Br. J. clin. Pharmac. (1989), **28**, 599–604

Morphine metabolism in children

I. A. CHOONARA[1], P. McKAY[2], R. HAIN[3] & A. RANE[1]
[1]Division of Clinical Pharmacology, University Hospital, S-751 85 Uppsala, Sweden, [2]Neonatal Unit, Leeds General Infirmary and [3]Department of Paediatrics, St James's University Hospital, Leeds

1 The metabolism of morphine was studied in 12 children and nine premature neonates on a continuous infusion of morphine (10–360 $\mu g\ kg^{-1}\ h^{-1}$).
2 The mean plasma clearance of morphine was significantly higher in children than neonates (25.7 and 4.7 ml $min^{-1}\ kg^{-1}$, respectively) ($P < 0.01$).
3 All the neonates and children had detectable concentrations of morphine-3-glucuronide (M3G) in plasma. All the children and five neonates had detectable concentrations of morphine-6-glucuronide (M6G) in plasma or urine.
4 The M3G/morphine ratios in plasma and urine, and M6G/morphine ratios in urine were significantly higher in children than neonates ($P < 0.01$), suggesting that morphine glucuronidation capacity is enhanced after the neonatal period.
5 There was no difference in the M3G/M6G ratio in children and neonates, indicating a parallel development of both glucuronidation pathways.

Keywords morphine glucuronidation neonates children

Introduction

Morphine is the drug of choice for patients with severe pain and its metabolism has been studied in volunteers and adult patients with malignancies (Säwe *et al.*, 1983). The major metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) which are present in plasma at significantly greater concentrations than morphine itself (Säwe *et al.*, 1983, 1985). Studies in adults have confirmed the analgesic activity of M6G (Osborne *et al.*, 1988), consistent with its binding to opioid receptors (Christensen & Jørgensen, 1987) and animal studies suggest that M6G is more potent than morphine itself (Shimomura *et al.*, 1971).

The importance of analgesia in children and neonates is now being recognised (Anand *et al.*, 1987; Choonara, 1989). Morphine infusions in children were used initially for the management of severe cancer pain (Miser *et al.*, 1980), but have since been established as being effective in the post-operative child (Bray, 1983; Dilworth & MacKellar, 1987). Only a few studies of the pharmacokinetics of morphine in children (Dahlström *et al.*, 1979; Nahata *et al.*, 1985; Vandenberghe *et al.*, 1983) and in the neonatal period (Koren *et al.*, 1985; Lynn *et al.*, 1987) have been published. There have been no studies of the metabolism of morphine in children or neonates. The metabolism of drugs by children is different from that of adults (Rane & Wilson, 1976; Rane, 1989), with age dependent differences for drugs that undergo oxidation (phenytoin, theophylline) as well as for drugs that undergo conjugation (oxazepam) (Tomson *et al.*, 1979). A decreased ability to conjugate paracetamol with glucuronic acid, with increased conjugation to paracetamol sulphate has been reported in prepubertal children (Miller *et al.*, 1976) and in foetal liver preparations (Rollins *et al.*, 1979).

The capacity for glucuronidation of morphine in childhood has not been evaluated. This

Correspondence: Dr I. A. Choonara, Institute of Child Health, Alder Hey Children's Hospital, Eaton Road, Liverpool L12 2AP

metabolic pathway is of clinical importance as morphine is the major analgesic used in neonates and children and also in view of the analgesic activity of M6G.

Methods

Plan of study

Informed consent was obtained from the parents and, where appropriate, the child, and the study was approved by the local ethics committee. Blood and/or urine samples were collected from 12 children and nine premature neonates. The clinical details of the patients are shown in Tables 1 and 2. Most of the children received morphine postoperatively (two had pain secondary to malignancy), whereas most of the neonates received morphine for sedation. All of the neonates had severe hyaline membrane disease and required ventilation *prior* to the morphine infusion. Urine samples were collected over a given time period in the children (up to 24 h) and from a single voiding in neonates.

Analytical methods

M3G and M6G in plasma and urine were measured by reversed phase ion-pair high performance liquid chromatography (Svensson *et al.*, 1982). The assay was modified slightly in that only one Sep-Pak C18 cartridge was used for sample purification instead of two. Urine samples were diluted with water (1:9). The same assay was used for the measurement of morphine in urine but was not sensitive enough for morphine in plasma. Plasma morphine concentrations were measured by organic extraction and reversed phase ion-pair high performance liquid chromatography (Persson *et al.*, 1989). The limit of assay for M3G and M6G was 40 ng ml^{-1} and for morphine it was 5 ng ml^{-1}.

Table 1 Clinical details of the children

	Age (years)	*Plasma creatinine ($\mu mol\ l^{-1}$)*	*Morphine ($\mu g\ kg^{-1}\ h^{-1}$)*	*Duration of infusion at time of sample collection (h)*	
				Blood	*Urine*
C1*	5	95	20	24	24–36
C2*	14	72	20	24	0–24
C3*	9	53	15	24	20–40
C4*	10	81	25	44	6–30
C5*	13	42	20	24	–
C6*	1	–	28	14	14–16
C7*	8	44	24	21	30–38
C8*	16	49	140	22	–
C9	14	62	115	14	–
C10	12	58	270	–	22–32
C11*	6	47	20	–	0–8
C12*	7	72	20	–	24–48

* post-surgery

Table 2 Clinical details of the neonates

	Age (days)	*Gestation (weeks)*	*Plasma urea ($mmol\ l^{-1}$)*	*Morphine ($\mu g\ kg^{-1}\ h^{-1}$)*	*Duration of infusion at time of sample collection (h)*
N1	5	24	11.7	20	48
N2	6	25	5.3	20	>48
N3	3	29	–	42	48
N4	2	29	5.8	40	24
N5	4	–	1.6	24	>48
N6*	5	33	–	15	48
N7	3	34	4.5	20	48
N8	12	36	2.4	17	48
N9	3	37	2.8	10	48

* post-surgery

Table 3 Pharmacokinetic data from nine children receiving an i.v. morphine infusion (15–140 μg kg^{-1} h^{-1})

Patient	*Plasma concentration (ng ml^{-1})* Morphine	M3G	M6G	*CL (ml min^{-1} kg^{-1})*	*Plasma M3G/morphine*
C1	12	338	51	27.9	28.2
C2	14	213	ND	24.3	15.2
C3	9	170	ND	27.3	18.9
C4	19	503	55	23.1	27.2
C5	10	312	ND	33.3	31.2
C6	16	460	69	30.7	29.7
C7	19	318	47	21.8	17.2
C8	132	3863	84	17.8	29.3
C9	76	1359	80	25.3	17.9
Mean	34	837	43	25.7	23.9
s.d.	42	1189	34	4.7	6.4

Table 4 Pharmacokinetic data from nine neonates receiving an i.v. morphine infusion (10–40 μg kg^{-1} h^{-1})

Patient	*Plasma concentration (ng ml^{-1})* Morphine	M3G	*CL (ml min^{-1} kg^{-1})*	*Plasma M3G/morphine*
N1	108	234	3.1	2.2
N2	139	123	2.4	0.9
N3	162	220	4.2	1.4
N4	210	401	3.4	1.9
N5	50	404	8.2	8.1
N6	26	371	9.6	14.3
N7	72	305	4.6	4.2
N8	44	411	6.3	9.3
N9	205	584	0.8	2.8
Mean	113	339	4.7	5.0
s.d.	70	136	2.8	4.6

Calculations

Previous studies have reported a plasma half-life for morphine of 2.1–3.9 h in children (Dahlström *et al.*, 1979; Lynn & Slattery, 1987; Nahata *et al.*, 1985) and 6.8 h in neonates (Lynn & Slattery, 1987), and a plasma half-life for M3G of 4 h in adults (Säwe & Odar-Cederlöf, 1987). Steady state plasma concentrations should therefore have been achieved by 24 and 48 h in children and neonates, respectively. Plasma clearance was determined by dividing the infusion rate by the steady state plasma drug concentration. All results are expressed as the mean ± s.d. and statistical analysis was by the Mann-Whitney U test or Spearman's rank correlation.

Results

Morphine and M3G were measurable in all the samples. Plasma concentrations of M6G were below the limit of assay (40 ng ml^{-1}) in all nine neonates and three children. M6G was measurable in all of the urine samples from the children and in samples from five neonates. The individual data are shown in Tables 3 and 4. The mean plasma clearance of morphine was significantly higher in children (25.7 ± 4.7 ml min^{-1} kg^{-1}) than in neonates (4.7 ± 2.8 ml min^{-1} kg^{-1}) (Mann-Whitney U test, $P < 0.01$). The M3G/morphine ratios in plasma and urine and M6G/morphine ratio in urine were used as indices of glucuronidation (see Table 5). All of these ratios were significantly higher in children than in neonates (Mann-Whitney U test, $P < 0.01$). The mean urinary M3G/M6G ratios were similar in children (9.9 ± 3.7) and neonates (10.3 ± 1.4).

There was a significant correlation between the M3G/morphine ratio in plasma and urine in the seven neonates who had both blood and urine samples analysed (Spearman's rank correlation ρ 0.893, $P < 0.02$). There was no correlation, however, between the M3G/morphine ratio in plasma and urine in the five children who had both blood and urine samples

Table 5 Urinary ratios of M3G and M6G to morphine

	Children Urine				*Neonates* Urine		
Patient	*M3G/M*	*M6G/M*	*M3G/M6G*	*Patient*	*M3G/M*	*M6G/M*	*M3G/M6G*
C1	12.8	1.54	8.3	N1	1.35	–	–
C2	16.6	2.26	7.3	N2	0.54	0.07	8.1
C3	14.4	1.38	10.5	N3	1.29	–	–
C4	20.4	2.13	9.6	N4	1.95	0.19	10.5
C6	–	–	6.9	N5	2.58	0.23	11.1
C7	7.9	0.66	11.9	N6	6.35	0.62	10.3
C10	7.6	0.61	12.5	N9	1.39	0.12	11.7
C11	7.0	1.47	4.7				
C12	16.4	0.95	17.2				
Mean	12.9	1.37	9.9		2.34	0.28	10.3
s.d.	5.0	0.62	3.7		2.08	0.24	1.4

Morphine was not measurable in patient C6 owing to an interfering chromatographic peak and M6G was not detectable in patients N1 and N3.

analysed (Spearman's rank correlation $P > 0.05$). This is probably related to the fact that the urine samples in the children were collected before steady-state plasma drug concentrations had been achieved.

Discussion

Our results show that preterm infants (even of 24–25 weeks gestation) can metabolise morphine by glucuronidation. This is consistent with previous results from our laboratory which demonstrated the *in vitro* glucuronidation of morphine by foetal liver microsomes (15–27 weeks gestation), albeit at considerably lower levels than by adult liver microsomes (Pacifici *et al.*, 1982).

The lower plasma clearance of morphine in neonates than children (4.7 and 25.7 ml min^{-1} kg^{-1} respectively) supports the single previous report directly comparing morphine kinetics in these two age groups (6.3 and 23.8 ml min^{-1} kg^{-1}) (Lynn & Slattery, 1987). Our findings are also consistent with previous studies of morphine kinetics in children (Nahata *et al.*, 1985; Vandenberghe *et al.*, 1983) and neonates (Koren *et al.*, 1985).

In contrast to previous studies our report includes data on the major metabolites of morphine, M3G and M6G. The plasma concentrations of M3G were similar in the children (Cl–C7) and neonates (N1–N9) who received a morphine infusion of 10–40 μg kg^{-1} h^{-1}. However, the plasma concentrations of morphine were significantly higher in the neonates, which in all probability is due to its reduced clearance. As a corollary the plasma M3G/morphine ratio was considerably higher in children than in neonates. A direct correlation between the *in vitro* glucuronidation of morphine to M3G in human liver microsomes and the M3G/morphine ratios in plasma and urine has been reported previously (Säwe *et al.*, 1985).

The lowered clearance of morphine in the neonate is probably due to a reduction in the metabolism of morphine. In addition, renal function in the newborn is usually impaired (Aperia *et al.*, 1981). The clearance of morphine in adult patients is not affected by renal failure (Aitkenhead *et al.*, 1984; Chauvin *et al.*, 1987; Säwe & Odar-Cederlöf, 1987). The impaired renal function in the newborn will, however, result in higher plasma concentrations of M3G as the glucuronides are excreted more slowly in patients with impaired renal function (Chauvin *et al.*, 1987; Säwe & Odar-Cederlöf, 1987). In spite of this the M3G/morphine ratios were lower in newborns. Thus, immature renal function is the most likely explanation for the similarity in the plasma concentrations of M3G in the children and neonates, and the lower ratios are a sign of a lower metabolic rate.

It is of interest that the M3G/M6G ratio was relatively constant in all of the patients studied, irrespective of age. This suggests that the glucuronidation of morphine to M3G and M6G is controlled by the same or similar regulatory mechanisms.

There was a significant correlation between the M3G/morphine ratio in plasma and urine in the seven neonates who had both samples collected simultaneously. This suggests that the urinary M3G/morphine ratio may be a useful tool to study the development of glucuronidation in the neonatal period. Using urine in this age group obviates the need for collection of blood samples in a sick neonate who has a small total

blood volume. Further studies are required to confirm the use of urinary M3G/morphine ratios as an accurate marker of morphine glucuronidation as there was no correlation between plasma and urine data in the five children who had both samples collected. This may be a reflection of the small number of samples or related to the timing of the urine collection in that up to 24 h urine was collected in the children whereas a single sample at steady-state was collected in the neonates.

Although M6G was not detected in the plasma of any neonate, this is related to the sensitivity of the assay (limit of sensitivity 40 ng ml^{-1}) and the limited plasma volume available for analysis, as M6G was detected in five of the seven neonatal urine samples. M3G is an inactive metabolite, whereas M6G is more potent than morphine in animals (Shinomura *et al.*, 1971). M6G has been shown to be an effective analgesic when given to adults and it has even been suggested that the analgesic activity of morphine is dependent on the formation of this metabolite (Osborne *et al.*, 1988). It is more likely however that both morphine and M6G contribute to the analgesic effect and, therefore, lower doses of morphine may be effective in premature neonates. The relationship between morphine, M6G and efficacy requires further study, in particular in the neonatal period when opioid receptors may not be fully developed (Leslie *et al.*, 1982).

I. A. Choonara is on a MRC Travelling Fellowship.

This work was supported by grants from the Swedish Medical Research Council (14X-04496), The Swedish Cancer Society, the Nordiska Samfundet mot Plågsamma Djurförsök and the Candlelighters.

We thank Mrs Annika Lundin for typing the manuscript and Mrs Lena Lenhammar for technical advice and assistance.

References

Aitkenhead, A. R., Vater, M., Achola, K., Cooper, C. M. S. & Smith, G. (1984). Pharmacokinetics of single-dose i.v. morphine in normal volunteers and patients with endstage renal failure. *Br. J. Anaesth.*, **56**, 813–819.

Anand, K. J. S., Sippell, W. G. & Aynsley-Green, A. (1987). Randomized trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet*, **i**, 243–247.

Aperia, A., Broberger, O., Elinder, G., Herin, P. & Zetterström, R. (1981). Postnatal development of renal function in pre-term and full-term infants. *Acta Paediatr. Scand.*, **70**, 183–187.

Bray, R. J. (1983). Postoperative analgesia provided by morphine infusion in children. *Anaesthesia*, **38**, 1075–1078.

Chauvin, M., Sandouk, P., Scherrmann, J. M., Farinotti, R., Strumza, P. & Duvaldestin, P. (1987). Morphine pharmacokinetics in renal failure. *Anesthesiol.*, **66**, 327–331.

Choonara, I. A. (1989). Pain relief. *Arch. Dis. Child.* (in press).

Christensen, C. B. & Jørgensen, L. N. (1987). Morphine-6-glucuronide has high affinity for the opioid receptor. *Pharmac. Tox.*, **60**, 75–76.

Dahlström, B., Bolme, P., Feychting, H., Noack, G. & Paalzow, L. (1979). Morphine kinetics in children. *Clin. Pharmac. Ther.*, **20**, 354–365.

Dilworth, N. M. & MacKellar, A. (1987). Pain relief for the pediatric surgical patient. *J. Pediatr. Surg.*, **22**, 264–266.

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

Leslie, F. M., Tso, S. & Hurlbut, D. E. (1982). Differential appearance of opiate receptor subtypes in neonatal rat brain. *Life Sci.*, **31**, 1393–1396.

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

Miller, R. P., Roberts, R. J. & Fischer, L. J. (1976). Acetaminophen elimination kinetics in neonates, children and adults. *Clin. Pharmac. Ther.*, **19**, 284–294.

Miser, A. W., Miser, J. S. & Clark, B. S. (1980). Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. *J. Pediatr.*, **96**, 930–932.

Nahata, M. C., Miser, A. W., Miser, J. S. & 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.

Pacifici, G. M., Säwe, J., Kager, L. & Rane, A. (1982). Morphine glucuronidation in human fetal and adult liver. *Eur. J. clin. Pharmac.*, **22**, 553–558.

Persson, K., Lindström, B., Spalding, D., Wahlström, A. & Rane, A. (1989). Determination of codeine and its metabolites in human blood plasma and in microsomal incubates by high performance liquid chromatography with ultra violet detection. *J. Chromatogr.* (in press).

Rane, A. (1989). Basic principles of drug disposition and action in infants and children. In *Pediatric Pharmacology*, ed. Yaffe, S. J. (in press).

Rane, A. & Wilson, J. T. (1976). Clinical pharmacokinetics in infants and children. *Clin. Pharmacokin.*, **1**, 2–24.

Rollins, D. E., von Bahr, C., Glaumann, H., Moldéus, P. & Rane, A. (1979). Acetaminophen: Potentially toxic metabolite formed by human fetal and adult

liver microsomes and isolated fetal liver cells. *Science*, **205**, 1414–1416.

Säwe, J., Kager, L., Svensson, J. O. & Rane, A. (1985). Oral morphine in cancer patients: in vivo kinetics and in vitro hepatic glucuronidation. *Br. J. clin Pharmac.*, **19**, 495–501.

Säwe, J. & Odar-Cederlöf, I. (1987). Kinetics of morphine in patients with renal failure. *Eur. J. clin. Pharmac.*, **32**, 377–382.

Säwe, J., Svensson, J. O. & Rane, A. (1983). Morphine metabolism in cancer patients on increasing oral doses – no evidence for autoinduction or dose-dependency. *Br. J. clin. Pharmac.*, **16**, 85–93.

Shimomura, K., Kanaat, O., Ueki, S., Ida, S., Oguri, K., Yoshimura, H. & Tsukamoto, H. (1971). Analgesic effect of morphine glucuronides. *Tohaku J. exp. Med.*, **105**, 45–52.

Svensson, J. O., Rane, A., Säwe, J., Sjöqvist, F. (1982). Determination of morphine, morphine-3-glucuronide and (tentatively) morphine-6-glucuronide in plasma and urine using ion-pair high-performance liquid chromatography. *J. Chromatogr.*, **230**, 427–432.

Tomson, G., Lunell, N. O., Sundsvall, A. & Rane, A. (1979). Placental passage of oxazepam and its metabolism in mother and newborn. *Clin. Pharmac. Ther.*, **25**, 74–81.

Vanderberghe, H., MacLeod, S., Chinyanga, M., Endrenyi, L. & Soldin, S. (1983). Pharmacokinetics of intravenous morphine in balanced anesthesia: studies on children. *Drug Metab. Reviews*, **14**, 887–903.

(Received 25 April 1989, accepted 30 June 1989)