Pralidoxime Methanesulfonate: Plasma Levels and Pharmacokinetics after Oral Administration to Man

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Abstract □ A new oral preparation of pralidoxime methanesulfonate was administered to 20 normal volunteers. The six subjects who ate before receiving the compound had higher plasma concentrations than those who had fasted. The biological half-time was 1.52 hr., and 31.9% of the dose was recovered in the urine. The renal clearance was 4.1 times the clearance of endogenous creatinine, and the volume of distribution was greater than the body volume. Plasma concentrations were equivalent on a molar basis to a comparable dose of pralidoxime chloride.

Keyphrases □ Pralidoxime methanesulfonate—plasma levels and pharmacokinetic parameters after oral administration, compared to pralidoxime chloride, man □ Plasma levels—pralidoxime methanesulfonate after oral administration, man □ Absorption—pralidoxime methanesulfonate after oral administration, compared to pralidoxime chloride, man □ Urinary excretion—pralidoxime methanesulfonate after oral administration, man □ Oximes, pralidoxime methanesulfonate—plasma levels and pharmacokinetic parameters after oral administration, compared to pralidoxime chloride, man

The oximes are valuable adjuncts to an anticholinergic drug in the therapy of anticholinesterase poisoning. For various reasons, there is not agreement from country to country on the oxime of choice. For example, in the United States, pralidoxime chloride (2-formyl-1-methylpyridinium chloride oxime) is the only oxime commercially available. In most of Europe, toxogonin [bis(4-hydroxyiminomethylpyridinium-1-methyl) ether dichloride] is the preferred compound; and in Great Britain and Canada, the methanesulfonate salt of pralidoxime is the one most commonly used.

Overall, there is probably little inherent therapeutic advantage of one oxime over another. Toxogonin is reportedly more potent (1, 2) (*i.e.*, a lower dose is required for therapeutic activity) but causes more side effects (at least in nonpoisoned subjects) and is poorly absorbed when taken orally (3). There seems to be little difference in therapeutic activity between the pralidoxime salts (4), and there are few data on which to base a direct comparison of pharmaceutical preparations.

This study was undertaken to evaluate a new oral preparation of pralidoxime methanesulfonate and to compare it with a commercial preparation of pralidoxime chloride studied earlier (5).

EXPERIMENTAL

Subjects—The subjects were healthy young men (ages 20–24), who underwent thorough physical and laboratory examinations[1] before being accepted into this study and who volunteered for the study after it was fully explained to them[2].

Materials—The pralidoxime methanesulfonate was in tablets[3], each containing 400 mg. of drug and 71 mg. of excipient with a dimethylaminoethyl methacrylate coating. Analysis indicated a 3% variation in active compound. Because the doses ranged from 2 to 8 g., the subjects took from 5 to 20 tablets over a 1–2 min. period.

Procedure—The tests were conducted in a hospital-type ward, with trained nurses and technicians in attendance at all times. The subjects were admitted the evening before the test and remained for 24 hr. after drug administration. They were awakened 1–2 hr. before receiving the drug, and control measurements of heart rate and blood pressure were made.

Fourteen subjects received no solids from 8 hr. before until 3 hr. after drug administration; six subjects ate breakfast (bacon, eggs, and toast) about 30–45 min. before the drug. All subjects were encouraged to drink approximately 1 l. of fluid during the 2 hr. before they received the drug and 250 ml. every 30 min. thereafter for 7 hr., mainly in the form of fruit juices and carbonated beverages.

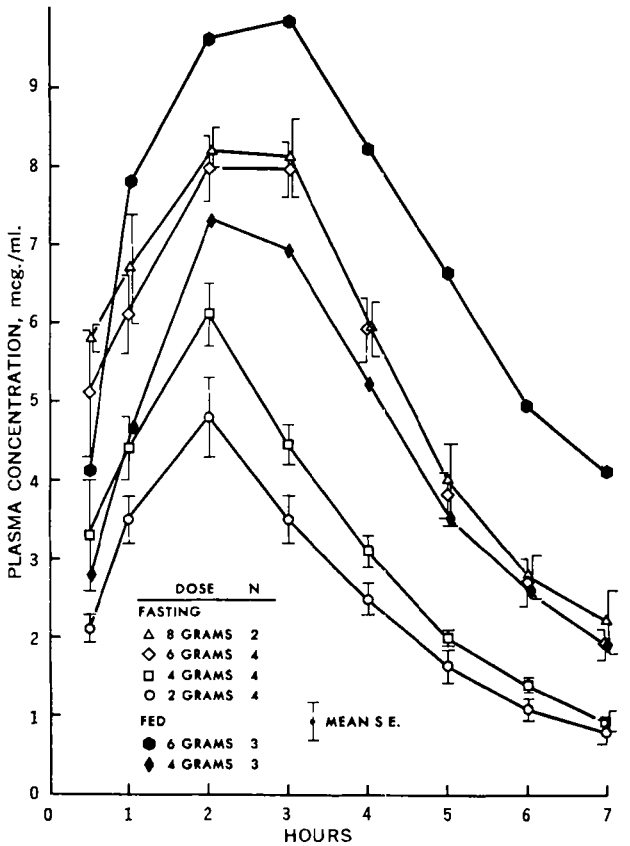

Figure 1—*Pralidoxime methanesulfonate: mean plasma concentrations* versus *time.*

[1] Chest X-ray, ECG, routine urinalysis including microscopic examination, hematocrit, hemoglobin, total and differential white blood cell counts, serum glutamic oxaloacetic transaminase (SGOT), blood urea nitrogen (BUN), creatinine, alkaline phosphatase, bilirubin, albumin, globulin, and serum (butyrl) and red cell (acetyl) cholinesterase.

[2] The volunteers in these tests were enlisted U. S. Army personnel. These tests were governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

[3] Developed, manufactured, and supplied by Philips-Duphar, Amsterdam, The Netherlands.

Table I—Urinary Excretion of Pralidoxime Methanesulfonate

Dose, g.	Amount Excreted, % of Total — Time, hr. 1	2	3	4	5	6	7	Percentage of Dose Excreted by 24 hr.	Amount Excreted by 24 hr., mg.
				Fasting					
2	14.9[a]	39.2	59.7	71.3	80.6	86.4	89.9	40.5	810
	5.4	7.3	7.6	6.9	6.7	6.4	5.5	4.4[c]	88
4	13.5	36.8	59.4	71.5	79.5	86.8	90.2	27.9[c]	1115
	2.7	5.7	5.4	3.5	3.3	1.9	2.2[b]	3.7	149
6	13.4	32.6	53.1	69.4	79.0	84.6	88.0	29.8	1789
	1.4	3.9	6.6	4.9	3.0	2.3	1.6	2.6	156
8	12.4	29.7	47.8	60.4	70.6	78.0	82.3	20.9	1669
	4.7	0.4	3.1	2.3	4.9	1.4	2.5	9.5	759
Mean	13.7	35.3	56.0	69.2	78.4	84.8	88.3		
	3.4	6.0	7.2	5.9	5.3	4.5	4.1		
				Fed					
4	11.2	32.9	48.6	65.6	74.0	81.4	86.1	34.8	1389
	4.1	4.0	8.0	7.1	3.6	1.8	1.5	3.3	132
6	8.2	23.8	41.4	61.0	71.6	80.4	86.4	33.1	1983
	2.2	3.9	4.4	6.2	3.8	2.1	1.3	4.2	254
Mean	9.7	28.4	45.0	63.3	72.8	80.9	86.2		
	3.4	6.1	7.0	6.5	3.6	1.8	1.2		
				Mean of All					
	12.5	33.2	52.7	67.5	76.7	83.6	87.7	31.9	
SD	3.8	6.7	8.7	6.5	5.4	4.3	3.6	6.9	

[a] Mean ± *SD*. [b] $p < 0.05$ by *t* test. [c] $p < 0.01$ by *t* test.

Blood was drawn for control and oxime measurements before the drug was given and at intervals thereafter for 7 hr. Urine was collected just before drug administration for routine analysis and as a control for oxime content, and the subjects were encouraged to void at hourly intervals for 7 hr. After 7 hr., no schedule was imposed, although the time of voiding was recorded. All urine voided for 24 hr. after the drug was analyzed for oxime content. The oxime content of plasma, red blood cells, and urine was measured by methods described previously (6). Each urine and blood sample was analyzed for creatinine using the Technicon procedure (7).

Heart rate and blood pressure were measured by the usual techniques twice on the evening of admission, thrice in the morning before drug administration, and just before each blood sampling thereafter. Each measurement was taken after the subject had lain supine for 10 min. The subjects were not restricted to bed except for 10 min. before measurement of heart rate and blood pressure.

At 24 hr. and at 7 days after the drug, urinalysis (including microscopic examination) was repeated and hematocrit, hemoglobin, total and differential white blood cell counts, SGOT, alkaline phosphatase, and BUN were measured. No abnormalities were found.

Four subjects participated each test day, and at least two doses were administered each day. The number of subjects by dose groups was four, four, four, and two for 2, 4, 6, and 8 g. fasting, respectively, and three for each of the fed groups (4 and 6 g.).

RESULTS

General—All subjects expressed surprise at the ease with which they were able to swallow the numerous tablets; and all, even those who took 20 tablets, were able to swallow the entire dose in less than 2 or 3 min., undoubtedly because of the methacrylate coating.

No subject had any symptoms, GI or otherwise, during the test period. There were no changes in heart rate or blood pressure.

Plasma Levels—Plasma concentrations of oxime, as the mean value for each dose group plotted against time, are shown in Fig. 1. The drug was rapidly absorbed, since the plasma levels were approximately 50% of their maximum within 30 min.

The average subject receiving 6 or 8 g. reached a plasma concentration of 4 mcg./ml. [considered to be a therapeutic level (8)] at about 20 min. and maintained a concentration above this amount for almost 5 hr. The average subject receiving 4 g. attained the therapeutic concentration about 45 min. after ingestion and exceeded it for about 2.5 hr. The average subject receiving 2 g. had a plasma level higher than 4 mcg./ml. only transiently at 2 hr.

There was no significant difference between the maximal plasma concentrations between subjects receiving 6 and 8 g. This correlates well with mean urinary excretion of oxime in these dose groups (1.79 g. for the 6-g. dose group and 1.67 g. for the 8-g. dose group, Table I).

The nonfasted subjects had slightly slower absorption (lower plasma concentrations at 30 min.) but eventually had higher plasma concentrations. The difference was not significant, however ($0.1 > p > 0.05$ by *t* test between maximal measured plasma concentrations of the fasting and fed subjects).

The slowing of gastric motility produced by the food may have allowed more time for absorption. One practical implication of this finding is that whether the subject has been fasting or eating makes no difference in the blood level of ingested oxime.

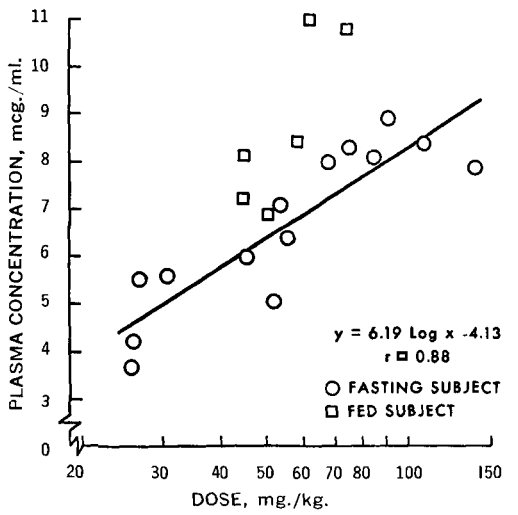

Figure 2—*Pralidoxime methanesulfonate: maximal measured plasma concentration for each subject (the regression line calculation did not include the fed subjects).*

Table II—Urinary Clearance of Pralidoxime Methanesulfonate

Case Number	Cl_{ox}[a], ml./min.	Cl_{ox}[b], ml./min.	Cl_{cr}[c], ml./min.	Cl_{ox}/Cl_{cr}
3541	537 ± 60[d]	514	125 ± 12.4	4.1 ± 0.4
3542	573 ± 196	535	124 ± 35	4.7 ± 0.5
3546	461 ± 25	466	154 ± 14	3.0 ± 0.3
3551	688 ± 163	680	139 ± 22	4.9 ± 0.5
3547	561 ± 87	581	125 ± 24	4.2 ± 0.7
3540	648 ± 62	656	147 ± 17	4.6 ± 0.6
3539	555 ± 37	551	144 ± 9	3.9 ± 0.1
3553	935 ± 550	874	167 ± 5	3.9 ± 0.6
3550	677 ± 233	708	144 ± 12	4.6 ± 1.6
3549	623 ± 66	645	151 ± 5	4.2 ± 0.6
3552	541 ± 97	566	130 ± 14	4.2 ± 1.0
3548	553 ± 166	609	125 ± 25	4.4 ± 0.4
3555	680 ± 227	561	147 ± 56	4.7 ± 0.8
3554	397 ± 94	392	95 ± 30	4.3 ± 1.0
3560	586 ± 65	606	180 ± 6	3.3 ± 0.5
3558	617 ± 204	661	125 ± 40	5.1 ± 1.1
3561	479 ± 42	487	161 ± 19	3.0 ± 0.4
3556	629 ± 164	668	170 ± 13	3.7 ± 0.7
3557	555 ± 152	590	158 ± 14	4.1 ± 0.9
3559	492 ± 67	500	152 ± 6	3.3 ± 0.5
Mean of all ±*SD*	576 ± 80	593 ± 104	143 ± 20	4.10 ± 0.61

[a] Renal clearance of oxime as $Cl = UV/P$. [b] Renal clearance of oxime calculated as slope of rate of urinary excretion *versus* plasma concentration. [c] Renal clearance of creatinine. [d] Mean (of at least four values) ±*SD*.

The highest plasma oxime concentration measured for each subject is plotted against his dose in Fig. 2. (When the regression line was calculated, data on the subjects who had eaten were excluded.)

Urinary Excretion—The mean percentage of the dose found in the urine over the 24-hr. period was 31.9, and 52.7% of this amount appeared within 3 hr. Table I shows the excretion data as the percentage per hour for the first 7 hr. and as the percentage of the dose excreted by dose group.

The percentage of the dose excreted decreased with increasing dose, although the only significant differences (by *t* test) were 2 g. *versus* 4 and 6 g. ($p < 0.01$ in each case) and 2 g. *versus* 8 g. ($p < 0.05$) (Table I). This result was reported previously for pralidoxime chloride and may be due to a saturation of the absorption sites or an increase in elimination by other routes. The lack of a proportional increase in plasma concentration as the dose was increased from 6 to 8 g. suggests the former.

Renal Clearance—The renal clearances of oxime and creatinine were calculated by the formula:

$$Cl_x = \frac{U_x V}{P_x} \qquad \text{(Eq. 1)}$$

where Cl_x is the renal clearance of compound x, U_x is the urinary concentration of x, V is the volume of urine produced per unit time, and P_x is the plasma concentration of x at the midpoint of the collection interval.

The P_x for oxime and creatinine was estimated from plasma concentrations measured hourly; since the plasma level of oxime was changing rapidly during the absorptive phase, only the values in or near the postabsorptive phase were used (arbitrarily, absorption was considered to be complete by 4 hr.).

Table II gives these clearance values and the ratio of oxime to creatinine clearance (no corrections for body surface area were made). Since endogenous creatinine clearance is an approximate measure of glomerular filtration rate, the clearance ratio of 4.1 indicates that the oxime must be actively secreted by renal tubular cells. This ratio approaches that of *p*-aminohippuric acid clearance to creatinine clearance [which is 5.28 (9)]. Since *p*-aminohippuric acid is a measure of effective renal plasma flow, this indicates that pralidoxime methanesulfonate is rather efficiently extracted from the plasma during its passage through the kidney.

In pharmacokinetics the renal clearance is taken as the slope of a regression line calculated from the rate of excretion of the drug *versus* the plasma concentration at the midpoint of the collection interval. This slope, or clearance, is the product of the elimination rate constant, the volume of distribution, and the fraction of drug excreted in the urine (10). Table II shows the clearances calculated by this method. The line (again, using the postabsorptive values only) frequently did not pass through the origin, but the 95% confidence limits of the intercept included zero and the clearance shown is the result of forcing the line through the origin.

The difference between the values for oxime clearance from the two methods of calculation was small and insignificant ($p > 0.5$ by paired *t* test).

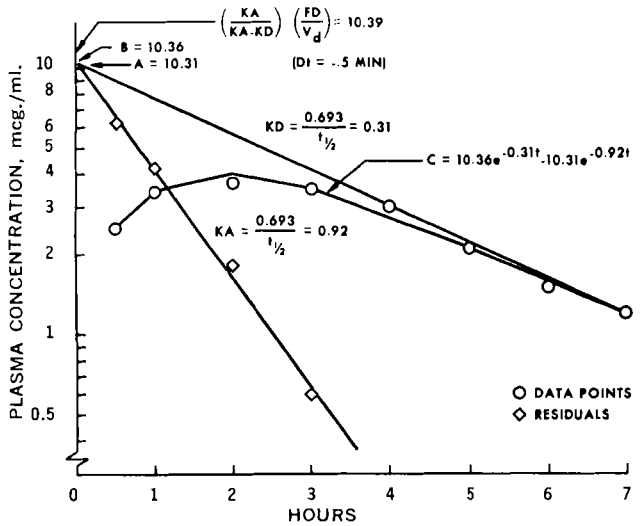

Figure 3—*Pralidoxime methanesulfonate: calculation of pharmacokinetic constants for a typical subject.*

PHARMACOKINETIC CONSIDERATIONS

General—By using the computer program of Mueller and Lieberman[4] (11) and the values for plasma level and time, the constants in Eq. 2 were calculated:

$$C_t = \frac{FD}{V_d}\left(\frac{KA}{KA - KD}\right)\left[e^{-KD(t-Dt)} - e^{-KA(t-Dt)}\right] \qquad \text{(Eq. 2)}$$

where F = fraction of the dose absorbed, D = dose, V_d = volume of distribution[5], KA = first-order rate constant for absorption, KD = first-order rate constant for elimination, Dt = "lag time" for the compound to appear in the plasma, and C_t = plasma concentration at time t.

[4] Kindly supplied by Mueller and Lieberman.

[5] The volume of distribution is the hypothetical volume in which the drug is present in the same concentration in which it is present in the plasma.

This equation describes a one-compartment model with first-order absorption and first-order excretion. The data from all subjects fit satisfactorily. The mean values by dose group for constants KA and KD and the ratio FD/V_d are shown in Table III. The data points and calculated response line for a typical subject are shown in Fig. 3.

Volume of Distribution—The volume of distribution can be calculated by several methods. The most direct is to divide the amount of drug in the body at time t by the plasma concentration at time t at a time when equilibrium has taken place. Although the amount entering the body cannot be measured directly when the drug is administered orally, the urinary output often may be assumed to be a direct reflection of this amount. Therefore, a good estimate of the amount of drug in the body at time t is the total amount excreted in the urine minus the amount excreted by time t; this amount, divided by the plasma level at time t, should give a good estimate of V_d (this ignores the 5–10 min. that the drug is in transit through the urinary tract). If the drug is not entirely eliminated through the kidneys, the V_d calculated by this method will underestimate the true V_d by a fraction equal to the fraction of drug eliminated by other means.

By using data from the postabsorptive state (after 3–4 hr.), V_d was calculated by this method. The dose group mean values are shown in Table III.

The volume of distribution can also be calculated from the plasma clearance (PC) as: $PC = V_d \times KD$. The plasma clearance is equal to the dose divided by the area under the plasma concentration *versus* time curve. Since the exact dose is not known (as the fraction absorbed is unknown), the dose was assumed to be equal to the amount excreted (an assumption that will result in an underestimation of V_d). The area under the plasma concentration–time curve was estimated by using the integral of the equation for the curve.

The values of V_d by this method were comparable to those previously calculated (Table III).

Absorption—The rate constant for absorption, KA, was not significantly different between any dose groups. Although the mean value was lower in the fed subjects than in the fasting subjects at the same doses, the difference was not significant ($0.4 < p < 0.5$ for the 4-g. groups, $0.8 > p > 0.7$ for the 6-g. groups, and $0.4 > p > 0.3$ for the combined groups).

Since the rate constant for elimination is the same for the fed or fasting groups, the time to maximal plasma level or t_{max}, calculated from (10):

$$t_{max} = \left(\frac{1}{KA - KD}\right) \ln\left(\frac{KA}{KD}\right) \qquad \text{(Eq. 3)}$$

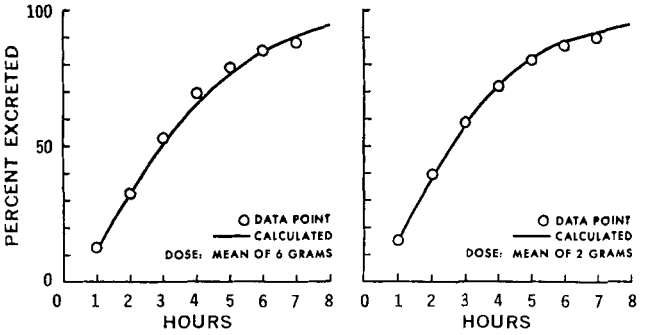

Figure 4—*Pralidoxime methanesulfonate: calculated* versus *actual urinary excretion.*

might be considered partially as a measure of rapidity of absorption. These times are shown in Table III. The mean times for the fasting 4- and 6-g. dose groups were 1.62 and 1.84 hr., respectively, and for the fed groups they were 2.02 and 2.22 hr., respectively. The differences are not significant ($0.1 < p < 0.2$ by t test). If one combines both dose groups, the differences are significant (fasting mean 1.73 hr., fed mean 2.12 hr.; $p < 0.05$). It is possible that had more subjects been used at each dose–eating condition, a more significant difference in absorption rate would have been detected.

Excretion—The rate constant for elimination, KD, was given by the computer program; the values are shown in Table III. There were no significant differences between dose groups or between groups receiving the same doses but with different eating conditions.

An alternative method of calculating KD is from the slope of a plot of the rate of urinary excretion in the postabsorptive phase (on a logarithmic scale) *versus* time (the midpoint of the collection interval). Again, absorption was assumed to be complete by 3–4 hr. The mean values shown in Table III are very similar to those obtained from plasma values. The $t_{1/2}$ for elimination based on the plasma value calculations is 1.52 hr.; from the urinary excretion rates, it is 1.60 hr. These half-times are longer than those found for pralidoxime chloride after intramuscular and intravenous administration (1.28 and 1.20 hr., respectively) (12), practically identical to those for pralidoxime chloride and pralidoxime methanesulfonate given orally in aqueous solution (13), and shorter than those for pralidoxime chloride given orally as a tablet (2.70 hr.) (5). However, in the latter study, plasma concentrations were measured only through 5 hr. in many subjects, and it is quite possible that not all values

Table III—Pharmacokinetic Data

Dose, g.	KA, hr.$^{-1}$	$t_{1/2}$ (0.693/KA), hr.	KD[a], hr.	$t_{1/2}$ (0.693/KD), hr.	(FD/V_d), mg./l.	KD[b], hr.$^{-1}$	t_{max}, hr.	V_d[c], l./kg.	V_d[d], l./kg.	Plasma Clearance, ml./min.
					Fasting					
2	1.02[e]	0.76	0.47	1.60	8.82	0.43	1.66	1.27	1.303	720
	±0.43	±0.26	±0.14	±0.49	±1.88	±0.10	±0.15	±0.89	±0.21	±146
4	0.85	0.88	0.52	1.37	12.56	0.46	1.62	1.39	1.169	770
	±0.45	±0.26	±0.11	±0.29	±2.20	±0.06	±0.14	±0.12	±0.25	±98
6	0.70	1.01	0.47	1.50	19.07	0.47	1.84	1.24	1.253	747
	±0.09	±0.13	±0.08	±0.27	±1.74	±0.06	±0.13	±0.22	±0.15	±149
8	0.93	0.89	0.42	1.83	17.85	0.45	1.68	1.91	1.523	613
	±0.52	±0.50	±0.19	±0.81	±4.83	±0.01	±0.27	±0.46	±0.81	±173
Mean	0.87	0.88	0.49	1.54	—	0.45	1.70	1.31	1.282	604
	±0.31	±0.25	±0.11	±140	—	±0.06	±0.17	±0.38	±0.31	±134
					Fed					
4	0.68	1.12	0.47	1.49	17.13	0.42	2.02	1.33	0.996	665
	±0.28	±0.38	±0.07	±0.23	±2.63	±0.06	±0.43	±0.11	±0.29	±155
6	0.66	1.19	0.34	1.74	1.74	0.40	2.22	1.03	1.058	543
	±0.25	±0.58	±0.06	±0.19	±8.88	±0.08	±0.49	—	±0.30	±98
Mean	0.67	1.16	0.41	1.61	—	0.41	2.12	1.23	1.027	726
	±0.24	±0.44	±0.09	±0.23	—	±0.06	±0.43	±0.19	±0.26	±131
					Mean of All					
	0.81	0.96	0.46	1.56	—	0.44	1.83	1.37	1.205	690
	±0.30	±0.33	±0.11	±0.36	—	±0.07	±0.33	±0.28	±0.31	±0.41

[a] From plasma data. [b] From urinary data. [c] Based on amount excreted. [d] From plasma clearance divided by KD. [e] Mean ± SD.

were from the postabsorptive state, which would tend to lengthen falsely the half-times.

If these data fit the one-compartment model with first-order absorption and first-order excretion rates, urinary excretion should fit the pattern described by the equation (10):

$$X_t = 100\left[1 - \left(\frac{1}{KA - KD}\right)(KAe^{-KDt} - KDe^{-KAt})\right] \quad \text{(Eq. 4)}$$

where X_t = the percentage of the amount finally excreted that is excreted by time t.

The data for most of the subjects and the mean values for the dose groups fit such a pattern; examples are shown in Fig. 4. This fit might be considered presumptive evidence that the model is correct.

DISCUSSION

The oral route is not the recommended way to administer an oxime to an individual with signs or symptoms of moderate to severe anticholinesterase poisoning, but there may be circumstances in which this route is acceptable. As suggested earlier (3, 5), these might include cases when the poisoning is mild, when the poisoning is by a compound undergoing *in vivo* transformation to a more toxic substance (*e.g.*, parathion to diethyl *p*-nitrophenyl phosphate[6]), or when the oxime is given for prophylaxis.

Kondritzer *et al.* (13) administered pralidoxime methanesulfonate as an aqueous solution in doses of 21.6 mmoles/70-kg. man (309 μmoles/kg.) and 8.6 mmoles/70-kg. man (123 μmoles/kg.) and reported maximal plasma oxime concentrations of about 30 and 17 μmoles/ml., respectively. Sundwall (14) administered this drug in gelatin capsules and obtained maximal plasma concentrations of about 5 mcg./ml. after doses of 45 mg./kg.; he also reported urinary recovery of 23% of the dose in 4 hr. Calesnick *et al.* (15) reported plasma levels of less than 4 mcg./ml. after oral administration of 45 mg./kg. as a hard gelatin capsule; they also noted a 24-hr. urinary recovery of 21% of the dose.

In this study of a new pharmaceutical preparation, plasma concentrations were at least as high and urinary recovery was 22% of the dose within 4 hr. This tablet appears to be at least as good as any of the previously reported dosage forms if availability is based on plasma concentrations.

This preparation was also similar to the pralidoxime chloride preparation studied earlier.

Plasma concentrations were comparable after similar molar doses, according to dose–plasma concentration regression lines. Doses of 100, 200, and 300 μmoles/kg. of the methanesulfonate should produce plasma concentrations of 22.1, 28.6, and 32.4 μmoles/ml., respectively, and equal doses of the chloride salt should produce plasma concentrations of 26.1, 35.4, and 40.8 μmoles/ml., respectively.

Absorption seemed to proceed at about the same rate, judging from plasma levels at 30 min., although absorption may be slightly more complete after the methanesulfonate salt (using urinary recovery at the 4- and 6-g. doses: 28.8 ± 3.2% for the methanesulfonate *versus* 22.4 ± 4.2% for the chloride). The biological half-lives are very similar and both compounds are rapidly excreted in the urine.

The urinary clearance of this salt is 4.1 times the simultaneously measured clearance rate of endogenous creatinine and approaches the clearance rate of *p*-aminohippuric acid, suggesting that the oxime is readily extracted from the plasma and secreted by the tubular cells. It is possible that its half-life may be prolonged by an appropriate drug to block this; probenecid, which blocks tubular secretion of many drugs, was reported to be ineffective (13).

The volume of distribution, calculated by several methods, is larger than body volume, indicating that large quantities of drug must enter and be concentrated in some body compartments, *i.e.*, tissues, although the site(s) of this sequestration is unknown.

[6] Paraoxon.

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