

PAEDIATRICS

I.V. acetaminophen pharmacokinetics in neonates
after multiple doses

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Background. Pharmacokinetics of an i.v. prodrug of acetaminophen (propacetamol) in neonates after repeat dosing are reported, with scant data for i.v. acetaminophen formulation.

Methods. Neonates from an intensive care unit received 6-hourly *prn* i.v. acetaminophen dosed according to postmenstrual age (PMA): 28–32 weeks, 10 mg kg⁻¹; 32–36 weeks, 12.5 mg kg⁻¹; and ≥36 weeks, 15 mg kg⁻¹. A maximum of five blood samples for assay and liver function tests (LFTs) were collected. A one-compartment linear disposition model (zero-order input; first-order elimination) was used to describe time–concentration profiles using population modelling (NONMEM).

Results. Fifty neonates, median (range) PMA 38.6 (32–45) weeks, mean (SD) weight 2.9 (0.7) kg, received a mean of 15 doses over a median 4 days with 189 serum acetaminophen and 231 LFT measurements. Standardized population parameter estimates for a term neonate were clearance (CL) 5.24 (CV 30.5%) litre h⁻¹ 70 kg⁻¹ and volume of distribution (V) 76 (29.6%) litre 70 kg⁻¹. CL increased with PMA from 4.4 litre h⁻¹ 70 kg⁻¹ at 34 weeks to 6.3 litre h⁻¹ 70 kg⁻¹ at 46 weeks. The presence of unconjugated hyperbilirubinaemia was associated with reduced CL: 150 μmol litre⁻¹ associated with 40% CL reduction. Acetaminophen concentrations between 10 and 23 mg litre⁻¹ at steady state are predicted after 15 mg kg⁻¹ 6-hourly for a neonate of PMA 40 weeks. Hepatic enzyme analysis of daily samples changed significantly for one patient whose alanine aminotransferase concentration tripled.

Conclusions. The parameter estimates are similar to those described for propacetamol. There was no evidence of hepatotoxicity. Unconjugated hyperbilirubinaemia impacts upon CL, dictating dose reduction.

Br J Anaesth 2008; **101**: 523–30

Keywords: analgesic techniques, i.v.; analgesics non-opioid, acetaminophen; pharmacokinetics, models

Accepted for publication: May 22, 2008

I.V. acetaminophen is gaining increasing use in children^{1–4} and neonates^{1 5 6} despite limited data concerning the pharmacokinetics of this formulation. Population pharmacokinetics of the i.v. prodrug (propacetamol) have been studied in neonates after single^{7 8} and repeat administration.⁹ There are limited neonatal i.v. acetaminophen pharmacokinetic data available for comparison with the prodrug pharmacokinetics in neonates; attributable in part to its off-label use in children weighing <10 kg.⁵ Dosing regimens used in some

institutions for neonates have been published,^{5 10} but there are no data validating these regimens. A case report concerning a 4-day-old 3.4-kg term neonate given i.v. acetaminophen 10 mg kg⁻¹ 4-hourly for 48 h after bowel surgery documents a trough concentration of ≤10 mg litre⁻¹ between the fifth and sixth dose,⁶ supportive of clearance (CL) estimates. CL determines maintenance dose and increases with postmenstrual age (PMA). The CL estimates from i.v. propacetamol data are 5.98 litre h⁻¹ 70 kg⁻¹ at 40 weeks PMA. This is

approximately one-third that of the 6–8-yr-old child's¹¹ or adult's⁸ value of 16–20 litre h⁻¹ 70 kg⁻¹. Licensing imposes no weight restriction in Australia, but the Australian product information for i.v. acetaminophen¹² does not consider the CL maturation with age in neonates in its dosing recommendations. The same dose of 15 mg kg⁻¹ 6-hourly is suggested for neonates more than 10 days of age and for infants and children up to 33 kg. A reduced dose of 7.5 mg kg⁻¹ 6-hourly is proposed in term neonates <10 days of age.¹²

Prescribing rights for i.v. acetaminophen were initially restricted to pain service practitioners in our institution.¹ Therapeutic drug monitoring was initiated after the introduction of this drug into neonatal unit (NNU) and broadening of prescribing rights to neonatologists. Analgesic serum concentrations for acetaminophen in neonates are unknown, but an effect site target concentration of 10 mg litre⁻¹ is proposed in children after tonsillectomy.¹³ We investigated i.v. acetaminophen pharmacokinetics after repeat dosing in neonates in the NNU. We wished to observe serum time–acetaminophen concentration profiles, investigate covariate effects on pharmacokinetics, to assess hepatic safety through liver transaminase enzyme testing and to revise dosing regimens in response to CL estimates.

Methods

This study was approved by the Ethics in Human Research Committee (EHRC) and performed in neonates nursed in the NNU at a tertiary paediatric centre. Parents of neonates were provided with written and verbal information and approached for written consent once their neonate had received at least two doses and required further i.v. acetaminophen (*Perfalgan*[®], Bristol Myer Squibb Pharmaceuticals, Noble Park, Australia). The neonates received i.v. acetaminophen, administered over 15 min, according to the proposed PMA adjusted 6-hourly *prn* dosing regimen: 28 to <32 weeks, 10 mg kg⁻¹; 32 to <36 weeks, 12.5 mg kg⁻¹; and ≥36 weeks, 15 mg kg⁻¹. This dosing regimen was calculated at 15% less than the current oral dosing regimen used within the NNU.

Blood samples (venous, arterial, or skin capillary) for acetaminophen assay were obtained and a daily liver function test (LFT) was performed opportunistically when other routine blood samples were obtained after enrolment into the study. Times for this sampling were not fixed. Volume of these additional samples was limited to <0.5 ml per patient, with a maximum of five samples per neonate. An EHRC requirement was to assay the samples in series (rather than batch analysis after storage at -20°C) to allow for individual patient dose adjustment in response to a trough concentration of >40 mg litre⁻¹ or LFT changes. The LFT panel included bilirubin (conjugated and unconjugated), alanine aminotransferase (ALT), gamma-glutamyl transaminase (GGT), alkaline phosphatase (ALP), albumin, and total protein. Where serum volumes were small, unconjugated bilirubin, albumin, and ALT were assayed preferentially. Doubling of ALT was

predefined as a marker of possible hepatotoxicity. Abnormal LFT concentrations were defined using the Vitros-950 analyser (Ortho-Clinical Diagnostics, Johnson and Johnson, Buckinghamshire, UK) neonatal reference ranges as: ALT, >55 U litre⁻¹; GGT, >255 U litre⁻¹; ALP, >355 U litre⁻¹; albumin, <23 g litre⁻¹; and total protein, <45 g litre⁻¹. An abnormal conjugated bilirubin was >10 µmol litre⁻¹ with postnatal age (PNA) <27 days (where date of birth is PNA Day 1) or >5 µmol litre⁻¹ with PNA ≥27 days. Unconjugated bilirubin was defined by PNA and abnormal if: >115 µmol litre⁻¹ with PNA <2 days, >155 µmol litre⁻¹ with PNA 2 to <6 days, >120 µmol litre⁻¹ with PNA 6 to <13 days, >80 µmol litre⁻¹ with PNA 13 to <20 days, >45 µmol litre⁻¹ with PNA 20 to <27 days or >10 µmol litre⁻¹ with PNA ≥27 days. Hypoproteinaemia was considered significant when albumin was <21 g litre⁻¹, total protein was <38 g litre⁻¹, or both, and mild for albumin between 21 and 23 g litre⁻¹, total protein between 38 and 45 g litre⁻¹, or both. In the absence of other LFT anomaly, mild hypoproteinaemia alone was classified as normal.

Covariate information included PMA and PNA, weight, diagnosis, or indication for i.v. acetaminophen and other parenteral therapy [i.v. analgesics, total parenteral nutrition (TPN), and i.v. antibiotics]. These data along with dose regimen and time concentration profiles were entered using Epidata 3.1 (The Epidata Association, Denmark, 2003–4). Data management and descriptive statistics were performed using Stata version 10.0 (Stata Statistical Software, Stata Corp LP, TX, USA). Normally distributed data are presented as means and range; non-normal are represented as medians and full ranges. Day-to-day changes in LFTs were assessed and presented graphically with an 80% bandwidth lowess curve for each plot. A lowess curve is a smooth non-parametric curve fitted by locally weighted regression.

Acetaminophen assay

Acetaminophen assays were performed on fresh or refrigerated (<52 h for weekend samples) centrifuged serum, returned to room temperature, using quantitative colorimetry-Vitros ACET (acetaminophen) slides and the Vitros-950 analyser. This system has high correlation with fluorescent polarization immunoassay (FPIA: 0.991) and high-performance liquid chromatography (HPLC: 1.0) assay techniques. The determination limit is 6 mg litre⁻¹ and precision is 0.8–2.1% over the concentration range of 19–166 mg litre⁻¹. The acetaminophen concentration is positively biased at high bilirubin concentrations, for example, for a bilirubin of 256 µmol litre⁻¹, an acetaminophen concentration of 30 mg litre⁻¹ has a positive bias of 4.2 mg litre⁻¹ (14%).

Pharmacokinetic analysis

Population parameter estimations. A one-compartment linear disposition model with first-order elimination was used to analyse time–concentration profiles. Population parameter estimates were obtained using non-linear mixed

effects modelling (NONMEM).¹⁴ This modelling accounts for population parameter variability (PPV, between and within subjects) and residual variability (random effects) and parameter differences predicted by covariates (fixed effects). The PPV in model parameters was modelled by a proportional variance model. A proportional term characterized the residual unknown variability. The population mean parameters, between subject and residual variances, were estimated using the first-order conditional interaction estimate method using ADVAN1 TRANS2 of NONMEM V. Convergence criterion was determined up to three significant digits. A Compaq Digital Fortran Version 6.6A compiler with Intel Celeron 333 MHz CPU (Intel Corp., Santa Clara, CA, USA) under MS Windows XP (Microsoft Corp., Seattle, WA, USA) was used to compile NONMEM.

The PPV is modelled in terms of random effect (η) variables. Each of these variables is assumed to have mean 0 and a variance denoted by ω^2 , which is estimated. The covariance between the two elements of η , for example, CL and V are a measure of statistical association between these two variables. Their covariance is related to their correlation (R), for example,

$$R = \frac{\text{covariance}}{\sqrt{\omega_{\text{CL}}^2 \cdot \omega_{\text{V}}^2}}$$

The covariance of CL and distribution volume (V) variability was incorporated into the model.

Covariate analysis. The parameter values were standardized for a body weight of 70 kg using an allometric model.¹⁵

$$P_i = P_{\text{std}} \cdot \left(\frac{W_i}{W_{\text{std}}} \right)^{\text{PWR}}$$

where P_i is the parameter in the i th individual, W_i is the weight in the i th individual, and P_{std} is the parameter in an individual with a weight W_{std} of 70 kg. This standardization allows the comparison of neonatal parameter estimates with those reported for adults. The PWR exponent was 0.75 for CL, 0.25 for half-times, and 1 for V .¹⁵

Exploration of a relationship between CL and unconjugated bilirubin (unbili) was explored using a slope parameter ($\text{SLP}_{\text{unbili}}$).

$$F_{\text{bili}} = \exp(-\text{SLP}_{\text{unbili}})$$

Covariate analysis included a model investigating age-related changes in CL and V using linear function:¹⁵

$$V = V_{\text{std}} \cdot \frac{W}{70} \cdot (1 + \text{SLP}_V \cdot \text{PNA}) \text{ litre}$$

$$\text{CL} = \text{CL}_{\text{std}} \cdot \left(\frac{W}{70} \right)^{0.75} \cdot F_{\text{bili}} \cdot \exp[\text{SLP}_{\text{CL}} \cdot (\text{PMA} - 40)] \text{ litre h}^{-1}$$

where V_{std} and CL_{std} are the population estimates for V and CL, respectively, standardized to a 70 kg person using

allometric models; PMA (weeks) is the postmenstrual age; PNA (weeks) is postnatal age; SLP_V and SLP_{CL} are constants describing age-related changes in V and CL, referenced to 40 weeks PMA or birth (PNA=0).

The quality-of-fit of the pharmacokinetic model to the data was sought by NONMEM's objective function and by visual examination of plots of observed vs predicted concentrations. Bootstrap methods¹⁶ provided a method to evaluate parameter uncertainty. Models were nested and an improvement in the objective function was referred to the Chi-squared distribution to assess the significance [e.g. an objective function change (OBJ) of 3.84 is significant at $\alpha=0.05$].

Simulation. A simulation study was performed using NONMEM software to investigate the acetaminophen concentration variability after a standard dose of i.v. acetaminophen 15 mg kg^{-1} 6 hourly in neonates of 34–44 weeks PMA. The drug was infused over 20 min. Simulated neonates ($n=1000$) were aged 39.4 (SD 2.88) weeks PMA with a weight 2.99 (0.66) kg (range: 1.2–4.5 kg). Pharmacokinetic parameter estimates and their variability from this current study were used to predict the individual time–concentration profiles.

Simulation was also used to investigate the steady-state concentrations after repeat doses in a term neonate. Two dose regimens were explored (7.5 and 15 mg kg^{-1} given 6 hourly). Mean time–concentration profiles were performed using *Berkeley Madonna*TM modelling and analysis of dynamic systems software (R. Macey and G. Oster, University of California, Berkeley, CA, USA).

Results

There were 50 neonates enrolled into the study. Most received i.v. acetaminophen for postoperative pain for 1–9 days. Table 1 lists patient characteristics, the number of doses received and if the dose given was correct for patients' PMA, therapy duration and indication for i.v. acetaminophen, other parenteral therapies and the number of acetaminophen assays performed. There were 189 acetaminophen serum concentration observations available for pharmacokinetic analysis. The median (range) value obtained was 17 (<6–50) mg litre^{-1} taken a median of 3.5 h after the preceding dose, after a median (range) of 5 (2–17) prior doses. There were 147 concentrations (81%) above 10 mg litre^{-1} ; 17 (9%) were <6 mg litre^{-1} , which occurred in 13 neonates a median of 10.1 h after dose. These reflect trough values in the setting of a median (range) of 4 (2–17) prior doses.

Population parameter estimates are listed in Table 2. Individual concentration predictions are based on values of maximum *a posteriori* Bayesian estimates of the parameters using the *post hoc* option, whereas predicted typical (population) concentrations are based on population parameters and covariate information. The

Table 1 Neonatal patient characteristics, number of doses, duration and indication for i.v. acetaminophen therapy, other parenteral therapies, and number of serum acetaminophen assays. TOF, tracheoesophageal fistula repair; CDH, congenital diaphragmatic hernia repair; NEC, necrotising enterocolitis

Neonatal patient characteristics	
PMA (weeks), median, range	38.6, 31.7–45.0
Preterm neonates (<37 PMA weeks), <i>n</i> (%)	11 (22)
PNA (days), median (range)	5 (1–144)
Weight at inclusion (kg), mean (SD)	2.9, 0.7
Males, <i>n</i> (%)	33 (66)
Number of i.v. acetaminophen doses received per patient	
Mean (SD)	15 (5)
Range	5–26
Dosing: doses, <i>n</i> (%)	
Correct for PMA	562 (79)
High for PMA	95 (13)
Low for PMA	59 (8)
Patients who received correct dosing for all doses, <i>n</i> (%)	31 (62)
Total duration of i.v. acetaminophen therapy (days), median (range)	3.8, 1–8.8
Indication for i.v. acetaminophen	
Laparotomy	30
Thoracotomy [TOF (<i>n</i> = 11), CDH (<i>n</i> = 3), cystic lobectomy (<i>n</i> = 1)]	15
Other surgery (gastrostomy for TOF, cardiac, pyeloplasty)	3
Non-surgical: medical management (NEC, hydrops fetalis)	2
Analgesics co-received, <i>n</i> (%)	
No additional analgesics required	10 (20)
I.V. tramadol (14%) or morphine (16%) or both (28%)	29 (58)
I.V. morphine and midazolam (10%) or combined with tramadol (2%)	6 (12)
Extrapleural alone (4%) or combined with i.v. tramadol (4%)	4 (8)
Epidural, i.v. morphine	1 (2)
Sucrose received in addition to above	8 (16)
Requiring TPN <i>n</i> (%)	
At any time during study	47 (94)
Commenced before i.v. acetaminophen	12 (24)
Duration of TPN before i.v. acetaminophen (days), median (range)	2, 1–18
Commenced same day or day after commencing i.v. acetaminophen	35 (70)
Overall duration of TPN (days), median (range)	9, 3–82
Requiring i.v. antibiotics, <i>n</i> (%)	44 (88)
Double (30%) or triple (58%) agent	
Number of acetaminophen serum concentrations per patient, median (range)	4, 1–6

Table 2 Population pharmacokinetic parameter estimates standardized for a 70 kg person. PPV, population parameter variability expressed as the square root of its variance; SE, standard error of the estimate; 95% CI, 95% confidence intervals for the population parameter estimates

Parameter	Estimate	% PPV	% SE	95% CI
CL _{std} (litre h ⁻¹ 70 kg ⁻¹)	5.24	30.5	5.8	4.66–5.85
V _{std} (litre 70 kg ⁻¹)	76	29.6	7.2	65.7–87.4
SLP _{CL}	0.0308	—	38.6	0.0029–0.0544
SLP _{unbili}	0.00 375	—	12.0	0.0029–0.0048
Proportional error	0.184%	—	19.1	0.148–0.217

correlation between subject variability for CL and *V* was 0.39. CL increased with increasing PMA: from 4.4 litre h⁻¹ 70 kg⁻¹ at 34-week PMA to 6.3 litre h⁻¹ 70 kg⁻¹ at 46-week PMA (Fig. 1, Table 3). There was no relationship between *V* and PMA or PNA.

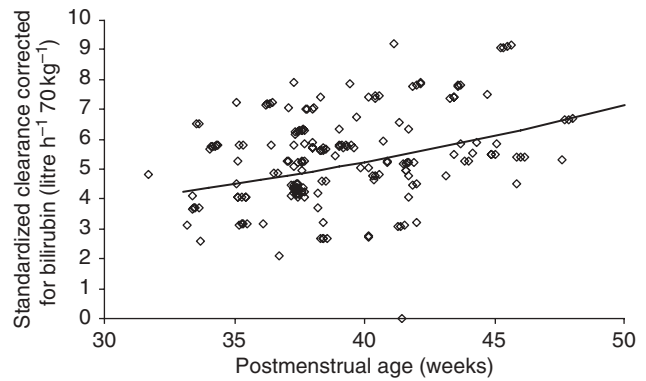


Fig 1 The relationship between PMA and individual Bayesian acetaminophen CL estimates.

Table 3 Maturation of CL with age

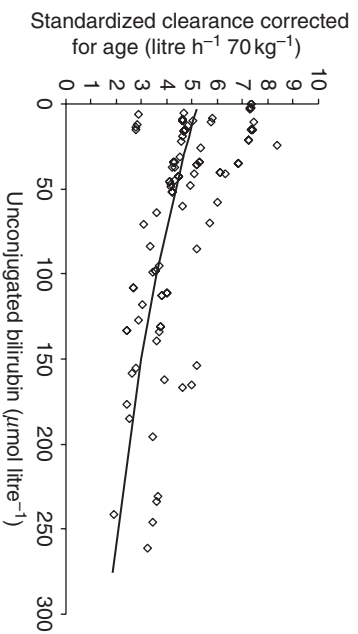
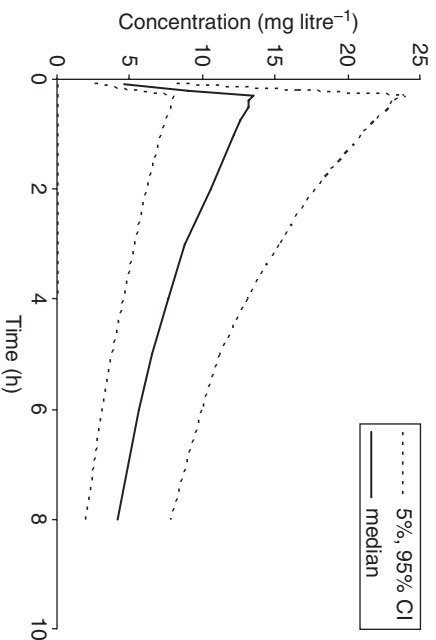
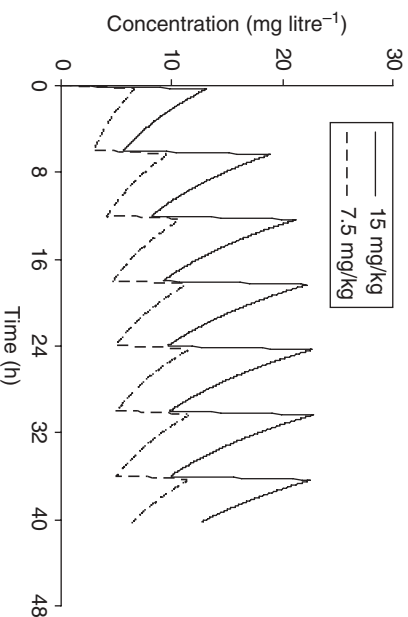
PMA (weeks)	Approximate weight (kg)	Allometric (litre h ⁻¹ 70 kg ⁻¹)	Absolute (litre h ⁻¹)	Per kilogram (litre h ⁻¹ kg ⁻¹)
34	2.4	4.35	0.35	0.145
36	2.8	4.63	0.41	0.148
40	3.3	5.24	0.53	0.161
44	4.2	5.93	0.72	0.171
46	4.6	6.30	0.82	0.177

There were 14 patients with pre-existing unconjugated hyperbilirubinaemia (Table 4). CL was reduced in the presence of unconjugated hyperbilirubinaemia; a concentration of 150 µmol litre⁻¹ was associated with 40% reduction in CL (Fig. 2). Figure 3 shows concentration variability after a standard dose of i.v. acetaminophen 15 mg kg⁻¹ 6 hourly in neonates of 34–44 weeks PMA. Figure 4 demonstrates the two predicted time–concentration profiles obtained with regular 6 h dosing of 7.5 and 15 mg kg⁻¹ for a 40-week PMA neonate. Steady-state concentrations are achieved after three doses with a trough concentration of 10 mg litre⁻¹ and a peak concentration of 23 mg litre⁻¹ after regular dosing with 15 mg kg⁻¹. The lower dose (7.5 mg kg⁻¹) achieved half of these concentrations.

Fifty patients had a mean of 4.6 LFTs performed (range: 2–8) with 231 available for an assessment, of which 84% were complete, 6% were partial panels, and 10% had only unconjugated and total bilirubin performed. At least one full panel was available for all 50 patients, while 30 patients (60%) had complete panels for all LFT assessments. For 23 patients, there was a baseline LFT set before commencement of i.v. acetaminophen and, for the remainder, the first set was taken on the day of the first acetaminophen assay. Table 4 lists the LFT findings and abnormal values for neonates according to PNA; the day-to-day changes in ALT, GGT, ALP, and unconjugated bilirubin for all patients are presented graphically in Figure 5. The lowess curve is below the normal values and flat (indicating no change for the majority) for ALT, GGT, and ALP for 48 h before through to 192 h after

Table 4 LFT findings for neonates ($n=50$) receiving i.v. acetaminophen. CDH, congenital diaphragmatic hernia

LFT findings and predominant abnormal values	<i>n</i>	TPN <i>n</i> (%)	Range of abnormal values	Other comment
Normal	14	13 (93)	—	These remained normal
Significant hypoproteinaemia	9	9 (100)	Albumin 15–20 g litre ⁻¹ Total protein 32–37 g litre ⁻¹	Present at time of i.v. acetaminophen commencement or developed during therapy
Hyperbilirubinaemia, unconjugated	14	13 (93)	58–195 µmol litre ⁻¹ (median 127)	Median PNA 3.5 (range 2–28) days
Hyperbilirubinaemia, conjugated	1	1 (100)	44–60 µmol litre ⁻¹	PNA 47 days: large intraventricular haemorrhage
Elevated GGT	5	5 (100)	280–652 U litre ⁻¹	One patient additionally had hyperbilirubinaemia (mixed). TPN started same day as i.v. acetaminophen or 1, 2, 6 and 18 days prior (2 had CDH, 3 had bowel tresspass)
Elevated ALP	3	3 (100)	361–722 U litre ⁻¹	One patient had isolated ALP elevation reflecting either metabolic bone disease or growth in a sick neonate.
Elevated ALT	4	3 (75)	86–174 U litre ⁻¹	Two patients had associated mild ALT elevation of 60–66 U litre ⁻¹ One persistent elevation, 2.3–2.6× with unconjugated hyperbilirubinaemia; 1 elevation 2.3× that normalized with mild unconjugated hyperbilirubinaemia; 1 mild elevation 1.6× with hypoproteinaemia; 1 isolated elevation 3.2× decreasing to 1.7×

**Fig 2** The relationship between unjugated bilirubin and CL. CL was reduced in the presence of unjugated bilirubin.**Fig 3** Median time-concentration profile for neonates 34–46 weeks PMA without hyperbilirubinaemia given a single dose 15 mg kg⁻¹. The 95% prediction interval is also shown.**Fig 4** Predicted time-concentration profiles in neonates at 40 weeks PMA with two regular 6 h dosing regimens of 7.5 and 15 mg kg⁻¹.

commencement of i.v. acetaminophen. Unjugated bilirubin decreased over that same time. There were four patients with elevated ALT; three received correct PMA based milligram per kilogram dosing, one initially received 15 mg kg⁻¹ corrected to 12.3 mg kg⁻¹ after two doses. They were all receiving i.v. antibiotics. One of

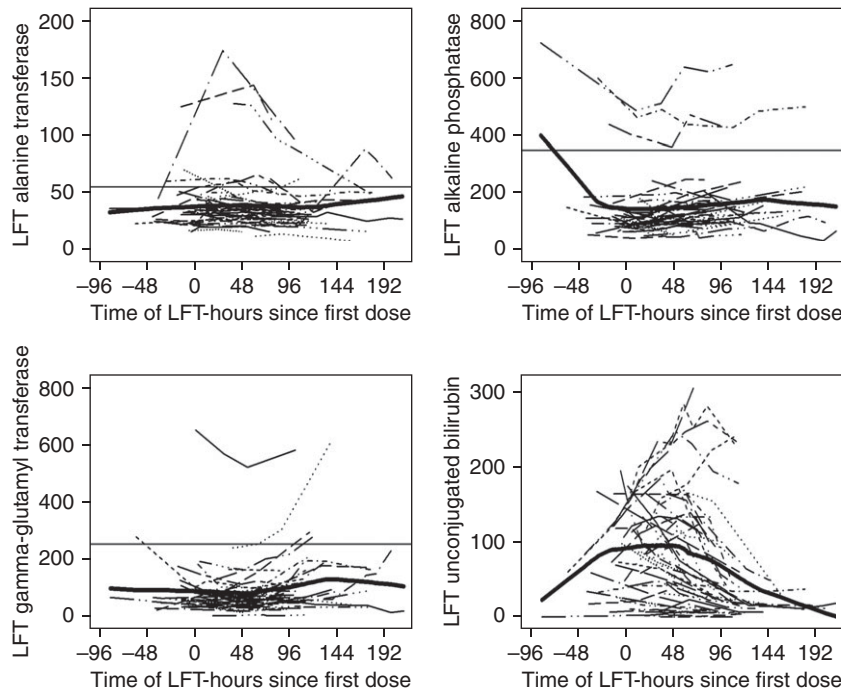


Fig 5 Graphs depicting changes in patients' LFTs in relation to the time of their first dose of i.v. acetaminophen. The thick line represents the 80% bandwidth lowestess curve fitted to each plot. Normal values for these LFTs (except unconjugated bilirubin) are indicated by the thin horizontal line.

these patients was a premature 2.2 kg neonate (PMA 35 weeks, PNA 11 days) with an unconjugated hyperbilirubinemia and a congenital diaphragmatic hernia whose baseline ALT was high and remained elevated (125, 144, 114 U litre⁻¹). Another near term 3.3 kg neonate (PNA 37 days) with imperforate anus and rectovaginal fistula had an elevated baseline ALT (128 U litre⁻¹) that decreased to normal. The third was a term 3.7 kg neonate (PNA 7 days) post-laparotomy for necrotizing enterocolitis whose ALT was mildly elevated (88 U litre⁻¹, after 7 days i.v. acetaminophen). The fourth 2 kg neonate (PMA 36.8 weeks, PNA 18 days) who required no TPN, had increased ALT from 45 U litre⁻¹ before operation to 174 U litre⁻¹ 2 days post-pyeloplasty for severe hydronephrosis (creatinine elevated at 0.04–0.05 mmol litre⁻¹) after his last of five i.v. acetaminophen doses; this decreased to 97 U litre⁻¹ on discharge 2 days later. This latter patient is the only one to satisfy the ALT criteria predefined to indicate possible hepatotoxicity, which occurred without any other LFT derangement in the context of resolving renal impairment.

Discussion

This is the first study to investigate pharmacokinetics after multiple doses of i.v. acetaminophen in term and preterm neonates, administered according to a PMA-adjusted dosing regimen. The estimate for CL (5.24 litre h⁻¹ 70 kg⁻¹) in this population of neonates is similar to that described for term neonates given enteral acetaminophen

(CL/Foral: 5.01 and 6.8 litre h⁻¹ 70 kg⁻¹)^{17 18} and to that reported in neonates given propacetamol (6.2 and 5.98 litre h⁻¹ 70 kg⁻¹).^{8 9} We were able to demonstrate CL maturation with PMA. There were only 11 premature neonates in this current analysis, but population CL estimates are similar to those reported for propacetamol.⁸ The volume of distribution decreases with PNA,^{8 17 18} but we were unable to reveal this trend in this current neonatal cohort. Dosing regimens for i.v. acetaminophen^{5 10} are based on the CL estimates from propacetamol data, and it is reassuring to note similar estimates for the i.v. acetaminophen formulation.

Measurement of unconjugated bilirubin concentration is a crude measure of hepatic conjugating ability. Both bilirubin and acetaminophen are cleared by glucuronosyltransferase; bilirubin by UGT1A1 and acetaminophen by UGT1A6. Acetaminophen is metabolized in neonates by both sulphate and glucuronide conjugation. Glucuronide:sulphate ratios range from 0.12 in premature neonates of 28–32 weeks post-conception,¹⁹ 0.28 in those at 32–36 weeks post-conception,¹⁹ and 0.34 in term neonates of 0–2 days old.²⁰ Bilirubin is also conjugated with glucuronide and increased unconjugated bilirubin may reflect immaturity of this process. Alternatively, increased unconjugated bilirubin may reflect increased bilirubin production. Increased unconjugated bilirubin concentration is a late sign of reduced CL; CL will be reduced before this marker is elevated, in the first few days of life (Fig. 5). CL is related more closely to PMA than PNA,¹⁵ rendering PNA a poor marker of conjugating ability. We therefore suggest that the dosing

recommendations not be exceeded in the first few days of life and that acetaminophen dose be reduced in the presence of unconjugated hyperbilirubinaemia.

Observed serum acetaminophen concentrations after multi-dosing in this patient population are generally above the target serum concentration of 10 mg litre⁻¹ after a median of three doses. Simulation (Fig. 4) demonstrates that mean concentrations above 10 mg litre⁻¹ are achieved in term neonates after 15 mg kg⁻¹ 6-hourly, but not after the lower dose of 7.5 mg kg⁻¹. In Europe, a loading dose of 20 mg kg⁻¹, independent of PMA, is recommended.^{5–10} This will achieve a higher initial peak serum concentration and earlier steady state with continued dosing, but the target concentration for analgesia is not established for neonates and the efficacy of this practice has not yet been assessed. A concentration–analgesic response relationship has only been described for tonsillectomy pain in children.¹³ The pain insults suffered by neonates in a NNU are different from tonsillectomy, and neuronal pathways transmitting or modulating pain are developing in neonates.²¹

Repeat administration of what was considered routine doses (75–90 mg kg⁻¹ day⁻¹) of acetaminophen can cause hepatotoxicity in children²² through production of highly reactive electrophilic arylating metabolites [e.g. *N*-acetyl-*p*-benzoquinone-imine (NAPQI)] by the hepatic cytochrome P-450-dependent mixed function oxidase enzyme system. Hepatotoxicity is dependent on the balance between the rate of NAPQI formation, the capacity of the safe elimination pathways of sulphate and glucuronide production, and the initial content and maximal rate of synthesis of hepatic glutathione. The balance of these factors in term and preterm neonates remains unknown. Neonates have been reported to have high serum acetaminophen concentrations after intentional maternal overdose prepartum.^{23–24} Delivered at 29 and 36 weeks gestational age, these neonates were managed with exchange transfusion postpartum and suffered no clinical hepatotoxicity. Recently, a case of neonatal hepatotoxicity has been reported in an ex-term (41 week) neonate who presented encephalopathic at PNA 5 days after 3 days of oral acetaminophen dosing—initially 156 mg kg⁻¹ day⁻¹ and then 78 mg kg⁻¹ day⁻¹. The patient had an unconjugated bilirubin at the high end of the normal range at 130 µmol litre⁻¹ with an elevated conjugated bilirubin of 25 µmol litre⁻¹ with a marked liver derangement on admission and recovered fully after receiving *N*-acetyl cysteine for more than 7 days.²⁵ Acetaminophen concentrations associated with increased NAPQI are not reported in neonates and the activity of CYP2E1, the major enzyme producing NAPQI, is unquantified, but thought to be reduced.²⁶ Consequently, it is currently difficult to predict ‘safe’ doses in this subpopulation.

There is no simple test to assess for potential hepatotoxicity. Kozer and colleagues²⁷ have demonstrated that ill children receiving repeated large doses of acetaminophen (>90 mg kg⁻¹ day⁻¹) may show abnormalities in liver function. Previous adult studies have shown that ALT

changes during long-term (1–12 month) chronic dosing for osteoarthritis are mild and resolve,²⁸ while recently ALT elevations (>3× normal) were documented more commonly in volunteers after 1 week of treatment with acetaminophen with or without opioids, while all placebo receivers had normal ALTs or ALTs remaining below 1–3 times normal.²⁹ Liver function was monitored in this neonatal cohort also by measuring ALT enzyme changes; all patients were nil by mouth, the majority co-receiving TPN. The one patient whose ALT rose significantly to three times normal (as seen in healthy adults) had renal impairment. This neonate also had low birth weight and was fasting perioperatively without TPN supplementation. His bilirubin was normal and his acetaminophen CL was within the neonatal range. His ALT rose in isolation and no conclusions can be drawn about the contribution of acetaminophen or coexisting pathology to the ALT changes seen.

I.V. acetaminophen is an attractive analgesic for neonatal use in the postoperative period and for those with restricted oral intake. It offers an alternative or supplement to opioid analgesia in term or preterm patients in whom the reduction of opioid associated side effects is frequently desirable. This study affirms serum concentrations after a PMA-based dosing regimen, which will continue to be used in our NNU. Serum unconjugated bilirubin concentration serves as a marker of reduced CL.

Funding

Dr Palmer received a Murdoch Children’s Research Institute grant for the cost of i.v. acetaminophen assays.

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