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Impact of disease on drug exposure and dosing recommendation for amoxicillin in neonatal sepsis

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Introduction: Serious bacterial infections remain a global health problem, especially during the neonatal period. Among the preferred treatment options when referral is not feasible (e.g. resource-limited settings), the WHO recommends the use of oral amoxicillin. The clinical pharmacology of amoxicillin has been studied in adults, but it is less characterised in children. It has also been shown that critical illness (e.g. sepsis) could modify the drug pharmacokinetics[1]. The objective of the analysis was to assess the feasibility of a simplified regimen for amoxicillin in septic (pre-)term infants (0 - 59 days) in resource-limited settings.

Method: A population pharmacokinetic model developed by Carlier et al[2], in which the pharmacokinetics of amoxicillin has been characterised in critically ill adults, was adapted for the analysis, using an approach proposed by Zhao et al[3], which relies on allometric concepts. The impact of other covariates was then evaluated using data from recent efficacy trials in the target population. The analysis was performed using nonlinear mixed effects modelling. Clinical trial simulations were implemented to explore the feasibility of a simplified dosing regimen. Measures of exposure to amoxicillin included plasma concentration vs. time profile, trough and peak concentrations, area under the concentration vs. time curve (AUC) and time above the minimum inhibitory concentration (T>MIC). Given the clinical evidence of the relevance of T>MIC for amoxicillin, dosing regimens were selected which maximise this parameter.

Results: Amoxicillin pharmacokinetics was best described by a two compartment model with first order absorption and elimination. Birth weight, post-natal age and serum albumin concentration were identified as significant covariates affecting amoxicillin clearance whereas body weight was found to affect the volume of distribution of central and peripheral compartments. Septic patients showed a 4-fold increase in the central and peripheral volume of distribution.

Conclusion: The predicted exposure to amoxicillin in a cohort of virtual patients shows that target levels can be achieved across the overall population by using two weight bands and fixed dosing regimen, namely: 250 mg b.i.d for patients < 4.0 kg and 500 mg b.i.d. for patients >4.0 kg. The proposed dosing regimen will warrant target drug levels minimising the risk of sub-optimal exposure. Further evidence of the suitability of the proposed regimen should be obtained by prospective evaluation of pharmacokinetics in target population.

References:

[1]Boucher et al (2006). Crit Care Clin 22(2): 255-271.

[2]Carlier et al (2013). J Antimicrob Chemother; 68: 2600-8.

[3]Zhao et al (2013). Clin Pharmacokin; 52: 1127-34.