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LETTER

No clinically relevant removal of meropenem by cytokine adsorber CytoSorb® in critically ill patients with sepsis or septic shock

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Dear Editor,

Sepsis and septic shock are life-threatening organ dysfunctions caused by a dysregulated host response to severe infection [1]. Inflammatory cytokines play a pivotal role in the progression of sepsis and cause dysregulation of vital organ functions, possibly leading to organ failure and death. To clear key cytokines in septic patients the cytokine adsorber CytoSorb® is increasingly used, despite absence of hard evidence for a beneficial effect on patient-centered outcomes [2]. Moreover, concerns have been raised that CytoSorb® unintentionally adsorbs drugs such as meropenem [3]. Previous in vitro experiments suggested that the CytoSorb® filter has an adsorptive capacity, for meropenem, of about 400 mg [3]. In a case report, removal of meropenem was suspected in a critically ill patient [5], yet recent in vivo data in healthy pigs suggested a negligible increase in clearance (6.3%) [4]. To date, reliable quantitative clinical data are missing [2].

We analyzed therapeutic drug monitoring data in critically ill patients undergoing continuous veno-venous hemodialysis with and without CytoSorb® treatment (44 CytoSorb® treatments, 25 patients, 333 serum samples including 114 during CytoSorb® treatment). Meropenem pharmacokinetics was characterized using nonlinear mixed-effect modeling (NONMEM 7.4). A classical two-compartment model best described the observed concentrations. To assess whether clearance differed without versus during CytoSorb® treatment, three approaches were applied: (i) quantification of a possible proportional increase in clearance during CytoSorb® treatment, (ii) investigation of (non)saturable adsorption at the CytoSorb filter using different adsorption submodels (constant adsorption, linear and hyperbolic decrease of adsorption); and (iii) model parameter re-estimation, excluding samples collected during CytoSorb® treatment and evaluating how well these parameters predicted the concentrations during CytoSorb® treatment (Supplementary File). However, none of these approaches revealed a significant ($p < 0.05$) or relevant effect of CytoSorb® therapy on meropenem concentrations. Both the proportional increase of approach (i) and the maximum adsorption estimated in approach (ii) were negligibly small (< 3.7% total clearance) and could not be estimated precisely (relative standard error ≥ 110%). The re-estimated model even revealed a small underprediction (0.42 mg/L, 2.6%) of concentrations during CytoSorb® treatment, whereas an overprediction would indicate adsorption. Figure 1 shows the predicted concentration–time profile of a representative patient, based on the pharmacokinetic model excluding CytoSorb® samples and the observed concentrations both during and without CytoSorb® treatment. Although not included in the model development, the samples taken during CytoSorb® treatment were well predicted by the model, showing that there was no clinically relevant reduction of meropenem concentrations. A similar figure supporting the same conclusion for all patients, as well as patient characteristics and details of

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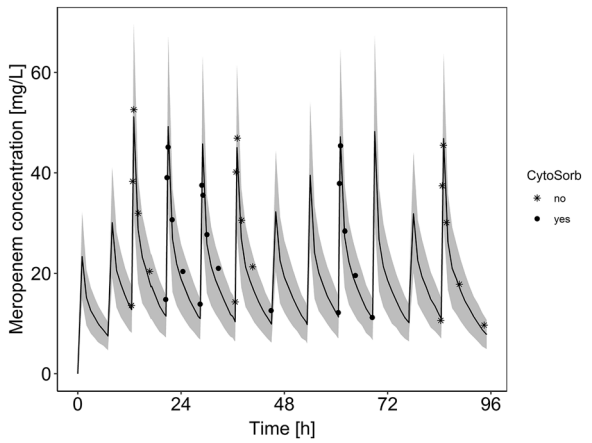

Fig. 1 Observed meropenem concentrations and meropenem concentration–time profile predicted on the basis of a pharmacokinetic model excluding CytoSorb® samples. The profile refers to one patient from the dataset. Black line: median prediction, Gray shading: 50% prediction interval, Symbols: meropenem samples with (points) and without (stars) CytoSorb® treatment

the modeling approach, can be found in the supplementary file.

Overall, no clinically relevant adsorption of meropenem by the cytokine adsorber CytoSorb® was observed in the investigated critically ill patient population. Consequently, neither additional dosing nor more frequent monitoring of meropenem is necessary during the application of CytoSorb®. Our findings most likely do not translate to other drugs and antibiotics, and we therefore emphasize that every drug needs to be investigated separately.

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Declarations

Conflicts of interest
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Ethics approval
This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval and consent were obtained from the Institutional Review Board of the Medical Faculty of the Ludwig-Maximilians-Universität München (Munich, Germany) [registration No. 428-12 and 18-578].

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