Penetration of Fosfomycin into Cerebrospinal Fluid across Non-inflamed and Inflamed Meninges

**Summary:** Serum and cerebrospinal fluid (CSF) concentrations of fosfomycin were evaluated in 45 patients. Mean serum concentration was 260.1 mg/l at 15 min postinfusion in 35 patients receiving a 5 g bolus dose, and 440 mg/l in five patients receiving a 10 g bolus dose. Mean distribution volume was 18.5 l (5 g dose), the total clearance was 118.8 ml/min, half-life was nearly 2 h, and the determined AUC were 420.95 mg/l • h (5 g dose) and 423.57 mg/l • h (10 g dose). The average peaks at 360 min in CSF reached 11.6 mg/l (5 g dose) and 17.7 mg/l (10 g dose). The CSF/serum ratio was 9.24% (5 g dose), and 13.81% (10 g dose). The CSF levels were not below 30 mg/l from the second day on in patients receiving 3 × 5 g fosfomycin per day. Meningeal inflammation increased the CSF concentrations from 30 mg/l at 6 h up to 150 mg/l at 120 h in the saturation phase, e. g., up to 300% more in comparison to non-inflamed meninges.

**Introduction**

Fosfomycin, (-)-(1R,2S)-(1,2-epoxypropyl)-phosphonic acid (1) is an antibiotic with a low molecular weight (138.1 Da), which is neither protein bound (2) nor metabolized. Fosfomycin possesses potent antimicrobial activity against commonly encountered pathogens (3, 4). Even today, especially cure of bacterial meningitis in patients at high risk is often limited by the low penetration rates of routinely used antibiotics into the CSF. Furthermore, it is highly desirable to get antibiotics showing sufficient penetration rates independent of the state of the blood-brain barrier. The objective of the current study was to evaluate CSF levels of fosfomycin, for which only limited information is available with inflamed (5-7) and non-inflamed (8, 9) meninges.

**Patients and Methods**

**Patients:** 45 patients were included in the study. Their mean age was 46.6 years (range 18 to 69 years). Each patient obtained an intraoperative or therapeutic (hydrocephalus occlusus) CSF drainage required for neurosurgical indication. The patients were informed about the intention of the study and the drug used. Consent was obtained prior to application. If patients were critically ill, they were excluded.

**Drug administration:** Fosfomycin was administered to 35 patients as a 5 g bolus dose, and to five patients as a 10 g bolus dose. Four suitable patients received a maintenance dose of 3 × 5 g per 24 h. Kinetics of this saturation dose were observed over a period of five days. The blood-brain barrier was considered to be largely intact, which was proved by normal cell count, total protein and glucose of CSF samples. Five patients showed meningal inflammation which was caused in three patients by *Staphylococcus aureus*, in one patient by a coagulasenegative-staphylococcus, and in one patient by *Pseudomonas aeruginosa*. All pathogens showed sensitivity to fosfomycin. The total dose of fosfomycin was infused, i. e. over approximately 30 min.

**Sample collection:** Samples were taken before administration, at time zero after, and at various times later. 283 blood samples and 240 CSF samples were investigated. The samples were stored at -70°C until assayed.

**Fosfomycin assay:** A bioassay was performed by a plate diffusion method (antibiotic agar Nr. 7; Oxoid) with *Escherichia coli* Nr. 108 (Boehringer Mannheim) as test organism. To determine the concentration, each sample was measured twice, and the quadruplicate method was used. The quantitation limit of the assay was 0.3 mg/l.

**Results**

**5 g bolus dose:** The concentration curves of blood and CSF of 35 patients receiving a 5 g bolus dose of fosfomycin are shown in Figure 1. The peak concentration in serum was 260.1 mg/l (s = ± 105.7 mg/l) 15 min after the end of infusion, and decreased to 2 mg/l (s = ± 0.8 mg/l).
**Figure 1:** Semilogarithmic plot of fosfomycin serum (○) and CSF concentrations versus time in 35 patients receiving a 5 g bolus dose. × = beginning, and O = end of i.v. infusion.

**Figure 2:** Semilogarithmic plot of fosfomycin serum (○) and CSF concentrations versus time in five patients receiving a 10 g bolus dose. × = beginning, and O = end of i.v. infusion.

**Figure 3:** CSF-concentrations (○) of fosfomycin in patients with noninflamed meninges. ▲ = single patients with meningeal inflammation.

15 h later. Following the open two-compartment model, we determined a mean distribution volume of 18.5 l in the central compartment, a \( \text{Cl}_{\text{to}} \) of 118.8 ml/min, a half-life of about 2 h, and an AUC of 420.95 mg/l • h.

The mean concentrations in the CSF were 8.6 mg/l at 180 min and 11.6 mg/l at 360 min, and decreased to 3 mg/l after 900 min. The AUC was determined as 38.89 mg/l • h, e. g., 9.24% when expressed as a ratio of CSF to serum concentrations.

**10 g bolus dose:** Serum and CSF concentrations of five patients receiving a 10 g bolus dose are shown in Figure 2. The peak serum concentration was higher (440 mg/l), but the elimination behaviour was comparable. The AUC was determined to be 423.57 mg/l • h, the mean distribution volume was 24.9 l. The time required to get higher concentrations of fosfomycin in the CSF could be clearly shortened. The mean concentration curve showed a more rapid increase, a longer constant phase, and a slower decrease than observed for the first group. The mean peak concentrations were 15.4 mg/l at 120 min, 17.7 mg/l at 360 min, and 7 mg/l at 900 min postinfusion. The AUC of the CSF was determined to be 58.49 mg/l • h, e. g., 13.81% of the AUC of the serum curve.

**Maintenance dose:** Four suitable patients received a maintenance dose of 3 × 5 g fosfomycin for five days (Figure 3). The concentration in the CSF increased from nearly 15 mg/l after 24 h to 30 mg/l after 48 h, and at least to more than 50 mg/l after 120 h. These data obtained in patients with non-inflamed meninges could be increased to 150 mg/l in five patients undergoing meningeal inflammation (Figure 3).

**Discussion**

Because of the high lethality, the progress of central nervous system infections has to be stopped as early as possible. Little or no inflammatory response is observed in endangered immunocompromised patients. Penetration into the CSF during the state of non-inflamed meninges is not sufficient for aminoglycosides (10), penicillins (11), and cephalosporins. Furthermore, the use of chloramphenicol (12), tetracyclines (13), and sulfonamides (14) is limited because of toxicity, allergy, and their activity on multiresistant nosocomial pathogens.

Oellers et al. (15) found fosfomycin concentrations in the serum of 275.3 mg/l at 10 min postinfusion in comparison to 260 mg/l of a 5 g bolus dose in the present study. The determined mean concentrations in CSF of 6.7 mg/l at 240 min and 10 mg/l at 450 min (15), and 10.3 mg/l at 240 min (9), respectively, were comparable to our own values. As reported by Friedrich et al. (16), the CSF concentrations ranged between 6.48 mg/l and 8.98 mg/l after administration of 15 g fosfomycin at 8 h intervals.

The higher initiation dose of 10 g fosfomycin had several advantages. First, the latency time to get the same concentrations as reached by a 5 g dose was clearly shortened by about 1 h; secondly, the plateau phase, and thirdly, the elimination phase, were prolonged. Although the CSF/serum ratios of the areas under the curves are of limited meaning, because at the time the experiment ended CSF-concentrations were still relatively high, they indicate a high penetration rate.

Administering the saturation dose of 3 × 5 g per day, the CSF concentrations did not fall below 30 mg/l from the second day on.