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The interaction potential of vigabatrin with phenytoin and carbamazepine

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Summary

The effect of vigabatrin on the pharmacokinetic profiles of orally coadministered doses of phenytoin (PT) and carbamazepine (CBZ) was examined in the rat. Plasma PT and CBZ levels were serially monitored over a 24 h period using an HPLC technique. Coadministration of vigabatrin markedly delayed drug absorption (i.e., longer T_{max}) and significantly reduced the plasma levels of PT and CBZ as assessed by the depression in the respective AUCs. These corresponded to a reduction of 21 and 17%, respectively. The effect on plasma drug concentration was not paralleled by any significant change in the elimination half-lives ($t_{1/2}$) of the drugs. The similarity in the pattern and magnitude of interaction observed with both drugs suggests a common underlying mechanism. In the absence of hepatic factors, and with vigabatrin's negligible influence on plasma protein binding, gastrokinetic property for vigabatrin is proposed as a likely mechanism to account for the interactions, but clearly further studies are needed to firmly establish this drug action.

Introduction

Phenytoin (PT), carbamazepine (CBZ) and vigabatrin belong to the class of anticonvulsant drugs. Despite their diverse chemical structures, they are all highly effective in the treatment of severe seizure disorders (Johnston, 1988). Vigabatrin, the newer member of the group, is a synthetic derivative of the central inhibitory neurotransmitter, γ -aminobutyric acid (GABA). Vi-

gabatin's anticonvulsant action is strongly linked to its ability to increase the synaptic concentrations of GABA by inhibiting the enzyme responsible for the degradation of the neurotransmitter. Clinically, vigabatrin has been successfully employed in the management of refractory seizures particularly of the complex partial types (Grant and Heel, 1991). In patients with these drug-resistant epileptic conditions, vigabatrin is generally given as an adjunctive therapy to other conventional antiepileptic drugs such as PT or CBZ. The chronic use of such drug combinations may precipitate clinically significant drug interactions. Indeed, the occurrence of drug interactions with and among the various antiepileptic drugs is well documented (Perucca and Richens, 1985).

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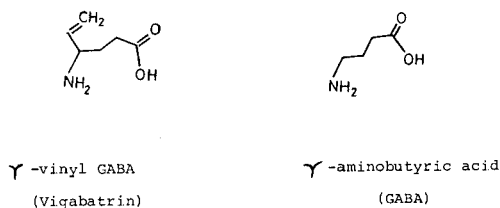


Fig. 1. Structural formulae of vigabatrin and GABA.

The reports to date on the interaction potential of vigabatrin with other anticonvulsant drugs are not consistent. In some of the studies Loiseau et al., 1986; Matilainen et al., 1988; Cocito et al., 1989; Luna et al., 1989; Tartara et al., 1989), the drug was reported as having no effect on the disposition profiles of coadministered CBZ, PT, Valproic acid, clonazepam and clobazam, while in others (Browne et al., 1987; Tassinari et al., 1987; Rimmer and Richens, 1989) it was seen to reduce the plasma concentrations of phenobarbitone, primidone, and PT. The latter studies also indicated that the interaction between vigabatrin and PT was of such magnitude as to represent clinical significance, but the mechanism(s) underlying the interaction has not been established (Rimmer and Richens, 1989).

The present study is designed to reassess the interaction potential of vigabatrin with the two most commonly used antiepileptic drugs, PT and CBZ. Potential interaction is evaluated by comparison of the pharmacokinetic parameters of these agents in the presence and absence of vigabatrin in the rat.

Materials and Methods

Subjects and study protocol

Male Sprague-Dawley rats weighing between 250 and 300 g were used in the study. Animals were randomly divided into four treatment categories. These consisted of the control groups which received a daily dose of either PT (25 mg kg^{-1}) or CBZ (20 mg kg^{-1}) for a period of 7 days. The remaining two groups (coadministration groups) received a combination of the primary drug (PT or CBZ) and vigabatrin (90 mg kg^{-1}) for the same period. Drug solutions were

freshly prepared and administered by gastric intubation.

At the end of the 7 day period, the animals were fasted overnight (with free access to water) and surgically prepared for continuous blood sampling. Briefly, this involved implanting under light ether anesthesia, a segment of heparinized polyethylene cannula (0.75 mm i.d., Jencons Sci., Beds, U.K.) in the abdominal aorta via the left femoral artery. The cannula was then exteriorized from the back of the neck and adapted for continuous blood sampling.

After recovery, the animals were orally challenged with the PT or CBZ dose alone (baseline controls) or a combination of either drug with vigabatrin before placing them in especially adapted cages. Blood sample (approx. 0.3 ml) was serially withdrawn via the indwelling cannula into small Eppendorff tubes at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, ..., 24 h after drug administration. Following each sample withdrawal, the cannula was flushed with an equal volume of heparinized saline to maintain the circulatory volume in the animal and also to ensure uninterrupted blood during the session. The blood samples were then immediately centrifuged, plasma samples separated and aliquots of 100 μl plasma stored at -20°C until assay.

Analytical techniques

Assay of PT and CBZ in plasma samples was performed by using the modified high-performance liquid chromatographic method of Asberg and Haffner (1987). The sample was deproteinized by adding 100 μl of acetonitriles containing 5 ppm of the internal standard (CBZ for PT samples and vice versa). After vortex-mixing and centrifugation at $1000 \times g$ for 15 min, 20 μl aliquots of supernatant were used in the assay.

The HPLC instrumentation consisted of a reverse phase Resolve C-18 cartridge column (5 μm , 10 cm \times 8 mm, i.d) connected to a solvent delivery system (M-501), an autosampler (WISP-712), UV detector (M-484), a systems controller (M-720) and an M-730 data module (Waters Associates, Milford, MA, U.S.A.).

The mobile phase, a mixture of methanol : acetonitrile : 10 mM phosphate buffer

(25:15:60), pH 6, was delivered at a flow rate of 2 ml per min. UV detection was at 220 nm and quantitation of drug levels was achieved by the use of calibration curves constructed from fresh rat plasma spiked with standard solutions (0.1 – $10.0 \mu\text{g ml}^{-1}$) and assayed on the same day.

Kinetic analysis

The plasma concentration-time profile of either PT or CBZ was constructed for each animal. The individual peak concentrations (C_{max} values) and the times to these peaks (T_{max} values) were estimated by inspection of the resulting curves. Terminal slopes, corresponding to the elimination rate constants (K_{el}), were determined by least-squares exponential regression and these in turn were used to compute the elimination half-lives ($t_{1/2}$). Area under the plasma concentration-time curve (AUC) was calculated using the trapezoidal rule. $\text{AUC}_{0-\infty}$ was estimated by dividing the last measurable plasma concentration by the elimination rate constant and adding the resultant value to the AUC_{0-12} . Differences in the mean values of the pharmacokinetic parameters between treatment groups were evaluated using a two-tailed Student's t -test. All values are reported as means \pm SE.

Results

Fig. 2 shows the mean plasma concentration-time profile of an oral dose of PT (25 mg kg^{-1}) administered alone or in combination with vigabatrin (90 mg kg^{-1}). The pharmacokinetic parameters (T_{max} , C_{max} , $t_{1/2}$ and AUC) derived from these data are listed in Table 1. The data appear to fit a one-compartment open model with first-order kinetics. PT absorption from the gastrointestinal tract (GIT) appears to be fairly rapid and complete with maximum plasma concentrations of 3.7 ± 0.33 and 2.85 ± 0.21 being attained at 1.65 and 2.3 h for the control and drug combination groups, respectively. The plasma profile also reveals considerable intersubject variability in drug levels as demonstrated by the relative size of the error bars in the curve. Plasma PT concentration was consistently lower during coadministration

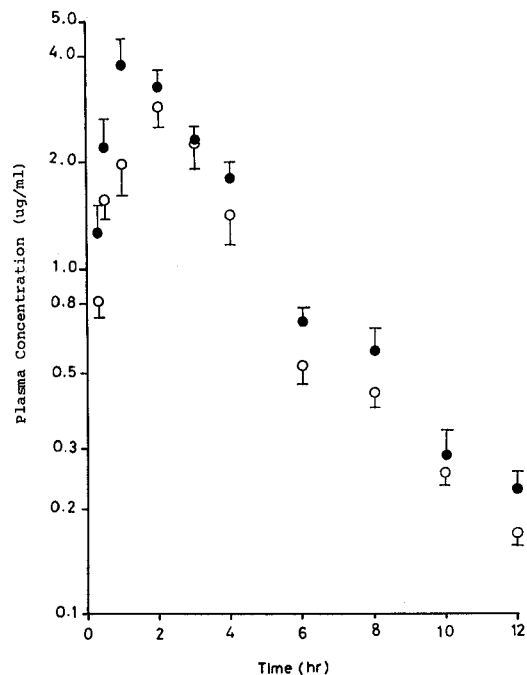


Fig. 2. Mean (\pm SE) plasma concentration vs time profile of an oral dose of PT administered alone (\bullet) or in combination with vigabatrin (\circ).

tion than when the drug was given alone. On closer examination, the two schedules of PT dosing were found to be significantly different ($P < 0.05$) in two of the four pharmacokinetic parameters studied (i.e., C_{max} and AUC). The relative values for the T_{max} and $t_{1/2}$ in the two groups were highly comparable (Table 1). Overall, coadministration of vigabatrin resulted in a reduction

TABLE 1

Pharmacokinetic parameters (mean \pm SE) for PT in animals given phenytoin alone (control) and in combination with vigabatrin ($n = 10$)

Parameter	Mean \pm SE	
	Control	Coadministration
T_{max} (h)	1.65 ± 0.20	2.30 ± 0.16^a
C_{max} ($\mu\text{g ml}^{-1}$)	3.70 ± 0.33	2.85 ± 0.21^a
$t_{1/2}$ (h)	3.35 ± 0.11	3.66 ± 0.21
AUC ($\mu\text{g h ml}^{-1}$)	16.66 ± 1.40	13.28 ± 1.30^a

^a Significantly different from control values ($P < 0.05$).

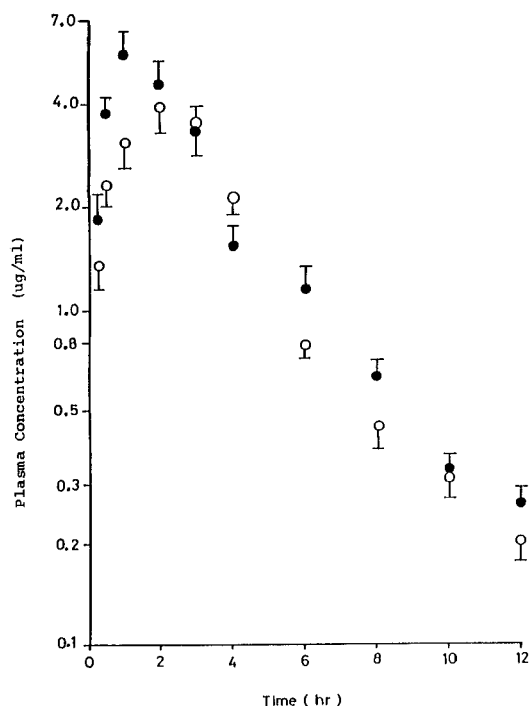


Fig. 3. Mean (\pm SE) plasma concentration vs time profile of an oral dose of CBZ administered alone (\bullet) or in combination with vigabatrin (\circ).

of PT levels by over 20% as assessed by the effect on the AUC.

The time course of the plasma concentration and the computed parameters for CBZ under the two schedules of administration (i.e., alone and in combination with vigabatrin) are illustrated in Fig. 3 and Table 2, respectively. The absorption profile closely parallels that of PT. The peak

TABLE 2

Pharmacokinetic parameters (mean \pm SE) for CBZ in animals given CBZ alone (control) and in combination with vigabatrin ($n = 10$)

Parameter	Mean \pm SE	
	Control	Coadministration
T_{\max} (h)	1.45 \pm 0.11	2.20 \pm 0.08 ^a
C_{\max} ($\mu\text{g ml}^{-1}$)	5.20 \pm 0.43	3.80 \pm 0.69 ^a
$t_{1/2}$ (h)	3.20 \pm 0.18	3.01 \pm 0.22
AUC ($\mu\text{g h ml}^{-1}$)	21.96 \pm 1.30	18.14 \pm 1.13 ^a

^a Significantly different from control values ($P < 0.05$).

absorption times (T_{\max}) were 1.45 and 2.2 h for the control and coadministration schedules, respectively. The plasma CBZ concentration corresponding to these times were 5.2 ± 0.43 and $3.8 \pm 0.69 \mu\text{g ml}^{-1}$ and the difference between the groups in this parameter was marginally significant. The CBZ concentration profile during coadministration was also characterized by lower plasma levels at most of the sampling time points resulting in a small but significant difference ($P < 0.05$), in the respective values of AUC. Comparison of the drug's elimination half-lives ($t_{1/2}$) in the two schedules, however, did not show a similar level of significance

Discussion

The results of the present study indicate that vigabatrin reduces both the rate and extent of absorption of coadministered doses of PT and CBZ without having any marked effect on the elimination rate constant of either drug. The percentage reduction in the plasma concentration of PT compares favourably to those reported in earlier studies (Browne et al., 1987; Tassinari et al., 1987; Rimmer and Richens, 1989). The depressant effect of vigabatrin on plasma CBZ profile, however, contrasts sharply with the findings of others (Loiseau et al., 1986; Cocito et al., 1989; Tartara et al., 1989), where no such influence was observed during the drugs' concurrent administration.

The few studies to date on the effect of vigabatrin on PT disposition relate to a reduction in the bioavailability of the latter, but the mechanism underlying this interaction has not been sufficiently characterized. PT and CBZ are extensively bound to plasma proteins and are principally cleared subsequent to their metabolism in the liver (Perucca and Richens, 1985). The apparent lack of effect of vigabatrin on the elimination half-life of these drugs rules out an interaction at the level of hepatic metabolism. Support for this may be found in the fact that vigabatrin itself, is not metabolized in the liver, and that it is principally eliminated by renal excretion as the unchanged drug (Haegle and Schechter, 1986). It

would therefore not be expected to influence the drug metabolizing capacity of microsomal enzymes. Furthermore, as a structural analogue of the endogenous substance, GABA (Fig. 1), vigabatrin might also share the latter's inertness with regards to influencing microsomal enzyme activity.

Rimmer and Richens (1989) examined the involvement of hepatic factors in the reported vigabatrin-PT interaction, but their findings were not conclusive. Their study design did not allow direct evaluation of the elimination rate constant of the primary drugs. They relied instead on an indirect method, the antipyrine test, to assess potential changes in hepatic enzyme activity following vigabatrin exposure. In the present study, elimination half-lives were directly estimated for PT and CBZ under the different schedules of drug administration. Comparison of the corresponding values in each drug category failed to show any difference between the single and coadministration schedule suggesting that vigabatrin has little or no effect on the hepatic disposition of either drug. As our study did not monitor the principal drug metabolites, however, subtle changes in microsomal activity cannot be totally ruled out.

As vigabatrin is poorly bound to plasma proteins (Mumford, 1988; Rimmer and Richens, 1989), it is very unlikely to influence the binding capacity of these molecules for PT and CBZ. Indeed, potential changes in plasma protein binding have been excluded as a likely mechanism for the interaction between PT and vigabatrin by previous investigators (Rimmer and Richens, 1989). Yet, the similarity in the pattern and the magnitude of the vigabatrin interaction with the two antiepileptic agents points to a common mechanism. Both PT and CBZ have limited aqueous solubility at the usual physiological pH values (Jung et al., 1980). This may, in part, explain the relatively large inter-subject variations in plasma levels of the drugs seen in the study. Subtle changes in the GIT milieu can markedly alter the absorption profiles of drugs with such characteristic features. As a weak acid, vigabatrin administration may decrease gastrointestinal pH and thereby enhance the absorption of acidic

drugs by suppressing their ionization. However, this was not reflected in our results which showed instead a reduction in plasma levels of the drugs. In the absence of hepatic, protein binding and pH factors, could vigabatrin-induced changes in gastric motility account for these interactions? A reduction in gastric emptying time (i.e., a shorter residence time) can adversely influence the rate and extent of drug entering systemic circulation from the GIT. Both these characteristics feature in the interactions of vigabatrin with the two antiepileptics. The proposed mechanism however, presupposes a potent gastrokinetic action for vigabatrin, which as yet, has not been adequately explored. In this respect, a further evaluation of the absorption phase will be needed for the characterization of vigabatrin interactions.

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