Comparative disposition of codeine and pholcodine in man after single oral doses

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1 Four healthy male subjects received single oral doses of 15, 30 and 60 mg of codeine and pholcodine according to a balanced cross-over design with an interval of 7 days between the six treatments. Blood samples were collected for 8 h after each drug administration. In phase 2 of the study six different male volunteers received single oral doses of 60 mg of codeine and pholcodine with a 14 day interval between successive drug treatments. Blood was sampled for 12 h after codeine and 121 h after pholcodine administration. Plasma concentrations of free (unconjugated) and total (unconjugated plus conjugated) codeine, pholcodine and morphine were determined by radioimmunoassay and selected pharmacokinetic parameters were derived from these data.

2 Pharmacokinetics of both drugs were independent of dose. Codeine was absorbed and eliminated relatively rapidly [elimination $t_{1/2} = 2.3 \pm 0.4$ h (mean $\pm$ s.d.)]. While codeine kinetics were adequately described by a one-compartment open model with first-order absorption, a two-compartment model was required to describe pholcodine elimination from plasma ($t_{1/2,z} = 37.0 \pm 4.2$ h).

3 Plasma concentrations of conjugated codeine were much greater than those of the unconjugated alkaloid. By contrast, pholcodine appeared to undergo little conjugation.

4 Biotransformation of codeine to morphine was evident in all subjects, although the extent of this metabolic conversion varied considerably between subjects. Morphine was not detectable in the plasma of any subject after pholcodine administration.

Keywords codeine pholcodine disposition

Introduction

Codeine (3-*O*-methyldmorphine: Figure 1) has a long history of use as a clinically effective antitussive and as an analgesic for the relief of moderate pain (Eddy *et al.*, 1970). Although metabolic *O*-dealkylation of codeine to morphine has been suggested (Sanfilippo, 1948) to be involved in the mechanism of analgesic action of codeine since the initial observation of the con-

version of codeine to morphine by incubation with rat liver slices (Bernheim & Bernheim, 1944), there is evidence that the antitussive action of this drug may be controlled by different receptor mechanisms (Pert & Snyder, 1973; Chau & Harris, 1980).

By contrast, pholcodine (3-*O*-morpholinoethylmorphine: Figure 1) has found clinical ap-

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Figure 1 Chemical structures of codeine and pholcodine.

plication only as an antitussive agent (Eddy *et al.*, 1970). Preclinical studies in rabbit, mouse, guinea pig and cat pharmacological models (Guidicelli *et al.*, 1951; Kelentey *et al.*, 1958; May & Widdicombe, 1954; Green & Ward, 1955, *inter alia*) generally indicated pholcodine to be a somewhat more potent antitussive than codeine, although the referenced studies are relatively old and no rigorous comparison has been published recently. Although many of the pharmacological effects of codeine and pholcodine have been reported to be similar, the toxicity of the latter drug was reported to be generally lower (Cahen, 1961). The analgesic potency of pholcodine, as well as several other central effects, is markedly less than those of codeine (Cahen, 1961).

Clinical trials (Chabrier *et al.*, 1950; Konar & Dasgupta, 1959; Bickerman & Itkin, 1960; Mulinos *et al.*, 1962; Snell & Armitage, 1957, *inter alia*) generally have shown equal or greater antitussive potency for pholcodine than codeine. However, these studies have suffered from the criticism of less control and sophistication than is applied to modern clinical trials. It has been demonstrated that pholcodine has essentially no addiction liability and, in large doses, fails to substitute for morphine in addicts (Eddy *et al.*, 1970; Cahen, 1961).

Although the disposition of codeine in man has been studied (Eddy *et al.*, 1970; Findlay *et al.*, 1977) and its metabolism demonstrated to give circulating levels of morphine in human plasma after therapeutic oral doses (Findlay *et al.*, 1978), similar studies of pholcodine disposition in man have not been reported. We have previously reported on the disposition of pholcodine in the rat (Butz *et al.*, 1983), including the demonstration that this drug has a longer elimination half-life and undergoes considerably less *O*-dealkylation than codeine. In a preliminary report Neuvonen *et al.* (1980) stated that [^{14}C]-pholcodine was metabolised and eliminated very slowly after oral or intravenous administration to healthy human volunteers.

The objective of the present study was to compare the pharmacokinetics and relative extents of *O*-dealkylation of pholcodine and codeine in healthy human subjects at doses in the range used for antitussive purposes (15 and 30 mg) and at the higher 60 mg dose level at which codeine is employed as an analgesic. It was of interest to see whether these parameters may correlate with any aspects of the clinical profile of these drugs. Some of this work was presented in preliminary form at the IUPHAR 9th International Congress of Pharmacology (Findlay *et al.*, 1984). The study protocol was approved by the independent Protocol Review Committee which considers all studies performed at The Wellcome Research Laboratories.

Methods

Clinical

Subjects Subjects in both Phases 1 and 2 were non-smokers in good health, exhibiting normal values on physical examination, blood chemistries, urinalysis, full blood count and electrocardiographic examination. No drugs were taken for 48 h before drug administration and for the duration of the study. Mean ages of subjects were 30.5 (range 25–36 years) in Phase 1 and 29.8 (25–36) years in Phase 2. All subjects gave informed consent and received an honorarium for participation in the study.

Phase 1 Four male volunteers (mean $\pm$ s.d. weight, 81.2 ± 8.6 kg) participated in a randomised, balanced cross-over study, with an interval of at least 7 days between each of six treatments consisting of single oral doses of 15, 30 and 60 mg of codeine and pholcodine. Both drugs were given in 20 ml aqueous solution and were followed by a 50 ml wash of water; codeine was given as the phosphate, while pholcodine was administered as the base. Subjects fasted for 8 h prior to drug administration and for 2.5 h

after, at which time a light breakfast was taken. Blood samples were collected into EDTA-containing evacuated glass tubes before drug administration and at 0.25, 0.5, 1, 1.5, 2, 4, 6 and 8 h thereafter. Plasma was separated by centrifugation and stored in stoppered vials at -20°C until analysed for drug content, as described below.

Phase 2 Six different male volunteers (mean $\pm$ s.d. weight, 73.9 ± 9.7 kg) received single oral doses of 60 mg of codeine and pholcodine in a crossover experiment, with an interval of 14 days between the two treatments. Drugs were administered in solution as above, and subjects fasted from 8 h before drug administration until 4 h thereafter, when a light lunch was given. Blood samples were obtained prior to dosing for both drugs and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h after codeine administration and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 32, 48, 56, 72, 96 and 121 h after dosing with pholcodine. Blood samples were processed as in Phase 1.

Analytical procedures

Chemicals and reagents [1-3H] Codeine (specific activity 20 Ci/mmol) and [1,6,7-3H] dihydromorphine (specific activity 81 Ci/mmol) were purchased from Amersham Corp. (Arlington Heights, IL). Codeine phosphate, morphine sulphate and pholcodine bitartrate for preparation of standard solutions were provided by Mallinckrodt, Inc., St. Louis, MO. Morphine-3-glucuronide and codeine-6-glucuronide were obtained from Applied Science Laboratories, Inc., State College, PA. Radioimmunoassay grade charcoal was purchased from Becton, Dickinson and Co., Rutherford, NJ and Dextran T-70 was obtained from Pharmacia Fine Chemicals, Piscataway, NJ. Aquasol-2 scintillation fluid was a product of New England Nuclear Corporation, Boston, MA, while β -glucuronidase [containing 2020 Fishman units of β -glucuronidase (EC 3.2.1.31) and 6200 units of arylsulphatase (EC 3.1.6.1) per mg] was purchased from Miles Laboratories, Inc., Elkhart, IN. The assay buffer used throughout these experiments was 0.05 M $\text{Na}_2\text{HPO}_4/\text{NaH}_2\text{PO}_4$, 0.15 M NaCl, 0.01 M EDTA- Na_2 , 0.1% gelatin, pH 7.0.

Codeine, morphine and pholcodine RIA The development of antisera to ethylmorphine-6-hemisuccinate-bovine serum albumin [used in radioimmunoassay (RIA) procedures for codeine and pholcodine] and to *N*-carboxypropyl-

normorphine-bovine serum albumin (used in the morphine RIA) has been described (Findlay *et al.*, 1977, 1981).

Codeine and pholcodine plasma concentrations were determined as described previously (Butz *et al.*, 1983) by solvent extraction of the drugs from basified plasma followed by RIA analysis. Morphine was determined directly without prior extraction. All analytical runs were accompanied by appropriate standard curves and control solutions ($1\text{--}1000$ ng ml^{-1}) for the respective alkaloids. The extent of conjugation of the alkaloids was investigated by RIA of plasma samples before and after overnight incubation with β -glucuronidase at pH 5.0, as described previously (Butz *et al.*, 1983).

Assay characteristics The antiserum used for analysis of codeine and pholcodine was raised to a conjugate of ethylmorphine-6-hemisuccinate and bovine serum albumin. This antiserum discriminates poorly between different 3-*O*-alkyl ethers of morphine but does distinguish (by cross-reactivity) between codeine and its *N*-demethylated metabolite, norcodeine. Thus pholcodine and codeine can be determined with a single antiserum, while *N*-demethylated metabolites of either would not cross-react. Solvent extraction of codeine from basified plasma removed the potential interference from the major metabolite, codeine-6-glucuronide.

The morphine RIA employed in this study has been applied to previous drug disposition studies in man (Findlay *et al.*, 1978). The morphine antiserum has excellent discriminatory characteristics for structural changes at the 3- and 6-positions of the morphine molecule, as in morphine-3-glucuronide, a major human metabolite of morphine, codeine, codeine-6-glucuronide, pholcodine and norcodeine, all of which could be present in some amounts in some plasma samples from the present study. Normorphine does crossreact extensively with this antiserum, but previous studies have demonstrated that normorphine is a minor primary metabolite of morphine in man (Brunk & Delle, 1974). In the present situation even less normorphine formation would be expected since this would be a secondary metabolic step.

Pharmacokinetic analysis

Model-independent In both phases of the study the maximum plasma concentration (C_{max}), the time at which maximum plasma concentration was attained (t_{max}) and the area under the plasma concentration-time curve (AUC) for parent drugs and morphine were determined from the

Figure 2 Plasma concentrations of unconjugated codeine and morphine after codeine administration. Data shown are mean $\pm$ s.e. mean. Open symbols are morphine data and closed symbols are codeine data.

observed data without curve fitting. All AUC values were determined by the trapezoidal rule from 0–8 h in Phase 1 and 0–24 h for codeine and 0–121 h for pholcodine in Phase 2 of the study.

Model-dependent Model-dependent pharmacokinetic parameters for codeine and pholcodine were determined only in Phase 2. Initial estimates of volume of distribution, absorption and elimination rate constants and lag time were derived from application of the curve-stripping program CSTRIP3, a modification of CSTRIP (Sedman & Wagner, 1976), to the plasma concentration–time data. These initial estimates were then applied to the analysis of the concentration–time data by the program NONLIN (Metzler *et al.*, 1974) with a weighting factor of $1/\text{concentration}^2$. Codeine plasma concentration–time data were adequately described by a one-compartment

open model with first-order absorption. However, pholcodine absorption was best described by a model that incorporated pseudo-zero order absorption to provide initial estimates of the major parameters for use in the NONLIN analysis.

Pupillometry and side effects

In Phase 2 of the study, photographs were taken before and hourly for 8 h after drug administration, using ring flash and a lens of fixed focal length. After development of the colour transparencies pupil diameters were measured. Data were analysed statistically using a paired *t*-test. At the same times subjects were requested to report side effects on a check list. Heart rates and blood pressure were also monitored.

Figure 3 Plasma concentrations of unconjugated pholcodine after pholcodine administration. Data shown are mean $\pm$ s.e. mean.

Results

The mean plasma concentration–time profiles for codeine in the four subjects who received single, oral 15, 30 and 60 mg doses of codeine in Phase 1 are shown in Figure 2. Similar data for these subjects after administration of the pholcodine doses are presented in Figure 3. Some model-independent pharmacokinetic parameters for codeine and pholcodine are listed in Table 1. The $t_{\max}$ values for codeine ranged from 0.5–1.5 h while those for pholcodine were in the range of 4–8 h on most occasions. Mean $C_{\max}$ and AUC values for pholcodine were lower than those for codeine, although AUC values for both drugs generally increased in direct proportion to dose, indicating that kinetics were independent of dose across the 4-fold range studied. Mean plasma concentrations of unconjugated codeine and pholcodine after separate administrations of single, oral 60 mg doses of these drugs (Phase 2)

are depicted in Figure 4. Model-independent kinetic parameters for both free (unconjugated) and total (unconjugated and conjugated) forms of both of these drugs are given in Tables 2 and 3. The relative extents of conjugation of these drugs are also illustrated in Figure 5. On average, more than 85% of circulating codeine was in the conjugated form while virtually no conjugated pholcodine was found in plasma.

Figure 2 presents the mean plasma concentrations of metabolically produced morphine after codeine administration to the subjects in Phase 1. Morphine was also detected in the plasma of subjects who participated in Phase 2 of the study after ingestion of the 60-mg dose of codeine. Some model-independent parameters for this metabolite are collated in Table 4, while AUC values are depicted in histogram form in Figure 5. After 60 mg of codeine, unconjugated morphine concentrations in plasma reached 6 ng ml⁻¹ or higher in subjects 2, 3 and 5. The unconjugated

Table 1 Model-independent pharmacokinetic parameters after 15, 30 and 60 mg codeine or pholcodine

	Subject	15 mg			30 mg			60 mg		
		C_{max} ($ng\ ml^{-1}$)	t_{max} (h)	AUC^* ($ng\ ml^{-1}\ h$)	C_{max} ($ng\ ml^{-1}$)	t_{max} (h)	AUC^* ($ng\ ml^{-1}\ h$)	C_{max} ($ng\ ml^{-1}$)	t_{max} (h)	AUC^* ($ng\ ml^{-1}\ h$)
Codeine	1	36	0.5	108	74	0.5	242	128	1.0	405
	2	28	0.5	104	71	0.5	229	111	1.0	435
	3	38	1.0	128	55	1.0	204	117	1.0	492
	4	27	0.5	85	43	1.0	190	100	1.5	423
	Mean s.d.	32 6	0.6 0.3	106 18	61 15	0.8 0.3	216 24	114 12	1.1 0.3	439 38
Pholcodine	1	10	4.0	61	17	4.0	122	32	2.0	214
	2	14	1.0	48	13	4.0	72	22	4.0	125
	3	8	6.0	49	16	4.0	97	32	6.0	187
	4	5	8.0	29	11	6.0	74	23	8.0	123
	Mean s.d.	9 4	4.8 3.0	47 13	14 3	4.5 1.0	91 23	27 6	5.0 2.6	162 46

*AUC 0-8 h

Figure 4 Mean plasma concentrations of codeine (▲) and pholcodine (●) after single 60-mg oral doses.

Table 2 Model-independent pharmacokinetic parameters for codeine after 60 mg oral codeine

Subject	Free			Total		
	C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC^* (ng ml ⁻¹ h)	C_{max} (ng ml ⁻¹)	t_{max} (h)	AUC^* (ng ml ⁻¹ h)
1	135	1.5	793	908	1.3	6082
2	227	0.5	945	1034	1.0	5288
3	167	2.0	820	1198	2.0	6257
4	167	1.0	631	1742	1.5	5850
5	253	0.8	1017	1300	1.0	6500
6	238	0.5	1014	2116	0.8	6937
Mean	198	1.1	870	1383	1.3	6152
s.d.	48	0.6	151	459	0.5	564

*AUC 0–24 h

morphine level peaked at 2 ng ml⁻¹ in the plasma from subject 2, while unconjugated morphine was undetectable in subject 4 and reached only very low levels in subject 6. Maximum plasma levels of total (unconjugated plus conjugated) morphine approached 100 ng ml⁻¹ in the three subjects with the highest concentrations of unchanged morphine. Total morphine AUCs in subjects 4 and 6 were less than 1% of their respective total codeine AUC values.

Plasma concentration–time data derived from the Phase-2 administration of 60-mg oral doses

of these two drugs were fitted with a model using the program NONLIN. Some model-dependent parameters resulting from this analysis are presented in Tables 5 (codeine) and 6 (pholcodine). Codeine was rapidly absorbed, as evidenced by the relatively short t_{max} values (Tables 1 and 2), and its elimination from plasma was adequately described by a one-compartment model with mean $\pm$ s.d. values of clearance (CL/F) and elimination half-life ($t_{1/2}$) of 1286 ± 255 ml min⁻¹ and 2.3 ± 0.4 h, respectively. Absorption of pholcodine was much slower (Tables 1 and 3)

Table 3 Model-independent pharmacokinetic parameters for pholcodine after 60 mg oral pholcodine

Subject	Free			Total		
	C_{max} ($ng\ ml^{-1}$)	t_{max} (h)	AUC^* ($ng\ ml^{-1}\ h$)	C_{max} ($ng\ ml^{-1}$)	t_{max} (h)	AUC^* ($ng\ ml^{-1}\ h$)
1	49.1	5.0	980	44.5	6.0	839
2	51.7	6.0	948	48.0	6.0	899
3	42.3	5.0	967	71.1	6.0	1089
4	42.6	5.0	806	49.9	5.0	838
5	59.1	5.0	951	66.6	5.0	1003
6	59.3	7.0	943	62.6	7.0	908
Mean	50.7	5.5	933	57.1	5.8	929
s.d.	7.5	0.8	64	11.0	0.8	99

*AUC 0–121 h

Figure 5 Plasma AUC values for unconjugated and total codeine, pholcodine and metabolically produced morphine after single, oral, 60 mg doses of codeine and pholcodine. Data shown are mean $\pm$ s.e. mean.

and was not adequately described as a first-order process. Elimination of pholcodine from plasma was biphasic, and mean $\pm$ s.d. values for CL/F and $t_{1/2}$ were $1001 \pm 82\ ml\ min^{-1}$ and $37.0 \pm 4.2\ h$, respectively.

Minimal side effects were observed after administration of either drug, and data were insufficient to subject to statistical analysis. No effects on heart rate or blood pressure were observed. Mean pupil diameters in the 8 h after codeine administration were significantly smaller ($P < 0.05$) than those after pholcodine (6.93 vs $7.97\ mm$, s.e. difference = 0.273).

Discussion

The data presented in this paper demonstrate that the nature of the 3-functional group in the morphine alkyl ether series can have a major impact on the disposition of these compounds in man. Thus, codeine (3-*O*-methyldmorphine) was absorbed and eliminated rapidly, with a mean $t_{1/2}$ of 2.3 h, which was in good agreement with earlier reports (Findlay *et al.*, 1977, 1978). Maximum plasma concentrations of codeine (C_{max}) were also attained within 0.5–1.5 h. Change in the functional group at position 3 to

Table 4 Model-independent pharmacokinetic parameters for morphine after 60 mg oral codeine

Subject	Free			Total		
	C_{max} (ng mL ⁻¹)	t_{max} (h)	AUC^* (ng mL ⁻¹ h)	C_{max} (ng mL ⁻¹)	t_{max} (h)	AUC^* (ng mL ⁻¹ h)
1	2.0	1.0	14.5	40.5	1.5	356
2	6.0	0.5	26.1	95.7	2.0	564
3	6.5	1.5	43.5	96.4	2.0	648
4	0.0	0.0	0.0	4.6	1.5	24
5	6.4	0.25	24.9	74.4	1.25	426
6	0.5	0.5	1.7	5.4	1.25	32

*AUC 0–12 h

Table 5 Model-dependent pharmacokinetic parameters for codeine

Subject	V/F (l) (l kg ⁻¹)		CL/F (mL min ⁻¹)	AUC^* (ng mL ⁻¹ h)	$t_{1/2,z}$ (h)
1	220	2.7	1330	752	1.9
2	235	3.8	1157	864	2.4
3	191	2.3	1324	755	1.7
4	380	4.6	1750	572	2.5
5	237	3.8	1102	907	2.5
6	250	3.4	1052	950	2.7
Mean	252	3.4	1286	800	2.3
s.d.	66	0.8	255	137	0.4

*AUC fitted 0–∞ by extrapolation from data to 12 h;
extrapolated area = $C(12)/\lambda_z$ **Table 6** Model-dependent pharmacokinetic parameters for pholcodine

Subject	V_1/F (l) (l kg ⁻¹)		V/F (l) (l kg ⁻¹)		CL/F (mL min ⁻¹)	AUC^* (ng mL ⁻¹ h)	$t_{1/2,z}$ (h)
1	392	5.0	3423	43.8	917	1091	43.1
2	252	4.0	2737	43.1	963	1038	32.8
3	179	2.2	3010	36.2	958	1044	36.3
4	487	5.9	4062	49.2	1147	872	40.9
5	136	2.1	3020	46.9	981	1019	35.6
6	141	1.9	2995	40.8	1040	961	33.3
Mean	265	3.5	3207	43.3	1001	1004	37.0
s.d.	145	1.7	473	4.6	82	77	4.2

*AUC fitted 0–∞ by extrapolation from data to 121 h; extrapolated area = $C(121)/\lambda_z$

morpholinoethyl, as in pholcodine (3-*O*-morpholinoethylmorphine), resulted in a compound which was absorbed and eliminated much more slowly than codeine. The t_{max} values for pholcodine were generally in the range of 4–8 h, while the mean elimination half-life was 37 h, or approximately 16-fold longer than that of codeine. The large difference in $t_{1/2}$ values for codeine and pholcodine may be directly related

to the marked difference in volume of distribution of these drugs rather than in clearance since AUC values of free drug were similar (Tables 5 and 6). However, this statement must be qualified since the fraction of bioavailable drug (F) was not determined in the present study. Although formal pharmacokinetics of pholcodine in man do not appear to have been reported before, Neuvonen and colleagues (1980) did observe

very slow metabolism and elimination of radio-labeled pholcodine in volunteers. An indirect indication of the slow elimination of pholcodine from humans was the observation (Svenneby *et al.*, 1983) that pholcodine administered as an antitussive to volunteers could still interfere in a radioimmunoassay for opiates in urine for 2–6 weeks after ingestion of single, therapeutic oral doses. By contrast, urinary drug levels fell below the assay sensitivity limit within 4 days of ingestion of a dose of codeine or ethylmorphine.

The relative extents of conjugation of these drugs with glucuronic and/or sulphuric acids (Tables 2 and 3, Figure 5) were also remarkably different. The bulk of the codeine circulating in plasma was conjugated, but pholcodine was not. The bulkier morpholinoethyl group at the 3-position may have created steric hindrance and thus limited access to the active site on the glucuronyl transferase in the case of pholcodine. These differences were noted previously in the rat (Butz *et al.*, 1983), which also eliminates pholcodine more slowly than it does codeine. Despite these differences in disposition, Phase 1 of the study showed that both drugs exhibited approximately linear pharmacokinetics over the 15 to 60-mg dose range studied. This observation must be qualified, however, because of the relatively short post-dose period (8 h) over which plasma concentration data were acquired compared to the half-life of pholcodine (37 h).

Although codeine pharmacokinetics after the single, oral, 60-mg dose (Phase 2) were similar to those found in earlier studies, pholcodine kinetics exhibited some unusual features. The absorption of pholcodine was not well described by either a first-order or zero-order process. Although maximum plasma concentrations were not achieved for 5–6 h, levels reached approximately half of this maximum value within 30 min of drug administration. The rate of rise in plasma concentrations then appeared to decrease. The first disposition phase after peak plasma concentrations were attained may reflect distribution of the drug from plasma into tissues. The unusual absorption profile of pholcodine might have resulted from its delaying gastric emptying, but the reported activity of pholcodine in the gastrointestinal tract (Cahen, 1961) is considerably less than that of codeine and there is no evidence of delayed transit or constipation with the use of this drug in man. The unusual absorption profile of pholcodine suggested by the present data cannot be explained yet.

A major difference in the disposition of these two agents is in the relative extents of their *O*-dealkylation to morphine (Table 4 and Figures 2, 3 and 5). Morphine, in unconjugated or con-

jugated form, was detectable in all six subjects participating in Phase 2 of the study (Table 4 and Figure 5). The morphine AUC values averaged 10% of those for the parent drug, codeine, although this metabolite was barely detectable in two of the subjects. This variability in the concentrations of circulating morphine in man, which arises from metabolism of codeine and has been noted previously (Findlay *et al.*, 1978; Rogers *et al.*, 1982), may well be due to a genetic polymorphism in the metabolic conversion of codeine to morphine. Confirmation of this hypothesis would require additional studies. Concentrations of morphine in three of the six subjects who received 60 mg of codeine orally in Phase 2 of this study were similar to those expected after a 2-mg intramuscular dose of morphine. This raises again the possibility that at least some of the mild analgesic and other central effects of codeine in man may be caused by its metabolite, morphine. Morphine (in conjugated or unconjugated form) was not detected in any plasma samples from subjects who took pholcodine during Phases 1 and 2 of the study. The rat, which extensively metabolises codeine to morphine produced much lower amounts of morphine from pholcodine by biotransformation (Butz *et al.*, 1983). The lack of significant analgesic activity of pholcodine (Cahen, 1961), as well as its very low addiction liability (Eddy *et al.*, 1970), may be directly related to the fact that no morphine appears to be formed by metabolism of this compound in man. On the other hand, pholcodine and codeine possess comparable antitussive potency (Eddy *et al.*, 1970) which in the case of pholcodine, can only be mediated by the parent drug or by some metabolite other than morphine. If antitussive and analgesic activities were mediated through different receptors, as Chau & Harris (1980) have suggested for codeine, pholcodine might only act on those responsible for antitussive effects. However, if cough control is mediated peripherally, a suggestion consistent with some animal findings (May & Widdicombe, 1954), the action of pholcodine may not involve opioid receptors at all, as previously proposed by Green & Ward (1955). In this respect, the lack of miotic effect of pholcodine is intriguing, as is the fact that the morphine circulating after the codeine doses was largely conjugated and thus diminished in its ability to exert its well-documented meiotic properties. Further work is required to evaluate these proposals, which could suggest new approaches to control of cough.

In their comprehensive review of alternatives to codeine for relief of pain and cough, Eddy *et al.* (1970) concluded that pholcodine was an

effective antitussive with less potential to produce dependence than codeine, but they assumed that it was similarly converted to morphine. The present study demonstrates that pholcodine is not metabolized to morphine in man and bears out experience with pholcodine in Europe over

the past 35 years that it is indeed a safe antitussive in adults and children. However, its long half-life suggests that current prescribing recommendations of relatively frequent dosing should be revised.

References

- Bernheim, F. & Bernheim, M. L. C. (1944). The oxidation *in vitro* of morphine by rat liver slices. *J. Pharmac. exp. Ther.*, **81**, 374–377.
- Bickerman, H. A. & Itkin, S. E. (1960). Further studies on the evaluation of antitussive agents employing experimentally induced cough in human subjects. *Clin. Pharmac. Ther.*, **1**, 180–191.
- Brunk, S. F. & Delle, M. (1974). Morphine metabolism in man. *Clin. Pharmac. Ther.*, **16**, 51–57.
- Butz, R. F., Jones, E. C., Welch, R. M. & Findlay, J. W. A. (1983). Pharmacokinetics and *O*-dealkylation of morphine-3-alkyl ethers in the rat. A radioimmunoassay study. *Drug. Metab. Dispos.*, **11**, 481–488.
- Cahen, R. (1961). The pharmacology of pholcodine. *Bull. Narcot.*, **13**, 19–36.
- Chabrier, P., Guidicelli, R. & Thuillier, J. (1950). Etude chimique, pharmacologique et clinique d'un nouveau sédatif de la toux: la morpholyléthylmorphine (M.E.M.). *Ann. Pharm. Franc.*, **8**, 261–273.
- Chau, T. T. & Harris, L. S. (1980). Comparative studies of the pharmacological effects of the *d*- and *l*-isomers of codeine. *J. Pharmac. exp. Ther.*, **215**, 668–672.
- Eddy, N. B., Friebel, H., Klaus-Jurgen, H. & Halbach, H. (1970). *Codeine and its alternates for pain and cough relief*, pp. 160–164. Geneva: World Health Organisation.
- Findlay, J. W. A., Butz, R. F. & Jones, E. C. (1981). Relationships between immunogen structure and antisera specificity in the narcotic alkaloid series. *Clin. Chem.*, **27**, 1524–1535.
- Findlay, J. W. A., Butz, R. F. & Welch, R. M. (1977). Codeine kinetics as determined by radioimmunoassay. *Clin. Pharmac. Ther.*, **22**, 439–446.
- Findlay, J. W. A., Fowle, A. S. E., Butz, R. F., Posner, J., Jones, E. C. & Welch, R. M. (1984). Comparative disposition of codeine and pholcodine in man. *IUPHAR 9th International Congress of Pharmacology*, London, Abstract 382.
- Findlay, J. W. A., Jones, E. C., Butz, R. F. & Welch, R. M. (1978). Plasma codeine and morphine concentrations after therapeutic oral doses of codeine-containing analgesics. *Clin. Pharmac. Ther.*, **24**, 60–68.
- Green, A. F. & Ward, N. B. (1955). The actions of analgesics and nalorphine on the cough reflex. *Br. J. Pharmac.*, **10**, 418–423.
- Guidicelli, R., Chabrier, P. & Kristensson, R. (1951). Etude chimique et pharmacologique de quelques nouveaux dérivés de la morphine. *Thérapie*, **6**, 146–154.
- Kelentey, G., Czollner, F., Stenszky, E., Meszaros, Z. & Szlavik, L. (1958). Darstellung und pharmakologische Untersuchung einiger morpholyläthylisierter Morphin-Derivate. *Arzneimittel-Forsch.*, **8**, 325–330.
- Konar, N. R. & Dasgupta, S. (1959). A chemical method for exciting cough reflex in human beings and its use in assessing the effectiveness of cough sedatives. *J. Indian med. Ass.*, **32**, 189–193.
- May, A. J. & Widdicombe, J. G. (1954). Depression of cough reflex by pentobarbitone and some opium derivatives. *Br. J. Pharmac.*, **9**, 335–340.
- Metzler, C. M., Elfring, G. L. & McEwen, A. J. (1974). A package of computer programs for pharmacokinetic modeling. *Biometrics*, **30**, 362.
- Mulinos, M. G., Nair, K. G. & Epstein, I. G. (1962). Clinical investigation of antitussive properties of pholcodine. *New York State med. J.*, **62**, 2373–2377.
- Neuvonen, P. J., Pentikainen, P. J. & Penttilä, A. (1980). Pharmacokinetics of pholcodine in man. *World Conference on Clinical Pharmacology and Therapeutics*, London, Abstract 0488.
- Pert, C. B. & Snyder, S. H. (1973). Properties of opiate-receptor binding in the rat brain. *Proc. Nat. Acad. Sci. USA*, **70**, 2243–2247.
- Rogers, J. F., Findlay, J. W. A., Hull, J. H., Butz, R. F., Jones, E. C., Bustrack, J. A. & Welch, R. M. (1982). Codeine disposition in smokers and nonsmokers. *Clin. Pharmac. Ther.*, **32**, 218–227.
- Sanfilippo, G. (1948). Contributo sperimentale all'ipotesi della smetilazione della codeina nell'organismo. I. Influenze della dose sull'assuefazione alla codeina. II. Assuefazione alla codeina attenuata con somministrazione prolungata di morphina. *Boll. Soc. Ital. Biol. Sper.*, **24**, 723–726.
- Sedman, A. J. & Wagner, J. G. (1976). CSTRIP. A fortran IV computer program for obtaining initial polyexponential parameter estimates. *J. pharm. Sci.*, **65**, 1006–1010.
- Snell, E. S. & Armitage, P. (1957). Clinical comparison of diamorphine and pholcodine as cough suppressants by a new method of sequential analysis. *Lancet*, **i**, 860–862.
- Svenneby, G., Wedege, E. & Karlsen, R. L. (1983). Pholcodine interference in the immunoassay for opiates in urine. *Forensic Sci. Int.*, **21**, 223–226.

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