Effect of flurbiprofen on the metabolism of antipyrine in man

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At the present time, there is a proliferation of new drugs for use in rheumatoid arthritis. Because pain in this condition is so difficult to control, most patients are taking two or more drugs simultaneously. It has become clear during recent years that drugs may interact with one another, for example with absorption, protein-binding in plasma, competition at receptor sites, and renal excretion (Prescott, 1969; Jeremy and Towson, 1970; Neuvonen, Gothoni, Hackman and Bjorksten, 1970; Beeley and Kendall, 1971; Kendall, Nutter and Hawkins, 1971). Drugs also interact by the interference of one with the metabolism of another (Conney, 1967 and 1969; Prescott, 1969 and 1971; McEwen and Stevenson, 1972), and several antirheumatic drugs (*e.g.* phenylbutazone) are known to produce such interactions by the induction of liver microsomal enzymes. It is important therefore to determine whether a new antirheumatic agent may influence the activity of microsomal enzymes.

The rate of disappearance of antipyrine from the plasma after a single oral dose has been shown to be a useful indicator in man of the drug-metabolizing capacity of the liver (O'Malley, Stevenson, and Alexander, 1970). Antipyrine is well-suited for this purpose as it is almost completely metabolized by the liver (Brodie and Axelrod, 1950) and there is little plasma protein binding (Soberman, Brodie, Levy, Axelrod, Hollander, and Steele, 1949). The clearance of antipyrine from the plasma is increased by known inducers of hepatic microsomal enzymes, *e.g.* phenobarbitone and insecticides (Vessel and Page, 1969; Kolmodin, Azarnoff, and Sjoqvist, 1969).

Flurbiprofen is a newly introduced antirheumatic agent which has been shown in a double-blind controlled trial to be effective in rheumatoid arthritis (Chalmers, Cathcart, Kumar, Dick, and Buchanan, 1972). In this paper, we report the results of a study of the effects of this drug on antipyrine clearance in healthy, normal subjects.

Material and methods

SUBJECTS

The study was performed on thirteen healthy young volunteers, seven males and six females. All were aged 20 or 21 years and all were Caucasian.

EXPERIMENTAL PROCEDURE

All subjects were seen on three occasions with intervals of 14 days between each visit. Each subject, having fasted overnight, ingested an oral dose of antipyrine of 18 mg./kg. body weight, at 08.00 hours. Serial blood samples were withdrawn at 09.30, 11.00, 12.00, 14.00, 15.30 and 17.00 hours. Each sample was anticoagulated with lithium-heparin and centrifuged as soon as possible after withdrawal. Supernatant plasma was decanted and stored under refrigeration at 4°C. pending antipyrine estimation which was performed the following day.

Samples withdrawn on the first two occasions were used for a study of the reproducibility of the technique. At the end of the second visit, each subject was issued with a 2-week supply of flurbiprofen (60 mg./day for females and 75 mg/day for males). The plasma samples withdrawn during the third visit were used for a study of the influence of flurbiprofen on antipyrine metabolism.

ANTIPYRINE ESTIMATION

This was performed according to the method of Brodie, Axelrod, Soberman, and Levy (1949). Each estimation was performed in duplicate and standards were run with each set of determinations. Before this study was begun, the precision of the method was tested by performing duplicate estimations on 22 plasma samples containing various amounts of antipyrine (4 to 40 µg/ml.). The mean value $\pm$ standard error for the first set of estimations was 14.29 ± 2.13 µg./ml. and that for the second 14.45 ± 2.11 µg./ml. The difference between these two figures is not significant by the Student's *t*-test for paired variables ($t = 1.20$; $P > 0.1$), which confirms the precision of the method. In order to exclude the possibility of interference by flurbiprofen with the analytical procedure, measured quantities of antipyrine were added to samples of plasma taken from patients before and after administration of therapeutic doses of flurbiprofen. Estimation of antipyrine in these samples revealed no difference between those with and those without flurbiprofen.

Results

The values obtained from the antipyrine estimations were used to determine plasma half-lives of the substance for each of the thirteen subjects at each of their three visits (see Table). The male subjects did not differ significantly from the females and all thirteen sets of figures are thus considered together. The mean plasma half-life $\pm$ standard error obtained on the first occasion was 8.5 ± 1.1 hrs and that obtained on the second occasion 7.1 ± 1.0 hrs. These two pre-treatment figures do not differ significantly ($t = 1.02$; $P > 0.1$) but there was wide individual variation (range 1.9 to 15.6 hrs). The combined mean for all pre-treatment values was 7.9 ± 0.8 hrs. This differed significantly from the mean plasma antipyrine half-life of 14.0 ± 1.6 hrs obtained after 2 weeks' treatment with flurbiprofen ($t = 3.91$; $P < 0.01$).

Discussion

A number of drugs and other compounds are known to influence hepatic microsomal enzymes. Of the antirheumatic drugs, phenylbutazone has been the most widely studied, and has been shown to have enzyme-inducing properties in animals (*in vitro* and *in vivo*) and in man (Chen, Vrindten, Dayton, and Burns, 1962; Conney, 1967; Kitagawa, Kamataki, and Yoshida, 1968). There is some evidence from animal experiments that corticosteroids may have a similar effect, but aspirin does not (Berlin and Schimke, 1965; Burns, Cucinell, Koster, and Conney, 1965). To our knowledge, the effect of other anti-rheumatic agents on hepatic drug-metabolizing enzymes has not been investigated, although several are known to inhibit lysosomal acid hydrolases from

the liver (Anderson, 1968). Since both aspirin and phenylbutazone have this inhibitory effect on lysosomal enzymes, this finding probably has no relevance to the study of drug metabolism.

The measurement of the plasma half-life of a drug is currently the most acceptable method of studying drug metabolism in man, and antipyrine is probably the most suitable agent for use in such studies (McEwen and Stevenson, 1972). In the present study, in healthy subjects not receiving specific medication, the mean plasma half-life of antipyrine did not vary significantly over a 14-day period. However, for individual subjects, quite markedly different values were obtained for the two measurements. In eight subjects, the half-life decreased by 0.2 to 11.0 hrs and in five it increased by 1.4 to 2.9 hrs. These figures support the use of antipyrine in studies of groups, but suggest that figures from individual subjects should be interpreted with caution because of an apparently random temporal variation.

After 14 days' treatment with flurbiprofen, there was a significant increase in mean antipyrine half-life. This finding suggests that the metabolism of antipyrine is inhibited by flurbiprofen. A possible mechanism for this is the inhibition of hepatic microsomal enzymes, although other influences on the liver cannot be excluded. Alterations in absorption and plasma-binding are unlikely, in view of the known properties of antipyrine (Soberman and others, 1949; Brodie and Axelrod, 1950). From the results obtained in the present study, we have been able to deduce that flurbiprofen produces no appreciable alteration in the volume of distribution of the test substance.

If enzyme inhibition does occur with the administration of flurbiprofen, an important practical implication is that the effect of concurrently adminis-

Table Plasma antipyrine half-lives before and after treatment with flurbiprofen

Sex	Case no.	Pre-treatment value			Post-treatment value	Percentage change after treatment
		First	Second	Mean		
Male	1	3.9	5.3	4.6	23.3	+407
	2	13.7	8.7	11.2	15.8	+41
	3	3.4	5.2	4.3	8.2	+91
	4	6.7	9.5	8.1	14.6	+80
	5	7.7	7.5	7.6	13.7	+80
	6	15.6	4.6	11.1	15.2	+37
	7	8.8	3.8	6.3	10.2	+62
Female	1	6.5	1.9	4.2	6.2	+48
	2	9.5	3.9	6.7	7.8	+16
	3	5.4	12.3	8.9	15.0	+69
	4	14.6	13.2	13.9	21.7	+56
	5	5.8	5.3	5.6	21.8	+289
	6	8.7	11.6	10.2	8.6	-16
Mean		8.5	7.1	7.9	14.0	97
$\pm$ SEM		± 1.1	± 1.0	± 0.8	± 1.6	± 33

tered drugs may be prolonged. This phenomenon is well recognized for other therapeutic agents, such as isoniazid, chloramphenicol, nortriptyline, and dicoumarol (Hansen, Kristensen, Skovsted, and Christensen, 1966; Kristensen and Hansen, 1967; Koch-Weser and Sellers, 1971; Kutt, 1971). Clinically significant interactions as a result of hepatic enzyme inhibition have occurred in many patients with chronic diseases who have been treated with these drugs. Another possibility is that flurbiprofen may inhibit its own metabolism and accumulate if given in the doses used in this study. A further interpretation of the present findings is that the change produced by the drug may be an early manifestation of hepatotoxicity (Sasame, Castro, and Gillette, 1968). However, no clinical or biochemical evidence of liver damage has been evident in twenty patients treated with therapeutic doses of flurbiprofen for up to 9 months (Cathcart, 1972). Further investigations of the effect of flurbiprofen on hepatic microsomal enzymes appear to be warranted, and clinical studies

to detect possible accumulation of the drug are also indicated.

Summary

A study in healthy young volunteers of the plasma half-life of antipyrine has shown that this is significantly increased after administration of the new anti-rheumatic drug, flurbiprofen. This finding suggests a possible inhibitory effect of the drug on hepatic microsomal enzymes. This, in turn, could conceivably produce a prolongation of the action of flurbiprofen itself and of other drugs metabolized by the liver.

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