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Pain Treatment of Newborns: Paracetamol Rectal Versus Intravenous Administration, A Randomised Open Clinical Trial

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Abstract

Background and aim: Early recognition and treatment of pain is of great importance in the neonatal period. Paracetamol is the most frequent prescribed medicine for pain treatment. Administration of rectal paracetamol has limitations and the effectiveness can be variable in neonates. This study is based on the hypothesis that intravenous (iv) paracetamol is well tolerated, less variable and therefore more reliable in preterm neonates compared to rectal paracetamol. We therefore compared the effectiveness of intravenous and rectal administration in (preterm) neonates during a period of sickness accompanied by pain.

Methods: We included 21 neonates with pain, post menstrual age (PMA) of 28-44 weeks. They received paracetamol rectal or intravenous according to Dutch guidelines. Serum concentrations at steady state (t = 0, 0.5, 1, 2, 4, 6 hours) were determined.

Results: Clearance was dependent of weight, not of PMA. Estimated mean serum concentrations after four administrations were 4,8 ± 0,7, 8,1 ± 1,9 and 10,2 ± 3,1 mg/L and after rectal administration 4,1 (n=1), 12,6 ± 6,0 and 14,0 ± 6,7 mg/L. Hepato- or renal dysfunction were not observed.

Conclusion: Rectal and intravenous administration of paracetamol is well tolerated in (preterm) neonates. Rectal administration gives no paracetamol absorption or a major variation with inter- and intra-individual variation, which turns out to be unreliable especially in (pre)term neonates. Dosing of paracetamol (rectal and iv) should be based on weight instead of PMA. Further research is needed to define the exact dosing regime and target concentration of intravenous paracetamol in (preterm) neonates in comparison to the pain experience especially in preterm neonates.

Keywords: Neonatology; Pain; Paracetamol; Pharmacology

Abbreviations: Cl: Clearance; Cl/F: Apparent Clearance, L/Hour; CYP: Cytochrome P450 Dependent Enzymes; F: Bioavailability; Iv: Intravenous; Ka/F: Absorption Rate, L/Hour; METC: Medical Ethics Commission; NEC: Necrotising Enterocolitis; NICU: Neonatal Intensive Care Unit; PD: Pharmacodynamics; PK: Pharmacokinetics; PMA: Post Menstrual Age; V: Distribution; V/F: Apparent Volume Of Distribution, I

Introduction

Early recognition and treatment of pain is of great importance in the neonatal period. Moreover, exposure to pain without effective treatment of pain in this period might influence not only early but also later development [1,2]. Paracetamol is the most frequent prescribed medicine for pain treatment excluding neonates. In the neonatal intensive care unit (NICU) neonates are frequently exposed to painful procedures but most medication used for pain are opioids (morphine and fentanyl). These opioids can have severe adverse effects in premature neonates (depression of breathing, hypotension, urine retention) [3]. On the other hand a clear description of the exposure of rectal paracetamol in preterm and term neonates is lacking [4,5]. In addition, the administration, of rectal paracetamol has limitations such as administration problems, loss of paracetamol suppository with defecation and immaturity of the porta-rectal system especially in preterms leading to a variable absorption. Moreover, in some clinical conditions rectal administration of paracetamol is contraindicated such as necrotising enterocolitis (NEC) and severe thrombocytopenia (< 50×10⁹/l).

Taken the adverse effects of opioids and limitations of rectal administration of paracetamol into account it is important to realize that (preterm) newborns has to be treated with medication characterized by good analgesic but less adverse effects or limitations in administration such as intravenous paracetamol. Currently rectal paracetamol is being used in preterm and terme neonates. We know that the effectiveness of rectal paracetamol can be variable in neonates [6,7]. Intravenous paracetamol being used in (preterm) neonates is not common. Improved understanding of the pharmacokinetics (PK) and pharmacodynamics (PD) of paracetamol will contribute to a safer, more effective and predictive analgesic dosing regimen for premature and term neonates. We think it is essential to estimate the effectiveness of intravenous paracetamol compared to rectal paracetamol, based on the hypothesis that intravenous paracetamol is well tolerated, less variable and therefore more reliable in preterm neonates compared to rectal paracetamol.

In the present study we used the paracetamol dosing regimen for optimal dosing exposure according to the Dutch guidelines and the described literature [8-10] The rectal and intravenous (iv) dosing is based on the post menstrual age (PMA) and weight in (preterm) neonates during a period of pain.

Methods

Study registration and ethics

This study was an open randomised clinical single center trial. The primary outcome was the PK of iv and rectal paracetamol administration in term and premature neonates. The secondary outcome was the PD (pain) and safety (hepatic and renal tolerance) of iv and rectal paracetamol administration in term and premature neonates. Twenty-four neonates were included following study registration, approval by the medical ethics commission (METC VU Medical Center, Amsterdam) and written parental informed consent.

Contra-indications for inclusion were, the absence of an arterial access (blood sampling for PK), renal- and/or hepatocellular dysfunction and severe thrombocytopenia (< $50 \times 10^9/l$), necrotising enterocolitis and rectal blood loss.

Clinical characteristics, medication, dosing regimen and blood sample strategy

Twenty-four neonates either preterm (28-37 weeks gestational age) or term (37-44 weeks gestational age) were included. Pain scores were collected by the Comfort NEO score (Dutch validated pain score system). Neonates with pain (Comfort NEO score > 14) received paracetamol iv or rectal after randomisation according to Dutch guidelines independent of the cause of pain (medical, postoperative, hematoma). Rectal dosing (28-31 weeks) loading dose 20 mg/kg followed by 20 mg/kg every 12 hour, (32-35 weeks) loading dose 30 mg/kg followed by 20 mg/kg every 12 hour and (36-44 weeks) loading dose 30 mg/kg followed by 20 mg/kg every 8 hour. Intravenous dosing (28-31 weeks) loading dose 20 mg/kg followed by 10 mg/kg every 12 hour, (32-35 weeks) loading dose 20 mg/kg followed by 10 mg/kg every 8 hour and (36-44 weeks) loading dose 20 mg/kg followed by 10 mg/kg every 6 hour.

The prescribed dose of intravenous paracetamol 10 mg/ml (Perfalgan©, Bristol-Myers Squibb) was administrated undiluted in 15 minutes. Paracetamol suppositories of 30 mg (UMC stRadboud, Pharmacy, Nijmegen, The Netherlands) and 60 mg (Centrafarm B.V, Etten-Leur, the Netherlands) were used to achieve the desired paracetamol dose. The suppository of 30 mg was fabricated for this study in a triglyceride base in gelatin capsules. Only complete suppositories were administrated. The correct handling was done by the nurse. Blood samples were taken through the arterial route at steady state around the fifth administration of paracetamol, samples were taken at t=0, 0.5, 1, 2, 4, 6 hour. These time points include the $C_{through}$ and C_{max} of neonates after administration of paracetamol either intravenous (15 minutes after infusion) or rectal paracetamol (1,5-5 hours).

Safety data are limited for paracetamol in neonates. It is difficult to predict acute liver or kidney injury in neonates. Renal and hepatocellular function has been measured with serum creatinine and alanine and aspartate aminotransferase. Thrombocyte count were measured by taken blood samples before randomisation and after the fifth administration of paracetamol.

Blood samples analysis

Plasma paracetamol samples were analysed by using a validated liquid chromatography tandem mass spectrometric (LC-MS/MS) (unpublished data on file, M Ris, ARC Laarman, JCG den Burger, DJAR Moes, AI Veldkamp, EL Swart, MM van Weissenbruch. Pharmacokinetic analysis of paracetamol after rectal or intravenous administration in neonates. VU Medical Center Amsterdam, The Netherlands) [11]. Linearity was established between 0,94 mg/L and 49,6 mg/L. The lower limit of quantification was 0,94 mg/L and variation coefficients of inter- and intra assay accuracy and precision were below 15%.

Exposure to paracetamol

Previous research has led to the development of two separate pharmacokinetic models in NONMEM (V6.2.0 Icon Development Solutions, Ellicott City, MD, USA) [12,13]. Intravenous administration was described best with a one compartmental pharmacokinetic model with first-order elimination. Random effect parameters for inter-individual variability were identified on clearance (Cl) and volume of distribution (V). Weight was the only identified covariate and described 54,9 % of variance. The data after rectal administration were described best with a two compartmental pharmacokinetic model with first order elimination. Random effect parameters for inter-individual variability were identified on Cl/F (apparent clearance, l/hour), V/F (apparent volume of distribution, l) and K_a/F (absorption rate l/hour) and not on F (bioavailability). Also here weight was the only identified covariate. Bioavailability (F) was fixed on 0,6 for achieving the same clearance as with intravenous administration [5]. In both models post menstrual age (PMA) did not significant predict inter-individual variance (unpublished data on file, M Ris, ARC Laarman, JCG den Burger, DJAR Moes, AI Veldkamp, EL Swart, MM van Weissenbruch. Pharmacokinetic analysis of paracetamol after rectal or intravenous administration in neonates. VU Medical Center Amsterdam, The Netherlands) [11]. With the developed pharmacokinetic models the individual clearance of paracetamol of each participant of the study was determined.

Exposure to paracetamol was calculated using the formula: Exposure = Dose*F / Cl and presented as average serum concentration (mg*h/L). If patients were excluded for PK-analysis the exposure was calculated of all the concentration-time points using the trapezoidal rule between the sampled time period (t=0 till t=6).

Statistics

Clinical characteristics were reported by mean, range and incidence. The differences between intravenous and rectal paracetamol dosing regimen, effect, exposure and serum concentrations were analysed with the Mann Whitney U test. A p-value < 0,05 was significant.

Results

Twenty-four neonates participated in the trial. Nine neonates have received iv paracetamol and fifteen neonates have received rectal paracetamol. The clinical characteristics and the indication for pain treatment in these 24 neonates are reported in Tables 1 and 2. Three neonates were excluded for analyses due to rectal administration problems and/or no absorption of paracetamol. There was no elevation of serum creatinine and alanine and aspartate aminotransferase. In all the patients the clearance of paracetamol was dependent on the actual weight during treatment instead of the regularly used PMA (Figure 1).

Paracetamol intravenous

In literature a target serum paracetamol concentration of >10 mg*h/l is described [14]. After four consecutive iv dosages the estimated serum concentrations (mean ±SD) of paracetamol were 4,8 ± 0,7 mg*h/l (PMA 28-31 weeks), 8,1 ± 1,9 mg*h/l (PMA 32-35 weeks) and 10,2 ± 3,1 mg*h/l (PMA 36-44 weeks).

Patient characteristics	PMA 28-31 weeks *1	PMA 28-31 weeks *1	PMA 32-35 weeks *2	PMA 32-35 weeks *2	PMA 36-44 weeks *3	PMA 36-44 weeks *3
Group	iv	rectal	iv	rectal	iv	rectal
N (total = 24)	3 (3 ♂)	3 (2 ♂)	3 (0 ♂)	4 (3 ♂)	3 (1 ♂)	8 (4 ♂)
Mean PMA (weeks + days) (at start)	30 4/7 (30 2/7-31 0/7)	29 4/7 (28 6/7-30 6/7)	32 3/7 (32 3/7-32 4/7)	34 3/7 (32 2/7-35 3/7)	39 2/7 (37 1/7-43 0/7)	38 3/7 (37 0/7-41 0/7)
Mean age (days) (birth - start)	3 (1-6)	11 (1-28)	4 (2-7)	2,5 (1-4)	8 (1-22)	4 (1-12)
Mean weight (gram)	1740 (1535-1890)	1225 (1005-1485)	1430 (1030-1750)	2395 (1710-2717)	3235 (2450-4555)	2845 (2115-4090)
Loading dose (mg/kg/day)	20.5 (20-21.5)	24.5 (20.2-29.8)	19.7 (19.4-30)	31.4 (24.4-35)	20.1 (19.8-20.4)	28.9 (24.5-34.2)
Dose (mg/kg/day)	20.7 (20-22.2)	49 (40.4-59.7)	29,6 (29.1-30)	50 (44.1-70)	40,1 (39.5-40.8)	69,9 (49.7-85.1)

Table 1: Patient characteristics and paracetamol loading dose intravenous and rectal in different patient groups: * 1: PMA 28-31 weeks, *2: PMA 32-35 weeks, *3 PMA 36-44 weeks.

Male = M	Weight	PMA	Rectal/ intravenous	Group	Reason Inclusion:
Female = F	gram	wk+day		PMA	
M	2185	39+3	rectal	a terme	hernia diafragmatica
M	2400	37+2	rectal	a terme	gastroschisis
F	2450	37+1	rectal	a terme	gastroschisis
M	3620	40+4	rectal	a terme	pain other cause
M	1890	30+2	intravenous	28-31	pain other cause
M	2717	35+2	rectal	32-36	jejunal atresia
F	1520	32+3	intravenous	31-36	esophageal atresia
F	2115	37+6	rectal	36-44	esophageal atresia
F	2700	37+1	intravenous	36-44	gastroschisis
M	1185	29+0	rectal	28-32	pain other cause
M	1800	30+3	intravenous	28-31	pain other cause
F	2450	34+6	rectal	32-36	duodenal web
F	1750	32+3	intravenous	31-36	pain other cause
F	2450	37+4	intravenous	36-44	duodenal atresia
M	1635	31+0	intravenous	28-31	pain other cause
M	1710	32+2	rectal	32-36	pain other cause
F	1030	32+4	intravenous	31-36	esophageal atresia
F	3050	37+0	rectal	36-44	hernia diafragmatica
M	4555	43+0	intravenous	36-44	lung biopsy
M	2700	35+3	rectal	32-36	central venous catheter
M	4090	41+0	rectal	36-44	esophageal atresia

Table 2: Patient characteristics.

Paracetamol rectal

The estimated serum concentrations (mean ± SD) of paracetamol after four consecutive rectal dosages were 4,1 mg*h/l (PMA 28-31 weeks), 12,6 ± 6,0 mg*h/l (PMA 32-35 weeks) and 14,0 ± 6,7 mg*h/l (PMA 36-44 weeks).

After rectal administration of paracetamol there was either no absorption or a major variation especially in the neonates with a PMA of 28-31 and 32-35 weeks. There was a major variation within the estimated serum paracetamol concentrations in all neonates after rectal administration. Almost all neonates, except one neonate with a PMA of 36-44 weeks, had reached the target serum paracetamol concentration>10 mg*h/l.

Two neonates with a PMA of 28-31 weeks were excluded for analyses due to rectal administration problems and/or no absorption of paracetamol. In addition, two neonates with a PMA of 36-44 weeks were excluded because of no increase but decline in serum paracetamol concentration compared to t=0 without signs of rectal administration problems (Figure 2).

Limitations of rectal paracetamol dosing versus iv paracetamol dosing

All neonates received paracetamol iv or rectal according to Dutch guidelines and almost all patients received the prescribed iv paracetamol dose in contrast to the rectal paracetamol dose. The iv paracetamol can easily be administrated in the exact prescribed dose.

For the rectal paracetamol it was impossible to administrate paracetamol in the exact prescribed dose because of the limitation of the suppository of 30 mg. Due to this limitation the administrated rectal paracetamol dose was higher than the prescribed paracetamol dose, especially in neonates with a PMA of 28-31 and 32-35 weeks.

All serum paracetamol concentrations were corrected for the administrated iv and rectal paracetamol dose. After four consecutive iv dosages the corrected serum concentrations (mean ± SD) of paracetamol were 4,7 ± 0,7 mg*h/l (PMA 28-31 weeks), 8,3 ± 1,9 mg*h/l (PMA 32-35 weeks) and 10,3 ± 3,3 mg*h/l (PMA 36-44 weeks). The corrected serum concentrations (mean ± SD) of paracetamol after four consecutive rectal dosages were 3,2 mg*h/l (PMA 28-31 weeks),
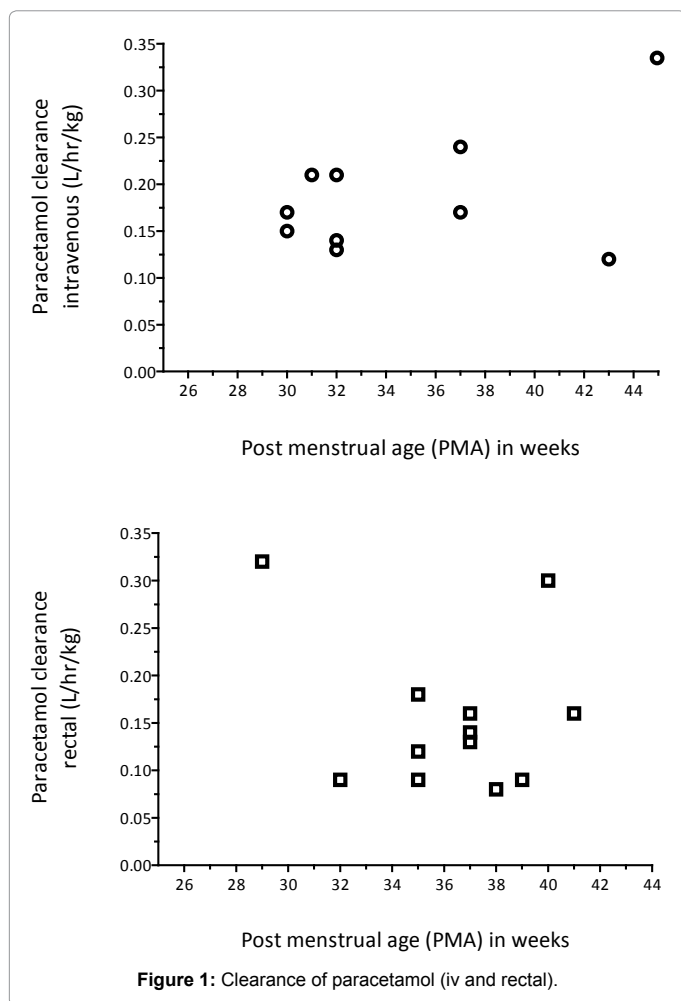
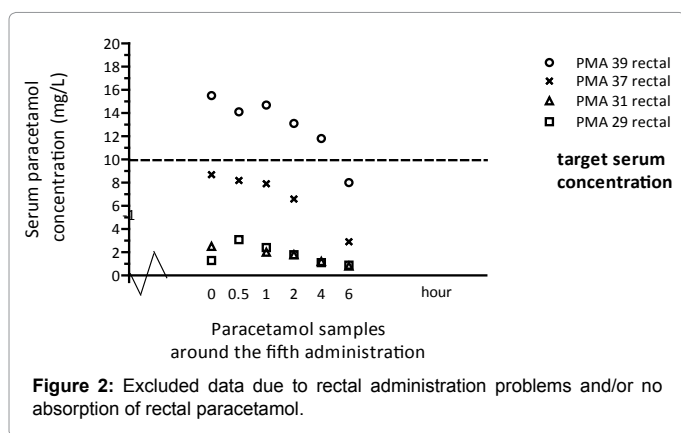**Figure 1:** Clearance of paracetamol (iv and rectal).

Figure 2: Excluded data due to rectal administration problems and/or no absorption of rectal paracetamol.

9,4 ± 2,9 mg*h/l (PMA 32-35 weeks) and 11,4 ± 4,3 mg*h/l (PMA 36-44 weeks).

The serum paracetamol concentration of iv paracetamol didn't change after correction for the administrated dose. The serum paracetamol concentration of rectal paracetamol was less variable and with nearly no difference in mean serum concentration after correction for the administrated dose (Figure 3).

Discussion

We here report that the clearance of paracetamol rectal and

intravenous was dependent of the neonatal weight during treatment instead of the regularly used PMA according to the current Dutch guidelines. Recent data from Allegaert et al. showed that variance in clearance of intravenous paracetamol is primarily explained by weight and suggests that dosing of intravenous paracetamol should be based on weight instead of PMA [15].

In our study the absorption of rectal paracetamol turns out to be very unreliable especially for the preterm neonates. Hansen et al. described a variable absorption of rectal paracetamol in neonates, with no clear description of paracetamol absorption in this population [4]. We observed either no absorption or a major variation in serum paracetamol concentration after rectal paracetamol administration in almost all neonates and especially in preterm neonates with a PMA of 28-31 weeks. In some patients studied, irrespective PMA, there were also problems with the route of rectal administration of paracetamol.

In general it is very difficult to administrate the rectal paracetamol in the exact prescribed dose because of the limitation of the suppository of 30 mg. Due to these limitations most of the neonates have received a higher rectal paracetamol dose than have been prescribed.

Therefore we have to be precautious with rectal paracetamol in both preterm and term neonates because rectal paracetamol might be very unreliable in these children. Tinner et al. described a possible increase of pain response, based on the neonatal pain and discomfort scale, in term and near term neonates who received rectal paracetamol soon after an assisted vaginal delivery [16].

We here showed that intravenous paracetamol administration is more accurate applicable in preterm and term neonates, with less variation in serum paracetamol concentration than rectal paracetamol administration. In almost all neonates the estimated serum paracetamol concentration was below the target serum concentration of 10 mg*h/l. Most of the neonates received co-medication such as opioids because
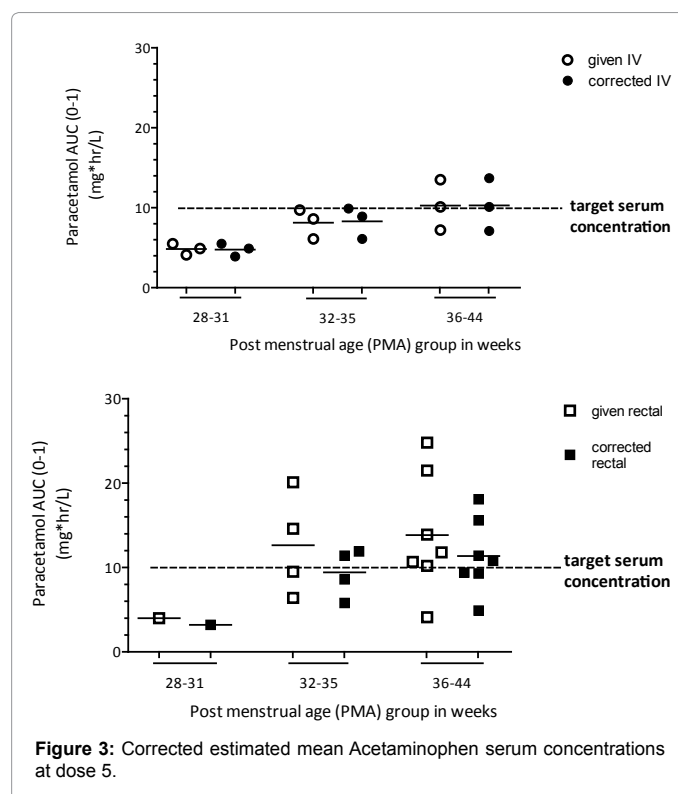

Figure 3: Corrected estimated mean Acetaminophen serum concentrations at dose 5.

of a surgical procedure, the iv or rectal paracetamol was added for pain treatment after the surgical procedure. Wong et al. described variable results in children who received perioperative paracetamol. Rectal paracetamol did not reduce the opioid requirements, but iv paracetamol reduced the opioid requirement in children aged 6-24 months [17].

So far it is not clear if the prescribed paracetamol dose is accurate enough for these neonates because of the low serum paracetamol concentrations. Otherwise the target serum paracetamol concentration of 10 mg*h/l might not be appropriate for these neonates especially in preterms. The use of co-medication makes it difficult to investigate this in a proper way. Pain experience can be another factor in these preterm neonates. They might experience pain different compared to older neonates.

Recent study from James et al. [18] showed that alanine aminotransferase and acetamionophen concentrations are less sensitive in predicting the development of acute liver injury. In our study we measured serum alanine and aspartate aminotransferase before and during rectal and intravenous paracetamol. We have observed no elevation of alanine and aspartate aminotransferase. As a result it is difficult to make any prediction regarding acetaminophen induced liver injury.

We are aware that the current report and study design have limitations. It is a small single center study in which we included only twenty-four neonates. Some neonates were treated with co-medication (morphine or fentanyl) which makes it impossible to evaluate if the target serum paracetamol concentration of >10 mg*h/l is optimal for the neonates studied with regard to the pain experience. We didn't evaluated metabolites of paracetamol in both plasma and urine of the neonates. These metabolites are important in further understanding the pharmacokinetics (PK) of paracetamol [19,20].

Based on these study results we are able to indicate inter- and intra-individual variation of absorption of paracetamol showing that the effectiveness of rectal paracetamol is unreliable in preterm and term neonates. Intravenous paracetamol administration, however, seems to be far more reliable, is well tolerated and more effective than rectal paracetamol administration in both preterm and term neonates. Further research is required to define pain experience especially in preterm neonates and for defining the dosing regime and target concentrations in using intravenous paracetamol in preterm and term neonates.

Conclusion

Rectal and intravenous administration of paracetamol is well tolerated in (preterm) neonates. Rectal administration gives no paracetamol absorption or a major variation with inter- and intra-individual variation, which turns out to be unreliable especially in (pre) term neonates. Dosing of paracetamol (rectal and iv) should be based on weight instead of PMA. Further research is needed to define the exact dosing regime and target concentration of intravenous paracetamol in (preterm) neonates in comparison to the pain experience especially in preterm neonates.

Acknowledgments

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