Intraperitoneal Meropenem for Polymicrobial Peritoneal Dialysis-Related Peritonitis

With the current rise in multiresistant gram-negative bacteria, carbapenems are more frequently used. Surprisingly, limited data exist on the pharmacokinetics of meropenem in peritoneal dialysis (PD)-related peritonitis. We report on the pharmacokinetics of repeated intraperitoneal (IP) meropenem during 21 days as treatment for polymicrobial multiresistant PD-related peritonitis.

Our current report supports daily doses of 125 mg/L intraperitoneal meropenem in all bags as an effective and safe modality in the treatment of PD-associated peritonitis with multiresistant microorganisms. No signs of over- or underdosing were found based on serial drug concentration measurements at fixed time points up to 21 days.

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With the current rise in multiresistant gram-negative bacteria, carbapenems are more frequently used. Meropenem is the drug of choice since its side effects on the central nervous system are less frequent than those of other carbapenems. Thus far, limited data exist on the pharmacokinetics of meropenem in peritoneal dialysis (PD)-related peritonitis (1). We report on the pharmacokinetics of repeated intraperitoneal (IP) meropenem during 21 days as treatment for polymicrobial multiresistant PD-related peritonitis. Guidelines advocate IP administration of antibiotics, since the IP route is considered to be superior to intravenous (IV) administration (2). The patient was an 84-year-old Asian woman on continuous ambulatory PD (CAPD) (4 1.5-L exchanges) for 5 years due to end-stage hypertensive nephropathy (creatinine clearance 4 mL/min, urinary output 560 mL/24 h). She had no prior episodes of PD peritonitis.

During a regular visit to our outpatient clinic she reported slightly turbid dialysate for a period of 2 weeks without abdominal complaints. Peritoneal dialysis fluid contained 3.4×10^9 /L leukocytes with 90% polymorphonuclear cells (PMNs). Empiric treatment with clindamycin (150 mg/L in all bags) and gentamicin (20 mg/L in overnight bag) was started. After an initial fall in PD fluid leukocytes to 1.8×10^9 /L within 3 days, a subsequent rise to 17.4×10^9 /L with 90% PMNs was observed on the 4th day. Our patient complained of general

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weakness and nausea. Peritoneal dialysis fluid grew *E. coli*, *S. milleri*, and *B. Fragilis*. All were sensitive to amoxicillin, except for the latter (only sensitive to metronidazole). Treatment was switched to IP amoxicillin, ciproxin, and gentamicin combined with IV metronidazole. Abdominal computed tomography (CT) scanning did not reveal bowel perforation or diverticulitis. A good clinical and biochemical response followed, with a fall in PD fluid leukocytes to $0.2 \times 10^9/L$ on day 11, when extended spectrum β -lactamase (ESBL) producing *E. Coli* was cultured from the PD fluid. This microorganism was resistant to all antibiotics, except for meropenem. Since no further decline of leukocytes in the peritoneal fluid was observed, treatment was changed to continuous IP meropenem (125 mg/L in all bags). Within 3 days after initiation, the leukocyte count in the peritoneal fluid decreased permanently to less than $0.1 \times 10^9/L$, and additional cultures of the peritoneal fluid were negative. Meropenem treatment was continued for 21 days. The patient gave informed consent to undergo additional blood and dialysate samples to monitor the pharmacokinetics of IP meropenem.

Blood and dialysate samples were drawn at $t = 0, 1, 2$, and 4 hours after the first dose of IP meropenem. In addition, blood was drawn at $t = 24, 144, 312$, and 480 hours after the first dose of IP meropenem. Twenty-four-hour dialysate was collected and sampled on days 1 and 7. The samples were immediately centrifuged and the dialysate and plasma were stored at $-80^\circ C$ until analysis. They were analyzed using high-performance liquid chromatography at the Free University Medical Center, Amsterdam, The Netherlands. In the samples at $t = 0, 2$, and 4 hours, creatinine and glucose were measured as well. Results are shown in Figure 1.

Figure 1 — Concentrations of meropenem (mg/L) in plasma (circles) and peritoneal fluid (squares) during continuous intraperitoneal (i.p.) treatment with meropenem 125 mg/L. Plasma concentrations were measured at 1, 2, 4, 24, 144, 312, and 480 hours after administration of the first dose of IP meropenem. Concentrations in peritoneal fluid were measured at 0, 1, 2, and 4 hours after administration of the first dose.

Dialysate/plasma creatinine at 4 hours was slightly higher (0.60) compared to the value at her recent peritoneal equilibration test (PET) (0.53), suggesting ongoing inflammation. Peritoneal dialysis fluid meropenem levels decreased over the dwell time, mainly reflecting diffusion to other body compartments and drug metabolism. Measured meropenem concentrations in pooled 24-hour PD fluid on day 1 and on day 7 were 27.0 mg/L and 30.8 mg/L. Mean PD fluid concentration was at least 27 mg/L. Plasma meropenem steady state levels ranged from 12.3 to 16.3 mg/L and were well above the minimal inhibitory concentration (MIC) for relatively unsusceptible microbes (2 – 4 mg/L) (3). In the biophase (peritoneum), meropenem levels are probably higher than in plasma and lower than in PD fluid. Following repeated intravenous (IV) administration of 1,000 mg meropenem, peak plasma levels are around 50 mg/L, substantially higher than those reached with IP administration of 125 mg/L in 4 bags (12.2 – 16.3 mg/L). These lower levels were therapeutic, well tolerated, and without side effects.

In conclusion, our current report supports daily doses of 125 mg/L IP meropenem in all bags as an effective and safe modality in the treatment of PD-associated peritonitis with multiresistant microorganisms. No signs of over- or underdosing were found based on serial drug concentration measurements at fixed time points up to 21 days.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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