International Journal of Pharmaceutics, 16 (1983) 285–294
Elsevier

An alternative method for calculating absorption and elimination rate constants in first-order processes: application to valproic acid

Meir Bialer [1], Ziad Hussein [1], Yuval Herishanu [2] and Yehezkel Melnik [3]

[1] *Department of Pharmacy, School of Pharmacy, Hebrew University of Jerusalem, P.O.B. 12065, Jerusalem 91120;* [2] *Department of Neurology, Soroka Medical Center, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel; and* [3] *Computer Unit, Hadassah Medical School, Hebrew University, Jerusalem (Israel)*

(Received January 7th, 1983)
(Modified version received March 15th, 1983)
(Accepted March 24th, 1983)

Summary

A simple method for calculating absorption and elimination rate constants from a single linear plot of plasma drug concentration data is presented. This method is applicable to the one-compartment open-body model with first-order processes. It allows an independent determination of the two rate constant values. As the two rate constants are found to be two square-roots of a quadratic equation, the proposed method obviates the fact that it cannot determine the identity of each rate constant from a single extravascular administration of a drug. Supplementary information is needed to complete this identity in order to make the proposed method globally identifiable. An application of the proposed method is presented using plasma data of valproic acid obtained after a single oral administration of the drug to two epileptic patients.

Introduction

In the one-compartment open-body model with first-order processes, the determination of the absorption and elimination rate constants (k_a and k_e, respectively) using only plasma drug concentration data is dependent on the magnitude of the differences between k_a and k_e. Generally, where $k_a \gg k_e$, k_e can be determined from the slope of the linear terminal slope of the log C_b vs t plot (C_b is concentration of the drug in body and t is time) and k_a can be determined by the

method of residuals (the "feathering" technique). Similarly, when $k_e \gg k_a$ (the so-called flip-flop case) k_a can be determined from the slope of the terminal phase of a log C_b vs t plot and k_e can be determined by the method of residuals (Dost, 1968; Gibaldi and Perrier, 1975; Wagner, 1975; Rowland and Tozer, 1980).

However, from a single extravascular (first-order input) administration it is impossible to determine whether a certain plasma drug concentration data set is included within the category of the general case (where $k_a \gg k_e$) or the flip-flop case (where $k_e \gg k_a$). Although the general case is the most common one in practice, in order to determine exactly the identity of one of the two rate constants, one has to administer the same drug by a different route of administration (preferably IV), or in a different dosage form to the same subjects(s) (Gibaldi and Perrier, 1975; Rowland and Tozer, 1980).

This paper presents a simple new method where from a single linear plot of plasma drug concentration data, obtained after a single extravascular (first-order input) administration, one can determine independently the values, but not the identities, of k_a and k_e. The two rate constants will be locally identifiable by the proposed method (Godfrey et al., 1980).

Theory

The drug concentration in the plasma (body) after a single dose administration in the one-compartment open-body model with first-order processes is described by the general Bateman equation (Eqn. 1) (Dost, 1968; Gibaldi and Perrier, 1975; Wagner, 1975).

$$C_b = \frac{FDk_a}{V(k_a - k_e)} \cdot (e^{-k_e t} - e^{-k_a t}) \tag{1}$$

where C_b is the concentration of the drug in the body, D is the dose administered, F is the fraction of the dose absorbed and V is the apparent volume of distribution. Differentiation of Eqn. 1 with respect to time will give Eqn. 2, which at $t = 0$ will be transformed into Eqn. 3.

$$\frac{dC_b}{dt} = \frac{FDk_a}{V(k_a - k_e)} \cdot \left(-k_e e^{-k_e t} + ka\, e^{-k_a t}\right) \tag{2}$$

$$\frac{dC_b}{dt} = \frac{FDk_a}{V} \tag{3}$$

Eqn. 3 is equal to the slope of the tangent to the C_b vs t plot at $t = 0$. A good estimation for this value can be determined from the quotient: $\frac{\Delta C_b}{\Delta t} = \frac{C_b - 0}{t - 0}$, where C_b is an early detectable plasma concentration obtained at time t close to zero ($t \sim 15$ min) (Figs. 1 and 2).

From a plot of C_b vs t, t_{max} and C_{bmax} can be determined by inspection and the AUC can be calculated by the trapezoidal rule (t_{max} = time of peak drug concentration, C_{bmax} = peak drug concentration, AUC = total area under the C_b vs time curve). Additionally, by using the trapezoidal rule, the AUC from t_{max} to infinity (AUC_2) can be calculated. The values of C_{bmax}, AUC (Dost, 1968; Gibaldi and Perrier, 1975; Wagner, 1978) and AUC_2 (Pidgeon and Pitlick, 1977, 1980; and appendix to this paper) are presented in Eqns. 4, 5 and 6.

$$C_{bmax} = \frac{FD}{V} \cdot e^{-k_e t_{max}} \tag{4}$$

$$AUC = \frac{FD}{Vk_e} \tag{5}$$

$$AUC_2 = \frac{C_{bmax}(k_a + k_e)}{k_a \cdot k_e} \tag{6}$$

By defining the quotient of AUC_2 to C_{bmax} as A and the quotient between dC_b/dt (at $t = 0$) and the AUC as B, Eqns. 7 and 8 can be derived.

$$A = \frac{AUC_2}{C_{bmax}} = \frac{k_a + k_e}{k_a \cdot k_e} \tag{7}$$

$$B = \frac{\frac{dC_b}{dt}}{AUC} = \frac{\frac{FDk_a}{V}}{\frac{FD}{k_e V}} = k_a k_e \tag{8}$$

From Eqns. 7 and 8 a quadratic equation for determining k_a (or k_e) can be derived (Eqns. 9, 10 and 11).

$$k_a = \frac{B}{k_e} \tag{9}$$

$$A = \frac{\frac{B}{k_e} + k_e}{\frac{B}{k_e} \cdot k_e} = \frac{B + k_e^2}{B \cdot k_e} \tag{10}$$

$$k_e^2 - ABk_e + B = 0 \tag{11}$$

Equation 11 is also applicable to k_a and thus:

$$k_a^2 - ABk_a + B = 0 \tag{12}$$

The solution to the two quadratic equations (Eqns. 11 and 12) is presented by Eqn. 13:

$$k_a, k_e = \frac{AB \pm \sqrt{A^2B^2 - 4B}}{2} \tag{13}$$

In general, where $k_a \gg k_e$, k_a will be equal to

$$\frac{AB + \sqrt{A^2B^2 - 4B}}{2}$$

and k_e will be equal to

$$\frac{AB - \sqrt{A^2B^2 - 4B}}{2},$$

but the situation reverses in the flip-flop case.

As k_a and k_e are found to be two square-roots of a quadratic equation, their identity could not be determined from Eqn. 13. Substitution of Eqn. 4 into Eqn. 5 leads to the double equality presented in Eqn. 14 (see also appendix).

$$C_{bmax} = AUC \cdot k_e \cdot e^{-k_e t_{max}} = AUC \cdot k_a e^{-k_a t_{max}} \tag{14}$$

Generally $k_a > k_e$, but there is also the theoretical possibility of the flip-flop case. In order to determine the identity of the two rate constants, additional information has to be known such as dosage form characteristics or urine data, etc.

Pidgeon and Pitlick (1977, 1980) presented a unique approach for the calculation of first-order absorption rate constants from blood or urine data. (This method will be designated herein as PP.) The performance of the method derived in this paper (designated MB) was assessed in comparison to the PP method by using theoretical data generated by Pidgeon and Pitlick. Additionally, an application of the MB method is presented, where data obtained after oral administration of sodium valproate (Gugler and von-Unruh, 1980) to two epileptic patients were used to calculate the pharmacokinetic parameters in comparison to the existing method (Dost, 1968; Gibaldi and Perrier, 1975; Wagner, 1975; Rowland and Tozer, 1980).

Materials and Methods

Two epileptic patients (S.H. and L.J.) were administered orally with 1 g of sodium valproate (5 × 200 mg of Depakine-Labaz, France). Blood samples (5 ml) were taken from the cubital vein into heparinized test-tubes at the following times after the drug administration: 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 23, 24, 30, 36, 42, 48 h. The blood samples were centrifuged (2000 rpm for 15 min) and the plasma was separated and stored at −20°C until analyzed.

Valproic acid was assayed by a Gas Liquid Chromatograph apparatus (Packard Model 7300) equipped with a flame ionization detector and a dual pen recorder (Unicorder U-225 M). The glass column (6 ft. × 2 mm i.d.) was packed with 5% free fatty acid phase (Jensen and Gugler, 1977) (FFAP, Applied Science Labs.) on 80–100 mesh Glass Chrom Q. The following flow rates were used: hydrogen, 40 ml/min; air, 400 ml/min; and carrier gas-nitrogen 40 ml/min. The system temperatures were: column 155°C, injector 180°C, detector 220°C. Stock solutions of sodium valproate (Labaz, France) were prepared by dissolving the drug (1 mg/ml) in water. Sodium caprylate (BDH, U.K.) was dissolved in water (1 mg/ml) and used as an internal standard.

Extraction procedure

To 0.5 ml of plasma containing the unknown concentration of drug were added 0.5 ml of H_2O, 1 ml of 10% solution of $Na_2WO_4 \cdot 2H_2O$ (Riedel, F.R.G.), 1 ml of 0.67 N, H_2SO_4, and 50 μl of the internal standard solution. The mixture was vortexed for 20 s and centrifuged for 10 min at 2000 rpm. The supernate was decanted and 0.1 ml of H_2SO_4 (0.67 N) and 0.1 ml of $CHCl_3$ were added. The mixture was vortexed and centrifuged as previously and 3 μl of the organic phase was injected into the gas chromatograph.

Results and Discussion

The MB method is an exact solution for k_a and k_e when the estimates are derived from error-free data obtained at small time intervals. However, since it was unlikely that C_{bmax} and t_{max} could be observed exactly experimentally, the theoretical time intervals were chosen to be 0.25 h for 3 h and then 1 h intervals, up to 20 h after administration of the dose. A set of data was generated for the various values of k_a, k_e, D, F and V, using Eqn. 13. (F/V and D were kept constant at values of 2.0 and 1000, respectively) (Pidgeon and Pitlick 1977). Estimates of k_a and k_e using the PP and MB methods are summarized in Table 1.

TABLE 1

ESTIMATES OF k_a AND k_e (AND PERCENT OF ERROR) DERIVED BY THE PP (PITLICK AND PIDGEON, 1977) AND MB METHOD ON THEORETICAL BLOOD LEVEL DATA WITHOUT ERROR

Input		Output					
		PP		MB			
k_a	k_e	k_a	(% error)	k_a	(% error)	k_e	(% error)
1.0	0.5	1.123	(12.35)	1.109	(10.9)	0.425	(15.0)
2.0	0.37	1.8805	(6.0)	1.851	(7.45)	0.46	(24.3)
3.0	0.3	2.191	(27.0)	3.51	(17.05)	0.31	(3.33)

TABLE 2

VALUES FOR k_a AND k_e ESTIMATED WITH THE PP AND MB METHODS CORRECTED FOR INACCURATE ESTIMATION OF C_{bmax} AND t_{max}

Input		Output					
		PP		MB			
k_a	k_e	k_a	(% error)	k_a	(% error)	k_e	(% error)
1.0	0.5	0.973	(2.7)	0.875	(12.5)	0.539	(7.8)
2.0	0.37	2.204	(10.2)	2.36	(18.0)	0.365	(1.35)
3.0	0.3	3.07	(2.4)	3.22	(7.3)	0.335	(11.67)

Values for k_a and k_e were recalculated using a correction factor for t_{max}. This factor is equal to the relative error between the theoretical estimated t_{max} and the observed one (Pidgeon and Pitlick, 1980). The data obtained are summarized in Table 2.

The method was also tested on the same data with 5% and 10% error, and compared to the PP method (Pidgeon and Pitlick, 1977, 1980). For each data set generated with a given ratio of k_a and k_e, a constant error of 5% and 10% was randomly introduced using a Fortran random number function (Pidgeon and Pitlick 1977, 1980) (Table 3).

A k_a estimate obtained by the PP method using the above-mentioned theoretical data with a k_a input of 2.0 gave output values of 1.92 and 2.22, for data with 5% and 10% error, respectively. The Wagner-Nelson method gave output values of 1.18 and 2.22 on the same data (Pidgeon and Pitlick, 1977).

The proposed method was applied to two sets of theoretical data with absorption lag times of 0.1 and 0.25 h with no errors and with 5% and 10% error in the data (Pidgeon and Pitlick, 1980). A comparative data calculation of these sets by the two methods is presented in Table 4.

The proposed method was also applied to the special case of equal absorption and elimination first-order rate constants (Gibaldi and Perrier, 1975). Theoretical data in

TABLE 3

ESTIMATION OF k_a AND k_e DERIVED BY THE PROPOSED METHOD (MB) ON THEORETICAL BLOOD DATA WITH 5% AND 10% ERROR IN ALL CONCENTRATIONS

Input		Output							
		5% error				10% error			
k_a	k_e	k_a	(% error)	k_e	(% error)	k_a	(% error)	k_e	(% error)
1.0	0.5	1.40	(40.0)	0.37	(26.0)	1.39	(39.0)	0.40	(20.0)
2.0	0.37	2.51	(25.5)	0.305	(17.6)	1.855	(7.25)	0.415	(12.2)
3.0	0.3	2.82	(6.0)	0.32	(6.67)	2.45	(18.33)	0.35	(16.7)

TABLE 4

EFFECT OF LAG TIMES ON THE ESTIMATES OF k_a AND k_e BY THE PP (PITLICK AND PIDGEON, 1980) AND MB METHODS

Input			Output					
			% error in data	PP		MB		
$t_{lag(h)}$	k_a	k_e		k_a	(% error)	k_a	(% error	k_e	(% error)
0.1	2.0	0.2	0	1.6	(20)	1.878	(6.1)	0.195	(2.5)
0.1	2.0	0.2	5	1.97	(1.5)	2.11	(5.5)	0.22	(10.0)
0.1	2.0	0.2	10	1.54	(23)	1.905	(4.75)	0.205	(2.5)
0.25	2.0	0.2	0	1.80	(10)	1.937	(3.15)	0.218	(9.0)
0.25	2.0	0.2	5	2.16	(8)	2.005	(0.25)	0.225	(12.5)
0.25	2.0	0.2	10	1.68	(16)	1.69	(15.5)	0.235	(19.0)

which $k_a = k_e = 0.5\ min^{-1}$ showed the following parameters: AUC = 20.6 mg/ml · min, $AUC_2 = 15.5\ \mu g/ml \cdot min$, $\frac{dC_b}{dt} = 4.8$ and $C_{bmax} = 3.7\ \mu g/ml$ (Bialer, 1980). The values of the two rate constants, obtained by the proposed method, were 0.535 min^{-1} and 0.435 min^{-1} (errors of 7% and 14%, respectively).

The present method was applied to experimental data obtained after oral administration of sodium valproate to two epileptic patients. The observed data were best

TABLE 5

A COMPARATIVE DATA CALCULATION OF THE TWO METHODS

Pharmacokinetic parameter	Patient 1 (S.H.)	Patient2 (L.J.)
Observed C_{bmax} ($\mu g/ml$)	76.85	82.17
Observed t_{max} (h)	4.1	1.0
AUC ($\mu g/ml \cdot h$)	1583.3	1823
AUC_2 ($\mu g/ml \cdot h$)	1449.6	1775
$\frac{dC_b}{dt}$ (at t = 0)	40.0	72.0
A (h)	$\frac{AUC_2}{C_{bmax}} = \frac{1449.6}{69.85} = 18.86$	$\frac{1775}{82.17} = 21.60$
B (h^{-2})	$\frac{\frac{dC_b}{dt}}{AUC} = \frac{40}{1583.3} = 0.0253$	$\frac{72}{1823} = 0.0395$
k_e [b] (h^{-1})	0.0605	0.0495
k_e^* [a] (h^{-1})	0.067	0.0464
k_a [b] (h^{-1})	0.4165	0.8041
k_a^* [a] (h^{-1})	0.5817	0.9818
Calculated C_{bmax} ($\mu g/ml$)	68.13	85.93

[a] k_e^* and k_a^* were calculated from linear terminal slope and the feathering technique.

[b] k_e and k_a were calculated by the proposed method.

[c] C_{bmax} was calculated by using Eqn. 14.

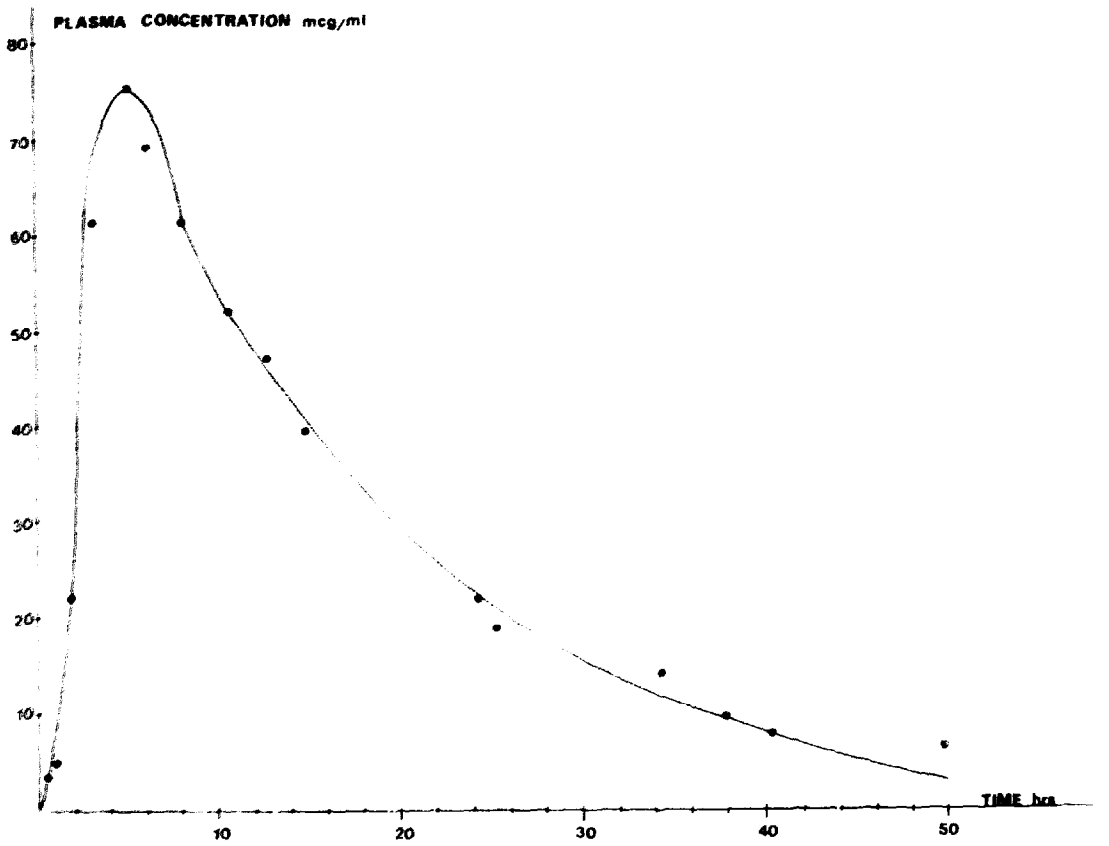

Fig. 1. Valproic acid plasma levels of patient 1 (S.H.).

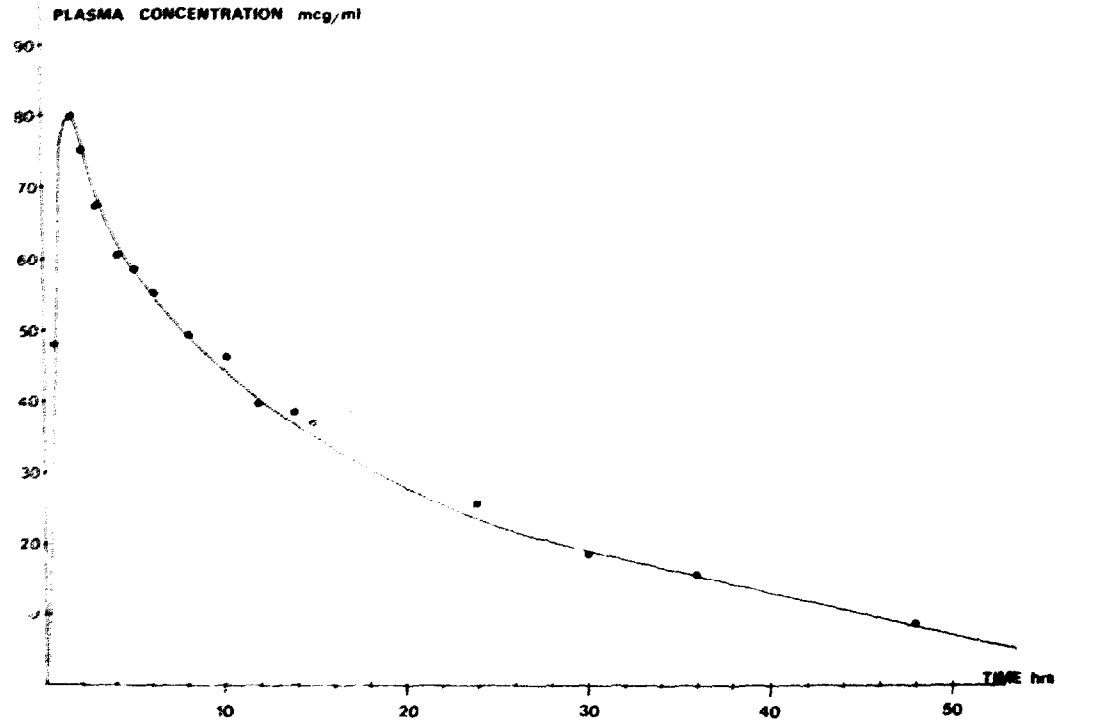

Fig. 2. Valproic acid plasma levels of patient 2 (L.J.).

fitted to a one-compartment open-body model similar to what has been reported previously in the literature after oral administration of sodium valproate to humans (Klotz and Antonin, 1977; Jordan et al., 1978).

All the observed data (mean ± S.D., n = 3) were fitted by using the NONLIN computer program (Metzler et al., 1979), which confirmed the initial estimates for k_e and k_a, obtained from the linear terminal slopes of log C_b vs t plot and from the feathering technique. The values obtained by this method for k_a and k_e are presented in Table 5 as k_e^* and k_a^*. In comparison, the same two rate constants were calculated by the proposed method using the linear plots presented in Figs. 1 and 2.

The differences in the values of k_a and k_e obtained by the two methods, as presented in Table 5, can be explained by the fact that the blood samples were taken hourly during the absorption phase (with the exception of two samples within the first hour).

Additionally, experimental data do not always completely fulfil all the pre-assumptions essential for the proposed method, especially the ones regarding the characterization of drug input.

Conclusion

Pidgeon and Pitlick (1977, 1980) presented a unique approach for calculation of first-order absorption rate constants from blood or urine data. The method used C_{bmax}, k_e and AUC_2 for the determination of k_a out of blood data. The method derived in this paper does not need to use k_e for the calculation of k_a. Moreover, it suggests a simple way of determining the values of k_a and k_e out of plasma data alone after single oral or any other first-order extravascular administration, though the two rate constants are only locally identifiable (Godfrey et al., 1980). In the general case, where $k_a > k_e$, the two rate constants are globally identifiable. This method is also applicable to unusual cases such as the "flip-flop case" or in the case in which k_a and k_e are of the same order of magnitude and there is no linear terminal slope in the log C_b vs t plot.

Appendix

Eqn. 6 which describes the value of AUC_2 is obtained by integrating Eqn. 1 from t_{max} and infinity and using the identity $k_e \cdot e^{-k_e t_{max}} = k_a \cdot e^{-k_a t_{max}}$. The exact way to derive Eqn. 6 is as follows:

$$AUC_2 = \int_{t_{max}}^{\infty} \frac{FDk_a}{V(k_a - k_e)} \cdot [e^{-k_e t} - e^{-k_a t}]dt$$

$$= \frac{FDk_a}{V(k_a - k_e)} \cdot \left[\frac{e^{-k_e t_{max}}}{k_e} - \frac{e^{-k_a t_{max}}}{k_a} \right]$$

$$= \frac{FDk_a}{V(k_a - k_e)} \left[\frac{e^{-k_e t_{max}}}{k_e} - \frac{k_e}{k_a^2} \cdot e^{-k_e t_{max}} \right]$$

$$= \frac{FDk_a(k_a^2 - k_e^2)\, e^{k_e t_{max}}}{V(k_a - k_e)k_e \cdot k_a^2} = \frac{FD(k_a + k_e)\, e^{-k_e t_{max}}}{V \cdot k_e \cdot k_a}$$

$$= \frac{C_{bmax}(k_a + k_e)}{k_a \cdot k_e} \qquad (6)$$

Acknowledgements

We would like to acknowledge the helpful assistance of the medical and nursing staff of the Neurology Unit at the Shaare Zedek Hospital, Jerusalem. This work was supported by a grant from the Joint Research Fund of the Hebrew University and Hadassah. Parts of this work are included in Mr. Ziad Hussein's M.Sc. dissertation project.

References

Bialer, M., A simple method for determining whether absorption and elimination rate constants are equal in the one compartment open model with first-order processes. J. Pharmacokin. Biopharm., 8 (1980) 111–113.

Dost, F.H., Grundlager der Pharmacokinetik, 2. Gufl. G. Thieme, Stuggart, 1968, pp. 38–47.

Gibaldi, M. and Perrier, D., Pharmacokinetics, Dekker, New York, 1975, pp. 33–43.

Godfrey, K.R., Jones, R.P. and Brown, R.F., Identifiable pharmacokinetic models, the role of extra input measurements. J. Pharmacokin. Biopharm., 8 (1980) 633–648.

Gugler, R. and von-Unruh, G.E., Clinical pharmacokinetics of valproic acid. Clin. Pharmacokin., 5 (1980) 67–83.

Jensen, C.J. and Gugler, R., Sensitive gas-liquid chromatographic method for determination of valproic acid in biological fluids. J. Chromatogr., 137 (1977) 188–243.

Jordan, B.J., Orwin, J.M., Nichols, J.D. and Henson, R., The bioavailability of sodium valproate (2-pp) from three Epilim formalities. Pharm. Weekl., 112 (1977) 347.

Klotz, U. and Antonin, K.H., Pharmacokinetics and bioavailability of sodium valproate. Clin. Pharmacol. Ther., 21 (1977) 736–743.

Metzler, C.M., Elfind, O.L. and McKwen, A.J., A user's Manual for NONLIN and Associated Program Research Biostatistics, Upjohn, Kalamazoo, 1974.

Pidgeon, C. and Pitlick, W.H., Unique approach for calculation of absorption rate constant. Res. Commun. Chem. Path. Pharmacol., 18 (1977) 467–475.

Pidgeon, C. and Pitlick, W.H., Unique approach for calculation of first-order absorption rate constants from blood or urine data. J. Pharmacokin. Biopharm., 8 (1980) 203–214.

Rowland, M. and Tozer, T. Clinical Pharmacokinetics, Lea and Febiger, 1980, pp. 293–295.

Wagner, J.G., Fundamentals of Clinical Pharmacokinetics, Drug Intelligence, Hamilton, 1975, pp. 74–82.