PK/PD of Colistin

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Colistin (polymyxin E) is a mixture of the cationic polypeptides Colistin A and Colistin B from the group of polymyxin antibiotics. It was discovered in 1949 and first used as an intravenous formulation in the 1950s. In the early 1980's, colistin use was largely abandoned due to reported nephrotoxicity and the availability of newer antibiotics. Because of its early registration, colistin was never subject to regulations in a modern kind of way, including systematic trials on pharmacokinetics, dose finding, pharmacokinetics and pharmacodynamics. The optimal dose and dosing regimens are still not fully known, partly because of its complex physicochemical properties. Colistin is administered as a prodrug (colistin methane sulfonate; CMS) that is converted to active drug over time and both CMS and colistin have mixed routes of renal and non-renal elimination. Adding further to the complexity is that protein binding has now been shown to be concentration dependent. The colistin mode of action is based on binding to the cell membrane of Gram-negative bacteria and thereby disrupting the membrane permeability. The result is a relatively rapid killing of the bacteria as determined from time-kill curves. Killing is concentration dependent, but is impaired by high inocula. As expected from its concentration dependent killing, the pharmacodynamic index correlated to efficacy has been shown to be the *f*AUC/MIC for Enterobacteriaceae*, P. aeruginosa* and *Acinetobacter spp*. in mouse models of infection. The amount necessary for a static affect seems to vary by species and is lower for *Acinetobacter spp*. Similar observations were made in in vitro pharmacokinetic models, exposing bacteria to various dosing regimens of colistin. Whereas the exposure response relationship is now reasonably well elucidated, this has not been translated yet to optimal dosing in humans. The pharmacokinetic properties have only recently become – incompletely – available, and appears to be highly variable between patients. Nevertheless, PK/PD properties clearly show that a loading dose is required and should be implemented in clinical dosing regimens.