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Editorial

Amikacin dosing in the ICU: we now know more, but still not enough...

Francesco G. De Rosa, Jason A. Roberts

There are perfect studies and there are useful studies, such as the paper by de Montmollin et al. [1] in this issue of Intensive Care Medicine, which uses a simple study design to provide a strong and clinically relevant message that is very useful for daily work in the intensive care unit (ICU). Although a standard dosage of 15 mg/kg once daily is commonly used for amikacin, the authors evaluated the effect of a higher fixed weight-based amikacin dose in critically ill patients, 25 mg/kg, on achievement of concentration targets in a heterogeneous patient cohort. They found that even with a 25 mg/kg loading dose, 33 % of patients still did not achieve C_{max}/MIC ratio [ratio of maximum concentration during dosing interval (C_{max}) to the minimum inhibitory concentration of the known/suspected pathogen (MIC)] of 8–10, assuming the highest MIC of susceptible pathogens.

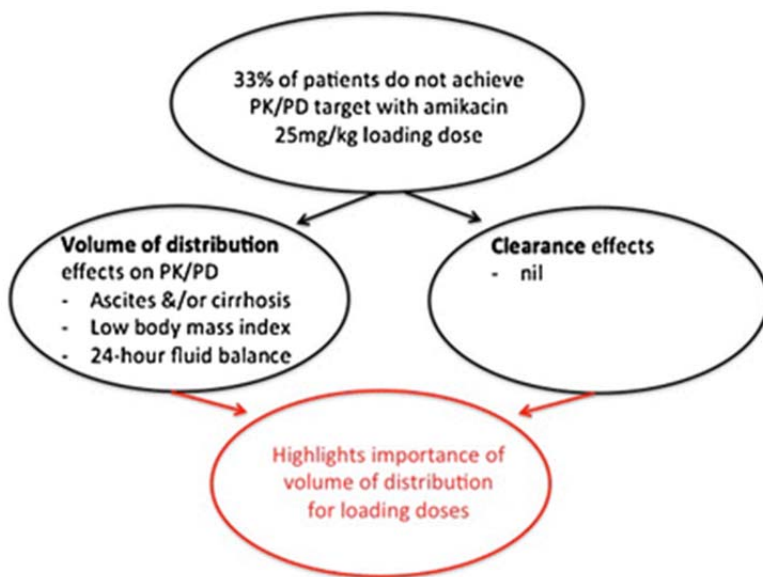
Why is this not a perfect study?

Firstly, the weight metric selected by the authors was total body weight and not an adjusted dosing weight, which is considered more appropriate, particularly for obese patients. Secondly, there are patients with acute kidney injury as well as patients treated with continuous renal replacement therapy which should require a slightly reduced loading dose compared with patients with better renal function. Thirdly, there was an insufficient patient enrolment to determine microbiological outcomes associated with altered concentrations. Finally, no analyses were provided to show how a clinician can overcome the inadequacies of a fixed dosing approach or even what dose should be used. Here a population pharmacokinetic analysis with dosing simulations would be preferred, but is unfortunately not possible with the current study design.

Why is this a useful study?

Antibiotic pharmacokinetics is clearly different in ICU patients compared with ward-based patients [2]. By including a large heterogeneous casemix of patients including those with different levels of renal function, different levels of fluid balance and different pathologies such as ascites and cirrhosis, the authors were able to statistically evaluate which factors were associated with suboptimal achievement of concentration targets. In fact the authors should be complimented for the large number of patients recruited. In the context of other pharmacokinetic studies in the ICU, this is a very large patient sample. The results of univariate analysis showed that the presence of ascites, cirrhosis and an increasing 24-h fluid intake or 24-h fluid balance were significantly related to lower C_{max}. Each of these factors logically would increase amikacin volume of distribution which would lead to a lower C_{max}. Interestingly, the multivariate analysis showed that only a body mass index (BMI) less than 25 kg/m² and the 24-h fluid balance were significantly associated with a lower C_{max}. As shown in Fig. 1, the data from this study is useful as it highlights the importance of factors that affect amikacin volume of distribution on the success of loading doses and that factors related to clearance are not relevant (although this may be because the authors did not choose a maximum accepted amikacin concentration).

Figure 1



Patient and treatment factors that affect amikacin volume of distribution rather than clearance and resulted in sub-optimal achievement of target concentration

Why is this study important, controversial and thought-provoking?

Given that BMI and not weight was shown to be a predictor of low amikacin concentrations, should we be dosing based on BMI? Drug dosing based on BMI has been proposed previously but is generally considered to be less accurate than other weight metrics like lean body weight or fat free mass [3]. The authors discuss why they used total body weight and not other weight metrics in this cohort that has few obese patients. However, in other countries there is no way that total body weight could be used because of the prevalence of obesity. Best evidence currently supports use of adjusted body weight in obese patients as highlighted by the authors in the discussion. Ideally a study design using lean or adjusted body weight would be appropriate for a hydrophilic drug like amikacin, but determining lean body weight in critically ill patients is technically difficult and so adjusted body weight is appropriate [4].

Since this is not the perfect paper but does target a basic question, it leaves us with some doubts: how many patients are treated with lower dose aminoglycosides, like amikacin, in other ICUs and how frequently are these patients not achieving target aminoglycoside concentrations? How many of these patients are given aminoglycoside doses which may increase the likelihood of generating and amplifying antibiotic resistance? The big question is in the conclusion: how much higher should empiric aminoglycoside doses be and which patients should receive them? These would be clinical messages that would further enhance our understanding of this area, although de Montmollin and colleagues have provided important data to help direct further research in this area. In the context of similar recent data from other antibiotics [5, 6], this problem should not be considered restricted to aminoglycosides. Indeed, quantification of the clinical advantages of an individualized approach to dosing is urgently required.

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