Cerebrospinal fluid impairs antimicrobial activity of fosfomycin in vitro—authors’ response

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Sirs,

Beer et al.1 have provided a Comment on our recent article2 regarding the activity of fosfomycin in cerebrospinal fluid (CSF). Essentially, we had reported reduced activity of fosfomycin against Staphylococcus aureus in CSF in vitro compared with in Mueller–Hinton broth, observing that a concentration of 8 × the MIC was required for sustained killing after 24 h.

In their Comment, Beer et al.3 express their skepticism that these in vitro data can be extrapolated to in vivo conditions and state that the reduced antimicrobial activity of fosfomycin in CSF is in contrast to their results from a previous in vivo pharmacokinetic study.3 However, we cannot see any contradiction in the results, since both studies do not seem to be comparable. While Pfausler et al.4 determined pharmacokinetic data in CSF and speculated on the clinical efficacy of the measured fosfomycin levels by referring to drug activity in Mueller–Hinton broth, our recent study5 investigated the activity of fosfomycin (pharmacodynamics) in CSF. The study by Pfausler et al.5 was clearly not designed to investigate the missing link between both studies, i.e. clinical outcome of fosfomycin therapy in ventriculitis, as all six patients of this pharmacokinetic study received at least two further antibiotics apart from fosfomycin.

As requested in the Comment on our work, we would like to provide some details on the pooled human CSF used for in vitro experiments. CSF was obtained only from patients who did not receive antibiotics, i.e. mainly from patients with ventricular drains where CSF was controlled, or from neurological investigations. Single samples of purulent CSF, or with visible blood contaminations, were not pooled. CSF was essentially not from people with cerebral infections, because such patients are mostly under antibiotic therapy precluding the use of CSF for microbiological experiments. The composition of pooled human CSF used on another occasion6 was as follows: glucose, 45 mg/dL; total protein, 280 mg/L; albumin, 185 mg/L; sodium, 105 mmol/L; and potassium, 2.4 mmol/L. Of these parameters, only glucose showed an essential change after 24 h of bacterial growth, sinking to 24 mg/dL in CSF in vitro.

Beer et al.1 further state that altered biochemical characteristics in the CSF of their patient population compared with our pooled CSF might result in different activity of fosfomycin. Though this relevant limitation was already mentioned in our manuscript,2 it should be noted that this issue remains rather speculative, since no data on the composition of CSF and, in particular, on the concentration of glucose-6-phosphate was given in the manuscript by Pfausler et al.3 Indeed, this topic would be worth being studied, as well as other possible reasons for bacterial regrowth in CSF at fosfomycin concentrations above the MIC.

In addition, we would like to recommend detailed consideration of the articles by Ribes et al.2 and Nau et al.6 who worked with in vivo meningitis models in rodents. Both groups reported good CSF penetration of fosfomycin, but stressed that fosfomycin concentrations of ≥8 × the respective MICs were necessary in CSF in vivo for sufficient bacterial killing during monotherapy. Hence, though observed in animals and not in humans, the assumption of lower fosfomycin activity in CSF than in other media was not only based on current in vitro experiments, but is in agreement with previous in vivo meningitis data. These results from animals should not be fully disregarded in the absence of randomized trials in humans reporting clinical outcomes of antibiotic therapy.

Finally, we would like to emphasize that fosfomycin must be administered in combination with other agents to avoid the emergence of resistance. Since enhanced activity of cephalosporins or vancomycin by the addition of fosfomycin is documented in vivo for meningitis in animals,5 and due to its excellent CSF penetration,3 fosfomycin remains an option for select patients with intracranial infections. The recent in vitro experiment2 was designed to contribute to the understanding of the results of the animal studies and the properties of fosfomycin—including its assets and drawbacks.

Transparency declarations
None to declare.

References
Letters to the Editor


