Can cytokine adsorber treatment affect antibiotic concentrations? A case report

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Keywords: drug monitoring, antibiotic therapy, septic shock, bacterial infections, meropenem, therapeutic drug monitoring, intensive care units, ICUs, in vivo, septicemia, 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. Recently, it has been shown that BetaSorb® (CytoSorbents) removes antibiotics in an in vitro system. 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 of Veterinary Hospital of Munich. The patient's condition was characterized by excessive inflammatory responses, presenting with 1700 μL of leucocytes (reference range 4000–11000 μL), 46 μg/L of procalcitonin (<0.1 μg/L) and 563000 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 ileoileostomy. 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, adjunct therapy with an extracorporeal arteriovenous cytokine filter system containing absorbent 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. The therapeutic target ranges were assumed for linezolid as trough levels between 2 mg/L and 10 mg/L, and for meropenem as 40% of the time with a serum level >8 mg/L.

Figure 1 shows that there was a substantial reduction in the level of IL-6 over the course of four CytoSorb® treatments from 563000 pg/mL on Day 1 to 19400 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%) than the assumed target range.
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. aUse of CytoSorb® according to clinical decisions. bLower peak levels compared with adjacent peak levels. cAdministration of 2 g of meropenem.
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 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

Advance Access publication 15 March 2015

Interaction between voriconazole and flucloxacillin during treatment of disseminated Scedosporium apiospermum infection

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Keywords: triazoles, metabolism, S. apiospermum

Sir,

Voriconazole is a broad-spectrum triazole used in the treatment of many fungal infections including those caused by Scedosporium spp. Along with significant side effects, voriconazole has a variable metabolism and multiple drug interactions, requiring regular monitoring. We present a case of disseminated Scedosporium apiospermum infection in a patient who was treated with voriconazole, but was unable to achieve therapeutic levels, with a resultant clinical relapse while on flucloxacillin for a Staphylococcus aureus bloodstream infection.

The patient’s infection involved the skin, lungs and brain, and occurred against a background of recently commenced low-dose prednisolone for polymyalgia rheumatica. Skin biopsies isolated S. apiospermum and flucloxacillin during...