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Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children

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Background. Descriptions of the pharmacokinetics and metabolism of morphine and its metabolites in young children are scant. Previous studies have not differentiated the effects of size from those related to age during infancy.

Methods. Postoperative children 0–3 yr old were given an intravenous loading dose of morphine hydrochloride (100 μg kg^{-1} in 2 min) followed by either an intravenous morphine infusion of 10 μg h^{-1} kg^{-1} (n=92) or 3-hourly intravenous morphine boluses of 30 μg kg^{-1} (n=92). Additional morphine (5 μg kg^{-1}) every 10 min was given if the visual analogue (VAS, 0–10) pain score was ⩾4. Arterial blood (1.4 ml) was sampled within 5 min of the loading dose and at 6, 12 and 24 h for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). The disposition of morphine and formation clearances of morphine base to its glucuronide metabolites and their elimination clearances were estimated using non-linear mixed effects models.

Results. The analysis used 1856 concentration observations from 184 subjects. Population parameter estimates and their variability (%) for a one-compartment, first-order elimination model were as follows: volume of distribution 136 (59.3) litres, formation clearance to M3G 64.3 (58.8) litres h^{-1}, formation clearance to M6G 3.63 (82.2) litres h^{-1}, morphine clearance by other routes 3.12 litres h^{-1} per 70 kg, elimination clearance of M3G 17.4 (43.0) litres h^{-1}, elimination clearance of M6G 5.8 (73.8) litres h^{-1}. All parameters are standardized to a 70 kg person using allometric 3/4 power models and reflect fully mature adult values. The volume of distribution increased exponentially with a maturation half-life of 26 days from 83 litres per 70 kg at birth; formation clearance to M3G and M6G increased with a maturation half-life of 88.3 days from 10.8 and 0.61 litres h^{-1} per 70 kg respectively at birth. Metabolite formation decreased with increased serum bilirubin concentration. Metabolite clearance increased with age (maturation half-life 129 days), and appeared to be similar to that described for glomerular filtration rate maturation in infants.

Conclusion. M3G is the predominant metabolite of morphine in young children and total body morphine clearance is 80% that of adult values by 6 months. A mean steady-state serum concentration of 10 ng ml^{-1} can be achieved in children after non-cardiac surgery in an intensive care unit with a morphine hydrochloride infusion of 5 μg h^{-1} kg^{-1} at birth (term neonates), 8.5 μg h^{-1} kg^{-1} at 1 month, 13.5 μg h^{-1} kg^{-1} at 3 months and 18 μg h^{-1} kg^{-1} at 1 year and 16 μg h^{-1} kg^{-1} for 1- to 3-yr-old children.

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Morphine is largely metabolized by uridine 5′-diphosphate glucuronosyltransferase UGT2B7 to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).[1] *In vitro* studies using liver microsomes from fetuses aged 15–27 weeks indicated that morphine glucuronidation was approximately 10–20% of that seen with adult microsomes.[2 3] Morphine glucuronidation has been demonstrated in premature infants as young as 24 weeks. Morphine clearance is reported as 23.6 (SD 8.5) ml min^{-1} kg^{-1} in infants and children greater than 11 days old.[4] Lynn and colleagues[5] report clearances greater on a per kg basis than those of adults at 3 months of age. In a systematic review of morphine metabolism, it was concluded that children older than 1 month metabolize morphine like adults.[6] The use of the per kilogram size model (ml min^{-1} kg^{-1}) has confused interpretation of morphine developmental pharmacokinetics; underestimation occurs as size decreases.[7] Anderson and colleagues[8] revised published clearance estimates from different age groups using a $\frac{3}{4}$ power allometric size model to demonstrate that adult values for clearance are reached at about 6 months.

We had the opportunity to examine morphine and metabolite serum concentrations in children 0–3 yr old given either intermittent boluses or morphine infusion.[9 10] These data have previously been analysed using multiple regression to investigate the effect of clinical variables, such as gestational age, sex, weight, the therapeutic regimens used and mechanical ventilation, on morphine requirements and plasma concentrations.[10] That analysis revealed that age was the most important factor affecting morphine requirements and plasma morphine concentrations. Significantly fewer neonates required additional morphine doses compared with all other age groups and neonates had significantly higher plasma concentrations of morphine.[10]

This study analysis further investigated and quantified the effect of age using a population-based approach that included size as the primary covariate in an effort to disentangle age-related factors from size-related factors. Age-related morphine metabolite pharmacokinetics in children have not been quantified previously.

Methods

The study was approved by the hospital medical ethics committee and written consent obtained from parents. The methods have been described in an earlier publication.[10] Children aged 0–3 yr, admitted to the paediatric surgical intensive care unit after non-cardiac thoracic and abdominal surgery, were considered for enrolment. Patients were excluded if they had received morphine within 6 h before surgery, or if they suffered from hepatic, renal or neurological disorders. Fentanyl, rather than morphine, was used in incremental doses intraoperatively: 5 μg kg^{-1} was given before orotracheal intubation, 5 μg kg^{-1} before surgical incision and additional doses of 2 μg kg^{-1} when HR and/or MAP were 15% above baseline values. The median amount of fentanyl used during surgery was 5.3 (25th–75th centile, 3.8–6.9) μg kg^{-1}. Patients were randomly assigned to receive either intravenous morphine hydrochloride infusion or intermittent morphine hydrochloride boluses. The pharmacists randomized and prepared all study drugs. Clinical staff were blinded to the study group allocation.

At the end of surgery, mechanical ventilation was continued in patients who required ventilator assistance after surgery. Directly after surgery, all patients were given an intravenous loading dose of morphine hydrochloride (100 μg kg^{-1} over 2 min), followed by either an infusion of 10 μg h^{-1} kg^{-1} combined with 3-hourly intravenous placebo (saline) boluses over 2 min or a continuous placebo infusion (saline) combined with 3-hourly intravenous morphine hydrochloride boluses of 30 μg kg^{-1}. Additional morphine (5 μg kg^{-1} every 10 min) was given if the visual analogue scale (VAS, 0–10) pain scores were ⩾4. No other analgesic or sedative drugs were used.

Arterial blood samples (1.4 ml) were taken after induction of anaesthesia (baseline), at the end of surgery, and 6, 12 and 24 h after surgery to determine serum concentrations of morphine, M3G and M6G.

Pain was assessed 3-hourly by nurses trained in the use of the behavioural part of the COMFORT score[11] and VAS (0–10). The VAS score was measured after the 2 min of observation needed for the COMFORT score.[11–14] Nursing interventions included pain assessment, blood sampling and administration of intermittent bolus (placebo or morphine) medication.

Morphine and metabolite assay

Serum aliquots (0.6 ml) were extracted with the Baker-10 extraction system (Baker Chemicals, Deventer, The Netherlands) fitted with 1-ml disposable cyclohexyl cartridges (C6H6, Baker, catalogue no. 7212-01). The extraction column was conditioned with two column volumes of methanol, two column volumes of water and 1 ml of 500 mM diammonium sulphate (pH=9.3). The serum (0.6 ml) was diluted with 0.6 ml 500 mM diammonium sulphate (pH=9.3) and washed with 2 ml of 50 mM diammonium sulphate (pH=9.3) after which it was allowed to dry for 15 s. The elution was carried out with 0.5 ml 0.01 M KH_2PO_4 buffer, pH=2.1, containing 11% acetonitrile. From this eluate, 50 μl was injected on the analytical column. The HPLC system comprised a Spectroflow 400 solvent delivery system (Kratos, Rotterdam, The Netherlands) equipped with a degasser (Separations, HI-Ambacht, The Netherlands), a Marathon auto sampler (Separations), a Spectroflow 773 UV detector at λ=210 nm (Separations), in sequence with an electrochemical detector (Interscience, Breda, The Netherlands) equipped with an analytical cell (Model 5010). All compounds leave the UV detector chemically intact, and so the electrochemically active components can be oxidized in the electrochemical cell. This type of electrochemical cell contains two separate analytical cells,

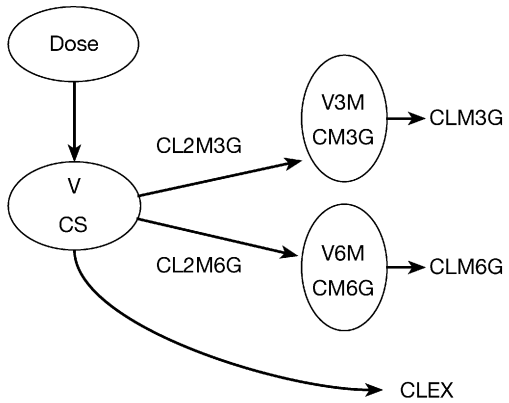

Fig 1 Pharmacokinetic model. V is the volume of distribution for morphine, CS is morphine serum concentration, CL2M3G is the formation clearance to M3G, CM3G is the serum M3G concentration, CL2M6G is the formation clearance to M6G, CM6G is the serum M6G concentration, CLM3G is the elimination clearance of M3G, CLM6G is the elimination clearance of M6G, VM is the volume of distribution of glucuronide metabolites, CLEX is unaccounted clearance, and Dose is the dose given.

which makes it possible to create a small window of applied potential. The detector 2 potential was set at 0.4 V, while the detector 1 potential was 0.3 V. This minimizes interfering peaks because only compounds with an oxidation potential from 0.3 to 0.4 V are recorded. Chromatographic separations were achieved using a Cp-Sper C8 column (250×4.6 mm) (Chrompack, Bergen op Zoom, The Netherlands). The mobile phase was a 0.01 M KH_2PO_4 buffer, pH=2.1, containing 11% acetonitrile and heptane sulphonic acid 0.4 g litre^{-1}.

In serum, all calibration graphs (containing six data points) were linear: for M3G the concentrations ranged from 25 to 580 ng ml^{-1} (r=0.9992); for M6G from 5 to 100 ng ml^{-1} (r=0.9982) and for morphine, from 5 to 90 ng ml^{-1} (r=0.9963). On average, the quantitation limit was 5 ng ml^{-1} for morphine and M6G and 25 ng ml^{-1} for M3G. However, in individual samples the quality of the chromatogram was inspected and allowed for a lower threshold when peaks were clearly separated from baseline. In this concentration range, the intra-day precision was less than 10% for all compounds and the bias was about 5%.[15 16] Standardized automated laboratory analysers measured serum concentrations of bilirubin and creatinine.

Morphine hydrochloride dose and M3G and M6G concentrations were converted to anhydrous morphine base equivalents using a molecular weight of 285 for morphine, 322 for morphine hydrochloride and 461 for the two glucuronide metabolites.

Modelling

Population parameter estimates were obtained using a nonlinear mixed effects model. This model accounts for random between-subject parameter variability and residual variability (random effects) as well as between-subject parameter differences predicted by covariates (fixed effects). The population parameter variability in model parameters was modelled by an exponential variance model. The covariance between clearance, distribution volume and absorption half-life was incorporated into the model. A proportional term characterized the residual unknown variability for morphine. An additive and a proportional term characterized the residual unknown variability for M3G and M6G concentrations. The population mean parameters, between-subject variance and residual variances were estimated using NONMEM version V release 1.1.[17] Estimation used the first-order conditional estimate method with the interaction option and ADVAN 6 with Tol=5. The convergence criterion was 3 significant digits. A Compaq Digital Fortran Version 6.6A compiler with Intel Celeron 333 MHz CPU (Intel, Santa Clara, CA, USA) under Microsoft Windows XP (Microsoft, Seattle, WA, USA) was used to compile NONMEM.

Differential equations were used to describe the pharmacokinetics of morphine and its metabolites.

$$CLT=CL2M3G+CL2M6G+CLEX$$

$$dCS/dt=(RATEIN–CS\times CLT)/V$$

$$dM3G/dt=(CL2M3G\times CS–CLM3G\times CM3G)/V3M$$

$$dM6G/dt=(CL2M6G\times CS–CLM6G\times CM6G)/V6M$$

The model is shown in Figure 1. CLT is total morphine clearance, V is the volume of distribution for morphine, CS is morphine serum concentration, CL2M3G is formation clearance to M3G, CM3G is the serum M3G concentration, CL2M6G is formation clearance to M6G, CM6G is the serum M6G concentration, CLM3G is the elimination clearance of M3G, CLM6G is the elimination clearance of M6G, VM is the volume of distribution of glucuronide metabolites, CLEX is morphine clearance by other routes, and RATEIN is the morphine infusion rate.

The metabolite volumes of distribution (V3M, V6M) cannot be identified with the present study design and were fixed at 23 and 30 litres per 70 kg, based on previous studies in adults.[18 19]

The parameter values were standardized for a body weight of 70 kg using an allometric model:[7 20]

$$P_i=P_{std}\times(W_i/W_{std})^{PWR}$$

where P_i is the parameter in the ith individual, W_i is the weight in the ith individual and P_{std} is the parameter in an individual with a weight (W_{std}) of 70 kg. The PWR exponent was 0.75 for clearance and 1 for distribution volumes.[20–23]

Exponential functions were applied to describe age-related developmental changes in the formation of metabolites (CL2M3G, CL2M6G), clearance of metabolites (CLM3G, CLM6G) and morphine volume of distribution (Table 3B):

Table 1A Pharmacokinetic parameter estimates. These estimates are standardized to a 70-kg person using an allometric size model. The metabolite volumes of distribution (V3M, V6M) cannot be identified with the current study design and were fixed at 23 and 30 litres per 70 kg, based on studies by Penson and colleagues[18] and Hanna and colleagues[19] in adults. CV=coefficient of variation for the population parameter estimate; SE=standard error of the estimate; CLT=population estimate for total morphine CL (litres h^{-1} per 70 kg); V=volume of distribution for morphine (litres per 70 kg); CL2M3G=formation clearance to M3G (litres h^{-1} per 70 kg); CL2M6G=formation clearance to M6G (litres h^{-1} per 70 kg); CLM3G=clearance of M3G (litres h^{-1} per 70 kg); CLM6G=clearance of M6G (litres h^{-1} per 70 kg); CLEX=unaccounted clearance; Err=residual error

Parameter	Estimate	CV (%)	SE (%)
CLT	71.1	–	
C2LM3G	64.3	58.8	18.0
CL2M6G	3.63	82.2	14.0
CLM3G	17.4	43.0	16.0
CLM6G	5.8	73.8	20.2
CLEX	3.12	117.0	133.7
V	136	59.3	11.0
V3M	23 fixed	–	–
V6M	30 fixed	–	–
Err morphine (proportional)	0.36		11.6
Err M3G (additive) (ng ml^{-1})	7.09		36.2
Err M3G (proportional)	0.34		27.0
Err M6G (additive) (ng ml^{-1})	0.45		26.0
Err M6G (proportional)	0.30		16.9

Table 1B Covariate models and estimates for pooled population parameters.

Volume of distribution (litres):

$V=[V_{std}\times(Wt/70)]\times\{1+\beta vol\times EXP[-PNA\text{ in days}\times Ln(2)/Tvol]\}$

βvol is a parameter estimating the fraction below V at birth; Tcl describes the maturation half-life of the age-related change for V; PNA is postnatal age.

Formation clearance (litres h^{-1}):

$CL2M3G=[CL2M3G_{std}\times(Wt/70)^{0.75}]\times\{1-\beta cl\times EXP[-PNA\text{ in days}\times Ln(2)/Tcl]\}$

$CL2M6G=[CL2M6G_{std}\times(Wt/70)^{0.75}]\times\{1-\beta cl\times EXP[-PNA\text{ in days}\times Ln(2)/Tcl]\}$

βcl is a parameter estimating the fraction below CL2M3G and CL2M6G at birth; Tcl describes the maturation half-life of the age-related change for CL2M3G and CL2M6G.

Metabolite clearance (litres h^{-1}):

$CLM3G=[CLM3G_{std}\times(Wt/70)^{0.75}]\times\{1-\beta rf\times EXP[-PNA\text{ in days}\times Ln(2)/Trf]\}$

$CLM6G=[CLM6G_{std}\times(Wt/70)^{0.75}]\times\{1-\beta rf\times EXP[-PNA\text{ in days}\times Ln(2)/Trf]\}$

βrf estimates the fraction below CLM3G and CLM6G and birth; Trf describes the maturation half-life of the age-related change for CLM3G and CLM6G.

Creatinine clearance[44] in children older than 1 week: creatinine clearance was standardized to a 40 year old person and centred about 85.947 μmol $litre^{-1}$. This empirical model used age (PNA) as a covariate to predict creatinine production rate with scaling constant (Kage); e.g.

$CLM3G=CLM3G_{std}\times(Wt/70)^{0.75}\times 85.947/creatinine\times EXP(Kage\times PNA/365-40)$

Relationship of bilirubin to CLM3G and CLM6G:

$CLM3G=CLM3G_{std}\times(Wt/70)^{0.75}\times EXP(bilirubin\times Kbili)$

Kbili is a scaling factor

Parameter	Estimate	SE (%)
βvol	0.391	28.4
Tvol (days)	26.3	72.2
βcl	0.834	6.4
Tcl (days)	88.3	37.4
βrf	0.832	9.7
Trf (days)	129	49.8
Kage	0.0141	139.7
Kbili	–0.00203	33.2

$$FCL2MxG=\{1-\beta cl\times EXP[-PNA\text{ in days}\times Ln(2)/Tcl]\}$$

$$FCLMxG=\{1-\beta rf\times EXP[-PNA\text{ in days}\times Ln(2)/Trf]\}$$

$$FV=\{1-\beta vol\times EXP[-PNA\text{ in days}\times Ln(2)/Tvol]\}$$

where βcl, βrf and βvol are parameters estimating the fraction below 'adult' values of parameters predicted at birth; Tcl, Trf and Tvol describe the maturation half-lives of the age-related changes in the parameters. FCL2MxG, FCLMxG represent the formation and elimination clearances of either M3G or M6G and FV morphine volume as a fraction of standard 70 kg adult values, i.e. when AGE is sufficiently large that the exponential expression tends to zero.

The effect of altered renal function on CLM3G and CLM6G was modelled using an estimate of renal function in children older than 1 week. Renal function was standardized to a 40-yr-old adult male with a creatinine clearance of 6 litres h^{-1} and a serum creatinine of 85.947 μmol $litre^{-1}$.[24] This empirical model used age (PNA) as a covariate to predict creatinine production rate with scaling constant (Kage) for age:

$$FRF=85.947/creatinine\times EXP(Kage\times PNA/365-40).$$

Serum bilirubin (μmol $litre^{-1}$) was used as a marker of hepatic function and its effect on CL2M3G and CL2M6G was modelled with an exponential function with a scaling constant (Kbili):

$$FBILI=EXP(bilirubin\times Kbili).$$

The clearance in a child with specific age, serum creatinine and bilirubin was then predicted by multiplying each of the covariate factors by the population parameter value for a standard 70 kg adult.

$$CL2M3G=CL2M3G_{std}\times FCL2M3G\times FBILI$$

$$CLM3G=CLM3G_{std}\times FCLM3G\times FRF.$$

The quality of fit of the pharmacokinetic model to the data was assessed by visual examination of plots of observed versus predicted concentrations. Models were nested and an improvement in the objective function was

Table 2 Covariance of pharmacokinetic parameters, expressed as the correlation of population parameter variability

	CL2M3G	CL2M6G	CLM3G	CLM6G	V
CL2M3G	1				
CL2M6G	0.255	1			
CLM3G	0.29	–0.19	1		
CLM6G	–0.17	0.76	0.066	1	
V	0.557	–0.02	0.342	–0.227	1

Table 3A Morphine and metabolite parameter estimate changes with age from the present study

Age (days)	V (litres per 70 kg	CL2M6G (litres h^{-1} per 70 kg)	CL2M3G (litres h^{-1} per 70 kg)	CLM3G (litres h^{-1} per 70 kg)	CLM6G (litres h^{-1} per 70 kg)	CLEX (litres h^{-1} per 70 kg)	CLT base (litres h^{-1} per 70 kg)
0	84	0.61	10.8	3.0	0.98	3.12	14.5
7	92	0.76	13.5	3.5	1.2	3.12	17.4
30	112	1.34	22.0	5.1	1.7	3.12	26.3
90	131	2.14	37.8	8.5	2.8	3.12	43.1
180	136	2.9	51.3	11.9	4.0	3.12	57.3
365	136	3.5	61.2	15.4	5.1	3.12	67.8
1000	136	3.63	64.3	17.3	5.8	3.12	71.1

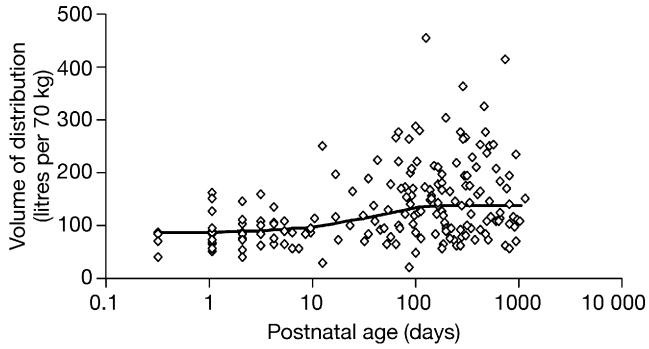

Fig 2 Volume of distribution change with postnatal age. Individual predicted volumes, standardized to a 70-kg person, from the NONMEM *post hoc* step, are plotted against age. The solid line represents the non-linear relation between volume of distribution and age.

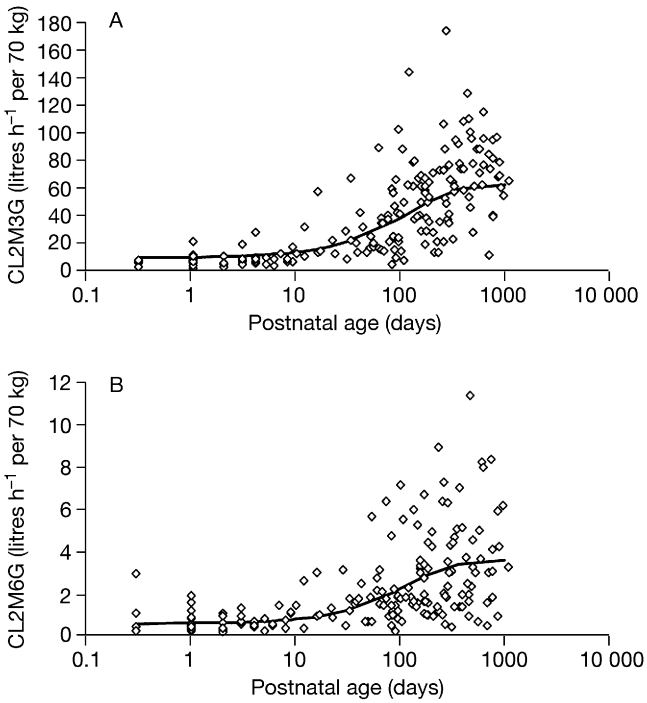

Fig 3 (A) Individual predicted formation clearances to M3G, standardized to a 70-kg person, from the NONMEM *post hoc* step, are plotted against age. The solid line represents the non-linear relation between clearance and age. (B) Individual predicted formation clearances to M6G, standardized to a 70-kg person, from the NONMEM *post hoc* step, are plotted against age.

referred to the Chi-squared distribution to assess significance; e.g. an objective function change (OBJ) of 3.84 is significant at α=0.05.

Results

The analysis used 1856 concentration observations from 184 subjects. The numbers of children given intermittent bolus and those given morphine infusion were the same (n=92). There were 106 boys and 78 girls. Mean (range) age and weight of the patients were 195 (0–1070) days and 5.9 (1.9–16.8) kg. Parameter estimates, standardized to a 70-kg, 40-yr-old person, are shown in Table 1A. Covariate analysis estimates are shown in Table 1B. The covariance of the pharmacokinetic parameters, expressed as the correlation of population parameter variability, was low (Table 2). Table 3A shows metabolite formation and elimination clearance estimate changes with age.

The volume of distribution of morphine increased exponentially with a maturation half-life of 26.3 days from 83 litres per 70 kg at birth to an adult value of 136 litres per 70 kg (Fig. 2); formation clearance to M3G (Fig. 3A) and M6G (Fig. 3B) increased with a maturation half-life of 88.3 days from 10.8 and 0.61 litres h^{-1} per 70 kg at birth to predicted values of 64.3 and 3.63 litres h^{-1} per 70 kg in adults respectively. At 6 months formation clearances were 80% of those predicted in adults. Formation maturation rates for both metabolites were the same. The objective function was not improved by using individual formation maturation parameters for each metabolite. Metabolite formation clearances decreased with increasing serum bilirubin concentration (Fig. 4).

Metabolite elimination clearance of M3G and M6G increased with a maturation half-life of 129 days from 3 and 0.98 litres h^{-1} per 70 kg at birth to predicted values of 17.3 and 5.8 litres h^{-1} per 70 kg in adults respectively (Fig. 5A and B). This maturation curve is similar to that described for the maturation of glomerular filtration rate in infants.[25] The effect of altered renal function (creatinine clearance) on

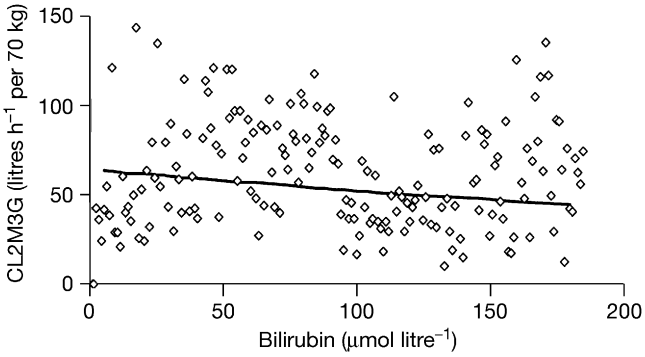

Fig 4 Individual *a posteriori* Bayesian estimates for CL2M3G corrected for size and age plotted against serum bilirubin. Formation clearance decreases as serum bilirubin increases.

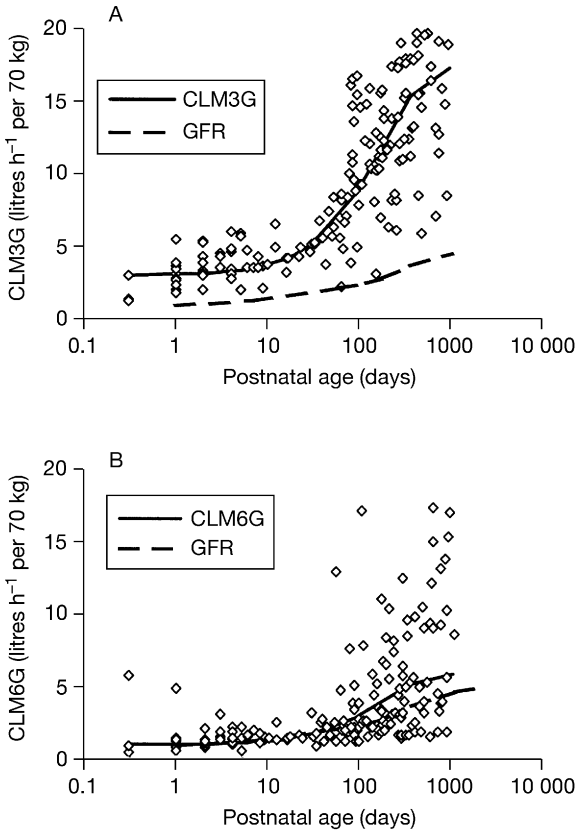

Fig 5 Individual *a posteriori* Bayesian estimates of CLM3G (A) are plotted against postnatal age. The dashed line represents the maturation of glomerular filtration rate (GFR; ml min^{-1} per 1.73 m^2), scaled to overlie CLM3G maturation (data from Bergstein).[25] (B) Individual *a posteriori* Bayesian estimates of CLM6G are plotted against postnatal age.

M3G elimination clearance unaccounted for by maturation is shown in Figure 6. This effect appears minimal.

Figure 7A–C demonstrates the quality of fit for pharmacokinetic data over the study time. The individual Bayesian predictions for serum concentration of morphine, M3G and M6G are compared with those observed. These predictions are based on maximum *a posteriori* Bayesian estimates of the parameters for each specific individual using their observed data. The fit is poorest for the prediction of serum metabolite concentration after the initial loading dose of morphine.

Total morphine clearance predictions (CLT) can be used to calculate morphine hydrochloride infusion rates required attaining steady-state serum concentration. Infusion rate is a product of clearance and desired concentration. A mean steady-state serum concentration of 10 ng ml^{-1} can be achieved in children after non-cardiac surgery in an intensive care unit with a morphine hydrochloride infusion of 5 μg h^{-1} kg^{-1} at birth (term neonates, 3.3 kg), 8.5 μg h^{-1} kg^{-1} at 1 month (4 kg), 13.5 μg h^{-1} kg^{-1} at 3 months (6 kg), 18 μg h^{-1} kg^{-1} at 1 yr (10 kg) and 16 μg h^{-1} kg^{-1} for 1- to 3-yr-old children (12–18 kg).

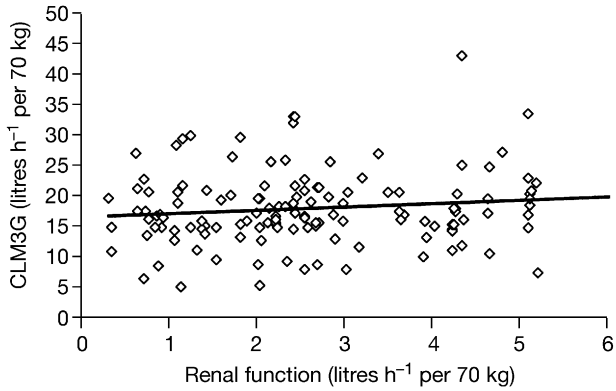

Fig 6 The relationship of creatinine clearance to metabolite elimination clearance of M3G, corrected for size and age. Changes in creatinine clearance are accounted for by maturation of M3G clearance.

Discussion

Size has considerable impact on the estimation and interpretation of pharmacokinetic parameters in children[7 8 26] and has been unaccounted for in paediatric morphine pharmacokinetic studies.[5 27–32] The impact of size is demonstrated in Table 3B and C, where reported clearance estimates, standardized to a 70-kg person with an allometric $\frac{3}{4}$ power model, show that clearance is similar to adults within 6–12 months. Size was the primary covariate used in our analysis of the effects of age and weight. This deliberate choice was based on known biological principles. A great many physiological, structural and time-related variables scale predictably within and between species with weight exponents of 0.75, 1 and 0.25 respectively.[21] We used these $\frac{1}{4}$ power models in this study rather than centred weight or some other function of weight, because the $\frac{1}{4}$ power models have sound biological principles. West and colleagues[22 23] have used fractal geometry to explain this phenomenon mathematically. The $\frac{3}{4}$ power law for metabolic rates was

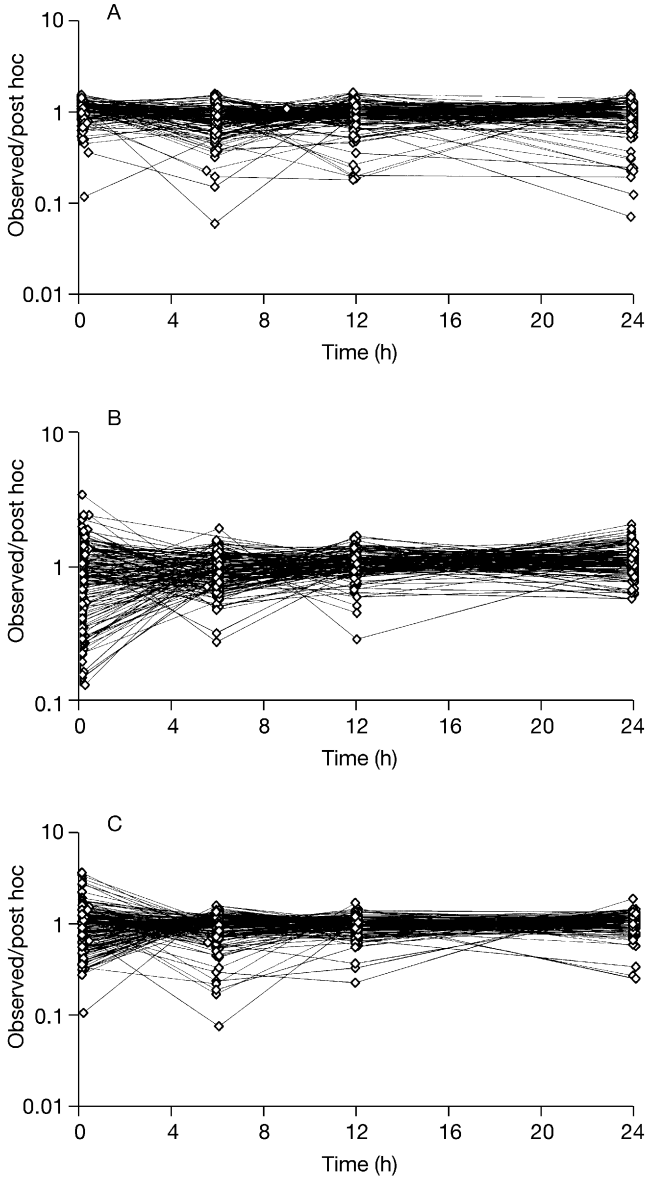

Fig 7 Quality of fit for pharmacokinetic data over the study time period. A line connects each subject's data. The individual *a posteriori* Bayesian predictions for serum concentration of morphine (A), M3G (B) and M6G (C) are compared with those observed. These predictions are based on maximum *a posteriori* Bayesian estimates of the parameters for each specific individual using their observed data.

derived from a general model that describes how essential materials are transported through space-filled fractal networks of branching tubes.[22 23] These design principles are independent of detailed dynamics and explicit models and should apply to virtually all organisms. By choosing weight as the primary covariate, the secondary effects of age could be investigated. We had no prior biological model for the effect of age on clearance or apparent volume, but assumed first order processes, which are common in biology.

The total body clearance (CLT) was 80% of that of adults by 6 months and 96% of that predicted in adults by 1 yr. Morphine HCl CLT and its rate of maturation fall between those described by McRorie and colleagues[32] and those described by others,[30 33] when their estimates are standardized to a 70-kg person with a $\frac{3}{4}$ power model (Table 3C). Our estimates are for the anhydrous morphine base rather than sulphate or hydrochloride salts and were determined using a population-based analysis. Differences may also be related to the population studied and the nature of the illness within that population.[5] McRorie and colleagues[32] and Lynn and colleagues[30] determined clearance by dividing infusion rate by steady-state concentration. Patients who did not achieve steady-state concentrations were excluded and it is unclear from their papers if the morphine salt used in the infusion and measured concentrations of morphine were corrected for molecular weight. We predict that morphine total clearance rises from 14.5 litres h^{-1} per 70 kg at birth to 71 litres h^{-1} per 70 kg in adults.

Based on the assumed values for metabolite volume of distribution, the predominant morphine elimination pathway is formation of M3G. Formation clearance to M3G and M6G increased with maturation half-life of 88.3 days from 10.8 and 0.61 litres h^{-1} per 70 kg at birth to predicted values of 64.3 and 3.63 litres h^{-1} per 70 kg at 3 yr respectively. There are few data concerning morphine metabolite formation or elimination clearance in neonates and children. Barrett and colleagues[34] studied the pharmacokinetics of morphine, M6G and M3G in 19 ventilated newborn infants (24–41 weeks gestation) who were given diamorphine infusions. The authors made the assumption that 55% of administered morphine is converted to M3G and 10% to M6G, based on adult literature.[35] The CLT reported by Barrett and colleagues [34] (4.6 ml min^{-1} kg^{-1}, 7.2 litres h^{-1} per 70 kg) is similar to that observed in the study by Scott and colleagues in premature neonates[29] (Table 3B), but the CL2M3G (2.5 ml min^{-1} kg^{-1}, 4.0 litres h^{-1} per 70 kg) is half of that in on our current study. We estimate the formation clearance of M3G in 1-yr-old infants accounts for 86% of morphine elimination. This has to be compared with a 55% contribution proposed in adults.[35] The CL2M6G (0.46 ml min^{-1} kg^{-1}, 0.72 litres h^{-1} per 70 kg) is similar to our estimate (0.61 litres h^{-1} per 70 kg). CLT observed in the present study in term neonates is greater than that described by others in premature neonates[28 29] (4.6 ml min^{-1} kg^{-1}, 7.2 litres h^{-1} per 70 kg), consistent with intrauterine development of glucuronidation.[1]

The volume of distribution increased exponentially with a maturation half-life of 26.3 days from 83 litres per 70 kg at birth to 136 (CV 117%) l/70 kg at 6 months. A literature review was unable to discern age related changes in volume of distribution.[4] However, the methods used in the literature to determine volume of distribution vary greatly and it is difficult to compare estimates. Individual studies, such as that by Pokela and colleagues,[36] report similar age-related changes to ours. The volume of distribution increased from 91 (SD 28) litres per 70 kg in neonates 1–4 days old, 126 (SD

56) litres per 70 kg at 8–60 days and 168 (SD 105) litres per 70 kg at 61–180 days of age.

The metabolite volumes of distribution in neonates and children are unknown. Penson and colleagues[18] report a volume of distribution for M3G (V3M) of 23.1 litres per 70 kg in adults. Adult estimates for the volume of distribution for M6G (V6M) are from 8.4 to 30 litres per 70 kg.[19 37–39] V6M is believed to be greater than V3M because of higher lipophilicity at physiological pH;[40] consequently a V6M of 30 litres per 70 kg was empirically chosen. The goodness of fit was poorest for the prediction of serum metabolite concentration after the initial loading dose of morphine (Fig. 7) and may be attributable to fixing VM at a set value with no associated variability. The total elimination clearance of M3G (CLM3G) of 17.4 (CV 43%) litres h^{-1} per 70 kg is greater than the renal M3G clearance described by Penson and colleagues[37] [10.1 (SD 2.9) litres h^{-1} 70 kg] in adults but total urinary morphine and metabolite recovery was only 74.6% in that study. Penson and colleagues[18] and Lotsch and colleagues[39] report a CLM6G of 9.4 (SD 2.8) litres h^{-1} per 70 kg and 9.24 (SD 1.68) litres h^{-1} per 70 kg respectively, greater than our estimate of 5.8 (CV 73.8%) litres h^{-1} per 70 kg in young children.

The morphine metabolites M3G and M6G are water-soluble compounds, enabling renal excretion. The time course of metabolite elimination clearance is similar to that of glomerular filtration rate (GFR), although clearance of morphine glucuronide metabolites is greater (Fig. 5). This may be attributable to renal tubular secretion[35 41 42] and non-renal elimination.[35 43] Changes in GFR are usually referenced to body surface area in children,[25] a model that approximates the $\frac{3}{4}$ power model but uses 2/3 as the weight exponent. Attempts to use the Cockcroft and Gault models[44] to predict creatinine production rate failed. An empirical formula based on age to predict creatinine production was used. Creatinine production increased with age (Kage 0.0141) as opposed to adults, in whom production decreases with age.[44] The increase in children is assumed to be a consequence of increasing muscle bulk with age as opposed to the decrease in muscle bulk that occurs with age in adults. The maturation of GFR is commonly estimated by creatinine clearance. However, creatinine clearance (CrCl) may result in overestimation as GFR declines because of tubular secretion, changes in metabolic state altering creatinine production, and measurement errors at low concentrations significantly altering CrCl estimation. We demonstrated minimal effect attributable to altered renal function (based on creatinine production) because maturation of metabolite elimination clearance, which mirrored GFR maturation, was already accounted for.

Serum bilirubin was used as a marker of hepatic function. This is a very crude marker of hepatic function because serum concentrations are dependent on both formation and clearance of bilirubin. Bilirubin is metabolized in the liver by another glucuronosyltransferase, UGT1A1, and does not compete for the same metabolic pathway as morphine.[1] Activity of this enzyme also increases immediately after birth, reaching adult values at 3–6 months.[45] It was possible to relate bilirubin to metabolite formation. Formation clearance to M3G in a 1-yr-old child, for example, is reduced from 60 litres h^{-1} per 70 kg when serum bilirubin is 5 μmol $litre^{-1}$ to 43 litres h^{-1} per 70 kg when bilirubin is 180 μmol $litre^{-1}$.

Routes other than glucuronidation clear morphine in humans. Renal clearance of unmetabolized morphine may contribute up to 19% of CLT in infants younger than 3 months, 13% in older infants and 11% in adults.[32] Sulphate metabolism for morphine and paracetamol is active in neonates and contributes approximately 6 litres h^{-1} per 70 kg for paracetamol clearance in 1-yr-old children and adults.[32 46] Faecal excretion and normorphine formation contribute minimally. We were unable to quantify elimination specifically by these other routes. Unaccounted for clearance of morphine contributed less than 5% in our analysis.

Table 3B Morphine clearance changes with postconception age. Data taken from Scott and colleagues[29] (from van Lingen and colleagues[47], with permission)

PCA (weeks)	Weight (kg)	Clearance (ml min^{-1} kg^{-1})	CLT_{std} (CV%) (litres h^{-1} per 70 kg)
24–27	1.1	2.27	3.378 (47)
28–31	1.4	3.21	5.07 (49)
32–35	2.2	4.51	7.98 (44)
36–39	3.6	7.8	15.6 (32)

Table 3C Morphine sulphate clearance changes with postnatal age in term neonates. Data taken from Lynn and colleagues[5] and McRorie and colleagues.[32] *Weights are estimates only. Adult data from Kart *et al.*[4]

Age (days)	Weight* (kg) (Lynn *et al.*)	Clearance (ml min^{-1} kg^{-1})	CLT_{std} (litres h^{-1} per 70 kg)	Weight (kg) (McRorie *et al.*)	Clearance (ml min^{-1} kg^{-1})	CLT_{std} (litres h^{-1} per 70 kg)
0–7	3	9.8	18.7 (12.0–30.6)	3.2	5.5	10.6 (6.2–16.3)
8–30	4	13.3	27.3	3.9	7.4	15.1 (6.9–38.4)
31–90	5.6	23.9	53.4 (37.3–74.4)	4.3	10.5	22.0 (20.5–42.0)
91–180	7.5	32.3	77.6 (44.5–125.2)	5.1	13.9	30.3 (18.2–52.6)
181–365	8.5	38.1	94.5 (44.6–172.1)	7.2	21.7	51.6 (13.7–68.0)
Adult	70	22	92.4 (CV% 38)			

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