CRITICAL CARE

LETTER

Beta-lactam antibiotics in continuous infusion in critically ill patients

Axel Jeurissen*[1] and Robert Rutsaert[2]

See related research by Taccone *et al.*, http://ccforum.com/content/14/4/R126

We read with great interest Taccone and colleagues' article [1], published in a recent issue of *Critical Care*, on the insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. While we fully agree with the authors' findings, we would like to offer some remarks.

Only 18 of their 80 patients (22.5%) were infected with *Pseudomonas aeruginosa*, but Taccone and colleagues used the European Committee on Antimicrobial Susceptibility Testing (EUCAST) minimal inhibitory concentration (MIC) breakpoints of *P. aeruginosa* to calculate the target pharmacokinetics (PK) profile in *all* of the patients. Because *Enterobacteriaceae* form a substantial part of infectious organisms in intensive care patients, it would be interesting to see how many patients would attain the PK profile for these microorganisms [2]. For cefepime, for instance, if the EUCAST sensitivity threshold of 1 mg/L were used, 17 of 19 patients (89%) would attain the target PK profile as compared with 3 of 19 patients (16%) for *P. aeruginosa*. Of course, we agree that, in an empirically started antibiotic regimen, the organisms, let alone the MIC, are not known to the clinician.

Furthermore, the data of Taccone and colleagues should be interpreted in light of local epidemiology and resistance data. In a Belgian multicenter study, all *P. aeruginosa* strains isolated from patients hospitalized in the intensive care unit (ICU) had an MIC_{90} (MIC required to inhibit the growth of 90% of organisms) for meropenem of 0.12 mg/L [3]. With this MIC, even more than 75% of the patients would have attained the target PK profile. In addition, we think that the initial loading dose should be followed immediately by an extended or continuous infusion in order to obtain an optimal PK/pharmacodynamics (PK/PD) profile [4].

Authors' response

Fabio Silvio Taccone, Jean-Louis Vincent and Frédérique Jacobs

We thank Jeurissen and Rutsaert for their interest in our study [1] and would like to reply to the important points they raise. In our patient population, one third of documented infections were due to *P. aeruginosa* as microbiological samples remained negative in 30% of patients with sepsis. Indeed, *P. aeruginosa* is frequently isolated in patients with comorbid illnesses or indwelling catheters or who are on mechanical ventilation or undergoing surgery, all of these conditions being typical in ICU patients [5]. *Pseudomonas* infections are associated with the highest mortality rate in this ICU patient population. For all of these reasons, it seems logical to develop an empirical strategy that targets this pathogen in patients with nosocomial infections.

We agree that *in vitro* studies on *Pseudomonas* susceptibility may show MICs that are much lower than the upper threshold of sensibility proposed by the EUCAST for carbapenems. However, in all epidemiologic studies, only the first isolated strain of *P. aeruginosa* is considered for MIC determination. Besides having an intrinsic resistance to a wide range of antimicrobials, *Pseudomonas* is able to acquire resistance via several mechanisms or under antimicrobial pressure. A recent study showed that *Pseudomonas* strains isolated from ICU patients are able to progressively increase the *in vitro* MIC level to different antibiotics during therapy [6].

Finally, we agree that the extended or continuous infusion of β-lactams can optimize the PK/PD profile of these drugs. Unfortunately, as only retrospective studies have provided evidence in favor of continuous infusion over intermittent infusion (especially in pathogens with higher

*Correspondence: axel.jeurissen@gza.be
[1]Department of Medical Microbiology, GZA St. Vincentius, St. Vincentiusstraat 20, 2018 Antwerp, Belgium
Full list of author information is available at the end of the article

MICs and in ventilator-associated pneumonia [7]), a prospective study in this setting is warranted.

Abbreviations

EUCAST, European Committee on Antimicrobial Susceptibility Testing; ICU, intensive care unit; MIC, minimal inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics.

Competing interests

FST, FJ, and J-LV have received lecture honoraria from AstraZeneca (London, UK). J-LV is on the speakers' list of GlaxoSmithKline (Uxbridge, Middlesex, UK). The other authors declare that they have no competing interests.

Author details

[1]Department of Medical Microbiology, GZA St. Vincentius, St. Vincentiusstraat 20, 2018 Antwerp, Belgium. [2]Department of Intensive Care Medicine, GZA St. Vincentius, St. Vincentiusstraat 20, 2018 Antwerp, Belgium.

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