Use of MULTDOS for Pharmacokinetic Analysis of Ethosuximide Data during Repetitive Administration of Single or Divided Daily Doses

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Abstract □ MULTDOS, a computer method to curve fit data obtained on multiple dosing, was used with either the 1969 or 1974 version of the NONLIN program to compare the pharmacokinetic parameters of ethosuximide during repetitive administration of single or divided daily doses. Elimination rate constants, excretion rate constants, and apparent volumes of distribution were similar between the two dosing regimens and essentially identical between the two nonlinear regression programs.

Keyphrases □ Computer analyses—MULTDOS and 1969 or 1974 NONLIN program, pharmacokinetic parameters of ethosuximide during single or divided daily doses compared □ Ethosuximide—pharmacokinetic parameters during single or divided daily doses compared using MULTDOS and 1969 or 1974 NONLIN computer program □ Pharmacokinetics—ethosuximide parameters during single or divided daily doses compared using MULTDOS and 1969 or 1974 NONLIN computer program □ Anticonvulsants—ethosuximide, pharmacokinetic parameters during single or divided daily doses compared using MULTDOS and 1969 or 1974 NONLIN computer program

Goulet *et al.* (1) compared once daily and three times daily ethosuximide administrations in healthy volunteers. Steady-state plasma ethosuximide concentrations and daily urinary excretion of unchanged drug and metabolite were comparable during either dosing regimen, supporting the use of a single daily dose for ethosuximide therapy.

Two recent articles concerned the pharmacokinetic analysis of data obtained during repetitive dosing (2, 3). The first report (2) considered the situation in which the pharmacokinetic parameters of the drug remain constant throughout, and the computer method employed is termed MULTDOS. The second report (3) concerned the development of a computer method, VARPARM, for those cases where there is dose-to-dose variation in one or more pharmacokinetic parameters. Both MULTDOS and VARPARM utilized the 1969 version of the nonlinear least-squares regression program NONLIN (4) as the main program. Inquiries as to the application of these methods with the 1974 version of NONLIN (5) led to the development of subroutines to be used with a modified version of the 1974 NONLIN.

The present report concerns the comparison of pharmacokinetic parameters obtained during repetitive dosing of ethosuximide as single or divided daily doses using the MULTDOS method with both the old and new versions of NONLIN.

EXPERIMENTAL

The basic MULTDOS method for fitting data was described previously (2). Utilization of the method with 1969 NONLIN has been modified since the original report so that the NONLIN package is self-sufficient; *i.e.*, the separate and independent DASCRU[1] subroutine need not be used. This modification was accomplished by having the multiple-dose routine call the numerical integration subroutine NUMINT in the NONLIN program. NUMINT subsequently calls a user-supplied subroutine F to solve the differential equations. Only a minor change is required in the NONLIN package to achieve this improvement[2].

Originally, we elected to input differential rather than integral equations (2, 3), and this approach is still favored. The use of differential equations is particularly convenient when fitting data to a complex, *e.g.*, nonlinear, pharmacokinetic model. On the other hand, if data are to be fit to a relatively simple pharmacokinetic model, the use of integral equations may be advantageous in that it requires less computer time and less modification of DFUNC.

The use of MULTDOS with 1974 NONLIN required modifications in the DASCRU, NONLIN, and SUMMARY subroutines, all of which are contained in the new NONLIN package, as well as in the user-supplied subroutine DFUNC[2]. The changes alter the logic so that the NONLIN program assumes the use of integrated functions even though differential equations are being used. The changes in DFUNC were required to follow the 1974 NONLIN logic.

The revised MULTDOS method with 1969 NONLIN and the newly developed MULTDOS method with 1974 NONLIN were tested successfully using ideal data before analyzing the ethosuximide data.

Plasma ethosuximide concentrations and urinary excretion rates during repetitive dosing were obtained from the study reported by Goulet *et al.* (1). Healthy subjects received 500 mg of ethosuximide, either as a single daily dose or as two 250-mg doses at 12-hr intervals for 14 days. The daily dose was then increased to 750 mg and administered either as a single daily dose or as three 250-mg doses at 6-, 6-, and 12-hr intervals each day for an additional 14 days. Blood and urine samples were collected for drug analysis at various times during the treatment and washout periods.

Average drug concentration data in plasma and urinary excretion rate data, weighted reciprocally, as well as initial parameter estimates for a one-compartment open model served as input for the programs. In each case, the plasma and urine data were fit simultaneously.

Table I—Comparison of Ethosuximide Pharmacokinetics Estimated by MULTDOS, Using 1969 NONLIN or 1974 NONLIN, from Simultaneous Curve Fits of Plasma Concentration and Urinary Excretion Data during Repetitive Administration of Single or Divided Daily Doses

Parameter[a]	Estimated with 1969 NONLIN[b]	Estimated with 1974 NONLIN[b]
	Single Daily Dose	
k_a	2.62 (545)	2.60 (675)
K	0.0132 (2)	0.0131 (2)
k_e	0.0026 (8)	0.0026 (12)
V/f	47.4 (4)	47.5 (4)
	Divided Daily Dose	
k_a	0.749 (29)	0.758 (29)
K	0.0138 (2)	0.0138 (2)
k_e	0.0029 (3)	0.0029 (7)
V/f	52.1 (2)	52.1 (2)

[a] k_a = absorption rate constant (hours^{-1}), K = elimination rate constant (hours^{-1}), k_e = urinary excretion rate constant, V = apparent volume of distribution (liters), and f = fraction of dose absorbed. [b] Mean estimate (*CV*, %).

RESULTS

The one-compartment model parameter estimates obtained by curve

[1] Available from IMSL, 6200 Hillcroft, Houston, TX 77036.

[2] Program information will be supplied on written request.

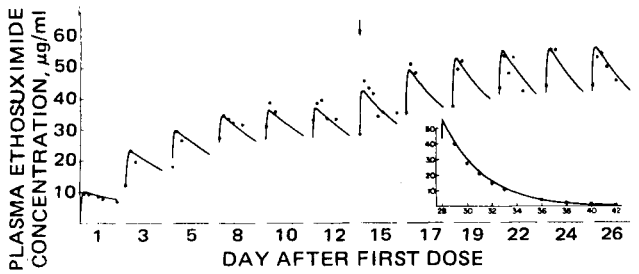

Figure 1—*MULTDOS curve fit to mean plasma ethosuximide concentrations during repetitive oral administration of single daily doses of 500 mg (Days 1–14) and 750 mg (Days 15–28). Inset shows plasma concentrations after the last dose.*

fitting the ethosuximide data using the MULTDOS method with either version of NONLIN are presented in Table I. The means and standard deviations for each parameter were, with one exception, quite similar between treatments (single daily doses *versus* divided daily doses) and were, in all cases, virtually identical between computer programs (1969 NONLIN *versus* 1974 NONLIN). The analysis suggests that there is more rapid absorption after the single compared to the divided daily doses. These differences, however, are of no significance in view of the large uncertainty associated with the absorption rate constant estimated from the single daily dose data. The reason for this uncertainty is that only one data point from the absorption phase was available each day for the pharmacokinetic analysis. When fitting the divided daily dose data, two or three such data points were available each day.

Plasma concentration–time data for the single and divided daily doses and the respective curve fits are shown in Figs. 1 and 2, respectively. Correlation coefficients of 0.991 and 0.996 were obtained between observed and predicted values for the respective treatments. As anticipated, differences between peak and trough levels of drug during a dosing interval at steady state were larger during the once-a-day dosing than during the divided daily dosing; but the mean steady-state plasma concentrations were quite similar, as previously reported (1).

The observed and predicted urinary excretion rates of ethosuximide

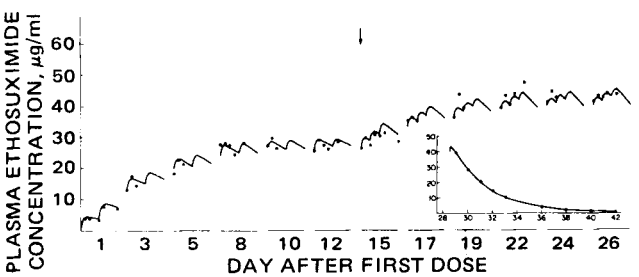

Figure 2—*MULTDOS curve fit to mean plasma ethosuximide concentrations during repetitive oral administration of divided daily doses of 500 mg (Days 1–14) and 750 mg (Days 15–28). Inset shows plasma concentrations after the last dose.*

Table II—Comparison of Observed and Predicted [a] Urinary Excretion Rates (Milligrams per Hour) of Ethosuximide during Multiple Dosing

Days	Single Daily Dose		Divided Daily Dose	
	Observed	Predicted	Observed	Predicted
0.5	1.3	1.1	1.0	0.6
7.5	3.7	3.8	3.3	3.7
11.5	4.4	4.1	4.6	4.0
13.5	4.8	4.1	4.4	4.0
14.5	5.2	4.7	4.8	4.7
21.5	5.8	6.1	6.3	6.2
25.5	5.3	6.2	5.4	6.4
27.5	6.6	6.3	6.5	6.4
29.5	3.5	3.3	3.8	3.7
31.5	1.4	1.8	1.8	1.9

[a] Predicted values were calculated by simultaneous curve fitting of plasma and urine data.

are presented in Table II. Correlation coefficients between observed and predicted data were 0.977 and 0.982 for the single and divided dose treatments, respectively. The correlation coefficients for the combined plasma and urine data were 0.994 and 0.997 for the respective treatments.

DISCUSSION

The present analysis of ethosuximide data obtained on multiple dosing indicates that the pharmacokinetic parameters are independent of the mode of administration. The elimination half-lives were 52.5 and 50.2 hr, and the apparent volumes of distribution (assuming complete absorption) were 47.4 and 52.1 liters for the single and divided daily doses, respectively. The results of this study also support the conclusion of Goulet *et al.* (1) that the use of single daily doses may be an effective regimen for ethosuximide therapy.

The data analysis further indicates that the MULTDOS method may be used with either version of NONLIN. Essentially identical parameter estimates, standard deviations, and correlation coefficients were obtained when using 1969 and 1974 NONLIN.

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