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LETTER

Persistence of piperacillin concentrations after treatment discontinuation: in cauda venenum?

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Dear Editor,

Antibiotic therapy is the mainstay of the treatment of severe infections. Antibiotics are administered as long as therapeutic drug concentrations are required, typically 5–10 days for most infections [1]. Due to changes in the pharmacokinetics of antibiotics in critically ill patients, and altered clearance of the drug [2], accumulation may occur, and antibiotic effects may persist after the administration has been stopped. It is unknown how long antibiotic concentrations remain detectable in the blood.

We studied the plasma concentration of piperacillin until 48 h after treatment discontinuation in 20 critically ill patients. We evaluated whether the remaining concentration reached the target (piperacillin concentration above 20 mg/l) and how long piperacillin concentrations in the plasma were detectable. Details of the study are available in the supplemental appendix.

Twenty patients were included, and full data sets from 18 patients were available for analysis. The median age of the patients was 62 years [interquartile range (IQR) 60–68]. Fourteen patients were treated for a respiratory infection, three patients for an abdominal infection, and in one patient the focus was unknown. The median Acute Physiology And Chronic Health Evaluation (APACHE) score was 27 (IQR 24–30). The median Sequential Organ Failure Assessment (SOFA) score was 9 (IQR 6–13) at the start of antibiotic treatment and 6 (IQR 5–7) at the time of antibiotic discontinuation. The median measured creatinine clearance (CrCl) was 77 ml/min (IQR 68–138). Two patients had a CrCl below 60 ml/min. The piperacillin concentrations after cessation of therapy are summarized in Table 1. No patients had a piperacillin concentration above 20 mg/l at 24 h or later. One patient had a concentration of 25.8 mg/l at 12 h. This patient had an average CrCl of 21 ml/min and received a reduced dose of 8 g over 24 h.

Table 1 Piperacillin plasma concentrations (mg/l) after cessation of therapy (median, with interquartile range)

Time point	End of therapy	12 h	24 h	36 h	48 h
All patients (18)	80.44 (58.63–123.41)	0.92 (0.30–3.29)	0.21 (0.09–0.47)	0.13 (0.05–0.47)	0.08 (0.03–0.12)
CrCL < 60 ml/min (2)	183.93 (155.29–212.56)	19.89 (16.92–22.85)	2.16 (2.00–2.31)	1.17 (0.78–1.55)	0.74 (0.52–0.87
CrCL 60–130 ml/min (11)	93.41 (71.50–127.27)	0.97 (0.61–3.21)	0.10 (0.07–0.32)	0.13 (0.03–0.54)	0.09 (0.03–0.11)
CrCL > 130 ml/min (5)	55.29 (36.45–61.06)	0.30 (0.20–0.92)	0.21 (0.20–0.34)	0.09 (0.06–0.14)	0.06 (0.04–0.07)

CrCL creatinine clearance

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Piperacillin concentrations no longer reached the predefined target 24 h after cessation of piperacillin/tazobactam (TZP) treatment in all patients. This indicates that the antibiotic is efficiently eliminated and that there is no longer a therapeutic effect 24 h after stopping therapy with TZP. In patients with impaired kidney function, however, concentrations may persist, as the renal clearance of the drug is the most important pathway for elimination of the drug.

Notably, after 48 h there was still a detectable concentration of piperacillin present in all patients. Considering, however, that these low concentrations beyond 24 h are still above the minimum inhibitory concentration (MIC) of many colonizing micro-organisms, this may still affect the microbiome of patients [3] and facilitate colonization with more resistant pathogens [4]. We did not measure antibiotic concentrations at the infection site or in the gut, and possibly the concentrations persist for a longer time at these sites. The implications of these persistent low concentrations with respect to development of antibiotic resistance—inside and outside the gut—need to be studied further.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5479-z) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
The authors report no conflict of interest.

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