Pharmacokinetics of Methsuximide and a Major Metabolite in Dogs

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Abstract □ The pharmacokinetics of methsuximide and its major metabolite 2-methyl-2-phenylsuccinimide were studied in dogs after single intravenous doses. Plasma methsuximide levels were described by a two-compartment open model, and those of the metabolite were described by a one-compartment open model. An expression was derived that describes both methsuximide and metabolite plasma levels after methsuximide administration. Excellent fits were obtained between observed data and those predicted from the model. The metabolite accounted for 40% of the overall elimination of methsuximide, and the half-life of the metabolite (15 hr) was much greater than that of the parent drug (1–3.5 hr). The results suggest that pharmacological effects after methsuximide administration may be due primarily to the metabolite, which may accumulate in the body during repeated doses.

Keyphrases □ Methsuximide and metabolite—pharmacokinetics in dogs after single intravenous doses, GLC analysis in plasma □ Pharmacokinetics—methsuximide and metabolite, after single intravenous doses in dogs □ GLC—analysis, methsuximide and metabolite, dog plasma □ Anticonvulsants—methsuximide and metabolite, pharmacokinetics in dogs after single intravenous doses, GLC analysis in plasma

Methsuximide is a succinimide derivative useful in the treatment of petit mal epilepsy (1–4). In rats, it is distributed rapidly into most major tissues and organs (5). Metabolism studies in rats, guinea pigs, dogs, and humans (6–8) indicate not only that methsuximide is metabolized extensively but also that a prime biotransformation route is *N*-demethylation, leading to 2-methyl-2-phenylsuccinimide, which is pharmacologically active (2, 5, 9). There is evidence that this metabolite is cleared slowly from the body relative to the parent drug (10–12). This phenomenon is not uncommon; several other antiepileptic drugs undergo *N*-demethylation to yield slowly cleared, active metabolites (13).

The *N*-demethylated metabolite may be responsible for the therapeutic activity of methsuximide. Plasma levels of methsuximide and the metabolite were measured by mass fragmentography in 17 patients receiving chronic methsuximide therapy (11). Plasma metabolite levels exceeded those of the parent drug by 700-fold. However, this number reflects the extremely low methsuximide concentrations that the assay was capable of detecting. Metabolite levels of less than 10 μg/ml were judged ineffective, while levels in excess of 40 μg/ml were toxic.

As exemplified in a recent case report (12), special caution must be exercised in the management of a methsuximide overdose. After ingestion of 10 g of methsuximide, the time course of toxicity was biphasic. The initial phase of toxicity was attributed to the high circulating level of the parent drug. After a period of improvement, the patient regressed into an extended, profound coma. This second phase of toxicity was attributed to the sustained, high concentrations of the metabolite in plasma, which were about 20 times those of the parent drug.

A primary objective of this study was to obtain the pharmacokinetic profiles in the dog of both methsuximide and the metabolite after single intravenous doses. By combining the individual models, it was then possible to quantitate the rate and extent to which methsuximide was biotransformed into the metabolite after single doses of the parent drug. This report also describes an improved, sensitive, and fast GLC assay for the simultaneous measurement of methsuximide and its metabolite in plasma.

EXPERIMENTAL

Pure samples of methsuximide[1], phensuximide[1], and 2-methyl-2-phenylsuccinimide[2] were the racemic forms. Two male beagle dogs were used; Dog A weighed 14 kg and Dog B weighed 17.5 kg. The dogs had free access to water at all times, but food was withheld 12 hr prior to an experiment.

Due to the limited water solubility of methsuximide (10), the intravenous dosage form, used in all experiments, consisted of 250 mg of methsuximide dissolved in 5 ml of an aqueous solution of 75% propylene glycol. For consistency, the metabolite was also administered in this dosage form.

Procedure—Each dog was placed in a restraining apparatus with its limbs held secure by pediatric limb restraints. A vein infusion set[3] was positioned in each of the two front limbs. One set was used to administer 5 ml iv (250 mg) of the drug solution by rapid injection (120 sec or less) and was then immediately flushed with 10 ml of normal saline solution to ensure quantitative delivery of the dose. This set was then removed. The other infusion set was used to collect multiple samples at short intervals during the 1st hr of the experiment. The set was kept open by filling with heparin sodium solution, 10 units/ml, between samples.

Blood samples (5 ml) were collected in vacuum tubes[4] at 0, 2–5, 10, 15, 30, 45, 60, and 120 min and then at longer time intervals up to 48 hr. After 3 hr, the infusion set was removed and the dog was freed from the restraints. Blood samples after this time were obtained by direct venipuncture. When the set was used, the blood collection procedure was to withdraw 5 ml of the heparin-diluted blood, draw the 5-ml blood sample, inject 5 ml of saline, reinject the diluted blood, and refill the set with about 1 ml of the dilute heparin solution. The blood samples were centrifuged, and the plasma was deep frozen until analyzed, usually within 1 week.

To eliminate the possibility of drug-related changes in the pharmacokinetic parameters, the minimum time between experiments on the same dog was 1 month.

Assay—The assay was a modification of that of Kinkel *et al.* (10). One milliliter of plasma, or blank plasma containing known quantities of methsuximide and metabolite, was pipetted into a 13-ml glass-stoppered centrifuge tube and acidified with 0.5 ml of 0.5 *N* hydrochloric acid. Five milliliters of chloroform[5] was added, and the tubes were shaken horizontally on a flat-bed shaker for 15 min and then centrifuged[6]. A 4-ml aliquot of the chloroform layer was transferred to clean tubes, and 1 ml of phensuximide solution (6 μg/ml in chloroform) was added as an external standard. The chloroform was evaporated to dryness carefully in a 40° water bath under a gentle stream of nitrogen. The residue was immediately redissolved in about 100 μl of carbon disulfide[7], and the samples were analyzed by GLC.

The gas chromatograph[8], equipped with flame-ionization detectors, was run isothermally using a U-shaped glass column (1.8 m × 2 mm i.d.) packed with 3% OV-17 on 100–120-mesh Gas Chrom Q[9]. The temperatures employed were: column, 175°; flame-ionization detector, 200°; and

[1] Donated by Parke-Davis and Co., Detroit, Mich.
[2] Aldrich Chemical Co., Milwaukee, Wis.
[3] Miniset vein infusion set, Travenol, Deerfield, Ill.
[4] Ten milliliter green stoppered with 143 units of heparin sodium, Becton-Dickinson, Rutherford, N.J.
[5] Analytical reagent, Mallinckrodt, as supplied.
[6] Dynac centrifuge, Clay Adams, Parsippany, N.J.
[7] Analytical reagent, Fisher Scientific Co.
[8] Nuclear Chicago 5000 dual-column, programmable gas chromatograph.
[9] Applied Science Laboratories, State College, Pa.

Table I—Summary of Experiments

Experiment	Dog	Compound Administered, Dose and Route
A	A[a]	Methsuximide, 250 mg iv
B	B	Methsuximide, 250 mg iv
C	B	Methsuximide, 250 mg iv
D	B	2-Methyl-2-phenylsuccinimide, 250 mg iv
E	B	2-Methyl-2-phenylsuccinimide, 250 mg iv

[a] Dog A had some difficulty adapting to the restraining apparatus and was replaced by Dog B.

injection block, 210°. The electrometer settings varied between 8 and 64 $\times 10^{-11}$ amp. Sample volume, introduced by the on-column injection technique, was 3 μl; the recorder chart speed was 38 cm/hr.

The flame gases were hydrogen and compressed air, and their flow rates were systematically adjusted until maximum flame-ionization detector response to the compounds was obtained at 20 and 200 ml/min, respectively. The carrier gas was nitrogen, and its optimal flow rate of 20 ml/min was obtained from an experimentally determined Van Deemter plot (14). Under the conditions used, the column had 321 and 435 theoretical plates/30.5 cm for methsuximide and the metabolite, respectively.

Compounds were quantitated using peak height ratios. This method was faster than, and as accurate as, peak area determination by disk integration or planimetry. The assay method was sensitive to plasma compound concentrations of 0.5 μg/ml.

Standard curves, run in triplicate on separate days, were constructed from the assay results of blank dog plasma containing known quantities of methsuximide and the metabolite at 10 concentrations over the range of 0.5–25.0 μg/ml. The standard curves were checked at the time of assay of unknowns by including in each run a blank plasma sample containing 10 μg of methsuximide and the metabolite; recoveries were 93 ± 3 (*SD*) and 88 ± 5%, respectively.

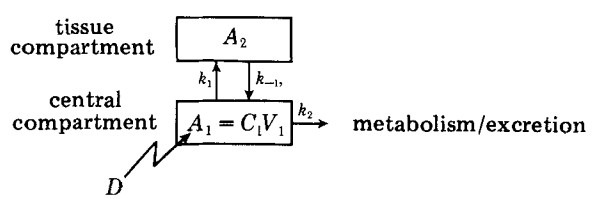
The experiments conducted are summarized in Table I.

Pharmacokinetic Analysis—Plasma level data were fitted to the appropriate pharmacokinetic equations by graphical methods (15). Improved estimates of pharmacokinetic parameters, including confidence limits and coefficients of determination, were obtained using the iterative nonlinear least-squares program NREG on a digital computer[10] as described previously (16).

RESULTS AND DISCUSSION

Assay—Carbon disulfide was substituted for chloroform as the final solvent for injection into the gas chromatograph, because flame-ionization detectors respond poorly to carbon disulfide and compound peaks are obtained from a flat baseline. Chromatograms obtained by the two methods are compared in Fig. 1. Although evaporation of chloroform solutions was reported to result in drug losses (10), no loss of methsuximide or metabolite was observed. The entire chromatogram was obtained within 6 min of injection.

Pharmacokinetic Model for Methsuximide—The decline in plasma methsuximide levels in Experiments A, B, and C was biphasic. A typical plasma profile from Experiment B is shown in Fig. 2. Therefore, these data were analyzed in terms of the two-compartment open model (17) as depicted in Scheme I. This model describes the instantaneous introduction of an intravenous dose, D, of drug into a rapidly accessible central or plasma compartment having an apparent distribution volume, V_1, and equilibration of this compartment with a less readily accessible tissue compartment. The quantities A_1 and A_2 refer to the amounts of unchanged drug in the central and tissue compartments, respectively. The disposition first-order rate constants k_1 and k_{-1} govern the transfer of drug between the compartments, while k_2 is the first-order rate constant representing loss of drug from the central compartment by all routes except k_1.



Scheme I

[10] Univac 1118.

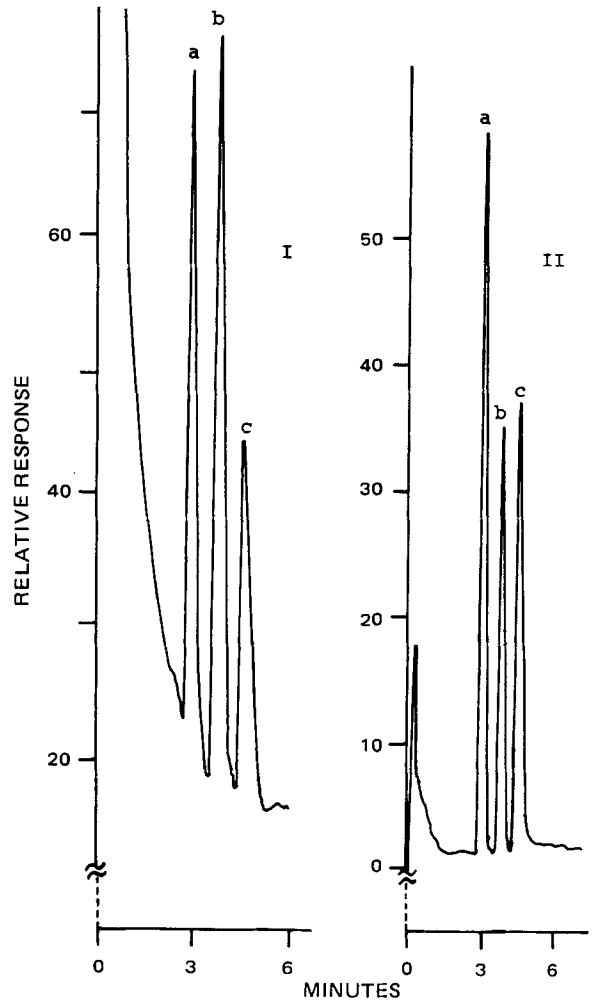


Figure 1—*Representative GLC chromatograms using chloroform (I) and carbon disulfide (II) as solvents. The lettered peaks and their retention times are:* (a) *methsuximide, 191 sec;* (b) *phensuximide external standard, 239 sec; and* (c) *2-methyl-2-phenylsuccinimide, 281 sec. Curves I and II are different plasma samples run at different chart speeds.*

Equation 1 describes the plasma drug concentration *versus* time profile appropriate to this model (17):

$$C_1 = \frac{D}{V_1(\alpha - \beta)}\left[(\alpha - k_{-1})\,e^{-\alpha t} + (k_{-1} - \beta)e^{-\beta t}\right] \qquad \text{(Eq. 1)}$$

where:

$$\begin{matrix}\alpha \\ \beta\end{matrix} = \tfrac{1}{2}\{(k_1 + k_{-1} + k_2) \pm [(k_1 + k_{-1} + k_2)^2 - 4k_{-1}k_2]^{1/2}\} \qquad \text{(Eq. 2)}$$

The composite rate constant β is the slope of the postdistributive log-linear phase of loss of drug from the body multiplied by −2.303, and α is the log-linear slope multiplied by −2.303 obtained by the method of curve stripping (17).

The broken line in Fig. 2 represents the computer fit to unweighted data. Low concentrations were consistently underestimated by the computer. Since NREG is a least-squares fitting routine, a small relative error in the higher concentrations contributes more to the sums of squares than an equivalent error in the lower concentration range. Thus, to make all concentrations contribute equally, data points were weighted by the reciprocal of their concentrations. This weighting scheme improved the curve fitting in all cases (solid line in Fig. 2) and was used in all nonlinear regression procedures.

Table II gives the computer-estimated parameters for Experiments A, B, and C. The distribution characteristics of methsuximide (k_1, k_{-1}, α, V_1, and T/P) differed between the two dogs, although they were of similar order of magnitude. There was more rapid equilibration of drug between compartments in Dog B (α, k_1, and k_{-1}), while Dog A had a

Table II—Pharmacokinetic Parameters after Intravenous Administration of Methsuximide to the Dog

Parameter[a]	Experiment A	Experiment B	Experiment C
k_1, hr^{-1}	2.80 (0.32–5.29)[b]	3.61 (1.02–6.32)	1.86 (0.074–3.65)
k_{-1}, hr^{-1}	1.47 (0.69–2.26)	3.40 (1.89–4.91)	3.28 (0.73–5.82)
k_2, hr^{-1}	0.63 (0.35–0.91)	1.67 (1.21–2.13)	0.84 (0.70–0.97)
D/V_1, mg/liter	23.3 (12.9–33.7)	18.5 (13.4–23.6)	11.1 (9.6–12.6)
D, mg	250	250	250
V_1, liters	10.7	13.5	22.5
α, hr^{-1}	4.71	8.03	5.48
β, hr^{-1}	0.20	0.71	0.50
$t_{1/2}$, hr	3.47	0.98	1.39
T/P[c]	2.20	1.36	0.67
R^2[d]	0.9930	0.9977	0.9972

[a] First four parameters are primary while the balance are derived. [b] The 95% confidence limits. [c] Amount of drug in the tissue compartment to that in the plasma compartment at equilibrium (17). [d] Coefficient of determination, $(\Sigma obs^2 - \Sigma dev^2)/\Sigma obs^2$.

greater amount of drug in the tissue compartment at equilibrium (T/P). The elimination characteristics (k_2, β, and $t_{1/2}$) also differed between the dogs, with Dog A eliminating and/or metabolizing methsuximide more slowly than Dog B.

The rate constant k_2 reflects excretion and metabolism of methsuximide. Since the metabolite was determined in all methsuximide experiments, it was possible to separate k_2 into components representing (*a*) formation of 2-methyl-2-phenylsuccinimide and (*b*) excretion of unchanged methsuximide and/or formation of any other metabolites. Before the metabolite data could be incorporated into Scheme I, its apparent distribution volume and individual pharmacokinetic model had to be obtained by intravenous administration of the pure metabolite.

Pharmacokinetic Model for Metabolite—Figures 3 and 4 are semilogarithmic plots of the data from Experiments D and E after intravenous metabolite administration (250 mg). Since the initial data points did not show sufficient curvilinearity to justify two-compartment model kinetics, the one-compartment open model (Scheme II) was used. The symbolism used in this model for the metabolite is equivalent to that used in Scheme I for unchanged drug.

The plasma metabolite level *versus* time profiles are described by:

$$C_m = \frac{D}{V_3} e^{-k_3 t} \qquad \text{(Eq. 3)}$$

so that, when plotted semilogarithmically, the concentration axis intercept is D/V_3 while the slope is $-k_3/2.303$. The solid lines in Figs. 3 and 4 are the lines of best fit as determined by linear regression analysis[11].

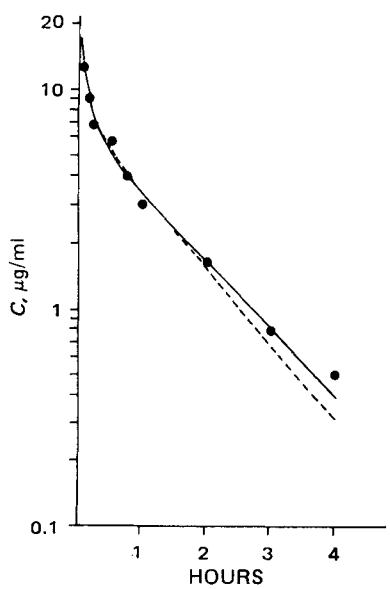
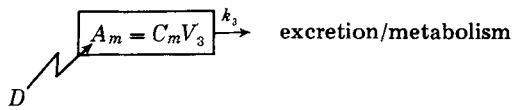


Figure 2—*Semilogarithmic plot of methsuximide concentration* versus *time data from Experiment B. The computer-determined equations of best fit using unweighted data* (- - -) *and data weighted by 1/C* (—) *are* $C_1 = 12.1e^{-9.95t} + 7.7e^{-0.81t}$ *and* $C_1 = 11.7e^{-8.03t} + 6.8e^{-0.71t}$, *respectively. See text for explanation.*

[11] Performed on a Compucorp 344 statistician microcomputer, Computer Design Corp., Los Angles, Calif.



Scheme II

Table III summarizes the regression-determined parameters of Scheme II.

The elimination rate constant k_3, representing excretion or further metabolism, was identical in both experiments and the biological half-life, $t_{1/2}$, was about seven times greater than that of the parent drug (*cf.*, Table II). The apparent distribution volumes of the two compounds were similar.

Since the models and pharmacokinetic parameters for methsuximide and its major metabolite in plasma were obtained independently, it was possible to develop a model to quantitate the rate and extent of formation of the metabolite after an intravenous dose of methsuximide.

Pharmacokinetics of Methsuximide Including Metabolite Formation—Scheme III depicts the model describing intravenous administration of methsuximide with subsequent formation of the metabolite. In Scheme III, D is the amount of methsuximide administered intravenously, k_1 and k_{-1} are as previously defined, k_{el} is the first-order rate constant describing excretion and metabolism of methsuximide to compounds other than 2-methyl-2-phenylsuccinimide, k_f is the first-order rate constant describing formation of the metabolite, and k_3 is the first-order rate constant representing excretion and/or further metabolism of 2-methyl-2-phenylsuccinimide. The remaining symbols are as in Schemes I and II.

The differential equations for the rate of change of C_1 and C_m, with time, can be solved to yield Eqs. 1 and 4:

$$C_m = \frac{WDk_f}{V_3}\left\{\left[\frac{k_{-1}-\alpha}{(k_3-\alpha)(\beta-\alpha)}\right]e^{-\alpha t} + \left[\frac{k_{-1}-\beta}{(k_3-\beta)(\alpha-\beta)}\right]e^{-\beta t} + \left[\frac{k_{-1}-k_3}{(\beta-k_3)(\alpha-k_3)}\right]e^{-k_3 t}\right\} \qquad \text{(Eq. 4)}$$

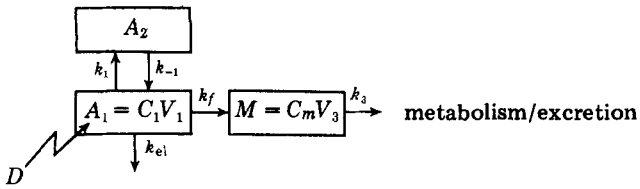
Since all concentrations are expressed on a mass per volume basis, the factor W, the molecular weight ratio of the metabolite to the parent drug (189/203), is required in Eq. 4.

The composite rate constants α and β are now defined by Eq. 5. The significance of these constants is the same as that in Eq. 2. However, in Eq. 5, k_2 from Eq. 2 is separated into $k_{el} + k_f$:

$$\begin{matrix}\alpha \\ \beta\end{matrix} = \tfrac{1}{2}\{(k_1 + k_{-1} + k_{el} + k_f) \pm [(k_1 + k_{-1} + k_{el} + k_f)^2 - 4(k_{-1}k_f + k_{el}k_{-1})]^{1/2}\} \qquad \text{(Eq. 5)}$$

Table III—Metabolite Pharmacokinetic Parameters after Intravenous Administration to the Dog

Parameter	Experiment D	Experiment E
D, mg	250	250
V_3, liters	14.6	11.8
D/V_3, mg/liter	17.1	21.1
k_3, hr^{-1}	0.047	0.047
$t_{1/2}$, hr	14.7	14.7



Scheme III

Figures 5 and 6 give the experimental data for methsuximide and the metabolite in Experiments B and C. Experiment A had to be terminated early, and the metabolite was followed over a time period less than its half-life (14.7 hr). Thus, this experiment could not be used to test the validity of the model in Scheme III.

Initial estimates of the parameters are needed for the computer analysis of the data in terms of Scheme III, but stripping of triexponential curves (Eq. 4) is an inaccurate procedure (18). However, initial estimates of α, β, k_1, and k_{-1} can be obtained from the computer values obtained from methsuximide alone (Table II). The estimate of k_3 can be obtained in two ways; it can be estimated from the independent metabolite experiments or from Eq. 4. Since it is already established that $\alpha > \beta > k_3$, after a certain time Eq. 4 will become essentially monoexponential and the resulting log-linear slope will equal $-k_3/2.303$. The volume V_3 can be estimated as the average volume obtained in Experiments D and E, and an estimate of k_f can be obtained by area analysis. Equations 1 and 4 can be integrated between the limits of zero and infinite time to yield Eqs. 6 and 7, respectively:

$$\text{area } C_1 = \frac{Dk_{-1}}{V_1\alpha\beta} \qquad \text{(Eq. 6)}$$

$$\text{area } C_m = \frac{Wk_fk_{-1}D}{V_3k_3\alpha\beta} \qquad \text{(Eq. 7)}$$

Combining Eqs. 6 and 7 and solving for k_f yield:

$$k_f = \frac{V_3k_3}{WV_1}\frac{\text{area } C_m}{\text{area } C_1} \qquad \text{(Eq. 8)}$$

The areas under the methsuximide and metabolite curves, area C_1 and area C_m, respectively, were determined using the trapezoidal rule; the areas from the time of the terminal data points to time infinity were calculated (17). The remaining parameter, k_{el}, was determined from:

$$k_{el} = \frac{\alpha\beta - k_{-1}k_f}{k_{-1}} \qquad \text{(Eq. 9)}$$

obtained directly from Eq. 5.

Table IV—Pharmacokinetic Parameters for Methsuximide and Metabolite after Intravenous Doses of Methsuximide

Parameter[a]	Experiment B	Experiment C
k_1, hr^{-1}	3.84 (0.52–7.17)[b]	0.71 (0.20–1.23)
k_{-1}, hr^{-1}	3.80 (1.92–5.68)	1.14 (0.26–2.02)
k_{el}, hr^{-1}	1.01 (0.69–1.33)	0.50 (0.42–0.58)
k_f, hr^{-1}	0.77 (0.54–1.00)	0.28 (0.24–0.31)
k_3, hr^{-1} (F)[c]	0.047	0.047
D/V_1, mg/liter	18.9 (12.8–25.0)	10.4 (9.3–11.5)
D/V_3, mg/liter (F)	18.9	18.9
V_1, liters	13.2	24.0
V_3, liters	13.2	13.2
α, hr^{-1}	8.64	2.24
β, hr^{-1}	0.78	0.40
$t_{1/2}$, hr (methsuximide)	0.9	1.7
$t_{1/2}$, hr (metabolite)	14.7	14.7
R^2 (methsuximide)	0.9979	0.9937
R^2 (metabolite)	0.9919	0.9914
R^2 (overall)	0.9950	0.9928

[a] First seven parameters are primary while the balance are derived. [b] The 95% confidence limits. [c] Indicates parameter was fixed in the regression analysis.

The methsuximide and metabolite data from Experiments B and C were simultaneously fitted to Eqs. 1 and 4. Since high correlations existed between some parameters, it was necessary to fix two of the seven primary parameters so that they would not contribute to the nonlinear regression analysis. Since V_3 was determined accurately in Experiments D and E and since identical values of k_3 were obtained by both initial estimate methods, these parameters were fixed. This procedure significantly reduced not only the correlations but also the 95% confidence limits of the parameters.

The computer parameter values are given in Table IV. The solid curves in Figs. 5 and 6 are the computer fits to the data. These figures and the R^2 values in Table IV indicate that Scheme III excellently describes the experimental data.

The simultaneous fitting only slightly changed the methsuximide parameters obtained in the absence of metabolite data (*cf.*, Table II).

Of particular interest is the relative importance of the rate of biotransformation of methsuximide to the metabolite, k_f, compared to the overall methsuximide elimination rate constant, $k_{el} + k_f$. This metabolic step accounted for 43 and 36% of the overall elimination of methsuximide in Experiments B and C, respectively. The large value of k_f together with the small k_3 led to sustained, high metabolite concentrations. This fact

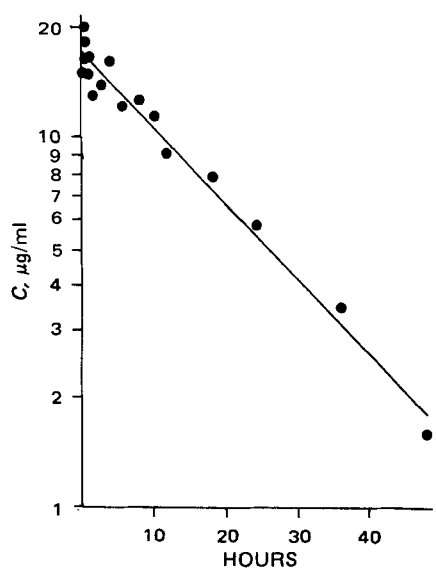


Figure 3—*Semilogarithmic plot of 2-methyl-2-phenylsuccinimide concentration* versus *time data from Experiment D after intravenous injection of this metabolite in the dog. The solid line was determined by linear regression analysis, the equation of which, including the 95% confidence limits, was log* $C_m = -0.0205(\pm 0.0015)t + 1.2326(\pm 0.0261)$.

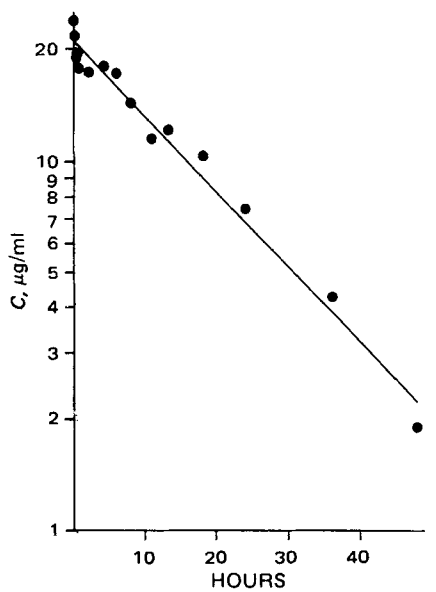


Figure 4—*Semilogarithmic plot of 2-methyl-2-phenylsuccinimide concentration* versus *time data from Experiment E after intravenous injection of this metabolite in the dog. The solid line was determined by linear regression analysis, the equation of which, including the 95% confidence limits, was log* $C_m = -0.0203(\pm 0.0017)t + 1.3245(\pm 0.0314)$.

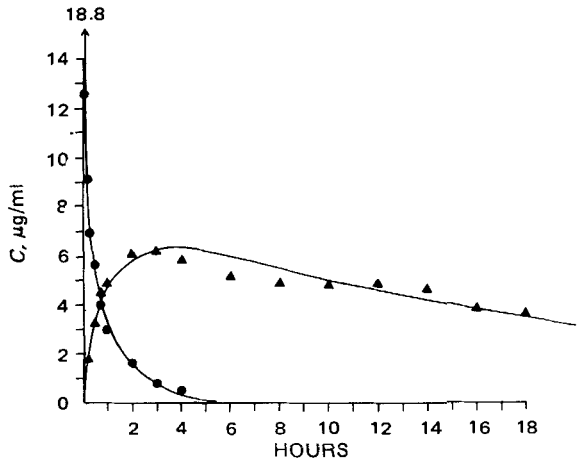


Figure 5—*Methsuximide and 2-methyl-2-phenylsuccinimide plasma level* versus *time profiles after a 250-mg intravenous injection of methsuximide (Experiment B). The computer-determined equations were: methsuximide* (●), $C_1 = 11.6e^{-8.64t} + 7.2e^{-0.78t}$; *and the metabolite* (▲), $C_m = -1.0e^{-8.64t} - 7.1e^{-0.78t} + 8.1e^{-0.047t}$.

lends support to the underlying assumption in this study that the dog is a suitable model for the pharmacokinetics of methsuximide in humans, since it has been shown that metabolite levels are also high and sustained in an overdose patient (12).

Multiple dosing of methsuximide results in induction of drug-metabolizing enzymes (10, 19). Thus, after multiple dosing, it might be expected that the metabolic step studied here would be increasingly important, both from a therapeutic and toxicological point of view. It cannot be discounted, however, that the metabolite may itself be responsible for some or all of the hepatic enzyme induction seen after repeated methsuximide doses.

Methsuximide is available for human use only as an oral dosage form. Since this drug is cleared from the body primarily by metabolism (7), the "first-pass effect," reported by Gibaldi *et al.* (20), may be an important phenomenon in methsuximide therapy. In light of the discussed enzyme induction and a possible first-pass effect, the pharmacological activity of methsuximide in humans may be due primarily to 2-methyl-2-phenylsuccinimide.

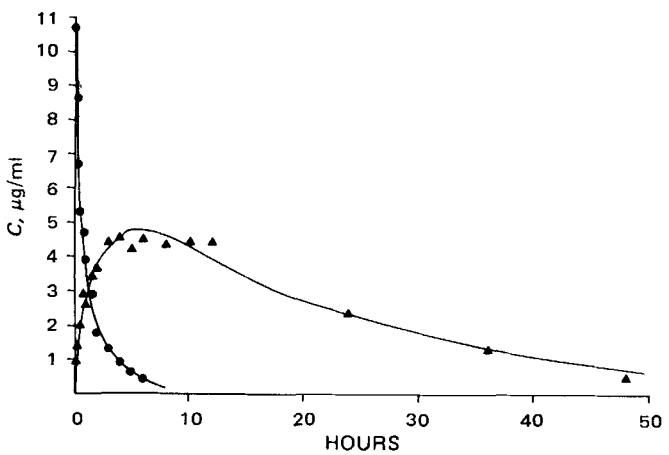


Figure 6—*Methsuximide and 2-methyl-2-phenylsuccinimide plasma level* versus *time profiles after a 250-mg intravenous injection of methsuximide (Experiment C). The computer-determined equations were: methsuximide* (●), $C_1 = 6.2e^{-2.24t} + 4.2e^{-0.40t}$; *and the metabolite* (▲), $C_m = -1.4e^{-2.24t} - 5.6e^{-0.40t} + 7.0e^{-0.047t}$.

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