Pharmacokinetics of pholcodine in healthy volunteers: single and chronic dosing studies

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1 The pharmacokinetics of pholcodine after two single doses and after chronic administration were studied in healthy human volunteers.

2 Six subjects received single oral doses of 20 and 60 mg of pholcodine according to a balanced cross-over design with an interval of 3 weeks between the two treatments. Blood and saliva samples and all urine were collected over 168 h after each dosage administration. Subsequently, the same subjects received 20 mg pholcodine 8 hourly orally for 10 days. Blood and saliva samples and all urine were collected during an 8 h dosing interval after the last dose on day 11.

3 Plasma, saliva and urine concentrations of pholcodine were determined by a high performance liquid chromatographic assay.

4 After the single doses, pholcodine was absorbed rapidly ($t_{\max} = 1.6 \pm 1.2$ h) and eliminated slowly with a mean half-life of 50.1 ± 4.1 h. The renal clearance of pholcodine was 137 ± 34 ml min⁻¹ and was inversely correlated with urine pH ($r = 0.60$) but not with urine flow rate. $26.2 \pm 3.3\%$ of the dose was excreted as unchanged pholcodine after both doses. The concentration of pholcodine in saliva was 3.6 times higher than in plasma.

5 After chronic administration, the pharmacokinetics of pholcodine were not statistically different from the single dose parameters.

6 Pholcodine did not appear to undergo conjugation. The plasma protein binding was 23.5%. Morphine, in unconjugated or conjugated form, was not detected in the urine of any subject after pholcodine administration.

Keywords pholcodine pharmacokinetics in humans

Introduction

Pholcodine (3-*o*-morpholinoethylmorphine, Figure 1), which belongs to the opioid family of compounds, is one of the most widely used antitussive drugs in paediatric and adult medicine. The antitussive potency of pholcodine as assessed in a variety of animal models has been reported to be equivalent to or superior to that of codeine (Cahen, 1961; Eddy *et al.*, 1969). The LD₅₀ of pholcodine is lower than that of codeine in several animal species (Cahen, 1961; Eddy *et al.*, 1969)

and pholcodine appears to be almost devoid of adverse effects in man (Jaffe & Martin, 1985).

Although pholcodine has been used as an antitussive drug for more than 30 years, little is known about its absorption and disposition in man. Neuvonen *et al.* (1980 and personal communication) reported in abstract form that following intravenous administration of [¹⁴C]-pholcodine, the mean half-life of total radioactivity in plasma was 230 h, and for 'unchanged

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Figure 1 Chemical structures of pholcodine, codeine and morphine

pholcodine' in urine 102 h. Findlay *et al.* (1986), using radioimmunoassay (RIA) examined the pharmacokinetics of pholcodine given as a single 60 mg oral dose and reported a mean terminal half-life of 37 h. The available data are thus in conflict and might have resulted from assay techniques whose specificities could be questioned. To our knowledge there are no data on the disposition of pholcodine following chronic administration.

The objective of the present study was to determine the pharmacokinetics of pholcodine, using a sensitive and specific analytical method, in human subjects given single and chronic oral dosages.

Methods

Six normal healthy volunteers, five male and one female, participated in the study, which was approved by the Human Ethics Committee of Royal Adelaide Hospital and the Committee on the Ethics of Human Experimentation of the University of Adelaide. The volunteers were aged between 23 and 47 (29.3 ± 8.2 , mean $\pm$ s.d.) years and weighed between 55 and 71 (63.8 ± 6.5) kg. They were in good health as judged by physical and biochemical examinations and all were non-smokers. Drugs and alcohol were prohibited for 2 days before pholcodine administration and for the duration of the study.

Study design

The study was in two parts. In part one, each subject received, in a balanced randomised order, 20 and 60 mg pholcodine as single doses of 20 ml and 60 ml Linctus Pectolin® (F. H. Faulding & Co. Ltd, Adelaide, Australia). Each 5 ml contained pholcodine base 5 mg, citric acid 50 mg, glycerol 1.5 ml, hydroxybenzoates 5 mg and

water to 5 ml. The doses were given at least 1 h after a light breakfast. The linctus dispenser was rinsed with successive washings of water (total volume 100 ml) which was ingested by the volunteer. Food was permitted after 4 h and normal fluid intake was allowed. The volunteers were ambulant but confined to the laboratory for the first 8 h of sampling. There was an interval of 3 to 4 weeks between the two doses. The second part of the study was conducted 3 to 8 weeks after completion of part one. Subjects received 20 mg of pholcodine (as 20 ml Linctus Pectolin®) 8 hourly (08.00, 16.00, 24.00 h) for 10 days. The final dose was given at 08.00 h on day 11 after a similar light breakfast. Venous blood samples (10 ml) were collected into heparinized plastic tubes via an indwelling catheter kept patent with a stylet (Jelco™, Critikon, Tampa, USA) placed in a forearm vein. The sampling times were for part one: 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 24, 32, 48, 72, 96, and 168 h; part two: 0, 2, 4, 6 and 8 h. Plasma was separated from blood cells by centrifugation. After chewing parafilm, mixed saliva samples (3 ml) were collected and saliva pH was recorded. The sampling times for saliva were: part one: 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8, 24, 32, 48, 72, 96, 120, 144 and 168 h; part two: prior to the dose (08.00 h) on days 1 to 11, and at 2, 4, 6, 8, 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240 h after the last dose. Urine was collected as follows, in part one: 0–8, 8–24, 24–32, 32–48, 48–72, 72–96, 96–120, 120–144 and 144–168 h after dosing; part two: 0–8 h on day 11 after the last dose. Urine pH and volume were recorded and an aliquot retained for analysis. All samples were stored in stoppered vials at -20°C until analysed for drug content.

Pholcodine analysis in biological fluids

Pholcodine concentrations were measured in plasma, saliva and urine by a recently described high-performance liquid chromatographic method using fluorescence detection (Chen *et*

al., 1988). This method has a sensitivity of 1.5 ng ml^{-1} and shows precision and accuracy to between 5 and 10%. The assay is also capable of detecting morphine in saliva and urine to a sensitivity of 1 ng ml^{-1} and 50 ng ml^{-1} respectively.

Pholcodine and morphine conjugates

The presence of conjugates of pholcodine and morphine in urine was inferred by the generation of pholcodine and/or morphine following enzymatic hydrolysis. The internal standard (codeine phosphate) was added to urine samples (0.3 ml) in 10 ml screw capped tubes. β -glucuronidase from *Helix pomatia* type H-1 (Sigma Chemical Co., St Louis, MO., USA) was added (0.3 ml of a 3500 u ml^{-1} in pH 5.0 acetate buffer), followed by incubation in a shaking water bath at 37°C for 14 h. Samples were analysed for pholcodine and morphine by the above method.

Plasma protein binding

The extent of binding of pholcodine to plasma proteins was assessed in a microultrafiltration system (Model MMC Amicon Corp., Danvers, Mass, USA) with Diaflo YM 10 membranes (Amicon Corp.) at 37°C . The 0, 2 and 4 hourly plasma samples from the chronic dosing study in each subject were used. The linearity of binding *in vitro* was assessed by spiking blank plasma with pholcodine at concentrations ranging from 5 to 200 ng ml^{-1} . The free fraction was calculated as the concentration in the ultrafiltrate divided by the concentration in the original sample.

Pharmacokinetic and statistical analysis

The concentrations of pholcodine in saliva up to 2 h after administration were not included in the calculations of the pharmacokinetic data, because of likely retention of part of the oral dose in the mouth during this time period.

The maximum plasma concentration ($C_{\max}$) and its time of occurrence ($t_{\max}$) were determined from the observed data. The area under the plasma or saliva concentration-time curves to the last sampling time (AUC_{0-168}) following single dose administration was calculated by the trapezoidal rule and the total AUC was calculated as

$$\text{AUC} = \text{AUC}_{0-168} + C_p^{168}/\lambda_z^p \text{ or } C_s^{168}/\lambda_z^s$$

where C_p^{168} and C_s^{168} are the plasma and saliva concentrations at 168 h respectively and λ_z^p and λ_z^s are the slopes of the terminal concentration-time curves determined by linear regression analysis of the terminal concentration-time curves

when plotted as their natural logarithm. Half-lives ($t_{1/2,z}$) in plasma and saliva were calculated as

$$t_{1/2,z} = 0.693/\lambda_z^p \text{ or } \lambda_z^s$$

The half-life of pholcodine was also calculated using urine data in which the natural logarithm of the rate of urinary pholcodine excretion was plotted against the mid-points of the urine collection time periods. The slope of this line (λ_z^u) was used to calculate the half-life as

$$t_{1/2,z} = 0.693/\lambda_z^u$$

Renal clearance (CL_R) was calculated as

$$\text{CL}_R = A_e(t_1 - t_2) / \text{AUC}(t_1 - t_2)$$

where A_e is the amount excreted unchanged and t_1 to t_2 represent time intervals.

The pharmacokinetic data from the 20 mg single dose study were used to predict the concentrations of pholcodine in plasma and in saliva during chronic administration. This prediction was made by using the equation:

$$C_{av} = \text{AUC}_{0-n\tau} / \tau$$

where τ is the dosing interval during chronic administration (8 h) and $\text{AUC}_{0-n\tau}$ is the area under the single dose concentration-time profile from time zero to n (the number of doses given) times the dosing interval (Chiou, 1979).

Differences in pharmacokinetic data between treatments were analysed for statistical significance by *t*-test. Linear regression analysis was used for correlations between plasma and saliva data and between renal clearance and urine pH and flow rate. All data are tabulated as mean $\pm$ s.d.

Results

Single dose studies

The mean plasma and saliva concentration-time profiles and urinary excretion rate vs mid-point time collections for pholcodine in six subjects following 20 and 60 mg oral doses are shown in Figure 2. Tables 1 and 2 contain the derived pharmacokinetic parameters. The values for $t_{\max}$ in plasma were not different between the two doses ($P > 0.05$). The maximum plasma concentration for the 60 mg dose was between 1.75 and 3.05 times that of the 20 mg dose. Following attainment of the peak plasma concentration, plasma pholcodine concentrations declined in a monoexponential manner. Tables 1 and 2 show that the elimination half-lives determined from plasma, saliva and urine excretion rate were not significantly different after the 20 mg dose and after the 60 mg dose ($P > 0.05$). There was no

Figure 2 Mean $\pm$ s.d. plasma (Δ) and saliva ($\square$) concentrations and urinary excretion rate ($\blacksquare$) of pholcodine after a single 20 mg (a) and 60 mg (b) oral dose.

Table 1 Pholcodine pharmacokinetic parameters after 20 mg oral pholcodine

Subject	$t_{1/2}$ (h)			t_{max} (h)	C_{max} (ng ml ⁻¹)	AUC (mg l ⁻¹ h)		CL_R (ml min ⁻¹)	Excretion of dose (%)
	plasma	saliva	urine			plasma	saliva		
1	41.9	81.1	53.6	4.0	12.1	0.70	4.17	123	30
2	54.5	52.7	57.6	3.0	9.6	0.66	2.62	129	26
3	44.0	37.3	42.0	0.75	11.1	0.62	1.63	141	26
4	34.9	46.0	32.8	0.25	25.4	1.05	1.95	63	24
5	47.4	66.8	51.7	2.0	9.7	0.67	4.91	136	32
6	49.8	50.0	49.8	2.0	8.9	0.62	2.19	162	27
Mean	45.4	55.6	45.5	2.0	12.8	0.72	2.91	126	27
s.d.	6.8	14.4	10.3	1.3	6.3	0.16	1.20	33	3

Table 2 Pholcodine pharmacokinetic parameters after 60 mg oral pholcodine syrup

Subject	$t_{1/2}$ (h)			t_{max} (h)	C_{max} (ng ml ⁻¹)	AUC (mg l ⁻¹ h)		CL_R (ml min ⁻¹)	Excretion of dose (%)
	plasma	saliva	urine			plasma	saliva		
1	53.3	45.0	36.0	1.0	36.7	1.52	4.97	133	20
2	39.2	49.6	39.2	0.25	29.3	1.44	7.53	171	25
3	52.0	47.9	55.5	1.0	28.6	1.51	5.19	181	27
4	76.0	40.4	76.4	0.5	43.5	2.34	6.09	95	22
5	45.7	51.2	45.7	3.0	26.2	1.65	8.72	171	28
6	44.9	45.9	60.7	2.0	26.3	1.55	7.18	146	23
Mean	51.9	46.7	52.1	1.3	26.3	1.67	6.61	150	24
s.d.	11.8	3.5	15.0	0.9	6.4	0.31	1.33	30	3

Figure 3 Correlation between the concentrations of pholcodine in saliva and plasma. ■ single dosing, △ chronic dosing.

difference in half-life between the two doses when determined using plasma, saliva or urine excretion rate data ($P>0.05$). The combined mean half-lives in plasma were 48.6 ± 10.4 h, saliva 51.2 ± 11.9 h and urine 50.0 ± 12.2 h. The mean area under the plasma concentration-time curve for the 60 mg dose was 2.3 ± 0.2 (range 2.2–2.5) times that of the 20 mg dose. This was significantly less than the expected ratio of 3.0 ($P<0.05$). The area under the saliva concentration-time curve for the 60 mg dose was 2.6 ± 1.0 (range 1.2–3.3) times that of the 20 mg dose and was not significantly different from the expected ratio of 3.0 ($P>0.05$). The mean area under the saliva concentration-time curve was 4.2 ± 2.1 times higher than under the plasma concentration-time curve for the 20 mg dose, and 4.1 ± 1.6 times for the 60 mg dose. There was a highly significant correlation ($r = 0.91$, $P<0.01$) between plasma and saliva concentrations (Figure 3).

The percent of the dose excreted unchanged after 20 mg and 60 mg was 27 and 24% respectively ($P>0.05$). There was no statistically significant difference ($P>0.05$) in renal clearance of pholcodine between the two doses. There was a statistically significant ($r = 0.60$, $P<0.01$) inverse relationship between urine pH and renal clearance (Figure 4a). There was however no correlation between urine volume and renal clearance (Figure 4b).

Chronic dose study

During the chronic dosing study, daily trough saliva concentrations reached a plateau by day 7 (Figure 5). The mean area under the saliva concentration-time curve during the dosing interval on day 11 was 1.97 ± 0.44 $\text{mg l}^{-1} \text{ h}$ which did not differ significantly ($P>0.05$) from the single dose area under the saliva concentration-

Figure 4 Correlations between the renal clearance of pholcodine and urine pH (a) and urine flow rate (b).

Figure 5 Mean $\pm$ s.d. plasma (Δ) and saliva ($\blacksquare$) concentrations of pholcodine after 20 mg oral pholcodine 8 hourly for 10 days. The concentration in saliva predicted ($\blacksquare$) from the single dose pharmacokinetics are shown. The inset contains the expanded inter-dose interval data after the last dose on day 11.

time curve ($2.91 \pm 1.20 \text{ mg l}^{-1} \text{ h}$), although in five of the six subjects, it was lower during the chronic study. By contrast, the mean area under the plasma concentration-time curve during the dosing interval on day 11 was $0.55 \pm 0.06 \text{ mg l}^{-1} \text{ h}$, being just significantly ($P = 0.05$) lower than the area obtained after the single dose ($0.72 \pm 0.16 \text{ mg l}^{-1} \text{ h}$). The mean elimination half-life ($53.5 \pm 2.3 \text{ h}$) in saliva was not significantly different from the single dose half-lives (Tables 1 and 2). Likewise the mean percentage of the dose excreted unchanged in urine (26.8 ± 3.5) was not significantly different from that following the two single doses (Tables 1 and 2). The mean ratio of saliva to plasma area under the concentration-time curves during the 8 h dosing interval was 3.64 ± 0.88 (range 2.40 to 5.06). The saliva pholcodine concentrations predicted from the single dose pharmacokinetic data are shown in Figure 5 and are not statistically different from the observed values ($P > 0.05$).

Morphine, and the conjugates of morphine after hydrolysis were not detected in urine (lower limit of assay sensitivity was 50 ng ml^{-1} in urine). Putative pholcodine conjugates were not detected in urine after hydrolysis although two additional peaks were noted in the chromatograms of the plasma extracts (60 mg dose and chronic dose), and in the extracts of urine and saliva samples after all doses. The identity of these peaks has not yet been established.

The extent of plasma protein binding was $23.2 \pm 5.6\%$ in the six subjects on chronic administration and was $21.5 \pm 3.1\%$ when pholcodine was added to drug free human plasma.

There were no adverse effects of pholcodine demonstrable in any of the volunteers during single or chronic studies.

Discussion

To our knowledge this is the first study to have used a specific chemical assay for the analysis of pholcodine in biological fluids in order to evaluate its disposition in man. The pharmacokinetics of pholcodine after single doses have been reported by Neuvonen *et al.* (1980) and Findlay *et al.* (1986). Differences exist in the results from these two studies compared with the present one. Firstly, the mean t_{max} of 4–6 h (Findlay *et al.*, 1986) was much longer than the 2 h reported here. This difference may relate to the fact that the subjects in Findlay *et al.* (1986) study had taken pholcodine in the fasting state whereas in our study, they had not. Secondly, after 60 mg of pholcodine in two separate studies, Findlay *et al.* (1986) reported a C_{max} of $27 \pm 6 \text{ ng ml}^{-1}$ and

$57 \pm 11 \text{ ng ml}^{-1}$ (mean $\pm$ s.d.) and Neuvonen *et al.* (1980) attained a C_{max} of about 80 ng ml^{-1} after a 30 mg dose (personal communication). The mean C_{max} of $26.3 \pm 6.4 \text{ ng ml}^{-1}$ achieved in this study is similar to one of the values cited by Findlay *et al.* (1986) but much lower than their second value. Thirdly, the mean plasma elimination half-life of $52 \pm 12 \text{ h}$ in our subjects is comparable to the value reported by Findlay *et al.* (1986) of $37 \pm 4 \text{ h}$, but is shorter than the $102 \pm 10 \text{ h}$ from urine reported by Neuvonen *et al.* (personal communication). Finally, the plasma AUC of $1670 \pm 310 \text{ ng ml}^{-1} \text{ h}$ is higher than that ($1004 \pm 77 \text{ ng ml}^{-1} \text{ h}$) found by Findlay *et al.* (1986). The reasons for these discrepancies are not clear.

We are not aware that the disposition of pholcodine after chronic administration to man has been previously studied. The fact that the observed concentrations in both saliva and plasma were similar to those predicted from the single dose pharmacokinetic parameters indicates that the absorption of pholcodine is not dose dependent and disposition obeys first order kinetics at the dosages studied in these volunteers. The similar terminal half-lives after single doses and on cessation of chronic dosing support the above contention. There was a trend for the AUC_{0-8} on day 11 for both saliva and plasma to be lower than the AUC following the single dose. The reasons for this are not clear.

The fate of pholcodine in humans is still unclear. The urinary recovery of unchanged drug of 25% indicates that a substantial proportion of the dose is not accounted for. The absorption of pholcodine was reported to be $88 \pm 26\%$ (Neuvonen *et al.*, 1980, personal communication). Thus most of the unaccounted portion must undergo metabolism, since only 5% of an intravenous dose was recovered as [^{14}C]-pholcodine in faeces (Neuvonen *et al.*, 1980). We could not recover any of the dose as glucuronide or sulphate conjugates in urine. It is likely that the two unidentified peaks which consistently appeared in all the urine and saliva chromatograms in every subject are pholcodine metabolites, whose identity is currently being sought.

There is evidence in the rat (Butz *et al.*, 1983) that morphine is a minor metabolite of pholcodine, accounting for less than 1% of the dose. In agreement with Findlay *et al.* (1986) and Neuvonen *et al.* (1980), we could not detect any morphine in urine even after enzymatic hydrolysis. Thus, pholcodine is unlikely to exert its pharmacological effect via morphine.

The saliva to plasma pholcodine concentration ratio was substantially greater than unity. This phenomenon results from a combination of

factors: pholcodine is a basic compound, it has a high pK_a (9.3, Moffat, 1986), low plasma protein binding (23%) and is highly lipophilic. Codeine has similar physico-chemical properties to pholcodine, and its saliva to plasma concentration ratio is similar to that of pholcodine (Lee *et al.*, 1986). Based on the Henderson-Hasselbach equation, we predict that the saliva to plasma ratio should be between 1.3 and 6.4 if saliva pH ranges from 6.5 to 7.2. The mean pH of saliva in our subjects was 6.8, which would result in a saliva to plasma ratio of 3.2. The mean ratio in our volunteers was 3.6. This somewhat higher than predicted value may reflect a contribution from ion trapping. The strong correlation between saliva to plasma pholcodine concentration ratio and saliva pH ($r = 0.804$) is consistent with the Henderson-Hasselbach equation and the known physico-chemical properties of pholcodine.

Pholcodine renal clearance ranged from 63 to 181 ml min⁻¹ and indicates that pholcodine must undergo tubular secretion in addition to glomerular filtration. In addition, the statistically significant inverse correlation between renal clearance and urine pH suggests that reabsorption must also occur. Our data do not allow us to determine the relative contribution of secretion and reabsorption to total renal clearance.

The elimination half-life of pholcodine is substantially longer than that of the other commonly used antitussive agents such as codeine (2.8 h, Vozech & Schmidlin, 1987) and dextromethorphan (3.0 h, Aylward *et al.*, 1984). The possible reasons for this difference may reside in a larger distribution volume and/or slower clearance rate. In support of the first hypothesis, we have calculated that the distribution volume of pholcodine ranges

between 30 to 40 l kg⁻¹, assuming complete bioavailability. This value is similar to that reported by Findlay and coworkers (1986). By comparison, the distribution volume of codeine is 5.4 l kg⁻¹ (Vozech & Schmidlin, 1987). We are not aware that the distribution volume of dextromethorphan has been reported. Secondly, the total body clearance of pholcodine, again assuming complete gastro-intestinal absorption, ranges between 400 and 600 ml min⁻¹, of which we know that renal clearance accounts for 25%. Thus, based on our data and calculations, pholcodine is likely to be a drug with a relatively low hepatic extraction ratio. Our clearance value is almost half of that reported by Findlay and coworkers (1986).

Although we did not objectively assess a pharmacodynamic response, none of our subjects experienced any of the usual opioid-like side-effects such as constipation, urinary hesitancy, drowsiness, dizziness, nausea and confusion, even though pholcodine had accumulated by a factor of 9 (Rowland & Tozer, 1980) on chronic administration over 10 days.

The currently recommended dosage regimen for pholcodine is 10 mg up to 6 times daily for adults (British National Formulary, 1985). The single dose data of Findlay *et al.* (1986) and now our additional information derived from chronic dosing, suggest that these dosing recommendations should be reconsidered.

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