

Colistin pharmacokinetics/pharmacodynamics and acute kidney injury: A difficult but reasonable marriage

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The worldwide rise of severe infections caused by multidrug-resistant Gram-negative bacteria in intensive care (IC) patients has propelled the “ancient warrior” antibiotic colistin back into the clinical arena.^[1] Concomitantly, the pharmacokinetic and pharmacodynamic (PK/PD) behavior of antibiotics became a key topic of investigation in the critically ill. Within this context, the recognition of colistin as a concentration-dependent antibiotic resulted in a continuous “upgrading” of its dose in an attempt to optimize therapeutic efficacy and to reduce resistance. However, this revived the old concerns about increased renal and neurological toxicity that once caused colistin’s demise from clinical use.^[1]

Basic Pharmacokinetics and Elimination of Colistin

Because colistin was abandoned for more than three decades, its PK/PD characteristics remained largely uninvestigated. Colistin has a relatively low (± 1748 Dalton) molecular weight and is predominantly nonrenally cleared in patients with normal kidney function.^[2,3] Renal handling of colistin is characterized by extensive (up to 80%) tubular reabsorption. Consequently, few colistin is excreted unchanged in the urine while a large fraction remains in the organism.

Being 55% protein-bound, hydrophilic, and with a distribution volume fluctuating from 0.09 to 0.34 L/kg, colistin is eliminated by continuous renal replacement therapy (CRRT).^[3] Colistin reabsorption does not occur when the drug is cleared by convection (as in continuous

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veno-venous hemofiltration [CVVH]).^[4-6] Moreover, CVVH counteracts colistin accumulation because the drug is continuously filtered and highly adsorbed in the bulk of the dialysis membrane. This explains, at least partly, why the colistin dose must be increased during CVVH.^[4,6]

Colistin Toxicity

Significant colistin toxicity is almost exclusively described in patients with acute kidney injury (AKI). Colistin neurotoxicity occurs infrequently and should be suspected in case of seizures, prolonged coma, or when a previously conscious patient suddenly fails to trigger the ventilator or develops unexplained respiratory muscle paralysis.^[1] Colistin-related nephrotoxicity is more common. Risk factors for this complication include older age, preexisting renal dysfunction, hypoalbuminemia, and concomitant use of intrinsically nephrotoxic drugs (e.g. nonsteroidal anti-inflammatory agents, aminoglycosides, and vancomycin).^[1]

Detecting colistin toxicity at the bedside is cumbersome, in particular when patients are mechanically ventilated. Measuring colistin serum levels is difficult, labor-intensive and only feasible in highly specialized laboratories. Moreover, any relationship between a distinct serum

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concentration and the occurrence of toxicity has not been demonstrated.^[4]

High-dose Colistin and Incidence of Acute Kidney Injury

Throughout the literature, a high incidence of colistin-induced nephrotoxicity has been reported, even with doses as low as 3 MU bid and in the absence of a high loading dose.^[1] In this issue of the Journal, Dewan and Shankat present interesting data on the incidence of AKI in critically ill IC unit patients treated with a colistin dose regimen in line with its predicted PK/PD profile, that is, a loading dose of 9.0 MU followed by 4.5 MU bid.^[7] Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg/L from baseline and severity of AKI was assessed by using the RIFLE criteria. Irrespective of creatinine clearance, all patients received the high loading dose. Thereafter, the maintenance dose was adapted to creatinine clearance by extending the dosing interval with decreasing creatinine clearance whilst conserving the same single 4.5 MU dose.^[2] AKI was observed in only 16% of the studied patients. This incidence is comparable with that reported previously in studies that used lower colistin doses and more fractionated regimens. Moreover, AKI was relatively mild, nonoliguric, short-lived, required no renal replacement therapy, and did not necessitate discontinuation of colistin. The authors concluded that a consistently high-dosed colistin regimen, favoring a high peak concentration to obtain an optimal bactericidal effect, did not increase the incidence of AKI, provided that dosing intervals were adapted when renal dysfunction developed.^[7]

Some important limitations of the study must be highlighted. Its single-center and observational design and inclusion of a limited number of patients precludes generalization of the results to a broad population of medico-surgical IC patients. Factors that might have affected kidney function in the studied patient population were insufficiently elaborated. No data on bacteriological or clinical outcome were presented. In addition, it must be emphasized that data on high-dose colistin treatment during CRRT are absolutely warranted. In fact, patients with preserved renal function may develop colistin resistance. Increasing the colistine maintenance dose up

to 4.5 MU tid may overcome this dramatic drawback. To allow the administration of such high-dose without enhancing the risk for eventual side-effects, patients have been successfully placed under “prophylactic” CVVH.^[3,8]

Conclusion

Despite inherent bias, the study of Dewan and Shankat elegantly proves the validity of applying PK/PD concepts on colistin administration in the critically ill. A high-dose colistin regimen appears to be safe in patients with normal kidney function. Significant nephrotoxicity can be avoided when the time interval between doses is prolonged rather than the dose reduced in case of renal dysfunction. Future research should focus on the use of colistin in conditions of (C) RRT and on the effect of applying even higher doses under a “prophylactic” CRRT shield to avoid or combat colistin resistance.

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