Pharmacokinetics, metabolism and tolerance of intravenous paracetamol in early life

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Abstract: Effective analgesia in neonates is still hampered due to the lack of data on pharmacokinetics and -dynamics of analgesics in this specific population. To a certain extent, this is even true for paracetamol. An intravenous formulation might improve prediction of concentration and consequent effect compared to enteral administration. There are limited pharmacokinetic data available concerning intravenous paracetamol in neonates that can be used to determine dosing while dosing regimens used in clinical practice vary from manufacturer recommendations. The impact of covariate information on dosing is uncertain. In this paper, we summarize the consecutive datasets we made to document aspects of pharmacokinetics, metabolism and aspects of safety (hepatic tolerance, haemodynamic stability and effects on body temperature) during exposure to intravenous paracetamol in neonates.

Key-Words: paracetamol – acetaminophen – newborn – pharmacokinetics - pharmacodynamics

1 Introduction
Adequate management of pain in neonates is a major issue, not only from an ethical perspective, but also to improve short and long term outcome [1]. Effective treatment of pain in this population is still in part hampered due to the limited volume of data on the pharmacokinetics and -dynamics of analgesics prescribed. To a certain extent, this is even true for paracetamol [1,2]. Paracetamol, N-acetyl-p-aminophenol, is a readily available antipyretic and analgesic agent. It is the most often prescribed drug for treatment of mild to moderate pain or fever in infants, including neonates and can be administered by oral, rectal but also by intravenous route [2].

Propacetamol (ProDafalgan®, Bristol-Myers Squibb, Brain-l’Alleud, Belgium) is a pro-drug of paracetamol and is hydrolysed by plasma esterase after intravenous administration such that 1g of propacetamol is hydrolysed to 0.5g of paracetamol. A new formulation of iv paracetamol (Perfusalgan®, Bristol-Myers Squibb, Brain-l’Alleud, Belgium) became more recently available [2].

The use of an intravenous administration might improve prediction of concentration and consequent effect compared to rectal and/or oral formulations by the elimination of plasma variability due to absorption kinetics and bio-availability. In addition, an intravenous route enables administration of paracetamol when the enteral route is not (yet) accessible [3]. In adults, paracetamol is almost exclusively eliminated by renal way after conjugation with either glucuronic acid to paracetamol-glucuronide (APAP-G, 47-62%) or with sulfate to paracetamol sulfate (APAP-S, 25-36%) resulting in a APAP-G/APAP-S ratio of about 2. Only limited amounts are excreted in the urine as free paracetamol or are metabolized through oxidation to N-acetyl-p-benzoquinone-imine (NAPQI) and into 3-hydroxy-APAP by the cytochrome p 450 enzyme system. If not depleted, glutathione conjugates with the hepatotoxic metabolite NAPQI resulting in cysteine and mercapturic acid metabolite. Uridinediphosphate-glucuronosyltransferases (UGT’s) are part of a superfamily of enzymes that catalyse the addition of a glycosyl group from a nucleotide sugar to a small molecule enhancing renal elimination of this molecule. Paracetamol is mainly metabolized by UGT-1A6 and to a much lesser extent by UGT-1A1 and UGT-1A9. This iso-enzyme specific activity depends at least in part on the concentration of the drug. A maturational trend with a progressive increase in APAP-G elimination has been described in several single dose enteral paracetamol studies in neonates, infants and children, based on a progressive increase in activity of the glucuronidation pathway during childhood only reaching an adult G/S ratio at the age of 8 to 10 year [4,5]. Data available on paracetamol metabolism in neonates were until recently limited to single dose administration and no data on safety assessment in neonates were available.

There are limited pharmacokinetic data available concerning intravenous paracetamol in neonates that can be used to determine dosing [6,7,8]. Dosing regimens used in clinical practice vary from manufacturer
recommendations [2,3]. The impact of covariate information on dosing is uncertain. In this review, we would like to summarize our stepwise approach to document intravenous paracetamol pharmacokinetics, metabolism and tolerance (hepatic, haemodynamic, thermodynamics in preterm and term neonates).

2 Paracetamol observations in neonates

2.1. Paracetamol pharmacokinetics in neonates

Maturational changes in drug disposition occur throughout childhood, but are most prominent in early life [9]. In general, neonates have an overall low clearance capacity. Between subject variability can be explained by covariates such as size, weight organ function, co-administration of drugs, genetic polymorphisms, growth restriction or disease characteristics [10].

Age, weight, growth restriction and unconjugated bilirubin concentration were available from three published investigations in literature [6,7,8] and were pooled with new observations from 60 neonates to describe covariate effects. The aim was to describe intravenous (IV) paracetamol pharmacokinetics, to determine major covariates and to suggest a dosing regimen for neonates 28-44 weeks postmenstrual age (PMA).

A population pharmacokinetic analysis of paracetamol time-concentration profiles (943 observations) from 158 neonates [PMA: 27 weeks-45 weeks] was undertaken using non-linear mixed effects models (NONMEM). A two-compartment (central, peripheral) linear disposition model was used [7,8,11,12]. Population parameter estimates (between subject variability, %) were central volume (V1) 51.9 (21.6%) L, 70kg, peripheral volume of distribution (V2) 22.7 L,70kg, clearance (CL) 5 (40%) L.h-1.70kg-1 and inter-compartment clearance (Q) 16.2 L,h-1.70kg-1.

Clearance estimates in the pooled analysis were similar to the smaller studies earlier reported [7,8]. Covariate information predicts 60.9% of the clearance variance. Weight was used to predict patient size and this was the major covariate contributing 57.5% of variance. Clearance expressed as mg.kg-1.h-1 increases only slightly with PMA (0.138 L/kg/h at 28 to 0.167 L/kg/h at 44 weeks PMA), and contributes to only 2.2% of variance. High unconjugated bilirubin levels only contributed an additional 1.2% of variance [8]. An increased volume of distribution supports the use of a loading dose for intravenous paracetamol in neonates. Size (described by patient weight) is the major covariate contributing to paracetamol clearance variance in neonates. Paracetamol clearance (mg.kg-1.h-1) increases only slightly with increasing postmenstrual age (PMA) in neonates. Consequently, we suggest a loading dose of 20 mg.kg-1 to compensate for the higher distribution volume, followed by 6 hourly dosing 10 mg.kg-1 independent of the PMA within the age range evaluated (28-44 weeks PMA).

2.2. Paracetamol metabolism in neonates

Compared with phase I isoenzymes, data on isoenzyme-specific phenotypic activity of uridine diphosphateglucuronosyltransferase (UGT) and its covariates in neonates are limited. In vivo observations on morphine, paracetamol (acetaminophen), and propofol disposition throughout childhood confirm the overall low glucuronidation activity in neonates observed in vitro studies [4,5,13]. In addition to the phenotypic low glucuronidation activity, in vivo observations of bilirubin (UGT1A1), morphine (UGT2B7), paracetamol (UGT1A6), and propofol (UGT1A9) glucuronidation in neonates display extensive interindividual variability, only in part explained by postmenstrual and/or postnatal age [12,13]. Based on urine collections during repeated intravenous paracetamol administration, we were able to illustrate that both postmenstrual and postnatal contributed to the interindividual variability in glucuronidation activity, quantified by the contribution of paracetamol-glucuronide to overall paracetamol urinary elimination (G/T) [13]. However, this only in part explained the interindividual variability in G/T ratio observed. We therefore decided to collect urine samples and portions during repeated intravenous paracetamol administration (PARANEO study) to explore the potential impact of disease characteristics (e.g. growth restriction, cardiopathy, indirect hyperbilirubinaemia) on this G/T ratio in neonates and pooled these observations with earlier reported observations in neonates.

Based on 24h urine collections, we also observed a trend to reduced paracetamol glucuronidation in the setting of increased bilirubinaemia. This makes sense, since both compounds (paracetamol and bilirubin) undergo glucuronidation to facilitate (renal) elimination. Palmer et al. also documented in their iv paracetamol study a link between reduced clearance and increased bilirubinaemia [8].

Secondly, during repeated administration, there was a progressive increase in the contribution of paracetamol-glucuronide to overall renal paracetamol elimination. This has been observed earlier and likely reflects adaptations in hepatic transport (biliary vs blood) capacity [13,14].

2.3. Aspects of paracetamol tolerance in neonates

2.3.1. Haemodynamics

Impaired haemodynamics following intravenous paracetamol administration in adult intensive care were recently published [15]. We therefore wanted to evaluate
haemodynamics of iv paracetamol in neonates. Pooled analysis of data on heart rate (bpm) and blood pressure (mean, systolic, diastolic) collected during iv paracetamol pharmacokinetic studies in neonates. Heart rate and blood pressure were recorded just before and 30, 60, 120, 180, 240, 300 and 360 minutes after iv paracetamol (paired, ANOVA). Clinical characteristics in hypotensive (mean mmHg < gestational age, weeks) cases were compared with controls (Mann Whitney U).

Based on observations in 72 neonates, heart rate decreased from 145 (SD 20) to 138 (21), 141(20), 137(20), 137(22), 140(20), 139(20) and 140(21) bpm (paired p<0.05, ANOVA p=0.36). There were no changes in systolic and diastolic pressure, but mean arterial pressure decreased from 46 (7) to 43(8) mmHg at 60 minutes (paired p<0.05, ANOVA p=0.75). Eight neonates developed hypotension. These cases had lower pre-administration arterial pressure (38 vs 47 mmHg, p<0.05) [16]. Although these data were collected following unblinded administration to alleviate (procedural) pain, it seems that haemodynamic effects iv paracetamol are modest (-8 bpm, -3 mmHg mean arterial pressure). We suggest to consider impaired haemodynamics a relative contra-indication for iv paracetamol in neonates [16].

2.3.2. Hepatic tolerance [17]

An intravenous (iv) formulation of paracetamol is available, but reports on its hepatic tolerance in neonates are limited. We therefore assessed hepatic tolerance of iv paracetamol in neonates. In a single centre retrospective study, clinical data and hepatic enzyme profiles (ALT, AST, \( \gamma \)GT) were collected in neonates treated with iv paracetamol.

Hepatic enzyme profiles were retrieved from 2 days before until 2 days after iv paracetamol administration. Mann-Whitney \( U \) test was used to compare hepatic enzymes before, during and after iv treatment. Correlations (Spearman rank) of hepatic enzymes with duration of treatment during iv administration were investigated.

2360 administrations in 189 cases {postmenstrual age 38 (range 30-55) weeks, postnatal age 5 (1-182) days} were documented and 1132 hepatic enzyme observations were available in 149/189 cases. There was no significant increase in ALT, AST or \( \gamma \)GT when pre-treatment observations (n=310) were compared with observations during (n=649) or during with after (n=173) treatment, nor was there a significant increase during administration. This retrospective study on hepatic tolerance provides evidence on safety aspects of iv paracetamol in neonates. Future studies should focus on dose-findings and pharmacodynamics of this formulation in neonates.

3.3.3. Thermodynamics

In the absence of reported observations on body temperature trends following iv acetaminophen administration in (pre)term neonates, we decided to pool data from two published pharmacokinetic (PK) studies on propacetamol disposition [6,7] and a recently finalised prospective study on PK, PD and safety of iv acetaminophen (PARANEO, www.clinicaltrials.gov) in neonates [16]. We aimed to evaluate the impact of iv acetaminophen on body temperature in neonates who were initially either normothermic or had fever.

Body temperature was recorded by skin probe and registered before and every 2 h following initiation of repeated iv acetaminophen administration up to 48 h. Clinical characteristics (age, weight) were collected and data reported by median and range, or mean and standard deviation. Repeated measures ANOVA and paired analysis were used to quantify differences following acetaminophen exposure.

The pooled analysis was based on 99 neonates [median weight 2.7 (range 0.5-5.4) kg, median postmenstrual age 37 (range 27-50) weeks]. Based on observations in 93 normothermic (<37.8°C) neonates and 6 neonates with fever, is was documented that acetaminophen administration does not affect body temperature in normothermic patients. In neonates with fever, the median decrease (-0.8°C) is most prominent in the first 2 hours (p<0.01) following acetaminophen administration with subsequent further normalisation. We therefore conclude that administration of iv acetaminophen does not result in hypothermia in initially normothermic neonates, while in those with fever, maximal temperature reduction is achieved within 2 hours following acetaminophen administration.

3 General discussion

More than one century after the introduction of paracetamol into clinical practice, still new observations on its disposition are unveiled and relevant questions can be formulated [2,3]. In a stepwise approach, we were able to describe aspects of disposition, metabolism and tolerance of intravenous paracetamol in preterm and term neonates [6,7,13,16,17]. Based on the need for adequate and well tolerated analgesia, intravenous paracetamol is a potential useful drug that should be considered in neonates [18].

Size is the single most important covariate for determining clearance in neonates during this initial slow maturation phase. Age has a greater contribution after this phase so that both age and size contribute 91% of variance of clearance throughout paediatric life [11,12]. Maintenance dosing (mg.kg\(^{-1}\).h\(^{-1}\)) should be based initially on clearance using total body weight as a measure (e.g. mean clearance 0.151 L.kg\(^{-1}\).h\(^{-1}\) at 36 weeks PMA). Mean clearance only differs by 10% from this value at
28 weeks PMA and at 44 weeks PMA. We suggest a loading dose of 20 mg kg\(^{-1}\) followed by 6 hourly dosing 10 mg kg\(^{-1}\) independent of the PMA within the age range evaluated (28–44 weeks PMA). Observations on renal metabolites suggest that besides age [13], other clinical covariates like hyperbilirubinaemia and repeated administration also contribute to the overall interindividual variability in glucuronidation activity.

When safety related issues are considered, it seems that this compound does not result in relevant negative effects when liver enzymes, haemodynamics or body temperature issues are considered [16,17].

### 4 Conclusions

Based on the available pharmacokinetic estimates, it seems that intravenous paracetamol is an attractive analgesic to be used in neonates, as an alternative or add-on therapy for opioid administration. After the documentation of the pharmacokinetics of paracetamol in neonates and in the absence of any data on pharmacodynamics of intravenous paracetamol in this population, prospective, well designed and appropriated powered pharmacodynamic studies in neonates focussing on analgesia are urgently needed.

### References