Intramuscular and Intravenous Administration of Small Doses of 2-Pyridinium Aldoxime Methochloride to Man

FREDERICK R. SIDELL and WILLIAM A. GROFF

Abstract □ Small doses (2.5, 5.0, 7.5, and 10.0 mg./kg.) of 2-pyridinium aldoxime methochloride were given intramuscularly and intravenously to groups of volunteers. After intramuscular administration, oxime plasma concentrations of greater than 4 mcg./ml. were attained only with the two higher doses and these concentrations were maintained for less than 1 hr. The half-times for elimination were almost identical (74 min. after intravenous and 77 min. after intramuscular administration), and the oxime was rapidly eliminated in the urine. Very transient symptoms were reported by the subjects receiving 2-pyridinium aldoxime methochloride intravenously.

Keyphrases □ 2-Pyridinium aldoxime methochloride—intramuscular, intravenous administration, man □ Anticholinesterase poisoning—administration of 2-pyridinium aldoxime methochloride

The efficacy of the pyridinium oximes as adjuvants to atropine in the therapy of anticholinesterase poisoning has been recognized for over a decade. Several early studies (1–3) and one recent study (4) demonstrated the value of small doses (5–7.5 mg./kg.) of 2-pyridinium aldoxime methochloride, but most recent publications recommended much higher doses (1–2.5 g./man) (5–7) intravenously. Although this may be optimal therapy, intravenous 2-pyridinium aldoxime methochloride should be given only by medical personnel, and this requirement may often preclude its immediate or early administration.

Atropine sulfate, the pharmacological mainstay in anticholinesterase poisoning, is available in self-injection (intramuscular) devices (containing 2 mg. of atropine sulfate)[1], which can be used immediately by an individual accidentally exposed to an anticholinesterase compound. Such devices possibly could also be used for oximes, so a poisoned individual or his coworker could administer an oxime intramuscularly before medical personnel arrive.

The dose contained in such a device would be limited by the volume of solution in the injector (most contain less than 2 ml.) and the concentration of 2-pyridinium aldoxime methochloride (concentrations above 30% w/v produce muscle necrosis in animals)[2]. It is, therefore, desirable to know the blood levels of oxime, the rapidity with which the oxime enters the circulation, and the side effects produced when low doses of 2-pyridinium aldoxime methochloride are administered intramuscularly to man. This study was undertaken to provide such information. In addition, low doses of 2-pyridinium aldoxime methochloride were administered intravenously, and the time course of the disappearance of oxime from the blood was compared with that noted in the intramuscular study.

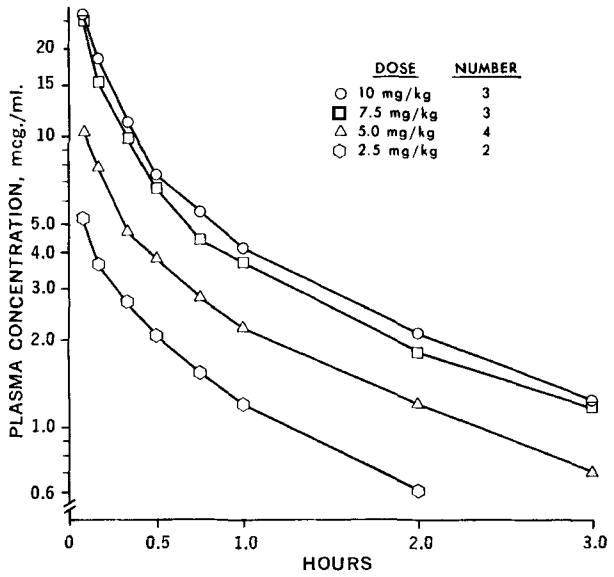

Figure 1—*Plasma concentration of 2-pyridinium aldoxime methochloride after intravenous administration.*

EXPERIMENTAL

Subjects[3]—The subjects were U. S. Army enlisted men who volunteered for this test after a thorough physical examination and laboratory examinations[4] had shown them to have no abnormalities. They were told they would receive a previously tested antidote for nerve agent poisoning and might experience mild symptoms.

Drug—The 2-pyridinium aldoxime methochloride was obtained commercially[5]. Each day a fresh solution (containing 300 mg./ml. for the intramuscular study and 100 mg./ml. for the intravenous study) was prepared from the powder, using isotonic saline as the diluent. The doses, given both intramuscularly and intravenously, were 2.5, 5.0, 7.5, and 10.0 mg./kg. The intramuscular injection was into the deltoid muscle.

Procedure—The subjects were admitted to the test ward the evening before the test. They were awakened about 2 hr. before receiving the drug; after they ate a light breakfast, they drank fluids to promote an adequate urinary output. For the first 3 hr. of the test, they drank at least 950 ml. hourly. Except to void, they remained in bed for this period.

Blood was drawn for oxime analysis just before injection of the drug and at frequent intervals thereafter (Figs. 1 and 3). An attempt was made to obtain urine specimens at half-hourly intervals for the first 3 hr., and all the urine collected in 12 hr. was analyzed for oxime.

Oxime Measurement—Plasma and urinary oxime concentrations were measured by the method described previously (8). Plasma

[1] Autoinjector, Rodana Research Corp., Bethesda, Md.; Ampin, Strong, Cobb and Co., Cleveland, Ohio; and atropine injection, E. R. Squibb and Sons, New York, N. Y.

[2] Unpublished data of J. E. Martin and J. F. Ferrell of this laboratory.

[3] These tests were governed by the principles, policies, and rules for medical volunteers as established in AR 70–25.

[4] Urine analysis, hematocrit, total and differential white blood count, blood urea nitrogen, serum glutamic oxaloacetic transaminase, alkaline phosphatase, total bilirubin, thymol turbidity, red blood cell and plasma cholinesterase, chest X-ray, and ECG.

[5] Protopam chloride, Ayerst Laboratories, New York, N. Y.

Table I—Urinary Excretion of 2-Pyridinium Aldoxime Methochloride

Dose, mg./kg.	Number of Subjects	Total Excreted by 12 hr., % of Dose	Amount Excreted, % of Total — Hours 0.5	1.0	1.5	2.0	2.5
			Intramuscular				
2.5	2	99	29	46	55	61	65
5.0	2	81	37	56	69	76	80
7.5	4	96	36	54	70	76	80
10.0	4	90	30	48	60	69	72
Mean ± *SD*		91 ± 10	33 ± 5	51 ± 6	64 ± 8	71 ± 8	75 ± 8
			Intravenous				
2.5	2	82	66	83	89	92	94
5.0	4	75	58	73	78	82	90
7.5	3	77	52	69	78	85	88
10.0	1[a]	94.5	53	66	71	74	77
Mean ± *SD*		80 ± 11	57 ± 8	73 ± 7	80 ± 6	84 ± 6	89 ± 5

[a] One subject accidentally discarded an early specimen; another had an unusual excretion pattern. Neither is included in this tabulation.

concentration was measured the day blood was drawn; urine samples were refrigerated and analyzed the following day. (Preliminary studies showed that oxime deteriorates less than 2% in refrigerated urine over a week's time.) In the study after intravenous administration, whole blood and red blood cell oxime concentrations were also measured.

Physiological Measures—Three baseline measurements of heart rate and blood pressure (supine) were taken in the morning before drug injection. Thereafter, heart rate and blood pressure were measured just before each blood sample was taken over a period of 2 hr. (intramuscular injection) or 3 hr. (intravenous injection).

RESULTS

Intravenous Administration—*Plasma Levels*—Mean plasma levels for each dose group are plotted against time in Fig. 1. In each case, the whole blood oxime concentration was roughly 45–50% of the plasma concentration, and the results are not shown. The studies on the red blood cell oxime concentration will be the subject of a separate report.

Urinary Excretion—Within the 12-hr. collection period, 80.4% of the dose was found unchanged in the urine. Fifty-seven percent of this amount (or 45.8% of the dose) was excreted within the first 30 min. and 73% (or 58.7% of the dose) within the 1st hr. (Table I). The total amount found in the urine was not as great as that found after intramuscular administration, but the difference is probably within the limits of experimental error.

One subject in the highest dose group had an unusual urinary excretion pattern. In contrast to the asymptotic line found with all the other subjects when percentage excreted was plotted against time (both on linear scales), a plot of the percentage of oxime he excreted against time (Fig. 2) was linear. No explanation is offered for this pattern.

Kinetic Considerations—The pattern of oxime disappearance from the plasma is described by the biexponential equation:

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}^6$$

Each of the constants, A, B, α, and β, was estimated graphically for each subject and is shown in Table II along with the biological half-time ($+0.693/\beta$), also known as the disposition half-time (10). Although the constants were estimated by graphic means, the error from the experimental values introduced by these estimations is not great, as indicated in Fig. 3 where the experimental values for one subject are plotted with a calculated line using the graphically estimated values for that subject.

The percent of the dose to be excreted in the urine that has not been excreted by time t is:

$$100 \times F \times \frac{A\beta e^{-\alpha t} + B\alpha e^{-\beta t}}{A\beta + B\alpha} \qquad \text{(Eq. 2)}^7$$

where F is the fraction of the total dose eventually eliminated in the urine. In Fig. 4, this relationship is shown for two subjects and for two dose groups, using mean values for the constants in the latter instance[8].

Physiological Measures and Side Effects—There was a slight and transient increase in heart rate, with a maximal increase of 10 beats/min. and a duration of less than 30 min. There was no significant change in blood pressure.

All subjects reported mild and very transient symptoms just after injection. Those at the lowest dose had slight dizziness; those receiving 5.0 mg./kg. had dizziness, and three complained of blurred vision. All at the 7.5-mg./kg. dose noted dizziness and blurred vision, and one complained of diplopia. Two at the highest dose complained of double and blurred vision, and the third stated he felt dizzy. All symptoms subsided within 3–4 min.

Intramuscular Administration—*Plasma Levels*—Figure 5 shows the mean plasma levels of oxime for each dose group plotted against time. By 5 min., the levels were more than 50% of the highest levels. If 4 mcg./ml. is needed for a therapeutic effect (13), only the two highest doses (7.5 and 10 mg./kg.) would be adequate. This level is reached rather rapidly (5–10 min.) with these doses.

Urinary Excretion—Overall, 91% of the oxime administered was excreted unchanged in the urine within the 12-hr. collection period.

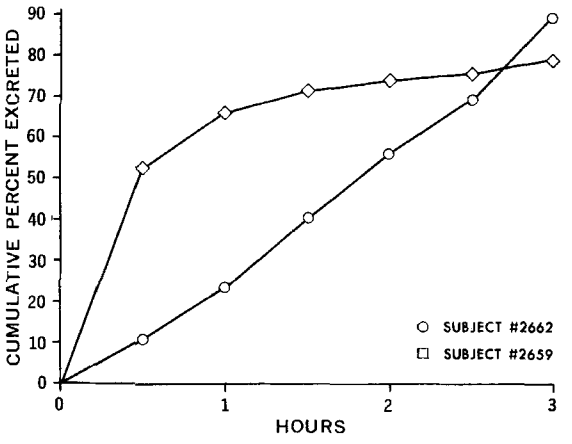

Figure 2—*Urinary excretion patterns of 2-pyridinium aldoxime methochloride in two subjects (dose 10 mg./kg.).*

[6] This equation was adequately discussed elsewhere (9–12), and only the definitions are given here. C_1 is the plasma level at time t; β is -2.303 times the slope of the terminal linear segment of the plot of plasma level on a logarithmic scale *versus* time on a linear scale, and B is the extrapolated zero-time intercept of this line. α is -2.303 times the slope of a line plotted by the method of residuals from the initial plasma level values, and A is the extrapolated zero-time intercept of this line. α and β are hybrid rate constants incorporating the rate constants for absorption, distribution, and metabolism or excretion in and out of the central (plasma) and peripheral (tissue) compartments. For further details, see pp. 124–133 of *Reference 12*.

[7] The derivation of this equation is given in the *Appendix* (Eq. A26).

[8] Note that there were inadequate data to determine A and α for one subject in the 5-mg./kg. group; his excretion data were also excluded for purposes of the figure.

Table II—Biological Half-Times and Kinetic Constants for 2-Pyridinium Aldoxime Methochloride Administered Intravenously

Subject Case Number	Dose, mg./kg.	$t_{1/2}$ (0.693/α), min.	$t_{1/2}$ (0.693/β), min.	A, mcg./ml.	B, mcg./ml.	α, min.$^{-1}$	β, min.$^{-1}$
2644	2.5	11	73	4.3	1.1	0.063	0.009
2653	2.5	11	87	5.0	2.1	0.063	0.008
Mean		11	80	4.7	1.6	0.063	0.0085
2645	5.0	7	63	8.7	4.3	0.099	0.011
2654	5.0	11	67	7.6	3.1	0.063	0.010
2651	5.0	7	69	14.7	4.6	0.099	0.010
2646	5.0	—	56	—	5.6	—	0.012
Mean		8.3	64	10.3	4.4	0.087	0.011
2652	7.5	6	60	25.5	7.2	0.115	0.012
2660	7.5	6	59	28.5	6.2	0.115	0.012
2661	7.5	10	112	29.5	4.9	0.069	0.006
Mean		7.3	77	27.8	6.1	0.100	0.010
2663	10	11	81	25.5	5.6	0.063	0.009
2659	10	8	71	24.0	7.0	0.087	0.010
2662	10	8.5	86	34.0	5.5	0.082	0.008
Mean		9.2	79	27.8	6.0	0.077	0.009
Mean of all subjects		8.8	73.7	—	—	0.083	0.010
± *SD*		2.0	15.2	—	—	0.020	0.002

Of this, 75% (or 69% of the dose) was excreted within the first 2.5 hr. As seen in Table I, about 50% of the total amount excreted (or 46% of the dose) was eliminated within the 1st hr., indicating a very rapid renal excretion of this compound.

Kinetic Considerations—Although the data fit a two-compartment model, the plasma level values after intramuscular administration were too meager to permit graphic dissection of similar constants (α, β, and, possibly, *k*, the rate constant for absorption) which might define a kinetic model for these data. [Wagner (14) recently commented on this problem, but the data were inadequate to pursue his suggested solution.]

By using the terminal points on a plasma concentration (logarithmic scale) *versus* time (on a linear scale) plot, the mean half-times by dose group were found to be 75 min. (2.5 mg./kg.), 72 min. (5 mg./kg.), 77 min. (7.5 mg./kg.), and 83 min. (10 mg./kg.). The corresponding rate constants for elimination were 0.0096, 0.0096, 0.0097, and 0.0084 min.$^{-1}$.

Theoretically, the urinary data should fit a plot calculated from the constants *k*, α, and β. Since the former two constants could not be separated on the basis of the data, this could not be done. The general shape of the curves, when amount not excreted (logarithmic) is plotted against time (linear), suggests a two-compartment model (Fig. 6).

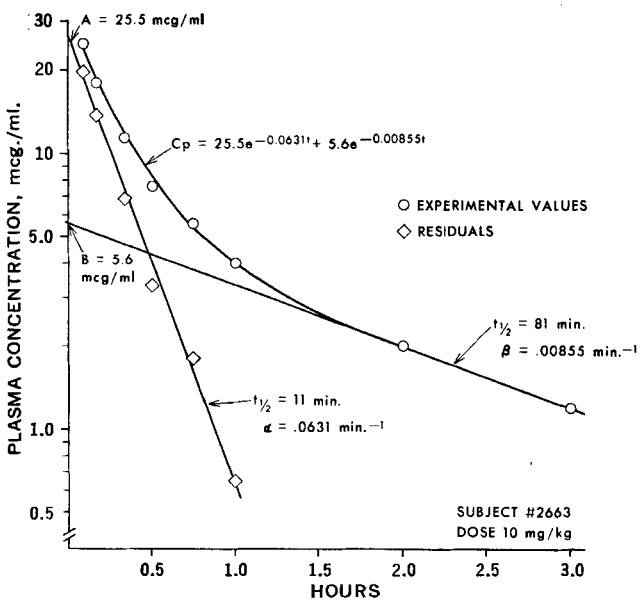

Figure 3—*Experimental values and calculated disappearance curve of 2-pyridinium aldoxime methochloride from plasma.*

Physiological Measures and Side Effects—There were no changes in heart rate or blood pressure. No subject had any signs or symptoms except mild pain at the site of injection which persisted for a few hours. There was slight tenderness to fist percussion at the injection site 24 hr. later.

DISCUSSION

Barkman *et al.* (15) found that 2-pyridinium aldoxime methanesulfonate, 10 mg./kg. i.m., produced maximal plasma concentra-

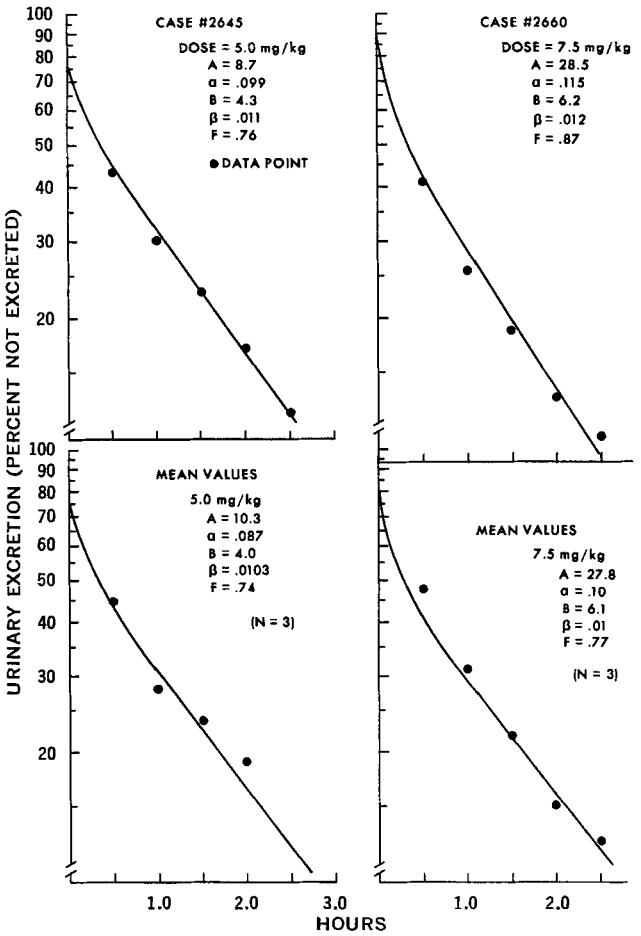

Figure 4—*Urinary excretion* versus *time: calculated and actual amounts.*

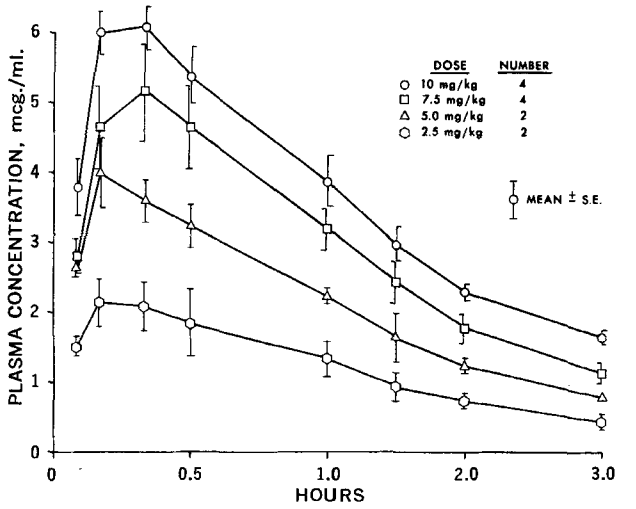

Figure 5—*Plasma concentration of 2-pyridinium aldoxime methochloride after intramuscular administration.*

tions of about 7 mcg./ml. and that a concentration of 4 mcg./ml. was maintained for about 90 min. A similar dose of 2-pyridinium aldoxime methochloride produced maximal concentrations of about 6 mcg./ml., and a concentration of greater than 4 mcg./ml. was maintained for only 50–55 min. Barkman *et al.* (15) did not measure urinary excretion; in the present study, it was found that 2-pyridinium aldoxime methochloride was eliminated in the urine very rapidly. If it is desired to maintain a high plasma level for a long period of time after a single intramuscular injection, it would appear that 2-pyridinium aldoxime methanesulfonate is preferable. However, because repeated injections would probably be given in practice and because intravenous therapy should be started within an hour under most conditions, it is doubtful if the difference between 2-pyridinium aldoxime methanesulfonate and 2-pyridinium aldoxime methochloride is of practical significance. Both oximes are absorbed rapidly and produce maximal plasma levels in about 5–15 min.

The rapid and rather complete urinary excretion of 2-pyridinium aldoxime methochloride was reported previously (16, 17). It is possible that 2-pyridinium aldoxime methochloride is not only not reabsorbed to any degree by the renal tubules after filtration but may be secreted by tubular mechanisms. Studies on the exact mechanisms by which the kidneys handle 2-pyridinium aldoxime methochloride are underway.

The half-life of 2-pyridinium aldoxime methochloride in the body is about the same whether administered by the intravenous or intramuscular route (74 min. *versus* 77 min.). This short half-life is the basis for the recommendation (5–7) that repeated doses be administered at intervals of an hour or so should the clinical circumstances warrant.

APPENDIX

If D is the total dose of drug administered intravenously, material balance at time t will be:

$$D = D_b + D_e \qquad \text{(Eq. A1)}$$

where D_b is the amount of drug in the body at time t, and D_e is the cumulative amount of drug eliminated from the body (by any means) by time t.

The fit of the plasma data to the biexponential equation infers a two-compartment model of the type described elsewhere (12). In this case, the total amount of drug in the body is the sum of the amount (D_1) in Compartment 1 (or central compartment) and the amount (D_2) in Compartment 2, or the peripheral (tissue) compartment. Thus,

$$D_b = D_1 + D_2 \qquad \text{(Eq. A2)}$$

In each case, the amount present is the product of concentration (C) times the volume of distribution (V) of that compartment, or:

$$D_1 = C_1 \times V_1 \qquad \text{(Eq. A3)}$$

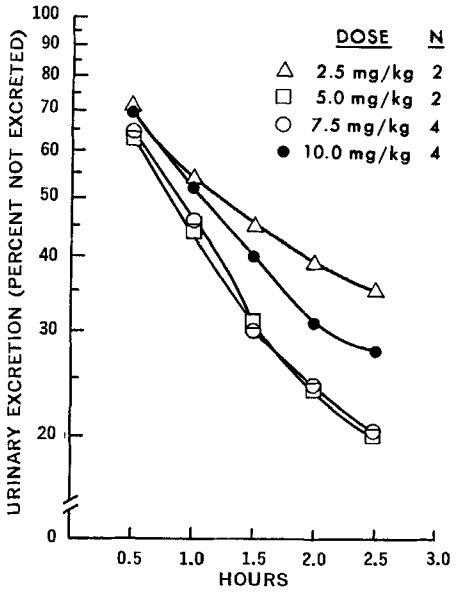

Figure 6—*2-Pyridinium aldoxime methochloride intramuscularly. percent not excreted* versus *time.*

and

$$D_2 = C_2 \times V_2 \qquad \text{(Eq. A4)}$$

In this case, C_1 is the plasma concentration; hence:

$$D_1 = V_1(Ae^{-\alpha t} + Be^{-\beta t}) \qquad \text{(Eq. A5)}$$

Since (12):

$$V_1 = \frac{D}{A + B} \qquad \text{(Eq. A6)}$$

this becomes:

$$D_1 = \frac{D}{A + B}(Ae^{-\alpha t} + Be^{-\beta t}) \qquad \text{(Eq. A7)}$$

C_2 was described (12) as:

$$C_2 = \frac{(K_1)(D)}{V_2(\alpha - \beta)}(e^{-\beta t} - e^{-\alpha t}) \qquad \text{(Eq. A8)}$$

where K_1 is the rate constant for transfer from Compartment 1 to Compartment 2.

The further definitions (12):

$$K_1 = \alpha + \beta - K_2 - K_{-1} \qquad \text{(Eq. A9)}$$

$$K_{-1} = \frac{A\beta + B\alpha}{A + B} \qquad \text{(Eq. A10)}$$

$$K_2 = \frac{\alpha\beta}{K_{-1}} \qquad \text{(Eq. A11)}$$

permit C_2 to be expressed in terms of the graphically defined α and β. Hence:

$$C_2 = \frac{(D)(AB)(\alpha - \beta)}{(A\beta + B\alpha)(A + B)(V_2)}(e^{-\beta t} - e^{-\alpha t}) \qquad \text{(Eq. A12)}$$

and

$$D_2 = \frac{D(AB)(\alpha - \beta)}{(A\beta + B\alpha)(A + B)}(e^{-\beta t} - e^{-\alpha t}) \qquad \text{(Eq. A13)}$$

By combining, $D_b = D_1 + D_2$, or:

$$D_b = \frac{D}{(A + B)}(Ae^{-\alpha t} + Be^{-\beta t}) + \frac{D}{(A + B)}\frac{(AB)(\alpha - \beta)}{(A\beta + B\alpha)} \times (e^{-\beta t} - e^{-\alpha t}) \qquad \text{(Eq. A14)}$$

By rearranging and combining, this becomes:

$$D_b = D\frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha} \qquad \text{(Eq. A15)}$$

The amount of drug eliminated from the body by time t can be represented by the expression:

$$D_e = Du + Dx \qquad \text{(Eq. A16)}$$

where Du is the cumulative amount of drug eliminated in the urine by time t, and Dx is the cumulative amount eliminated by other routes or means (metabolism, *etc.*).

If F is the fraction of the dose eliminated in the urine by $t = \infty$, or:

$$F = \frac{Du_\infty}{D} \qquad \text{(Eq. A17)}$$

then:

$$Du = F \times D_e \qquad \text{(Eq. A18)}$$

or since $D_e = D - D_b$ (from Eq. A1):

$$Du = F(D - D_b) \qquad \text{(Eq. A19)}$$

The fraction of drug eliminated by other means is $(1 - F)$ and:

$$Dx = (1 - F)(D - D_b) \qquad \text{(Eq. A20)}$$

By combining Eqs. A16, A19, and A20:

$$D_e = F(D - D_b) + (1 - F)(D - D_b) \qquad \text{(Eq. A21)}$$

and by combining A21 and A1:

$$D = D_b + F(D - D_b) + (1 - F)(D - D_b) \qquad \text{(Eq. A22)}$$

By dividing by D, this becomes:

$$1 = \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha} + F\left(1 - \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha}\right) + (1 - F)\left(1 - \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha}\right) \qquad \text{(Eq. A23)}$$

The fraction excreted into the urine by time t is:

$$\frac{Du}{D} = F\left(1 - \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha}\right) \qquad \text{(Eq. A24)}^9$$

and the fraction yet to be excreted is the total fraction excreted by $t = \infty$, F, minus this, or:

$$F - F\left(1 - \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha}\right) \quad \text{or}$$

$$F \times \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha} \qquad \text{(Eq. A25)}$$

Thus the percent yet to be excreted is:

$$100 \times F \times \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha} \qquad \text{(Eq. A26)}$$

If the total dose is eliminated unchanged into the urine, $F = 1$, and the percent remaining to be excreted at time t is $100 \times [A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]/A\beta + \beta\alpha$, which is the percent remaining in the body.

[9] A slightly different derivation of this is to combine Eq. A19, where $Du = F(D - D_b)$, and Eq. A17, $F = Du_\infty/D$, producing:

$$Du = \frac{Du_\infty}{D}(D - D_b) \qquad \text{(Eq. A27)}$$

or

$$Du = Du_\infty\left(1 - \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha}\right) = Du_\infty - \left(Du_\infty \times \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha}\right) \qquad \text{(Eq. A28)}$$

When $F = 1$, this becomes:

$$Du = D\left(1 - \frac{[A\beta e^{-\alpha t} + B\alpha e^{-\beta t}]}{A\beta + B\alpha}\right) \qquad \text{(Eq. A29)}$$

This states that the cumulative amount of drug in the urine at time t is the total amount excreted in the urine ($t = \infty$) minus the fraction of this amount still in the body.

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ACKNOWLEDGMENTS AND ADDRESSES

Received August 28, 1970, from the *Clinical Medical Sciences Department, Medical Research Laboratory, Research Laboratories, Edgewood Arsenal, MD 21010*

Accepted for publication April 30, 1971.

The authors thank the nurses and ward technicians of the Clinical Medical Sciences Department for the ward care of the subjects, Mr. Andris Kaminskis for assisting with the laboratory analyses, and Mrs. Marion P. Royston and LTC James S. Ketchum, M.C., for editorial assistance and criticism.

The authors wish also to thank Dr. Berton E. Ballard for his many helpful suggestions and comments on the pharmacokinetic aspects of this report.