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Morphine metabolism in neonates and infants

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The metabolism of morphine was studied in seven fullterm neonates and five infants receiving a continuous infusion of morphine. All the patients had detectable plasma concentrations of morphine 3-glucuronide (M3G) and 10 had detectable concentrations of morphine 6-glucuronide (M6G). The mean plasma clearance of morphine was 20.1 ml min^{-1} kg^{-1} in neonates and 23.4 ml min^{-1} kg^{-1} in the group as a whole. The M3G/morphine ratio (7.3) was higher than that previously reported for preterm neonates (5.0) but lower than that reported for children (23.9).

Keywords morphine glucuronidation neonates infants

Introduction

The importance of analgesia in children and neonates has been recognised (Anand *et al.*, 1987; Choonara, 1989, 1992). Morphine is the most commonly used drug for paediatric patients with severe pain and its metabolism has been studied in adults (Säwe *et al.*, 1983) and children (Choonara *et al.*, 1989). The major metabolites of morphine are morphine 3-glucuronide (M3G) and morphine 6-glucuronide (M6G) which are present in plasma in significantly greater concentrations than morphine itself in both adults (Säwe *et al.*, 1983, 1985) and children (Choonara *et al.*, 1989). M6G has significant analgesic properties (Osborne *et al.*, 1988; Shimomura *et al.*, 1971) and we have previously reported that newborn infants are capable of forming the active metabolite M6G, by confirming its presence in urine (Choonara *et al.*, 1989). We were, however, unable to measure plasma concentrations of M6G previously because of both the volume of blood required from each infant and also the sensitivity of the assay. More sensitive assays for the measurement of morphine metabolites are now available, allowing more detailed studies to be undertaken.

Methods

Plan of study

Written informed consent was obtained from parents and the study was approved by the Hospital Ethics Committee. Blood samples were collected from 12 neonates and infants. The clinical details of the patients are shown in Table 1. All were born at 37–40 weeks gestation except for patient B1 who was preterm (28 weeks gestation). All had a plasma creatinine within the normal range (20–90 μmol l^{-1}) except for patient A5 who had a plasma creatinine of 105 μmol l^{-1}. Most of the patients were receiving other medication including vecuronium and antibiotics.. All were patients on the Regional Paediatric Intensive Care Unit and at the time of the study were ventilated and receiving morphine by infusion for analgesia. A single blood sample (1 ml) was collected after at least 48 h of constant rate infusion of morphine.

Table 1 Clinical details of the infants

Patient	*Age (days)*	*Weight (kg)*	*Diagnosis*	*Morphine infusion rate (μg kg^{-1} h^{-1})*
A1	3	3.0	Gastroschisis	33.6
A2	6	3.1	Diaphragmatic hernia	51.3
A3	3	2.2	Gastroschisis	18.2
A4	3	2.6	Diaphragmatic hernia	19.6
A5	6	2.7	Bowel resection	22.2
A6	3	3.0	Gastroschisis	20.0
A7	15	3.3	Cystic hygroma	12.1
	(months)			
B1	4	2.5	Bronchiolitis	8.0
B2	4	6.4	Brain tumour	47.2
B3	6	8.4	Bronchiolitis	11.9
B4	8	8.7	Pneumonia	23.0
B5	11	8.5	Encephalitis	23.5

Analytical methods

Analysis of morphine and its metabolites, M3G and M6G, was performed by h.p.l.c. employing fluorescence

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Table 2 Plasma concentrations of morphine and its glucuronides and associated pharmacokinetic parameters in neonates and infants

Patient	Plasma concentration (ng ml^{-1}) Morphine	M3G	M6G	CL (ml min^{-1})	CL (ml min^{-1} kg^{-1})	Plasma M3G/M	M6G/M	M3G/M6G
A1	29	181	94	59	20	6.3	3.3	1.9
A2	41	194	84	65	21	4.8	2.1	2.3
A3	9	216	92	74	34	23.9	10.2	2.3
A4	8	77	34	101	39	9.2	4.1	2.3
A5	ND	275	63	–	–	–	–	4.4
A6	79	116	32	11	4	1.5	0.4	3.6
A7	66	145	42	10	3	2.2	0.6	3.5
B1	ND	10	6	–	–	–	–	1.8
B2	66	162	52	76	12	2.5	0.8	3.1
B3	4	30	19	463	55	8.2	5.4	1.5
B4	ND	53	ND	–	–	–	–	–
B5	ND	17	ND	–	–	–	–	–
Mean				53	23	7.3	3.4	2.7
s.d.				36	18	7.3	3.3	0.9
Mean for neonates A1–A7				108	20	8.0	3.4	2.8
s.d.				147	15	8.3	3.6	1.1

detection, according to the method of Venn & Michalkiewicz (1990). The h.p.l.c. system consisted of an LKB 2249 gradient pump with an LKB 2156 solvent conditioner and an LKB 2157 autosampler. A Merck-Hitachi F1050 fluorescence detector (excitation wavelength 280 nm, emission wavelength 335 nm) was coupled to a JCL6000 chromatography data system. The column used was a Techsphere 5C8 (250 mm × 4.6 mm i.d., 5 μm particle size, HPLC Technology, Macclesfield, UK) with an octyl precolumn. All solvents were of h.p.l.c. grade. Data were quantified by comparing the peak areas with those of standards run daily. The limit of determination for all three analytes was 1 ng ml^{-1}. The coefficients of variation for the assays of morphine, M3G and M6G at 2 ng ml^{-1} ranged from 2.3 to 3.7. The coefficients of variation for day to day variability ranged from 1.6 to 2.9. The recoveries of 2 ng in 200 μl plasma for morphine, M3G and M6G ranged from 94.9% to 97.9% (coefficients of variation 2.1 to 4.1).

Calculations

Steady state plasma drug concentrations in neonates are achieved by 48 h (Lynn & Slattery, 1987). Plasma clearance was calculated by dividing the infusion rate by the steady state plasma drug concentration. All results are expressed as the mean ± s.d.

Results

M3G was measurable in all the samples. M6G was detectable in all but two of the samples whereas morphine was detectable in all but four of the 12 samples. The concentrations of M3G, M6G and morphine are shown in Table 2 alongside the plasma clearance of morphine and the ratios of the metabolites to morphine and the ratio of M3G to M6G. The mean plasma clearance of morphine was 20.1 ml min^{-1} kg^{-1} in the seven neonates and 23.4 ml min^{-1} kg^{-1} in the group of infants as a whole.

Discussion

The results confirm that neonates have a well-developed mechanism for the glucuronidation of morphine at both the 3- and 6-positions. In ontogenetic terms morphine UDP-glucuronosyl transferase activity is present at an early stage in human gestation, being demonstrated in liver samples from a 15 week old foetus (Pacifici *et al.*, 1982).

In all cases plasma M3G concentrations were higher than those of morphine, while plasma M6G concentrations were greater than those of morphine in 7 of the 10 infants in whom M6G was detectable. This is consistent with our previous findings in children where M3G concentrations in both plasma and urine, and M6G in urine were higher than those of morphine (Choonara *et al.*, 1989). Studies in adults have shown that these two metabolites are present in plasma at significantly higher concentrations than morphine itself (Säwe *et al.*, 1985).

The plasma M3G/morphine ratio is a useful index of glucuronidation in the presence of normal renal function and this study in fullterm neonates and infants demonstrated a higher ratio (7.3) than that found in preterm neonates (5.0) but lower than that found in children (23.9) (Choonara *et al.*, 1989). This is consistent with studies suggesting that the clearance of morphine is dependent on the level of glucuronidation and that this is lower in neonates and more markedly so in preterm neonates (Choonara *et al.*, 1989).

The mean plasma clearance of morphine in the fullterm neonates in this study was 20.1 ml min^{-1} kg^{-1} and this is higher than that previously reported in preterm infants (4.7 ml min^{-1} kg^{-1} (Choonara *et al.*, 1989), 3.4–15.5 ml min^{-1} kg^{-1} (Bhat *et al.*, 1990), and 3.6 ml min^{-1} kg^{-1} (Barrett *et al.*, 1991)). The study by Bhat and co-workers reported increasing clearance with increasing gestational age (3.4 ml min^{-1} kg^{-1} in infants under 30 weeks gestation, 9.6 ml min^{-1} kg^{-1} in infants of 31–37 weeks gestation, and a value of 15.5 ml min^{-1} kg^{-1} in the 3 fullterm infants studied). There was considerable inter-individual variation in both clearance and indices of glucuronidation (M3G and M6G to

morphine ratios). This is consistent with previous studies of the pharmacokinetics of morphine in preterm infants (Bhat *et al.*, 1990). Owing to the small number of patients in this study we are unable to comment on differences in clearance and glucuronidation between neonates and infants and further studies are required to document any changes in glucuronidation through infancy.

Both M3G and M6G retain significant pharmacological properties and are therefore of importance. M6G is a potent opioid agonist (Osborne *et al.*, 1988), whereas M3G functionally antagonises some of the effects of both morphine and M6G (Gong *et al.*, 1991). Considering these opposing properties, the proportions of the two metabolites formed are clearly relevant. In this respect the ratio of M3G:M6G found in neonates is markedly lower than previously demonstrated in adults or children. In adults, chronic oral morphine treatment produces variable plasma ratios of M3G:M6G, with reported mean ratios of 10:1 (Hand *et al.*, 1987), 6:1 (Venn *et al.*, 1990) and 5:1 (McQuay *et al.*, 1990). A study of a single intravenous dose of morphine in adults found a plasma ratio of M3G:M6G of 8.5 (Hasselström *et al.*, 1990). Urinary ratios of 10:1 for M3G:M6G have been observed in children (Choonara *et al.*, 1989). However, the present data show a mean plasma ratio for M3G:M6G of less than 3:1 in neonates.

There is now overwhelming evidence that UDPGTs exist as a multigene family resulting in a range of isoenzymes (Mulder *et al.*, 1990), and at least eleven different forms of UDPGT have been identified (Mackenzie & Haque, 1988). Moreover, morphine has been demonstrated to be metabolised to M3G by more than one UDPGT isoenzyme (Miners *et al.*, 1988). More recently, however, a functional heterogeneity has been observed between the isoenzymes responsible for the glucuronidation of morphine in the 3- and 6-positions (Lawrence *et al.*, 1992). Therefore, the possibility exists that the low ratio of M3G:M6G observed could represent a differential development of these UDP-glucuronosyl transferases.

It is not possible to say what plasma concentrations of morphine and M6G are associated with satisfactory analgesia in infants and also the dose requirements will vary with the medical diagnosis and other procedures. Our study does, however, show that newborn infants can form the active metabolite M6G and that further studies are needed to assess the plasma concentrations of morphine and M6G in terms of analgesic activity.

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