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Editorial Open Access

Gentamicin Use – More Clinical Outcome Evidence Needed

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Statement of the Problem

There is currently a looming world-wide problem in antimicrobial resistance. Methods to make antimicrobial prescribing more appropriate and incorporate quality use of medicines guidelines have clearly been ineffective. Further there is a dearth of 'new' antimicrobials in the pharmaceutical industry pipeline. The optimal use of older, effective drugs are therefore of clinical relevance. Gentamicin is an antibiotic that is inexpensive and has proven efficacy. However, its use is becoming restricted, due to toxicity concerns. Research to improve knowledge in this area is thus urgently needed.

Editorial

Gentamicin is an aminoglycoside antibiotic widely used as it is effective in the treatment of gram negative infections and its rate of resistance has remained low. However, there are severe side effects including nephro toxicity and vestibule toxicity, which although they may be detected early, can be irreversible. Currently, although there is clinical evidence for once daily dosing in most groups of patients, clinicians do not have a clear monitoring strategy for Gentamicin that has been validated using clinical endpoints to ensure effectiveness and prevent toxicity.

In order to reduce the risk of side effects, serum Gentamicin concentrations are integral in attempts to individualize dosage regimens (dose and dose interval) with the goal of attaining the desired response as quickly as possible. The dilemma is that currently most dosing and monitoring strategies are aimed at achieving a therapeutic exposure, defined in terms of a high serum peak concentration (to ensure effectiveness) and a low serum trough concentration (to avoid toxicity). However, in a recent retrospective case series Gentamicin vestibulotoxicity was seen to occur with any dose, in any dosing regimen, at any serum concentration. Of most concern was that even when vestibule toxicity was present, it was often not recognized [1].

Although this case series lacked significant clinical information and a comparator group, it was enough for clinicians to consider whether toxicity was actually related to sustained trough concentrations greater than 0.5 mg/L, as had been proposed for many years. A subsequent comment suggested that aminoglycosides should still have a role as initial therapy i.e. up to 48 hours, pending culture results, and then converting to a safer therapy when the results are known [2]. In clinical practice however, some patients require longer therapy (greater than 48 hours).

There are two major questions to be answered. First, whether the risk of side effects has been prospectively shown to reduce with short, rather than long courses. Second, what the appropriate dosing and monitoring strategies are to reduce toxicity and maintain effectiveness in patients needing more than a short course of Gentamicin therapy. The manuscript by Martin et al. in this journal discusses the latter issue although it does not provide new data for guidance. Thus, while the questions raised in this manuscript are being researched, traditional methods will continue to be used in the clinical setting. The question is whether better recommendations for dosing can be made in the meantime.

In general, as efficacy is related to a high peak concentration (greater than the Mean Inhibitory Concentration (MIC)) and toxicity with sustained elevated trough concentrations, once daily dosing regimen is used, and has been demonstrated to improve patient outcomes when compared to multiple daily dosing [3,4]. However, as discussed in the paper, there are a large number of dosing and monitoring methods. These range from empirical dosage adjustment, basic pharmacokinetic (PK) methods using peak or trough concentrations, or area under the concentration-time curve (AUC), and population based nomograms [3]. Nomogram based methods are common as they are 'simple', do not require complex PK modeling and have a strong pharmacodynamic rationale in the sense that AUC is a measure of total body exposure to Gentamicin over a dosing interval. Unfortunately, most nomograms were developed in patients with stable renal function and are not suitable for many hospitalised patients such as the geriatric and paediatric populations and special groups such as burns, cystic fibrosis, ascites or pregnancy where the PK of Gentamicin are highly variable. Recent studies have shown the deficits of these methods [5,6] in achieving a therapeutic target.

Gentamicin is a hydrophilic drug that has wide intra- and inter-individual variability in its PK and methods for dose estimation should reflect these complexities. For hospitalized patients, methods of dose individualization that combine population derived PK models with relevant patient factors such as lean body weight and renal function, are necessary in populations such as the obese and elderly. Bayesian statistical methods can then be used to accurately predict the time-course of Gentamicin concentrations in an individual and thereby allow clinicians to individualize dosing strategies [7]. Whilst this method has been shown to better estimate target concentrations when compared to nomogram methods [8] the effect on real patient outcomes (such

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as survival, duration of hospital stay, episodes of nephrotoxicity), as opposed to differences in surrogate markers of efficacy such as AUC/MIC or AUC per se, has not been demonstrated.

It is now time to undertake the definitive study, appropriately powered for clinical outcomes, to compare model-based dosing with nomograms dosing for Gentamicin. In the meantime we need to be using evidence-based guidelines which take into account patient specific factors such as renal function, body size and composition, MIC and comorbidity.

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