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Pharmacokinetics of 300 mg/d Intraperitoneal Daptomycin: New Insight from the DaptoDP Study

The DaptoDP (NCT 2012-005699-33) study aimed to evaluate the pharmacokinetic parameters of daptomycin (DAP) in peritoneal dialysis-related peritonitis (PDRP) patients following intraperitoneal (IP) administration. The authors have already reported the findings on the 200-mg dosing and present here the follow-up results of the 300-mg dosing. The primary endpoint was a dialysate concentration of DAP above the effective concentration *in situ* during 6 hours of dwell time i.e., 16 mg/L. Secondary endpoints were to avoid the toxic threshold of 120 mg/L DAP and to be above 16 mg/L DAP for 2 hours in plasma. Pharmacokinetic parameters were evaluated on days 1 and 5. Safety data were evaluated on days 1 to 14 based on clinical and biological parameters. Daptomycin was administered in Nutrineal during 6 hours of dwell time for 14 days plus the usual antibiotic therapy in a separate dwell. Because the 200-mg dosing objectives were not reached, a higher DAP dose of 300 mg was tested in the next 3 patients. Effective dialysate and plasma concentrations were achieved at the 300-mg of DAP dose with the plasma concentration well below the toxic threshold, even at steady state, during which the accumulation factor never exceeded 3. The optimal DAP dose of 300 mg daily by the IP route, as determined by the pharmacokinetic data, needs to be clinically confirmed prior to routine use. The good peritoneal bioavailability of DAP supports using the IP route as an alternative to the intravenous route for peritonitis and systemic infections.

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KEY WORDS: Intraperitoneal route; peritoneal dialysis; peritoneal dialysis-related peritonitis; continuous ambulatory peritoneal dialysis; renal failure.

Peritoneal infection is still a frequent complication in peritoneal dialysis (PD) patients and is referred to as peritoneal dialysis-related peritonitis (PDRP). Based on the recommendations of the International Society for Peritoneal Dialysis (ISPD), the intraperitoneal (IP) route is recommended to obtain a maximal concentration at the site of infection (1).

According to ISPD guidelines, given the clinical efficacy and favorable profile of adverse reactions, daptomycin (DAP) is probably the first-line antibiotic of choice for peritoneal infection episodes caused by vancomycin-resistant *enterococcus* (VRE). Daptomycin may also be useful in peritoneal infection episodes caused by *Staphylococci* or vancomycin-resistant *Streptococci* (1). Therefore, we performed a pharmacokinetic study of DAP administered intraperitoneally in patients on continuous ambulatory peritoneal dialysis (CAPD) with PDRP to determine an effective and safe dose.

METHODS

The DaptoDP study is a prospective, open-label, non-randomized pharmacokinetic (PK) single-center study. We chose to test a fixed dose of DAP, which was added to 2 liters of dialysis solution. To be effective, due to activity-dependent concentrations, the concentration of DAP needs to be at least 4 times the minimal inhibitory concentration (MIC). The critical concentration of DAP for the treatment of *enterococci* is 4 mg/L (2). As a result, the authors concluded that the plasma concentration of DAP had to be above 16 mg/L for 2 hours and that the intraperitoneal IP concentration of DAP had to be above 16 mg/L during the 6 hours of dwell time.

To be safe, the plasma concentration of DAP should be lower than 120 mg/L, as this is the upper limit in healthy patients treated with DAP by the intravenous (IV) route. The stability of DAP in peritoneal dialysisPD fluids (PDFs) has been confirmed (3). In addition, DAP is known to be more effective in Nutrineal PD solution than in Physioneal PD solution (Baxter Healthcare Corporation, Deerfield, IL, USA) (4).

The authors wanted to examine the potential efficacy of DAP based on PK parameters. Clinical efficacy was not the objective, but the authors chose to study infected patients because inflammation increases the permeability of the peritoneal barrier. Therefore, patients received the usual care with empiric IP antibiotic therapy (for 14 or 21 days according to guidelines) in the first dwell time (in Dianeal for 6 hours) and then received experimental DAP (for 14 days) in a second dwell time (in Nutrineal for 6 hours) followed by Physioneal (4 hours) and Extraneal (8 hours) (Baxter Healthcare Corporation, Deerfield, IL, USA). For more details on the methodology, please refer to a previous publication (5).

Sample Size: In the first part of the study, the investigators chose to test the first experimental dose of 200 mg per day in 3 patients. The results were then published. After the first PK analysis, efficacy outcomes were not achieved (5). A dose adjustment was necessary to achieve effective concentrations; therefore, the investigators decided to test a higher dose of 300 mg per day on the next 3 patients. The results are presented in this article.

RESULTS

During the second part of the DaptoDP study, 4 patients were enrolled; 1 was excluded because of an exclusion criterion on day 1 (PDRP with *Pseudomonas aeruginosa* only), and 3 patients were analyzed. The period of recruitment was from March 2014 to December 2016.

The baseline characteristics of the 3 patients were as follows: age, 64 ± 30.8 years; body mass index (BMI), 25.7 kg.m^{-2}; albumin, 33.0 g/L ± 6.7; and PD duration, 6.0 months ± 2.6. The estimated residual renal function (sum of the urea and creatinine clearance divided by 2) of patient number 1 and 3 was 3.26 and 6.9 mL/min, respectively; patient number 2 was anuric.

In all cases, patients were successfully cured of their PDRP; patient number 1, 2, and 3 were cured on day 26, day 24 and day 14, respectively (decreased white blood cell count in PD

fluid at the end of therapy and the absence of clinical signs). The PD effluents respectively started to improve on day 1, 3, and 1 and were completely cleared up on day 5, 6, and 2. No safety concerns emerged during the study.

Figure 1 illustrates the change in DAP plasma and dialysate concentrations in the 3 patients treated with a single daily IP dose of DAP (300 mg in a 2-L dialysis bag during the 6-h dwell time) on day 1 and 5. Daptomycin concentrations relative to the administered dose were measured in urine collected during the 24-h period after DAP administration was initiated and were 1.4 % and 6.7 % on day 1 and 5, respectively, for patient 1, and 3.7 % and 11.5 % on day 1 and 5, respectively, for patient 3 (no data for the anuric patient 2).

The PK parameters calculated on day 1 and 5 from data determined using both plasma and dialysate fluids are listed in Table 1. To better inform the reader, the previously published mean PK parameters obtained with the lower 200-mg daily dose are provided in brackets (5).

DISCUSSION

The present follow-up PK study conducted on 3 patients undergoing CAPD with a higher dose of 300 mg of DAP by the IP route generally verifies findings that the authors previously obtained in 3 patients treated with 200 mg of DAP.

The T1/2 values were longer in DAP-treated subjects than in subjects with normal renal function, confirming that DAP elimination is prolonged in patients with impaired renal function. These values, however, are close to those previously obtained in patients with end-stage renal disease on hemodialysis or patients on CAPD, corroborating the moderate effect of these epuration modes on DAP excretion. The distribution volume and total and peritoneal clearances were confirmed to be very low using approximated values obtained in patients with severe renal failure.

Using a daily regimen of 300 mg/2 L of dialysis solution during a 6-h dwell time, blood concentrations of DAP were mostly above 16 mg/L (proposed effective concentration) and well below 120 mg/L (proposed toxic concentration), even at steady state, during which accumulation never exceeded 3. Based on this new evidence, for safe and efficient treatment of patients on CAPD, the authors recommend a daily DAP dose of 300 mg instead of 200 mg. It is important to note that the European Public Assessment Report of Cubicin recommends the administration of 200 mg of DAP every 2 days by the IV route; however, it might be of doubtful relevance due to an

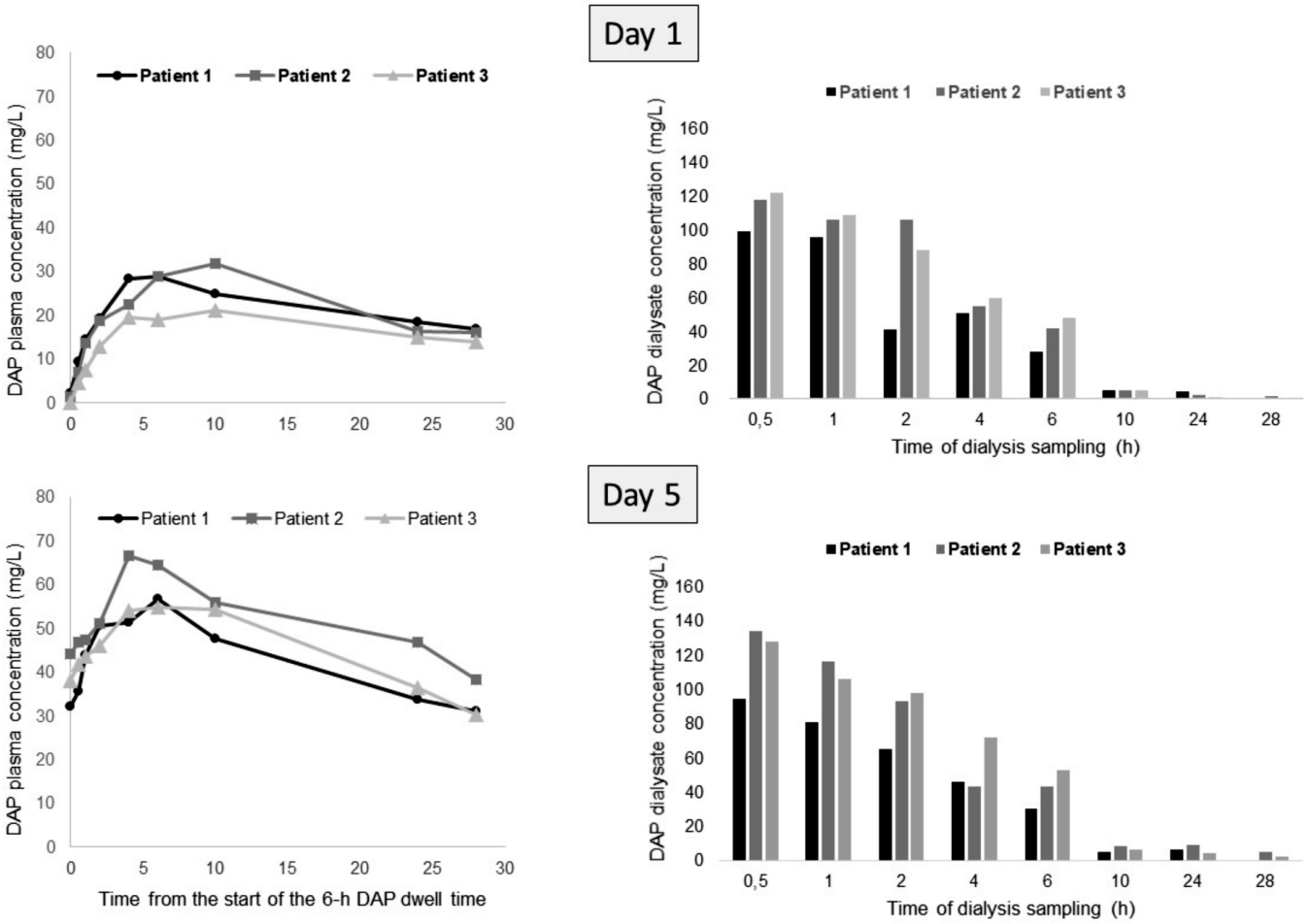

Figure 1 — Concentration of daptomycin (DAP) in plasma and dialysate obtained during and after intraperitoneal administration of 300 mg of DAP in 2 L of dialysis solution (Nutrineal) during the 6-h dwell time on day 1 and day 5.

TABLE 1
Pharmacokinetic Parameters of Daptomycin[a]

Study day			1				5	
Patient number	1	2	3	Mean	1	2	3	Mean
Absorbed dose (%)	81	72	68	74 (82)*	80	71	65	72 (86)
k_e (h^{-1})	0.026	0.036	0.026	0.029 (0.033)	0.028	0.021	0.028	0.026 (0.025)
$t_{1/2}$(h)	27	19	26	24 (22)	25	33	25	28 (29)
C_{max} (mg/L)	28,8	31,9	21,1	27 (9)	56,7	66,6	54,7	59 (13)
t_{max} (h)	6	10	10	9 (6)	6	4	6	5 (5)
$AUC_{0\text{-}24h}$ (mg/L.h)	528	552	409	496 (143)	1072	1302	1146	1173 (266)
$AUC_{0\text{-}infinite}$ (mg/L.h)	1236	1043	1006	1095 (293)				
V_{area} (L)	7.7	5.8	7.8	7.1 (18)				
V_{ss} (L)					8.1	7.9	5.5	7.2 (22)
CL (Lh^{-1})	0.20	0.21	0.20	0.2 (0.58)				
CL_{ss} (Lh^{-1})					0.21	0.16	0.17	0.18 (0.66)
CL_p (Lh^{-1})	0.04	0.03	0.03	0.03 (0.13)	0.03	0.04	0.02	0.03 (0.09)

k_e = first-order rate constant; $t_{1/2}$ = apparent elimination half-life; C_{max} = peak plasma DAP concentration; t_{max} = time to C_{max}; $AUC_{0\text{-}24h}$ = area under the concentration time curve from time zero to 24 hours post-dose; $AUC_{0\text{-}infinite}$ = area under the concentration time curve from time zero to infinite; V_{area} = volume of distribution; V_{ss} = volume of distribution calculated at steady state; CL = systemic clearance; CL_p = peritoneal clearance; * = data in brackets correspond to 3 other patients administered with a 200 mg dose (reported in a previous paperB); PDRP = peritoneal dialysis-related peritonitis.
[a]Determined in 3 patients with PDRP when administered at a single daily intraperitoneal dose of 300 mg for 6 hours.

increased risk of underdosing. Nevertheless, further investigations to specifically study the clinical effects and safety of DAP treatment are required to confirm this recommendation based only on PK data.

Moreover, the small amount of DAP recovered in dialysate bags at the end of the 6-h peritoneum infusion again demonstrated the good DAP absorption when administered via the peritoneal route (nearly 70 % of the administered dose) and confirmed this administration route as an alternative in patients with damaged venous access, even for the treatment of systemic infections. One potential limitation of this conclusion is the presence of peritonitis in our patients, in whom peritoneal permeability may be increased, thus resulting in faster drug absorption and increased peritoneal drug clearance during no-drug dwell times.

The 2 major limitations of the study are the small number of patients evaluated in the DaptoDP study and the heterogeneity of the residual renal function.

CONCLUSION

The optimal DAP dose of 300 mg by the IP route needs to be confirmed by a larger efficacy and safety study prior to its routine use to treat PDRP. Our study indicates also that the IP route can be an alternative to the intravenous route for the treatment of PDRP as well as systemic infections.

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