Table 1. Percentage reduction of food consumed by dogs 1 h after a meat meal.

Compound	Dose mg kg^{-1} p.o.	% Reduction 0–1 h
3	10	−53 ± 9·0
3a	10	−75 ± 9·5
3b	10	+3 ± 7·5
11	5	−90 ± 5·0
Placebo	—	+6 ± 9·0

suppressant effect found for the morpholine (**3**) compared with the standard drug (**11**) was, however, considered sufficient to predict clinical use in man provided that subsequent testing failed to reveal the attenuated stimulant properties characteristic of many clinically used appetite suppressants. In the acute test, using a Latin Square design, the morpholine (**3**) had an ED50 for the 0–1 h effect of 3 mg kg^{-1} compared to 2 mg kg^{-1} for the standard drug (**11**). A lower ED50 of 5·5 mg kg^{-1} for the 0–2 h effect of 2-benzylmorpholine (**3**) fell to an ED40 of 9 mg kg^{-1} for the 0–4 h effect.

Consideration of the enantiomers **3a** and **3b** showed that whereas the (+)-enantiomer (**3a**) caused a 75% fall in meat consumed after 1 h the corresponding (−)-enantiomer (**3b**) was without significant effect.

Dogs given oral doses of 200 mg kg^{-1} of the morpholine (**3**) were free of behavioural effects and stereotype actions. Under similar test conditions diethylpropion (**11**) caused overt stimulation at 5 mg kg^{-1} p.o.

An additional drawback in the use of appetite suppressants such as amphetamine (**1**) and phenmetrazine (**2**) is that they become less effective on repeated dosing. Thus a chronic dosing study involving 20 days oral dosing to three dogs at 10 mg kg^{-1} of the morpholine (**3**) was carried out. An average reduction of 75% in meat consumed at 1 h after meat was supplied on days 3, 4 and 5 declined to 35% by days 17–20 of the test.

Chronic dosing with the active (+)- enantiomer **3a** was not studied but it is unlikely that the presence of the inactive enantiomer **3b** in the racemate would have affected the outcome of the tolerance test.

In conclusion 2-benzylmorpholine (**3**) is a potent appetite suppressant agent in dogs when dosed orally. Resolution of the compound showed that appetite suppressant activity was confined to the dextrorotatory enantiomer (**3a**). In contrast to clinically used appetite suppressants of the central stimulant class, no stimulant or stereotype actions were seen for 2-benzylmorpholine (**3**). However, a chronic dosing study of morpholine (**3**) in dogs at its active dose level showed an unacceptable fall in the appetite suppressant effect indicating the development of tolerance.

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Phenytoin–bupropion interaction: effect on plasma phenytoin concentration in the rat

A. TEKLE, KHALIL I. AL-KHAMIS, *Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Kingdom of Saudi Arabia*

Abstract—The effect of coadministration of bupropion (50 mg kg^{-1}, p.o.) on the disposition profile of phenytoin has been studied in the rat. Plasma phenytoin concentration was measured serially for 10 h by HPLC. Bupropion had little or no effect on the pharmacokinetic parameters of an acutely administered dose of phenytoin. Following multiple doses of phenytoin however (i.e. steady state) the coadministration of bupropion resulted in significant increases in the elimination half-life ($t_{\frac{1}{2}}$), the area under the plasma concentration-time curve (AUC) and the time to maximum plasma concentration (t_{max}). Allowing for the limitations of single dose studies, these results point to a possible pharmacokinetic interaction between bupropion and phenytoin—the clinical significance of which needs to be assessed.

Phenytoin is a primary anticonvulsant drug in the treatment of partial and generalized epilepsy with convulsive disorders. The drug has a narrow therapeutic range (10–20 μg mL^{-1}) and displays dose-dependent disposition kinetics around this range (Gugler et al 1976). Furthermore, its biotransformation has been shown to be markedly influenced by the concomittant use of other drugs (Kutt 1972; Perruca 1982). The antidepressants are one such group that would be coadministered with phenytoin for the treatment of depressed epileptic patients and in conditions such as post herpetic neuralgia (Raftery 1979).

Bupropion, a novel antidepressant drug has some common biotransformational features with phenytoin. It is both highly bound to plasma proteins (Findlay et al 1981) and extensively metabolized by hepatic microsomal enzymes (Schroeder 1983). Concomittant use of bupropion and phenytoin may thus present a potential for pharmacokinetic drug interaction.

The present study was designed to investigate any such interaction by studying the effect of a single dose of bupropion on the kinetics of a single/repeated dose of phenytoin in the rat.

Correspondence to: A. Tekle, Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.

Materials and methods

Male Wistar rats, 300–350 g, were fasted overnight while having free access to water. The following day, under light ether anaesthesia, the right femoral artery was surgically exposed, rostrally ligated with cotton thread at one end and clamped with an artery clip at the other. A small incision was made into the artery and one end of a cannula (flexible polyethylene tubing, i.d. 0·75 mm) inserted deep into the artery. The other end of the cannula was connected (via a 25 G needle) to a syringe containing heparinized 0·9% NaCl. After establishing patency of the cannula and flushing it with heparinized saline, the tubing was secured by a further cotton thread ligature(s). A wire plug was then fitted and the whole assembly was pulled under the skin to emerge at the back of the neck and the site sutured. The cannula remained functional for over 48 h with periodic flushing with heparinized saline.

Experimental procedure. There were four separate drug treatment groups each with at least 10 rats. Acute phenytoin (25 mg kg^{-1} p.o.), acute phenytoin plus bupropion (50 mg kg^{-1} p.o.), chronic phenytoin (i.e. animals received a daily dose of 25 mg kg^{-1} phenytoin for 2 weeks)—challenged with either phenytoin alone or with a combination of phenytoin and buproprion.

The doses of phenytoin and bupropion were prepared in 0·9% NaCl (saline) from their Na^+ and HCl salt forms, respectively and administered as soon as the animals had recovered from surgical anaesthesia. Blood (0·3 mL) was withdrawn via the indwelling cannula into small heparinized Eppendorff tubes before drug administration and thereafter at 0·25, 0·5, 1·0, 1·50, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h. The cannula was flushed with an equal volume of saline after each sample withdrawal. The blood samples were immediately centrifuged and from the resulting plasma, 100 μL samples were stored at −20 C until assay.

Sample pretreatment. To 100 μL plasma samples, was added 10 μL of phenacetin (10 μg mL^{-1} stock soln) the internal standard, and the sample vortex mixed for 30 s. This was then extracted with 0·5 mL of isopropanol and ethyl acetate mixture (4:96 v/v). After centrifugation at 4000 *g* for 10 min, the organic layer was transferred into fresh 1 mL Eppendorff tubes and allowed to dry under a stream of nitrogen. The dried extract was finally reconstituted with 100 μL of the mobile phase and a 50 μL amount used for drug analysis.

Drug analysis. This was by a reversed phase HPLC technique using a Waters Associates Chromatograph equipped with a variable wavelength UV detector and a Rheodyne sample injector. The column was a Resolve C18 (5 μm) cartridge (100 × 8 mm i.d.) and the mobile phase a mixture of methanol 0·01 M phosphate buffer (45:55 v/v), adjusted to pH 6. The effluent was monitored at 220 nm with the flow rate set at 2 mL min^{-1}.

Statistical analysis. The apparent elimination rate constant (K_{el}) was determined by linear regression analysis of the plasma concentration versus time data of the terminal phase. Elimination half-life, $t_{\frac{1}{2}}$ was calculated from the relationship $t_{\frac{1}{2}} = 0{\cdot}693/K_{el}$ while area under the curve (AUC) was calculated using the trapezoidal rule. The significant difference between respective treatment groups was calculated by paired Student's *t*-test ($P \leqslant 0{\cdot}05$).

Results

Acute study. Fig. 1 shows the mean plasma concentration versus time profiles of phenytoin administered alone or in combination with bupropion. The data fitted a one compartment open model with first order kinetics and the pharmacokinetic parameters derived from these data are summarized in Table 1. In both treatment categories the absorption process was complete with median t_{max} of 1·43 ± 0·13 and 1·6 ± 0·10 h for the phenytoin alone and drug combination groups, respectively. The bupropion-induced shift in the t_{max} of phenytoin was not statistically significant ($P > 0{\cdot}05$). The distribution phase was fairly short in both groups—a concentration decay being evident within 2 h of drug administration. Comparison of the other parameters failed to show significant differences in either peak drug levels attained (C_{max}) or the mean elimination half-lives ($t_{\frac{1}{2}}$). These findings were

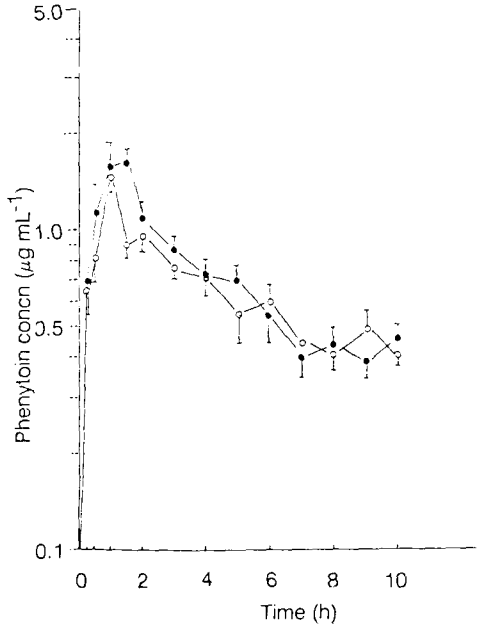

FIG. 1. Mean (±s.e.m.) plasma concentration vs time profile of acutely administered phenytoin (○) alone or in combination (●) with bupropion.

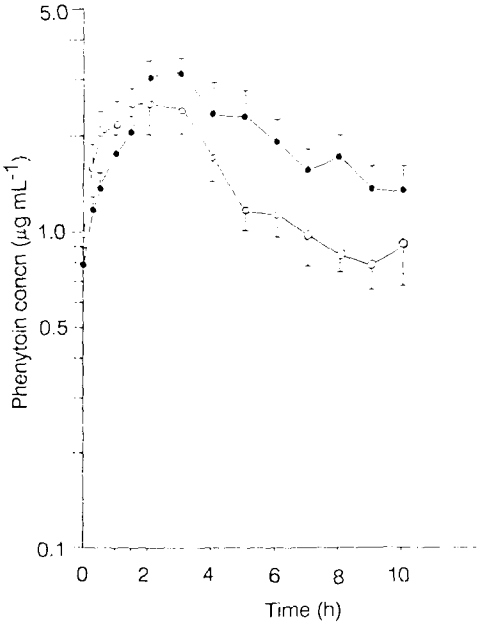

FIG. 2. Mean (±s.e.m.) plasma concentration vs time profile of phenytoin administered (○) alone or in combination with (●) bupropion in chronically bupropion treated rats.

Table 1. Mean pharmacokinetic parameters after a single oral dose of phenytoin alone or in combination with bupropion (n = 10).

Parameter	Mean ± s.e.m. Alone	Combination	P
Time to maximum concn (t_{max} (h))	1·43 ± 0·13	1·68 ± 0·10	NS
Maximum concn (C_{max} μg mL^{-1})	1·28 ± 0·03	1·66 ± 0·22	NS
Terminal log-linear half-life ($t_{\frac{1}{2}}$ (h))	6·98 ± 0·60	7·84 ± 0·32	NS
AUC up to 10 h (μg min mL^{-1})	6·49 ± 0·30	7·09 ± 0·70	NS

NS = not significant

Table 2. Mean parameters after challenge dose(s) of phenytoin alone or in combination with bupropion in chronically phenytoin-treated rats (n = 10)

Parameter	Mean ± s.e.m. Alone	Combination	P
Time to maximum concn (t_{max} (h))	1·94 ± 0·15	3·26 ± 0·23	< 0·05
Maximum concn (C_{max} μg mL^{-1})	2·80 ± 0·33	3·40 ± 0·30	NS
Terminal log-linear half-life ($t_{\frac{1}{2}}$ (h))	5·89 ± 0·23	6·90 ± 0·34	< 0·05
AUC up to 10 h (μg min mL^{-1})	14·00 ± 1·89	20·01 ± 2·33	< 0·05

NS = not significant

further reflected in the lack of significant difference between the respective AUC values.

Repeated dose (chronic) study. The concentration decay of the phenytoin dose administered alone or in combination with bupropion in phenytoin primed rats is presented in Fig. 2, the corresponding parameters listed in Table 2. The mean steady state level of phenytoin was 0·8 ± 0·03 μg mL^{-1}. Coadministration of bupropion markedly delayed phenytoin absorption. Significant differences were also observed between the treatment groups in their respective $t_{\frac{1}{2}}$ and AUC values; comparison of the C_{max} values showed that a higher level of the drug was attained in the combination group but this increase was not statistically significant.

Discussion

Changes in the metabolic and distribution phases (e.g. displacement from plasma protein binding) are often considered the principal features of phenytoin interaction with other drugs (Perruca 1982).

Data from our single dose (i.e. acute phase) study indicate that bupropion has little or no effect on the disposition characteristics of a coadministered dose of phenytoin. When steady-state levels of phenytoin have been attained however, bupropion markedly alters the pharmacokinetic parameters of coadministered phenytoin. There were significant increases in the values of t_{max}, $t_{\frac{1}{2}}$ and AUC. The effect on the rate of absorption (t_{max}) may be largely due to bupropion induced pH changes in the gastric milieu. (Bupropion as a weak base may have non-specifically interacted with phenytoin, a weak acid, to cause the delay in absorption.)

Increases in $t_{\frac{1}{2}}$ and AUC appear to suggest an inhibitory role for bupropion on the microsomal enzymes responsible for phenytoin metabolism. Earlier studies on phenytoin interaction with tricyclic antidepressant drugs have not all been conclusive. Imipramine was reported to cause a substantial rise in phenytoin levels (Perruca & Richens 1977) but the closely related amitriptyline and nortriptyline were without effect when coadministered with phenytoin (Braithwaite et al 1975; Pond et al 1975). Comparison of the plasma phenytoin concentration profiles obtained following single and multiple doses of phenytoin showed a faster concentration decay pattern in multiple phenytoin dosing. This was reflected in a shorter half-life—possibly as a result of auto-enzyme induction (Perruca 1978; Goodman & Gilman 1985).

Within the limitations of single dose studies, our results preliminarily suggest some degree of pharmacokinetic interaction between bupropion and phenytoin, particularly when bupropion is administered following multiple doses of phenytoin. Since therapeutically both phenytoin and most antidepressant drugs are routinely employed on repeated dose schedules, further studies are clearly needed to assess the clinical significance of this interaction.

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