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Clinical Pharmacological Studies in the Neonatal ICU with Intravenous Paracetamol

Authors

Karel Allegaert

Neonatal ICU Gasthuisberg UZ Leuven, Belgium

Dept. of Paediatric Surgery

Sophia's Children Hospital Rotterdam, The Netherlands

Jan de Hoon

Center for Clinical Pharmacology Gasthuisberg UZ

Leuven, Belgium

Hugo Devlieger

Neonatal ICU Gasthuisberg UZ

Leuven, Belgium

Dick Tibboel

Dept. of Paediatric Surgery

Sophia's Children Hospital Rotterdam, The Netherlands

Brian Anderson

Dept. of Anaesthesiology, University of Auckland

New Zealand

Correspondence

karel.allegaert@uz.kuleuven.ac.be

The relevance, feasibility and methodology of pharmacokinetic studies in neonates during intensive care are illustrated by some recently published studies on intravenous paracetamol.

Introduction

Many drugs in neonates and children are still prescribed off-label or are unlicensed. Although this problem is already of relevance in the out-hospital setting (30%), it is most prominent in paediatric (70%) and neonatal (90%) intensive care settings (Turner et al. 2003). It is therefore obligatory that population-specific data on drug-specific pharmacokinetics and -dynamics are collected to secure quality, safety and evidence based prescription of drugs in the near future. The high off-label prescription rate in intensive care patients further emphasizes the necessity for clinical research in the intensive care setting.

Studying Neonatal Populations: Measures and Methodologies

Although general principles of clinical pharmacology also apply in neonates, the characteristics of this population warrant a specific approach. Body water content, fat disposition and muscle mass are markedly different, all hepatic clearance processes have a distinct iso-enzyme specific ontogeny and renal clearance in early neonatal life is low (Kearns et al. 2003; Van den Anker 1996). Besides biological changes, there are also population-specific methodological issues which need consideration, such as scaling and sampling.

Relevant co-variables of pharmacokinetics in neonates are postnatal, postconception age and weight (Kearns et al. 2003; Van den Anker 1996). Weight is often the first co-variable evaluated in paediatric populations, but it is important to appreciat the limitations of the scaling for size (Anderson and Meakin 2002; Anderson et al. 2000). While body weight is most commonly used, a non-linear relationship is recognized between weight and dose. Body surface area is also used, but the allometric ¾ power model may be a more appropriate scaling, based on the observation that the logarithmic of basal metabolic rate with weight produces a straight line with a slope of 3/4.

In this article, we illustrate the feasibility and relevance of pharmacokinetic studies during childhood through recently published studies on intravenous paracetamol disposition.

Pharmacokinetics and Metabolism of Intravenous Paracetamol in Neonates

Paracetamol is a readily available analgesic and antipyretic. It is the most often prescribed drug for treatment of mild to moderate pain in infants, including neonates (Allegaert et al. 2004). In adults, paracetamol is almost exclusively eliminated by the kidney after conjugation to either glucuronic acid (paracetamolglucuronide, 50-60%) or sulphate (paracetamol sulphate, 25-35%). A maturational trend with a progressive increase in paracetamol-glucuronide elimination has been described in several single dose paracetamol studies, reaching an adult pattern at the age of 8-10 years (Allegaert et al. in press; Anderson et al. 2002; Miller et al. 1976).

Due to lack of data, we first performed a single dose study in neonates (day 1) (Allegaert et al. 2004). We were hereby able to document the gestational age-based maturation of paracetamol terminal elimination half life (see figure 1).

Based on these findings, a repeated dose scheme was developed and studied. All concentration-time profiles were entered in a population pharmacokinetic analysis using a non-linear mixed effects model (NONMEM) to describe maturational aspects of pharmacokinetics of intravenous paracetamol in term and preterm neonates. Clearance increased from 2.85 L/70kg, CV 40.7% at 27 weeks PCA, to reach 7.05 L/h/70kg by 42 weeks PCA (standardised to a 70 kg person using allometric “1/4 power” models). These observations directed agespecific repeated dose regimes. A mean paracetamol steady state target concentration above 10 mg/L at trough can be achieved by loading dose of 40 mg/kg and maintenance doses:

– 20 mg/kg 6 h at 28-weeks,

– 25 mg/kg 6 h at 32 weeks,

– 30 mg/kg 6 h at 36 weeks, and

– 20 mg/kg 4 h at 40 weeks PCA.

Warning: propacetamol doses, for intravenous paracetamol 50% of dose (Allegaert et al. 2004).

Finally, to study metabolism, urinary samples were collected in neonates who were administered repeated intravenous propacetamol. A significant increase in the relative contribution of APAP-G to overall urinary paracetamol elimination (i.e. G/T ratio) with increasing postnatal ($p<0.0001$) (see figure 2) and postconception age ($p=0.0055$) was observed while an increase ($p=0.0005$) in G/T ratio was documented during repeated administration and remained a significant variable to explain G/T ratio ($p<0.01$) in a multiple regression model (Allegaert et al. in press).

Discussion

We have used studies on paracetamol pharmacokinetics as a model to illustrate the feasibility and relevance of such studies in the intensive care setting.

A population pharmacokinetic approach enabled us to study the pharmacokinetic variability based on a limited number of samples/individual. With conventional approaches, a model is defined for each individual, based on the concentration/time profiles available. Pharmacokinetic variables are estimated based on these concentration/ time profiles and can further be described and compared using a statistical approach. There are important prerequisites to using such a conventional approach (Anderson and Meakin 2002; Anderson et al. 2000). The number of observations in every individual should be adequate enough and a stringent interindividual sampling strategy is required to further reduce variability. In addition, within subject variability should be limited since estimated pharmacokinetic parameters are used as measured variables, resulting in limited accuracy to explore variability. Unfortunately, interindividual variability in pharmacokinetics is the most relevant question in neonates, while a frequent sampling strategy is more difficult to implement because of ethical considerations.

In a population approach, the entire population is modelled, which therefore eliminates the need to acquire sufficient data from every individual to define a predictive model. Population pharmacokinetics hereby provides a tool to learn more about what we need to know, providing data on degree and source of variation in the determinants of drug concentration-time profiles. In a non-linear mixed effects modelling (NONMEM)

approach, all data from all individuals are fitted together with individual data on potential relevant biological variables, using a non linear regression analysis approach. Assumptions must be made regarding the form of variation in each parameter between individuals and regarding the distribution of the measurement error. Individual parameter values for some of the structural parameters are assumed to vary around the mean population value by a normal distribution. Variation between and within individuals is explained using statistical parameters within the modelling process (Anderson and Meakin 2002).

In conclusion, clinical trials of various medicines in neonates are required to provide evidence for safe and effective drug prescription in the near future. This will become an increasingly important issue in intensive care, with the very high prescription rate of off-label drugs. All contributors to paediatric drug development – regulatory authorities, ethics committees, physicians, the patient and his/her family and industry – need to play a role towards developing adequate and safe pharmacotherapy. In line with earlier initiatives, the activities within the European Medicines Evaluation Agency (EMEA) and the Paediatric Draft regulation reflect the increased awareness and scrutiny of 'the public'. Here we have illustrated the necessity, feasibility and methodology of such studies in neonates and young children, using intravenous paracetamol as a model.

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