state trough concentration greater than 6 mg/L. Sime et al. [18] developed a population pharmacokinetics model in 30 critically ill patients with severe TBI or SAH without renal dysfunction. For every 40 mL/min/1.73 m^2 increase in urinary CrCl, levetiracetam CL increased by 50% and the median trough concentrations were reduced by 50%. They performed dosing simulations with dosages ranging from 1000 mg every 12 h to 2000 mg every 8 h and concluded that for urinary CrCl greater that 120 mL/min/1.73 m^2, none of the simulated regimens had a probability of 80% or above of achieving trough concentrations higher than 12 mg/L. Similarly, Ong et al. [20] developed a PPK model in 20 neurosurgical patients. They also performed Monte Carlo simulations showing a low probability of reaching trough concentrations > 6 mg/L with the 500 mg twice daily dosing regimen. Finally, our group also reported a population pharmacokinetic model in 27 critically ill patients [17], not restricted to neurocritical patients. CrCl demonstrated a significant influence on the levetiracetam CL. Dosing simulations showed that the administration of at least 500 mg every 8 h or 1000 mg every 12 h would be needed in patients with normal renal function and that higher doses or shorter dosing interval would be needed in patients with ARC.

According to these PPK models, the dosage regimen of 500 mg every 12 h is insufficient to achieve a PTA of at least 80% in ICU patients with a normal renal function. However, this is a widely used dosage in clinical practice, especially in the prophylactic context, where between 34 and 100% of patients received this dosage [17–20]. Furthermore, the maximum dosage approved for levetiracetam, 3000 mg daily in short infusion, also resulted in subtherapeutic levels in patients with ARC. Our results confirm that the target plasma levels would only be reached in ARC patients with the administration of at least 3000 mg in 4-h infusion (in patients with CrCl of 160 mL/min) or in continuous infusion (in patients with CrCl of 200 mL/min). Although extended and continuous infusions are not included in the SPC of levetiracetam, they may be an alternative that avoids the use of doses higher than 3000 mg. However, in patients with CrCl of 240 mL/min, it is not possible to reach the target plasma levels with the maximum authorized dose regardless of the mode of administration, and higher doses are compulsory.

For an adequate management of these patients, however, the ARC should be considered as a dynamic and temporary situation and, consequently, patients' renal function should be assessed daily to adjust dosing regimens if necessary [6, 16]. Equations that estimate glomerular filtration rate have been shown to be inappropriate in critically ill patients [41], and specifically in patients with ARC as they tend to underestimate the value of CrCl in this population [6]. For this reason, creatinine clearance measured in urine should be the routine technique for calculating CrCl in ICU patients, and this value should be used to adjust the dosing regimens of drugs affected, such as levetiracetam.

Several factors are needed to be considered before considering applying in the clinical practice these results obtained by means of pharmacokinetic simulations, that is, the feasibility of the proposed dosage strategies must be pondered from different approaches. In the case of levetiracetam, there is sufficient experience to consider safe its administration in prolonged infusions [29–34]. However, it is important to take into account that extended infusions do not allow reaching therapeutic levels from the beginning of the treatment; therefore, in patients who were not undergoing previous treatment with the drug, it is necessary to consider a loading dose. Considering levetiracetam Vd is not affected by patient`s CrCl, the required loading dose would be the same as in patients without ARC (1000–1500 mg). On the other hand, it should be noted that the administration in extended or continuous infusion makes sense in situations in which we want to maintain stable drug levels in the blood for prolonged time. Therefore, these strategies

would not be suitable for example in the acute treatment of status epilepticus, where high single dose bolus is usually recommended (1 to 3 g at a rate of 2 to 5 mg/kg/min or 40 to 60 mg/kg as a single dose infused over 5–15 min in combination with a parenteral benzodiazepine, and with a maximum dose of 4.5 g) [21]. Finally, one potential drawback to prolonged or continuous infusion is the need for a venous access site in patients with limited lumens available.

The safety of administering doses higher than those authorized in the SPC must be considered. Our dosing simulations suggest the need to administer up to 6000 mg of levetiracetam daily to reach the target plasma level. To date, available evidence shows a good safety profile with the use of high doses of levetiracetam [40]. Nevertheless, the objective of our simulations is to reach levels within the therapeutic range in a group of patients in which, due to their characteristics, the clearance of the drug is increased. For this reason, the use of high doses in this context can be considered safe, although it is necessary to closely monitor patients and, if possible, perform therapeutic monitoring of the drug.

Finally, when administering a drug in extended or continuous infusion, the information on drug stability is critical. Indeed, short post-dilution stability can prevent the drug from being administered in this way. However, different stabilities have been set for levetiracetam by different regulatory agencies, which can condition the proposal of new dosage regimens. On the one hand, EMA [20] accepted that levetiracetam is stable for at least 24 h at room temperature; on the other hand, FDA [21] limited it to 4 h. This discrepancy might suppose the use of extended and prolonged perfusions impossible under FDA criteria, whereas feasible in Europe. Therefore, it would be desirable to re-examinate the current recommendations about drug stability and to achieve an international consensus regarding this issue.

Although this research reached its aims, it has certain limitation: first of all, there is a limited number of PPK studies of levetiracetam including ARC condition and all the results are obtained from simulations based on a previously published study carried out in a relatively small population, which included patients with CrCL > 50 mL/min, but only 37% had ARC. Second, the objective of our simulations was to evaluate the adequacy of currently levetiracetam dosage regimens to achieve plasma levels within the range established by the ILAE. However, there is a lack of consensus about which the target concentrations for levetiracetam treatment are, and no specific target has been defined in prophylactic use. Although, the dosage regimens used in prophylactic context are usually the same as those listed for seizure treatment and the majority of clinical trials in which the efficacy of levetiracetam in prophylaxis has been evaluated use same guidelines, the relationship between levetiracetam plasma levels and its efficacy or toxicity needs to be further characterized in both situations. That is, even if there are studies that analyze the influence of the ARC in the achievement of plasma levels within the currently accepted range, there is no data linking this situation with higher incidence of seizures. Therefore, further investigations overcoming these limitations are needed to confirm these results in the clinical setting.

Conclusions

This study states that conventional dosage regimens do not allow obtaining drug plasma concentrations among the therapeutic range of levetiracetam in critically ill patients with ARC, and highlights the need to implement new dosing guidelines that include specific recommendations for patients in this subpopulation. The recommended regimens must take into account biopharmaceutical and pharmacokinetic aspects that condition the probability of treatment success, such as the controversial stability of the drug in solution or the duration of perfusion. We proposed new dosage recommendations, to be implemented in critically ill patients with ARC, which meet feasibility criteria that allow them to be transferred to the clinical environment with safety and efficacy. According to simulation results, sometimes extended or continuous infusions would be needed, and in other situations, it would be necessary to administer doses higher than those authorized. Nevertheless, further clinical studies are needed to confirm these results.

Abbreviations

ARC: Augmented renal clearance; CL: Clearance; CrCl: Creatinine clearance; ICU: Intensive care unit; ILAE: International League Against Epilepsy; PPK: Population pharmacokinetic model; PTA: Probability of target attainment; SAH: Subarachnoid hemorrhage; SPC: Summary of product characteristics; TBI: Traumatic brain injury.

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Author contributions

IB, AI, MAS, AR and HB conceived the study. HB, JM and JASI carried out data collection. IB and EA performed data analysis. IB, HB, MS and AI drafted the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The population PK model used for simulations has been published at: Bilbao-Meseguer et al. [17].

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Pharmacokinetic, Nanotechnology and Gene Therapy Group (PharmaNanoGene), Faculty of Pharmacy, Centro de Investigación Lascaray Ikergunea, University of the Basque Country UPV/EHU, Paseo de la Universidad 7, 01006 Vitoria-Gasteiz, Spain. [2]Bioaraba, Microbiology, Infectious Disease, Antimicrobial Agents, and Gene Therapy, Vitoria-Gasteiz, Spain. [3]Department of Pharmacy, Cruces University Hospital, Plaza de Cruces 12, Barakaldo, 48903 Bizkaia, Spain. [4]Bioaraba, Intensive Care Unit, Vitoria-Gasteiz, Spain. [5]Osakidetza Basque Health Service, Araba University Hospital, Intensive Care Unit, c/ Olaguibel no. 29, Vitoria-Gasteiz, Spain. [6]Inserm U1070: Pharmacologie des anti-infectieux, Pôle Biologie Santé-Bâtiment B36, Université de Poitiers, 1 rue Georges Bonnet, 86022 Poitiers, France. [7]Intensive Care Unit, Doce de Octubre Hospital, Avda de Córdoba, s/n, 28041 Madrid, Spain. [8]Present Address: PharmaMar, Avda. De los Reyes, 1, Pol. Ind. La Mina-Norte, Colmenar Viejo, 28770 Madrid, Spain.

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