Journal of Pharmacokinetics and Biopharmaceutics, Vol. 6, No. 3, 1978

Novel Method of Estimating Volume of Distribution of a Drug Obeying Michaelis–Menten Elimination Kinetics[1]

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Received September 12, 1977—Final December 7, 1977

The novel method of estimating the volume of distribution involves (a) administering an appropriate bolus intravenous dose of the drug, (b) starting a constant-rate intravenous infusion of the drug at the same time, (c) maintaining the infusion for a given number of hours, (d) measuring the drug concentration over the entire time course, (e) computer-fitting the post-infusion data to obtain estimates of V_m and K_m, (f) estimating the total area under the concentration–time curve from zero time to infinity, and (g) iteratively solving a cubic equation to obtain the estimate of the volume of distribution. The method was applied to ethanol in the cat and yielded an average value of 635 ml/kg (63.5% of body weight) with a coefficient of variation of 23.0%. This is equivalent to total body water in the cat.

KEY WORDS: ethanol; volume of distribution; Michaelis–Menten elimination kinetics.

INTRODUCTION

The volume of distribution of a drug is an essential parameter in many pharmacokinetic calculations, and it may or may not have physiological implications. This article describes a novel method of estimating the volume of distribution of a drug which obeys Michaelis–Menten elimination kinetics. The experimental procedure involves the administration of a

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0090-466X/78/0600-0197$05.00/0

bolus intravenous dose of the drug and the initiation of a constant-rate intravenous infusion of the drug at the same time. The infusion is maintained over a period of T hours. The drug concentration in blood is measured as a function of time from zero (time of the bolus dose and initiation of the infusion) until a period of time after T hours when the drug has, for all practical purposes, disappeared from the blood. The total area under the concentration–time curve from zero to infinite time (A_∞) is estimated as well as the concentration at time zero (C_0). The concentration at time T (C_T) is an observed value. The postinfusion data are fitted to the integrated form of the Michaelis–Menten equation via computer to obtain estimates of V_m and K_m. A cubic equation involving the volume of distribution (V), A_∞, C_0, C_T, V_m, K_m, and T is then solved iteratively via digital computer to obtain the estimate of V. The method was applied to ethanol in the cat, where C refers to the whole blood concentration of ethanol (mg/ml).

EXPERIMENTAL

The cat experiments were run as described by Wagner *et al.* (1). During each study, blood pressure, heart rate, body temperature, respiratory rate, blood alcohol concentration, and blood acetaldehyde concentration were measured as a function of time, but only the blood alcohol

Table I. Experimental Conditions for Cat Studies

Cat No.	Study No.	Date of study	Weight (kg)	Loading dose (ml 95% alcohol)	Infusion rate[a] [mg/(kg×hr)]	Other drug: Drug	Other drug: Dose[b] (mg/kg)
1	16	4/9/76	4.0	2.5	125	None	
	17	4/12/76	4.0	1.9	110	None	
	18	4/20/76	4.0	1.9	110	None	
	19	4/27/76	4.0	2.5	125	None	
2	20	5/27/76	3.4	1.4	125	None	
3	22	6/9/76	3.15	1.3	125	None	
4	25	7/8/76	2.7	1.12	125	None	
5	27	7/14/76	3.5	1.44	125	None	
2	21	5/28/76	3.4	1.4	125	Pentobarbital	12.5
3	23	6/10/76	3.15	1.3	125	Digoxin	0.0286
4	26	7/9/76	2.7	1.12	125	atropine sulfate	0.04
5	28	7/15/76	3.5	1.44	125	Isproterenol HCl	0.001

[a] Infusion continued for 4 hr in each experiment.
[b] Dose administered as a bolus intravenously at 4 hr.

concentrations are reported herein. Body temperature was maintained constant at 100–101°F (rectal) during each experiment. Table I lists the study conditions for 12 studies in five different cats. In eight of the studies in the five cats, ethanol was the only drug involved (studies 16–19, 20, 22, 25, and 27). In four of the cats, ethanol was given only on 1 day and on the next day the same type of experiment was run with alcohol, but just as the infusion of ethanol ended a bolus intravenous dose of another drug was administered (see cat 2, studies 20 and 21; cat 3, studies 22 and 23; cat 4, studies 25 and 26; cat 5, studies 27 and 28). Ethanol and acetaldehyde were measured in whole arterial blood by the head-space, gas chromatographic method described by Wagner *et al.* (1).

THEORETICAL

Assuming that the "body" acts as a single compartment, equations 1 and 2 are applicable to the experimental conditions in the interval $0 \leq t \leq T$.

$$dC/dt = k_0/V - (V_m C)/(K_m + C) \tag{1}$$

$$C_0 = D_L/V \tag{2}$$

where C is the whole blood concentration of ethanol (mg/ml), t is time (hr), V is the volume of distribution (ml/kg), k_0 is the constant infusion rate [mg/(kg×hr)], V_m is the maximal velocity of elimination [mg/(ml×hr)], K_m is the Michaelis constant (mg/ml), C_0 is the estimated initial concentration of ethanol at time zero (mg/ml), and D_L is the loading dose of ethanol given by bolus intravenous injection (mg/kg). To estimate C_0, the value of 600 ml/kg was used for V; this does introduce a small error into the final estimate of V derived from the cubic equation derived later, but the error is very small.

After the infusion ceases at time T (i.e., for $t \geq T$), the blood alcohol concentration obeys

$$dC/dt = -(V_m C)/(K_m + C) \tag{3}$$

Integration of equation 1 yields

$$\begin{aligned} t = {} & VK_m/(k_0 - V_m V) \ln [\{(k_0 - V_m V)C + k_0 K_m\}/\{k_0 - V_m V)C_0 + k_0 K_m\}] \\ & + \{V/(k_0 - V_m V)\}(C - C_0) - \{k_0 K_m V/(k_0 - V_m V)^2\} \\ & \times \ln [\{(k_0 - V_m V)C + k_0 K_m\}/\{(k_0 - V_m V)C_0 + k_0 K_m\}] \end{aligned} \tag{4}$$

Integration of equation 4, to obtain the area under the concentration–time curve from 0 to T, yields equation 5, where C_T is the concentration at time T:

$$\begin{aligned}\text{AUC } 0\text{–}T &= \int_0^T C(t)\,dt = \int_{C_T}^{C_0} t(C)\,dt + C_T T \\ &= \{V/(k_0 - V_m V)\}[-C_T^2/2 - C_0^2/2 + C_0 C_T \\ &\quad + K_m\{k_0 K_m/(k_0 - V_m V) + C_T\} \ln\{(k_0 - V_m V)C_0 + k_0 K_m\} \\ &\quad + K_m(C_T - C_0) - K_m\{((k_0 - V_m V)C_T + k_0 K_m)/(k_0 - V_m V)\} \\ &\quad \times \ln\{(k_0 - V_m V)C_T + k_0 K_m\}] - \{k_0 K_m V/(k_0 - V_m V)^2\} \\ &\quad \times [\{k_0 K_m/(k_0 - V_m V) + C_T\} \ln\{(k_0 - V_m V)C_0 + k_0 K_m\} \\ &\quad + C_T - C_0 - \{(k_0 - V_m V)C_T + k_0 K_m\}/(k_0 - V_m V) \\ &\quad \times \ln\{(k_0 - V_m V)C_T + k_0 K_m\}] + C_T T \end{aligned} \tag{5}$$

Integration of equation 3, to obtain the area under the concentration–time curve from T to ∞, yields

$$\text{AUC } T\text{–}\infty = C_T/V_m[C_T/2 + K_m] \tag{6}$$

Addition of equations 5 and 6 yields the total area, A_∞. Rearrangement of the resulting equation for A_∞ yields

$$AV^3 + BV^2 + C'V + D + \{EV^3 + FV^2\} \ln[(G - HV)/(I - JV)] = 0 \tag{7}$$

where

$$\begin{aligned} A &= V_m^2[A_\infty V_m - C_T^2 - C_0^2/2 + C_0 C_T \\ &\quad + K_m C_T - K_m C_0 - V_m C_T T - C_T K_m] \end{aligned} \tag{8}$$

$$\begin{aligned} B &= k_0 V_m[3K_m C_T + (5/2)C_T^2 + 3V_m C_T T \\ &\quad + K_m C_0 - K_m C_T - 2C_0 C_T + C_0^2 - 3A_\infty V_m] \end{aligned} \tag{9}$$

$$C' = k_0^2[3A_\infty V_m - 2C_T^2 - C_0^2/2 + C_0 C_T - 3V_m C_T T - 3C_T K_m] \tag{10}$$

$$D = (k_0^3/V_m)[C_T^2/2 + C_T K_m + V_m C_T T - A_\infty V_m] \tag{11}$$

$$E = K_m V_m^2 C_T \tag{12}$$

$$F = -[k_0 K_m^2 V_m + k_0 V_m K_m C_T] \tag{13}$$

$$G = k_0 C_0 + k_0 K_m \tag{14}$$

$$H = V_m C_0 \tag{15}$$

$$I = k_0 C_T + k_0 K_m \tag{16}$$

$$J = V_m C_T \tag{17}$$

Since the parameters C_0, k_0, C_T, T, V_m, K_m, and A_∞ are readily estimated or known from experimental data, V may be obtained from equations 7–17. An iterative digital computer program (given in the Appendix) was employed to obtain V. The program includes equations 8–17.

To obtain estimates of V_m and K_m, the postinfusion C, t data were fitted to the integrated form of equation 3, namely equation 18, by numerical integration of equation 3, using the program NONLIN (2) and the AMDAHL 470V/6 digital computer. Details of such fittings with ethanol data are given elsewhere (3–7). In equation 18, C_T is the estimated value of the blood alcohol concentration at cessation of the infusion and the other symbols have already been defined.

$$C_T - C + K_m \ln [C_T/C] = V_m(t - T) \tag{18}$$

RESULTS

The estimated initial and the observed ethanol concentrations are listed in Table II. The sensitivity of the assay was such that essentially the total area under the concentration–time curve was obtained by application of the trapezoidal rule. This was checked by using equation 6 as well as the trapezoidal rule to estimate AUC T–∞, where for the trapezoidal rule only the concentration up to the last sampling time (Table II) was employed. For the 12 sets of data the means were 0.834 and 0.824 mg/(ml × hr) (paired $t = 0.37$, $p > 0.25$) for the area from equation 6 and by trapezoidal rule, respectively. This also provides a check on the pharmacokinetic model.

Table III lists the estimated values of V_m, K_m, and A_∞ as well as the estimated values of V, obtained via computer with equations 7–17.

DISCUSSION

For cat 1, studied four times with ethanol alone, the mean volume of distribution was 571 ml/kg, with a coefficient of variation of 7·4%. In calculating the other means, this mean of 571 ml/kg was employed to represent cat 1. For the five cats given ethanol alone, the mean volume of distribution was 635 ml/kg, with a coefficient of variation of 23.0%. For the experiments in cats 2–5, where another drug was given by bolus intravenous injection at 4 hr, the mean volume of distribution was

Table II. Estimated Initial Blood Alcohol Concentrations at Zero Time and Observed Blood Alcohol Concentrations over an $8\frac{1}{2}$-hr Period in Each Study

Time (hr)	Blood concentration of ethanol (mg/ml) for indicated study No.											
	16	17	18	19	20	21	22	23	25	26	27	28
0	0.781[a]	0.594	0.594	0.781	0.515	0.515	0.516	0.516	0.519	0.519	0.514	0.514
0.083	0.891	0.649	0.676	0.941	0.460	0.577	0.523	0.566	0.429	0.418	0.498	0.440
1	0.722	0.492	0.537	0.671	0.381	0.500	0.397	0.384	0.359	0.357	0.412	0.392
1.5	0.735	0.464	0.509	0.666	0.397	0.462	0.407	0.398	0.354	0.357	0.417	0.413
2	0.679	0.447	0.539	0.676	0.444	0.484	0.403	0.409	0.335	0.377	0.405	0.418
3	0.695	0.432	0.502	0.682	0.485	0.525	0.449	0.381	0.333	0.384	0.437	0.427
4	0.695[b]	0.409	0.461	0.659	0.528	0.541	0.445	0.457	0.318	0.411	0.497	0.450
4.5	0.616	0.305	0.372	0.537	0.432	0.518	0.363	0.328	0.256	0.337	0.348	0.382
5	0.509	0.194	0.324	0.480	0.356	0.433	0.250	0.260	0.210	0.254	0.275	0.327
5.5	0.398	0.130	0.220	0.370	0.296	0.379	0.229	0.164	0.148	0.175	0.192	0.238
6	0.349	0.056	0.142	0.320	0.263	0.291	0.143	0.107	0.084	0.123	0.133	0.182
6.5	0.247	0.010	0.087	0.219	0.229	0.225	0.075	0.040	0.040	0.084	0.071	—
7	0.179	0.001	0.026	0.138	0.171	0.188	0.030	0.009	0.071	0.025	0.020	0.056
7.5	0.086	0.0005	0.004	0.061	0.103	0.121	0.006	0.003	0.003	0.004	0.003	0.012
8	0.019	—	0.0008	0.008	0.074	0.060	0.002	0.001	0.0004	0.002	0.001	0.002
8.5	0.003	—	—	0.001	0.034	0.018	0.0007	0.003	0.0003	0.001	0.0008	0.0008

[a] Concentrations in this row are the estimated C_0 values obtained with equation 2, using $V = 600$ ml/kg.
[b] Concentrations in this row are the C_T values used in estimating V with equations 7–17.

Table III. Trapezoidal Areas, A_{∞}, and Estimated Values of V_m, K_m, and V

Cat No.	Study No.	V_m [mg/(ml×hr)]	K_m (mg/ml)	A_{∞} [mg/(ml×hr)]	V (ml/mg)	
1	16	0.210	0.0603	4.25	609	Mean = 571 C.V. (%) = 7.4
	17	0.259	0.0813	2.33	535	
	18	0.172	0.0294	2.82	534	
	19	0.193	0.0414	4.10	607	
2	20	0.138	0.0772	2.90	876	
3	22	0.176	0.0579	2.40	633	
4	25	0.210	0.125	1.90	614	
5	27	0.250	0.129	2.40	483	
				Mean	635	
				C.V. (%)	23.0	
2	21	0.165	0.0634	3.30	799	
3	23	0.211	0.0505	2.26	538	
4	26	0.216	0.111	2.12	550	
5	28	0.159	0.0370	2.50	724	
				Mean	653	
				C.V. (%)	19.8	
				Grand mean	643	
				C.V. (%)	20.3	

653 ml/kg, with a coefficient of variation of 19.8%; when these same cats received ethanol alone, the mean volume of distribution was 652 ml/kg, with a coefficient of variation of 25.5% (paired $t = 0.016$, $p > 0.25$). Hence there was no real evidence that the other drugs administered altered the volume of distribution of ethanol. However, the experimental design was not a good test of alteration of the volume of distribution of ethanol by another drug. If the alcohol infusion had been continued beyond the time of injection of the second drug, as in the studies of Wagner *et al.* (1), the design would have been better to test such an effect.

Table IV lists estimates of total body water in the adult cat taken from Altman and Dittmer (8). The weighted mean total body water is 593 ml/kg, and the mean value for 11 cats, based on the urea method, is 630 ml/kg. These values agree very closely with the volume of distribution of ethanol estimated in our studies (Table III), strongly suggesting (a) that ethanol is distributed in total body water as has been reported before (9,10) and (b) that the method described herein, using ethanol, may be a useful method for determining total body water.

The volume of distribution estimated in such studies by the method outlined is not necessarily just the "V_d of the one-compartment open model." Under the conditions of the studies, various body

Table IV. Estimates of Total Body Water in Adult Cats (8)

No. animals	Total body water (ml/kg)	Method
1	666	Desiccation
1	580	Desiccation
3	677	Desiccation
1	615	Deuterium oxide
8	500	Sodium chloride
11	630	Urea
Weighted mean	593	

"compartments" are essentially "filled" with drug within about a 1-hr period after administration of the bolus intravenous dose and the initiation of the constant-rate intravenous infusion. Hence a multicompartment open model essentially becomes a one-compartment open model within a short time after initiation of the experiment. The fact that there was little, if any, evidence of a distribution phase in the postinfusion data supports this. A similar but linear pharmacokinetic example, with a drug having an apparent elimination half-life of 11.5 hr, was reported by Paalman *et al.* (11); when an infusion of their drug was administered over 0.5 hr, the postinfusion data were fitted by a biexponential equation, but when the same drug was infused over a 24-hr period the postinfusion data were fitted with only a single exponential term. Unfortunately, in that article (11) the captions for Figs. 2 and 3 were reversed.

Table V. Results of Tests for Steady-State Alcohol Levels

Cat No.	Study No.	Time period (hr)	N^a	Slope of C, t plot	t^b	p value	Mean C (mg/ml)	C.V. (%)
1	16	1–4	5	−0.0107	1.19	$p>0.10$	0.705	3.2
	17	1–4	5	−0.0254	6.98	$0.01>p>0.001$	0.449	7.0
	18	1–4	5	−0.0227	2.94	$0.10>p>0.05$	0.510	6.2
	19	1–4	5	−0.00176	0.43	$p>0.25$	0.671	1.3
2	20	1.5–4	4	0.0498	8.25	$0.01>p>0.001$	0.464	12.1
3	22	1–4	5	0.0187	3.74	$0.05>p>0.02$	0.420	5.9
4	25	2–4	3	0.00606	1.89	$p>0.10$	0.329	2.8
5	27	1–4	5	0.0276	3.36	$0.05>p>0.02$	0.434	8.6
2	21	1.5–4	4	0.0321	6.84	$0.05>p>0.02$	0.503	7.2
3	23	1–4	5	0.0178	1.68	$p>0.10$	0.406	7.6
4	26	1–4	5	0.01805	7.02	$0.01>p>0.001$	0.377	5.9
5	28	1–4	5	0.01698	6.66	$0.01>p>0.001$	0.420	5.0

[a] N = number of concentration–time pairs (see Table II) used to estimate the slope of the C, t plot.
[b] t = Absolute value of slope/standard error of slope.

A test was made for attainment of steady-state alcohol blood levels in each of the 12 studies in the cats. The method employed was to test the significance of difference of the slope of the C, t plot from zero by t test in the expected steady-state period. Results are given in Table V. In five (studies 16, 18, 19, 23, and 25) the slope of the C, t plot was not significantly different from zero, indicating attainment of steady state. Table V also lists the mean concentrations and their coefficients of variation calculated from the same concentration values as used to estimate the slopes. There was a strong correlation ($r = 0.949$, $p < 0.001$) for the linear regression of these coefficients of variation vs. the absolute value of the slope. This suggests that the larger coefficients of variation were associated with lack of attainment of steady state and were not the result of error in the essay.

APPENDIX

```
      PROGRAM MAIN(INPUT,OUTPUT,TAPE5=INPUT,TAPE6=OUTPUT)
C     THE PROGRAM TO CALCULATE THE VOLUME OF DISTRIBUTION
C     WRITTEN BY YI-JONG LIN  20 JULY, 1976
C     KO IS THE INFUSION RATE , MG OF ALCOHOL/KG/HOUR
C     VM IS THE MAXIMAL VELOCITY OF MICHAELIS-MENTEN KINETICS , MG/ML*HR
C     KM IS THE IN VIVO MICHAELIS CONSTANT , MG/ML
C     CO IS THE ALCOHOL CONCENTRATION AT ZERO TIME
C     CT IS THE ALCOHOL CONCENTRATION WHEN INFUSION WAS CEASED
C     XT IS THE TIME WHICH ALCOHOL INFUSION WAS CEASED
C     AREA IS THE AREA UNDER THE BLOOD CONCENTRATION CURVE FROM
C     0 HOUR TO INFINITE
C     VO IS THE STARTING POINT FOR V
      REAL KO,KM
    7 READ(5,101) ID
      IF(EOF(5))470,999
  999 CONTINUE
  101 FORMAT(I10)
      WRITE(6,212)ID
  212 FORMAT(1H1,"ALCOHOL STUDY WITH CAT NO.",I10)
      READ(5,100)KO,VM,KM,CO,CT,XT,AREA,VO
  100 FORMAT(8F10.5)
      WRITE(6,210)
  210 FORMAT(////8X,"KO",10X,"VM",10X,"KM",10X,"CO",10X,"CT",10X,"XT",
     18X,"AREA",10X,"VO")
      WRITE(6,211)KO,VM,KM,CO,CT,XT,AREA,VO
  211 FORMAT(//8(2X,F10.5))
      A=VM**2.0*(AREA*VM-CT**2.0-(CO**2.0)/2.0+CO*CT+KM*CT-KM*CO-
     1VM*CT*XT-CT*KM)
      B=KO*VM*(3.0*KM*CT+5.0*CT**2.0)/2.0+3.0*VM*CT*XT+KM*CO-KM*CT-
     12.0*CO*CT+CO**2.0-3.0*AREA*VM)
      C=KO**2.0*(3.0*AREA*VM-2.0*CT**2.0-(CO**2.0)/2.0+CO*CT-3.0*VM*CT
     1*XT-3.0*CT*KM)
      D=(KO**3.0/VM)*((CT**2.0)/2.0+CT*KM+VM*CT*XT-AREA*VM)
      E=KM*VM**2.0*CT
      F=-(KO*KM**2.0*VM+KO*VM*KM*CT)
      G=KO*CO+KO*KM
      H=VM*CO
      XI=KO*CT+KO*KM
      XJ=VM*CT
      WRITE(6,203)
  203 FORMAT(/" THE EQUATION WAS F(V)=A*V**3.0+B*V**2.0+C*V+D+(E*V**3.0+
     1F*V**2.0)LN((G-H*V)/(XI-XJ*V))")
      WRITE(6,204)
```

```
  204 FORMAT(//8X,"A",14X,"B",14X,"C",14X,"D",14X,"E",14X,"F",14X,
     1"G",14X,"H")
      WRITE(6,201)A,B,C,D,E,F,G,H
  201 FORMAT(//8F15.5)
      WRITE(6,205)
  205 FORMAT(//7X,"XI",13X,"XJ",13X,"VO")
      WRITE(6,202)XI,XJ,VO
  202 FORMAT(/3F15.5)
      V=VO
    1 IF(V .GT. 900.) GO TO 30
      FL=((G-H*V)/(XI-XJ*V))
      IF(FL-0.0)50,40,40
   40 FLN=ALOG(FL)
      FV=A*V**3.0+B*V**2.0+C*V+D+(E*V**3.0+F*V**2.0)*FLN
      IF(ABS(FV)-5.00)20,20,10
   10 V=V+1.
      GO TO 1
   20 WRITE(6,200)V
  200 FORMAT(/" THE ESTIMATE VOLUME OF DISTRIBUTION WAS =",F10.2,"ML/KG"
     1)
      V=V+1.
      GO TO 1
   30 WRITE(6,220)
  220 FORMAT(/" THE GOOD ESTIMATE VOLUME OF DISTRIBUTION WAS NOT FOUND")
      GO TO 7
   50 WRITE(6,221)
  221 FORMAT(/" FL WAS NEGATIVE THE ESTIMATE VOLUME OF DISTRIBUTION WAS
     1 NOT FOUND")
      GO TO 7
  470 STOP
      END
```

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