Blood Levels of Oxime and Symptoms in Humans after Single and Multiple Oral Doses of 2-Pyridine Aldoxime Methochloride

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Abstract □ Single and repeated doses of a commercially available tablet of 2-pyridine aldoxime methochloride (2-PAMCl) were given to volunteers. A single dose of 5 g. was required to produce a plasma level of 4 mcg./ml., and higher doses (to 9 g.) produced plasma levels up to 11 mcg./ml. However, there was much variation in blood levels among individuals receiving the same dose. Although it was possible to maintain blood levels of more than 4 mcg./ml. when the oxime was given in doses higher than 3 g. at 4-hr. intervals, all subjects who received multiple doses over 48 hr. had gastrointestinal symptoms. The mean urinary excretion was 20–25% of the dose administered; the plasma $t_{0.5}$ was 2.7 hr. and the $t_{0.5}$ for excretion into the urine was 2.4 hr.

Keyphrases □ 2-Pyridine aldoxime methochloride (2-PAMCl)—oxime blood levels □ Oxime levels—blood, urine □ Pharmacological effects—2-PAMCl □ Biological half-life—2-PAMCl □ Dose-response—2-PAMCl

2-Pyridine aldoxime methochloride (2-PAMCl) is known to be a potent reactivator of cholinesterase (ChE) which has been inhibited by certain organophosphorus compounds; the oxime, therefore, has been widely accepted as part of the therapeutic armamentarium against poisoning by these compounds. Most studies and recommended doses are based on the intravenous use of the drug. Although 2-PAMCl is marketed in an oral preparation,[1] there are relatively few data showing rate of absorption and blood levels attainable after administration in this form to human subjects.

This study was undertaken to provide data on blood levels of oxime that can be attained after a single oral dose of 2-PAMCl, blood levels that can be maintained by repeated oral doses, and man's tolerance to these doses.

SUBJECTS, MATERIALS, AND METHODS

The subjects were U.S. Army enlisted men who volunteered for this study. They were found to be completely normal after stringent physical, mental, and laboratory examinations (including electrocardiogram, chest X-ray, hemoglobin, total and differential white blood cell count, bilirubin urea nitrogen, serum glutamic oxalacetic transaminase, lactic dehydrogenase, and alkaline phosphatase) before they were accepted into this study.

The subjects were admitted to a special study ward the evening before the test. Those men who received only one dose received no food from 8 hr. before they were given 2-PAMCl until 3 hr. afterwards; the subjects who received multiple doses ate meals at the usual times. To insure adequate urine output, both groups were encouraged to take fluids. The subjects on the single-dose study were restricted to the ward area, but those on the longer study were allowed to leave the ward. All subjects rested in bed for 10 min. preceding measurement of vital signs. Blood pressure and heart rate were measured twice during the evening before the test, three times in the morning before the drug was given, every hour thereafter for the single-dose group, and at the time blood was taken for the 48-hr. group. Venous blood for oxime analysis was withdrawn by the nursing staff at specified times. For the multiple-dose group, this was immediately before each dose and during the daytime hours, at the midpoints between doses.

Plasma from heparinized blood and urine were analyzed for oxime content by the method of Groff and Ellin (1). Plasma specimens were analyzed the day drawn; urine specimens, which were often refrigerated overnight, were analyzed the following day.

The 2-PAMCl (Ayerst Laboratories, control No. E4323) was in the form of tablets, each containing 0.5 g. of the oxime. Each subject took the assigned number of tablets within 2 to 4 min. Midway through one phase of the multiple-dose study, 2-PAMCl tablets were not available, and from 2800 hr. (experimental time) onward the subjects received gelatin capsules containing 0.5 g. of crystalline 2-PAMCl, which were prepared in this laboratory. This may have affected the results obtained after this time with Subjects J.B. and T.M. (2 g. every 4 hr.), T.Y. (4 g. every 6 hr.), and R.M. and C.P. (5 g. every 6 hr.).

RESULTS

Single-Dose Group—*Plasma and Urine Oxime Levels*—Plasma levels of oxime are listed in Table I, and the average values for several doses are shown in Fig. 1.

Within each dose group there was extreme variation in blood levels, presumably due to variation in rate of absorption and amount absorbed. For example, 30 min. after a 7-g. dose, one subject had a level of 3 mcg./ml. and another had a level of 10.5 mcg./ml. Three hours after the 7-g. dose, the range among the four subjects was 3.6–5.7 mcg./ml., which was very close to the range for the 3-g. group (3.2–5.5 mcg./ml.). Also, the range at 2 hr. for the 7-g. group (4.5–6.0 mcg./kg.) was similar to that for the 5-g. group (4.0–7.5 mcg./kg.). Results seemed more consistent at the two highest doses, but because it is impractical to administer 16 or 18 tablets as a

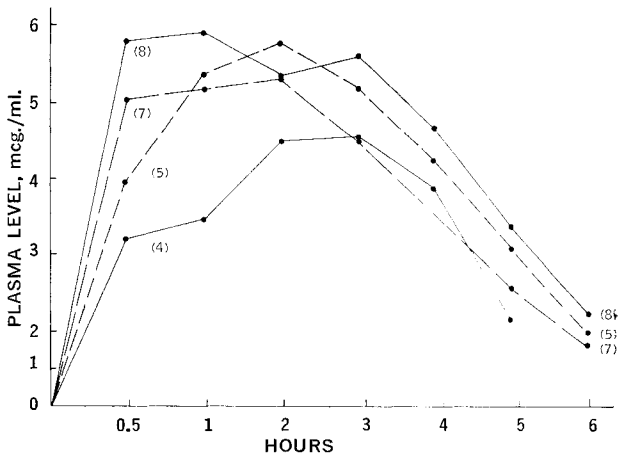

Figure 1—*Plasma levels of oxime after oral administration of 2-PAMCl to men. Key: ( ), dose in grams. See Table I for mM equivalents.*

[1] Protopam tablets containing 0.5 g., Ayerst Laboratories, Inc., New York, N. Y.

Table I—Plasma Level of 2-PAMCl After Oral Administration to Humans

Subject	Dose, g.[a]	Oxime in Plasma, mcg./ml. — Time, hr. 0030	0100	0200	0300	0400	0500	0600	Plasma, hr. $t_{0.5}$	Plasma, hr. k	Urinary, hr. $t_{0.5}$	Urinary, hr. k
J.F.	3	—	3.05	5.0	5.50	4.50	—	—	[b]	—	—	—
R.Co.	3	3.6	3.6	4.0	4.6	4.3	3.4	—	[b]	—	—	—
M.M.	3	2.5	3.1	3.5	3.2	3.2	2.4	—	[b]	—	—	—
R.Cr.	3	2.8	3.1	4.4	3.7	3.0	2.3	—	3.22	0.215	3.5	0.198
Av.		2.96	3.2	4.20	4.2	3.7	2.7	—	—	—	—	—
L.D.	4	1.45	2.85	4.45	4.95	4.60	—	—	—	—	—	—
R.F.	4	6.05	4.95	4.45	4.10	3.20	2.0	—	3.25	0.213	—	—
E.D.	4	2.10	2.55	4.55	4.60	3.85	2.35	—	[b]	—	—	—
Av.		3.2	3.45	4.48	4.55	3.88	2.17	—	—	—	—	—
J.A.	5	3.4	3.4	4.0	3.1	2.12	1.6	—	2.21	0.314	—	—
C.B.	5	3.0	3.6	5.1	5.0	4.5	3.4	—	[b]	—	—	—
W.Ba.	5	5.0	4.6	5.2	5.1	4.25	2.6	—	[b]	—	2.1	0.330
W.Bo.	5	4.45	5.6	6.55	6.4	5.5	3.6	—	[b]	—	—	—
J.G.	5	3.4	7.8	7.5	6.3	5.4	4.4	—	4.70	0.147	2.7	0.257
D.H.	5	3.2	4.4	4.7	4.1	3.5	2.8	—	4.05	0.171	2.0	0.347
W.M.	5	4.2	5.0	6.3	5.9	4.6	3.2	2.1	2.47	0.281	2.9	0.239
B.W.	5	7.0	11.1	7.3	5.5	4.0	2.8	1.7	1.93[c]	0.359	—	—
A.B.	5	1.8	2.6	4.9	4.8	4.4	3.2	—	[b]	—	—	—
Av.		3.93	5.34	5.72	5.13	4.25	3.06	1.9	3.07	0.254	2.4	0.293
R.L.	6	8.9	7.0	5.7	4.0	3.1	2.1	1.4	2.15[c]	0.322	—	—
D.H.	6	6.1	6.4	6.4	6.3	5.2	3.5	2.5	2.19	0.316	2.8	0.248
J.I.	6	3.6	4.7	6.0	6.1	4.2	2.9	—	1.86[c]	0.373	2.1	0.33
R.M.	6	6.9	7.1	5.3	3.8	2.3	1.6	—	1.82[c]	0.381	—	—
Av.		6.37	6.3	5.85	5.05	3.7	2.52	1.95	2.00	0.348	2.45	0.289
M.H.	7	3.3	4.4	5.6	4.9	4.4	3.1	2.1	2.87	0.241	2.0	0.347
M.G.	7	3.0	4.6	5.0	3.6	2.3	1.5	1.1	1.78[c]	0.389	2.1	0.33
A.K.	7	10.5	7.8	6.0	5.7	4.8	3.3	2.1	2.73[c]	0.254	2.0	0.347
D.L.	7	3.3	3.9	4.5	3.8	2.9	2.4	1.7	2.88[c]	0.241	2.6	0.267
Av.		5.02	5.17	5.27	4.5	3.6	2.57	1.75	2.57	0.281	2.2	0.323
D.B.	8	7.1	7.1	5.9	5.7	4.9	3.5	2.3	3.30	0.21	3.0	0.231
J.A.	8	4.5	4.7	5.0	5.5	4.5	3.2	2.1	2.15	0.322	2.2	0.315
Av.		5.8	5.9	5.45	5.6	4.7	3.35	2.2	2.73	—	2.6	0.273
J.H.	9	6.7	8.9	9.2	8.1	5.3	3.9	3.0	2.33	0.297	2.6	0.267
G.H.	9	6.7	9.4	7.9	7.1	4.5	3.7	2.6	2.65[c]	0.262	2.0	0.346
Av.		6.7	9.15	8.55	7.6	4.9	3.8	2.8	2.49	0.280	2.3	0.307
Mean									2.66	0.279	2.44	0.293

[a] Doses in millimoles are: 3 g. = 17.35 mmoles; 4 g. = 23.12 mmoles; 5 g. = 28.90 mmoles; 6 g. = 34.68 mmoles; 7 g. = 40.46 mmoles; 8 g. = 46.24 mmoles; 9 g. = 52.02 mmoles. [b] Not significant at 0.01 level. [c] $p<0.001$

therapeutic or prophylactic measure, few subjects were tested at these doses.

Oxime levels in urine were measured over either the 8- or 12-hr. period after oxime ingestion. Results (Table II) show that about 20 to 25% of the dose was excreted in the urine within this period, indicating that at least this amount was absorbed.

Side Effects.—Symptoms were exhibited only by the four subjects receiving the highest doses. The two men receiving 9-g. and one (D.B.) receiving 8g. each had three episodes of diarrhea in the 5 hr. following ingestion of 2-PAMCl; the other man (J.A.) receiving 8 g. had one diarrheal stool approximately 4 hr. after the 2-PAMCl.

Physiological Measures.—There were no significant deviations from control values for heart rate or blood pressure.

Multiple-Dose Group—Various regimens of dose and time of administration were used in an attempt to keep the blood level of oxime above 4 mcg./ml. without causing symptoms. A 48-hr. period was selected for the repeated dose study because (*a*) man probably would not have to take prophylactic oximes for a longer period; (*b*) the test period was not too long; and (*c*) the number of venipunctures required was not unreasonable.

Plasma Oxime Levels—The results of the plasma analyses for oxime are given in Table III and Figs. 2 and 3. When oxime was given every 4 hr., Fig. 2, a blood level of at least 4 mcg./ml. was usually maintained. A 2-g. dose given at this interval produced levels above 4 mcg./ml. during the first 24 hr., after which all values were above 4 mcg./ml. Blood levels attained after 3-g. doses were usually above 4 mcg./ml. and those after 5 g. were even higher. However, symptoms (see below) increased with the higher doses.

Given every 6 hr. (Fig. 3) 4 g. did not maintain the desired level. Five grams did, but also produced symptoms after the sixth dose.

Side Effects—No man was asymptomatic. In the 2-g. dose group one subject (J.B.) reported anorexia and malaise the morning of the second day and the other (T.M.) had six diarrheal stools between 12 and 48 hr after the first dose. Of the two subjects receiving 3 g. every 4 hr., one (R.K.) had nine episodes of diarrhea starting 30 hr. after the first dose and the other (F.S.) had seven diarrheal stools between 10.5 and 38 hr. For both subjects doses were withheld because of this (Table III). One man (R.B.) who received 5 g. every 4 hr. had nine episodes of diarrhea starting 10 hr. after the first dose. The other subject on this schedule (D.N.) began having diarrhea 6 hr. after the first dose and was still having frequent loose bowel movements when he was discharged from the test ward. In addition, he vomited twice between 36 and 48 hr. and had nausea there-

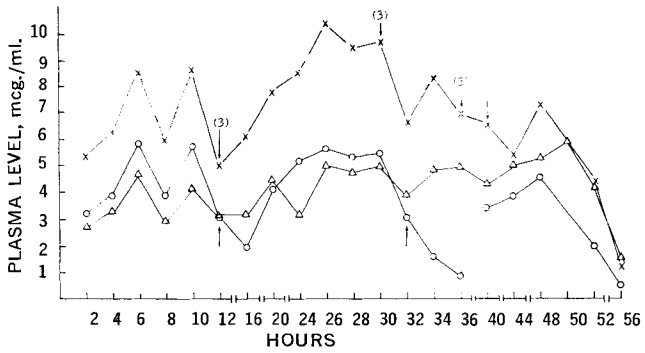

Figure 2—*Mean plasma oxime levels in subjects receiving 2-PAMCl orally through 48 hr. Key:* △—△, *2 g. every 4 hr. (N=2);* ○—○, *3 g. every 4 hr. (N=2):* ×—×, *5 g. every 4 hr. (N=2).* ↑, *one or both subjects received no oxime (see Table III).* (*3*) ↓ *one subject received only 3 g. (see Table III).*

after. Doses were reduced or omitted several times in each man because of these symptoms.

The man (T.Y.) who received 4 g. every 6 hr. had diarrhea throughout the test. One man (R.M.) who got 5 g. every 6 hr. had eight episodes of diarrhea starting at 25 hr. after the first dose and lasting until he was discharged from the ward; he also was nauseated most of the second day. The other subject at this dose (C.P.) had anorexia, complained that he did not feel well the second morning, was nauseated and had diarrhea starting about 48 hr. after the first dose. Although these symptoms were as severe as those in the other dose groups, it was decided to continue the dosage.

Physiological Measures—No subject's blood pressure or heart rate differed significantly from his control values.

DOSE RESPONSE

The relationship between the single dose administered and the maximal plasma level of oxime is significant, $r = 0.54$, ($p < 0.01$). The dose-response plot is shown in Fig. 4.

BIOLOGICAL HALF-LIFE

It has been demonstrated that the rate of decline of the blood level of a drug as a function of time often follows first-order kinetics (2).

The equation to define this can be expressed as

$$C = C_0 e^{-kt}$$

or

$$\log C = \log C_0 - \frac{kt}{2.303}$$

where C = the concentration at time t, C_0 the concentration at zero time or the intercept on the concentration axis, and k = the velocity constant characterizing drug elimination from the blood stream.

Values of C and t were fitted into this regression equation by the method of least squares and where the correlation was significant ($p < 0.05$) the half time was determined and k calculated. Results are shown in Table I.

Figure 5 shows the calculated disappearance curves and the actual blood level data from which they were derived for several subjects.

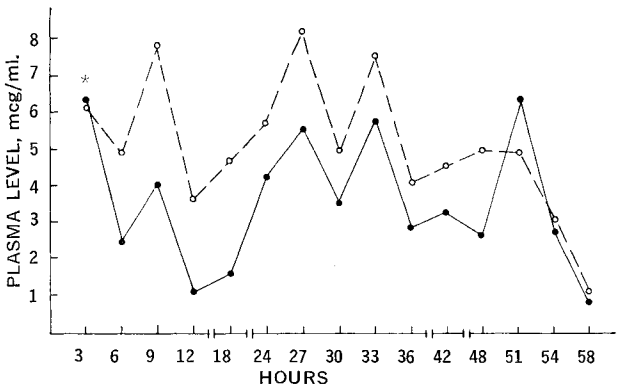

Figure 3—*Mean plasma oxime levels in subjects receiving 2-PAMCl orally through 48 hr. Key: —, 4 g. every 6 hr. (N = 1); - - - 5 g. every 6 hr. (N = 2). *, 5 g. given to all subjects at zero time.*

URINARY HALF-TIMES

In a similar manner the half time for elimination of a compound from the body and its appearance in the urine can be calculated.

Table II—Urinary Excretion of 2-PAMCl Administered Orally to Humans[a]

Subject	Dose, g.	Time, hr.	Amount Excreted, mg.	%
J.F.	3	0200	556	58
		0800	400	100
Total			956	
% of dose			31.9	
M.M.	3	0400	614.4	81
		0530	105.6	95
		0830	43.2	100
Total			763.2	
% of dose			25.4	
L.D.	4	0600	920	87
		0700	142	100
Total			1062	
% of dose			26.5	
J.A.	5	0100	104.4	15
		0200	234.0	49
		0400	192.2	77
		0500	116.8	94
		0800	45.0	100
Total			692.4	
% of dose			13.8	
W.Ba.	5	0330	287	46
		0530	282	91
		0800	61	100
Total			630	
% of dose			12.6	
A.B.	5	0125	15.9	16
		0310	389.4	40
		0510	438.6	84
		0800	158.4	100
Total			1002.3	
% of dose			20.0	
R.Co.	3	0300	351.0	49
		0515	235.2	81
		0600	66.0	90
		0800	62.9	100
Total			715.1	
% of dose			23.8	
R.Cr.	3	0030	33.6	5
		0200	162.0	29
		0300	162.0	53
		0510	171.6	78
		0800	156.0	100
Total			685.2	
% of dose			22.8	
E.D.	4	0530	788	90
		0800	89	100
Total			877	
% of dose			21.9	
C.B.	5	0150	319.2	27
		0400	400.0	61
		0600	324.0	89
		0800	119.7	100
Total			1162.9	
% of dose			23.3	
W.Bo.	5	0400	797	69
		0535	249	91
		0800	112	100
Total			1158	
% of dose			23.2	
R.M.	6	0135	267.3	25
		0310	600.0	82
		0445	184.8	100
Total			1052.1	
% of dose			17.5	
D.L.	7	0120	165.8	20
		0240	180.0	42
		0350	184.0	65
		0630	144.9	82
		0840	62.7	90
		1200	79.2	100
Total			816.6	
% of dose			11.7	

(*continued on next page*)

Table II—(*continued*)

Subject	Dose, g.	Time, hr.	Amount Excreted, mg.	%
M.H.	7	0230	363.0	41
		0300	132.0	56
		0500	273.0	86
		0800	127.6	100
Total			895.6	
% of dose			12.8	
J.A.	8	0200	596.0	39
		0430	453.6	68
		0500	88.5	74
		0700	239.2	90
		1100	99.0	96
		1200	65.0	100
Total			1541.3	
% of dose			19.3	
B.Wa.	5	0120	434.6	29
		0245	451.5	59
		0400	267.0	77
		0700	264.0	94
		0900	89.6	99
		1200	17.3	100
Total			1524.0	
% of dose			30.5	
W.M.	5	0120	257.1	20
		0240	401.5	51
		0450	292.1	73
		0640	258.5	93
		0830	52.2	97
		0900	17.2	98
		1200	34.2	100
Total			1312.8	
% of dose			26.3	
D.H.	5	0100	170.4	13
		0200	387.0	42
		0300	253.5	61
		0500	331.5	86
		0800	195.0	100
Total			1337.4	
% of dose			26.7	
R.L.	6	0145	808.5	49
		0300	488.8	79
		0530	221.0	92
		0800	120.9	99
Total			1639.2	
% of dose			27.3	
J.I.	6	0200	499.2	47
		0300	246.0	70
		0500	186.0	87
		0800	141.0	100
Total			1072.2	
% of dose			17.9	
A.K.	7	0130	328.5	24
		0240	367.5	51
		0350	252.0	70
		0630	246.0	88
		0900	98.0	95
		1200	56.3	100
Total			1348.3	
% of dose			19.3	
J.G.	5	0010	0	0
		0200	61.2	5
		0330	440.7	39
		0700	780.0	100
Total			1281.9	
% of dose			25.6	
D.H.	6	0145	410.0	29
		0300	487.6	64
		0600	408.0	93
		0800	106.0	100
Total			1411.6	
% of dose			23.5	
G.H.	9	0230	943.2	41
		0500	952.0	82
		0630	171.1	89
		0800	85.5	93
		1100	124.5	98
		1200	44.0	100
Total			2320.3	
% of dose			25.8	
M.G.	7	0145	297.0	49
		0300	190.0	80
		0530	37.5	86
		0800	81.0	100
Total			605.5	
% of dose			8.7	
D.B.	8	0230	434.0	33
		0400	381.5	62
		0745	347.2	88
		1000	100.0	96
		1200	40.0	100
Total			1302.7	
% of dose			16.3	
J.H.	9	0230	336.0	22
		0300	231.8	37
		0500	148.4	47
		0530	459.0	77
		0700	210.0	90
		1200	135.5	99
Total			1522.7	
% of dose			16.9	

[a]

Dose, g.	Mean % Excretion (total)	Dose, g.	Mean % Excretion (total)
3	26.0	7	13.1
4	24.3	8	17.8
5	25.3	9	21.4
6	21.6		

The exact calculation using the above equation requires knowledge of the amount of drug entering tissues and the total magnitude of excretable drug, which are not known. These are not needed if the differential form of the first-order rate equation (3) is used:

$$\log \frac{dC}{dt} = \frac{-kt}{2.303} + K$$

where $K = \log(-kC_0)$; C = the amount of unexcreted substance at time t; C_0 = the maximal amount of excretable material; and k = the specific velocity constant for elimination.

A plot of the change in C for each interval of t when these intervals are reasonably equal produces a straight line. From the slope, the biological half-lives and velocity constants can be approximated. The mean half-life of 2.44 hr. and k of 0.29 compare favorably with corresponding plasma values of 2.66 hr. and 0.28. Table I gives values for $t_{0.5}$ and k for some subjects. Considering the approximations used in the urinary calculations, this agreement is surprising.

DISCUSSION

A factor to be considered before administering oximes by the oral route is the variation in blood levels among individuals obtained by a given dose. This variation was quite marked in the single-dose group and, although less prominent, it was still significant in the repeated-dose group. When a definite blood level is needed, this variability will influence the dose required.

There is a good ($p < 0.01$) correlation between dose and blood level (Fig. 4). However, there is enough variation among individuals to make it impossible to predict a blood level for a particular subject after a given dose.

Half-time data presented here suggest that increasing the dose does not increase the half-time, which is consistent with first-order kinetics for elimination. This has been demonstrated for other drugs (2).

Table III—Blood Levels of 2-PAMCl After Repeated Oral Doses

Subject	Oxime in Blood, mcg./ml. — Experimental Time, hr.											
	0200	0400	0600	0800	1000	1200	1400	1600	1800	2000	2200	2400
						2 g. every 4 hr.						
T.M.	2.4	3.6	4.6	2.3	3.9	1.8	—	1.5	—	3.4	—	2.8
J.B.	3.0	3.0	4.7	3.6	4.4	4.5	—	4.9	—	5.5	—	3.6
						3 g. every 4 hr.						
R.K.	3.4	2.4	4.7	4.3	5.6	3.8	4.4	3.3	5.1	4.7	4.9	5.0
F.S.	3.1	5.3	6.9	3.4	5.7	2.3[a]	1.2	0.6	5.0	3.4	6.5	5.2
						5 g. every 4 hr.						
D.N.	5.3	6.8	8.2	5.3	8.5	4.8[b]	7.2	5.5	10.4	8.7	10.9	9.4
R.B.	5.4	5.6	8.8	6.5	8.8	5.1	8.2	6.6	8.2	6.8	9.3	7.5
	2600	2800	3000	3200	3400	3600	4000	4400	4800[c]	5000	5200	5600
						2 g. every 4 hr.						
T.M.	4.6	3.2	4.1	2.5	3.5	3.0	3.0	3.8	3.8	4.7	4.1	1.3
J.B.	5.4	6.2	5.7	5.3	6.2	6.9	5.5	5.1	6.6	7.1	4.3	1.6
						3 g. every 4 hr.						
R.K.	5.5	4.6	4.9	2.6[a]	1.5	0.8	3.5	4.1	5.4[a]	—	2.4	0.8
F.S.	5.6	5.9	5.9	3.4[a]	1.6	0.9	3.3	3.4	3.5[a]	—	1.4	0.2
						5 g. every 4 hr.						
D.N.	11.5	10.6	11.9	8.1	9.8	9.0	7.7[a]	4.0	6.9[a]	—	3.4	1.5
R.B.	9.1	8.3	8.4[b]	5.1	6.7	4.8[b]	5.4	6.8	7.5[a]	3.3	1.1	—
	0300	0600	0900	1200	1800	2400	2600	3000	3300	3600	4200	4800[a]
						4 g. every 6 hr.						
T.Y.	6.4[d]	2.5	4.0	1.1	1.6	4.3	5.6	3.6	5.9	2.9	3.3	2.7
						5 g. every 6 hr.						
R.M.	6.1	3.6	7.4	2.7	3.1	5.5	7.8	3.7	6.6	3.2	3.9	4.6
C.P.	6.4	6.2	8.3	3.6	6.3	6.0	8.7	6.2	9.5	5.0	5.3	5.4[a]
	5200	5400	5800									
						4 g. every 6 hr.						
T.Y.	6.4	2.8	0.9	—	—	—	—	—	—	—	—	—
						5 g. every 6 hr.						
R.M.	7.0	1.6	1.3	—	—	—	—	—	—	—	—	—
C.P	2.9	4.6	0.9	—	—	—	—	—	—	—	—	—

[a] No oxime given at this time. [b] Dose reduced to 3 g. [c] Time of last dose. [d] First dose was 5 g.

The half-times are longer than those previously reported by Kondritzer *et al.* (2.7 hr. *versus* 1.7 hr.) (4). It is suggested that this is because of the different preparation used. They used 2-PAM dissolved in water, and this mixture may be absorbed more rapidly than the commercial tablets used in this study which have to be broken down in the gastrointestinal tract before they can be absorbed.

The blood levels of oxime necessary for therapy of anticholinesterase intoxication are unknown, although there is some evidence that 4 mcg./ml. might be considered the minimum useful level (5). A factor that must be considered is the time after poisoning at which the oxime must be given; it would seem that in other than very mild poisoning, there would not be enough time for sufficient oxime to be absorbed and to reach the tissue sites in adequate amounts.

Several investigators have given oximes prophylactically for anticholinesterase poisoning, but both gave atropine after the poisoning. Crook *et al.* (6) saved 14 dogs which received 5.5 to 9.4 LCt_{50}'s of sarin at a time their mean blood level of oxime was 6.76 mcg./ml., but 18 others, with a mean oxime blood level of 5.03 mcg./ml., died. All received 5 mg./kg. of atropine in 1 min. after exposure. Zvirblis and Kondritzer (7) found that oxime blood levels of 4 and 8.1 mcg./ml. in rats increased the LD_{50} of sarin by factors of 2 and 2.46 over the LD_{50} obtained when the animals were treated with 17 mg./kg. of atropine alone. Data on the prophylactic value of oximes alone are not available.

The extent of symptoms produced in the repeated dose study, particularly by the lower doses, was unexpected. The exact cause is unknown, but since comparable blood levels of oxime resulting from intravenous administration do not cause symptoms, it is felt that the symptoms are due to a local effect of the oxime on the gastrointestinal tract (perhaps pH change or direct irritation to the

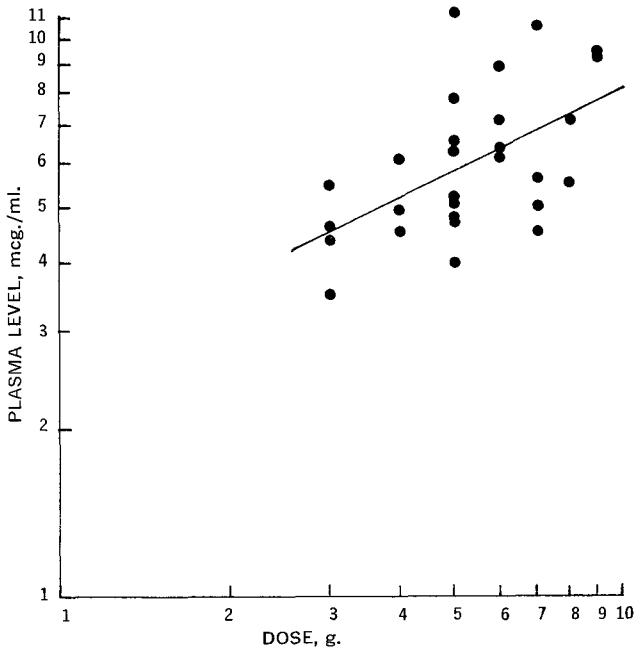

Figure 4—*Maximal plasma level of oxime after oral administration of 2-PAMCl. Key:* ●, *one subject. Log* y = *0.4 18* + *0.495 log* x. r = *0.54.*

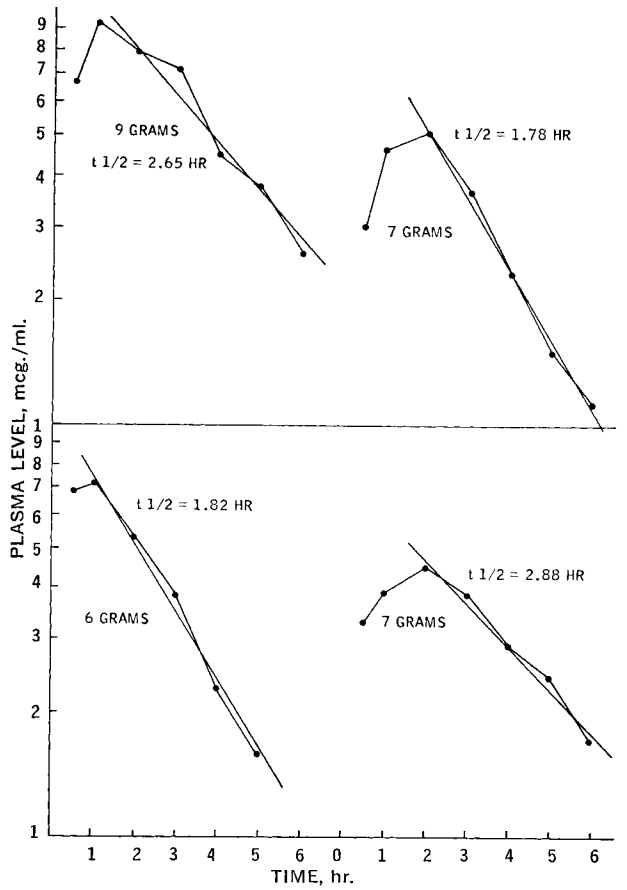

Figure 5—*Calculated disappearance curves and blood level data of plasma oxime levels in several subjects.*

mucosa) rather than to a systemic effect. This degree of side effects would probably preclude chronic administration.

SUMMARY AND CONCLUSIONS

Single and repeated doses of a commercially available tablet of 2-PAMCl were given to volunteers. Five grams was required to produce a plasma level of 4 mcg./ml. after a single dose, and higher single doses (to 9 g.) produced plasma levels up to 11 mcg./ml. However, there was much variation in blood levels among individuals receiving the same dose. Although it was possible to maintain blood levels of more than 4 mcg./ml. when the oxime was given in doses higher than 3 g. at 4-hr. intervals, all subjects who received multiple doses over 48 hr. had gastrointestinal symptoms. The mean urinary excretion was 20–25% of the dose administered; the plasma $t_{0.5}$ was 2.7 hr. and the $t_{0.5}$ for excretion into the urine was 2.4 hr.

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Enhancement of Percutaneous Absorption by the Use of Volatile: Nonvolatile Systems as Vehicles

M. F. COLDMAN, B. J. POULSEN, and T. HIGUCHI

Abstract □ Using *in vitro* techniques the penetration of ^{14}C labeled fluocinolone acetonide and its acetate ester through human skin at 37° has been examined with vehicle mixtures of isopropanol and isopropyl myristate or propylene glycol. Little penetration was found from either of the nonvolatile solvents. As the formulation was changed to include increasing amounts of volatile component, however, penetration could be increased up to 8 to 10 times. Precipitation of steroid prevented greater increases.

Keyphrases □ Percutaneous absorption—enhancement □ Volatile: nonvolatile vehicles—percutaneous absorption □ Fluocinolone acetonide and fluocinolide, ^{14}C-labeled—percutaneous absorption □ Scintillometry—analysis □ Radiochromatography—analysis

The penetration of corticosteroids through the intact human epidermis has been shown to be very poor (1, 2) and occlusive techniques are commonly used to increase penetration (3, 4). However, these methods are neither convenient nor pleasing to the patient and this investigation has studied another means of enhancing penetration that may make occlusion unnecessary.

Based on theoretical models, Higuchi (5) derived equations outlining parameters of percutaneous absorption and other workers (6–8) have investigated some aspects of vehicle effects on the degree of penetration of topically applied drugs. This report is primarily concerned with the effect, on penetration, of concentrating the drug into a small fraction of the vehicle following topical application. This can be accomplished by the use of appropriate volatile:nonvolatile solvent systems such that the large bulk of the vehicle is lost by evaporation immediately following application. The concentra-