Antibiotics on the intensive care unit: continuous infusion or intermittent bolus?

Sepsis is common among patients admitted to hospital and especially to the intensive care unit (ICU). Early antibiotic administration forms the mainstay of treatment. Correct antibiotic dosing, optimal duration of treatment, monitoring of levels when appropriate and avoidance of drug interactions are vital in achieving appropriate tissue levels of antibiotics. Secondary objectives include avoiding toxicity and prevention of emergence of antibiotic resistance (Kollef, 2001). Given altered pharmacokinetics and a high prevalence of resistant pathogens among the severely sick ICU patients, should infusions of antibiotics be used or should tried and tested intermittent bolus regimens be adhered to? Can that impact on clinical outcome?

Continuous infusion is better

Understanding antibiotic pharmacodynamics is important for appropriate use of these drugs. In general antibiotics can be divided into two groups. The first group are concentration-dependent (e.g. aminoglycosides or quinolones) where the ratio of plasma antibiotic concentration to minimum inhibitory concentration (MIC) determines bactericidal activity. The second group are time-dependent (e.g. beta-lactams, macrolides or glycopeptides) where duration when plasma antibiotic concentration is in excess of MIC is important. The second group may be more efficacious when administered as an infusion. Failure to appreciate that may result in poor treatment outcomes (Ley et al, 1996).

Numerous studies have looked at pharmacokinetic rather than clinical end points of using continuous infusion of antibiotics in both healthy volunteers and in real patients. The results of the majority of these studies indicate that, compared with intermittent bolus, continuous infusion achieves an equivalent or greater percentage of time above MIC in plasma and tissues when administering betalactams such as ceftazidime, pipercaillin-tazobactam or cefepime. For beta-lactams to have a bactericidal effect, the concentration has to exceed MIC for 60–70% of the dose interval time for cephalosporins, 50% for penicillins and 40% for carbapenems (Drusano, 2004). This is achieved more easily with a continuous infusion.

Continuous infusion also offers the potential for less drug to be given, therefore reducing cost and toxicity. The same reduction in cost and toxicity is also true of vancomycin (James et al, 1996; Kitzis and Goldstein, 2006). An additional benefit of using vancomycin is that drug levels can be monitored easily. Blood samples can be taken at any time, irrespective of the timing of the last dose. From a practical standpoint intermittent dosing is also likely to suffer when patients are out of the department (e.g. in theatre or X-ray department).

Continuous infusion is not necessary

Pharmacokinetic studies in existence, while generally supportive of continuous infusions, are often small in number and frequently conducted in healthy volunteers. Many of these studies are also not controlled for the degree of hepatic or renal impairment and usually do not assess the clinical impact of such intervention. MIC as a benchmark provides only incomplete and in vitro information about antibiotic effect on pathogens.

A meta-analysis comparing continuous infusion and intermittent bolus regimens noted lower rates of clinical failure with continuous infusion but without statistical significance (Kasiakou et al, 2005). There was also no difference in mortality or nephrotoxicity. A limitation of the meta-analysis was the small size and heterogenous nature of the studies included. Continuous infusion also requires equipment in the form of infusion pumps as well as training of staff and introduction of additional protocols. Also the lack of adequate data regarding the biochemical stability of antibiotic infusions affects drug licensing with regards to administration.

Conclusions

There are strong theoretical grounds for using intermittent infusions of time-dependent antibiotics, which are supported by pharmacokinetic data. Progress in understanding the complexity of antibiotic pharmacodynamics, including areas such as inter-individual variability and time–concentration kill rate relationship, is likely to lead to a more rational approach to antibiotic administration (Drusano, 2004). Meanwhile large clinical studies confirming the benefit of continuous infusions are lacking. Potential costs of additional equipment necessary for continuous infusion may be offset by a reduction in the total dose of antibiotic given, decreased rates of antimicrobial resistance and less treatment failures. Until further clinical comparisons become available the intermittent bolus regimen is likely to remain in use. BJHM

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