A PHARMACOKINETIC INTERACTION IN MAN BETWEEN PHENOBARBITONE AND FENOPROFEN, A NEW ANTI-INFLAMMATORY AGENT

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- 1 The effect of repeated administration of phenobarbitone on the plasma disposition of fenopropfen ($\pm$ -2-(3-phenoxyphenyl) propionic acid) was investigated in rats and man.
- 2 The plasma elimination rate constants increased significantly and the rats excreted proportionately more metabolized fenopropfen in the urine. These findings are consistent with an increase in the rate of metabolism of fenopropfen.
- 3 This interaction between phenobarbitone (and presumably other inducers of drug metabolizing enzymes) and fenopropfen should be considered when evaluating the clinical usefulness of fenopropfen.

Introduction

We are currently evaluating the clinical utility of fenopropfen ($\pm$ -2-(3-phenoxyphenyl) propionic acid), a new anti-inflammatory, antipyretic analgesic. Our experience in man and animals has indicated that fenopropfen does not affect its own metabolism upon repeated administration (Rubin, Rodda, Warrick, Ridolfo & Gruber, 1971). With its potential widespread usage, however, this agent could be administered with a variety of drugs, some of which might affect the metabolism (and hence the pharmacology) of fenopropfen. Therefore, we decided to determine whether the plasma disposition of fenopropfen in man was altered by repeated administration of the prototype enzyme-inducer, phenobarbitone. The data indicate that both the plasma elimination rate constant and the apparent volume of distribution for fenopropfen increase following phenobarbitone pretreatment.

Methods

Analytical methods

Fenopropfen concentrations in plasma were measured by GLC analysis of hexane extracts of deproteinized plasma (Nash, Bopp & Rubin, 1971); total [¹⁴C]-fenopropfen equivalents and non-metabolized fenopropfen were assayed in urine,

and in hexane extracts of urine, respectively, by liquid scintillation spectroscopy (Rubin, Rodda, Warrick, Ridolfo & Gruber, 1972a, Rubin, Warrick, Wolen, Chernish, Ridolfo & Gruber, 1972b). Antipyrine concentrations in plasma were estimated by the method of Brodie, Axelrod, Soberman & Levy (1949).

Pharmacokinetics

The first order elimination rate constants, apparent volumes of distribution and areas under curves were computed by least squares estimation techniques assuming a single-compartment open model. Intravenously administered fenopropfen can be more appropriately described by a two-compartment model (Rubin *et al.*, 1971), but inadequate blood sampling during early periods prohibited its use in this case. The limited sampling of blood was not an oversight; we felt that the simpler model was adequate if a significant effect existed.

Study I

Male Sprague-Dawley rats, weighing between 40 and 50 g, were housed under conditions of controlled temperature, humidity, and light. No pesticide usage was permitted in the animal area. Purina Laboratory Chow and water was available to the animals *ad libitum*.

The rats were separated randomly into two groups of 40 rats each: the control group was

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pretreated with 0.9% w/v NaCl (physiological saline; 10 ml/kg i.p.) once daily for six days, the drug group received 50 mg/kg of phenobarbitone in 10 ml of solution/kg i.p. once daily for six days. Twenty-four hours after the last pretreatment injection 35 animals from each group were injected (i.p.) with fenopropfen sodium (10 mg/kg as the acid equivalent in 10 ml of physiological saline/kg). At selected time periods after the fenopropfen injection, blood samples from five unanaesthetized animals from each group were collected into heparinized tubes by puncture of the retro-orbital sinus. Each animal was bled once only. The remaining five animals in each group were used for study of urinary excretion of fenopropfen and metabolites. They were injected (i.p.) with a mixture of unlabelled fenopropfen sodium and tracer amounts of [^{14}C]-fenopropfen labelled in the carboxyl group (10 mg/kg as the acid equivalent in 10 ml of physiological saline/kg). The specific activity of the labelled compound was 0.25 $\mu\text{Ci}/\text{mg}$, and each rat received about 0.1 μCi . Pooled urines from each group were collected 0-1, 1-2, 2-4, 4-6, 6-8 and 8-20 h after the fenopropfen injection.

Study II

The plasma half-life of antipyrine was determined in 40 male volunteers. A single oral dose of 15 mg/kg antipyrine in aromatic elixir U.S.P. was given to fasted subjects with 180 ml of water. Food was withheld for an additional 2 h after the dose was ingested. Blood was drawn at 8, 12 and 16 h after the dose for analysis of antipyrine concentration in the plasma and for subsequent estimation of the antipyrine half-life.

Eighteen subjects (13 caucasian, 5 negro) with the longest antipyrine half-lives were selected for the remainder of the study. They were between the ages of 20 and 41 years (mean 26.2); their weights ranged from 55.8 to 105.3 kg (mean 76.3). Informed consent forms were signed by each subject before his participation and after discussion of the study with each subject. All underwent routine clinical and laboratory examinations and exhibited no overt evidence of disease.

The subjects were separated into three groups of six men each; individuals with comparable antipyrine half-lives were represented among the groups. Group 1 swallowed a placebo capsule every 6 h; groups 2 and 3 swallowed 15 and 60 mg phenobarbitone every 6 h, respectively, until a total of 40 doses of placebo or phenobarbitone had been ingested. Twenty-four hours after the last dose, each subject received fenopropfen sodium i.v. (200 mg acid equivalents dissolved in 4 ml water for injection and diluted to 10 ml with 0.9%

Fig. 1 Plasma concentrations of fenopropfen in rats pretreated with saline (10 ml/kg i.p.) once daily for six days (●), or phenobarbitone (50 mg/kg i.p.) once daily for six days (○). The results are the means for five rats per time period.

w/v NaCl solution, injected over a 1 min interval). Blood was drawn into heparinized containers at 1, 2, 3, 4, 5, 6 and 8 h after the fenopropfen injection for determinations of plasma concentrations of fenopropfen.

Results

Rats; Study I

Mean plasma concentrations of fenopropfen from the control and phenobarbitone treated rats are shown in Figure 1. A dramatic reduction of plasma concentrations of fenopropfen followed phenobarbitone pretreatment. In fact, no valid estimate of the half-life of fenopropfen was possible in the group pretreated with phenobarbitone because of the rapid disappearance of fenopropfen and our limited sampling of blood at the terminal phase of the plasma-disposition curve.

Figure 2 shows the cumulative urinary excretion of fenopropfen and its metabolites in the rats pretreated with saline or phenobarbitone. The data suggest that induction of fenopropfen-metabolizing enzymes occurred in the rats pretreated with phenobarbitone, there being proportionately more metabolized fenopropfen excreted in the phenobarbitone-treated group than in the saline controls. *In vitro* studies of the metabolism of fenopropfen in livers from these animals were not conducted; the animal study was undertaken primarily as a preface to a human study.

Man; Study II

Figure 3 shows the mean concentrations of fenopropfen in human plasma for each treatment group:

Fig. 2 Cumulative urinary excretion of fenopropfen (■, ●) and metabolites (□, ○) in rats pretreated with saline, 10 ml/kg, i.p. once daily for six days (■, □) or phenobarbitone, 50 mg/kg i.p. once daily for six days (●, ○). Urines were pooled from five rats per time period.

Fig. 3 Plasma concentrations of fenopropfen in human subjects pretreated with placebo capsules (●), phenobarbitone 15 mg (○), or phenobarbitone 60 mg (△) every 6 h for 10 days. The results are the mean values $\pm$ s.e. mean for six men per treatment group.

Table 1 Pharmacokinetic estimates (area under plasma fenopropfen concentration v. time curve, the apparent first order elimination rate constant (k_d) and the apparent volume of distribution (V_d)) for fenopropfen disposition in subjects pretreated with placebo capsules, phenobarbitone 15 mg, or phenobarbitone 60 mg every 6 h for 10 days

Dose schedule (four times daily $\times$ 10 days)	Subject no.	Area under curve ($\mu\text{g} \times \text{h} \times \text{ml}^{-1}$)	k_d (min^{-1})	V_d (l)
Placebo	1	43	0.0041	19
	2	74	0.0043	11
	3	32	0.0047	10
	4	56	0.0048	12
	5	43	0.0052	15
	6	61	0.0063	9
	mean	52	0.0047	13
15 mg phenobarbitone	7	48	0.0047	15
	8	36	0.0048	19
	9	35	0.0059	16
	10	36	0.0060	15
	11	35	0.0060	16
	12	49	0.0081	8
	mean	40	0.0057	15
60 mg phenobarbitone	13	30	0.0042	26
	14	29	0.0052	22
	15	28	0.0059	20
	16	48	0.0061	11
	17	36	0.0063	20
	18	28	0.0065	18
	mean	33	0.0056	20
s.d. (from analysis of variance)		10.05	0.0029	4.04

placebo, 15 and 60 mg phenobarbitone. Estimates of the pharmacokinetic parameters of these curves (Table 1) indicated a decrease in area under the fenopropfen plasma curve and an increase in the apparent first order elimination rate constant (k_d) for fenopropfen after phenobarbitone pretreatment. An increased apparent volume of distribution of fenopropfen was also evident in the barbitone-treated group. Analysis of variance for each measure failed to show a significant difference between 15 and 60 mg phenobarbitone but did indicate a significant difference between the phenobarbitone and placebo groups when both phenobarbitone groups were treated as a unit. These conclusions could be made with confidence with respect to elimination rate constants and area, but inferences about apparent volumes of distribution (V_d) must be made cautiously. Because we did not draw blood samples during the rapid decline in the curve during the 0-1 h interval, our estimates of V_d may be biased. Thus, values of V_d may not be given a precise pharmacokinetic interpretation and must be considered only as inexact indexes.

Discussion

Fenopropfen is extensively metabolized in rats and in man. About 2.5% of an i.v. or oral dose of fenopropfen in man is excreted in the urine as 4'-OH-fenopropfen and 45% as 4'-OH-fenopropfen glucuronide (Rubin *et al.*, 1972a, 1972b). The demonstrated increase in the elimination rate constant of fenopropfen in phenobarbitone treated subjects would be expected if phenobarbitone increased the rate of metabolism of fenopropfen.

The interpretation of an increased apparent volume of distribution for the phenobarbitone treated group is not clear. One explanation is that

in addition to a more rapid disappearance of fenopropfen from the plasma during the *terminal* phase of the plasma concentration time curve, enhanced metabolism shortly after injection would be reflected as a decrease in fenopropfen concentration in plasma. In the one-compartment open model this could lead to an under-estimation of the apparent volume of distribution. The study was designed to estimate half-lives, and for this reason, we did not look at early time points in detail. Thus as stated above, we may only speculate what may have happened during the first hour following injection of fenopropfen. We do not know whether the reduction of fenopropfen concentrations in plasma caused by phenobarbitone treatment is clinically significant. Surely, our selection of human subjects having low elimination rate constants for antipyrine is likely to favour the observation of an inductive effect of phenobarbitone on the drug metabolizing enzymes. In fact, Vesell & Page (1969) have demonstrated that phenobarbitone will depress the antipyrine half-life more in subjects having longer initial antipyrine half-lives.

Although the phenobarbitone effect was not as marked in man as in rats, clinicians evaluating the potential utility of fenopropfen in patients receiving phenobarbitone (or other drugs and chemicals known to be enzyme inducers in man (Remmer, 1962)) should be aware of the *potential* for this metabolic interaction. If this interaction caused a clinically significant increase in the rate of metabolism of fenopropfen to pharmacologically inactive metabolites, the clinical evaluation of fenopropfen could be complicated in subjects receiving fenopropfen and phenobarbitone (or other inducers of the drug metabolizing enzyme systems).

Requests for reprints should be sent to A.R.

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(Received January 7, 1974)