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IS HYPERBILIRUBINAEMIA A CLINICAL USEFUL INDICATOR OF REDUCED DRUG CLEARANCE CAPACITY IN NEONATES?

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Background: There is extensive variability in clearance between neonates, mainly explained by age or size. We aimed to assess if hyperbilirubinaemia also contributes as covariate, using reported paracetamol [1] and propofol datasets [2] since both compounds undergo glucuronidation.

Methods: Population pharmacokinetic analysis of 943 paracetamol observations in 158 neonates was undertaken (NONMEM, two-compartment linear disposition). A similar approach (three-compartment) was performed on a dataset of 235 propofol concentration-time points in 25 neonates. Covariates were postmenstrual and postnatal age (PMA, PNA), weight and indirect hyperbilirubinaemia (dichotomous, PNA adapted fixed cut-off values [3])

Results: For the paracetamol clearance, covariate information predicted 60.9% of variance [weight 57.5, PMA 2.2, unconjugated bilirubin 1.2 %]. For propofol, the age (PMA+PNA) model described the data most accurately. The covariates PMA+PNA explained 67% of the interindividual variability compared to 45% with PMA+bilirubin. Introduction of bilirubin into the PMA+PNA model did not improved this model.

Conclusions: Ontogeny itself, reflected by age (PMA, PNA) or size are the dominant covariates of drug clearance in neonates. Hyperbilirubinaemia appears to be only a very modest clinical indicator of (reduced) drug clearance in neonates for drugs that undergo glucuronidation.

[1] Allegaert K et al. *Arch Dis Child* doi:10.1136/adc.2010.204552;

[2] Allegaert K et al. Br J Anaesth 2007;99:864-70;

[3] Palmer GM et al. Br J Anaesth 2008;101:523-30