Successful Treatment of a Pacemaker Infection with Intraperitoneal Daptomycin

We investigated the pharmacokinetics of intraperitoneal administration of daptomycin in a peritoneal dialysis (PD) patient treated for a pacemaker infection with *Staphylococcus epidermidis*. After initial start of intravenous daptomycin at 9 mg/kg body weight every 48 hours, the therapy was switched to intraperitoneal administration of 5.3 mg/kg body weight in 1 L icodextrin 7.5% with a dwell time of 12 hours overnight every 48 hours. Therapeutic drug monitoring (TDM) was performed at 4 hours and 24 hours after dose administration. Due to high peak concentration above target peak concentration, the dose was reduced to a final maintenance dose of 3.2 mg/kg body weight. Data from this single case suggest that serum drug concentration above the minimal inhibitory concentration (MIC) can be easily achieved with intraperitoneal administration of daptomycin every 48 hours even with a lower dose, as recommended for the intravenous administration, but measurement of serum concentration and dose adjustments are mandatory in such cases.

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Intraperitoneal antibiotic administration is the treatment of choice for the management of intraperitoneal infections in patients undergoing peritoneal dialysis (PD) (1). Depending on the antibiotic's protein-binding capacity and permeability across the peritoneal membrane, significant plasma antibiotic concentrations can also be achieved after intraperitoneal application, particularly if the peritoneal membranes are inflamed (2). Antibiotics with a high protein-binding capacity can be rapidly taken up across the peritoneal membrane (3) and can

therefore also be administered intraperitoneally for systemic infections or infections outside of the peritoneal cavity (4). Daptomycin is a new cyclic lipopeptide antibiotic used for the treatment of infections caused by gram-positive organisms, especially resistant strains of *Staphylococcus* and vancomycin-resistant *Enterococci* (5). It exhibits concentration-dependent killing (5). Its plasma protein-binding is 90 – 93% (5), so systemic uptake after intraperitoneal administration is expected. Data, however, are limited to a single case report describing measurement of relevant plasma daptomycin concentrations after intraperitoneal administration of 7 mg/kg body weight for the treatment of presumed *S. aureus* peritonitis (6). Daptomycin has a volume of distribution of 0.1 L/kg body weight in healthy adult subjects and is water soluble (5). It is largely renally cleared, with a clearance of 4 – 7 mL/h/kg. The pharmacokinetics of intraperitoneally applied daptomycin are not known.

MATERIALS AND METHODS

We describe a case in which intraperitoneal daptomycin administration was used to successfully treat a systemic infection and in which dosing was guided by therapeutic drug monitoring (TDM). As trough daptomycin concentrations above 24 mg/L are associated with an increased risk of muscle toxicity (7), a target trough level of < 24 mg/L was set. Data regarding target peak (C_{max}) daptomycin concentrations for the treatment of *S. epidermidis* in humans are lacking. However, data from a mouse model of *S. aureus* infection show that a C_{max}/minimum inhibitory concentration (MIC) of approximately 150 is associated with 2 log killing (8), corresponding to a peak concentration (C_{max}) of 37.5 mg/L in this case. Due to the lack of more specific data for *S. epidermidis*, it seemed reasonable to set the target peak daptomycin concentration range at 32.5 – 42.5 mg/L. Daptomycin was measured in serum using a fully validated liquid chromatography–mass spectrometry (LC-MS)/MS method according to Jourdil and colleagues with some modifications (9). Blood samples were centrifuged at 3,000 rpm for 10 minutes and the serum supernatant removed and stored at 20°C until analysis. The patient gave written, informed consent for publication of her case.

RESULTS

A 54-year-old female patient (94 kg) on long-term hemodialysis (HD) due to thrombotic microangiopathy and without residual renal function developed sepsis after insertion of a pacemaker for the treatment of symptomatic third-degree heart block. *Staphylococcus epidermidis* sensitive to daptomycin grew in all 4 blood culture samples. The daptomycin MIC was 0.25 mg/L. Due to thrombosis of the superior vena cava, the pacemaker system could not be explanted, and an extensive course of antibiotics was required. Intravenous daptomycin was commenced at 9 mg/kg body weight (850 mg) every 48 h after HD (Table 1). Co-medication was with unfractionated heparin, buprenorphine, pantoprazole, laxatives, mirtazapine, paracetamol, and sevelamer.

Problems arose with her venous dialysis access 5 days after the start of daptomycin. Renewed central venous access was not possible due to the high chance of catheter infection in the setting of a not yet fully treated infected indwelling pacemaker system (as evidenced by elevated C-reactive protein [CRP] – Table 1). It was therefore decided to convert from HD to PD on day 5. Peritoneal dialysis was initially unsuccessful due to PD-catheter dysfunction, so regular effective PD was started with some delay on day 9. During this time, confusion arose regarding the timing of intravenous daptomycin, and the patient inadvertently received more frequent doses than intended. Therapeutic drug monitoring (TDM) confirmed peak levels 4 times above target on day 7 (Table 1), and the patient also developed nausea, requiring treatment with antiemetics. She did not experience any other daptomycin-related adverse effects and creatine kinase (CK) measurements remained normal throughout (Table 1).

Peripheral venous access subsequently failed on day 11 and, despite several attempts, could not be re-established. The decision was made to administer daptomycin 500 mg (5.3 mg/kg) intraperitoneally every 48 h, with the first administration taking place on day 11. A lower dose of only 5.3 mg/kg was given, due to persistent peak drug levels above the target range (37.5 ± 5 mg/L) on days 7 and 10 and concern that intraperitoneal daptomycin may have 100% bioavailability. Icodextrin 7.5% (1 L) was chosen as the PD fluid and a dwell time of 12 h overnight was used. Therapeutic drug monitoring was performed before, 4 h after, and 24 h after this first intraperitoneal dose (Table 1). During the daytime, the patient was treated with automated PD over 6 h with a total volume of 8.4 L (1.5% glucose). The 4-h sampling time point was chosen, as this was the time at which the peak concentration was reached in the previously published case (6). The 24-h post-dose sample was performed in order to determine the daptomycin clearance of intraperitoneal dialysis. As daptomycin dosed at 5.3 mg/kg every 48 h achieved above-target peak concentrations, the dose was empirically reduced to 400 mg (4.3 mg/kg) every 48 h and then subsequently to 3.2 mg/kg every 48 h. Target trough and peak concentrations were achieved on day 22, and the dose was maintained at 300 mg (3.2 mg/kg) intraperitoneally every 48 h (Table 1) until day 32, when treatment was converted to oral rifampicin (600 mg/d) and fusidic acid (1.5 g/d) for a further 10 weeks. Blood cultures remained negative on completion of treatment. Six months later, the patient underwent cadaveric renal transplantation. One year later, the patient is well and her pacemaker remains functional. On direct questioning about her experience of intraperitoneal daptomycin application, she said she was grateful that she could be treated ‘without needles’ and that she did not experience any side effects from the treatment.

DISCUSSION

To our knowledge this is the first case report describing the intraperitoneal administration of daptomycin for the

TABLE 1
Dosing, Administration Route, Modality of Renal Replacement Therapy, Measured Daptomycin Concentrations, CRP, Symptoms, and CK-measurements

Treatment day	Renal replacement therapy	Daptomycin dose (mg)	Dose (mg/kg)	Route	Pre-dose ('trough') concentration (mg/L) after HD	Post-dose concentration (hours post dose)	CRP (mg/L)	CK (U/L)	Symptoms
1	HD	850 after HD	9	IV			199	11	
2	—	0	0				123	33	
3	HD	850 after HD	9	IV	30.3	86.9 (1)			
4	—	0	0						
5	—	720	7.7	IV					
6	HD	350 after HD	3.7	IV			94	66	
7	—	720	7.7	IV	54.2	160 (1)			Nausea
8	HD	0	0				66	32	
9	PD	720 (morning)	7.7	IV					
10	HD + PD	0	0		52.8				
11	PD	500 (evening)	5.3	IP	34.4	33.1 (0); 57.3 (4); 50.0 (24)			
12	PD	0	0				25	38	
13	PD	500 (evening)	5.3	IP			22	73	
14	PD	0	0						
15	PD	400 (evening)	4.3	IP	38.8	57.1 (4); 57.4 (6)			
16	PD	0	0				34	87	
17	PD	300 (evening)	3.2	IP					
18	PD	0	0						
19	PD	300 (evening)	3.2	IP	25.9	36.2 (4)			
20	PD	0	0						
21	PD	0	0						
22	PD	300 (morning)	3.2	IP	17.1	33.8 (4)	35	40	
23	PD	0	0				30	37	
24	PD	300 (morning)	3.2	IP			38	37	
25	PD	0	0				33	39	
26	PD	300 (morning)	3.2	IP					
27	PD	0	0				31	30	
28	PD	300 (morning)	3.2	IP			30	29	
29	PD	0	0				30	30	
30	PD	300 (morning)	3.2	IP			28	26	
31	PD	0	0						
32	PD	Daptomycin stopped	0				25	33	

CRP = C-reactive protein; CK = creatine kinase; HD = hemodialysis; PD = peritoneal dialysis; IV = intravenous; IP = intraperitoneal. All concentrations were direct measurements.

treatment of a systemic gram-positive infection. A single previous report of intraperitoneal administration of 7 mg/kg/body weight used to treat peritonitis (absolute dose of 280 mg daptomycin) showed that peak drug serum concentrations of approximately 20 – 30 mg/L can be achieved (6).

The type of PD fluid used in the previously published case was not reported. Daptomycin was initially considered to be unstable in dextrose solutions. However an *in vitro* study showed that daptomycin was stable at 25°C and 37°C in dextrose and amino-acid solutions for at least 6 hours (10). Data on the stability of daptomycin in icodextrin could unfortunately not be obtained in this latter study due to measurement problems. Additionally, *in vitro* data show continued bactericidal effects in different dextrose solutions at 37°C for up to 24 h, with the best

bactericidal effect being achieved by daptomycin in icodextrin 7.5% solution (11). Another *in vitro* study using PD solutions of varying pH and high calcium concentration (75 mg/L) did not show a significant reduction in daptomycin's antibacterial activity over a period of 4 h (12). Furthermore, daptomycin showed good antibacterial activity under these conditions, whereas vancomycin and cefazolin did not (12). We found that peak serum concentrations were already reached after 4 hours (data from day 15, Table 1), suggesting that a shorter dwell time might have achieved the same systemic drug exposure.

Our patient did not have peritonitis, so systemic drug exposure to daptomycin in cases of inflamed peritoneal membranes is likely to produce different results, and our dosing strategy may not be applicable in such cases. Indeed, much

lower daptomycin doses (20 mg/L compared with 300 mg/L dialysate) have been used in cases of peritoneal infection (13). On the basis of intravenous pharmacokinetic data, steady state plasma concentrations are achieved within 3 days when administered every 24 hours (5). Further studies would need to be performed to determine exactly when steady state is achieved for intraperitoneal application; however, the data from this single case suggest it is also achieved within a similar time-frame when applied in 1 L of dialysate with a dwell time of 12 hours every 48 hours.

In conclusion, in patients with systemic infectious diseases and poor vascular access undergoing PD, intraperitoneal administration of antibiotics might present a feasible route of application. Since pharmacokinetic studies after intraperitoneal application are lacking for most antibiotics, measurement of serum concentrations and dose adjustments to maintain therapeutic, non-toxic concentrations is possible and meaningful in this context. The case presented here suggests that icodextrin is a suitable application solution for daptomycin. However, further studies are needed.

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DISCLOSURES

The authors have no financial conflicts of interest to declare.

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