Is Intraperitoneal Antibiotic Administration Inadequate/Insufficient Therapy in PD Peritonitis?

Peritonitis is a prevalent complication in patients on peritoneal dialysis (PD). Gram-positive organisms account for about one-third of all cases of PD peritonitis in India.[1] Vancomycin is a frequently used intra-peritoneal antibiotic given for PD peritonitis treatment before culture reports are ready. The International Society of Peritoneal Dialysis (ISPD) recommends a dose of 15-30 mg/kg once in every 5-7 days to treat peritonitis in patients on continuous ambulatory peritoneal dialysis (CAPD).[2] Therapeutic drug monitoring of vancomycin in the treatment of PD peritonitis has often been discussed but remains rarely accessible to clinicians in India.

Sampath E *et al.*[3] studied the serum and dialysate vancomycin levels in patients being treated for PD peritonitis. As per the ISPD guidelines for PD peritonitis treatment, intermittent vancomycin instillation was done at 15 mg/kg every 5–7 days. They measured the serum vancomycin levels at 1, 12, 24, and 96 hours after the vancomycin instillation. Similarly, dialysate antibiotic levels were measured at 24 and 96 hours. Median therapeutic serum vancomycin levels achieved at 1, 12, 24, and 96 hours were 2.9, 3.3, 2.7, and 2.2 µg/mL, respectively. These were much lower than the expected therapeutic trough levels (>15 mg/mL). At 96 hours, none of the patients achieved trough levels >12-15 mg/mL. This raises the question of whether the administration of 15 mg/kg vancomycin as per the ISPD guidelines achieves adequate drug (serum and dialysate) levels. This concerns developing countries where the monitoring of drug levels of vancomycin is not universal.

In a single center experience in the UK, when patients with PD peritonitis were treated with vancomycin at 25 mg/kg (higher than the doses in the current study), only 9.2% (anuric) and 16.2% (non-anuric patients) of patients with CAPD failed to achieve adequate drug levels (>12 mg/mL).[4] They concluded that the dosing schedule recommended by the ISPD achieved adequate drug levels in most patients. In another study by the same group, a 30 mg/kg IP vancomycin dose in patients with PD peritonitis achieved adequate (>12 mg/mL) drug levels in 98% of patients with a 19.3 mg/mL mean trough vancomycin level on day 5.[5] They also measured the D5 PD effluent levels of vancomycin. Only 23% of patients had PD effluent levels <4 mg/L – which is more than the MIC of many Gram positive organisms. The authors concluded that although adequate serum levels were achieved, intermittent vancomycin dosing may not consistently result in dialysate concentrations markedly greater than the MICs of many important pathogens (23% of patients had inadequate PD effluent levels).[5] However, this is in stark contrast to the current study, where PD effluent vancomycin levels > 4 mg/L were seen in only 7% of patients. In another Australian study that treated patients with PD peritonitis with 30 mg/kg of vancomycin, D2 vancomycin levels of <15 mg/mL were seen in 46% of cases.[6] Reassuringly, peritonitis cure rates were not associated with trough vancomycin levels in any of the above studies, including ours. However, due to the small number of patients included in these studies, this may reflect a beta error rather than a true effect.

Multiple studies have shown that 25-30 mg/kg vancomycin doses achieves adequate serum drug levels in most patients with PD peritonitis. Whether the lower dose (15 mg/kg – mean weight of patients being 53.9 kg) administered in the current study caused low serum drug levels need to be further understood. If so, the current dose recommendations by ISPD guidelines will need to be modified, as a 15 mg/kg dose of vancomycin is used widely without drug level monitoring. Also concerning is the possibility of batch-to-batch variability and the use of generic drug formulations without proven therapeutic bioequivalence to the innovator molecule. Although the same generic drug was used in all patients, this may have contributed to the lower trough levels. Because this is a single-center study, it needs to be replicated in other Indian centers to ensure that the results are uniform, irrespective of the site or brand. Attention must also be given to the pharmacokinetic profile of intermittently administered vancomycin in PD peritonitis. Vancomycin, being a middle molecule, has a lower D/P ratio and lower peritoneal clearance than urea or creatinine.[7] However, as the antibiotic dwell time was 8 hours, there was sufficient duration for systemic absorption. Inflammation of the peritoneum should have theoretically increased the D/P values, enhancing vancomycin absorption. Several factors, such as the presence or absence of peritonitis, the presence and extent of residual renal function, dwell times, dialysate volume, the effect of antibiotic-free PD exchanges, and age, influence vancomycin clearance.[8] How these factors influenced the result needs evaluation.

A recent study examined a population pharmacokinetic model, for intraperitoneally administered vancomycin to evaluate intraperitoneal and plasma exposure after administering dosing schedules recommended by the ISPD. In this model, the peritoneum did not receive the target exposure (AUC_{24}) >400 mg/h/L by intermittent dosing (30 mg/kg every 5-7 days) of vancomycin for most of the days.[9] Despite insufficient peritoneal exposure

to the drug, even with dosing every five days, a large proportion of oliguric patients experienced an overdose after the second administration. In patients with preserved diuresis, continuous dosing (LD 20 mg/kg followed by MD = 25 mg/L in each subsequent dwell) was deemed to be borderline efficacious. Based on the presented model, they proposed optimal dosing (LD = 20 mg/kg followed by MD = 50 mg/L) to increase the intraperitoneal vancomycin exposure without overdosing the patients with excessive plasma levels. Their simulations showed that intermittent vancomycin dosing may lead not only to intraperitoneal underexposure but also to possible systemic overexposure. However, in a Cochrane review of studies with low-quality evidence, intermittent and continuous administration of IP antibiotics led to similar cure and relapse rates.[10] Summarizing, this study questions whether the current dosing recommendations of intraperitoneal vancomycin proposed by the ISPD, achieve adequate drug levels in the Indian population. More pharmacokinetic studies on serum vancomycin AUC/MIC ratio and dialysate vancomycin levels from multiple centers in India are urgently required to prevent insufficient vancomycin dosage in Indian patients with PD peritonitis. Further high-quality studies are also needed to answer conclusively whether continuous administration of IP antibiotics offers clinical benefits over intermittent administration in this population.

Conflicts of interest: There are no conflicts of interest.

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