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PHARMACOKINETIC DATA

Pharmacokinetic Parameters Estimated from Intravenous Data by Uniform Methods and Some of Their Uses

John G. Wagner[1,3] and coworkers[2]

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This article summarizes pharmacokinetic parameters of 20 different drugs. The parameters were estimated by uniform methods for an n*-compartment open mammillary model in which elimination was assumed to occur only from the central compartment. For various reasons, some of the reported parameters differ appreciably from those reported in the original articles. Some uses of the parameters are discussed.*

KEY WORDS: pharmacokinetic parameters; volumes of distribution; steady-state plasma levels; loading doses; intravenous infusion doses.

INTRODUCTION

This article summarizes pharmacokinetic parameters of 20 different drugs. The parameters were estimated by uniform methods for an n-compartment open mammillary model in which elimination was assumed to occur only from the central compartment. For various reasons, some of the reported parameters differ appreciably from those reported in the original articles. Some uses of the parameters are discussed.

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[1]College of Pharmacy and Upjohn Center for Clinical Pharmacology, The University of Michigan, Ann Arbor, Michigan 48109.

[2]See Acknowledgments.

[3]Address correspondence to Dr. John G. Wagner, Upjohn Center for Clinical Pharmacology, University of Michigan Center, Ann Arbor, Michigan 48109.

EXPERIMENTAL

Raw Data

The raw data were either obtained from the original articles or obtained after request from the senior author. The drugs and references are as follows: ampicillin (1), diazepam (2), diphenhydramine (3), nortriptyline (4), phenytoin (5), tranexamic acid (6), warfarin (7), acetylsalicylic acid and salicylic acid (8), cefazolin (9), clindamycin phosphate and tobramycin (10,11), digoxin (12–16), griseofulvin (17), pentobarbital (18), pindolol (19), quercetin (20), spectinomycin (21), sulfisoxazole (22), and cephalexin (23).

Methods

For acetylsalicylic acid (8), diazepam (2), digoxin (12), griseofulvin (17), and salicylic acid (8), the coefficients and exponents of the polyexponential equations which the original authors had fitted to the data were employed.

In all other cases, the procedure was as follows. Each set of plasma (or serum) concentration–time data observed either following bolus intravenous injection or subsequent to the termination of a constant-rate intravenous infusion was evaluated by the program CSTRIP (24) and a digital computer. The operator requested the program to print out the optimum polyexponential equation for one, two, three, and four exponential terms. The "optimum," decided by the program, is the equation which arises from the grouping of the points for each exponential term which yields the minimum sum of squared deviations. For each data set, the operator then decided the appropriate number of exponential terms for a nonlinear least-squares fit. The latter was usually decided by the regression analysis of $\hat{C}$ vs. C and use the percentage improvement in r_2^2, the coefficient of determination, which is printed out by the program; criteria used in the decision are shown in Table I.

In practice, in most cases the decision was made quite easily, since, for example, if the optimum number of terms was two, the r_2^2 value for the two-term equation was higher than for a three-term or four-term equation. Sometimes an asymptotic r_2^2 value was reached at the two-term level such that the r_2^2 values for the two-term, three-term, and four-term polyexponential equations were the same. Each set of data was then fitted to the appropriate polyexponential equation using the program NONLIN (25) and a high-speed digital computer; the preliminary estimates of the coefficients and exponents used as input for NONLIN were those obtained from the program CSTRIP. If there was any doubt about the required number of

Table I. Goodness-of-Fit Criteria to Estimate the Number of Exponential Terms Needed

r_2^2 value for polyexponential equation with n terms[a]	Percent improvement in r_2^2 value required to choose a polyexponential equation with $n+1$ terms
$r_2^2 \leq 0.75$	10
$0.75 < r_2^2 \leq 0.90$	5
$0.90 < r_2^2 \leq 0.95$	2.5
$0.95 \leq r_2^2$	1.5

[a] r_2^2 = coefficient of determination

$$= 1 - \left\{ \sum_{i=1}^{m} (C_i - \hat{C}_i)^2 \Big/ \sum_{i=1}^{m} C_i^2 - \left[\left(\sum_{i=1}^{m} C_i \right)^2 \Big/ m \right] \right\}$$

where m is the number of plasma concentration measurements.

exponential terms needed, then NONLIN least-squares fits with both n and $n+1$ terms were obtained and the F test described by Boxenbaum *et al.* (26) was used. In each fitting, the squared deviations were weighted according to the reciprocals of the observed concentrations. All fittings were performed to the general polyexponential equation 1 for bolus intravenous data and to equation 2 for post-constant-rate infusion data.

$$C_p = \sum_{i=1}^{n} C_i e^{-\lambda_i t} \tag{1}$$

$$C_p = \sum_{i=1}^{n} Y_i e^{-\lambda_i t} \tag{2}$$

In equations 1 and 2, C_p symbolizes the plasma (or serum) concentration at time t, C_i is the coefficient of the ith exponential term for bolus intravenous data, Y_i is the coefficient of the ith exponential term for post constant-rate intravenous infusion data, and λ_i is the exponent of the ith exponential term.

If only one infusion had been administered over T hours, then the equation of the form of equation 2, obtained from postinfusion data, was converted to the corresponding equation 1 (simulating the situation if the total infused dose had been given as a bolus intravenous injection) by use of

$$C_i = \lambda_i T Y_i / (e^{+\lambda_i T} - 1) \tag{3}$$

Such a correction of the coefficients should be made even though only very short infusions have been administered. Several authors (6, 18, 20) failed to adjust the coefficients by means of equation 3 (or did not fit data to an equation which was appropriate for an infusion), and hence all their reported pharmacokinetic parameters were subject to error.

In the case of nortriptyline (4), multiple infusions were administered. Five infusions, each containing 11.4 mg of nortriptyline hydrochloride in 25 ml of saline, were given over 10-min periods with intervals of 5 min between infusions. In this case, C_p is given by

$$C_p = \sum_{i=1}^{n}\left[\frac{C_i}{\lambda_i\theta q}\left\{\frac{[e^{+\lambda_i q}-1][e^{+\lambda_i m'(p+q)}-1]}{[e^{+\lambda_i(p+q)}-1]}+e^{+\lambda_i t^*}-e^{+\lambda_i m'(p+q)}\right\}\right]e^{-\lambda_i t}$$

$$= \sum_{i=1}^{n} Z_i\, e^{-\lambda_i t} \tag{4}$$

where Z_i represents everything within the square brackets and the coefficient is obtained by fitting postinfusion data. Equation 5 was then used to convert the Z_i values to C_i values:

$$C_i = \lambda_i\theta q Z_i/\{P_i\} \tag{5}$$

where $\{P_i\}$ represents everything in the same type of braces in equation 4. In equation 4, $q = 10$ min (0.166 hr) and is the duration of each infusion; $p = 5$ min (0.083 hr) and is the interval between infusions, $p+q = 0.25$ hr; $m' = 4$ and is the number of $p+q$ periods; $t^* = 1.166$ hr $= (\theta-1)(p+q)+q$; $\theta = 5$ and is the number of infusion periods; and t is the time from the start of the first infusion.

The pharmacokinetic parameters were calculated using equations 6–11, reported by Wagner (27).

$$V_p = D\Big/\sum_{i=1}^{n} C_i \tag{6}$$

$$V_{dss} = D\sum_{i=1}^{n} C_i/\lambda_i^2\Big/\left[\left(\sum_{i=1}^{n} C_i/\lambda_i\right)^2\right] \tag{7}$$

$$V_{d\text{area}} = D/\left(\lambda_1\sum_{i=1}^{n} C_i/\lambda_i\right) \tag{8}$$

$$V_{d\text{ext}} = D/C_1 \tag{9}$$

$$\text{Cl}_p = D\Big/\sum_{i=1}^{n} C_i/\lambda_i \tag{10}$$

$$t_{1/2} = 0.693/\lambda_1 \tag{11}$$

In equations 6–11, D is the intravenous dose; C_1 and λ_1 are the coefficient and exponent, respectively, such that λ_1 is the smallest of the λ_i's of the polyexponential equation; V_p is the volume of the plasma (reference) compartment, V_{dss} is the volume of distribution steady state; $V_{d\text{area}}$ is that volume which, when multiplied by C_p in the log-linear phase (when only

$C_1 e^{-\lambda_1 t}$ is making a significant contribution to C_p), is equal to the amount of drug in the body, and also such that $Cl_p = V_{d\text{area}} \cdot \lambda_1$; $V_{d\text{ext}}$ is the extrapolated volume of distribution; Cl_p is the plasma (or serum) clearance; and $t_{1/2}$ is the apparent elimination half-life.

In order to avoid arithmetic errors, equations 6–11 were programmed on an electronic calculator. Input was the dose and the coefficients and exponents; output was the left-hand sides of equations 6–11 in numerical form. In addition, the students calculated the parameters separately, providing an additional check on accuracy.

RESULTS

The numbers of exponential terms used in the NONLIN fittings are summarized in Table II.

Table II. Number of Exponential Terms in Polyexponential Equations

Drug	Number of data sets giving the indicated number of exponential terms			Coefficients and exponents used
	1	2	3	
Ampicillin[a]		8		T[c]
Diazepam[a]			4	O[d]
Diphenyhydramine[b]		2		T
Nortriptyline[b]		4		T
Phenytoin[a]			6	T
Tranexamic acid[b]		2		T
Warfarin[a]		9		T
Tobramycin[b]	2	3		T
Acetylsalicylic acid[a]		6		O
Cefazolin[a]		5		T
Clindamycin phosphate[b]	2	8		T
Digoxin[a,b]		18		T(2), O(16)
Griseofulvin[a]		8		O
Cephalexin[b]		8		T
Pentobarbital[b]		5		T
Pindalol[b]	2	3		T
Quercetin[b]		6		T
Salicylic acid		4		O
Spectinomycin[a]		5		T
Sulfisoxazole[a]		7		T

[a] Bolus intravenous data evaluated.
[b] Post constant-rate intravenous infusion data evaluated.
[c] T = This study (means coefficients and exponents obtained by methods outlined in this article).
[d] O = Original (means that the coefficients and exponents reported in the original article were used).

In all cases reported, the NONLIN fits of individual data sets were excellent as judged by the r_1^2 values obtained:

$$r_1^2 = 1 - \left[\sum_{i=1}^{m} (C_i - \hat{C}_i)^2 \Big/ \sum_{i=1}^{m} C_i^2 \right]$$

These usually exceeded 0.995. Several of the data sets of clindamycin phosphate in subjects under dialysis and in uremic subjects and of pentobarbital fell in the region $0.988 < r_1^2 < 0.995$.

The data of subject 3, given cefazolin (9), were excluded, since the fit was not good ($r_1^2 = 0.861$, Corr = 0.982), particularly at the tail end of the curve.

Table III lists doses and pharmacokinetic parameters for eight drugs where data came from articles which listed the body weights of the individual subjects or patients. For these eight drugs, the volumes are given in liters/kg and the clearance in liters/(kg × hr); this is a distinct advantage since such parameters usually have smaller coefficients of variation than corresponding values expressed in liters and liters/hr, respectively.

Tables IV and V list doses and pharmacokinetic parameters of 12 drugs where the data came from articles which did not list the body weights of individual subjects. Hence for these drugs volumes are given in liters and clearances in liters/hr. Tables III–V also list the number of subjects or patients for which data were evaluated, the type of subjects or patients, and the mean, range, and coefficient of variation of each estimated parameter.

The data given in Table IV for digoxin were calculated using the coefficients and exponents of biexponential equations reported by Koup *et al.* (12); these were obtained by the simultaneous fitting of both serum concentration and urinary excretion data. The individual subject values calculated in this study are listed in Table VI, along with variance ratios (F values) and results of paired t tests comparing bolus intravenous and infusion methods. It should be noted that paired t tests are valid even when the variances are not homogeneous (i.e., the F value is significant at $p \leq 0.05$). Table VII lists the digoxin pharmacokinetic parameters obtained from postinfusion data of Wagner *et al.* (16). Table VIII lists (for the first time) the apparent elimination half-lives of digoxin estimated from terminal oral data following digoxin tablets (Burroughs & Wellcome) in the study of Wagner *et al.* (16).

DISCUSSION

There is no doubt that the method of data analysis used in this article results in improved parameter estimates. However, they are still potentially subject to computer- and methodological-derived error. The NONLIN is

Table III. Summary of Pharmacokinetic Parameters Calculated from Plasma (or Serum) Concentrations After Bolus Intravenous Injection or Post Constant-Rate Intravenous Infusion: Drugs from Articles Where Body Weights of Subjects Were Given

	Ampicillin	Diazepam[a]	Diphen-hydramine	Nortriptyline	Phenytoin	Tranexamic acid	Warfarin	Tobramycin
Number of subjects	8	4	2	4	6	2	6 (9 data sets)	5
Dose (mg/kg)								
Mean	8.75	0.135	0.517	0.742	3.9	14.6	2.4	1
Range	6.60–11.6	0.113–0.157	0.462, 0.572	0.663–0.803	3.4–4.4	14.5, 14.6	0.714–8.00	None
C.V. (%)	21.7	17.0	—	7.8	9.5	—	92.3	—
V_p (liters/kg)								
Mean	0.186	0.339	1.46	5.81	0.204	0.130	0.0725	0.262
Range	0.146–0.259	0.205–0.498	0.854, 2.07	3.92–6.81	0.0912–0.323	0.129, 0.130	0.0510–0.0981	0.140–0.314
C.V. (%)	20.3	35.7	—	22.8	44.2	—	20.1	27.3
V_{dss} (liters/kg)								
Mean	0.286	1.62	2.98	20.3	0.541	0.229	0.110	0.339
Range	0.235–0.375	1.36–1.79	2.69, 3.27	16.2–25.8	0.480–0.583	0.192, 0.266	0.0875–0.128	0.257–0.455
C.V. (%)	14.3	11.2	—	21.0	7.4	—	10.5	26.4
V_{darea} (liters/kg)								
Mean	0.475	1.87	3.68	21.1	0.574	0.241	0.111	0.346
Range	0.292–0.823	1.62–2.05	2.98, 4.38	17.2–26.7	0.496–0.656	0.195, 0.286	0.0881–0.131	0.257–0.464
C.V. (%)	42.2	10.1	—	20.0	11.4	—	11.0	26.1
V_{dext} (liters/kg)								
Mean	1.26	2.18	4.93	22.1	0.624	0.255	0.112	0.353
Range	0.334–3.57	1.96-2.57	3.32, 6.53	18.3–27.7	0.513–0.776	0.199, 0.310	0.0887–0.135	0.257–0.474
C.V. (%)	90.4	12.5	—	19.1	18.7	—	11.6	26.0
Cl_p [liters/(kg × hr)]								
Mean	0.289	0.0417	0.517	0.672	0.0231	0.169	0.00280	0.0168
Range	0.232–0.348	0.0374–0.0476	0.499, 0.584	0.572–0.879	0.0177–0.0313	0.158–0.180	0.00142–0.0052	0.011–0.023
C.V. (%)	16.0	11.0	—	21.6	24.7	—	48.9	29.2
$t_{1/2}$ (hr)								
Mean	1.18	31.3	5.16	22.5	17.8	1.01	33.1	15.2
Range	0.71–2.23	26.7–36.5	3.54, 6.77	14.7–27.8	14.3–22.3	0.754, 1.26	16.2–52.1	8.99–21.4
C.V. (%)	50.3	13.9	—	26.9	16.8	—	41.2	35.6
Type of subjects	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Chronic renal on dialysis

[a] Based on whole blood levels.

Table IV. Summary of Pharmacokinetic Parameters Calculated from Plasma (or Serum) Concentrations After Bolus Intravenous Injection or Post Constant-Rate Intravenous Infusion: Drugs from Articles Where Body Weights of Subjects Were Not Given

			Clindamycin phosphate				
	Acetylsalicylic acid	Cefazolin	Peritoneal dialysis	Uremics	Digoxin	Griseofulvin	Cephalexin
Number of subjects	5 (6 data sets)	5	3	7	8 (16 data sets)	5 (8 data sets)	8
Dose (mg)							
Mean	—	1000	600	300	0.75	119	1000
Range	325 or 650	—	—	—	—	58–180	—
C.V. (%)	—	—	—	—	—		—
V_p (liters)							
Mean	6.4	5.15	41.7	21.4	35.7	54	11.3
Range	5.5–7.6	0.41–7.74	39.5–45.6	16.3–28.0	21.6–61.6	42–64	8.41–15.7
C.V. (%)	13	57.9	8.1	20.2	26.6	15	30.8
V_{dss} (liters)							
Mean	11	8.23	52.7	44.7	608	103	24.4
Range	9.4–13	5.43–10.3	39.5–75.1	20.1–87.8	418–792	92–115	11.7–36.9
C.V. (%)	13	24.4	37.0	60.4	18.0	7.7	35.2
V_{darea} (liters)							
Mean	15	9.79	61.1	57.4	754	115	38.4
Range	13–19	8.16–11.5	39.5–99.9	20.1–109	440–1120	97–135	14.5–59.7
C.V. (%)	15	21.6	55.2	65.2	24.3	11	41.1
V_{dext} (liters)							
Mean	21	12.2	76.5	88.7	944	130	69.3
Range	16–30	8.85–16.7	39.5–146	20.1–160	503–1596	104–164	18.6–112
C.V. (%)	23	26.6	78.7	65.9	32.4	16	45.5
Cl_p (liters/hr)							
Mean	40.8	3.76	12.5	5.01	12.9	6.3	14.9
Range	37–42	3.33–4.19	8.21–18.8	2.72–7.06	7.21–24.6	3.4–9.0	11.8–20.4
C.V. (%)	4.6	11.3	44.6	43.3	35.2	37	20.0
$t_{1/2}$ (hr)							
Mean	0.25	1.80	3.84	11.0	42.1	14	1.86
Range	0.23–0.32	1.47–2.20	1.62–6.60	2.48–31.5	31.5–53.3	9.2–20	0.673–3.50
C.V. (%)	13	15.1	65.9	104	18.2	28	50.0
Type of subjects	Normal	Normal	Chronic renal (on dialysis)	Uremics	Normal	Normal	Normal

Table V. Summary of Pharmacokinetic Parameters Calculated from Plasma (or Serum) Concentrations After Bolus Intravenous Injection or Post Constant-Rate Intravenous Infusion: Drugs from Articles Where Body Weights of Subjects Were Not Given

	Pentobarbital	Pindolol	Quercetin	Salicylic acid	Spectinomycin	Sulfisoxazole
Number of subjects	5	5	6	4	5	7
Dose (mg)						
Mean	50	5	100	500	500	2000
Range	—	—	—	484–508	—	—
C.V. (%)	—	—	—	2.3	—	—
V_p (liters)						
Mean	41.7	121	20.9	5.43	4.28	8.69
Range	37.1—46.7	45.2–233	11.2–38.4	4.81–5.90	2.89–6.27	7.17–10.3
C.V. (%)	9.9	70.7	48.4	8.9	35.0	13.3
V_{dss} (liters)						
Mean	122	142	66.9	9.10	8.63	12.0
Range	94.5–147	58.4–233	31.0–135	8.19–10.1	5.98–10.5	7.51–14.3
C.V. (%)	18.8	52.4	53.1	9.6	22.3	20.2
V_{darea} (liters)						
Mean	124	154	77.2	9.19	10.5	13.8
Range	96.0–148	63.3–233	34.7–146	8.26–10.2	6.38–15.3	8.22–16.0
C.V. (%)	18.4	46.5	47.7	9.6	34.7	25.4
V_{dext} (liters)						
Mean	126	182	99.1	9.29	13.9	17.2
Range	97.9–150	70.0–233	39.1–158	8.33–10.4	6.83–26.6	11.7–30.5
C.V. (%)	18.1	37.2	43.6	10.0	57.5	41.0
Cl_p (liters/hr)						
Mean	1.80	32.1	47.2	1.41	4.73	1.49
Range	1.39–2.77	18.0–47.3	19.4–90.9	1.35–1.50	3.40–4.84	1.18–1.88
C.V. (%)	31.6	37.1	63.2	4.5	12.9	15.5
$t_{1/2}$ (hr)						
Mean	51.5	3.23	1.55	4.53	1.66	6.49
Range	26.5–73.6	2.44–4.17	0.506–3.65	4.13–5.25	0.96–2.19	4.28–10.0
C.V. (%)	35.6	24.3	80.7	11.0	29.2	29.6
Type of subjects	Normal	Normal	Normal	Normal	Normal	Normal

Table VI. Pharmacokinetic Parameters for Digoxin Calculated Using the Coefficients and Exponents Reported by Koup *et al.* (12) Where B Represents Bolus Intravenous Injection and I Represents Infusion

	6-day urinary excretion[a] (μg)		V_p(liters)		V_{dss} (liters)		$V_{d\ area}$(liters)		Cl_p(liters)		$t_{1/2}$(hr)		Total AUC [(ng/ml)×hr]	
Subject	B	I	B	I	B	I	B	I	B	I	B	I	B	I
RRM	516	636	31.9	31.0	584	690	726	809	13.1	10.5	38.5	53.3	57.4	71.3
JMS	623	606	48.2	32.9	651	623	806	769	13.7	13.8	40.8	38.5	54.8	54.2
RRG	601	612	31.7	26.4	385	584	440	686	8.36	9.60	36.5	49.5	89.7	78.1
DJG	588	588	61.6	33.3	792[b]	764	1120	1048	24.6[b]	16.8	31.5[b]	43.3	30.4[b]	44.7
JKW	587	635	44.8	21.6	615[b]	645	704	797	12.0	11.2	40.8	49.5	62.7	67.2
DWD	560	614	33.5	39.6	500	669	554	772	7.21	12.4	53.3	43.3	104	60.7
JR	565	610	33.2	28.2	532	621	599	902	7.79	18.0	53.3	34.7	96.3	41.6
AJS	491	576	38.4	35.1	418	652	485	846	10.2	17.8	33.0	33.0	73.6	42.2
Mean	566	610	40.4	31.0	560	656	679	829	12.1	13.8	41.0	43.1	71.1	57.5
C.V. (%)	7.8	3.4	26.1	18.0	23.5	8.3	32.0	13.1	46.2	24.5	20.4	17.1	34.7	24.4
F[c]	4.56		3.60		5.86		4.01		2.75		1.27		3.08	
	($0.05>p>0.025$)		($0.10>p>0.05$)		($0.025>p>0.01$)		($0.05>p>0.025$)		($p\approx0.10$)		($p>0.25$)		($0.10>p>0.05$)	
Paired t	2.71		2.26		2.72		2.68		0.80		0.51		1.45	
	($0.05>p>0.02$)		($0.10>p>0.05$)		($0.05>p>0.02$)		($0.05>p>0.02$)		($p>0.25$)		($p>0.25$)		($p>0.10$)	
Overall mean	588		35.7		608		754		12.9		42.1		64.3	
Overall C.V.(%)	6.8		26.6		18.0		24.3		35.2		18.2		32.1	

[a] Means are considerably different than those reported by Greenblatt *et al.* (14).
[b] Value is considerably different than that calculated from the same data by Koup *et al.* (12).
[c] F = variance ratio.

Table VII. Pharmacokinetic Parameters of Digoxin Calculated from the Coefficients and Exponents of Biexponential Equations Fitted to the Postinfusion Data of Wagner *et al.* (16)

Parameter	Subject 1	Subject 2	Average
V_p (liters)	90.8	69.0	79.9
V_{dss} (liters)	739	759	749
V_{darea} (liters)	813	842	828
Cl_p (liters)	10.7	12.0	11.4
$t_{1/2}$ (hr)	52.5	48.8	50.7[a]
AUC [(ng/ml) × hr]	44.6	41.8	43.2[b]

[a] The average and range from the data of Koup *et al.* (12) was 42.1 (33.0–53.3) hr.
[b] The average for the 0.75-mg dose from the data of Koup *et al.* (12) was 64.3, which is equivalent to (0.5/0.75) × 64.3 = 42.9 for a 0.5-mg dose, hence agreement is excellent.

Table VIII. Apparent Elimination Half-Lives of Digoxin Estimated from Digoxin Plasma Concentrations in the 24–96 hr Time Range and 0.04–0.3 ng/ml Concentration Range Following Oral Administration of Lanoxin Tablets in the Study of Wagner *et al.* (16)

Subject	Half-life (hr)
1	38.7
2	30.1
3	33.3
4	34.3
5	69.1
6	42.2
7	72.8
8	25.9
Mean	43.3[a] (38.3)[b]
C.V. (%)	41.1

[a] The average (and range) in the intravenous study of Koup *et al.* (12) was 42.1 (33.0–53.3) hr, hence agreement is excellent.
[b] Value in parentheses is the harmonic mean half-life.

one of the better programs for nonlinear analysis, but is still subject to false minima. Fell and Stevens (28) showed that the NONLIN program resulted in relatively poor estimates of the parameters from data derived for one- and two-body-compartmental models. The use of r^2 for selection of the number of exponential terms and as a criterion of fit is subject to error since it is a measure of overall fit to the model.

Variability of Parameters

Of the volumes V_{dss}, V_{darea}, and V_{dext}, there is a general tendency for the coefficients of variation (C.V.) to increase in the order given, as well as the magnitudes of the volumes. That is, in general, V_{dss} not only is the smallest of these three volumes but also has the smallest C.V. This is fortunate since V_{dss} is probably the most useful volume pharmacokinetically. The C.V. of V_{dss} is less than the C.V. of V_{darea} for ampicillin, phenytoin, digoxin, griseofulvin, cephalexin, spectinomycin, and sulfisoxazole. The C.V. of V_{dss} is approximately equal to the C.V. of V_{darea} for diazepam, nortriptyline, warfarin, tobramycin, ASA, clindamycin phosphate, pentobarbital, quercetin, and salicylic acid.

The C.V. of Cl_p is greater than the C.V. of V_{dss} for phenytoin, warfarin, digoxin, griseofulvin, pentobarbital, and quercetin. The C.V. of Cl_p is approximately equal to the C.V. of V_{dss} for ampicillin, diazepam, nortriptyline, tobramycin, and clindamycin phosphate. The C.V. of V_{dss} is greater than the C.V. of Cl_p for ASA, cefazolin, pindolol, salicylic acid, spectinomycin, and sulfisoxazole (see Tables III–V).

As pointed out earlier by Koup *et al.* (12), the C.V. of each pharmacokinetic parameter when digoxin was given by intravenous infusion is less than the corresponding C.V. when the drug was given by bolus intravenous injection (see Table VI). The variance ratios for bolus/infusion are significant ($p \leq 0.05$) for 6-day urinary excretion, V_{dss}, and V_{darea}, but are not significant ($p > 0.05$) for V_p, Cl_p, $t_{1/2}$, and AUC.

The variabilities of the pharmacokinetic parameters for tobramycin (Table III) and clindamycin phosphate (Table IV) in chronic renal patients undergoing dialysis are quite large, indicating considerable patient-to-patient variability.

V_{dext}

The extrapolated volume of distribution, V_{dext}, is probably the most common "volume of distribution" reported in the medical literature, yet it is the most inappropriate volume from a pharmacokinetic standpoint. Many assume that $Cl_p = V_{dext} \cdot \lambda_1$, but this has no foundation in pharmacokinetic theory. If the model is the simple one-compartment open model, then $V_{dext} = V_{darea} = V_{dss}$ and the clearance is equal to $V_{dext} \cdot \lambda_1$. However, in all other cases $Cl_p = V_{darea} \cdot \lambda_1$. Hence, in most cases, the only time that V_{dext} is useful in a pharmacokinetic sense is when V_{dext} is only slightly larger than V_{darea} and can be used as an estimate of V_{darea}. Of the 20 drugs studied, this approximation holds for only seven drugs (35%), namely for nortriptyline, tranexamic acid, warfarin, tobramycin, griseofulvin, pentobarbital, and salicylic acid (see Tables III–V). For the other 13 drugs, V_{dext} is of little use pharmacokinetically, except as noted below (see equation 17).

Use of Equations 3–5

Readers' attention is drawn to the importance of applying equations 3–5 to infusion data, even though constant-rate infusions are given over only a few minutes. A bolus injection in the pharmacokinetic sense means injection of the entire dose all at once at zero time, and the bolus intravenous equations have been derived with that assumption. In applying equation 3, the biggest difference in the Y_i's and corresponding C_i's will occur with Y_2 and C_2 for a biexponential equation and in Y_2 and C_2 and Y_3 and C_3 for a triexponential equation. Also, if the investigator wishes to give a short infusion for safety purposes, the infusion should be administered at a constant rate and the infusion time accurately determined for each subject, so that equation 3 may be applied correctly.

Reporting Body Weights

It is a distinct advantage to report the body weights of individual subjects or patients in pharmacokinetic papers. The C.V.'s of the various pharmacokinetic parameters are almost always lower when corrections have been made for body weight than when they have not. This was tested with the drugs given in Table III and found to be true, and that is why the volumes are expressed in units of liters/kg and the clearances in liters/(kg × hr). Thus, if one is going to make estimates for a particular subject or patient from the tabled numbers, the body weight corrected value multiplied by the particular patient's body weight will provide a better estimate of a mean value and the possible range of the value. It is suggested that journal editors accept pharmacokinetic articles only when individual body weights have been listed. The senior author of this article also believes that all raw data should be included in an article, particularly when they are intravenous data. Showing data in graphical form does not allow future reevaluation of data, such as is done in this article. It is really the raw data which have archival value, not someone's interpretation of the data. Theory and methods change with time, and reevaluation of data is often necessary at some later date. In the present instance, the senior author believed such a comparison of pharmacokinetic parameters should be done only when all data were evaluated by uniform methods.

Number of Exponential Terms

The type of data evaluated (i.e., either bolus intravenous or postinfusion) and the number of exponential terms used in the fittings are summarized in Table II. The table also indicates whose exponents and coefficients were used in applying equations 6–11.

It should be noted that the same number of exponential terms are not always required to fit each member's data in a given panel administered a given drug. In the case of tobramycin, clindamycin phosphate, and pindolol, two data sets for each drug required only one exponential term, while the remainder required two exponential terms. We evaluated the phenytoin data of Gugler *et al.* (5) with triexponential equations, whereas the original authors used biexponential equations. Although the data evaluated for both phenytoin and salicylic acid fit the linear model at the low doses employed, it should be realized that these drugs obey Michaelis–Menten kinetics at higher doses.

Digoxin

Koup *et al.* (12) stated: "Urinary excretion data are essential for proper pharmacokinetic analysis of digoxin disposition and reveal a slower elimination rate than that suggested by earlier studies which determined only serum concentrations." This statement is true for the earlier study of Kramer *et al.* (13), but not for the earlier study of Wagner *et al.* (16). The reason lies in the assay method published by Stoll *et al.* (29), which showed that lower plasma and serum levels of digoxin can be measured than those reported by either Kramer *et al.* (13) or Koup *et al.* (12). The pharmacokinetic parameters, particularly Cl_p, $t_{1/2}$, and AUC, estimated from the plasma digoxin concentrations after bolus intravenous administration in the study of Wagner *et al.* (16), shown in Table VII, are very similar to those obtained from the data of Koup *et al.* (12), shown in Table VI. Also, the apparent elimination half-lives of digoxin, not formerly reported but now shown in Table VIII, which were estimated from plasma digoxin concentrations measured by radioimmunoassay (29) following oral dosing with digoxin (Burroughs & Welcome tablet) are essentially the same as those reported by Koup *et al.* (12). As indicated by the table heading of Table VIII, the log-linear phase of digoxin elimination does not commence until about 24 hr, when the digoxin concentration is about 0.3 ng/ml, requiring a more sensitive assay than the routine radioimmunoassay and sampling each day in the 24–96 hr range after a single dose. In the studies of Kramer *et al.* (13), digoxin concentrations were measured down only to about 0.5 ng/ml, and in the studies of Koup *et al.* (12) concentrations in serum were measured down only to about 0.3 ng/ml.

Greenblatt *et al.* (14) recommended use of digoxin given by slow infusion over a 1-hr period and 6-day urinary excretion of apparent digoxin as bioavailability standard. Table VI, derived from the data of Koup *et al.* (12), indicates that mean 6-day urinary excretion of apparent digoxin was 566 μg for bolus and 610 μg for infusion; the 8% difference is significant

($0.05 > p > 0.02$) by paired t test. However, in both cases the C.V.'s are very small, being 7.8% for bolus and 3.4% for infusion. It should also be noted that the total AUC (obtained by integrating the polyexponential equations between the limits of 0 and ∞) averages 71.1 for *bolus* and 57.5 for *infusion*—a 24% difference, which did not test significant ($0.10 > p > 0.05$). Stoll and Wagner (15) pointed out that the bolus–infusion difference in 6-day urinary excretion could be caused by the nonspecific radioimmunoassay used (26) and the higher ratio of metabolites/digoxin in urine than in plasma.

USE OF THE PHARMACOKINETIC PARAMETERS

Baseline Data for Disease State Studies

Most of the tabled values were calculated from data obtained when normal volunteers were given the drugs intravenously. Hence they may serve as baseline data for comparison purposes with similar values estimated from data obtained after administration of the same drugs intravenously to patients with various specific diseases.

Constant-Rate Intravenous Infusion Therapy

The mean values of the parameters may be most useful for *initiating* therapy with one of the drugs in a given patient. Some examples are given below, but these are not intended to be exhaustive or complete.

1. A safe method for rapidly achieving a desired steady-state plasma concentration, C_p^{ss}, for drugs whose plasma concentration is describable by a biexponential equation was given by Wagner (30). The solution is such that the steady state is achieved as rapidly as possible after a final infusion rate is commenced. The method involves administration of two consecutive constant-rate infusions—one at a rate Q_1 over T hours, and the second at a rate Q_2 starting at T hours and maintained as long as steady state is desired. The needed infusion rates are calculated with equations 12 and 13, using the nomenclature of this article. Suggestions for choosing the time T were given in the original article (30). The method was later generalized by Vaughan and Tucker (31).

$$Q_2 = \mathrm{Cl}_p \cdot C_p^{ss} \tag{12}$$

$$Q_1 = Q_2/(1 - e^{-\lambda_1 T}) \tag{13}$$

The mean values of the exponents, $\overline{\lambda_1}$, $\overline{\lambda_2}$, and $\overline{\lambda_3}$, obtained in the fittings reported in this article are shown in Table IX.

Table IX. Mean Values, $\overline{\lambda_1}$, $\overline{\lambda_2}$, and $\overline{\lambda_3}$, and Coefficients of Variation

Drug	$\overline{\lambda_1}$ (hr^{-1})	C.V. (%)	$\overline{\lambda_2}$ (hr^{-1})	C.V. (%)	$\overline{\lambda_3}$ (hr^{-1})	C.V. (%)
ASA	2.82	11	15.0	17	—	—
Ampicillin	0.616	37.7	3.54	69.7	—	—
Cefazolin	0.392	14.8	5.15	57.9	—	—
Cephalexin	0.473	56.1	3.15	73.2	—	—
Clindamycin phosphate						
Dialysis	0.247	66.8	3.31	—	—	—
Uremics	0.133	70.0	0.880	79.1	—	—
Diazepam	0.023	13.8	0.411	60.1	8.42	111.0
Digoxin	0.017	18.0	1.99	16.5	—	—
Diphenhydramine	0.149	—	7.7	—	—	—
Griseofulvin	0.054	30.0	0.67	28	—	
Nortriptyline	0.0329	31.3	1.97	7.7	—	—
Pentobarbital	0.0153	43.9	2.15	35.6	—	—
Phenytoin	0.0399	16.0	0.563	71.5	6.44	68.1
Pindolol	0.224	23.1	1.19	56.3	—	—
Quercetin	0.740	65.3	14.7	69.8	—	—
Salicylic acid	0.155	10.3	11.4	22.3	—	—
Spectinomycin	0.454	35.8	7.24	72.9	—	—
Sulfisoxazole	0.115	27.8	0.808	75.0	—	—
Tobramycin (dialysis)	0.0513	39.4	0.881	25.5	—	—
Tranexamic acid	0.735	—	26.6	—	—	—
Warfarin	0.0254	49.5	1.94	66.4	—	—

Example 1: Suppose one wished to attain a steady-state serum concentration of ampicillin of 25 μg/ml in a 70-kg man. Then, $C_p^{ss} = 25$; from Table IX under ampicillin we obtain $\lambda_1 = 0.616\ hr^{-1}$ and from Table III we obtain $\overline{Cl_p} = 0.289$ liters/(kg × hr). Let $T = 0.5$ hr. Then substituting these values into equations 12 and 13 gives

$$Q_2 = (0.289)(70)(25) = 506 \text{ mg/hr} \tag{14}$$

$$Q_1 = 506/(1 - e^{-(0.5)(0.616)}) = 1909 \text{ mg/hr} \tag{15}$$

Thus these estimates suggest an initial infusion rate of about 1900 mg/hr for $\frac{1}{2}$ hr, then an abrupt change to an infusion rate of about 500 mg/hr.

2. Alternative method of calculation: The theophylline example used by Wagner (32) is employed for illustration purposes. For this example, the parameter values were $Cl_p = 0.0864$ liters/(kg × hr), $C_p^{ss} = 10$ μg/ml, $V_p = 0.277$ liters/kg, $V_{dss} = 0.520$ liters/kg, $V_{dext} = 0.548$ liters/kg, $\lambda_1 = 0.162\ hr^{-1}$, $\lambda_2 = 5.99\ hr^{-1}$, and $T = 0.5$ hr. The bolus loading dose, D_L, is given by

$$\text{Bolus } D_L = V_{dss} \cdot C_p^{ss} = (0.520)(10) = 5.20 \text{ mg/kg} \tag{16}$$

However, it is not usually safe to give the loading dose all at once at zero time, then start the infusion at the same time. Let us assume we wish to give a loading dose over 0.5 hr. Then we must calculate how much of the bolus D_L is lost in 0.5 hr, then add this amount to the bolus D_L to get the correct loading dose to administer as an infusion over 0.5 hr.

One can "synthesize" the typical bolus intravenous equation using equation 17, reported by Wagner (30):

$$C_p = \left(\frac{D_{\text{i.v.}}}{V_{d\text{ext}}}\right) e^{-\lambda_1 t} + \left(\frac{D_{\text{i.v.}}}{V_p}\right)\left(1 - \frac{V_p}{V_{d\text{ext}}}\right) e^{-\lambda_2 t} = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \tag{17}$$

The matching of coefficients indicates that $C_1 = D_{\text{i.v.}}/V_{d\text{ext}}$ and $C_2 = (D_{\text{i.v.}}/V_p)(1 - V_p/V_{d\text{ext}})$. Substitution of the values for theophylline and using $D_{\text{i.v.}} = 5.55$ mg/kg (value which was formerly calculated which had to be given at the rate Q_1) gives

$$C_p = 10.128e^{-0.162t} + 9.908e^{-5.99t} \tag{18}$$

For a constant-rate infusion over 0.5 hr, the coefficients, X_1 and X_2, are given by

$$X_1 = C_1/\lambda_1 T = 10.128/[(0.162)(0.5)] = 125.0 \tag{19}$$

$$X_2 = C_2/\lambda_2 T = 9.908/[(5.99)(0.5)] = 3.31 \tag{20}$$

Hence during the 0.5-hr infusion the plasma concentration, C_p^{dur}, will be given by

$$\begin{aligned} C_p^{\text{dur}} &= 125.0(1 - e^{-0.162t}) + 3.31(1 - e^{-5.99t}) \\ &= 128.31 - 125.0e^{-0.162t} - 3.31e^{-5.99t} \end{aligned} \tag{21}$$

The amount eliminated in 0.5 hr, $A_e^{0.5}$, is given by

$$\begin{aligned} A_e^{0.5} &= \text{Cl}_p \int_0^{0.5} C_p^{\text{dur}}\, dt \\ &= 0.0864\left[(128.31)(0.5) - \frac{125.0}{0.162}(1 - e^{-(0.162)(0.5)}) \right. \\ &\quad \left. - \frac{3.31}{5.99}(1 - e^{-(5.99)(0.5)})\right] = 0.31 \text{ mg/kg} \end{aligned} \tag{22}$$

Hence the total needed loading dose is given by

$$\text{Total } D_L = \text{bolus } D_L + A_e^{0.5} = 5.20 + 0.31 = 5.51 \text{ mg/kg} \tag{23}$$

By the method of Wagner (27), the Q_1 rate obtained was 11.1 mg/kg/hr for $T = 0.5$ hr. Thus in 0.5 hr the dose delivered was 5.55 mg/kg, which is essentially the same as the total D_L of 5.51 mg/kg calculated above. Hence the method of Wagner (27) compensates for the drug lost from the body during infusion at the rate Q_1, as well as providing for rapid attainment of steady state.

3. For a single infusion at a rate equal to Q, two useful equations are

$$Q = \mathrm{Cl}_p \cdot C_p^{ss} \tag{24}$$

$$A_b^{ss} = V_{dss} \cdot C_p^{ss} \tag{25}$$

In equation 25, A_b^{ss} is the amount of drug in the body at steady state. By solving both equations 24 and 25 for C_p^{ss} and then equating the right-hand sides, one obtains

$$A_b^{ss} = \frac{V_{dss} \cdot Q}{\mathrm{Cl}_p} \tag{26}$$

Thus one could make various estimates of A_b^{ss} for different infusion rates Q, using tabled mean values of V_{dss} and Cl_p.

Intermittent Bolus Intravenous Therapy

Approximations for clinical use may be made with equation 17.

Example 2: Suppose we use the mean tabled values for digoxin (Tables IV and IX). These are $\overline{D}_{\mathrm{i.v.}} = 0.75$ mg (750 μg), $\overline{\mathrm{Cl}}_p = 12.9$ liters/hr, $\overline{V}_p = 35.7$ liters, $\overline{V}_{d\mathrm{ext}} = 944$ liters, $\overline{\lambda}_1 = 0.017$ hr^{-1}, and $\overline{\lambda}_2 = 1.99$ hr^{-1}. Substituting these values into equation 17 gives

$$\begin{aligned} C_p &= (750/944)\, e^{-0.017t} + (750/35.7)(1 - 35.7/944)\, e^{-1.99t} \\ &= 0.794 e^{-0.017t} + 20.2 e^{-1.99t} \end{aligned} \tag{27}$$

Now, integration of equation 27 between the limits of 0 and ∞ gives an AUC of 56.9 (ng/ml) $\times$ hr. The mean AUC based on 16 data sets (Table VI) was 64.3, hence agreement is reasonable.

Suppose one wished to predict the steady-state level, $\overline{C_p^{ss}}$, and the minimum steady-state level, $C_p^{\min}$, if 0.5 mg of digoxin was given as a bolus intravenous dose once a day ($\tau = 24$ hr). The steady-state concentration at any time t after a dose of 0.5 mg at steady state will be estimated by equation 28, in which the coefficients have been corrected for dose.

$$\begin{aligned} C_p &= (0.5/0.75)[0.794/(1 - e^{-(0.017)(24)})]\, e^{-0.017t} + (0.5/0.75) \\ &\quad \times [20.2/(1 - e^{-(1.99)(24)})]\, e^{-1.99t} \\ &= 1.580 e^{-0.017t} + 13.5 e^{-1.99t} \end{aligned} \tag{28}$$

The average steady-state level is given by

$$\overline{C_p^{ss}} = D_{i.v.}/(Cl_p \cdot \tau) = 500/(12.9 \times 24) = 1.61 \text{ ng/ml} \quad (29)$$

$\overline{C_p^{ss}}$ is also given by the more difficult equation 30:

$$\overline{C_p^{ss}} = \int_0^{\tau} C_p^{ss}\, dt/\tau = [(1.580/0.017)(1 - e^{-(0.017)(24)}) + (13.5/1.99) \times (1 - e^{-(1.99)(24)})]/24$$
$$= 1.58 \text{ ng/ml} \quad (30)$$

The discrepancy in the "answers" given by equations 29 and 30 does not reside in the equations, but rather in the fact that the "answer" was obtained using mean values of V_p and V_{dext}, while the other "answer" was obtained using the mean value of Cl_p. For clinical purposes, the discrepancy is not important.

The minimum plasma level at steady state is estimated with

$$C_p^{min} = 1.580e^{-(0.017)(24)} + 13.5e^{-(1.99)(24)} = 1.05 \text{ ng} \times \text{ml} \quad (31)$$

Equation 31 was obtained from equation 28 by letting $t = \tau$. One must be aware that such estimates are based on average parameter values and that parameter values for individual patients and subjects are not the same. In addition, with digoxin, one must be aware that with *oral dosing* there is the additional variable of the fraction of an oral dose which is absorbed.

Estimation of Cl_p for a Particular Patient

Suppose the tabled $\overline{V_{darea}}$ (mean value) has a reasonably small coefficient of variation (C.V.) and one has some method of estimating λ_1 with endogenous creatinine clearance, such as given by Wagner (33), or from a correlation of $t_{1/2}$ with serum creatine concentration, then obtaining λ_1 with equation 11. Then one can estimate the clearance for a particular patient from

$$Cl_p = \overline{V_{darea}} \cdot \lambda_1 \quad (32)$$

The range of possible values could be estimated using the estimated range of V_{darea} obtained with

$$\text{Estimated range of } V_{darea} = \overline{V_{darea}} \pm 2(\text{C.V.}(\%)/100)(V_{darea}) \quad (33)$$

Use of V_{dext} as an Estimate of V_{darea}

V_{dext} may be estimated from the dose and terminal log-linear plasma concentrations, hence is much easier to obtain experimentally than V_{darea},

which requires sampling at sufficient points to define the entire C_p, t curve after a single dose. Hence, for those drugs such as nortriptyline, tranexamic acid, warfarin, tobramycin, griseofulvin, pentobarbital, and salicylic acid where $V_{d\text{ext}}$ is approximately the same as $V_{d\text{area}}$, in future studies only $V_{d\text{ext}}$ really needs to be measured. However, until one knows that these are essentially equivalent, use of $V_{d\text{ext}}$ is not sound.

Oral Therapy

Equation 34 is equivalent to equation 24 when therapy is by the oral route.

$$D_m/\tau = (\mathrm{Cl}_p/FF^*)\overline{C_p^{ss}} \tag{34}$$

In equation 34, D_m/τ is the "dose rate," where D_m is the maintenance dose and τ is the uniform dosing interval; FF^* is the "bioavailability factor," where F is the fraction of the dose in the dosage form which is absorbed and F^* is the fraction of that drug absorbed which reaches the general circulation as a result of the "first-pass" effect. Hence, to use the Cl_p values listed in this article to make predictions for oral therapy, one must know the value of FF^* for *the particular drug and the particular dosage form of the drug which is used.* For example, Jusko and Lewis (1) reported that for ampicillin oral capsules, sold by Bristol Laboratories, FF^* averaged 0.32, with a range of 0.21–0.46. Work in several laboratories has indicated that the mean value of FF^* for digoxin tablets, manufactured by Burroughs & Wellcome, is 0.6. For warfarin, given in 5-mg tablets, sold by Endo Laboratories, the value of FF^* is essentially unity (i.e., all the drug is absorbed and there is essentially no "first-pass" effect).

If the $\overline{\mathrm{Cl}_p}$ values tabled in this report are used, and an estimate of FF^* is known, then an estimate of the "dose rate" needed to attain a desired average steady-state plasma level, $\overline{C_p^{ss}}$, may be made with equation 34. Once the ratio, D_m/τ is obtained, then a reasonable value of τ (i.e., 4, 6, 8, 12, or 24 hr) and a reasonable value of D_m (i.e., something available from a commercial product, such as one tablet, one-half tablet, etc.) are chosen, so that one obtains the required "dose rate." Obviously, the smaller the value of τ, the less fluctuation there will be in the steady-state levels, i.e., the smaller the difference between C_{ss}^{max} and C_{ss}^{min}.

If *oral* plasma level data are available, then an estimate of Cl_p/FF^* may be obtained with equation 35, without knowing the individual values of Cl_p and FF^*. In equation 35, $D_{\text{p.o.}}$ is the dose given orally and $(\mathrm{AUC})_{\text{p.o.}}$ is the total area under the plasma concentration–time curve from zero to infinite

time after a single dose or the area under the curve during a dosage interval at steady state.

$$Cl_p/FF^* = D_{p.o.}/(AUC)_{p.o.} \tag{35}$$

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