Individualised antimicrobial dosing in critically ill patients undergoing continuous renal replacement therapy: focus on total drug clearance

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Received 24 September 2016

Revised 16 December 2016

Accepted 20 December 2016

Published Online First

13 January 2017

EAHP Statement 4: Clinical Pharmacy Services

ABSTRACT

Background Continuous renal replacement therapy (CRRT) is common practice in critical care patients with acute renal failure.

Objectives To evaluate the adequacy of antimicrobial doses calculated based on the total drug clearance and dose recommended by different guides in critically ill patients undergoing CRRT.

Methods Retrospective observational study. Patients admitted to a critical care unit during May 2014 to May 2016 and subjected to CRRT were included. The recommended dose was established as the product of the usual dose of the drug by total drug clearance.

Results 177 antimicrobial agents, used in 64 patients were analysed; 45 (25.4%) antimicrobials were given in an insufficient dose (<20%) according to the theoretical calculation. Following the recommendations in the revised guidelines, between 10% and 20% of antimicrobials were given in insufficient doses. A higher success rate of treatment in those patients not receiving a low drug dosage was seen (35.2% vs 24.0%).

Conclusions There is a great disparity between the antimicrobial dose prescribed, recommended and calculated based on drug clearance in critically ill patients undergoing CRRT.

The aim of this study is to evaluate the correlation between the doses calculated based on a theoretical model and the doses used in clinical practice as well as those recommended in various clinical guides.

METHODS

We designed a retrospective observational study. Adult patients (>18 years of age) admitted to the intensive care unit in the period May 2014–May 2016, and subjected to CRRT and antimicrobial therapy, were included.

Patient characteristics were collected, including demographics, the reason for admission to the unit, date of start of antimicrobial treatment, doses used, duration and the final outcome, defining final success by the patients' clinical improvement.

Calculation of the clearance (Cl) of the drug was performed using the formula given by Bugge,¹⁰ considering the baseline renal clearance present in the patient (mL/min), the non-renal drug clearance and the clearance given by CRRT, which was defined as the product of the free drug (considered equivalent to the sieving coefficient) and the effluent flow rate (ultrafiltrate+dialysate) at the beginning of the renal replacement process. The theoretical dose was established as the product of the usual dose of the drug by total drug clearance (Cl).

- CRRT dose: dose desired × total drug Cl
- Total drug Cl = (renal Cl × non-renal Cl × HDFVC equipment Cl) / normal Cl
- CRRT equipment Cl = sieving coefficient × effluent flow (mL/min)

We compared the prescribed dose, the calculated theoretical dose and the dose recommended by two antimicrobial treatment guides (*Antimicrobial Therapy Guide 2014* (Mensa J)¹¹ and *The Sanford Guide to Antimicrobial Therapy 2014* (Gilbert D)¹² and the reviews of Azanza *et al.*¹³ and Trotman *et al.*¹⁴ The antimicrobial dose was prescribed according to physicians' criteria, following different sources of information. The percentage of prescriptions with variations in dose >20% of the calculated dose was obtained according to the theoretical calculation model and compared with doses considered by the guides.

The difference was also evaluated from the success rate of antimicrobial treatment among those patients who achieved the calculated doses and those receiving an infra-low dose, defined as a prescribed dose at least 20% lower than that calculated by the theoretical model.

INTRODUCTION

Acute renal failure is one of the most frequent complications of critically ill patients, often appearing as a complication associated with severe sepsis.^{1–2} In these patients, the use of continuous renal replacement therapy (CRRT) is one of the mainstays of treatment.³ The use of these techniques leads to a modification of the pharmacokinetic parameters of many drugs as much by altering the volume of distribution as solute removal which occurs during the procedure.⁴ In the case of antimicrobial agents, several authors have warned of the high risk of an infra-low dosage and consequent therapeutic failure in this group of patients.^{5–6}

Non-renal clearance during CRRT is influenced by the characteristics of the drug and the equipment,^{7–9} presenting high interpatient variability depending on dose and the system employed. However, doses of antibiotics recommended in several clinical guidelines and revisions do not consider differences in the total clearance of the drug derived from the flow used in this technique, recommending the use of the same dose for all patients.

To cite: Ruiz J, Favieres C, Broch MJ, *et al.* *Eur J Hosp Pharm* 2018;**25**:123–126.

Clinical response to treatment was defined as the disappearance of the signs and symptoms present at the time of diagnosing the infection (fever, haemodynamic instability, leucocytosis, a reduction in procalcitonin or C reactive protein of >80% compared with the baseline value). For patients with a diagnosis of pneumonia, the modifications suggest by Ioanas *et al*¹⁵ were followed—namely, an improvement in gas exchange, patient temperature returning to normal, the disappearance of purulent secretions, a reduction of at least 50% in the lung infiltrations on a chest X-ray examination and haemodynamic stability after 72 hours of antibiotic treatment.

Study protocol was approved by the hospital institute's committee on human research.

RESULTS

During the study a total of 64 patients undergoing CRRT and antimicrobial treatment were included. The demographic and clinical characteristics of these patients are shown in table 1.

The CRRT procedure was started an average of 5.8 (95% CI 3.8 to 7.6) days after admission, with an initial average effluent flow of 30.6 (95% CI 26.6 to 36.6) mL/kg/hour.

For the 64 patients enrolled, a total of 177 antimicrobials were prescribed, 45 (25.4%) of which were inadequate doses (<20%) according to the theoretical dose calculated. The infra-low dose percentages by therapeutic group are shown in table 2. The β -lactam drugs (n=8; 13.6%), azoles (7; 100%) and co-trimoxazole (9; 100%) were the groups with the highest number of infra-low dosages.

A higher rate of drug treatment success was seen for those patients who did not receive low dosages relative to the calculated dose, although no statistically significant differences were achieved (35.2% vs 24.0%, Fisher; p=0.355).

Table 1 Characteristics of patients included in the study (n=64)

Age (years), mean (SD)	60.3 (14.9)
Male	46 (71.9)
Obesity (BMI ≥ 30 kg/m ²)	12 (18.8)
ICU stay before RRT (days), median (IQR)	2 (1–7)
APACHE II score, median (IQR)	23 (16–26)
Mechanical ventilation	40 (62.5)
Comorbidities	
COPD	7 (10.9)
Diabetes	17 (26.6)
Liver cirrhosis	22 (34.4)
Immunosuppression	9 (14.1)
Neutropenia	18 (28.1)
Infection focus	
Lung	25 (39.1)
Abdominal	18 (28.1)
Catheter	5 (7.8)
Sepsis without focus	9 (14.1)
Other	5 (7.8)
Unclear focus	9 (14.1)
Initial renal status	
Creatinine (mg/dL), median (IQR)	2.4 (1.6–3.8)
Urea (mg/dL), median (IQR)	132 (95–182)
Anuria	54 (84.4)
Initial effluent flow (mL/kg/h), mean (95% CI)	30.6 (26.6 to 36.6)

Results are shown as number (%) unless stated otherwise.

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; RRT, renal replacement therapy.

Antimicrobial prescriptions with a dose prescribed or recommended by the reviewed guidelines at least 20% lower than the dose calculated by the theoretical model are shown in table 2. The percentage of antimicrobials with an infra-low dose recommended compared with the dose calculated by the theoretical model was superior in the Azanza review (n=30; 17.7%), followed by the Sandford guide (23; 15.9%), Trotman review (20; 15.9%) and the Mensa guide (23; 13.0%). The largest number of antimicrobials with an infra-low dose recommended corresponded to the β -lactams group (Sandford: 18 (33.3%); Mensa: 17 (28.8%); Azanza: 20 (33.9); Trotman: 16 (32.7%)).

In addition, 49 (27.7%) drugs had more than 20% of the theoretical calculation overdosage, including, glycopeptides (1; 100%), antiviral agents (1, 100%) and β -lactams (33; 49%) had a higher percentage of overdosage (100%). The percentage of overdosage with respect to the theoretical calculation was higher for the Sandford guide (40.0%), followed by the Trotman *et al* review (39.7%), Mensa guide (37.5%) and Azanza review (34.7%).

Eleven (6.2%) of the antimicrobial agents were removed owing to toxicity (five aminoglycosides; four β -lactams and two amphotericin B), having presented in five of them doses 20% higher than those calculated according to the theoretical calculation model.

DISCUSSION

According to our results, there are important differences between the doses calculated by the theoretical model and the doses prescribed to patients, as well as the recommended clinical practice guidelines. These differences are more common for β -lactam antibiotics, co-trimoxazole and azoles.

The prescription of appropriate doses of antimicrobials during a CRRT procedure is a challenge for health professionals. Treatment guidelines base their recommendations on published studies, usually from a small group of patients. However, it is important to consider that for those drugs partially removed during the procedure, a high variability of concentrations is achieved, both published by different authors and in the concentrations obtained within a single study. This means that insufficient information is obtained to permit extrapolation to another group of patients with other systems or haemodiafiltration dosage. This is particularly relevant for β -lactam antibiotics or azoles.^{16–17} This high variability of concentrations is largely due to changes in the patient with renal failure (including weight, plasma proteins and non-renal clearance of drugs)^{18–19} and the equipment used (haemofiltration system, flow or membrane used by the system).^{5–20–21}

This phenomenon has led to the application of mathematical formulas for calculating the appropriate dose which is of particular importance for patients. Although these formulas have not been validated in clinical practice, the idea of adapting the dose of antimicrobial, taking into account its elimination, makes the process of haemofiltration appealing.

Several authors have shown that the flow rate of haemofiltration correlates with various antimicrobial concentrations obtained in patients.^{22–23} Prescribed variations in the efficiency of the renal replacement technique and in CRRT dose can lead to large changes in the clearance of drugs. However, prospective studies are needed to evaluate the role of haemofiltration flow as a possible modifier of the prescribed antimicrobial dose in critically ill patients.

In our study, azoles, such as co-trimoxazole, are the drugs with the highest percentage of infra-low dose calculated by the theoretical model. Several authors have demonstrated a

Table 2 Antimicrobial prescriptions with a dose prescribed or recommended by the reviewed guidelines at least 20% lower than the dose calculated by the theoretical model

Antimicrobial prescription	n	Prescribed (n=177)	Mensa (n=177)	Sanford (n=145)	Azana (n=169)	Trotman
Aminoglycosides	18	5 (27.8)	3 (17.7)	0 (0.0)	4 (22.2)	2 (13.3)
Antiviral agents	5	0 (0.0)	2 (40.0)	2 (40.0)	2 (50.0)	1 (33.3)
Azoles	7	7 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
β -Lactams	59	8 (13.6)	17 (28.8)	18 (33.3)	20 (33.9)	16 (32.7)
Echinocandins	17	0 (0.0)	1 (5.9)	ND	1 (5.9)	0 (0.0)
Co-trimoxazole	9	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	ND
Fosfomycin	1	1 (100.0)	0 (0.0)	ND	ND	ND
Glycopeptides	2	2 (100.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
Lincosamides	1	0 (0.0)	0 (0.0)	ND	1 (100.0)	1 (100.0)
Lipopeptides	6	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Macrolides	2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	ND
Nitroimidazoles	1	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	ND
Others	4	0 (0.0)	ND	1 (100.0)	1 (100.0)	ND
Oxazolidones	22	3 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Polyene	3	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Polymyxins	5	3 (60.0)	0 (0.0)	0 (0.0)	ND	0 (0.0)
Quinolones	11	2 (18.2)	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)
Tetracyclines	4	0 (0.0)	0 (0.0)	ND	0 (0.0)	ND
Total	177	45 (25.4)	23 (13.0)	23 (15.9)	30 (17.7)	20 (15.9)

ND, not done.

significant increase in the clearance of these drugs during the renal replacement process, and have found it necessary to increase the doses of these drugs.^{24 25} The need to increase the prescribed dosage of these drugs is not reflected, however, in the revised guidelines.

In the case of β -lactam drugs, the results of the many studies published show a high disparity, particularly for meropenem and piperacillin/tazobactam. Most studies agree that there is a significant clearance of these drugs during haemofiltration, and consider the need to increase or maintain the doses used in patients without renal failure to cover bacteria that are more resistant to these drugs.^{26 27} However, the guidelines continue to recommend low doses in this patient group. It is necessary to evaluate in prospective studies the impact of different doses and forms of administration on the treatment response and associated toxicity in this group of patients.

The infra-low dose of antimicrobials in critically ill patients is not a trivial matter. Severe sepsis is a common cause of acute renal failure in critically ill patients, due to the need for a renal replacement therapy (RRT) implant in up to 70% of patients.²⁸ In this group of patients, it has been shown that inadequate dosing of antimicrobials leads to an increased risk of treatment failure and mortality.²⁹ In our study, we identified a high percentage of patients with treatment failure, consistent with findings published by other authors. Improper dosing of antimicrobials may partly explain this failure.

On the other hand, it must be considered that certain antimicrobial agents may accumulate during these procedures, with an increased risk of toxicity. In our study, 11 antimicrobial agents had to be suspended owing to toxicity, although only four had high doses according to the theoretical model. It has been suggested that the toxicity associated with the use of antimicrobial drugs is due to other factors, including concomitant medication or an individual's metabolising capacity.

Limitations of this study include the small number of patients with certain groups of antimicrobials, which has prevented conclusions being drawn for certain groups of drugs. On the other

hand, it would have been of great interest to have determined plasma concentrations to establish an adequate correlation between the dose administered and calculated and the achievement of the pharmacokinetic/pharmacodynamic (PK/PD) objectives in our patients. It must be noted that although the use of mathematical formulas is a more logical approach to dosing patients with antimicrobial RRT, some authors have shown that more aggressive doses of haemofiltration may not be sufficient.³⁰ Furthermore, the use of these formulas does not consider the use of different doses of antimicrobials, such as high or continuous perfusion of β -lactams, to obtain PK/PD objectives.

Given the importance of the adequacy of the dosage of antimicrobials in patients with severe infection in an environment of increased resistance to them, it is necessary to implement new monitoring techniques to ensure proper dosage of these drugs.

What this paper adds

What is already known on this subject

- ▶ Continuous renal replacement therapy (CRRT) is common practice in critical care patients with acute renal failure.
- ▶ Doses of antibiotics recommended for patients with CRRT do not consider differences in the total clearance of the drug derived from the flow used in these techniques

What this study adds

- ▶ There is a great disparity between the antimicrobial dose prescribed, recommended and calculated based on drug clearance in critically ill patients undergoing CRRT.
- ▶ Variables of the patient and the renal replacement system should be considered when adjusting the dose of antibiotics in this group of patients.

CONCLUSION

There is a significant disparity in antimicrobial doses calculated based on the total clearance of the drug and those prescribed and recommended for these patients. Despite the support given by the clinical guidelines, prospective studies are needed to evaluate the effect of the prescription dose of antimicrobial agents based on the patient's own variables and the CRRT system.

Contributors JR: design of the study, data collection and statistical analysis. PR: co-ordination and design of the study, and helped to draft the manuscript. MG, AQ: data collection. EV: design of the study and statistical analysis. CF: collection and analysis of microbiological data. MJB, ACO: design, coordination and review of the manuscript. All authors read and approved the final manuscript.

Competing interests None declared.

Ethics approval Hospital La Fe Bioethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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