Journal of Antimicrobial Chemotherapy Advance Access published March 18, 2015

Journal of Antimicrobial Chemotherapy

J Antimicrob Chemother
doi:10.1093/jac/dkv068

Can cytokine adsorber treatment affect antibiotic concentrations? A case report

Michael Zoller[1]*, Gundula Döbbeler[1], Barbara Maier[2], Michael Vogeser[2], Lorenz Frey[1] and Johannes Zander[2]

[1]*Department of Anesthesiology, Hospital of the Ludwig-Maximilians-University of Munich, Munich, Germany;* [2]*Institute of Laboratory Medicine, Hospital of the Ludwig-Maximilians-University of Munich, Munich, Germany*

*Corresponding author. E-mail: michael.zoller@med.uni-muenchen.de

Keywords: drug monitoring, antibiotic therapy, septic shock, bacterial infections, meropenem, therapeutic drug monitoring, intensive care units, ICUs, *in vivo*, septicaemia, linezolid

Sir,

Cytokine adsorbers, such as CytoSorb® (CytoSorbents, Monmouth Junction, NJ, USA), play an increasingly important role in the treatment of critically ill patients suffering from excessive inflammatory responses. Cytokine adsorption as a treatment during severe sepsis contains the excessive systemic expression of pro- and anti-inflammatory substances during septic conditions.[1] Recently, it has been shown that BetaSorb® (CytoSorbents) removes antibiotics in an *in vitro* system.[2] The removal of vitally important antibiotics by cytokine-adsorbing devices *in vivo* may result in insufficient and low antibiotic levels and a poor outcome and may finally promote the development of antibiotic resistance. However, to date, no *in vivo* data are available on the removal of these drugs by a cytokine filter. Here, we report, for the first known time, the use of *in vivo* pharmacokinetic monitoring of linezolid and meropenem during treatment with CytoSorb®.

A patient with septic shock and multiple organ failure was admitted to the ICU at the University Hospital of Munich. The patient's condition was characterized by excessive inflammatory responses, presenting with 1700/μL of leucocytes (reference range 4000–11 000/μL), 46 μg/L of procalcitonin (<0.1 μg/L) and 563 000 ng/L of IL-6 (<5.9 ng/L). An initial laparotomy showed an ischaemic bowel with peritonitis. The patient was immediately given intravenous meropenem (2 g) and underwent a segmental resection of the jejunum and colon with the surgical formation of an ileotransverse colostomy. A culture from an intra-abdominal smear revealed meropenem-susceptible Enterobacteriaceae and a linezolid-susceptible strain of *Enterococcus faecalis* during the subsequent course of the disease. In addition to meropenem, linezolid treatment was started 5 h after admission. Both antibiotics were administered intravenously with short infusion times (15–60 min). Because of the excessive cytokine storm, adjuvant therapy with an extracorporeal arteriovenous cytokine filter system containing adsorbent polymer beads (CytoSorb®) was initiated (four times within 96 h). The first use of the cytokine filter had to be stopped because a second look surgery was required to achieve haemostasis. Over the following days, the patient's condition substantially improved (i.e. there was an improvement in renal and liver function and cardiorespiratory status, etc.). However, after 4 weeks and seven further repeat laparotomies, the patient died from multiple organ failure.

In the context of an observational study (DRAK, ClinicalTrials.gov, NCT01793012), serum samples were primarily collected to quantify linezolid levels. The serum samples from the arterial line for antibiotic determination were collected during routine blood sampling at multiple timepoints before, during and after antibiotic administration (giving a total of 25 samples). The medical staff recorded the exact time of blood sampling. Samples were immediately sent to the Institute of Laboratory Medicine, centrifuged, aliquotted into polypropylene tubes and stored within 1 h at −80°C. The serum linezolid concentrations as well as meropenem concentrations were determined using a highly accurate LC–MS/MS method.[3] The therapeutic target ranges were assumed for linezolid as trough levels between 2 mg/L and 10 mg/L,[4] and for meropenem as 40% of the time with a serum level >8 mg/L.[5]

Figure 1 shows that there was a substantial reduction in the level of IL-6 over the course of four CytoSorb® treatments from 563 000 pg/mL on Day 1 to 19 400 pg/mL on Day 4. Using a high loading dose of linezolid (4×600 mg on Day 1) and meropenem (4 g on Day 1) because of critical illness, post-operative bleeding and the use of a cytokine filter, all of the measured antibiotic concentrations were above the lower limit of the therapeutic target range. However, we observed a high intra-patient variability for the linezolid and meropenem levels (range of lowest to highest peak level for linezolid = 11.90–20.01 mg/L and range of lowest to highest peak level for meropenem = 38.40–66.20 mg/L). The peak levels of linezolid were substantially lower (22%–40%) for administrations during CytoSorb® use than for the adjacent peak levels. Finally, the meropenem peak level during the second period of CytoSorb® use was substantially lower than the peak level before use.

The observed substantially lower linezolid peak levels during CytoSorb® use might be due to adsorption by the cytokine filter. Indeed, different endogenous substances, apart from cytokines, are reported to be adsorbed by cytokine filters.[6] Adsorption would also explain the lower peak level of meropenem during the second use of CytoSorb®. However, blood samples were not collected at optimal timepoints for meropenem; hence, the information for this antibiotic is limited. It should be mentioned that the high intra-individual variability observed for both antibiotics might also be due to the effects of critical illness.[4,7] However, because of the possible adsorption of antibiotics by cytokine filters, therapeutic drug monitoring (TDM) might be especially important for patients using such systems. Indeed, first guidelines already recommended the use of TDM in critically ill patients.[8,9] If TDM is not available, high loading doses or shorter intervals between antibiotic administrations could be used to achieve adequate antibiotic levels. The results suggest that further studies

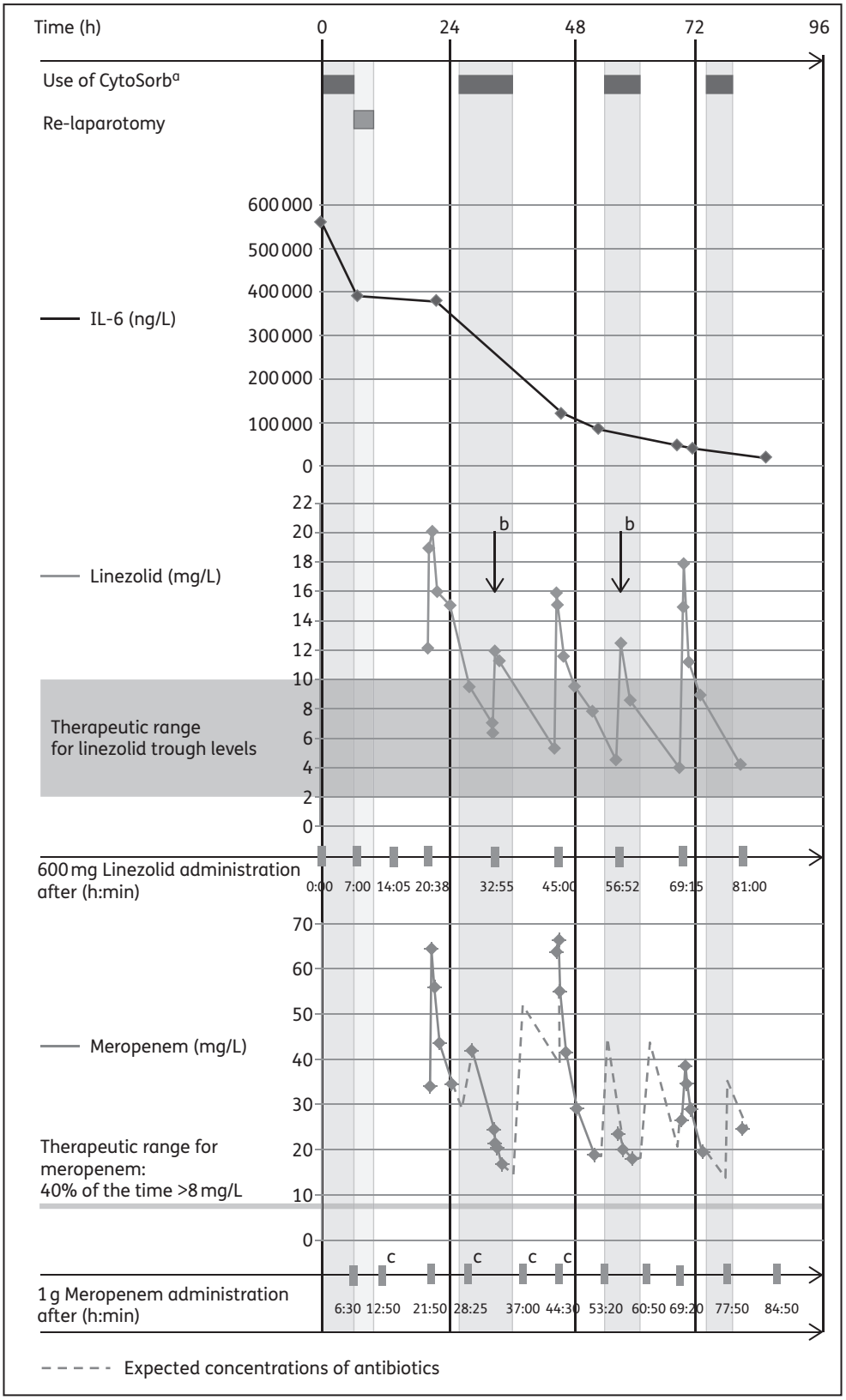

Figure 1. Effects of CytoSorb® use and antibiotic administration on the serum concentrations of IL-6, linezolid and meropenem. The first 96 h after the start of CytoSorb® use are shown. [a]Use of CytoSorb® according to clinical decisions. [b]Lower peak levels compared with adjacent peak levels. [c]Administration of 2 g of meropenem.

are needed to understand the impact of cytokine filters on the concentrations of different antimicrobials.

Funding

This study was supported by a Mérieux Research Grant (Institut Mérieux, Lyon, France).

Transparency declarations

None to declare.

We affirm that this manuscript is an honest, accurate and transparent account of the case being reported, and that no important aspects of the case have been omitted.

References

1 Bello G, Di Muzio F, Maviglia R *et al*. New membranes for extracorporeal blood purification in septic conditions. *Minerva Anestesiol* 2012; **78**: 1265–81.

2 Reiter K, Bordoni V, Dall'Olio G *et al*. In vitro removal of therapeutic drugs with a novel adsorbent system. *Blood Purif* 2002; **20**: 380–8.

3 Zander J, Maier B, Suhr A *et al*. Quantification of piperacillin, tazobactam, cefepime, meropenem, ciprofloxacin and linezolid in serum using an isotope dilution UHPLC-MS/MS method with semi-automated sample preparation. *Clin Chem Lab Med* 2014; doi:10.1515/cclm-2014-0746.

4 Zoller M, Maier B, Hornuss C *et al*. Variability of linezolid concentrations after standard dosing in critically ill patients: a prospective observational study. *Crit Care* 2014; **18**: R148.

5 Wong G, Brinkman A, Benefield RJ *et al*. An international, multicentre survey of β-lactam antibiotic therapeutic drug monitoring practice in intensive care units. *J Antimicrob Chemother* 2014; **69**: 1416–23.

6 Kuntsevich VI, Feinfeld DA, Audia PF *et al*. In-vitro myoglobin clearance by a novel sorbent system. *Artif Cells Blood Substit Immobil Biotechnol* 2009; **37**: 45–7.

7 Roberts JA, Abdul-Aziz MH, Lipman J *et al*. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. *Lancet Infect Dis* 2014; **14**: 498–509.

8 Bodmann KF, Grabein B. Empfehlungen zur kalkulierten parenteralen Intitialtherapie bakterieller Erkrankungen bei Erwachsenen. Update 2010. *Chemother J* 2010; **19**: 179–255.

9 Dellinger RP, Levy MM, Rhodes A *et al*. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **41**: 580–637.