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# Toxogonin and Pralidoxime: Kinetic Comparison after Intravenous Administration to Man

**FREDERICK R. SIDELL▲, WILLIAM A. GROFF, and ANDRIS KAMINSKIS**

**Abstract** □ After intravenous administration to humans, the chloride and methanesulfonate salts of pralidoxime were found to have identical pharmacokinetic characteristics. Toxogonin had a much smaller volume of distribution and a lower renal clearance rate. These findings explain the fivefold difference in plasma concentrations after similar doses of toxogonin and pralidoxime.

**Keyphrases** □ Toxogonin–pralidoxime—kinetic comparison after intravenous administration, man □ Pralidoxime–toxogonin—kinetic comparison after intravenous administration, man □ Volume of distribution—review of definitions and interrelationships of various terms □ Anticholinesterase intoxication therapy—kinetic comparison of toxogonin and pralidoxime, intravenous administration, man □ Pyridinium oximes—kinetic comparison of toxogonin and pralidoxime, intravenous administration, man □ Pharmacokinetics—comparison of toxogonin–pralidoxime, intravenous administration, man, volume of distribution terms reviewed and compared

The pyridinium oximes are widely accepted as valuable adjuncts to atropine in the therapy of anticholinesterase intoxication. Pralidoxime chloride (2-pyridine aldoxime methochloride) is the preparation used in this country, and toxogonin [*N,N'*-oxydimethylene bis(pyridinium-4-aldoxime)dichloride] is preferred in Europe. The two structures are basically similar, but toxogonin consists of two pyridinium rings linked by an oxygen molecule. Thus, it is about twice the size and weight of pralidoxime chloride.

Previous studies with pralidoxime chloride and toxogonin showed a marked difference in the relationship between apparent dose and plasma concentration between these two closely related materials. After intramuscular administration of equal doses (milligrams per kilogram), plasma levels of the oxime produced by toxogonin were four times higher than those produced by pralidoxime chloride (1, 2). Urinary excretion of both oximes was quite high: 84% of the dose for toxogonin and 91% of the dose for pralidoxime chloride.

These findings strongly suggest a difference in the volume of distribution for these compounds. To investigate this further, the two drugs, along with pralidoxime methanesulfonate, were given intravenously to volunteer subjects.

Although in principle its meaning should be clear, the term "volume of distribution" has been defined in various ways (3). A brief review of these definitions and their interrelationships is also given in this report.

## EXPERIMENTAL

**Subjects**—The subjects were U. S. Army enlisted men who volunteered to participate after the test was discussed with them. Each had a complete medical evaluation including a physical examination, chest X-ray, ECG, and laboratory tests [hematocrit, total and differential white blood cell count, urinalysis, blood urea nitrogen (BUN), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase, bilirubin, creatinine, and red blood cell and plasma cholinesterase] and were found to be free from abnormality before being accepted into the study.

**Methods**—Ideally, this study should have had a crossover design; however, the subjects were available for only a short time, and multiple venipunctures twice in this period did not seem warranted.

The subjects were admitted to the test ward on the evening before the test. On the morning of the test, they were given a light breakfast and thereafter they were urged to drink large amounts of

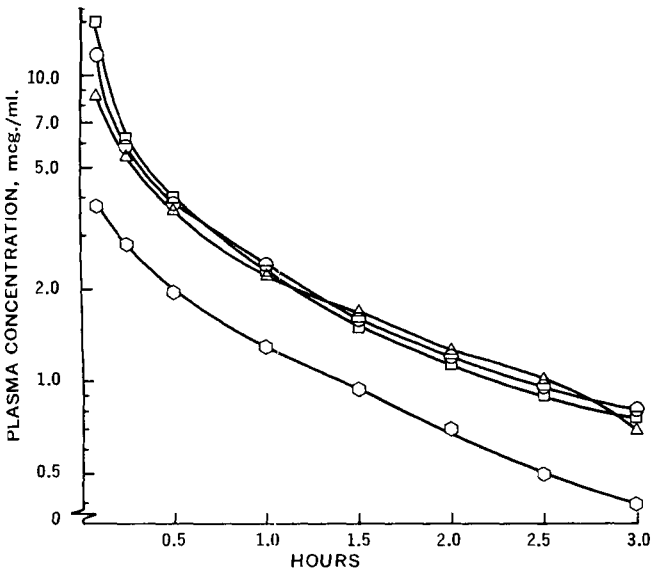


**Figure 1**—*Plasma concentrations after intravenous administration to humans of pralidoxime chloride* (○), *pralidoxime methanesulfonate* (□), *and toxogonin* (△, *1.0 mg./kg.*; ⬡, *0.5 mg./kg.*).

fluid to maintain a copious urinary output. The subjects who received pralidoxime chloride and pralidoxime methanesulfonate were asked to void at hourly intervals for the first 8 hr. of the study; such a rigid schedule was not asked of the subjects who received toxogonin, but they voided spontaneously at frequent (1–3-hr.) intervals, at least during the early part of the study.

Heart rate and blood pressure were measured before and at close intervals after drug administration. As the results did not differ from those previously reported after administration of these compounds, they are not reported.

Plasma was collected at the times shown in Fig. 1; these samples and all urine specimens for 24 hr. were analyzed for oxime content by the method described elsewhere (4). As mentioned (4), in this method the fluid to be analyzed is dialyzed twice through a small pore membrane which filters out proteins, so the method measures only the free drug; since recovery of oxime from human plasma (even with added protein) is almost the same as from water, it would appear that the oximes are negligibly bound to plasma proteins. Each plasma and urine specimen from the pralidoxime subjects was analyzed for creatinine content by standard methods (5).

Although they were allowed to be out of bed *ad libitum*, most subjects remained in bed (except to void) for the first 3 hr.

Although Levy (6) reported a 27% increase in the volume of distribution of benzylpenicillin in subjects at bed rest over ambulatory subjects, the limited, although *ad libitum*, ambulation of the present subjects was not a significant factor in the results because: (*a*) subjects in all groups had about the same amount of bed rest and ambulation, *i.e.*, they stayed in bed most of the morning and were up most of the afternoon; and (*b*) the differences in the volume of distribution, rate constants for elimination and metabolism, amount of drug excreted, and renal clearance noted by Levy for the same drug under different conditions of rest or nonrest, although perhaps significant in the continuous administration of the same drug to unhealthy and healthy patients, were rather small in magnitude compared to the interdrug differences noted in this study.

Toxogonin, from the same lot described previously (1), was mixed to a concentration of 100 mg./ml. The pralidoximes were dissolved to the same concentration. Since there were data on the pralidoximes given intravenously (2, 7), only one dose (5 mg./kg.) was given; two doses of toxogonin, 0.5 mg./kg. (two subjects) and 1.0 mg./kg. (three subjects), were given. The drugs were given intravenously over a 20–30-sec. interval.

## RESULTS

**Plasma Concentration**—Figure 1 shows the mean plasma concentrations for each of the four groups. The group receiving 1.0 mg./kg. of toxogonin had a plasma concentration *versus* time curve very similar to those of the groups receiving 5.0 mg./kg. of the pralidoximes.

**Urinary Recovery and Renal Clearance**—Of the toxogonin administered, 68 ± 8% (mean ± *SD*) of the dose was recovered in the urine within 24 hr. Total urinary recovery of pralidoxime chloride was 89.8 ± 2.6% of the dose, and it was 87.1 ± 20% of the dose of pralidoxime methanesulfonate. For the pralidoximes, about half of the total recovered was recovered within the 1st hr. and about 70% within the first 2 hr. Since the subjects receiving toxogonin did not follow a regular voiding schedule, comparable values are not available, but most of the recovered drug was found in their early specimens.

Renal clearance of oxime was calculated by four methods: (*a*) the standard technique of dividing urinary excretion rate by plasma level at the midpoint of the collection period, using only the excretion and plasma levels in the postabsorptive phase (assumed to be after 3 hr.); (*b*) from the slope of a linear plot of the excretion rate *versus* the plasma level at the midpoint of the collection interval (8); (*c*) by dividing the total amount excreted by the total area under the plasma concentration *versus* time plot (8); and (*d*) by dividing the cumulative amount excreted by the cumulative area under the plasma concentration *versus* time curve and averaging these values for the duration of the study (9). Kwan *et al.* (9) indicated that fluctuations from one time period to the next (which presumably are due to experimental error or slight physiological variation) are minimized by Method (*d*), while Method (*c*) has the advantages of necessitating only one urinary collection and analysis and of eliminating the need for multiple, carefully timed urine specimens.

As shown in Table I, the four values for each subject are in good agreement, with several exceptions. The low fraction excreted and the low cumulative values for clearance make one suspect that Subject 3656 may have discarded an early specimen which would have changed these particular values more than the other clearance values.

In the six subjects receiving pralidoxime, simultaneous creatinine clearances were measured (Table I) and were roughly 18% of the pralidoxime clearances. Thus, these compounds appear to measure renal plasma flow because their clearances are about the same as that of *p*-aminohippuric acid (10). Other data[1] indicate that the renal clearance of toxogonin is less than that of simultaneously measured creatinine clearance, although obviously this conclusion cannot be shown from the data in Table I. Thus, it appears that the two similar compounds, pralidoxime and toxogonin, are handled differently by the kidneys. The net effect for pralidoxime is tubular secretion; for toxogonin it is reabsorption.

The general agreement found between the methods of renal clearance calculation adds support to the argument of Kwan *et al.* (9) that an accurate, valid renal clearance can be obtained after intravenous drug administration by dividing the amount excreted over a given time by the area under the plasma concentration *versus* time curve, provided that the area under the curve can be estimated accurately.

**Kinetic Considerations**—*General*—When plotted against time, the plasma concentration data fit the line described by the biexponential equation:

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

where $C_p$ = plasma concentration, $\beta = -2.303$ times the slope of the terminal linear segment (when plasma concentration is on a logarithmic scale and time is on a linear scale), and $B$ is the intercept of this line. $A$ and $\alpha$ are similar parameters for a line drawn from the residuals. These parameters were calculated by the least-squares method using the method of residuals.

From these parameters, the rate constants and volumes of distribution were calculated by standard methods (8); $k_{12}$ is the first-order rate constant describing the rate of drug transfer from the central to the peripheral compartment, $k_{21}$ describes drug transfer from the peripheral to the central compartment, $k_{13}$ is the rate constant for drug elimination (assumed to be from the central compartment), $V_1$ is the volume of the central compartment, and $V_2$ is the volume of the peripheral compartment (Table II).

The half-times for drug elimination from plasma ($0.693/\beta$) are similar for all three compounds: 1.20 hr. for toxogonin, 1.41 hr.

[1] F. R. Sidell and W. A. Groff, unpublished data.

**Table I**—Renal and Plasma Clearances of Oximes

| Case Number | Dose, mg./kg. | Weight, kg. | Renal Clearance, ml./min. Standard[a] | Slope[b] | Cumulative[c] | 24-hr. Cumulative[d] | Creatinine Clearance[e], ml./min. | $Cl_{ox}/Cl_{cr}$ | Plasma Clearance, ml./min. | $f/(Cl_r/Cl_p)$ [g] | $f$, Fraction of Dose Recovered in Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Toxogonin** | | | | | | | | | | | |
| 3139 | 0.5 | 71 | 97 ± 30[h] | 87 | 82 | 83 | — | — | 128 | 0.648 | 0.647 |
| 3140 | 0.5 | 71 | 91 ± 6 | 82 | 77 | 83 | — | — | 137 | 0.605 | 0.595 |
| 3141 | 1.0 | 70 | 82 ± 1 | 80 | 79 | 86 | — | — | 129 | 0.667 | 0.658 |
| 3142 | 1.0 | 70 | 118 ± 14 | 110 | 104 | 123 | — | — | 151 | 0.815 | 0.811 |
| 3143 | 1.0 | 63.1 | 87 ± 8 | 79 | 76 | 84 | — | — | 120 | 0.700 | 0.694 |
| Mean | | | 95 | 88 | 83 | 92 | — | — | 133 | 0.687 | 0.681 |
| *SD* | | | 14 | 13 | 12 | 17 | — | — | 12 | 0.079 | 0.081 |
| **Pralidoxime Chloride** | | | | | | | | | | | |
| 3658 | 5.0 | 84.5 | 582 ± 292 | 738 | 775 | 726 | 129 | 5.6 | 784 | 0.926 | 0.915 |
| 3655 | 5.0 | 71.8 | 620 ± 224 | 679 | 679 | 662 | 99 | 6.7 | 733 | 0.903 | 0.911 |
| 3657 | 5.0 | 90.3 | 616 ± 170 | 634 | 666 | 648 | 142 | 4.6 | 745 | 0.870 | 0.869 |
| Mean | | | 606 | 638 | 707 | 679 | 123 | 5.6 | 754 | 0.900 | 0.898 |
| *SD* | | | 21 | 44 | 60 | 42 | 22 | 1.0 | 27 | 0.028 | 0.026 |
| **Pralidoxime Methanesulfonate** | | | | | | | | | | | |
| 3654 | 5.0 | 67.3 | 659 ± 396 | 735 | 747 | 713 | 100 | 7.1 | 718 | 0.993 | 0.978 |
| 3659 | 5.0 | 78.2 | 603 ± 521 | 587 | 748 | 700 | 120 | 5.8 | 685 | 1.022 | 1.000 |
| 3656 | 5.0 | 85.9 | 670 ± 114 | 593 | 369 | 402 | 116 | 3.5 | 633 | 0.635 | 0.636 |
| Mean | | | 644 | 638 | 621 | 605 | 112 | 5.5 | 679 | 0.883 | 0.871 |
| *SD* | | | 36 | 84 | 219 | 176 | 11 | 1.8 | 46 | 0.216 | 0.204 |

[a] From *UV/P*. [b] From slope of rate of excretion *versus* plasma concentration. [c] From mean of ratios of cumulative amount excreted to cumulative area under the plasma concentration *versus* time curve. [d] Ratio of the total amount excreted to the total area under the plasma concentration *versus* time curve. [e] Not corrected for body surface area. $Cl_{cr}$ not done in toxogonin subjects. [f] Using 24-hr. cumulative $C_{ox}$. [g] Calculated $f$, using 24-hr. cumulative renal clearance. [h] Mean ± *SD* (at least four values for each subject).

for pralidoxime methanesulfonate, and 1.31 hr. for pralidoxime chloride.

*Plasma Clearance*—For a two-compartment model, the plasma clearance ($Cl_p$) may be defined as (8):

$$Cl_p = V_1 k_{13} \qquad \text{(Eq. 2)}$$

or by the identical term:

$$Cl_p = \frac{D}{AUC} \qquad \text{(Eq. 3)}$$

where $AUC$ is the area under the plasma concentration *versus* time curve, and $D$ is the dose entering the circulation (assumed to be the total dose after intravenous administration).

By using the integral of the equation for plasma concentration *versus* time (Eq. 1), the total $AUC$ (from $t = 0$ to $t = \infty$) was estimated and then the $Cl_p$ was calculated for each subject (Table I).

The fraction of drug entering the circulation that is excreted unchanged in the urine ($f$) is also theoretically the ratio of the renal clearance to the plasma clearance (8). The comparison between the actual $f$ (measured urinary excretion divided by dose) and theoretical $f$ (renal clearance divided by plasma clearance) is shown in Table I. The clearance values using the total amount excreted divided by the total area under the plasma concentration *versus* time curve agreed most closely with the experimental values, and they were the ones used for this calculation.

*Volume of Distribution*—The volume of distribution is the hypothetical volume in which the drug is present in the same concen-

**Table II**—Pharmacokinetic Constants

| Case Number[a] | $A$, mcg./ml. | $\alpha$, hr.$^{-1}$ | $B$, mcg./ml. | $\beta$, hr.$^{-1}$ | $t_{1/2}$, hr. | $k_{12}$, hr.$^{-1}$ | $k_{21}$, hr.$^{-1}$ | $k_{13}$, hr.$^{-1}$ | $V_1$, ml./kg. | $V_2$, ml./kg. | $(V_d)_{ss}$ ml./kg. | $(V_d)_\beta$, ml./kg. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Toxogonin** | | | | | | | | | | | | |
| 3139 | 2.205 | 4.95 | 2.788 | 0.667 | 1.04 | 1.476 | 3.058 | 1.080 | 100.1 | 48.3 | 148.4 | 161.8 |
| 3140 | 2.340 | 3.58 | 1.914 | 0.522 | 1.33 | 1.224 | 1.896 | 0.984 | 117.5 | 75.9 | 193.4 | 222.0 |
| 3141 | 4.656 | 4.26 | 4.546 | 0.576 | 1.20 | 1.422 | 2.394 | 1.020 | 108.7 | 64.6 | 173.3 | 193.0 |
| 3142 | 10.129 | 5.67 | 3.954 | 0.667 | 1.04 | 2.442 | 2.070 | 1.824 | 71.0 | 83.8 | 154.8 | 194.5 |
| 3143 | 5.849 | 3.96 | 3.60 | 0.498 | 1.39 | 1.560 | 1.818 | 1.080 | 105.8 | 90.8 | 196.6 | 230.5 |
| Mean | | 4.48 | | 0.586 | 1.20 | 1.625 | 2.247 | 1.198 | 100.6 | 72.7 | 173.3 | 200.4 |
| *SD* | | 0.83 | | 0.079 | 0.16 | 0.473 | 0.504 | 0.353 | 17.7 | 16.7 | 21.8 | 27.2 |
| **Pralidoxime Chloride** | | | | | | | | | | | | |
| 3658 | 12.456 | 6.65 | 3.68 | 0.518 | 1.34 | 3.454 | 1.916 | 1.789 | 309.9 | 558.6 | 868.5 | 1075 |
| 3655 | 17.120 | 6.43 | 2.66 | 0.484 | 1.43 | 3.199 | 1.282 | 2.423 | 252.78 | 630.5 | 883.3 | 1266 |
| 3657 | 15.24 | 8.10 | 4.85 | 0.590 | 1.17 | 4.298 | 2.403 | 1.989 | 248.9 | 445.15 | 694.0 | 839 |
| Mean | 14.94 | 7.06 | 3.73 | 0.531 | 1.31 | 3.650 | 1.867 | 2.070 | 270.5 | 544.8 | 815.2 | 1060 |
| *SD* | 2.35 | 0.91 | 1.10 | 0.05 | 0.13 | 0.575 | 0.562 | 0.320 | 34.1 | 93.4 | 105.3 | 214 |
| **Pralidoxime Methanesulfonate** | | | | | | | | | | | | |
| 3654 | 18.776 | 6.72 | 2.34 | 0.466 | 1.46 | 3.325 | 1.159 | 2.702 | 236.8 | 678.5 | 915.2 | 1373 |
| 3659 | 25.04 | 8.74 | 2.87 | 0.432 | 1.60 | 4.950 | 1.286 | 2.936 | 179.5 | 689.6 | 868.7 | 1218 |
| 3656 | 23.90 | 7.69 | 5.0 | 0.610 | 1.14 | 3.909 | 1.835 | 2.559 | 173.0 | 368.6 | 541.6 | 725 |
| Mean | 22.57 | 7.717 | 3.40 | 0.503 | 1.41 | 4.061 | 1.427 | 2.732 | 196.3 | 578.6 | 775.2 | 1105 |
| *SD* | 3.34 | 1.01 | 1.41 | 0.09 | 0.24 | 0.823 | 0.359 | 0.190 | 35.2 | 182.5 | 204.0 | 338 |

[a] See Table I for doses.

tration as it is in the plasma. Or, the volume of distribution ($V_d$) is the ratio of the amount of drug in the body ($D_b$) to the plasma concentration ($C_p$).

A basic assumption is that $V_d$ is constant, so this definition should be true for all values of $C_p$ (*i.e.*, from $t = 0$ to $t = \infty$). If a drug behaves as though it is distributed in a single compartment, this assumption would be valid. However, the distribution and excretion patterns of many drugs appear to follow two-compartment model kinetics and, under these circumstances, a single volume of distribution over the entire time course is not as easily defined.

After rapid intravenous administration of a drug, the concentration in the blood (which is part of the central compartment) usually falls rapidly for a period and then declines more gradually. The concentration is highest immediately after the injection (or at zero time). The concentration in the tissue (or peripheral) compartment is zero at zero time. The tissue concentration increases to a maximum and then declines in parallel with the plasma concentration (the $\beta$ phase). Since the plasma and tissue concentrations maintain a constant relationship during the $\beta$ phase, a single volume of distribution [designated as $(V_d)_\beta$, which is exactly equivalent to $(V_d)_{area}$] can relate the amount of drug in the body to the plasma concentration during this period (11), but a single expression of volume of distribution cannot hold true over all time periods.

By using separate volumes for each compartment, the amount of drug in the body is defined by:

$$D_b = C_p \cdot V_1 + C_t \cdot V_2 \qquad \text{(Eq. 4)}$$

where $V_1$ and $V_2$ are as previously defined, and $C_t$ is the concentration in the peripheral compartment. This expression, using two volumes for the two-compartment model, accounts for the amount of drug in the body over all time periods.

The steady-state volume of distribution[2], $(V_d)_{ss}$, is the ratio of the amount of drug in the body to the plasma concentration at steady-state conditions, *i.e.*, when the rate of drug transfer into the peripheral compartment is equal to the rate of transfer back to the central compartment (11). This phenomenon is momentary, and only at this instant does $(V_d)_{ss}$ relate the amount of drug in the body to the plasma concentration.

Although conceptually they are unlike, algebraically it can be shown[3] that:

$$(V_d)_{ss} = V_1 + V_2 \qquad \text{(Eq. 5)}$$

Unfortunately, the different notations used for the volume of distribution have apparently masked this mathematical relationship. Although the single term $(V_d)_{ss}$ does not relate the plasma and tissue concentrations to the amount of drug in the body at any time except for a single instant, it is the sum of two volumes, $V_1$ and $V_2$, which do for all time periods. If a single value is to be used when speaking of a single volume of distribution of a two-compartment model, it would seem more appropriate to use this sum of the two valid compartmental volumes rather than a volume [*e.g.*, $(V_d)_\beta$] that really describes neither.

Some experimental evidence suggests that $(V_d)_{ss}$ may be the preferred value. Wagner *et al.* (12) showed that the calculated tissue concentration of LSD paralleled scores on a performance test (which they assumed was a direct reflection of tissue concentration) over all time periods. Their calculations were based on a two-compartment model with $V_d = V_1 + V_2$ which, as indicated, is algebraically identical to $(V_d)_{ss}$. Sidell and Groff (2) used the two-compartment model to estimate the amount of drug remaining in the body at all times after intravenous 2-pyridinium aldoxime methochloride. This mathematical expression was verified by material balance experiments in man.

A similar calculation can be made using the present data. The amount in the body ($D_b$), from $t = 0$ to $t = \infty$, over time is given by the following equation which is based on the two-compartment model (2):

$$D_b = \frac{D}{A\beta + B\alpha}(A\beta e^{-\alpha t} + B\alpha e^{-\beta t}) \qquad \text{(Eq. 6)}$$

If the entire dose were eliminated into the urine, the dose less the amount in the body should equal the amount excreted. Since urinary recovery is often less than 100%, the calculated amount excreted must be adjusted by this factor. This adjustment was made, and Fig. 2 shows the result with experimental data for one subject along with the mean data points for one drug group. The experimental data (amount excreted) agree with the calculated line in each case.

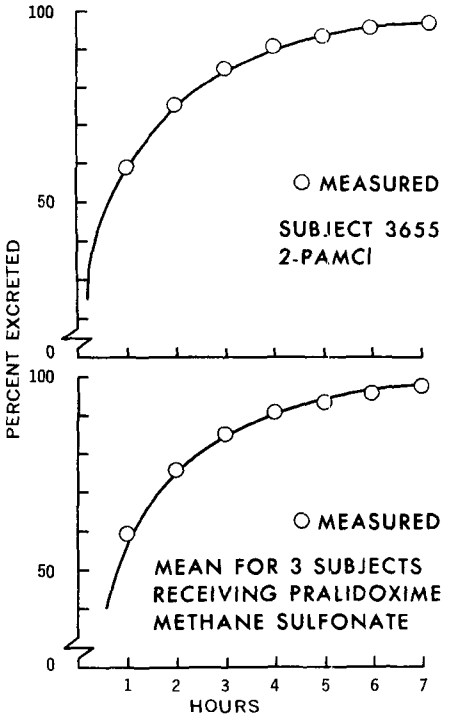


**Figure 2**—*Calculated and experimental urinary excretion values of pralidoxime chloride and pralidoxime methanesulfonate.*

Table II gives the values for $V_1$, $V_2$, $(V_d)_{ss}$, and $(V_d)_\beta$ [or $(V_d)_{area}$ by different terminology] for each subject.

The total volumes of distribution for the pralidoxime salts do not differ notably from salt to salt, and both are larger by a factor of 4–5 than the volumes for toxogonin. The fivefold difference in volume of distribution accounts for the fivefold difference in dose of toxogonin needed to produce similar plasma levels of oxime, as found in this and previous studies.

## DISCUSSION

From these results it would appear that toxogonin produces higher plasma concentrations of oxime than pralidoxime after equal doses because the volume of distribution of toxogonin is much less.

The rate constants for exit from the central compartment ($k_{12}$ and $k_{13}$) are less than half those for pralidoxime. For toxogonin, the central volume is larger than the peripheral, while for the pralidoximes the opposite is true. These comparisons indicate that toxogonin slowly diffuses through membranes or into tissues while pralidoxime diffuses rather freely. The reasons for this difference are not clear at present. The compounds have similar chemical functional groups and nearly identical pKa values, but they differ in charge and molecular volume. The exact relationship between these factors and differences in membrane permeability is under investigation[4].

The high renal clearance of pralidoxime suggests that it is actively secreted by the renal tubular cells; toxogonin appears to be reabsorbed but whether by active or passive mechanisms is unknown.

Renal clearances of these compounds estimated by several commonly described methods were not equal but, in most cases, were in reasonably close agreement. If clearance is to be measured after a single injection of a drug, the method of using the ratio of the total amount of drug excreted to the total area under the plasma con-

[2] See *Appendix* for the relationship of $(V_d)_{ss}$ to $(V_d)_\beta$.
[3] See *Appendix* for this proof.

[4] R. I. Ellin, personal communication.

centration *versus* time curve has the advantage of eliminating the need for multiple, exactly timed urine specimens.

Comparative data on the therapeutic efficacy of the two oximes (summarized in *Reference 1*) indicate that at equimolar doses toxogonin is several times more effective in treating animals poisoned with anticholinesterases. The plasma oxime concentrations were not measured in these studies, but it can be assumed that after equal doses the plasma concentration of toxogonin would be higher than the plasma concentration of oxime after toxogonin.

The two-compartment open model appears adequate to describe the pharmacokinetics of these compounds in man. Constants derived from data from one compartment (plasma) were used in equations derived on a theoretical basis from the model and predicted in a reasonable manner the observed values independently measured in another compartment (urine).

The definitions of volume of distribution and its varying notations were discussed. Several that are usually designated by different symbols were noted to be identical. In the interest of clarity, the symbols should be standardized and the equivalencies recognized.

## APPENDIX

**Definitions**—The values for the rate constants, volumes, and $C_t$ have been mathematically defined as follows (8):

$$k_{21} = \frac{A\beta + B\alpha}{A + B} \qquad \text{(Eq. A1)}$$

$$k_{13} = \frac{\alpha\beta}{k_{21}} \qquad \text{(Eq. A2)}$$

$$k_{12} = \alpha + \beta - k_{13} - k_{21} \qquad \text{(Eq. A3)}$$

$$V_1 = \frac{D}{A + B} \qquad \text{(Eq. A4)}$$

$$V_2 = \frac{k_{12}}{k_{21}} \cdot V_1 \qquad \text{(Eq. A5)}$$

$$C_t = \frac{k_{12} \cdot D}{(\alpha - \beta)(V_2)} (e^{-\beta t} - e^{-\alpha t}) \qquad \text{(Eq. A6)}$$

where $A$, $B$, $\alpha$, $\beta$, and $D$ are as defined in the text.

By substitution and rearrangement, these can be expressed in terms of graphically defined $A$, $\alpha$, $B$, and $\beta$ as follows:

$$k_{13} = \frac{\alpha\beta(A + B)}{A\beta + B\alpha} \qquad \text{(Eq. A7)}$$

$$k_{12} = \frac{AB(\alpha - \beta)^2}{(A + B)(A\beta + B\alpha)} \qquad \text{(Eq. A8)}$$

$$V_2 = \frac{D}{A + B} \frac{AB(\alpha - \beta)^2}{(A\beta + B\alpha)^2} \qquad \text{(Eq. A9)}$$

$$C_t = \frac{A\beta + B\alpha}{\alpha - \beta} \cdot [e^{-\beta t} - e^{-\alpha t}] \qquad \text{(Eq. A10)}$$

**Equivalency of $(V_d)_{ss}$ and $(V_1 + V_2)$**—$(V_d)_{ss}$ has been defined (11) as:

$$(V_d)_{ss} = \frac{k_{21} + k_{12}}{k_{21}} \cdot V_1 \qquad \text{(Eq. A11)}$$

By substitution and rearrangement:

$$(V_d)_{ss} = \frac{D(A\beta^2 + B\alpha^2)}{(A\beta + B\alpha)^2} \qquad \text{(Eq. A12)}$$

Also by substitution:

$$V_1 + V_2 = \frac{D}{A + B} + \left[\frac{D}{A + B}\right] \cdot \left[\frac{AB(\alpha - \beta)^2}{A\beta + B\alpha)^2}\right] \qquad \text{(Eq. A13)}$$

or:

$$V_1 + V_2 = \frac{D(A\beta^2 + B\alpha^2)}{(A\beta + B\alpha)^2} = (V_d)_{ss} \qquad \text{(Eq. A14)}$$

**Relationship between $(V_d)_\beta$ and $(V_d)_{ss}$**—It was reported (11) that:

$$(V_d)_\beta = \frac{V_1}{f_c} \qquad \text{(Eq. A15)}$$

where $f_c$ = the fraction of the amount of drug in the body that is in the central compartment, or:

$$f_c = \frac{C_2}{C_2 + C_2'} \qquad \text{(Eq. A16)}$$

where:

$$C_2 = \frac{B}{A + B} \qquad \text{(Eq. A17)}$$

and:

$$C_2' = \frac{k_{12}}{(\alpha - \beta)} \qquad \text{(Eq. A18)}$$

By substitution and rearrangement:

$$(V_d)_\beta = \frac{\alpha D}{A\beta + B\alpha} \qquad \text{(Eq. A19)}$$

Since:

$$(V_d)_{ss} = \frac{D(A\beta^2 + B\alpha^2)}{(A\beta + B\alpha)^2} \qquad \text{(Eq. A20)}$$

it follows that:

$$(V_d)_\beta = \frac{\alpha(A\beta + B\alpha)}{A\beta^2 + B\alpha^2} \cdot (V_d)_{ss} \qquad \text{(Eq. A21)}$$

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