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α,α-Diphenylsuccinimide: Evaluation of Anticonvulsant and Hydrophobic Properties

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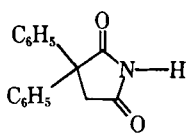
Received December 13, 1982, from the *Department of Pathology, Texas College of Osteopathic Medicine, Fort Worth, TX 76107.* Accepted for publication January 13, 1983. *Present address: Physiology Department, University of Utah, Salt Lake City, UT 84117.

Abstract □ The anticonvulsant potencies (ED_{50}) of α,α-diphenylsuccinimide, phenytoin, and phenobarbital were evaluated in mice by a standard maximal electroshock technique. Potencies were expressed in terms of intraperitoneal dosage and blood and brain concentrations. Overt neurotoxicity (TD_{50}) was assessed by the rotorod method. These data were compared with relative hydrophobicities for the above compounds and three others [carbamazepine, cyheptamide, and (diphenylacetyl)urea] taken from the literature. An approximate parabolic dependence of anticonvulsant potency on hydrophobicity was observed regardless of the means of expressing potency (intraperitoneal dosage, blood concentration, or brain concentration); approximate optimal hydrophobicities were in the range of 2.18–2.23 (log P). Calculated therapeutic indices (TD_{50}/ED_{50}) also displayed a parabolic dependence on hydrophobicity, while toxic potency (TD_{50}) displayed a linear dependence (within the limited range of log P values studied). Implications of the parabolic dependence of anticonvulsant potency and linear dependence of toxic potency on hydrophobicity are discussed with respect to the possible mechanisms involved.

Keyphrases □ α,α-Diphenylsuccinimide—anticonvulsant potency, hydrophobic properties, overt neurotoxicity, maximal electroshock screen in mice □ Anticonvulsants—α,α-diphenylsuccinimide, hydrophobic properties, overt neurotoxicity, maximal electroshock screen in mice □ Hydrophobicity—α,α-diphenylsuccinimide, anticonvulsant potency, overt neurotoxicity, maximal electroshock screen in mice

The synthesis of α,α-diphenylsuccinimide (I) was reported by Miller and Long in 1951 (1). The anticonvulsant profile of the compound was evaluated in rats by a pentylenetetrazole model and in mice by a maximal electroshock (MES) model of epilepsy (1, 2). The compound was judged ineffective (500 mg/kg) in the prevention of pentylenetetrazole-induced seizures. However, sufficient dosage conferred complete protection against MES seizures; the ED_{50} (oral) in the MES model was 45 mg/kg (1, 2). A quantitative estimate of neurotoxicity was not provided. Since this early work, additional reports on the pharmacology of this compound have not appeared, and after three decades its profile remains unclear.

The present study was undertaken (*a*) to evaluate the anticonvulsant, neurotoxic, and hydrophobic properties of α,α-diphenylsuccinimide, phenytoin, and phenobarbital and (*b*) to compare these properties with the same properties for carbamazepine, cyheptamide, and (diphenylacetyl)urea (3, 4). Relative anticonvulsant potencies, determined using a standard MES model of epilepsy (5), are expressed in terms of intraperitoneal dose and blood and brain concentrations. Neurotoxicity was assessed using a rotorod method (6). Relative neurotoxicities and therapeutic indices are reported on the basis of intraperitoneal dose. Relative hydrophobicities were approximated using hydrophobic π-constants (7). Inspection of the data suggests that the potency of α,α-diphenylsuccinimide is subject to the same parabolic dependence on hydrophobicity already described for other compounds (8).



I

EXPERIMENTAL

Drugs—Phenytoin sodium[1] and phenobarbital sodium[2] were gifts. α,α-Diphenylsuccinimide was prepared utilizing a modification of a method described previously (1). The procedure involved the addition of ethyl bromoacetate to a mixture of diphenylacetonitrile in sodium ethoxide. The intermediate ethyl β-cyano-β,β-diphenylpropionate was hydrolyzed, initially in potassium hydroxide to β-cyano-β,β-diphenylpropionic acid and subsequently in concentrated hydrochloric acid to α,α-diphenylsuccinic acid. At this point the synthesis deviated from the published procedure. α,α-Diphenylsuccinic acid was heated at reflux in acetyl chloride to give the anhydride, an ethereal solution of which was treated with ammonia. The intermediate α,α-diphenylsuccinamic acid was removed by filtration and heated at reflux with acetyl chloride to give α,α-diphenylsuccinimide, which was recrystallized from methyl alcohol, mp 140–142°C (reported mp (1) 140–142°C). This material showed one spot on TLC (silica gel, alumina; chloroform). IR (chloroform): 1770 and 1740 cm^{-1} (5-membered ring, imide C=O's); ^1H-NMR (deuterochloroform): δ 3.38 (s, 2, CH_2), 7.16 (s, 10, ArH), and 8.84 ppm (s, 1, NH).

Animal Studies—Phenytoin sodium was suspended in 30% polyethylene glycol 400, and α,α-diphenylsuccinimide was suspended in 5% gum acacia. Phenobarbital sodium was dissolved in 0.9% NaCl. The suspensions were sonicated (probe-type) for ~5 min to produce a fine suspension. The drugs were administered intraperitoneally in a volume of 0.01 mL/g of body weight to male CF_1 mice[3], average weight 22 g. The mice, 30–32 d of age when received, were allowed several days to acclimatize before testing. Food and water were given *ad libitum*.

The anticonvulsant activity of each drug was evaluated by a standard MES test (5). A 60-Hz alternating current (50 mA) was applied for 0.2 s *via* corneal electrodes. Protection was defined as the absence of tonic

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hind limb extension greater than a 90° angle with the trunk. The time of peak anticonvulsant effect was determined as described previously (9). Complete dose-response profiles were determined for each drug at its time of peak effect.

Immediately after the MES test, 100 μL of blood was collected in 2% sodium fluoride, and the animal was decapitated. The entire brain was removed and blotted on filter paper. The specimens (including blood) were stored at −80°C until assayed. Blood and brains from 10 mice were pooled for each dose, and at least five doses were employed for each drug.

Relative neurotoxicity was assessed by the rotorod method (6) in which the rodent is placed on a 2.54-cm diameter knurled rod, rotating at 6 rpm. Minimal neurological deficit was defined as the inability of a mouse to remain on the rotating rod for 1 min in at least two of three trials.

The anticonvulsant and neurotoxicity data were evaluated with 95% confidence limits by a quantal statistical method (10). The relative anticonvulsant potencies (ED_{50}) are expressed in terms of blood and brain concentrations, as well as intraperitoneal dosage. The relative neurotoxicity data (TD_{50}) are expressed in terms of intraperitoneal dosage only.

Analytical Methods—The blood and brain concentrations for each drug were assayed by GC. The method for extraction from blood and brain is similar for all three compounds. Aqueous suspensions of blood and homogenized whole brain were saturated with ammonium sulfate and acidified with concentrated hydrochloric acid. These suspensions were extracted with toluene, and the toluene layer was back-extracted with tetramethylammonium hydroxide. The drugs were then derivatized with methyl iodide (11) and extracted into chloroform in the presence of excess 1 M monobasic potassium phosphate. 5-(*p*-Methylphenyl)-5-phenylhydantoin was used as internal standard for the analysis of phenytoin and α,α-diphenylsuccinimide, and 5-ethyl-5-tolylbarbituric acid was used for the phenobarbital assay. Phenytoin was recovered from brain and blood specimens with 77 and 86% efficiency, respectively. Phenobarbital and α,α-diphenylsuccinimide were recovered from either specimen with at least 86% efficiency. Each drug was chromatographed using Supelcoport, 80–100 mesh.

Blood and brain extracts of phenytoin were assayed isothermally at 230°C on 3% OV-17 (injector port and detector temperature 300°C). The retention times for phenytoin and its internal standard were 5.9 and 8.3 min, respectively. Phenobarbital was assayed isothermally in brain extracts at 210°C on 3% OV-17 (injector port temperature 280°C, detector temperature 300°C) and in blood extracts at 170°C on 3% OV-101 (injector port temperature 270°C, detector temperature 340°C). The retention times for phenobarbital and its internal standard were 2.3 and 3.3 min, respectively, for the brain extract, and 2.2 and 3.3 min, respectively, for the blood extract. α,α-Diphenylsuccinimide (I) in brain extracts was assayed with a programmed run from 170°C to 240°C (10°C/min) on 3% OV-17 (injector port and detector temperature 300°C). Assay of I in blood extracts was programmed as follows: 130°C held for 2 min, followed by a 10°C/min increase to 210°C, where it was held for a final 2 min (3% OV-101; injector port temperature 270°C, detector temperature 300°C). The retention times for α,α-diphenylsuccinimide and its internal standard were 8.3 and 3.1 min, respectively, for the brain extract, and 8.9 and 3.7 min, respectively, for the blood extract.

Each method employed flame-ionization detection. The carrier gas (nitrogen), flow rates (50 mL/min), and column dimensions (2-mm i.d. × 1.83 m) were also common for the three drugs, in both blood and brain extracts. An example of a typical chromatogram for α,α-diphenylsuccinimide extracted from brain tissue is depicted in Fig. 1.

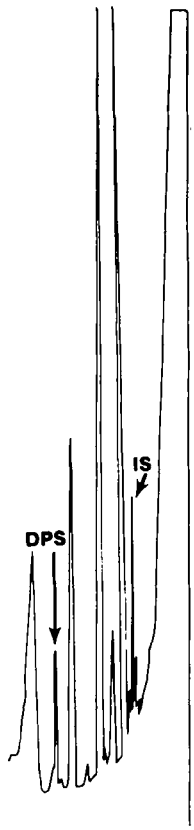

Figure 1—*Chromatogram of α,α-diphenylsuccinimide (DPS) from brain extract. Internal standard (IS) was 5-(p-methylphenyl)-5-phenylhydantoin. See text for methods.*

RESULTS AND DISCUSSION

α,α-Diphenylsuccinimide produced qualitatively the same alteration of MES-induced seizure pattern as that produced by phenytoin or phenobarbital; *i.e.*, the tonic hind limb extension was abolished with sufficient dosage of each drug. The ED_{50} (intraperitoneal dosage) for α,α-diphenylsuccinimide was 26.5 mg/kg (95% confidence limits: 23.4–30.0) (Table I). This is lower than the 45 mg/kg estimate reported for an oral dosage (1, 2). (The apparently greater potency by the intraperitoneal route can likely be ascribed to the greater surface area for absorption by this route.) In comparison, phenytoin and phenobarbital are more potent than α,α-diphenylsuccinimide when estimates are based on intraperitoneal dosage (Table I). However, the difference in potency among these drugs is much smaller when estimates are based on blood or brain concentrations. In fact, α,α-diphenylsuccinimide is more potent than phenobarbital when blood or brain concentration forms the basis of comparison (Table I).

Much of the variation in anticonvulsant potency among these drugs can be explained by a parabolic dependence of potency on hydrophobicity, already described for other agents (8). This is evident if one compares the potency and log P (logarithm of the partition coefficient) values of phenobarbital, carbamazepine, phenytoin, α,α-diphenylsuccinimide, cyheptamide, and (diphenylacetyl)urea (Table I). It will be seen that potency (expressed in terms of intraperitoneal dosage or blood concentrations) increases from phenobarbital to carbamazepine to phenytoin, with the increase of log P from 1.63 to 2.18 to 2.23, respectively. However, potency decreases from phenytoin to α,α-diphenylsuccinimide to cyheptamide to (diphenylacetyl)urea, with the continued increase of log P from 2.23 to 2.63 to 2.74 to 2.83, respectively. If expressed in terms of brain concentrations, potency increases from phenobarbital to carbamazepine with the increase of log P from 1.63 to 2.18, respectively; further increases in log P result in decreased potency. Thus, the optimal hydrophobicity among these compounds is expressed by log P values in the range of 2.18–2.23. This is not too different from the optimal hydrophobicities (log P_O) predicted by others for antielectroshock activity in rats (1.8) and mice (3.7) (12) and for hypnotic activity in rats and mice (2.0) (13). (The fact that log P_O for anticonvulsant activity does not differ significantly from log P_O for hypnotic activity indicates that changes in hydrophobicity alone may not result in more selective anticonvulsant agents.)

A conceptual explanation for the parabolic dependence of potency on hydrophobicity is that molecules must possess a certain degree of lipid solubility in order to "dissolve" in and penetrate the lipid matrix of membranes, and increases in lipophilicity (hydrophobicity) will, within limits, facilitate this process. However, increases beyond a certain optimal hydrophobicity (log P_O) result in lower potency because the molecules increasingly partition within the lipid matrix of the membrane. Because the probability of membrane penetration is thus diminished, higher concentrations of drug are necessary to permit an eventual efficacious engagement of receptors.

If the data in Table I are arranged to express brain–blood concentration ratios, it will be seen that the distribution of drug between the two compartments also follows an approximate parabolic relationship with hydrophobicity. The ratios increase from phenobarbital (0.87) to carbamazepine (2.04) to phenytoin (2.41) with increases in log P up to 2.23;

Table I—Anti-Maximal Electroshock Potency (ED_{50}), Overt Neurotoxicity (TD_{50}), and Calculated Log P of α,α-Diphenylsuccinimide, Phenytoin, Phenobarbital, Carbamazapine, Cyheptamide, and (Diphenylacetyl)urea

	Phenobarbital (III)	Carbamazepine	Phenytoin (II)	α,α-Diphenyl-succinimide (I)	Cyheptamide	(Diphenyl-acetyl)urea
ED_{50} intraperitoneal, mg/kg	19.0(17.1–21.2)	9.7(8.5–11.0)	7.1(6.5–7.8)	26.5(23.4–30.0)	81.0(52.0–127.0)	406(349–472)
blood, μg/mL	17.2(15.5–19.1)	2.4(2.2–2.7)	2.2(1.8–2.8)	5.0(3.4–7.2)	5.5(3.9–7.8)	23(12.6–42.1)
brain, μg/g	15.0(13.6–16.5)	4.9(4.1–5.7)	5.3(4.7–5.9)	8.4(6.4–11.1)	8.9(7.5–10.6)	40(25.5–62.8)
TD_{50}, mg/kg ip[a]	66(62–71)	71[b]	91(84–98)	220(200–241)	170[b]	—[c]
Therapeutic index[d] Log P	3.5(3.1–3.9)	7.6	12.8(11.4–14.3)	8.3(7.3–9.5)	2.1	—[c]
	1.63[e]	2.18[f]	2.23[f]	2.63[g]	2.74[f]	2.83[f]

[a] Overt toxicity was assessed by the rotorod method (Ref. 6). [b] Obtained from the literature (Refs. 15 and 16). [c] Not available from the literature. [d] Calculated for each drug as the ratio TD_{50}/ED_{50} with respect to the intraperitoneal dose (mg/kg). [e] Calculated by π (barbiturate function) + π (C_6H_5) + π (ethyl) = −1.35 (Ref. 13) + 1.96 (Ref. 7) + 1.02 = 1.63 (Ref. 7). The calculated log P was used in preference to the experimental value (1.42, Ref. 13) to maintain consistency among calculated values. [f] Obtained from the literature (Refs. 3 and 4). [g] Calculated by π (succinimide) + 2π(C_6H_5) = −1.29 (Ref. 12) + 3.92 = 2.63.

further increases in log P result in lower ratios. (The only compound which is in poor compliance with this relationship is (diphenylacetyl)-urea.) This, of course, is expected on the basis of the conceptual framework discussed above. Each membrane interposed along the pharmacokinetic path a drug might follow to its receptor will lessen the probability that the drug will ever engage its receptor. The greatest reduction in such probability occurs at extreme values of the partition coefficient. Since one or more membranes must separate the blood from the brain (and receptor) compartments, the decrease in the brain–blood ratios with either very low or very high log P values is likely the result of a failure to enter the lipid bilayer or a failure to penetrate once entry has been made, respectively.

After a comparison was made of the average potency ratios among the above drugs within each category (*i.e.*, intraperitoneal dosage, blood concentration, and brain concentration), it was found that the smallest average potency ratio (3.1, $SD = 2.2$, $n = 15$) was for potencies expressed in terms of brain concentrations; the largest average ratio was for potencies expressed in terms of intraperitoneal dosage (12.1, $SD = 16.5$, $n = 15$), and the average ratio in terms of blood concentrations (4.2, $SD = 3.1$, $n = 15$) was intermediate. This also can be explained within the conceptual framework already discussed. As the number of membranes a drug must penetrate increases, the probability of a particular molecule penetrating all of the membranes decreases; this decrease is disproportionately greater for drugs with hydrophobicities at either extreme. Hence, the smaller average potency ratios expressed on the basis of brain concentrations might simply be an expression of a smaller difference in probability permitted by fewer barriers separating the drug from its receptor. In the formalism of shallow *versus* deep compartmentalization (14), the receptors exist in a relatively more shallow compartment when potency is expressed in terms of brain concentrations than when expressed in terms of intraperitoneal dosage or blood concentration.

Another factor which might partially explain the larger average potency ratios for intraperitoneal dosage is limited aqueous solubility. The log P value is an index of relative solubility in a hydrophobic *versus* aqueous solvent; it is not a measure of the absolute aqueous solubility of a compound. Thus, the role that variance in log P might play in the parenteral absorption of the above drugs might be insignificant in comparison with the variance imposed by significant differences in absolute aqueous solubility. If the drug is not sufficiently soluble in water to permit intimate association with the membrane, the role of hydrophobicity in drug absorption will be minimized.

In contrast with the MES data, overt neurotoxicity assessed by the rotorod method did not exhibit an apparent parabolic dependence on log P. Neurotoxicity data are not available for (diphenylacetyl)urea, but the rotorod TD_{50} values for carbamazepine and cyheptamide in mice are 71 (15) and 170 mg/kg (16), respectively (the estimate for cyheptamide was based on oral dosage). Thus, neurotoxicity seems to be inversely related to log P; higher log P values are associated with lower toxic potency (*i.e.*, higher TD_{50} values). This observation is supported by regression analysis of 16 compounds (15) which provided the following:

$$\log 1/C = 15.94\log MW - 0.97\log P + 0.55\mu - 33.19 \quad \text{(Eq. 1)}$$

where C is the dose producing (in mice) measurable toxicity in 50% of the test population (*i.e.*, TD_{50}), MW is the molecular weight, and μ is the dipole moment. If one compares the above equation with one of several equations which have been written to characterize anti-MES potency, it becomes apparent that overt neurotoxicity is not simply an extension of anticonvulsant activity. For example, anti-MES potency in mice has been characterized by:

$$\log 1/C = -0.22(\log P)^2 + 1.15\log P - 0.37\mu + 2.99 \quad \text{(Eq. 2)}$$

where C is the dose conferring protection against seizures in 50% of the test population (*i.e.*, ED_{50}). Thus, there is considerable evidence for a linear dependence of neurotoxicity on log P (within the dosage range evaluated) and a parabolic dependence of anticonvulsant potency on log P. Furthermore, neurotoxic potency is directly proportional to μ, whereas anticonvulsant potency is inversely proportional to μ. Therefore, it is apparent that the mechanisms conferring toxicity are fundamentally different than those that confer an anticonvulsant effect.

This can also be rationalized if one compares the therapeutic indices (TD_{50}/ED_{50}) for the above drugs. These indices exhibit the same parabolic dependence on log P as does anticonvulsant potency. For example, the therapeutic indices increase from phenobarbital (3.5) to carbamazepine (7.6) to phenytoin (12.8) with successive increases in log P, but the indices decrease from phenytoin (12.8) to α,α-diphenylsuccinimide (8.3) to cyheptamide (2.1) with continued increases in log P (the therapeutic index is not yet known for (diphenylacetyl)urea). This parabolic dependence of therapeutic ratio would not be expected if the toxic and anticonvulsant actions were the result of identical mechanisms.

Although at first thought it might seem that the uniqueness of mechanisms involved might make it easier to design more selective (less toxic) anticonvulsant compounds, the parabolic dependence of therapeutic index on log P severely limits the utility of this parameter in such design. However, it is also apparent that other indices, such as dipole moment, should be explored more thoroughly. As is apparent from the above equations, larger dipole moments might be associated with lower anticonvulsant potency, but greater toxic potency. Thus, it might make sense to screen hypothetical compounds for dipole moment as well as hydrophobicity. Furthermore, as the quantitative structure–activity relationships (QSAR) of anticonvulsant compounds become more fully documented, it is distinctly possible that other physicochemical or empirical indices will contribute still more to rational drug design. The potency data provided herein should be useful in QSAR studies of anticonvulsant compounds, in particular because potency expressed in terms of brain concentration appears more suited for such analysis than potency expressed as parenteral dosage.

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Pharmacokinetic Analysis of Concentration–Time Data Obtained Following Administration of Drugs that are Recycled in the Bile

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Received October 4, 1982, from the *Department of Pharmacokinetics and Biopharmaceutics, Hoffmann-La Roche Inc., Nutley, NJ 07110.* Accepted for publication January 18, 1983.

Abstract □ A pharmacokinetic model for calculating the pharmacokinetic parameters for a compound that is recycled in the bile is presented and tested using theoretical as well as experimental data. The results indicate that this method is stable and only slightly susceptible to sampling and recycling times. It is apparent from the present study that pharmacokinetic terms that have been used in classical situations are not directly applicable to drugs that enter the enterohepatic circulation. Effective half-life and effective clearance are used to describe the intrinsic ability of the eliminating organs to remove drug from the blood, whereas net half-life and net clearance are used to describe the irreversible elimination of the drug from the body.

Keyphrases □ Pharmacokinetics—biliary recycling of drugs, theoretical model, applications to cimetidine and isotretinoin □ Biliary excretion—incorporation in pharmacokinetics, model, applications to cimetidine and isotretinoin □ Mathematical models—incorporation of biliary recycling in pharmacokinetics, application to cimetidine and isotretinoin

The ability to predict plasma concentration–time profiles observed following repetitive doses from data obtained following a single dose is an important aspect of pharmacokinetic analysis. In most cases, drugs that follow linear pharmacokinetic models allow these predictions to be made with reasonable certainty. However, when plasma concentration–time data cannot be adequately described by classical pharmacokinetic equations, *i.e.*, saturable processes or enzyme induction, this predictive capability becomes impaired. When a compound is excreted in the bile and subsequently reabsorbed from the GI tract, a similar situation exists in that classical equations cannot be used to sufficiently characterize the erratic and fluctuating plasma concentration–time curves. The purpose of the present investigation was to develop a biliary recycling model, to test its susceptibility to sampling times and experimental error, and to apply it to experimental data from drugs that are known to recycle in the bile.

THEORETICAL

Two distinct types of compounds must be considered when discussing biliary excretion and enterohepatic circulation. In the first category, there are compounds that are recycled but still are eliminated in ≤24 h; indomethacin (1), cimetidine (2), and imipramine (3) are examples from this category. In the second category are compounds that persist for much longer than 24 h; isotretinoin (4), digitoxin (5), and phenprocoumon (6) are examples from this category of substances. For compounds that are eliminated from the body in ~24 h or less, extensive sampling of body fluids is required over the entire interval, whereas for compounds that take substantially longer than 24 h to be eliminated from the body, extensive sampling during the first 24 h and subsequent samples at 24-h intervals are required. The modeling procedure developed herein considers both types of compounds.

Model Development—The following compartmental models (Fig. 1) are among those applicable to the study of blood concentration–time data profiles of compounds that undergo enterohepatic circulation. The models differ only in the sites of elimination. It can be shown that models

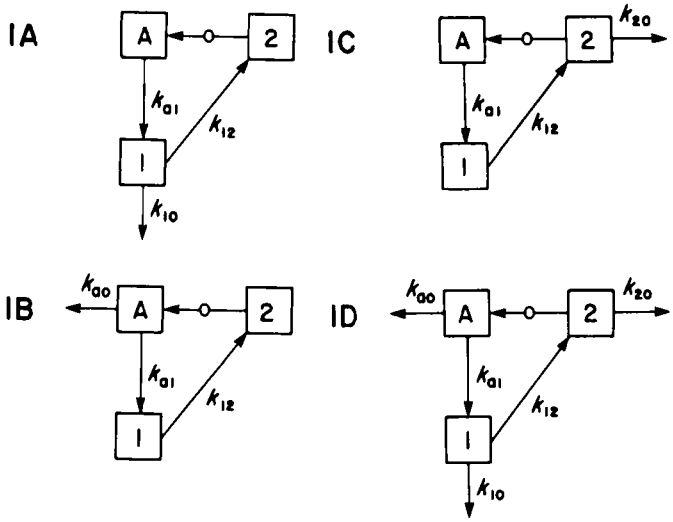

Figure 1—*Four possible enterohepatic recycling models. Compartment A is the absorption site, compartment 1 is the sampled blood compartment, and compartment 2 is the storage compartment that includes the gallbladder and the transit-time factor. The first-order rate constants* k_{a1} *and* k_{12} *represent the transfer of drug from the absorption site to the sampled blood compartment and from the sampled compartment to the gallbladder storage compartment whereas* k_{a0}, k_{10}, *and* k_{20} *are rate constants that represent first-order elimination from the absorption site, sampled compartment, and gallbladder storage compartment. The arrow between compartments 2 and A represent the discontinuous emptying process of the gallbladder such that the amount of drug in the gallbladder is transferred instantaneously to the absorption site at the time* (t_{bile}) *that reabsorption begins and V is the volume of the sampled compartment.*

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