Colistin: The PK, PD and TD Characteristics of this 'Old' Antibiotic Provide the Basis for TDM

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Colistin, also known as polymyxin E, was first isolated in 1947 from a spore-bearing soil bacillus (*Paenibacillus polymyxa*). Colistin, like the other clinically used member of the polymyxin antibiotic family (polymyxin B), has significant antibacterial activity against many species of pathogenic Gram-negative bacteria, especially *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. Because early pre-clinical investigations revealed substantial potential for development of nephrotoxicity, colistin was developed as an inactive prodrug called colistimethate or colistin methanesulphonate (CMS) as it was believed that this would ameliorate the risk of nephrotoxicity. In 1959, CMS was approved for clinical use *via* parenteral administration. While the nephrotoxic potential was reduced by administration of colistin in the form of CMS, it was not eliminated. Subsequently, as other antibiotics with activity against Gram-negative bacteria and perceived lower potential for nephrotoxicity became available during the 1970s, the use of CMS declined substantially. However, over the last decade, a very substantial increase in the proportion of Gram-negative isolates that are multi-drug resistant to other commonly used antibiotic classes (e.g. β-lactams, aminoglycosides, fluoroquinolones) has occurred, especially among critically-ill patients. In many cases, isolates of *P. aeruginosa*, *A. baumannii* and *K. pneumoniae* from these patients are susceptible to only colistin. Thus, colistin administered parenterally as CMS has become an important 'last resort' antibiotic for the treatment of life-threatening infections in very sick patients.

CMS/colistin was approved for clinical use almost 60 years ago and was never subjected to contemporary pre-clinical and clinical drug development procedures. Even the studies that were conducted in the 1950s used methods that led to very misleading results. For example, the basic pharmacokinetic (PK) studies conducted used microbiological assays. Such methods are incapable of accurately quantifying colistin (the active antibacterial and nephrotoxic entity) present in a sample at the time of its collection from a patient, because of the concomitant presence of CMS in the sample and its ongoing conversion to colistin during the microbiological incubation period. Thus, clinicians needing to resort to CMS for the treatment of a life-threatening infection have not had useful knowledge of many aspects of

the pharmacology and toxicology of this 'last-line' antibiotic. Fortunately, over the last few years much information has emerged on the PK, pharmacodynamics (PD) and toxicodynamics (TD) of CMS/colistin, and of important PK/PD and PK/TD relationships.

From studies involving use of modern bioanalytical methods, we now understand the PK in critically-ill patients of CMS (the inactive prodrug) and of the colistin formed from it *in vivo*. It has emerged that CMS is a very inefficient prodrug. In patients with 'good' renal function only ~20% or less of each dose of CMS is converted *in vivo* to colistin, because the prodrug is avidly cleared by renal excretion. Although colistin itself is cleared by renal excretion to only a very small extent, its overall disposition is influenced greatly by renal function which is the only patient factor identified as influencing PK of formed colistin in a large population PK study in critically-ill patients. This influence occurs because as renal function declines a greater fraction of each administered dose of CMS is available for conversion to colistin. Importantly, even at a given creatinine clearance there is ~10-fold variability in the apparent clearance of colistin, and hence in the daily dose of CMS required to achieve a desired average steady-state plasma colistin concentration. This characteristic alone provides a compelling case for TDM.

Studies conducted in animal infection models have provided essential information on the PK/PD of colistin. In particular, the relationship between exposure to plasma-unbound colistin and the extent of bacterial killing has been defined for important Gram-negative pathogens. With appropriate recognition of differences in plasma protein binding between animals and critically-ill patients, results from these PK/PD studies have been translated to the clinical setting to inform the plasma exposure of colistin likely needed to achieve antibacterial effect in patients. Administration of CMS can lead to >50% of critically-ill patients developing colistin-associated acute kidney injury (AKI), which is the major adverse effect limiting the use of CMS/colistin. Recent clinical PK/TD studies have identified the relationship between plasma exposure to colistin and the risk of developing AKI. Importantly, from the afore-mentioned PK/PD and PK/TD studies it is very clear that the therapeutic window of colistin is very narrow. Indeed, the plasma concentrations of colistin that may be required to elicit an antibacterial effect in a patient overlap extensively with those that may increase the risk of AKI. The very narrow therapeutic window provides another compelling case for TDM.

As summarised above, there is substantial interpatient variability in PK even after accounting for creatinine clearance, the only patient factor identified as influencing the apparent clearance of colistin. Moreover, the very narrow therapeutic window severely complicates use of this 'old' antibiotic. A CMS dosing regimen cannot be individualised and optimised on clinical observation alone, especially in the early period that is a critical determinant of prognosis in patients with life-threatening infections caused by Gram-negative pathogens. Moreover, if therapy is unsuccessful there are potential dire consequences (inadequately treated infection for the patient concerned, emergence of resistance with possible nosocomial spread). The lecture will present an overview of the PK, PD and TD and of the PK/PD and PK/TD relationships that provide the rationale for TDM. There are several key considerations in the implementation of TDM for colistin and these will also be discussed.