Optimising PK-PD in Critically Ill Patients

John Turnidge

Women's and Children's Hospital, Australia

The conventional approach to antimicrobial dosing in critically ill patients has been to assume that drug clearance is impaired and adjust dosages downwards and/or increase dosing intervals, reducing overall drug exposure. While this cautious approach appears rational, it has recently been recognised that in many critically ill patients that the opposite pharmacokinetic conditions apply. Critically ill patients tend to have a hyperdynamic circulation that increases blood flow to many organs. Well documented changes in patient pharmacokinetics in severe sepsis include: (i) augmented renal clearance, (ii) increased volume of distribution, (iv) microvascular changes, including the use of vasoactive agents, that reduce tissue penetration, (iii) decreased albumin leading to less protein binding. The first three of these lead to lower drug exposures at the site of infection, especially for renally-cleared drugs, while the last factor will tend to increase exposure for highly protein bound drugs. The net effect of some or all of these changes is that many patients will not achieve the known pharmacodynamic targets when given the standard recommended doses of antimicrobials. This has been highlighted by the poor outcomes noted in three prospective comparative trials on the treatment ventilator-associated pneumonia with doripenem, ceftobiprole and tigecycline.

For critically ill patients with acute kidney injury, while they do not have augmented renal clearance, their pharmacokinetic profile is further complicated by the use of continuous renal replacement therapy (CRRT). There is a diverse range of approaches to CRRT, meaning that there is no simple formulaic approach to dosage adjustment when CRRT is being used. Population PK models are currently being investigated in an attempt to overcome this significant problem.

One potential solution to many of these problems is to individualise the approach to treatment. If a pathogen has been isolated, it is a simple matter for the laboratory to measure an MIC as part of a routine or additional susceptibility test. Second, the plasma levels (ideally the free drug levels) of the administered agent could be measured to get an estimate of drug exposure. This requires the establishment of a broad range of assays which can be turned around quickly. Once these data are available, it is a simple matter of estimating the pharmacodynamic index of interest in that particular patient, comparing it to the known PD targets, and making any necessary adjustments to the dosing regimen. Unfortunately few laboratories serving intensive care units have the capacity for a wide range of drug assays, nor rapid turnaround of results. Novel rapid methods need to be developed to service the growing need to need to optimise antimicrobial treatment in the critically ill patient.