Kinetics of Absorption and Elimination of Pralidoxime Chloride in Dogs

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Abstract □ The kinetics of the absorption and elimination of pralidoxime chloride were investigated in the dog. Similar apparent elimination rate constants were obtained after intravenous, intramuscular, and oral administration. Although oral absorption occurred slowly, intramuscular absorption proceeded rapidly. With *in situ* techniques, it was found that no absorption occurred from the isolated stomach and duodenum but that absorption did take place from the jejunum and ileum.

Keyphrases □ Pralidoxime chloride—absorption and elimination kinetics in dogs □ Absorption, GI—pralidoxime chloride, kinetics in dogs □ Elimination—pralidoxime chloride, kinetics in dogs □ Kinetics—absorption and elimination of pralidoxime chloride in dogs □ Cholinesterase reactivators—pralidoxime chloride, absorption and elimination kinetics in dogs

Most charged drugs are poorly absorbed after oral administration. However, quaternary ammonium compounds that are charged and have low lipid solubility undergo varied absorption. About 10% of a dose of tetraethylammonium chloride was absorbed at the end of 3 hr, using *in vivo* intestinal loops in dogs (1). The disappearance of 10–30% of a dose of a number of quaternary ammonium anticholinergics was found in the rat using isolated intestinal loops (2, 3). *N,N*-Bis(phenylcarbamoylmethyl)-dimethylammonium chloride, an antiarrhythmic agent, was poorly and erratically absorbed in rats (4) and humans (5). The bioavailability of thiazinamium methylsulfate after oral administration in humans is approximately 10% (6).

Levine and Steinberg (7) reported almost complete absorption of the methanesulfonate, phosphate, methochloride, and methiodide salts of pralidoxime in the rat. However, other investigators indicated that large doses of this drug were required to obtain significant plasma levels in humans (8–10).

To understand more fully the erratic absorption behavior of quaternary ammonium compounds, the complete absorption and elimination profile of pralidoxime chloride (2-[(hydroxyimino)methyl]-1-methylpyridinium chloride) was investigated in the dog. This drug is used clinically to reactivate cholinesterase in the therapy of organophosphate poisoning.

EXPERIMENTAL

Test Animals—Thirty-one male mongrel dogs, 8.6–11.4 kg, were permitted to adjust to the environment for at least 48 hr. Water was permitted *ad libitum*, and food was withheld for 24 hr prior to use.

Chemicals—Pralidoxime chloride[1] was used as received. All other chemicals were reagent grade.

Anesthesia—Pentobarbital sodium, given intravenously at a dosage of 30 mg/kg, was used as the anesthetic.

Blood Sampling—Venous blood sampling in anesthetized animals was accomplished with inside needle catheters[2].

The catheter was inserted in the femoral vein after anesthesia, and heparin sodium was then administered at a dosage of 1000 units/kg as an anticoagulant. Venous blood samples were collected in heparinized tubes[3]. In unanesthetized animals, samples were obtained by venipuncture.

Pralidoxime Assay—A previously described analytical technique, (11) was utilized to determine the pralidoxime content in biological fluids. Standard aqueous solutions containing 0.750–9.00 mg of pralidoxime/ml were prepared; to each 10.0-ml sample, 0.40 ml of 20% NaOH was added. The standard curve obeyed the Beer–Lambert law.

Intravenous Administration—The drug was dissolved in 10 ml of sterile water for injection and administered intravenously *via* the cephalic vein over 3 sec. Three dogs received a 150-mg dose, and three other dogs received a 300-mg dose. Blood samples, 3 ml, were taken from each dog at 0, 1, 2, 3, 4, 6, 8, 10, 15, 20, 25, 30, 40, 60, 75, 90, 105, 120, and 150 min.

Drug Disappearance from GI Tract—*Stomach*—A midline abdominal incision was made 8 cm in length and equidistant from the base of the sternum. The stomach was exposed and kept moist by bathing in physiological saline at 37°. The stomach was tied off just below the entry of the esophagus and just above the pyloric sphincter. A small slit was made in the cardiac portion and in the pyloric region of the stomach approximately 2 cm from each tie. Foley catheters[4] were inserted into each slit, inflated, and fixed in position using a purse string suture.

The stomach was returned to the abdominal cavity and rinsed with 100 ml of physiological saline at 37° by way of a syringe attached to the catheter at the cardiac portion. After rinsing, air was forced through the syringe to expel any remaining wash. A 50-ml vented calibrated syringe was attached to each catheter; 15 min after washing, 1 g of drug dissolved in 50 ml of water at 37° was administered through the catheter at the cardiac portion. A positive backward pressure was exerted on each catheter to prevent inward movement.

At 0, 15, 30, 45, 60, 75, 90, 105, and 120 min after drug administration, the total volume of the stomach contents was measured by withdrawing the fluid into the syringe at the pyloric portion. A 0.20-ml sample was removed and analyzed.

Duodenum, Jejunum, and Ileum—The procedure used was similar to that described for the stomach. The entire duodenum, with blood, nerve, and lymph supplies intact, was isolated and tied at the pylorus and the duodenal–jejunal flexure and catheterized as described previously. The bile duct and pancreatic duct were ligated. Washing, drug administration, and sampling procedures were identical to those used with the stomach.

A 1-g dose of pralidoxime chloride in 50 ml of water at 37° was administered to four dogs. Duodenal contents were removed by way of the distal syringe, the volume was determined, and a 0.20-ml sample was removed for assay at 0, 15, 30, 45, 60, 75, 90, 105, and 120 min after drug administration. During each experiment, 3-ml blood samples also were taken at 15-min intervals up to 2 hr.

Jejunal and ileal washing, drug administration, and sampling techniques were as described for the stomach and duodenum. The midsection of the jejunum was isolated; a segment drained by three branches of the common mesenteric vein was tied off with its blood, nerve, and lymph supplies intact. A slit was made central to each ligation, and a catheter was inserted. The loop was then returned to the abdominal cavity.

For ileal disappearance, the ileum was isolated. A section drained by three branches of the common mesenteric vein (starting at the second

[1] Aldrich Chemical Co., Milwaukee, Wis.

[2] Bardic, C. R. Bard.

[3] Vacutainer, Becton-Dickinson.

[4] Bardex, C. R. Bard.

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Table I—Pharmacokinetic Parameters after Rapid Intravenous Injection of Pralidoxime Chloride

Dose, mg	Dog	A, μg/ml	α, min^{-1}	C, μg/ml	γ, min^{-1}	B, μg/ml	β, min^{-1}
150	1	190	2.06	68	0.201	12	0.0179
	5	680	1.69	82	0.110	14	0.0131
	16	220	1.51	88	0.173	14	0.0124
							0.0145 ± 0.006[a]
300	1	450	1.40	150	0.120	27	0.0171
	17	290	0.82	94	0.116	34	0.0180
	18	420	1.58	78	0.140	19	0.0167
							0.0173 ± 0.0013[a]

[a] Mean ± 95% confidence limits.

branch after the ileocecal juncture) was ligated. The segment was catheterized and returned to the abdominal cavity. Jejunal and ileal contents were removed by the distal syringe, the volume was determined, and a 0.20-ml sample was removed for assay. Blood samples, 3 ml, also were taken at 15-min intervals up to 4 hr.

Back-diffusion of drug from the plasma into each GI area was determined by isolating the area as described previously and injecting a 300-mg iv dose at 0 and 60 min. Samples, 0.2 ml, were taken from the isolated areas at 0, 15, 30, 45, 60, and 120 min and assayed.

Oral Administration—Pralidoxime chloride, 1 g, was administered *via* stomach tube to unanesthetized dogs as solutions (50 ml) and as tablets[5]. Three dogs were used for each dosage form. Immediately after administration of the tablets, 50 ml of water was given by way of a stomach tube. Blood samples were taken at 1, 3, 5, and 7 hr after administration and analyzed for drug. Three days later, the animals were dosed again and blood samples were taken at 2, 4, 6, and 8 hr.

The same procedure was followed for oral administration in anesthetized dogs. Tablets were administered just prior to anesthesia. Blood samples, 3 ml, were taken at 30-min intervals up to 11 hr.

Intramuscular Administration—Drug, 150 mg in 3 ml of sterile water for injection, was administered into the triceps muscle. Blood samples were taken for assay at 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, 120, and 135 min.

Statistical Comparison—Statistical comparisons were made using analysis of variance. Significance was tested at the $p \leq 0.05$ level.

RESULTS

Intravenous Administration—The plasma concentration–time profiles after rapid intravenous injection of pralidoxime chloride at both 150 and 300 mg were characterized by a triexponential equation:

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

This equation can be represented as a three-compartment open model for drug disposition. Table I lists the values for the various parameters for each dog. There was no significant difference between elimination rate constants (β) obtained with the 150- and 300-mg doses. Also, there was no difference within each dose. In a single experiment where ether was used as the anesthetic instead of pentobarbital, an elimination rate constant of 1.77×10^{-2} min^{-1} was obtained after a 150-mg dose.

Drug Disappearance from Different Segments of GI Tract—No measurable disappearance of plasma pralidoxime levels was observed at any time in experiments utilizing isolated stomach or duodenum.

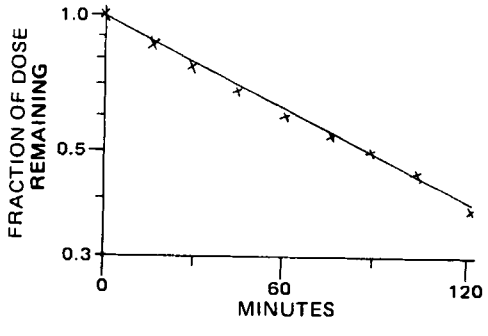

Figure 1—*Fraction of dose remaining in jejunal loop (Dog 25).*

[5] Protopam tablets, 0.5 g, Ayerst.

Drug disappearance from the isolated jejunum followed first-order kinetics, where the observed rate constant was defined as k_a (Fig. 1).

Similar results were observed for drug disappearance from the ileum, except that first-order loss was not observed until approximately 60 min. The pattern for the initial period in all dogs was similar; the data illustrated erratic behavior and nonlinearity when plotted for first-order kinetics. The best estimates of k_a, the disappearance rate constants, were obtained from the terminal linear segment using regression analysis. As can be seen in Table II, the rate constants and percent losses observed after 2 hr from the ileum were significantly greater than those obtained from the jejunum. No differences were observed within each set of animals at each intestinal area.

Plasma levels after intestinal drug administration indicate higher levels from the ileum than from the jejunum (Fig. 2). Although the results shown are for Dogs 9 and 17, similar results were obtained for the other two dogs in each set. Longer blood sampling in the jejunum experiments may have shown a slow, continual rise in plasma levels since this trend was observed in all three animals. However, since blood levels beyond the 2-hr experiment were difficult to obtain, this hypothesis could not be verified. Since samples also were not collected at every interval or with every dog within the 2-hr interval, average results have not been given.

No detectable amounts of drug could be found in the stomach, the duodenum, the jejunum, or the ileum at 0, 15, 30, 45, 60, and 120 min following the intravenous administration of a 300-mg dose at 0 and 60 min, indicating no back-transfer of drug into these areas. Two dogs were observed at each level.

Oral Administration—No plasma levels were observed in anesthetized dogs following oral administration of 1 g of pralidoxime chloride as a solution and as tablets. Tablets passed compendial standards for disintegration, weight variation, and potency and contained an average of 511 mg of drug. Mean plasma levels after oral administration of a 1-g dose in solution and as tablets to three unanesthetized dogs are presented in Figs. 3 and 4.

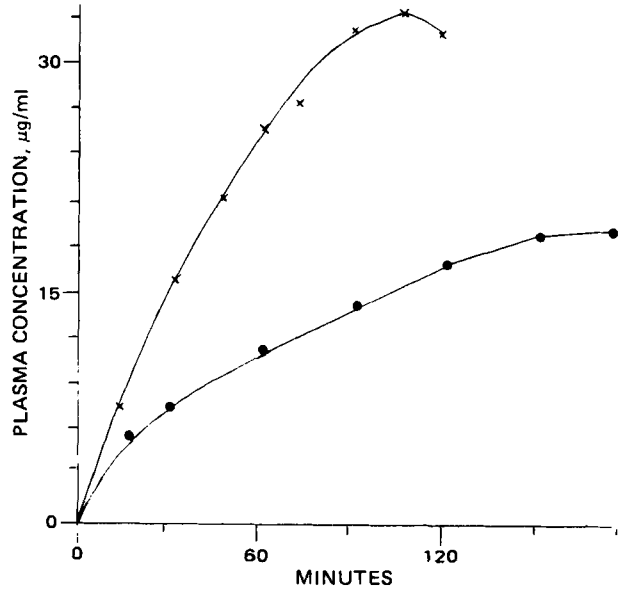

Figure 2—*Plasma concentration after jejunal and ileal administration of 1 g of pralidoxime chloride. Key: ●, jejunal, Dog 9; and ×, ileal, Dog 17.*

Table II—Disappearance Rate Constant, k_a, and Percent Loss of Pralidoxime Chloride from the *In Situ* Isolated Stomach, Duodenum, Jejunum, and Ileum

GI Area	Dog	$k_a \times 10^3$, min^{-1}	Loss after 2 hr, %
Stomach	36, 43	—	—[a]
Duodenum	19, 20, 22, 24	—	—[a]
Jejunum	9	6.87	56.8
	12	7.79	58.4
	15	8.81	63.7
	25	8.12	64.3
		7.89 ± 1.09[b]	60.8 ± 5.18[b]
Ileum	17	18.8	83.7
	21	17.7	84.2
	23	17.0	80.8
	26	16.3	80.5
		17.5 ± 1.46[b]	82.3 ± 2.65[b]

[a] No measurable loss. [b] Mean ± 95% confidence limits.

The individual and average data were fitted adequately to a one-compartment open model with first-order absorption. The following equation describes the plasma level after administration with both dosage forms:

$$C_p = P_1'(e^{-k_a't} - e^{-\beta t}) \qquad \text{(Eq. 2)}$$

where P_1' is a constant, k_a' is the apparent absorption rate constant, β is the elimination rate constant, and C_p is the plasma level at time t.

A tetraexponential equation would be expected since a three-compartment model was observed after intravenous administration. However, this model is difficult to observe after oral administration since it is not feasible to obtain the large number of blood samples required to describe absorption and disposition adequately. For this reason, a less complicated model is often used to delineate blood level curves after oral drug administration (12).

The parameters of Eq. 2 were obtained using the method of residuals and nonlinear least-squares regression analysis to obtain the best estimates of the constants (13). Individual apparent absorption rate constants, elimination rate constants, areas under the plasma level–time curve from zero to infinity, and bioavailabilities, F, are presented in Table III.

There was no significant difference in the absorption rate constants and elimination rate constants obtained with either the solution or tablet. No difference was observed for values obtained within each dosage form. However, the area under the curve from zero to infinity for the solution

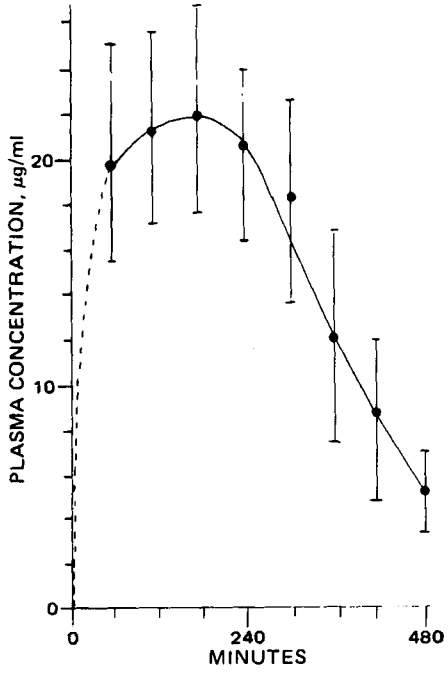

Figure 3—*Mean plasma concentration ± 95% confidence limits after oral administration of 1 g of pralidoxime chloride in solution.*

Table III—Absorption Rate Constants, Elimination Rate Constants, Area under the Plasma Level–Time Curve from Zero to Infinity, and Bioavailability Obtained after Oral Administration of 1 g of Pralidoxime Chloride

Dosage Form	Dog	$k_a' \times 10^3$, min^{-1}	$\beta \times 10^2$, min^{-1}	Area under Curve, μg-hr/ml	Bioavailability, F[a]
Solution	40	8.13	1.24	118	0.61
	41	6.21	1.15	145	0.75
	42	7.46	1.21	153	0.79
		7.26 ± 1.96[b]	1.20 ± 0.092[b]	139 ± 20.7[b]	0.72[c]
Tablet	43	7.08	1.72	76.6	0.40
	44	7.10	1.23	80.1	0.41
	45	7.78	1.09	89.2	0.46
		7.32 ± 0.74[b]	1.35 ± 0.67[b]	82.0 ± 7.36[b]	0.42[c]

[a] Calculated using the average of the individual areas under the curve for the 150-mg iv dose. [b] Mean ± 95% confidence limits. [c] Mean value.

was 70% larger than for the tablet, and these values were statistically different. Using the average of the individual areas under the curve for the 150-mg iv dose, the approximate bioavailabilities for the solution and tablet were 0.72 and 0.42, respectively.

Intramuscular Administration—Mean plasma levels after administration of 150 mg of pralidoxime chloride to three dogs are shown in Fig. 5. The following equation describes the plasma levels after intramuscular administration:

$$C_p = P_1''(e^{-\beta t} - e^{k_a''t}) \qquad \text{(Eq. 3)}$$

where P_1'' is a constant, β is the elimination rate constant, k_a'' is the apparent absorption rate constant, and C_p is the plasma level at time t.

Although a tetraexponential equation would be expected since a three-compartment model was observed after intravenous injection, as discussed under *Oral Administration*, less complicated models are often observed with other routes of administration.

The parameters of Eq. 3 were obtained using the method of residuals and nonlinear regression analysis to obtain the best estimates of the constants. Individual absorption rate constants and elimination rate constants are given in Table IV.

No significant difference was observed among the elimination rate constants obtained after intravenous, oral, or intramuscular administration. Values obtained within each route of administration were similar. The absorption rate constant after intramuscular administration was approximately eight times larger than after oral administration. Table V summarizes the results for each route.

DISCUSSION

After intravenous drug administration, the elimination kinetics are readily analyzed because no simultaneous absorption processes are oc-

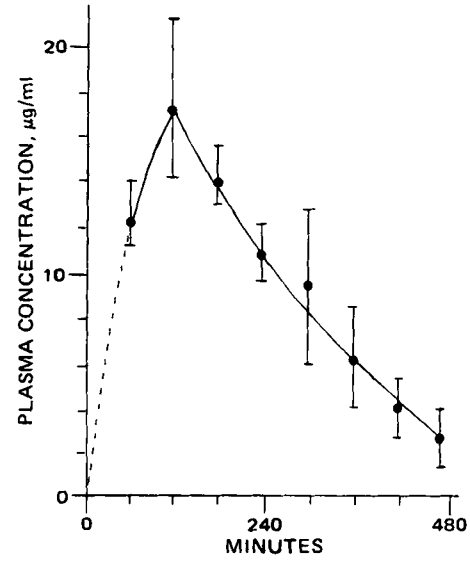

Figure 4—*Mean plasma concentration ± 95% confidence limits after oral administration of two 0.5-g pralidoxime chloride tablets.*

Table IV—Apparent Absorption Rate Constants and Elimination Rate Constants Obtained after Administration of 150 mg im of Pralidoxime Chloride

Dog	$k_a'' \times 10^2$, min^{-1}	$\beta \times 10^2$, min^{-1}
43	7.16	1.18
44	5.20	1.69
45	5.11	1.50
	5.82 ± 2.35[a]	1.46 ± 0.52[a]

[a] Mean ± 95% confidence limits.

curring. The intravenous study of pralidoxime was undertaken to determine the elimination rate constant. Plasma levels after intravascular drug administration in dogs at doses of 150 and 300 mg were described by a triexponential equation.

A three-compartment open model after rapid intravenous injection also was described for 5-(dimethyltriazeno)imidazole-4-carboxamide in the dog (14). A two-compartment open model was used to describe the pharmacokinetics for pralidoxime given intravenously to humans (15). In this latter study, blood sampling was not initiated until 5 min after injection, and only four samples were obtained between 5 and 30 min. Had samples been obtained at earlier times, perhaps a more complex model would have been observed, as was found in the dog where blood sampling began at zero time. Delayed sampling and a lack of frequent sampling at very early times may place the starting point of the plasma curve at a point in time beyond which the value of the first exponential is significant.

In addition to obtaining a plasma level profile of pralidoxime, the objective of the intravenous study was to determine the elimination rate constant, β. After intravenous injection of 150- and 300-mg doses, mean β values of 1.45×10^{-2} and 1.73×10^{-2} min^{-1} were found, respectively. No significant difference existed between these values, indicating that changing the dose within the range utilized had no effect on the drug elimination pattern in dogs. Elimination rate constants of 0.0128 min^{-1} (16) for pralidoxime iodide, 0.0084 min^{-1} (17) for pralidoxime methanesulfonate, and 0.010 min^{-1} (15), 0.0089 min^{-1} (17), and 0.00973 min^{-1} (18) for pralidoxime chloride were reported after intravenous administration to humans.

The rapid drug disappearance from the plasma in both dogs and humans probably is due to the fact that pralidoxime is eliminated from the kidneys by both glomerular filtration and tubular secretion (19). The excreted substances are the unchanged drug and an altered derivative, possibly an aldehyde (19).

When ether was used in place of pentobarbital as the anesthetic, a β of 1.77×10^{-2} min^{-1} was obtained. This value, which is of the same magnitude as those obtained with pentobarbital anesthesia, indicates that the latter probably has no effect on plasma pralidoxime disappearance after a single dose.

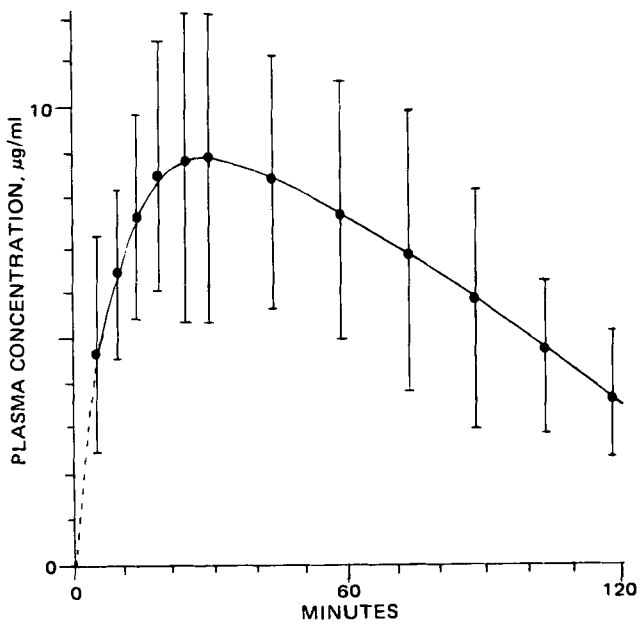

Figure 5—*Mean plasma concentration ± 95% confidence limits after intramuscular administration of 150 mg of pralidoxime chloride.*

Table V—Results for Each Route of Administration

Route of Administration	Dose	β ± 95% Confidence Limits, min^{-1}	k_a ± 95% Confidence Limits, min^{-1}
Intravenous	150 mg	0.0145 ± 0.006	—
	300 mg	0.0173 ± 0.0013	—
Oral solution	1 g	0.0120 ± 0.00092	0.00726 ± 0.00196
Oral tablets	1 g	0.0135 ± 0.0067	0.00732 ± 0.00074
Intramuscular	150 mg	0.0146 ± 0.0052	0.0582 ± 0.0235
Jejunum	1 g	—	0.00789 ± 0.00109
Ileum	1 g	—	0.0175 ± 0.00146
Stomach	1 g	—	0.00
Duodenum	1 g	—	0.00

Once a profile of elimination from the plasma after intravenous administration was obtained, the absorption pattern and absorption rates from the various areas of the GI tract were examined in an *in situ* preparation. The method involved the use of isolated areas of the GI tract, which permitted serial sampling from the area and also blood sampling. No detectable loss of drug was observed from the isolated stomach or duodenum after administration of a 50-ml solution containing 1 g of drug. Plasma levels were also not detectable after drug instillation into each area. Based on these results, it appears that absorption of the compound from the isolated stomach and duodenum of anesthetized dogs is negligible. Kakemi *et al.* (20), using the isolated stomach of the rat, also reported no absorption of pralidoxime methiodide.

The lack of absorption is predictable based on the physicochemical properties of quaternary ammonium compounds. Since the drug is a charged compound and not lipid soluble, passage through a lipid barrier would be expected to be low. The lack of absorption probably cannot be attributed to inadequate blood flow since blood flow in the stomach and duodenum is sufficient in the pentobarbital-anesthetized dog (21).

However, drug disappearance from the isolated jejunum and ileum was observed. The loss of pralidoxime from the jejunum exhibited first-order kinetics. In the ileum, the drug disappeared rapidly, although erratically, during the initial 60 min, followed by a slower, first-order disappearance. This behavior may be the result of some interaction of pralidoxime with the ileal mucosa, resulting in the establishment of a pseudoequilibrium condition or the secretion of fluid in the ileum, which could possibly slow drug absorption. A rapid initial absorption rate with a subsequent decline in the rate for pralidoxime chloride and other monoaldoximes in rats was observed previously (7).

In the jejunum and ileum, the mean absorption rate constants were 7.89×10^{-3} and 1.75×10^{-2} min^{-1} and the percent loss after 2 hr was 61 and 82%, respectively. These results illustrate that drug absorption from the jejunum proceeded at a slower rate than from the ileum in isolated segments of the dog. The differences are probably not the result of a change in pH since the pH of the intestinal contents during the experiment was 7.3 in both segments. Also, blood flow in the jejunum and ileum was reported as identical in the pentobarbital-anesthetized dog (21).

The differences observed in absorption from the jejunum and ileum were possibly the result of differences in some membrane characteristic or constituent. Ion-pair formation may play a role in the absorption of quaternary ammonium compounds (4, 22); adjunctive substances present in the membrane may combine with the drug and facilitate its absorption (23). The absorption rate of the methiodide salt of 2-pyridine aldoxime in the rat reached a maximum with an increasing concentration of drug (20), which is consistent with ion-pair formation or may suggest the possible existence of another transport system.

If such substances or transport systems do, in fact, exist, variability in the nature and distribution in different areas of the GI tract could possibly cause differences in the absorption rate. Pralidoxime may possibly be absorbed *via* the pore route since the pores are not static structures. The ability of the pores to change dimensions may differ at the various levels of the GI tract. Based on elasticity theory, a small change in the linear dimension of a membrane will cause a much greater change in the dimensions of the pores (24).

Plasma levels after drug administration in the isolated jejunum and ileum indicate a more rapid rise from the ileum than from the jejunum. This result is consistent with more rapid absorption from the ileum than from the jejunum. Plasma levels beyond the 2-hr experiment were difficult to obtain since clotting occurred and excessive bleeding was en-

countered when surgically prepared animals were heparinized. Therefore, it is not known whether plasma levels would have continued to increase slowly had sampling been successful beyond approximately 2 hr.

No back-transfer of drug was observed from the plasma into the isolated stomach, duodenum, jejunum, or ileum after intravenous administration at 0 and 60 min. This finding indicates that the disappearance results of pralidoxime from the various areas of the GI tract of the dog were measures of absorption. The *in situ* preparation used in studying absorption from the various areas of the GI tract of the dog appears to be a good technique and provides a means of kinetically following drug disappearance from the isolated area.

After absorption in certain isolated areas of the GI tract was observed, studies were conducted to investigate absorption of drug in the intact animal following oral administration. No absorption occurred in pentobarbital-anesthetized dogs; this result may possibly be explained in terms of the lack of absorption from the stomach. In the anesthetized dog, stomach emptying may be delayed or eliminated, preventing drug absorption from the intestinal tract. In the unanesthetized dog, stomach emptying is not affected and, therefore, absorption occurs.

Plasma levels after oral administration of both dosage forms to unanesthetized dogs were described by Eq. 2. Evaluation of the data showed that the terminal phase of the plasma level–time profile represented the apparent absorption rate constant rather than the elimination rate constant. This effect can occur if absorption is slower than elimination (25). The rate constants were assignable since the elimination rate constant was known from the prior intravenous study.

Byron and Notari (26) clearly demonstrated the problems associated with assignment of rate constants when absorption is assumed to be rate limiting. In recognition of these problems, the use of apparent absorption rate constants was adopted.

The mean apparent absorption rate constants after oral administration of drug in solution and as tablets were 7.26×10^{-3} and 7.32×10^{-3} min^{-1}, respectively. These values are of the same magnitude as the apparent absorption rate constant obtained from the jejunum, 7.89×10^{-3} min^{-1}. This result suggests that absorption may occur principally from the jejunum, as would be predicted since the jejunum constitutes the major portion of the small intestine. However, the isolated ileal experiments showed a faster absorption rate constant. Therefore, if drug is still available during intestinal transit, it could also be absorbed in this region.

This discussion may provide an explanation for the discrepancy between the reported constants after intravenous and oral administration of pralidoxime salts in humans. Elimination rate constants of 0.010 (15), 0.00973 (18), and 0.0089 (17) min^{-1} were reported after intravenous administration while values of 0.0047 (10), 0.0068 (9), and 0.0068 (27) min^{-1} were found after oral administration. Sidell *et al.* (27) utilized the usual one-compartment open model with a first-order absorption equation to obtain values for the various constants. However, the assignments were in error since the elimination rate constant was larger than the absorption rate constant. Reevaluation of the data in the oral studies indicated that the elimination rate constants were 0.0122 (10), 0.0133 (9), and 0.0112 (27) min^{-1}, respectively. These values are of the same magnitude as those obtained following intravenous administration, suggesting that the reported constants are apparent absorption rate constants.

No statistically significant difference was observed in rate constants obtained after oral administration of drug in solution and as tablets to dogs. A difference between the area under the curve obtained with the solution and with tablets was observed. This result indicated that, although the absorption rate was not affected, the drug was less available from the tablet dosage form.

Since the same dogs were not used in the oral and intravenous studies, only an approximate measure of the bioavailability of drug from the solution and tablet dosage forms could be obtained.

The results indicate that although pralidoxime is a charged molecule, considerable intestinal absorption occurs, supporting similar evidence reported by Levine and Steinberg (7).

After intramuscular administration, however, the opposite is observed. Reasonable plasma levels are obtained with a dose of 150 mg, and the descending portion of the plasma level–time curve corresponds to apparent elimination since absorption is rapid. Generally after intramuscular administration of drugs in aqueous solution, absorption is rapid and complete. An elimination rate constant of 0.0093 min^{-1} was reported in humans (15) as compared to a mean of 0.0146 min^{-1} obtained in this investigation.

Elimination with intravenous, intramuscular, and oral administration was rapid. Comparison of apparent elimination rate constants for different routes of administration indicates no significant difference in these values.

In the dog, large oral doses of drug apparently are necessary to achieve measurable plasma levels since elimination occurs at a faster rate than absorption. This conclusion can be reached only after comparison of intravenous and oral administration. Low plasma pralidoxime levels may, therefore, result from slow absorption coupled with rapid elimination rather than negligible or poor absorption. In contrast, after intramuscular administration, absorption is more rapid than elimination and low doses produce measurable plasma levels.

CONCLUSIONS

The results suggest that, in dogs, pralidoxime is absorbed best in the jejunal and ileal areas of the small intestine. Absorption from the isolated stomach and duodenum is negligible. Based on the results of intravenous and oral administration, it was concluded that although there is reasonable bioavailability of drug from oral dosage forms, low plasma levels are observed due to more rapid elimination than absorption. The reverse was observed with intramuscular administration.

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