Methods for Optimising Neonatal Antimicrobial Use: Time- and Concentration-Dependent Agents

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Introduction Most medicines prescribed for neonates are unlicensed or off-label, and lack rational dosing guidelines. Population pharmacokinetic investigations are increasingly conducted to address this problem, but many published studies do not go beyond describing the data. Where dose recommendations are attempted, most authors rely on simulation from the final model. Exploring dose recommendations by simulation is time-consuming and limited to the regimens chosen by the investigator. This study uses utility functions to define optimal guidelines based on pre-specified criteria, and as such provides an elegant and efficient way of defining the optimal dose.

Antimicrobials are one of the main types of medicine used in neonates, and pharmacodynamics are closely linked with pharmacokinetics. For time dependent agents, fraction of dose interval above the minimum inhibitory concentration (%fT>MIC) maximises effect, whereas for concentration-dependent agents the ratio of C_{max}:MIC is important.[1] Whilst many time-dependent agents have a wide therapeutic index, concentration-dependent agents such as the aminoglycosides exhibit dose-dependent toxicity.

Research Questions

What infusion duration for meropenem maximises %fT>MIC?

What is the optimal dose of gentamicin to balance efficacy and toxicity?

Methods Pharmacokinetic modelling and dose optimisations were performed with NONMEM VII. A meropenem pharmacokinetic model was derived from data in pre-term neonates[2] receiving 0.5 or 4 hour infusions. A 1-compartment model with physiological parameterisation[3] for CL was used. A large population of simulated subjects was generated using demographics from a neonatal database and individual pharmacokinetic parameters from the model. The usual off-label dose of 20 mg/kg was fixed, and the target %fT>MIC was set to 100%. Based on this target and the parameters in the simulated dataset, infusion duration was optimised. In the first instance, MIC values were randomly assigned in a non-parametric fashion to simulated subjects based on Eucast *E.coli* data.[4] Secondly infusion duration for ascending MIC values was optimised.

A gentamicin pharmacokinetic model was derived from data in neonates undergoing routine TDM.[4] A 2-compartment model with similar physiological parameterisation[3] for CL adequately described the data, and as with the meropenem example, pharmacokinetic parameters were generated for a simulated population. As gentamicin is a narrow therapeutic index agent, the utility function consisted of benefit and risk. Meta-analysis of clinical studies gives the relationship between C_{max}/MIC ratio and clinical response shown in Figure 1.[5] Figure 2 shows the relationship between gentamicin serum concentration and uptake in renal cortical cells.

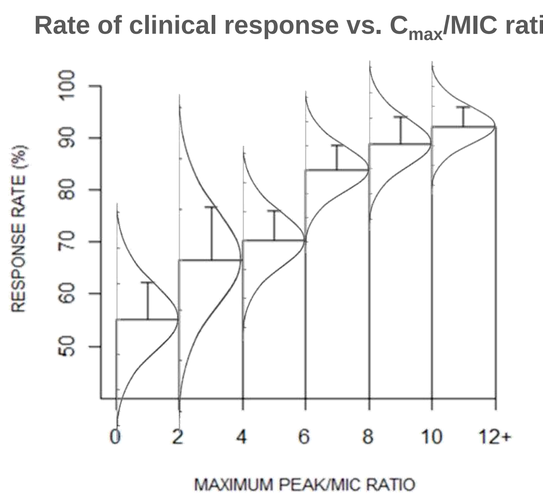

Figure 1 Clinical response rate versus C_{max}/MIC ratio from meta-analysis of clinical studies. Adapted from Moore et al[5]

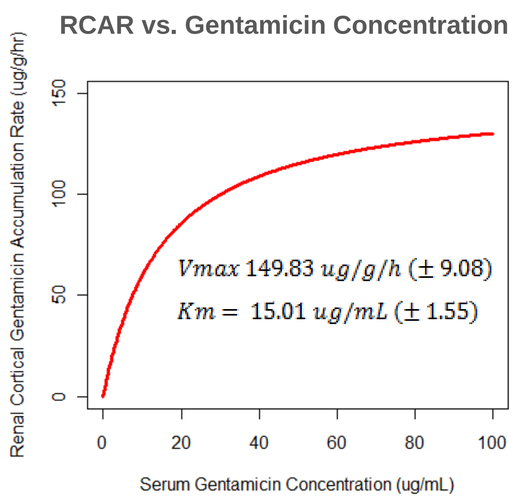

Figure 2 Renal cortical cell uptake of gentamicin. Adapted from Giuliano et al[6]

The efficacy target was set at 100%, with individual efficacy being defined according to Figure 1. Uncertainty within each C_{max}/MIC bin was incorporated by assuming normally distributed variability and a monotonic constraint applied within subjects. The toxicity target was set at 0% accumulation at the end of the dosing interval scaled versus the worst-case scenario of V_{max}*time. Uncertainty in toxicity was incorporated through assigning subjects V_{max} and K_m values according to those reported by Giuliano et al.[6] As 100% efficacy could only be achieved in a minority of subjects (Figure 1) and toxicity could not be 0% if dose>0, the utility function seeks the optimum balance. MIC values were randomly assigned to simulated subjects based on Eucast distributions for *E.coli,*[4] followed by optimising dose for ascending MIC values.

Results For meropenem there was no single optimal infusion time when *E.coli* MIC values were randomly assigned. This was clear because optimal times varied widely when datasets with different simulated MIC values were tested. Upon investigation of iOFV values, a small number of outliers drove OFV, with other iOFV values close to 0, and these outliers were those subjects randomly allocated high MIC values. With fixed ascending MIC optimal infusion time rose steeply, and then fell back as MIC reached C_{max}. Standard errors were very small except for infusion durations of around 6 hrs (Figure 3).

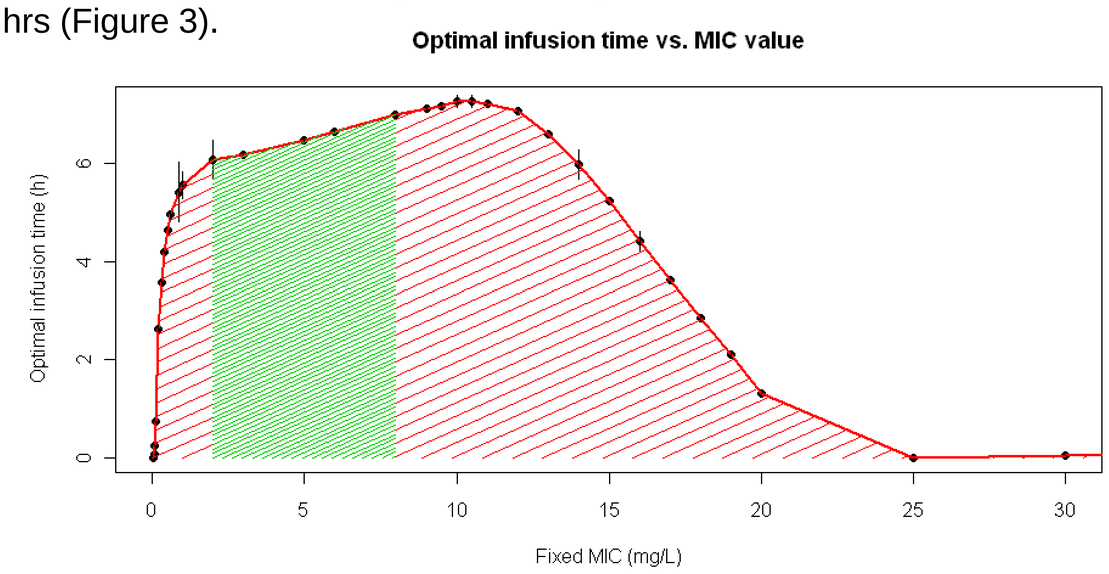

Figure 3 Optimal infusion time plotted against MIC for meropenem. Green shaded area represents Eucast *E.coli* breakpoints of 2 and 8mg/L

Distributions of %fT>MIC are given in Figure 4 and show that for 2 mg/L infusion length is of little significance, but for pathogens that are borderline resistant (MIC 8mg/L) increasing infusion length ensures the majority of subjects have higher %fT>MIC.

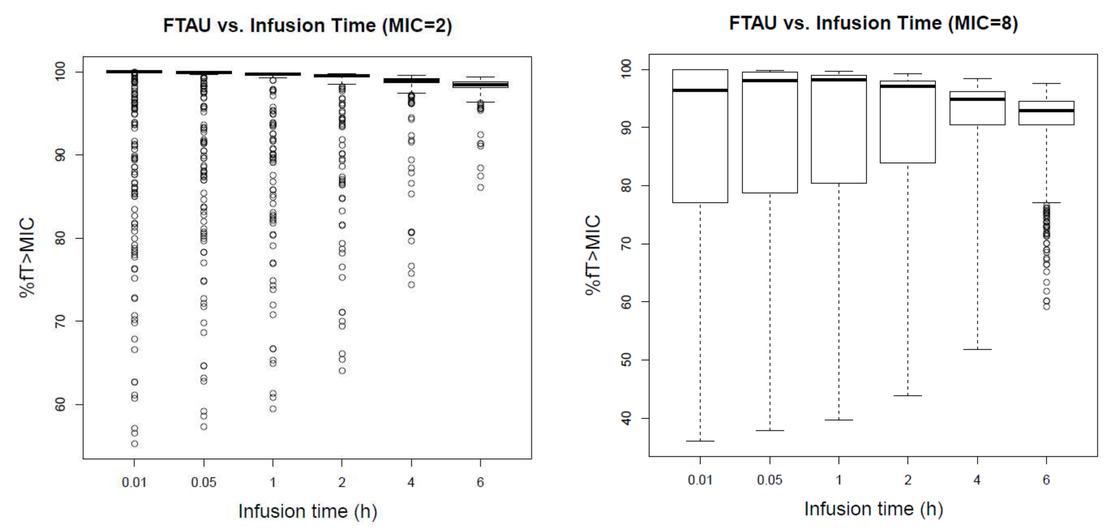

Figure 4 Adjusted box plots[7] of %fT>MIC versus infusion duration for meropenem Eucast *E.coli* breakpoints of 2 and 8mg/L.

For gentamicin the optimal dose for randomly assigned MIC values was 2.25mg/kg. Optimal doses for sensitivity and resistance breakpoints of 2 and 4mg/L were 4.54 and 6.74mg/kg respectively (Figure 5). The sensitivity of changing the dose interval, and therefore risk target, was explored as shown in Table 1.

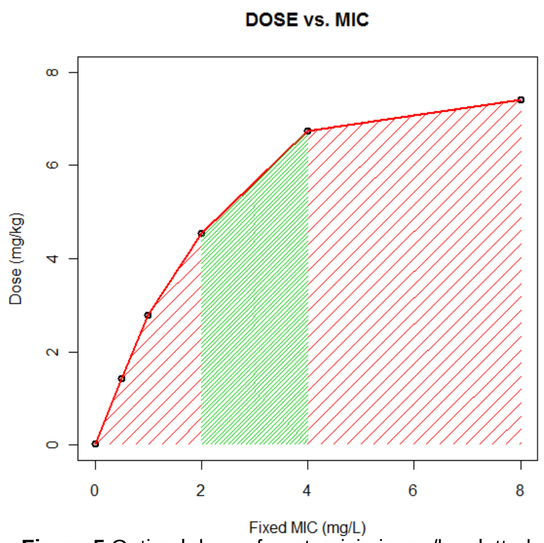

Figure 5 Optimal dose of gentamicin in mg/kg plotted against MIC. Green shaded area represents Eucast *E.coli* breakpoints of 2 and 4mg/L

Efficacy target	Risk target	MIC	Optimal dose
100 at 1 hour	0 at 1 hours	2	2.63 mg/kg
100 at 1 hour	0 at 6 hours	2	3.35 mg/kg
100 at 1 hour	0 at 12 hours	2	3.65 mg/kg
100 at 1 hour	0 at 24 hours	2	4.54 mg/kg
100 at 1 hour	0 at 36 hours	2	4.57 mg/kg
100 at 1 hour	0 at 48 hours	2	5.04 mg/kg

Table 1 Effect of increasing dose interval on optimal dose. No firm data were found on the concentration of gentamicin at which cortical cell lysis would occur. For this reason the toxicity function was scaled against a worst case scenario of maximal cortical cell uptake for the whole dose interval. The toxicity part of the utility function is hence somewhat subjective and so simulations were performed to investigate dose recommendations for different dose intervals. Reassuringly for the typical dose intervals used in neonates (24-48 hours) little change in optimal dose was seen.

Conclusions Optimising utility functions provides a more efficient method than exploring dose recommendations by simulation. Increasing meropenem infusion duration is only necessary if resistant infections are suspected. The optimal balance between nephrotoxicity and probability of clinical response for gentamicin is with a starting dose of 4.5 mg/kg.

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