Comparative Pharmacokinetic and Pharmacodynamic Analysis of Phthaloyl Glycine Derivatives with Potential Antiepileptic Activity

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Glycine, in addition to GABA, is one of the most important neurotransmitter amino acids. The described structure pharmacokinetic pharmacodynamic relationships (SPPR) study explored the possibility of utilizing phthaloyl derivatives of glycine as new antiepileptics. This was carried out by investigating the pharmacokinetics and pharmacodynamics (anticonvulsant activity and neurotoxicity) of the following four phthalimide derivatives: phthaloyl glycine, phthaloyl glycinamide, N,N-diethyl phthaloyl glycinamide and N,N-diisopropyl phthaloyl glycinamide. Phthaloyl glycine did not demonstrate anticonvulsant activity, possibly because of its poor pharmacokinetics, high clearance, low volume of distribution and short half life. The three glycinamide derivatives showed anticonvulsant activity and had better pharmacokinetic profiles, longer half life and mean residence time, than phthaloyl glycine. Phthaloyl glycinamide was more potent than one of the major antiepileptic agents—valproic acid and showed a better margin between activity and neurotoxicity. The four investigated phthaloyl glycine derivatives did not operate as chemical drug delivery systems (CDDS) of glycine, but acted rather as drugs on their own. Phthaloyl glycine was excreted unchanged in the urine while the urinary metabolites of the glycinamide derivatives were phthaloyl glycine and phthaloyl glycinamide. In this analogous series of phthalimide derivatives, minor chemical changes affected dramatically the compounds' pharmacokinetics. The current study demonstrates the benefit of the SPPR approach in developing and selecting a potent antiepileptic compound in intact animals based not only on its intrinsic pharmacodynamic activity, but also on its better pharmacokinetic profile.

KEY WORDS: phthaloyl glycine; phthaloyl glycinamide and its N,N-dialkyl analogues; anticonvulsant activity; structure pharmacokinetic pharmacodynamic relationships (SPPR).

INTRODUCTION

GABA is an inhibitory neurotransmitter, which plays an important role in the control of neuronal activity in the mammalian central nervous system (CNS). A deficiency in brain GABA levels has been found to cause convulsions or epilepsy (1,2). Therefore, drugs which increase the amount of GABA available in the brain for neurotransmission have the potential of becoming antiepileptic agents. The first GABA derivative to become an antiepileptic was progabide which was approved in France in the mid 1980's (3). Two of the five newest antiepileptics recently approved; vigabatrin and gabapentin, contain GABA in their molecule (4). Vigabatrin, γ-vinyl GABA, was designed to increase GABA brain levels by inhibiting GABA transaminase (5). Gabapentin contains a GABA molecule symmetrically integrated into a lipophilic cyclohexane system, which unlike GABA has the ability of crossing the blood brain barrier (4,6). However, at present it appears that gabapentin has a novel mechanism of action which is unrelated to its original design as a GABA analogue (6).

Next to GABA, glycine is one of the most important inhibitory neurotransmitter amino acids. Glycine has also been incorporated into a new antiepileptic agent—milacemide-I (7). Recent reports have shown that in several rats models, co-administration of glycine together with other antiepileptics, such as phenytoin, phenobarbital and vigabatrin, potentiate their anticonvulsant activity due to synergism (8–11).

In spite of their intrinsic potency neither GABA nor glycine are effective upon oral or systemic administration, due to their inability to cross the blood brain barrier (BBB) and their liver metabolic deactivation which minimizes their availability to the brain (12). The delivery of these two inhibitory neurotransmitters into the brain can be accomplished by designing active lipophylic derivatives which will act as drugs on their own, or as chemical drug delivery systems (CDDS) which will serve as BBB penetrative carriers (13,14).

Recently, it was reported that the new compound taltrimide—(2-phthalimidoethanesulphon-N-isopropylamide-II) and its dealkylated metabolite showed promising anticonvulsant activity in animal models (15). Taltrimide, which is currently undergoing clinical trials, is a phthalimide derivative of taurine, which like glycine is a neuroinhibitory transmitter (15,16). A second phthalimide derivative, phthaloyl GABA (III) also has been reported to possess antiepileptic activity in different animal models (17,18).

A comparative analysis of the structures of milacemide, taltrimide and phthaloyl GABA led us to the idea of designing and evaluating several glycine derivatives of phthalimide with potential antiepileptic activity. These phthalimide derivatives could serve as CDDS for glycine and glycinamide or may become potent glycine derivatives on their own. Consequently, glycine brain penetrability will be enhanced leading to glycine derivatives with anticonvulsant activity in intact animals. The purpose of the current study was to comparatively evaluate the pharmacokinetics and pharmacodynamics (anticonvulsant activity and neurotoxicity) of the following four phthalimide derivatives (Fig 1): phthaloyl glycine (IV), phthaloyl glycinamide (V), N,N-diethyl phthaloyl glycinamide (VI) and N,N-diisopropyl phthaloyl glycinamide (VII). The analysis was carried out utilizing a structure pharmacokinetic pharmacodynamic relationship (SPPR) study. This approach enabled pharmacokinetic pharmacodynamic correlation as well as investigation of how the in vivo performance (pharmacokinetics in intact animals) affected the anticonvulsant activity in a series of analogous phthaloyl glycine derivatives.

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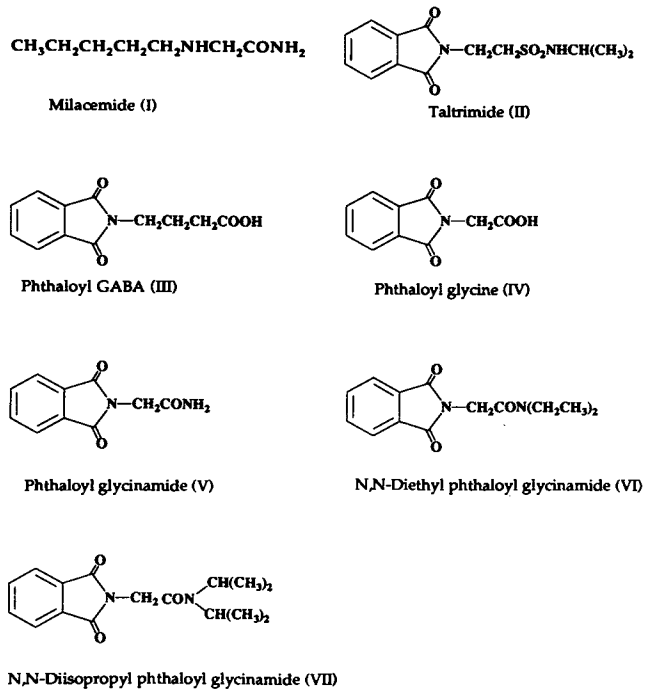

Figure 1 Chemical structures of the phthaloyl glycine derivatives investigated and evaluated in this study.

MATERIALS AND METHODS

Materials

Phthaloyl glycine, phthalimide and tert-butyl methyl ether were purchased from Aldrich, Wisconsin, USA. Phthaloyl glycinamide (V) was synthesized by a classical method, reacting N-carboethoxy phthalimide with glycinamide. The N,N- diethyl and N,N-diisopropyl phthaloyl glycinamides were prepared by reacting phthaloyl glycine with diethylamine and diisopropylamine, respectively. Phthaloyl GABA (III) (17,18) was also synthesized (for comparative means and for utilization as an internal standard) by reacting N-carboethoxy phthalimide with GABA. All reagents used were of analytical grade or HPLC pure. The chemical structures of the synthesized phthaloyl derivatives were confirmed by nuclear magnetic resonance (NMR) and elemental microanalysis.

Pharmacokinetic Studies

Dogs

The pharmacokinetic studies were carried out on four mongrel dogs ranging in weight between 18 and 21 kg. In a randomized cross over design, each dog was intravenously injected (into one of the cephalic veins) with the following phthaloyl derivatives: phthaloyl glycine (400 mg), phthaloyl glycinamide (400 mg), N,N-diethyl phthaloyl glycinamide (510 mg) and N,N-diisopropyl phthaloyl glycinamide (562 mg). The doses of the latter two compounds were equivalent to 400 mg of phthaloyl glycinamide.

Protocol. Venous blood samples (6 ml) were collected via an indwelling catheter (from the other cephalic vein) at specified intervals following injection (0, 5, 10, 15, 20, 30, 40 and 50 min, and 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hr). The plasma was immediately separated by centrifugation at 3000 g for 15 min and stored at −20°C. Before each assay, the plasma was allowed to reach room temperature, was vortexed, centrifuged, and the residual clot removed. Plasma concentrations of the investigated phthaloyl derivatives were monitored by an HPLC assay whose details are described below. Urine was collected systematically at 1 hour intervals for 12 hours after dosing, by means of an indwelling catheter. Urine levels of the phthaloyl derivatives were assayed by HPLC.

Rats

Pharmacokinetic studies were carried out on Sabra rats weighing 250–260 g placed in metabolic cages. In three parallel studies the rats were intravenously (20 mg) injected with phthaloyl glycine (IV), phthaloyl glycinamide (V) and N,N-diethyl phthaloyl glycinamide (IV).

Protocol. Following each administration, four rats were sacrificed and blood collected at each of the following time intervals; 5, 15, 30, 45, 60 min 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 7, 8, 9, and 10 hours following dosing. Urine was collected systematically at one hour intervals for 12 hours after dosing, utilizing the metabolic cages. The remainder of the protocol was as described above for the dog studies.

Assay Methodology

A new HPLC assay was developed, which allowed simultaneous monitoring and quantification of phthaloyl glycine, phthaloyl glycinamide, N,N-diethyl phthaloyl glycinamide and N,N-diisopropyl phthaloyl glycinamide.

The assay procedure was as follows: To 0.25 ml plasma (containing the above mentioned phthalimide derivatives), internal standard solution (10 ul of phthaloyl GABA solution, 1 mg/ml in acetonitrile), and methanol (1 ml) were added. The mixture was vortexed for 30 minutes and 1 ml of acetonitrile was added followed by a 30 min vortex. The mixture was then centrifuged for 10 minutes at 3000 g and tert. butyl methyl ether (3 ml) was added, followed by a 30 second vigorous vortex. The mixture was centrifuged for 10 minutes at 3000 g and the organic phase was separated, and evaporated (using a vortex evaporator) to dryness. To the dry residue, mobile phase (120 ul) was added, the mixture was vortexed and 20 ul were injected into the HPLC apparatus (LDC Milton Roy, USA).

HPLC Conditions: Column —RP-18 reverse phase column (Lichrosphere—RP-18 5 μ—Merck, Germany) equipped with a precolumn. Mobile phase: acetonitrile 35%, bidistilled water 65%, and trifluoroacetic acid (TFA) 0.1%. UV wave length—220 nm. The minimum quantifiable concentration of the assay was 0.1 mg/L. The interday coefficient of variation among replicates ranged between 5 and 9.5%.

Pharmacokinetic Calculations

The linear terminal slope (β) of the log C (the plasma concentration of the appropriate phthalimide derivative) versus t (time) plot, was calculated by the method of least squares. The terminal half-life of each compound (t1/2β) was calculated from the quotient: 0.69/terminal slope (19). The AUC (area under the C versus t curve) was established by using the trapezoidal rule with extrapolation to infinity, by dividing the last experimental plasma concentration by the terminal slope. The total body clearance (CL) of each compound was found by using the quotient of the iv dose (D) and the AUC. The volume of distribution (Vβ) could then be calculated by using the quotient of the clearance and the linear terminal slope (19). The volume of distribution at steady state (V_{ss}) and the mean residence time (MRT) were calculated by classical methods (19). The fraction excreted unchanged (fe) of each of the phthaloyl glycine derivatives was calculated from the ratio of the cumulative amount excreted in the urine to the dose. The fraction metabolized of a phthaloyl derivative (eg. phthaloyl glycinamide) to its urinary metabolite (eg. phthaloyl glycine) was calculated from the dose normalized ratio of the fe obtained after iv administration of the parent compound and its corresponding metabolite. All of the pharmacokinetic parameters were calculated in a non-compartmental manner based on the statistical moment theory (19,20).

Pharmacodynamic Evaluation of Anticonvulsant Activity and Neurotoxicity

The following compounds: phthaloyl GABA (III), phthaloyl glycinamide (V), phthaloyl glycine (IV), phthalimide, N,N-diethyl phthaloyl glycinamide (VI) and N,N-diispropropyl phthaloyl glycinamide (VII) were screened in mice and rats for their anticonvulsant activity and neurotoxicity in collaboration with the NIH Epilepsy Branch (21). The screening procedure involved the following: 1. The maximal electroshock (MES) test which measures seizure spread. 2. The subcutaneous pentylenetetrazol (sc Met) test which measures seizure threshold and 3. The rotorod ataxia test which assesses neurotoxicity.

RESULTS

Figure 2 depicts the mean plasma levels of phthaloyl glycine, phthaloyl glycinamide, and N,N-diisopropyl phthaloyl glycinamide, obtained following their iv administration to four dogs. Unlike the above three compounds, following the iv administration of N,N-diethyl phthaloyl glycinamide (VI), a metabolite—phthaloyl glycine (IV) was also detected and monitored in the plasma. Figure 3 depicts the mean plasma levels of compound VI and its metabolite-phthaloyl glycine (IV) obtained following its iv administration to the same four dogs. Table I summarizes the mean pharmacokinetic parameters of the four phthaloyl glycine derivatives in dogs. Figures 4 and 5 depict the mean plasma levels of phthaloyl glycine, phthaloyl glycinamide and N,N-diethyl phthaloyl glycinamide (and its metabolites—compounds IV and V) obtained following their iv administration to rats and Table II summarizes the pharmacokinetic parameters of these compounds in rats.

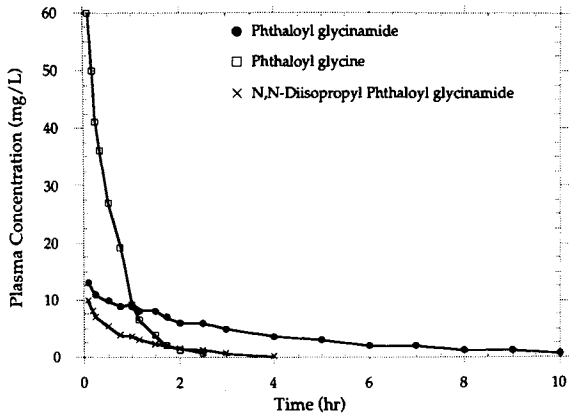

Figure 2 Mean plasma levels of phthaloyl glycinamide, phthaloyl glycine and N,N-diisopropyl phthaloyl glycinamide obtained following iv administration (at a dose equivalent to 400 mg of phthaloyl glycinamide) to four dogs.

Anticonvulsant testing showed that phthaloyl glycine and phthaloyl GABA were inactive. However, phthaloyl glycinamide and its two dialkyl analogues (VI and VII) showed better anticonvulsant potency in the MES and had better safety margins (as indicated by their protective index PI—the ratio of the ED_{50} in the MES test to the TD_{50} in the neurotoxicity test) than one of the major antiepileptic drugs valproic acid—VPA. Table III compares the anticonvulsant performance of phthaloyl glycinamide and its two dialkyl analogues with VPA and phthalimide, after ip administration to mice, and oral administration to rats. In mice, phthaloyl glycinamide was twice as active (or potent as an anticonvulsant) and three times less neurotoxic than VPA and thus, had a protective index (PI) of greater than 6.4 relative to a VPA-PI value of 1.4. In rats, the difference in anticonvulsant activity was even more favourable; phthaloyl glycinamide and its disopropyl analogue were 16 times more potent than VPA and half as toxic. They had a PI value of 16 relative to a VPA-PI value of 0.6. N,N-diethyl phthaloyl glycinamide was the most active compound being 2.5 times more potent than the other two glycinamide derivatives.

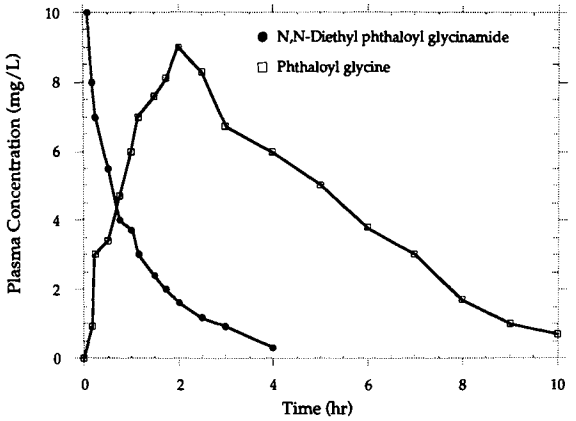

Figure 3 Mean plasma levels of N,N-diethyl phthaloyl glycinamide and phthaloyl glycine obtained (at a dose equivalent to 400 mg phthaloyl glycinamide) following iv administration of N,N-diethyl phthaloyl glycinamide to four dogs.

Table I. Mean Pharmacokinetic Parameters of Phthaloyl Glycine (PHT-GLN), Phthaloyl Glycinamide (PHT-GLD), N,N-diethyl Phthalyl Glycinamide (DIE) and N,N-diisopropyl Phthaloyl Glycinamide (DIP) Obtained following iv Administration (at a Dose Equivalent to 400 mg of Phthaloyl glycine) to Four Dogs

	Mean ± SD			
	PHT-GLN	PHT-GLD	DIE	DIP
$t_{1/2}$ β (hr)	0.37 ± 0.11	3.4 ± 0.7	1.1 ± 0.3	2.1 ± 0.3
AUC (mg/L hr)	38 ± 16	49 ± 9	11 ± 6	254 ± 18
CL (L/hr)	12 ± 4.4	8.5 ± 1.6	48 ± 1.4	2.2 ± 0.2
Vss(L)	6.6 ± 1.9	46 ± 13	71 ± 11	6.8 ± 0.7
Vβ (L)	6.1 ± 1.9	48 ± 13	71 ± 24	6.8 ± 1.3
MRT (hr)	0.58 ± 0.14	4.6 ± 0.9	1.5 ± 0.3	3.1 ± 0.2
fe (%)	92 ± 4	7 ± 0.7	5 ± 0.4	3.6 ± 0.5
fm to PHT-GLN (%)		34 ± 3	27 ± 2	
fm to PHT-GLD (%)			57 ± 6	

DISCUSSION

Pharmacokinetic analysis showed that phthaloyl glycinamide had a lower clearance value than its corresponding acid, phthaloyl glycine. However, the major pharmacokinetic difference between phthaloyl glycine and phthaloyl glycinamide was in their volume of distribution (V_{ss} or Vβ). The volume of distribution of phthaloyl glycinamide was 7 times larger than that of phthaloyl glycine. The great difference in volume of distribution and the relative lower clearance value led to phthaloyl glycinamide being retained in the body for a much longer period of time than phthaloyl glycine as reflected by the MRT values.

The half-life of drugs in general is affected by their clearance and their volume of distribution (19). Comparison of the three major pharmacokinetic parameters; CL, V and t½ shows that the relative decrease in the t ½ of phthaloyl glycine was mainly due to a decrease in volume of distribution and, to a lesser degree to an increase in clearance.

In dogs, N,N-diethyl phthaloyl glycinamide had a short half life as a result of its larger clearance. Diisopropyl phthaloyl glycinamide had a shorter half life than phthaloyl glycinamide due to its lower volume of distribution. The current study shows that increasing the lipophilicity of phthaloyl glycinamide by the synthesis of the above two analogues did not affect the pharmacokinetics of these derivatives in the same way (Table I). In comparison to its two N,N-dialkyl analogues, phthaloyl glycinamide demonstrated the best pharmacokinetic performance in dogs; a low clearance and a large volume of distribution, which led to the longest half life and mean residence time (MRT) values (Table I). Contrary to their chemical similarity, the pharmacokinetics of the two N,N-dialkyl analogues of phthaloyl glycinamide was quite different. Both compounds demonstrated anticonvulsant activity (MES test), although in the case of N,N-dialkyl phthaloyl glycinamide, a major active metabolite monitored in plasma—phthaloyl glycinamide, may also contribute to the anticonvulsant activity of the parent compound.

Similarly to dogs, in rats phthaloyl glycine had a large clearance and low volume of distribution, with consequently a short half life of less than ten minutes. Phthaloyl glycine was eliminated intact by urinary excretion in both species. Both, phthaloyl glycinamide and its N,N-dialkyl analogue had a smaller clearance and a larger volume of distribution and therefore these two compounds were retained in the

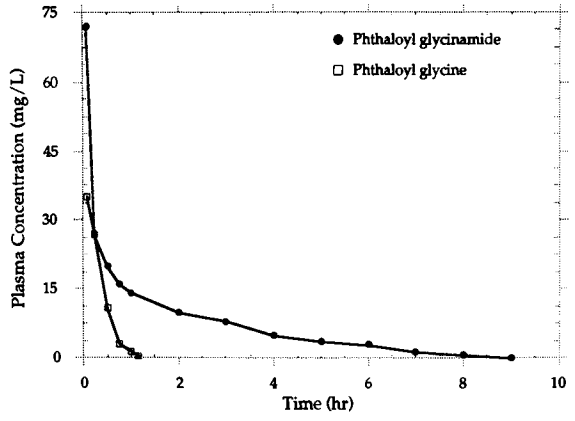

Figure 4 Mean plasma levels of phthaloyl glycine and phthaloyl glycinamide obtained following their iv administration (20 mg) to rats.

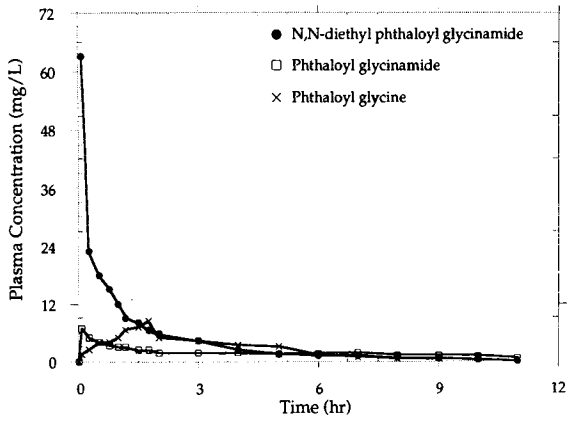

Figure 5 Mean plasma levels of N,N-diethyl phthaloyl glycinamide and its two metabolites obtained following its iv administration (20 mg) to rats.

Table II. Pharmacokinetic Parameters of Phthaloyl Glycine (PHT-GLN), Phthaloyl Glycinamide (PHT-GLD) and N,N-diethyl Phthaloyl Glycinamide (DIE) Obtained Following Their IV Administration (20 mg) to Rats

Pharamcokinetic parameters	PHT-GLN	PHT-GLD	DIE
$t_{1/2}\beta$ (hr)	0.17	1.4	3.0
AUC (mg/L · hr)	14	65	49
CL (L/hr)	1.4	0.31	0.41
Vss (L)	0.44	0.67	1.02
Vβ (L)	0.36	0.62	1.78
MRT (hr)	0.31	2.2	2.5
fe (%)	99	24	1.4
fm to PHT-GLN (%)		3.6	10
fm to PHT-GLD (%)			56

body for a longer period of time. N,N-dialkyl phthaloyl glycinamide had the longest half life and MRT values due to its larger volume of distribution. Phthaloyl glycinamide was excreted partially unchanged in the urine (fe = 24%) and the fraction metabolized (fm) to phthaloyl glycine was small (fm = 3.6%). N,N-dialkyl phthaloyl glycinamide was excreted virtually unchanged and was mainly eliminated by metabolism to phthaloyl glycinamide (fm = 56%) and phthaloyl glycine (fm = 10%). Comparison of the pharmacokinetics of the two glycinamides in dogs and rats showed that phthaloyl glycinamide demonstrated a better pharmacokinetic performance in dogs, while its N,N-dialkyl analogue demonstrated a better pharmacokinetic profile in rats. In both species, N,N-dialkyl phthaloyl glycinamide was metabolized to phthaloyl glycinamide to a similar extent, while the fraction metabolized to phthaloyl glycine was greater in dogs than in rats.

In the literature, there are several reports regarding the anticonvulsant activity of phthalimidoxy derivatives (22) and the hypolipidemic activity of N-substituted phthalimide derivatives (23). In addition, there are conflicting reports regarding the anticonvulsant activity of phthaloyl GABA. Blowmick et al. (18) reported that phthaloyl GABA was more potent than VPA against bicuculline induced seizures. These reports are in contrast to a report by Weichert (17) and our findings, in which phthaloyl GABA failed to demonstrate anticonvulsant activity in the MES and the sc Met tests. Phthaloyl GABA has also been reported to possess analgesic (24) and antiulcer properties (25).

Amide derivatives (or N-alkyl analogues of phthaloyl gabamide) were recently reported to possess activity against different chemically induced seizures and some also showed moderate hypnotic activity (26). Other phthalimide derivatives have been reported to possess different biological activities. Several phthaloyl glycinamides possess antispasmotic activity (27). Methyl N-phthalimidoxyacetate was convulsant at high doses of 100 mg/kg, but showed anticonvulsant activity in the MES test at lower doses (28). Phthaloyl-DL-α-alaninamide and phthaloyl glycinamide demonstrated analgesic activity (29), while N-phthaloyl gabamide exhibited central depressive activity (30). Anticonvulsant testing showed that unlike phthaloyl glycine, phthaloyl glycinamide demonstrated anticonvulsant activity in mice and rats. This compound was more potent (in the MES test) than one of the major antiepileptic agents—valproic acid (VPA) in mice and rats, and showed a better margin between activity and neurotoxicity. N,N-diethyl and N,N diisopropyl of phthaloyl glycinamides also possessed anticonvulsant activity, with the former being the most potent compound, having an ED_{50} value similar to phenytoin and carbamazepine (21).

This study showed good pharmacokinetic-pharmacodynamic (anticonvulsant activity) correlation. Phthaloyl glycine may lack antiepileptic activity because of its poor pharmacokinetics (high clearance and low volume of distribution). The four investigated phthaloyl glycine derivatives did not serve as chemical drug delivery systems (CDDS) of glycine in dogs and rats. Nevertheless, phthaloyl glycinamide and its two dialkyl analogues were active as drugs on their own. In spite of the chemical similarity of the investigated compounds, only the compounds with the better pharmacokinetic profiles demonstrated promising antiepileptic activity.

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Table III. The Anticonvulsant Activity of Phthaloyl Glycinamide (PHT-GLD) N,N Diethyl Phtaloyl Glycinamide (DIE) and N,N-diisopropyl Phthaloyl Glycinamide (DIP) Compared to Phthalimide and Valproic Acid (VPA) in Mice (ip) and Rats (po)

	Mice			Rats			
	PHT-GLD	Phthalimide	VPA	PHT-GLD	DIE	DIP	VPA
Test							
MES,ED_{50} (mg/kg)	94	224	200	31	13	36	490
sc Met,ED_{50} (mg/kg)	>400	328	146	>250	>250	>250	180
Neurotoxicity, TD_{50}	>600	305	283	>500	264	>500	280
PI, MES[a]	>6.4	1.3	1.4	>16.1	>20	>14	0.6
PI, sc Met[a]	1.5	0.9	1.9	—	—	—	1.6

[a] PI = TD_{50}/ED_{50}.

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