Infants and young children metabolise codeine to morphine. A study after single and repeated rectal administration

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- 1 Codeine was administered rectally to thirteen infants and young children undergoing elective surgery. Nine infants (6–10 months old) received a 4 mg suppository and four children (3–4 years old) an 8 mg suppository. Codeine and its metabolite morphine were measured in plasma by GC/MS.
- 2 The mean concentrations of codeine at 3, 4 and 5 h after administration were 240, 163 and 123 nmol l⁻¹ in the younger and 309, 251 and 169 nmol l⁻¹ in the older patients. The corresponding concentrations of morphine were 8.3, 7.4 and 4.5 nmol l⁻¹ and 6.8, 5.5 and 2.8 nmol l⁻¹ respectively. One patient in each age group had no detectable amounts of morphine.
- 3 In the four children, the rectal dose was repeated 6-hourly for four doses. The plasma concentrations of codeine and morphine following the fifth dose were similar to those after the first dose. The mean AUC(0,5 h) of morphine was 1.6% that of codeine.
- 4 In the infants the mean plasma half-lives of codeine and morphine were 2.6 and 2.5 h. The two infants with the lowest body weights had the longest half-lives.
- 5 The mean morphine/codeine concentration ratio was 4.3% in the infants and 1.6% in the children, suggesting impaired glucuronidation of morphine in the former group. The hourly concentration ratios were almost identical following the first and fifth dose in the children.
- 6 We conclude that at the age of 6 months infants are capable of *O*-demethylating codeine to morphine.

Keywords infants children codeine morphine *O*-demethylation rectal administration

Introduction

Although codeine has been widely used for about 150 years, its pharmacokinetics in man have been investigated mainly during the last 10 years (Guay *et al.*, 1987; Findlay *et al.*, 1977, 1978, 1986; Quiding *et al.*, 1986; Rogers *et al.*, 1982). In two studies (Guay *et al.*, 1987; Quiding *et al.*, 1986) the plasma concentrations of codeine and its *O*-demethylated metabolite morphine were determined after single and repeated oral administration in healthy adult volunteers. The hypothesis that codeine acts through biotransformation to morphine was proposed over 40 years ago (Sanfilippo, 1948). Furthermore, the 6-glucuronide metabolite of morphine seems to exert an analgesic effect in man (Hanna *et al.*, 1990; Osborne *et al.*, 1988).

No pharmacokinetic study of codeine seems to have

been conducted in children. However, it was shown that human foetal liver microsomes cannot *O*-demethylate codeine (Ladona *et al.*, 1989). The present investigation was undertaken to determine whether infants and young children are capable of demethylating codeine to morphine. In addition, the plasma concentrations of codeine and morphine following the first dose were compared with those achieved at apparent steady state, i.e. following repeated administration over 24 h. The study was conducted in infants and children undergoing elective surgery and codeine was administered rectally.

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Methods

Thirteen infants and children participated in the study. Nine were between the ages of 6 and 10 months and four were between 3 and 4 years. All were scheduled for elective surgery (repair of coarctation aorta, ligation of patent ductus arteriosus and repair of gastro-oesophageal reflux). The surgery was performed under general anaesthesia and an arterial catheter was inserted for the purpose of anaesthetic monitoring. The children were premedicated with atropine and/or diazepam 30–60 min before induction of anaesthesia with thiopentone. Intubation was performed after injection of pancuronium or suxamethonium and the anaesthetic was maintained with isoflurane and N₂O/O₂. Ventilation was controlled using a Servoventilator 900 B. In the older age group three patients received additional analgesic treatment with pethidine in the postoperative period. Informed consent was obtained from the parents and the study was approved by the Ethics Committee of the Karolinska Hospital, Stockholm, Sweden.

After induction of anaesthesia one suppository of 4 mg codeine phosphate was administered to the infants while the children received an 8 mg codeine phosphate suppository. In the latter group another suppository (8 mg) was administered every 6th hour for a total of five doses. Plasma samples were taken from the indwelling arterial catheter at 3, 4 and 5 h after the administration of the first suppository. Plasma samples were also drawn from the children at 0, 1, 2, 3, 4 and 5 h after the administration of the fifth suppository on the day after surgery. In one of the infants one plasma sample was taken after 1 h instead of after 4 h. All samples were centrifuged within 2 h and the plasma was separated and stored at –20° C until analysis.

The suppositories contained codeine phosphate and Witepsol H15 and were specially prepared and supplied by Astra Läkemedel AB, Södertälje, Sweden. The morphine content in the suppositories was less than 0.01% of that of codeine. The analyses of unconjugated codeine and morphine in plasma were carried out by gas chromatography-mass spectrometry and the lower limits of determination were 3.3 and 1.4 nmol l⁻¹, respectively. The analytical procedure has been described in detail elsewhere (Quiding *et al.*, 1986). The disposition rate constants (λ_z) for codeine and morphine were calculated from the plasma drug concentration-time curves using linear regression analysis. Data at 3, 4 and 5 h were used for the first dose and data from 1 to 5 h for the fifth dose. The half-lives were obtained from $\ln 2/\lambda_z$. Using the trapezoidal rule, the area under the plasma drug concentration-time curve was calculated from 0 to 5 h AUC(0,5) during steady conditions, i.e. after the fifth dose. The logarithmic trapezoidal rule was applied to the declining part of the curve. For two patients having morphine concentrations below the limit of determination at hour 5, this concentration was estimated by extrapolation using the disposition rate constant.

Results

Demographic data for the nine infants (6–10 months) and the four young children (3–4 years) are given in Table 1. Their mean weights were 7.9 and 15.0 kg, respectively. The dose kg⁻¹ body weight ranged from 0.4 to 0.8 mg in the infants and from 0.4 to 0.7 mg in the children.

Individual plasma concentrations of codeine and its metabolite morphine are shown in Figures 1 and 2. One

Table 1 Demographic data and half-lives of codeine and morphine after rectal administration of codeine to infants (6–10 months) and children (3–4 years)

Patient	Sex	Age (months)	Weight (kg)	Dose of codeine (mg) phosphate	First dose		Fifth dose	
					t _{1/2} Codeine (h)	t _{1/2} Morphine (h)	t _{1/2} Codeine (h)	t _{1/2} Morphine (h)
6–10 months								
1	M	10	9.2	4	1.9	1.6	—	—
2	F	6	6.9	4	1.1	1.6	—	—
3	F	8	6.2	4	4.6	4.4	—	—
4	F	6	5.2	4	6.9	4.8	—	—
5	F	7	8.0	4	1.1	1.3	—	—
6	M	6	8.2	4	1.5	*	—	—
7	F	9	8.5	4	2.4	1.9	—	—
8	M	8	8.8	4	2.3	2.2	—	—
9	F	10	10.3	4	1.9	**	—	—
Mean		7.8	7.9		2.6	2.3		
s.d.		±1.6	±1.6		±1.9	±1.4		
3–4 years								
1	M	31	11.0	8	2.0	2.1	1.8	1.8
2	M	52	15.5	8	4.3	2.0	1.8	1.5
3	F	43	15.3	8	2.0	0.8	1.6	3.5
4	F	40	18.0	8	2.1	*	2.7	*
Mean		42	15.0		2.6	1.6	2.0	2.3
s.d.		±8.7	±2.9		±1.1	±0.7	±0.5	±1.1

* Not calculated—all plasma concentrations (3, 4 and 5 h) below the limit of determination.

** Not calculated—plasma concentration at 3 h below the limit of determination.

Figure 1 Individual plasma concentrations of codeine and morphine in infants aged 6–10 months after rectal administration of a suppository containing 4 mg codeine phosphate.

Figure 2 Individual plasma concentrations of codeine and morphine in children aged 3–4 years after rectal administration of a suppository containing 8 mg codeine phosphate.

patient in each age group had no detectable morphine ($<1.4 \text{ nmol l}^{-1}$). The plasma concentration-time profiles were similar both within and between the age groups. Mean plasma drug concentrations are shown in Table 2. The maximum plasma concentrations of codeine and morphine occurred at or before the first hour after drug administration.

Individual and mean half-lives of codeine and morphine are listed in Table 1. The mean half-lives of codeine and morphine were 2.6 and 2.5 h in the infants while the corresponding values were 2.6 and 1.6 h after the first dose and 2.0 and 2.3 h after the fifth dose in the children. After the fifth dose the mean values of AUC (0,5) for codeine and morphine were $1447 \text{ nmol l}^{-1} \text{ h}$ (range 687–1915) and $25.9 \text{ nmol l}^{-1} \text{ h}$ (range 0–52.6), respectively. The mean AUC(0,5) of morphine was 1.6% (range 0–3.0%) that of codeine. The hourly mean plasma concentration ratios of morphine/codeine are shown in Table 2. After the first dose the individual ratios for hours 3 to 5 ranged from 0 to 11.4% (mean 4.3%) in the infants and from 0 to 3.7% (mean 1.6%) in the children. Detectable concentrations of morphine were obtained in eight infants and three children and in these patients the mean ratios of morphine/codeine were 4.9, 5.7 and 4.7% and 2.4, 2.3 and 1.8% respectively, at 3, 4 and 5 h after the first dose. The Wilcoxon two-sample test at 3, 4 and 5 h ($P = 0.18$, $P = 0.04$ and $P = 0.05$, respectively) indicated that infants had a higher ratio than children.

Discussion

The pharmacokinetics of codeine have not been investigated previously in infants or children. The present results were obtained in patients undergoing surgery and an influence of the anaesthetic procedures cannot be excluded. Because of ethical considerations only a limited number of blood samples could be taken. After the first dose the estimation of the half-life was based on three samples and should therefore be considered as an approximation. However, the plasma concentrations of codeine and morphine showed a fairly consistent pattern both within and between the two age groups. One of the children weighed only 11 kg and the plasma drug concentrations in this child were somewhat higher than those in the other children of this age group. The absorption of codeine and its demethylation to morphine were rapid as both compounds had reached maximum plasma concentrations in the first sample 1 h after the fifth dose.

In the infants the mean half-lives of both codeine and morphine were about 2.5 h. However, the two infants (numbers 3 and 4) with the lowest body weights had half-lives which were about 2 h longer. One explanation for this could be a reduced metabolic capacity. In the children the mean half-lives of codeine and morphine were 2.6 and 1.6 h after the first administration and 2.0 and 2.3 h after the fifth dose. The AUC (0,5) of morphine as a percentage of the AUC(0,5) of codeine

Table 2 Mean plasma concentrations of codeine and morphine after rectal administration of codeine to nine infants and four young children

	First dose						Fifth dose					
	Infants			Children			Children			Children		
	3 h	4 h	5 h	3 h	4 h	5 h	0 h	1 h	2 h	3 h	4 h	5 h
C_{codeine} (nmol l ⁻¹)	240	163	123	309	251	169	125	527	378	258	180	113
s.d.	±85	±71	±65	±121	±99	±57	±50	±220	±148	±104	±58	±38
C_{morphine} (nmol l ⁻¹)	8.3	7.4	4.5	6.8	5.5	2.8	3.3	10.2	6.1	5.2	3.5	1.1
s.d.	±5.1	±3.5	±2.7	±6.8	±6.3	±3.5	±2.4	±9.1	±6.0	±4.3	±3.1	±2.1
$\frac{C_{\text{morphine}}}{C_{\text{codeine}}} \times 100(\%)$	3.9	5.0	4.2	1.8	1.8	1.3	2.3	1.6	1.3	1.8	1.9	1.1
s.d.	±3.4	±3.4	±3.2	±1.5	±1.5	±1.5	±1.8	±1.3	±1.2	±1.4	±1.7	±2.2

ranged from 0 to 3.0% after the fifth dose. These results correspond with those obtained after multiple oral dosing with 60 mg codeine to 12 adult healthy volunteers, using the same method of drug analysis (Quiding *et al.*, 1986). The half-lives of codeine and morphine in the adult volunteers were 2.2 and 2.9 h after the second dose and 2.5 and 4.2 h after the seventh dose. The AUC(0,8) of morphine as a percentage of the AUC(0,8) of codeine ranged from 0 to 4.4% after the seventh dose.

In adults codeine is predominantly metabolised by glucuronidation but may also undergo *N*- and *O*-demethylation to form norcodeine and morphine, respectively. A genetic polymorphism in *O*-demethylation has been shown in adult healthy volunteers (Chen *et al.*, 1988, Yue *et al.*, 1989) and *in vitro* using liver biopsies (Dayer *et al.*, 1988; Mortimer *et al.*, 1990). In foetal human liver microsomes codeine *O*-demethylation does not occur while *N*-demethylation is comparable with that in adults (Ladona *et al.*, 1989). The present results show that infants of 6 months of age are capable of *O*-demethylating codeine to morphine. The absence of morphine in two patients may reflect a genetic inability to carry out this reaction. Neonates (Choonara *et al.*, 1987) and newborns (Lynn & Slattery, 1987) appear to have a reduced capability of forming the glucuronide conjugates of morphine. The sulphation of morphine is more marked in neonates than in children but it is a minor pathway (Choonara *et al.*, 1990). In foetal liver microsomes the *N*-demethylation of

morphine to normorphine is comparable with that in adults (Ladona *et al.*, 1989). In this study the mean plasma concentration ratio of morphine/codeine was 4.3% in the infants and 1.6% in the children. It is unlikely that polymorphism could explain the difference in ratios as this would mean that virtually all of the children were poor metabolisers whereas the infants were not. It is more probable that the glucuronidation of morphine and possibly of codeine, is somewhat impaired in the infants. However, measurement of the metabolites of both codeine and morphine would be necessary to confirm this.

The chemical analyses measured free and protein bound drugs together. Although children may have a decreased plasma protein binding and consequently an increased unbound fraction it is believed that the free concentrations of codeine and morphine would only be marginally affected since the extent of protein binding in adults is only about 30% (Judis, 1977; Kurz *et al.*, 1977). Our plasma drug concentration data indicate that a rectal dose of codeine of about 0.5 mg kg⁻¹ to children results in concentrations of codeine and morphine which are similar to or somewhat higher than those after a 60 mg oral dose of codeine to healthy adult male volunteers (Quiding *et al.*, 1986).

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