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Morphine kinetics after diamorphine infusion in premature neonates

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1 The pharmacokinetics of morphine were studied in 26 newborn premature neonates (26–38 weeks gestational age) who were given a loading dose of 50 $\mu g\ kg^{-1}$ of diamorphine followed by an intravenous infusion of 15 $\mu g\ kg^{-1}\ h^{-1}$ of diamorphine. Plasma concentrations of morphine were measured during the infusion at steady-state and for 24 h after the cessation of the diamorphine infusion.

2 The mean steady-state plasma morphine concentration (± s.d.) for a diamorphine infusion rate of 15 $\mu g\ kg^{-1}\ h^{-1}$ was 62.5 ± 22.8 $ng\ ml^{-1}$.

3 Morphine clearance was 3.6 ± 0.9 $ml\ min^{-1}\ kg^{-1}$, the elimination half-life was 8.9 ± 3.3 h and the volume of distribution was 2.7 ± 1.0 $l\ kg^{-1}$.

4 Morphine elimination kinetics were described by a mono-exponential function.

5 There was a direct relationship between the gestational age of the patients and the clearance ($r^2 = 0.31$, $P = 0.003$) and half-life ($r^2 = 0.35$, $P = 0.01$) of morphine, but no relationship was found between gestational age and volume of distribution.

6 The results suggest that the currently used dosing regimen of diamorphine achieves a safe and effective morphine concentration in the premature newborn but that the loading dose could be modified to achieve a more rapid onset of analgesia.

Keywords diamorphine morphine pharmacokinetics premature newborn intravenous infusion dose regimen

Introduction

Opioid drugs have been widely used as analgesics in the adult population but not in infants and newborn babies. However, recent work has shown the benefit of these drugs in the neonate (Anand *et al.*, 1987) and they are now being increasingly used in neonatal units to provide analgesia and sedation. Between 1984 and 1988 the use of sedation in British neonatal units increased from 8% to 18% (Marlow *et al.*, 1990). This substantial rise in the use of opioids in the neonate has led to concern over the choice of a safe and effective dosing regimen because of the undesirable side-effects of these drugs at high doses. These concerns have been addressed by several studies on the pharmacokinetics of the opioid analgesics in both infants and neonates. The pharmacokinetics of morphine, the most widely used analgesic in neonates, and of several other opioids have been shown to vary with age in the newborn and in young children (Choonara *et al.*, 1989; Collins *et al.*, 1984; Davis *et al.*, 1989; Lynn & Slattery, 1987; Marlow *et al.*, 1990). This observation, also noted for many drugs other than opioids, suggests that care should be taken in extrapolating from an adult dose to the neonatal dose. However, opioids have not been well studied in the premature neonate, a group which has been reported to be sensitive to the side-effects of opioids but which often receives these drugs as part of treatment during intensive care.

Diamorphine (3,6-diacetylmorphine) is a semi-synthetic derivative of morphine which is widely used in adults for the relief of acute pain, and is now being used to treat patients in neonatal intensive care units in the UK. The drug is believed to exert its pharmacological activity *via* its active metabolites (Figure 1), principally morphine, and has been considered as a pro-drug for morphine (Boerner *et al.*, 1976; Inturrisi *et al.*, 1983). Compared with an equivalent dose of morphine, an intravenous dose of diamorphine is reported to have a more rapid onset of action and a greater potency. The greater water solubility of diamorphine compared with morphine makes it more suitable for intravenous administration (Bruce-Scott, 1988). Satisfactory analgesia and sedation have been observed with diamorphine infusions in the newborn, using a dosing regimen based upon that

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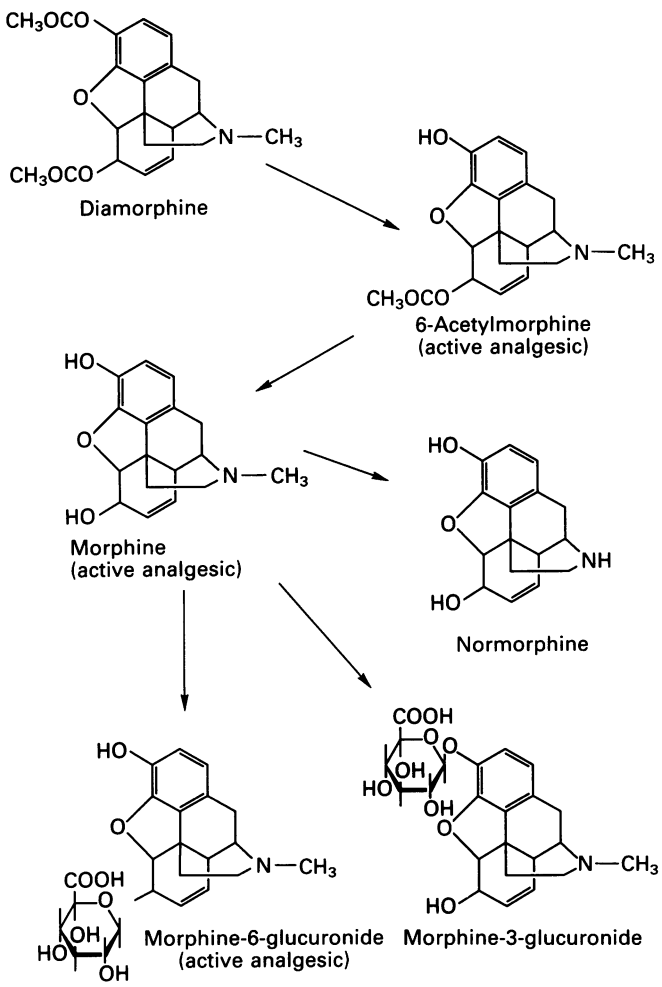

Figure 1 Pathways of diamorphine metabolism in man.

for morphine in the neonate, but to date plasma drug concentrations have not been measured nor the pharmacokinetics of the drug examined.

This study was designed to measure the plasma concentrations of morphine achieved with our currently used infusion rate of diamorphine, and to evaluate the pharmacokinetics of morphine during such infusions in the premature neonate.

Methods

Patients

Twenty-six neonates, gestational age 25 to 40 weeks (mean 30.7 ± 3.5), postnatal age, 1 to 37 days (mean 3.3 ± 6.9) and birth weight, 0.74 to 3.56 kg (mean 1.56 ± 0.61 kg) were studied. The clinical details are shown in Table 1. The majority of the infants received diamorphine for sedation to synchronise their own breathing with that of the mechanical ventilator. Approval for the study was obtained from the Hospital Ethics Committee and informed consent was given by the parents.

Dosing regimen

Patients received a diamorphine loading dose of 50 μg kg^{-1} as an infusion over 30 min followed by a continuous infusion of 15 μg kg^{-1} h^{-1}. For clinical reasons certain patients received a different loading dose or infusion rate of diamorphine, and in some patients the infusion rate was changed during the study. These changes were taken into account when calculating the pharmacokinetic

Table 1 Clinical details of infants

Subject number	*Postnatal age (days)*	*Gestational age (weeks)*	*Weight (kg)*	*Loading dose (μg kg^{-1})*	*Infusion rate (μg kg^{-1} h^{-1})*	*Duration of infusion (h)*	*Diagnosis*
1	1	29	0.88	50	15	75	RDS
2	2	28	1.10	50	15	90	RDS
3	3	32	1.60	50	15	33	RDS
4	1	28	1.30	50	15	48	RDS
5	2	36	2.30	50	15	40	Perforated caecum*
6	3	40	3.56	none	15	37	TOF*
7	1	32	1.97	51	15	40	RDS
8	2	32	1.63	50	14	18	RDS
9	37	26	1.20	none	15	14	Apnoea
10	2	29	1.30	50	15	41	RDS
11	2	38	2.97	50	15	104	RDS
12	1	36	1.43	50	15	17	RDS
13	3	31	2.01	50	15	80	RDS
14	3	25	0.74	50	15	46	RDS
15	1	28	1.10	50	15	24	RDS
16	2	31	1.80	50	15	62	Pneumothorax
17	5	31	1.24	50	30	83	RDS
18	1	29	1.30	50	25	63	RDS
19	1	29	1.44	55	16	76	RDS
20	1	28	1.38	22	15	97	RDS
21	1	28	1.14	50	15	149	RDS
22	1	31	1.44	55	15	93	RDS
23	2	31	1.24	48	22	93	Pneumothorax
24	2	31	1.64	49	21	44	RDS
25	3	30	1.42	49	8.8	25	RDS
26	2	30	1.46	50	15	74	RDS

RDS = Respiratory distress syndrome; TOF = Tracheo-oesophageal fistula; * = Post-operative subjects.

parameters. The duration of the infusion ranged from 14 to 149 h (mean 60.2 ± 32.9 h). All patients received regular monitoring of respiratory rate, temperature, heart rate, blood pressure, transcutaneous pO_2, ventilator settings, urine output and blood glucose measurement. Blood levels of creatinine, bilirubin and urea were also monitored before and during the study.

Blood sampling and analysis

Arterial blood samples (0.5 ml) were collected before the study, after the loading dose, two to five times during the continuous infusion and serially ten times in the 24 h after discontinuation of the diamorphine infusion. Plasma was separated and stored at −30° C until analysed. Samples from eight subjects were analysed by a high-performance liquid chromatography (h.p.l.c.) method for morphine and 6-acetylmorphine. The method is briefly described here: The plasma sample (0.1 ml) was mixed with internal standard (nalorphine), buffered to pH 9.0 and extracted with a Bond-Elut C18 cartridge. The methanolic eluate from the Bond-Elut cartridge, containing the analytes, was dried under nitrogen and the residue was reacted with dansyl chloride (20 min, 45° C, pH 9.0) to produce highly fluorescent derivatives of the analytes. After extraction of the derivatised analytes from the reaction mixture with toluene (0.2 ml), aliquots (0.1 ml) were injected for analysis by h.p.l.c. The analysis was performed using a Spherisorb CN column and a mobile phase comprising hexane/2-propanol/0.88 SG ammonia solution (95/5/0.25). Detection was by fluorescence of an excitation wavelength 340 nm and an emission wavelength 500 nm. The lower limit of the assay was 10 ng ml^{-1} for morphine and 25 ng ml^{-1} for 6-acetylmorphine. The inter-assay coefficient of variation was 5.7% and 6.4% for morphine and 6-acetylmorphine, respectively, at a plasma concentration of 75 ng ml^{-1}. The remaining samples from 18 subjects were analysed for morphine alone by a Coat-A-Count radioimmunoassay (r.i.a.) method (Diagnostic Products Ltd) which was highly specific for morphine. The r.i.a. method showed low cross reactivity (< 0.5%) to diamorphine, 6-acetylmorphine and other metabolites of morphine, it had a lower limit of 2.5 ng ml^{-1} and had an inter-assay coefficient of variation of 7.2% at 75 ng ml^{-1}. Good agreement was achieved between the r.i.a. and h.p.l.c. methods. Morphine concentrations are reported in terms of morphine base.

During the study drugs other than diamorphine were administered to the infants. The most common were penicillin, gentamicin, flucloxacillin, metronidazole and cefotaxime. There was no evidence that they interfered with the assays for morphine in plasma.

Pharmacokinetic analysis

All the pharmacokinetic data in this study relate to morphine. Clearance was calculated by dividing the infusion rate (in morphine equivalents) by the steady state plasma concentration of morphine. Half-life was determined from the slope of the plot of the logarithm of morphine concentration *vs* time (by linear regression) and the elimination rate constant was calculated by dividing 0.693 by the elimination half-life. The volume of distribution was calculated by dividing clearance by the elimination rate constant. The steady-state concentration was taken as the plasma morphine concentration at the end of the diamorphine infusion, or as a mean of values during infusion where these values were within ± 10% of each other. Pharmacokinetic simulations were performed using the PCNONLIN software package (Statistical Consultants Inc. Lexington, USA).

Data analysis

Statistical analysis of the relationship between gestational age and pharmacokinetic parameters was performed using a Student's *t*-test on the regression coefficient of the appropriate sets of data.

Results

Plasma morphine concentration

Morphine was detected in the plasma of all study subjects at concentrations ranging from 20 to 98 ng ml^{-1} (Table 2). The mean steady state morphine concentration during the diamorphine infusion was 62.5 ± 20.8 ng ml^{-1} (n = 19) for all patients who received diamorphine at an infusion rate of 15 μg kg^{-1} h^{-1}. 6-acetylmorphine was detected in low concentrations in two plasma samples from one subject but not in the remaining seven subjects when analysed by the h.p.l.c. method.

Pharmacokinetics

The pharmacokinetic parameters of clearance, elimination rate constant, half-life and volume of distribution for all the subjects are shown in Table 2. The plasma morphine concentration *vs* time profiles during and after termination of the diamorphine infusion for three representative subjects are shown in Figures 2 and 3. The mean clearance of morphine was 3.6 ± 0.9 ml min^{-1} kg^{-1} (n = 26), the mean elimination rate constant was 0.078 ± 0.029 h^{-1} (n = 17), the mean elimination half-

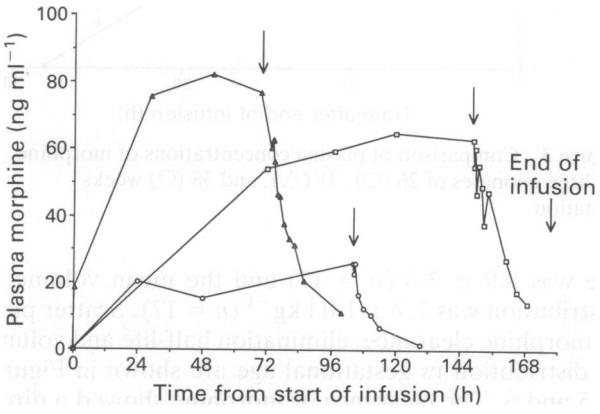

Figure 2 Plasma morphine concentrations during and after diamorphine infusion (15 μg kg^{-1} h^{-1}) in three premature neonates. □ 28 weeks gestation, △ 30 weeks gestation, ○ 38 weeks gestation.

Table 2 Morphine pharmacokinetic data from diamorphine infusion

Subject number	*Analysis method*	*Infusion rate*† ($\mu g\ kg^{-1}\ h^{-1}$)	*Morphine steady state concentration* ($ng\ ml^{-1}$)	*Half-life* (*h*)	*Clearance* ($ml\ min^{-1}\ kg^{-1}$)	*Volume of distribution* ($l\ kg^{-1}$)	*Elimination rate constant* (h^{-1})
1	h.p.l.c.	11.6	46.0		4.2		
2	r.i.a.	11.6	88.1	9	2.2	1.7	0.077
3	h.p.l.c.	11.6	98.0	7.3	2.0	1.2	0.095
4	h.p.l.c.	11.6	81.0	18.3	2.4	3.8	0.038
5	h.p.l.c.	11.6	82.9		2.3		
6	h.p.l.c.	11.6	20.0		9.7		
7	h.p.l.c.	11.6	57.0	7.3	3.4	2.1	0.095
8	r.i.a.	10.8	76.8	6	2.3	1.2	0.116
9	h.p.l.c.	11.6	48.0	11.9	4.0	4.1	0.058
10	r.i.a.	11.6	46.9	12.2	4.1	4.4	0.057
11	r.i.a.	11.6	26.1	6.3	7.4	4.0	0.110
12	r.i.a.	11.6	77.8		2.5		
13	h.p.l.c.	11.6	53.7	4.2	3.6	1.3	0.165
14	r.i.a.	11.6	56.3		3.4		
15	r.i.a.	11.6	63.8		3.0		
16	r.i.a.	11.6	71.5		2.7		
17	r.i.a.	23.2	95.1	6.5	4.1	2.3	0.107
18	r.i.a.	19.3	92.2		3.5		
19	r.i.a.	12.4	78.5	11.5	2.6	2.6	0.060
20	r.i.a.	11.6	89.5		2.2		
21	r.i.a.	11.6	63.0	9.8	3.1	2.6	0.071
22	r.i.a.	11.6	56.8	9.1	3.4	2.7	0.076
23	r.i.a.	16.6	69.8	8	4.0	2.7	0.087
24	r.i.a.	16.2	45.9	7.6	5.9	3.9	0.091
25	r.i.a.	6.8	30.1	5.6	3.8	1.8	0.124
26	r.i.a.	11.6	60.3	10	3.2	2.8	0.069
Mean (± s.d.)			62.5 ± 22.8* (n = 19)	8.9 ± 3.3 (n = 17)	3.6 ± 0.9 (n = 26)	2.7 ± 1.0 (n = 17)	0.078 ± 0.029 (n = 17)

s.d. = standard deviation; † morphine equivalents; *man of 11.6 $\mu g\ kg^{-1}\ h^{-1}$ rate (15 $\mu g\ kg^{-1}\ h^{-1}$ diamorphine).

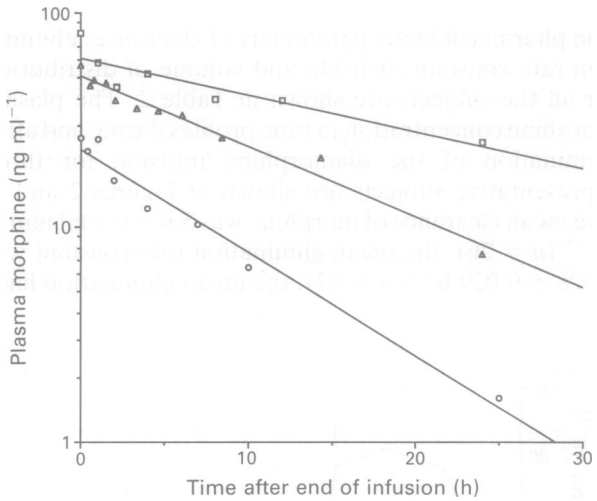

Figure 3 Comparison of plasma concentrations of morphine in three neonates of 26 (□), 31 (△), and 38 (○) weeks gestation.

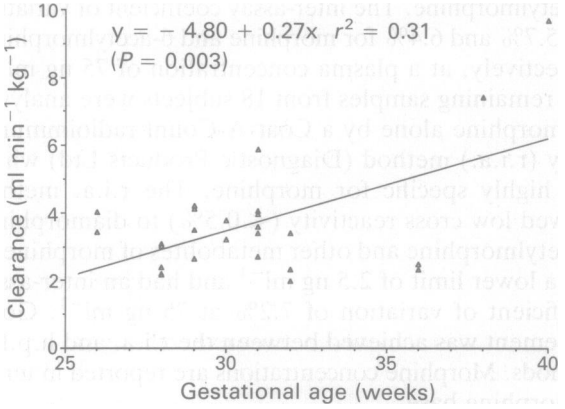

Figure 4 Relationship between morphine clearance and gestational age.

life was 8.9 ± 3.3 (n = 17) and the mean volume of distribution was 2.7 ± 1.0 l kg^{-1} (n = 17). Scatter plots of morphine clearance, elimination half-life and volume of distribution *vs* gestational age are shown in Figures 4, 5 and 6. The clearance of morphine showed a direct relationship with gestational age (r^2 = 0.31, P = 0.003) and the half-life of morphine showed a similar relationship (r^2 = 0.35, P = 0.01). There was no significant relationship between volume of distribution and gestational age.

Pharmacokinetic simulation

The post-infusion elimination of morphine in all subjects was best described by a mono-exponential function. For the purposes of simulating morphine concentration-time profiles a volume of distribution of 2.7 l kg^{-1} and an elimination rate constant of 0.078 h^{-1} were used (mean values obtained from the study data). A target steady-state morphine concentration of 50 ng ml^{-1} was assumed (see discussion) and the simulation was established to calculate plasma morphine concentrations for a 30 min constant rate loading infusion followed by a 72 h continuous infusion of diamorphine.

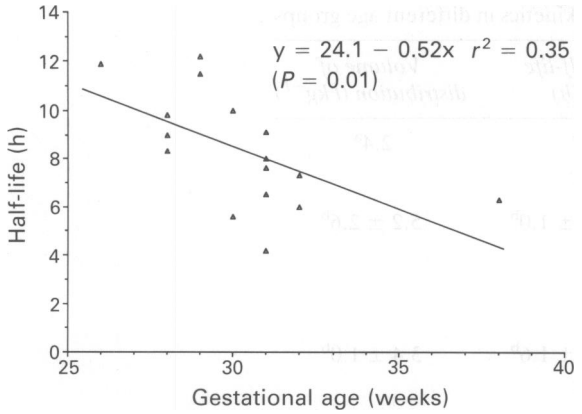

Figure 5 Relationship between morphine half-life and gestational age.

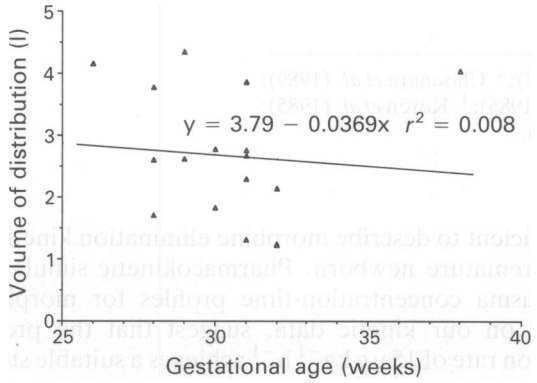

Figure 6 Relationship between morphine volume of distribution and gestational age.

Discussion

The range of plasma morphine concentrations in our study of between 20 to 98 ng ml^{-1} (mean 62.5 ng ml^{-1}) compare with the reported minimum concentrations required for analgesia in adults of between 20 and 65 ng ml^{-1} (Berkowitz *et al.*, 1975; Dahlstrom *et al.*, 1979, 1982). Thus, it appears that the diamorphine infusion rate used in the study produces an effective plasma concentration of morphine. However, there are several complicating factors relating to diamorphine analgesia in the premature newborn infant which must be considered. The contribution of 6-acetylmorphine, the intermediary metabolite between diamorphine and morphine, to the analgesic effect of diamorphine is unknown, although the compound is known to have pharmacological activity (Inturrisi *et al.*, 1983). This compound was not detected in any plasma samples from this study, but it is reasonable to assume that 6-acetylmorphine would be found in plasma samples following a diamorphine infusion if the assay had been sufficiently sensitive. Hence, it is likely that 6-acetylmorphine does enhance the analgesic effect of morphine, and, because of its higher lipid solubility compared with morphine, is more likely to cross the blood-brain barrier rapidly in the premature infant and induce a faster onset of analgesia than morphine. Studies in adults have confirmed that morphine-6-glucuronide, a major metabolite of morphine (Figure 1), also has significant analgesic activity (Osborne *et al.*, 1988) though a recent study failed to detect this compound in neonatal plasma after morphine administration (Choonara *et al.*, 1989). Hence, there is a complex relationship between these three pharmacologically active metabolites which will determine the degree of analgesia produced by diamorphine. This relationship has not been studied and our knowledge of diamorphine and morphine induced analgesia would benefit from its further investigation.

In this study diamorphine has been administered and the pharmacokinetics of the major metabolite, morphine, have been determined. There are no reports of diamorphine kinetics in the paediatric population but a single study has been performed in adults, which showed that diamorphine itself is rapidly metabolised (half-life less than 5 min in plasma) to 6-acetylmorphine and further deacetylated to morphine. Diamorphine was not assayed in the present study and no 6-acetylmorphine was detected in the plasma samples; it is therefore more instructive to compare the pharmacokinetic data in this study with previous reports of morphine kinetics in the paediatric population.

The value for morphine clearance of 3.6 ± 0.9 ml min^{-1} kg^{-1} is in agreement with a value of 4.7 ± 2.8 ml min^{-1} kg^{-1} calculated for nine neonates in the single previous study of morphine clearance in pre-term neonates (Choonara *et al.*, 1989). This value is significantly lower than the two reported values for clearance of morphine in the mature neonate of 6.3 ± 2.2 ml min^{-1} kg^{-1} (Lynn & Slattery, 1987) and 7.8 ± 1.9 ml min^{-1} kg^{-1} (Koren *et al.*, 1985). In older infants, clearances of 23.8 ± 13.5 (Lynn & Slattery, 1987), 25.7 ± 4.7 (Choonara *et al.*, 1989), 20.5 ± 2.8 (Vandenberghe *et al.*, 1983) and 25.4 ± 14.8 (Nahata *et al.*, 1985) ml min^{-1} kg^{-1} have been reported. There is strong evidence from this study that morphine clearance in premature neonates is reduced compared with that in mature neonates and continues to increase to a maximum value during childhood. In adults, morphine clearance is reduced compared with that of younger children, with a value of 11.5 ml min^{-1} kg^{-1} (Stanski *et al.*, 1982).

The half-life of morphine determined in this study of 8.9 ± 3.3 h compares with a value of 10.3 ± 1.0 h reported in five premature neonates (Mercurio *et al.*, 1989). In mature neonates the half-life of morphine is shorter at 6.8 ± 1.6 h (Lynn & Slattery, 1987) and in children it is further reduced to 3.9 ± 1.0 h (Lynn & Slattery, 1987) and 3.2 ± 2.5 h (Nahata *et al.*, 1985). This trend towards a prolonged half-life of morphine at a lower gestational age confirms a previous observation of such a trend in a small group of neonates of 24 to 38 weeks gestation (Mercurio *et al.*, 1989). The volume of distribution of morphine in premature neonates has not been reported previously and the value determined in this study of 2.7 ± 1.0 l kg^{-1} compares with 3.4 ± 1.0 l kg^{-1} and 5.2 ± 2.6 l kg^{-1} in mature neonates and children (Lynn & Slattery, 1987).

Table 3 shows previously published morphine pharmacokinetics in different age groups compared with those calculated from this study. These data indicate that morphine clearance is reduced and elimination half-life prolonged in infants younger than 1 month and further reduced in newborn and premature newborn babies.

Table 3 Summary of morphine pharmacokinetics in different age groups

	Clearance ($ml\ min^{-1}\ kg^{-1}$)	*Half-life* (*h*)	*Volume of distribution* ($l\ kg^{-1}$)
Adults	11.5[a] 6.2[h]	2.0[a] 2.1[h]	2.4[a]
Children (0–5 years)	25.7 ± 4.7[c] 23.8 ± 13.5[b] 20.5 ± 2.8[d] 25.4 ± 14.8[e]	3.9 ± 1.0[b]	5.2 ± 2.6[b]
Neonates (full term)	6.3 ± 2.2[b] 7.8 ± 1.9[f]	6.8 ± 1.6[b]	3.4 ± 1.0[b]
Premature neonates	4.7 ± 2.8[c]	10.3 ± 1.0[g]	—
Present study neonates (25–38 weeks)	3.6 ± 0.9	8.9 ± 3.3	2.7 ± 1.0

[a] Stanski *et al.* (1982); [b] Lynn & Slattery (1987); [c] Choonara *et al.* (1989); [d] Vandenberghe *et al.* (1983); [e] Nahata *et al.* (1985); [f] Koren *et al.* (1985); [g] Mercurio *et al.* (1989); [h] Moore *et al.* (1984).

This trend is continued over the range of gestation (25 to 38 weeks) of the present study group. It is likely that this relationship between pharmacokinetics and gestational age would be continued to the extreme premature newborns (gestational age 24–27 weeks) but there were insufficient data in this study to demonstrate this with certainty. The same trend has been noted for other opioid analgesics and is probably the result of the immaturity of the enzymes responsible for drug metabolism in the neonatal liver (Morselli, 1989). The reduced clearance and prolonged half-life means that premature infants will achieve a higher plasma concentration of morphine for a longer duration than will be observed in the mature newborn and young children.

Morphine and other opioids are known to depress respiration and it has been suggested that young infants are particularly sensitive to this effect (Lynn & Slattery, 1987; Way *et al.*, 1965). The reasons for this increased sensitivity have not been determined but possible explanations include developmental changes in pharmacokinetics, metabolism, opoid receptors or in the blood-brain barrier. The observation of a strong relationship between gestational age and pharmacokinetics in this study and the previous reports of age-related changes in pharmacokinetics of opioids suggest that this observation represents at least part of the explanation for the respiratory depression noted in neonates and preterm infants. In attempting to recommend a safe and effective dosing regimen for diamorphine in the neonate it is necessary to proceed with caution for the reasons given above. It is, however, possible to make an estimate of the required dosing regimen.

Previous studies of morphine pharmacokinetics in adults and children have suggested that the elimination profile is best described by either a bi-exponential or tri-exponential process (Dahlstrom *et al.*, 1979; Moore *et al.*, 1984; Nahata *et al.*, 1985). We have found no evidence in the data reported here for such multi-exponential behaviour and consider that a single exponential function is sufficient to describe morphine elimination kinetics in the premature newborn. Pharmacokinetic simulations of plasma concentration-time profiles for morphine, based on our kinetic data, suggest that the present infusion rate of 15 $\mu g\ kg^{-1}\ h^{-1}$ achieves a suitable steady state plasma morphine concentration in the majority of subjects. However, the pharmacokinetic simulation predicts that a loading dose of 50 $\mu g\ kg^{-1}$ would result in a delay of several hours in the attainment of a therapeutic plasma concentration of morphine (Figure 7). This is confirmed by the slow accrual in plasma morphine concentrations observed over the first 24 h of the infusion. The same kinetic simulation suggests that a higher loading dose of 200 $\mu g\ kg^{-1}$ of diamorphine would result in the attainment of an effective plasma morphine concentration in less than 1 h after dosing (Figure 7). However, with the loading dose of 50 $\mu g\ kg^{-1}$ used in this study small but significant decreases in both heart rate and blood pressure occurred (data not shown). It is probable that these related primarily to the reduction of stress in the infant due to the sedative effect of the opioid drug, rather than to the unwanted side-effect of respiratory depression. Because of the importance of safety when

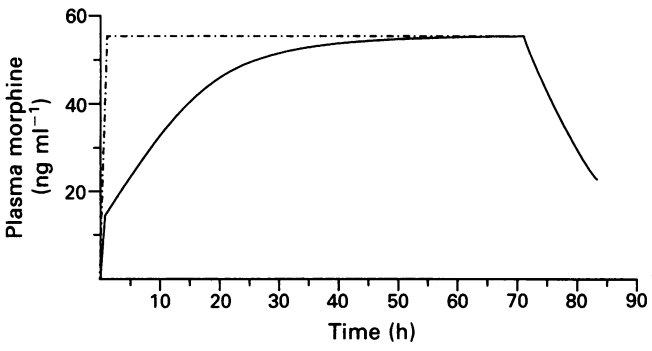

Figure 7 Simulation of plasma morphine concentrations after a diamorphine infusion (15 $\mu g\ kg^{-1}\ h^{-1}$) with loading doses of 50 (—) and 200 $\mu g\ ml^{-1}$ (—·—).

recommending a new dosing regimen and taking into account the complex nature of diamorphine analgesia we would recommend that the lower 50 $\mu g\ kg^{-1}$ loading dose is still used until the clinical effects of the 200 $\mu g\ kg^{-1}$ loading dose have been studied carefully.

This study has not addressed the problem of determining the pharmacokinetics of diamorphine itself and its intermediary metabolite, 6-acetylmorphine. Diamorphine is difficult to measure because of its instability in plasma, its very short half-life of less than 5 min in adults and a lack of sensitive analytical procedures. The necessary procedures to stabilise diamorphine in plasma (Umans *et al.*, 1982) could not be carried out in the neonatal intensive care unit and hence no attempt was made to measure diamorphine or to assess its stability in neonatal plasma. 6-Acetylmorphine was found to be stable in neonatal and adult plasma for up to 24 h at room temperature (data not shown), thus excluding any possible degradation which would lead to an overestimation of the plasma morphine concentration. That no 6-acetylmorphine was detected in this study was unexpected since steady-state concentrations of greater than 25 $ng\ ml^{-1}$ have been reported during diamorphine infusion in adults (Inturrisi *et al.*, 1984). The absence of 6-acetylmorphine may be explained by the lack of assay sensitivity or because a different pathway of metabolism of diamorphine exists in the premature neonate.

This pharmacokinetic study suggests that the dosing regimen described does achieve plasma concentrations indicative of effective analgesia. The maximum plasma concentration in the study of 98 $ng\ ml^{-1}$ was well within the therapeutic window for morphine (Dahlstrom *et al.*, 1979, 1982). This indicates that the infusion dose has a good margin of safety, considering the possibility of raised morphine plasma concentrations in very premature infants.

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References

Anand, K. J. S., Sipell, W. G. & Aynsley-Green, A. (1987). Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effect on the stress response. *Lancet*, **i**, 243–248.

Berkowitz, B. A., Ngai, S. H., Yang, J. C., Hempstead, J. & Spector, S. (1975). *Clin. Pharmac. Ther.*, **17**, 629–635.

Boerner, U., Abbot, S. & Roe, R. L. (1975). The metabolism of morphine and heroin in man. *Drug Metab. Rev.*, **4**, 39–73.

Bruce-Scott, D. (ed.) (1988). *Diamorphine*. England: Woodhead-Faulkener Ltd.

Choonara, I. A., McKay, P., Hain, R. & Rane, A. (1989). Morphine metabolism in children. *Br. J. clin. Pharmac.*, **28**, 599–604.

Collins, C., Koren, G., Crean, P., Klein, J., Roy, W. L. & Macleod, S. M. (1984). The correlation between fentanyl pharmacokinetics and pharmacodynamics in preterm infants during PDA ligation. *Anesthesiology*, **61**, A442.

Dahlstrom, B., Bolme, P., Feychting, H., Noack, G. & Paalzow, L. (1979). Morphine kinetics in children. *Clin. Pharmac. Ther.*, **26**, 354–365.

Dahlstrom, B., Tamsen, A., Paalzow, L. & Hartvig, P. (1982). Patient-controlled analgesic therapy. IV. Pharmacokinetic and analgesic concentrations of morphine. *Clin. Pharmacokin.*, **7**, 266–279.

Davis, P. J., Killian, A., Stiller, R. L., Cook, D. R., Guthrie, R. D. & Scierka, A. M. (1989). Pharmacokinetics of alfentanil in newborn premature infants and older children. *Dev. Pharmac. Ther.*, **13**, 21–27.

Inturrisi, C. E., Max, M. B., Fley, K. M., Schultz, M., Shin, S. U. & Houde, R. W. (1984). The pharmacokinetics of heroin in patients with chronic pain. *New Engl. J. Med.*, **310**, 1213–1217.

Inturrisi, C. E., Schultz, M., Shin, S., Umans J. G., Angel, L. & Simon, E. J. (1983). Evidence from opiate binding studies that heroin acts through its metabolites. *Life Sci.*, **33**, 773–776.

Koren, G., Butt, W., Chinyanga, H., Soldin, S., Tan, Y.-K. & Pape, K. (1985). Post-operative morphine infusion in newborn infants: assessment of disposition characteristics and safety. *J. Paediatrics*, **107**, 963–967.

Lynn, A. M. & Slattery, J. T. (1987). Morphine pharmacokinetics in early infancy. *Anesthesiology*, **66**, 136–139.

Marlow, N., Weindling, A. M., Van Peer, A. & Heykants, J. (1990). Alfentanil pharmacokinetics in preterm infants. *Arch. Dis. Child.*, **65**, 349–351.

Mercurio, M., Nelli, C., Gettner, P., Sherwonit, E., Williams, J. & Ehrenkranz, R. (1989). Morphine pharmacokinetics in premature newborns. *Paediatric Res.*, **25** (71A), A408.

Moore, R. A., Baldwin, D., Allen, M. C., Watson, P. J. Q., Bullingham, R. E. S. & McQuay, H. J. (1984). Sensitive and specific morphine radioimmunoassay with iodine label: pharmacokinetics of morphine in man after intravenous administration. *Ann. clin. Biochem.*, **21**, 318–325.

Morselli, P. L. (1989). Clinical pharmacology of the perinatal period and early infancy. *Clin. Pharmacokin.*, **17**, (Suppl. 1), 13–28.

Nahata, M. C., Miser, A. W. & Reuning, R. H. (1985). Variation in morphine pharmacokinetics in children with cancer. *Dev. Pharmac. Ther.*, **8**, 182–188.

Osborne, R., Joel, S., Trew, D. & Slevin, M. (1988). Analgesic activity of morphine-6-glucuronide. *Lancet*, **i**, 828.

Stanski, D. R., Paalzow, L. & Edlund, P. O. (1982). Morphine pharmacokinetics: GLC assay versus radioimmunoassay. *J. pharm. Sci.*, **71**, 314–317.

Umans, J. G., Chiu, T. S. K., Lipman, R. A., Schultz, M. F., Shiu, S.-U. & Inturrisi, C. E. (1982). Determination of heroin and its metabolites by high performance liquid chromatography. *J. Chromatogr.*, **233**, 213–225.

Vandenberghe, H., MacLeod, S., Chinyanga, H., Endrenyi, L. & Soldin, S. (1983). Pharmacokinetics of intravenous morphine in balanced anaesthesia: studies in children. *Drug Metabolism Reviews*, **14**, 887–903.

Way, W. L., Costley, E. C. & Leong Way, E. (1965). Respiratory sensitivity of the newborn infant to meperidine and morphine. *Clin. Pharmac. Ther.*, **6**, 454–461.

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