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Pharmacokinetics of codeine and its metabolites in Caucasian healthy volunteers: comparisons between extensive and poor hydroxylators of debrisoquine

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1 The kinetics of codeine and seven of its metabolites codeine-6-glucuronide (C6G), norcodeine (NC), NC-glucuronide (NCG), morphine (M), M-3 (M3G) and 6-glucuronides (M6G), and normorphine (NM) were investigated after a single oral dose of 50 mg codeine phosphate in 14 healthy Caucasian subjects including eight extensive (EM) and six poor (PM) hydroxylators of debrisoquine. The plasma and urine concentrations of codeine and the metabolites were measured by h.p.l.c.

2 The mean area under the curve (AUC), half-life and total plasma clearance of codeine were 1020 ± 340 nmol l^{-1} h, 2.58 ± 0.57 h and 2.02 ± 0.73 l h^{-1} kg^{-1}, respectively. There were no significant differences between EM and PM in these aspects.

3 PM had significantly lower AUC of M3G, the active metabolites M6G, NM and M ($P < 0.0001$), and lower partial metabolic clearance by *O*-demethylation ($P < 0.0001$). In contrast, the PM had higher AUC of NC ($P < 0.05$) than the EM. There was no difference between PM and EM in the AUC of C6G and NCG, nor in the partial clearances by *N*-demethylation and glucuronidation.

4 Among EM, the AUC of C6G was 15 times higher than that of codeine, which in turn was 50 times higher than that of M. The AUCs of M6G and NM were about 6 and 10 times higher than that of M, respectively. The partial clearance by glucuronidation was about 8 and 12 times higher than those by *N*- and *O*-demethylations, respectively.

5 The total recovery of drug-related material in 48 h urine collections ranged from 71% to 106% of the dose and did not differ between EM and PM. Six percent of the dose was *O*-demethylated in EM and the majority of the metabolites produced through this pathway were conjugated. Unconjugated M accounted for less than 0.2% of the dose. In PM, only 0.33% of the dose was metabolized by *O*-demethylation and M was negligible (0.001% of the dose). However, PM had a significantly higher recovery of NC ($P < 0.001$) than EM. There was no significant difference between EM and PM in the recovery of codeine, C6G and NCG, and in the renal clearance of codeine or any of its metabolites.

6 Data from a chronic dosing study including three EM and three PM confirmed the results of the single dose study.

7 The clinically important findings were the negligible plasma concentration of the *O*-demethylated active metabolites M6G, NM and M in PM, and the relatively high concentrations of M6G and NM in EM. Considering the low plasma concentration of M as well as the potent analgesic effects of M6G and NM, the latter compounds might play an important role in the analgesic effect of codeine.

Keywords codeine metabolism active metabolites pharmacokinetics pharmacogenetics Caucasian debrisoquine phenotype

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Introduction

Codeine is a commonly used analgesic and antitussive drug. Its pharmacokinetics in man (Findlay *et al.*, 1977, 1978; Guay *et al.*, 1987; Quiding *et al.*, 1986) and the influence of smoking (Rogers *et al.*, 1982), alcohol (Bodd *et al.*, 1987) as well as renal disease (Guay *et al.*, 1988) have been investigated. The hypothesis that codeine may exert its moderate analgesic potency through partial biotransformation to morphine (M) has been proposed (Sanfilippo, 1948), and the biotransformation of codeine to M in man by *O*-demethylation has been demonstrated (Findlay *et al.*, 1978; Guay *et al.*, 1987, 1988; Quiding *et al.*, 1986; Rogers *et al.*, 1982). Apart from M, two other metabolites of codeine *O*-demethylation, morphine-6-glucuronide (M6G) and normorphine (NM), have also been shown to be active. Much stronger analgesic potency has been reported for M6G compared with M (Hand *et al.*, 1987; Joel *et al.*, 1985; Osborne *et al.*, 1988; Paul *et al.*, 1989; Shimomura *et al.*, 1971; Yoshimura *et al.*, 1973). Figure 1 shows the major metabolic pathways of codeine.

It is well recognised that some drugs are metabolised by pathways that are under monogenic control. Among the best studied pathways showing genetic polymorphism is debrisoquine-type hydroxylation; 5–10% of Caucasians are classified as 'poor hydroxylators' (PM) while the remainder are 'extensive hydroxylators' (EM) (Mahgoub *et al.*, 1977; Steiner *et al.*, 1988). *O*-demethylation of codeine, leading to the formation of the active metabolites M, M6G and NM, has been found to co-segregate with the debrisoquine oxidation polymorphism (Chen *et al.*, 1988; Dayer *et al.*, 1988; Yue *et al.*, 1988, 1989a, 1989b). We have now studied the pharmacokinetics of codeine and its metabolites in PM and EM of debrisoquine.

Methods

Fourteen healthy Caucasians, including eight EM and six PM of debrisoquine, participated in this single dose study which was approved by the Ethics Committee of Huddinge University Hospital. Informed consent was obtained from all subjects. The subject characteristics and debrisoquine metabolic ratios (MR) are presented in Table 1. Each subject was phenotyped with a single 10 mg oral dose of debrisoquine hemisulphate (Declinax, Hoffmann-La Roche). The ratio of parent drug and the 4-hydroxy-metabolite (D/4-OH-D) was measured in an aliquot of a 8 h urine collection. Debrisoquine and 4-OH-D were measured by gas chromatography with flame-ionization detection according to Lennard *et al.* (1977). A PM was defined as having a MR > 12.6 (Evans *et al.*, 1980).

On a separate occasion, the subjects were given a single oral dose of 50 mg codeine phosphate (Kodein®, ACO Drugs AB, Sweden) following an overnight fast. Blood samples (10 ml) were obtained through an indwelling intravenous catheter into heparinized Vacutainer® tubes before and 0.17, 0.33, 0.5, 0.67, 1, 1.5, 2, 3, 4, 5, 7, 9, 11 and 24 h after the dose. The samples were centrifuged and the plasma was stored at −20° C until analysis. Serial urine samples were collected for 48 h from 0–2, 2–4, 4–6, 6–8, 8–10, 10–12, 12–24, 24–36 and 36–48 h. Urine volumes and pH were measured and aliquots were stored at −20° C until analyzed.

Another six healthy volunteers, including three EM with MRs between 0.34 and 0.68 (aged 27 to 33 years) and three PM with MRs between 37 and 64 (aged 28 to 41 years), received multiple doses of codeine. Following the first dose, blood and urine samples were collected for 24 h. From day 2 (after 24 h), codeine (50 mg) was administered regularly every 6 h for nine doses. Blood samples were collected for 30 h and urine samples for 48 h after the last dose.

Codeine and its seven known metabolites morphine (M), M-3- (M3G), and M-6-glucuronide (M6G), normorphine (NM), codeine-6-glucuronide (C6G), norcodeine (NC), NC-glucuronide (NCG) in both plasma and urine were measured using ion-pair high performance liquid chromatography by a modification of the method of Svensson (1986) as described in Yue *et al.* (1989a). For the sources of all the chemicals see Yue *et al.* (1989a) and Svensson (1986).

The area under the curve (AUC) of codeine was calculated by the linear trapezoidal rule and extrapolated

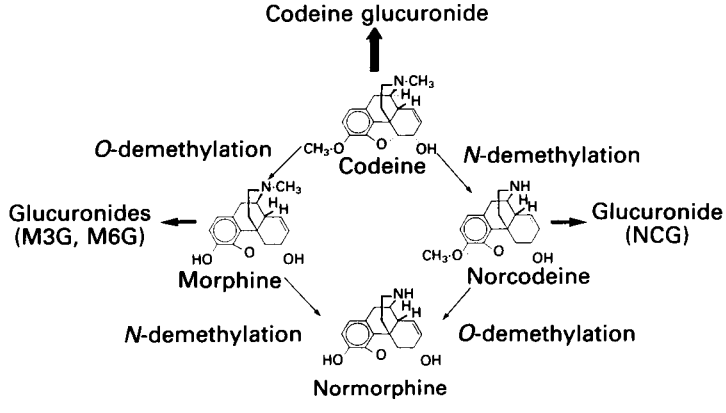

Figure 1 The major metabolic pathways of codeine. M3G = Morphine-3-glucuronide; M6G = Morphine-6-glucuronide; NCG = Norcodeine glucuronide.

to infinity by use of the last measured plasma concentration and the elimination rate constant (λ_z), which was determined by log-linear regression analysis of the terminal concentration-time points. The elimination half-life ($t_{1/2}$) was obtained by dividing ln2 by λ_z. The plasma clearance (CL) of codeine was calculated from the ratio of dose and AUC. Renal clearance (CL_R) and metabolic clearance of codeine through different pathways were calculated using the following equations:

$$CL_R = Ae(\text{codeine})_{t_1-t_2}/AUC_{t_1-t_2}$$
$$CL_{\text{glucuronidation}} = Ae(C6G)_{t_1-t_2}/AUC_{t_1-t_2}$$
$$CL_{O\text{-demethylation}} = Ae(M+M3G+M6G+NM)_{t_1-t_2}/AUC_{t_1-t_2}$$
$$CL_{N\text{-demethylation}} = Ae(NC+NCG+NM)_{t_1-t_2}/AUC_{t_1-t_2}$$

$Ae_{t_1-t_2}$ is the urinary recovery of compound over the urine collection interval t_1–t_2, and $AUC_{t_1-t_2}$ is the area under the plasma codeine concentration *vs* time curve over the urine collection interval t_1-t_2. It was assumed that codeine is absorbed completely from the g.i. tract (Bechtel & Sinterhauf, 1978). Another assumption was that the final elimination of the metabolites occurs only by renal excretion. Maximum plasma concentrations (C_{max}) and time to attain C_{max} (t_{max}) were estimated from observed plasma concentration *vs* time data.

The unpaired Student's *t*-test (or U-test for *O*-demethylation data) was used for the comparison between the two phenotypic groups.

Results

The individual kinetic parameters in 14 subjects (eight EM and six PM) are shown in Table 1. The AUC of codeine ranged from 537 to 1728 (mean ± s.d. = 1020 ± 340) nmol l^{-1} h in all the subjects. The ranges of plasma codeine half-life and plasma clearance were between 1.55 and 3.29 (2.58 ± 0.57) h and between 1.23 and 3.95 (2.02 ± 0.73) l h^{-1} kg^{-1} respectively.

Representative plasma-concentration *vs* time curves for codeine and its metabolites in one PM and one EM are shown in Figure 2 and the average AUC values for all subjects are listed in Table 2. There was no difference between EM and PM in the AUC and plasma clearance of codeine (Tables 1 and 2). However, there were pronounced differences in the formation of metabolites between EM and PM (Figure 2 and Table 2). PM had significantly lower AUC values of M3G, M6G, NM and M ($P < 0.0001$), and lower partial metabolic clearance by *O*-demethylation ($P < 0.0001$, Table 1 and 2). Five of six PM did not have a detectable amount of M and one PM had an AUC of M less than 2 nmol l^{-1} h. The AUC values of M6G and NM were more than 20× lower in PM compared to EM (Table 2).

In contrast, the PM had higher AUC values of NC ($P < 0.05$) than the EM (Table 2). There was no significant difference between PM and EM in the AUCs of C6G and NCG, nor in the partial clearances by *N*-demethylation and glucuronidation (Tables 1 and 2).

Table 1 Subject characteristics, debrisoquine ratio and kinetic parameters of codeine and metabolites after a single oral 50 mg (123 μmol) of codeine phosphate to 14 healthy Caucasian subjects (eight EM and six PM)

Subject	*Age/sex/weight* (years) (kg)	*DB MR*[a]	C_{max} (nmol l^{-1})	t_{max} (h)	$t_{1/2}$ (h)	*CL* (l h^{-1} kg^{-1})	*Partial metabolic clearance*[b] *O-dem* (l h^{-1} kg^{-1})	*N-dem* (l h^{-1} kg^{-1})	*Glucu* (l h^{-1} kg^{-1})
EM									
1	35/F/58	0.34	462	0.5	1.23	1.23	0.09	0.09	0.77
2	40/F/68	0.51	272	1.5	2.51	1.38	0.09	0.11	0.89
3	31/M/70	0.46	250	1.0	2.91	1.88	0.25	0.17	1.42
4	38/F/58	0.21	206	1.5	1.58	3.95	0.27	0.33	2.24
5	31/M/78	0.43	165	1.0	2.88	2.13	0.20	0.14	1.34
6	29/M/80	3.10	327	0.5	1.55	2.39	0.06	0.22	1.31
7	31/F/65	3.30	272	1.0	2.84	1.83	0.04	0.12	1.52
8	32/F/52	7.48	378	1.0	1.89	2.04	0.01	0.21	1.86
Mean	33/–/66	1.98	292	1.0	2.43	2.10	0.12	0.17	1.42
s.d.	34/–/10	2.57	95	0.38	0.58	0.84	0.10	0.08	0.48
PM									
9	27/F/67	250	432	0.67	3.29	1.24	0.002	0.16	0.81
10	40/F/67	37	179	1.5	2.73	2.36	0.004	0.16	1.47
11	23/F/55	26	173	0.67	3.20	2.81	0.017	0.38	2.18
12	27/M/85	97	154	1.0	2.79	1.73	0.009	0.15	1.60
13	31/F/61	380	249	1.0	2.21	2.11	0.004	0.27	1.50
14	31/M/78	31	505	0.33	3.18	1.24	0.004	0.15	1.03
Mean	30/–/69	137*	282	0.86	2.90	1.92	0.007*	0.21	1.43
s.d.	6/–/11	146	150	0.40	0.41	0.63	0.006	0.09	0.48

[a]DB MR = debrisoquine metabolic ratio;
[b]*O*-dem = *O*-demethylation; *N*-dem = *N*-demethylation; Glucu = glucuronidation;
*$P < 0.0001$. U-test between EM and PM.

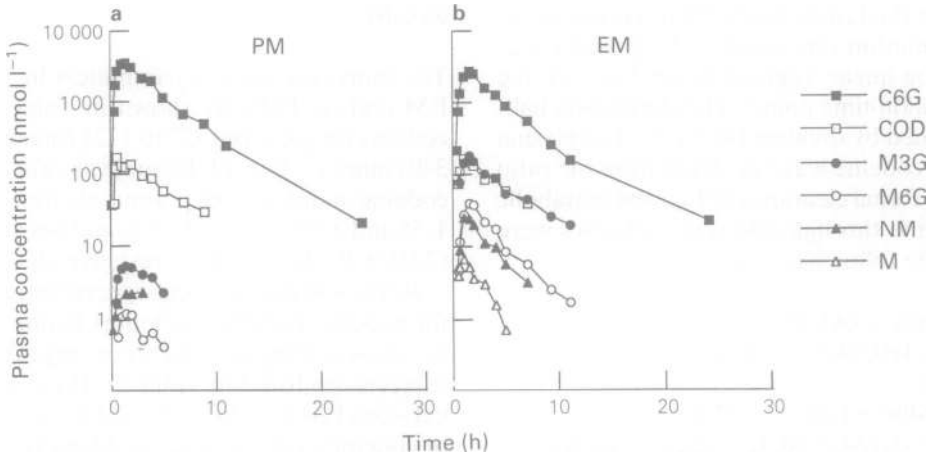

Figure 2 Plasma concentration-time curves of codeine and its metabolites in a PM (a) and EM (b) of debrisoquine after a single oral dose of 50 mg codeine phosphate. (Data for NC and NCG were excluded for the sake of clarity.)

Table 2 Plasma AUC and urinary recovery of codeine and its metabolites in eight EM and six PM of debrisoquine (mean ± s.d.)[a]

	Plasma AUC (nmol l^{-1} h)		*Urinary recovery (% of dose)*	
	EM	*PM[b]*	*EM*	*PM[b]*
Codeine	1010 ± 391	1020 ± 292	3.33 ± 1.52	3.56 ± 0.85
C6G	15200 ± 2690	17700 ± 2710	68.4 ± 7.7	75.3 ± 11.3
NC	163 ± 87	289 ± 117*	2.3 ± 1.6	5.7 ± 1.2**
NCG	772 ± 351	976 ± 380	4.4 ± 0.7	5.3 ± 1.7
M3G	807 ± 808	25.4 ± 10.4***	3.5 ± 2.7	0.16 ± 0.07***
M6G	117 ± 95	5.2 ± 2.8***	0.83 ± 0.63	0.14 ± 0.12***
M	20 ± 20	< 2[c]	0.18 ± 0.16	0.001 ± 0.002***
NM	191 ± 157	< 9***	1.50 ± 0.87	0.029 ± 0.05***
Total			84.4 ± 15.9	90.2 ± 15.3

[a]The U-test was used to compare EM and PM with respect to M3G, M6G, M and NM and the *t*-test was used for the remaining metabolites.
[b]Difference between EM and PM *($P < 0.05$); **($P < 0.001$); ***($P < 0.0001$).
Statistic comparisons were not possible since M could be detected in only one PM.

Among EM, the partial clearance by glucuronidation (Table 1) was more than 8 times higher than that by *N*-demethylation and about 12 times higher than that by *O*-demethylation (Table 1). The AUC of C6G was 15 times greater than that of codeine, which in turn was 50 times greater than that of M. The AUC values of active M6G and NM were about 6 and 10 times higher than that of M, respectively (Table 2).

In 48 h urine collections, the total recovery of drug-related material ranged from 71% to 106% of the dose and did not differ between EM and PM (Table 1). The pattern of urinary recovery was similar to that of plasma AUC for both codeine and the metabolites (Table 2). Six percent of the dose was *O*-demethylated in EM and the majority of the metabolites formed by this pathway were conjugated; M accounted for less than 0.2% of the dose. In PM, only 0.33% of the dose was metabolised by *O*-demethylation and M recovery was negligible (0.001% of the dose). However, PM had a significantly higher recovery of NC ($P < 0.001$) than the EM (Table 2). No significant difference was observed in the recovery of codeine, C6G and NCG between EM and PM (Table 2). The renal clearance of codeine did not differ significantly between EM and PM.

The results of the single dose study were confirmed in an extended study with chronic dosing. These data are presented in Tables 3 and 4.

Three of the 14 volunteers experienced slight side effects including tiredness (one EM and two PM) and headache (one PM) after single dose, and five of six subjects reported tiredness (two EM and two PM), dizziness (two EM) nausea (one EM and one PM) or headache (one PM) after multiple doses.

Discussion

The results indicate significant interindividual differences in the capacity to form morphine from codeine. Individuals who were PM phenotypes for debrisoquine hydroxylation had very low or undetectable concentrations of the active compounds M, M6G and NM.

No major alteration of codeine pharmacokinetics occurred during multiple dose administration, in accord with the findings of others (Guay *et al.*, 1987). With regard to the accumulation of M after chronic dosing, contradictory results have been reported (Guay *et al.*,

Table 3 Pharmacokinetics of codeine and its metabolites after single (S) and repeated (R) oral doses of codeine in three EM (mean ± s.d., $n = 3$)

	C_{max} (nmol l^{-1})		t_{max} (h)		$t_{1/2}$ (h)		AUC[a] (nmol l^{-1} h)		CL_R (l h^{-1} kg^{-1})	
	S	R	S	R	S	R	S	R	S	R
Codeine	411 ± 219	318 ± 129	0.9 ± 0.9	2.0 ± 2.6	1.71 ± 0.63	2.46 ± 0.82	757 ± 179	1050 ± 475	0.051 ± 0.026	0.064 ± 0.028
C6G	4090 ± 3380	4300 ± 1540	1.1 ± 0.4	2.3 ± 2.3	3.32 ± 0.82	3.71 ± 0.73	15000 ± 3710	15100 ± 3670	0.084 ± 0.032	0.094 ± 0.028
NC	48 ± 26	39 ± 8	0.6 ± 0.3	2.0 ± 2.6	3.64 ± 1.50	3.74 ± 3.02	205 ± 76	186 ± 77	0.19 ± 0.06	0.23 ± 0.04
NCG	108 ± 44	153 ± 15	2.2 ± 0.8	3.0 ± 1.7	2.99 ± 0.85	3.12 ± 0.69	587 ± 149	566 ± 153	0.12 ± 0.04	0.12 ± 0.02
M3G	186 ± 121	252 ± 51	1.2 ± 0.7	2.7 ± 2.9	6.49 ± 3.38	14.3 ± 4.8	889 ± 152	1140 ± 581	0.090 ± 0.03	0.087 ± 0.017
M6G	41 ± 23	53 ± 14	1.8 ± 1.0	2.5 ± 2.2	15.4 ± 5.2	14.2 ± 2.9	321 ± 55	197* ± 24	0.11 ± 0.03	0.11 ± 0.01
NM	41 ± 33	65 ± 26	1.6 ± 1.3	2.5 ± 2.2	8.5 ± 5.1	9.8 ± 3.0	220 ± 41	257 ± 52	0.13 ± 0.05	0.11 ± 0.02
M	27 ± 23	21 ± 9	0.7 ± 0.5	2.0 ± 2.6	5.7 ± 2.8	9.9 ± 7.2	37 ± 13	35 ± 11	0.11 ± 0.03	0.06 ± 0.03

*$P < 0.01$ Student's t-test
[a] 0–6 h after multiple dosing.

Table 4 Pharmacokinetics of codeine and its metabolites after single (S) and repeated (R) oral doses of codeine in three PM (mean ± s.d., $n = 3$)

	C_{max} (nmol l^{-1})		t_{max} (h)		$t_{1/2}$ (h)		AUC[a] (nmol l^{-1} h)		CL_R (l h^{-1} kg^{-1})	
	S	R	S	R	S	R	S	R	S	R
Codeine	239 ± 60	349 ± 56	1.8 ± 1.0	0.8 ± 0.3	2.68 ± 0.94	2.38 ± 0.38	798 ± 69	982 ± 163	0.046 ± 0.015	0.044 ± 0.015
C6G	3890 ± 949	6110* ± 65	1.8 ± 1.0	1.3 ± 0.3	3.16 ± 0.56	3.48 ± 0.36	16600 ± 1420	16700 ± 1400	0.090 ± 0.009	0.070 ± 0.039
NC	48 ± 13	92 ± 44	1.7 ± 1.2	1.3 ± 0.8	2.31 ± 0.74	4.12 ± 0.89	229 ± 163	315 ± 141	0.23 ± 0.02	0.20 ± 0.11
NCG	146 ± 8	250* ± 36	2.2 ± 0.8	1.7 ± 0.3	2.90 ± 0.3	3.21 ± 0.06	1050 ± 156	1020 ± 151	0.10 ± 0.02	0.085 ± 0.034
M3G	9.1 ± 8.2	16 ± 5.7	1.3 ± 0.9	1.3 ± 0.6	11.8 ± 7.4	5.6 ± 4.7	56 ± 45	25 ± 13	0.083 ± 0.03	0.083 ± 0.025
M6G	ND[b]	ND	ND	ND	ND	ND	ND	ND	ND	ND
NM	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
M	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

*$P < 0.01$ Student's t-test.
[a]0–6 h after multiple dosing.
[b]ND = Not detectable.

1987; Quiding *et al.*, 1986). We found a significant increase in the C_{max} of C6G and NCG (in PM, Table 4) during multiple-dose administration. However, no increase was observed for other metabolites of codeine.

It is commonly cited that approximately 10% of an oral dose of codeine is recovered in urine as free and conjugated M (Goodman & Gilman, 1985). These figures are based primarily on results obtained using radioimmunoassays (Findlay *et al.*, 1977, 1978; Rogers *et al.*, 1982). The corresponding figures in our study were 6% in EM and less than 0.4% in PM. M accounted for less than 0.2% of the dose in the EM and was essentially absent in the PM. The % relative plasma AUC of M to codeine varied from 0.19 and 4.5% in EM and from 0 and 0.13% in PM. These results are in agreement with earlier data obtained by a GC-MS method with values ranging from 0 and 4.4% in 12 volunteers after oral doses of 60 mg at steady-state (Quiding *et al.*, 1986). The mean plasma C_{max} values of M were 8.4 nmol l^{-1} in EM and less than 2 nmol l^{-1} in PM, which compare with a reported value of 3.5 ng ml^{-1} (9.3 nmol l^{-1}) (Quiding *et al.*, 1986). The mean minimum effective plasma concentration of M for the relief of pain in patients after abdominal surgery has been estimated to be 16 ng ml^{-1} (42.7 nmol l^{-1}) (Dahlström *et al.*, 1982). Considering the very low plasma concentration of M detected at the usual doses of codeine used in the treatment of pain it is unlikely that this metabolite contributes much to the analgesic effect of codeine in man.

M6G is another active metabolite of codeine formed by *O*-demethylation to M and further glucuronidation at the 6-position. The analgesic potency of this metabolite has been recognized for more than a decade (Shimomura *et al.*, 1971; Yoshimura *et al.*, 1973), but its potential clinical importance with respect to analgesic action has only been appreciated recently (Hand *et al.*, 1987; Joel *et al.*, 1985; Osborne *et al.*, 1988). Thus, M6G has been shown to have an analgesic effect approximately twice that of M when given subcutaneously in mice. However, when injected either intracerebroventricularly or intrathecally, M6G was approximately 90- and 650-fold more potent an analgesic than M, respectively (Paul *et al.*, 1989). The greater potency of M6G has also been reported in rats (Abbott & Palmour, 1988; Sullivan *et al.*, 1989). The increased degree and duration of effect of M in patients with renal dysfunction has focused attention on the active metabolites of M (Hasselström *et al.*, 1989; Osborne *et al.*, 1986; Säwe, 1986). The i.v. administration of 0.5–1 mg 70 kg^{-1} M6G to cancer patients resulted in analgesic activity, and it has been suggested that most of the analgesic effect occurring after M treatment is due to this metabolite (Osborne *et al.*, 1988, 1990). However, M6G is a water soluble compound and its movement through the blood brain barrier may be limited. In the present study, the AUC of M6G was almost six times higher than that of M after codeine administration, which is in accordance with the reported mean M6G to M AUC ratio after oral M (Osborne *et al.*, 1990; Säwe *et al.*, 1985). In conjunction with the demonstration of the pharmacological activity of M6G, the findings of the present study suggest that M6G plays a more important role than M in the analgesic effect of codeine.

NM which is formed from codeine by both *N* and *O*-demethylation also has analgesic effect (Lasagna & de Kornfeld, 1958; Sullivan *et al.*, 1989). NM was equipotent with M after intrathecal injection into rats (Sullivan *et al.*, 1989). When given to relieve postoperative pain in man, NM was approximately one-fourth as potent as M (Lasagna & de Kornfeld, 1958). In view of the almost 10-fold higher AUC of NM compared to that of M observed in this study, NM might also make a significant contribution to analgesia after administration of codeine.

The values of C_{max}, t_{max}, AUC and $t_{1/2}$ of codeine observed in this study were similar to those reported by others (Findlay *et al.*, 1977, 1978; Quiding *et al.*, 1986) and there were no significant differences between EM and PM. The AUC and urinary recovery of C6G were also similar in EM and PM. As far as we know, C6G has not been shown to have any analgesic effect. However, PM had a significantly higher AUC and urinary recovery of NC compared to EM which is interesting since it has been reported that NC has analgesic activity (Miller & Anderson, 1954). These differences confirm observations made in a population study in which urine samples from several hundred healthy volunteers were analysed (Yue *et al.*, 1989b). The difference in the concentrations of NC was less than two-fold between the two phenotypes and the efficacy of NC appears not to be greater than that of codeine (Miller & Anderson, 1954). Therefore, higher concentrations of NC would not be expected to compensate for the differences between EM and PM in the formation of *O*-demethylated metabolites.

The clinical significance of debrisoquine oxidation polymorphism has been reviewed (Brøsen & Gram, 1989; Sjöqvist, 1989a, 1989b). In general it is important only when the kinetics of the drug are significantly dependent on the specific isoenzyme cytochrome P450IID6. Codeine might be an exception to this. Although *O*-demethylation of codeine is only a minor metabolic route and the kinetics of the parent drug are not significantly influenced by this pathway, it could be of clinical importance because of the activity of the metabolites associated with this pathway. It has been suggested that codeine is ineffective in PM, but only one PM volunteer was included in the study (Desmeules *et al.*, 1989). A more detailed investigation of the analgesic effect of codeine is indicated using a larger sample size.

In conclusion, Caucasians who are PM of debrisoquine have very low or undetectable plasma concentrations of the *O*-demethylated metabolite morphine, as well as low concentrations of the two other important active metabolites morphine-6-glucuronide and normorphine. The plasma clearance of codeine is similar in Caucasian EM and PM.

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