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Inhibition of antipyrine metabolism by interferon

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Antipyrine clearance was measured before and 1 day after administration of a single intramuscular dose of recombinant human leukocyte αA interferon. In the nine patients studied, antipyrine clearance was reduced after interferon from 0.49 (0.21–1.13) ml kg^{-1} min^{-1} (median (range)) to 0.41 (0.20–1.07) ml kg^{-1} min^{-1}, $P < 0.01$. In individual patients, the decrement in antipyrine clearance was variable, ranging from 5–47% (median, 16%). This study provides the first direct evidence that interferon inhibits hepatic oxidative drug metabolism in humans and alerts clinicians to the possibility of potentially toxic drug–drug interactions.

Keywords drug metabolism antipyrine clearance interferon hepatitis B

Introduction

Recent observations that viral infections (Renton, 1978). influenza vaccination (Meredith *et al.*, 1985), and BCG innoculation (Gray *et al.*, 1983) are associated with impairment of hepatic oxidative drug metabolism have led to the suggestion that interferon, produced as a result of infections or vaccinations, inhibits hepatic drug metabolism. This concept is supported by observations in laboratory animals that interferon-inducing agents and interferon itself depress hepatic mixed function oxidase activity (El Azhary *et al.*, 1980; Singh & Renton, 1984; Renton *et al.*, 1984). The purpose of the present study was to examine directly the effect of interferon on hepatic drug metabolism.

Methods

Subjects studied

The protocol was approved by the Parramatta Hospitals Human Ethics Committee. Nine patients (seven males, two females; aged 20–63 years) participating in a trial of recombinant leukocyte αA interferon (F. Hoffman-La Roche) for the treatment of chronic active hepatitis B were studied using a longitudinal design and antipyrine clearance as an indicator of hepatic mixed function oxidase activity. Patients were not taking drugs known to induce or inhibit hepatic mixed function oxidase activity. Daily alcohol intake was less than the equivalent of 20 g ethyl alcohol and only one patient smoked cigarettes.

Experimental design

Two point antipyrine clearance studies were performed 2 days before and 1 day after a single intramuscular dose of interferon (4.5–18.0 megaunits) according to the method of Farrell & Zaluzny (1984).

Antipyrine half-life ($t_{½}$), apparent volume of distribution (V) and total body clearance (CL) were calculated by conventional methods (Farrell & Zaluzny, 1984).

Comparison of antipyrine clearance before and after interferon was made using the Wilcoxon matched pairs sign rank test.

Results

The median baseline value for antipyrine clearance of 0.49 (0.21–1.13) ml kg^{-1} min^{-1} (median

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(range)) was within the normal range for our laboratory of 0.34–1.02 ml kg^{-1} min^{-1} (Farrell & Zaluzny, 1984) (Table 2). However, individual results varied widely with two patients above and three patients below the normal range (Table 1). One day following administration of the single dose of interferon the median antipyrine clearance had decreased by 16% to 0.41 (0.20–1.07) ml kg^{-1} min^{-1} ($P < 0.01$) (Table 2). In all nine patients, antipyrine metabolism was reduced with decrements ranging from 5 to 47% (Table 1). Although there was a corresponding increase in antipyrine half-life following administration of interferon, this was not significant (Table 2). The volume of distribution was unchanged (Table 2). There was no apparent relationship between the dose of interferon and the extent of inhibition of antipyrine clearance (data not shown).

Table 1 Antipyrine clearance before and after interferon

Patient	*Antipyrine clearance (ml kg^{-1} min^{-1})*	
	Baseline	*After interferon*
1	0.44	0.41
2	0.27	0.21
3	1.13	1.07
4	0.32	0.28
5	0.49	0.26
6	0.21	0.20
7	0.66	0.61
8	0.79	0.71
9	1.03	0.87

Discussion

This study provides the first direct evidence that interferon inhibits hepatic drug metabolism in humans. This possibility had previously been suggested to explain the observations that metabolism of theophylline and other drug substrates of hepatic mixed function oxidases is impaired during viral infections and following vaccinations. In the present study, antipyrine was used as a marker compound for *in vivo* assessment of hepatic oxidative drug metabolism since its elimination is almost completely dependent on hepatic mixed function oxidase activity and it fulfils other safety and pharmacokinetic parameters of a marker compound for hepatic drug metabolism (Vesell, 1979). Many studies in healthy subjects have shown that clearance of antipyrine is very stable with time (Vesell, 1979). Hence in the longitudinal design of the present study patients served as their own controls.

The decrease in antipyrine clearance attributable to interferon, is greater than that reported with cimetidine (Roberts *et al.*, 1981). Moreover, some inhibition of antipyrine metabolism, from 5% to 47% occurred in every subject. Thus the potential importance of inhibition of hepatic drug metabolism by interferon will vary between individuals in an unpredictable way. Correlation between rates of antipyrine metabolism and those of other clinically relevant drug substrates of hepatic mixed function oxidases such as theophylline, warfarin and phenytoin are often poor (Vesell, 1979). It is therefore now crucial to examine the effect of interferon on elimination of clinically relevant drugs in humans since, as in the case of cimetidine, these may well be affected to a greater extent than antipyrine. Since interferons vary in their effects on mouse hepatic mixed function oxidases *in vitro* (Renton *et al.*, 1984), and *in vivo* (Taylor *et al.*, 1985), it will also be important to study the effects of γ-interferon and other interferons in humans at the time they are released for clinical trials.

The mechanism of inhibition of hepatic oxidative drug metabolism by interferon is uncertain. Studies in laboratory animals have demonstrated that interferon inducing agents increase degradation of the haem moiety of cytochrome P-450 (El Azhary *et al.*, 1980) and depress the rate of synthesis of the apoprotein of cytochrome

Table 2 Pharmacokinetic parameters for antipyrine before and after interferon

	V (*l kg^{-1}*)	$t_{½}$ (*h*)	*AP CL (ml kg^{-1} min^{-1})*
Baseline	0.68 (0.43–1.07)	15.1 (7.1 to 35.5)	0.49 (0.21 to 1.13)
After interferon	0.73 (0.44–1.08)	16.1 (6.0 to 38.9)	0.41 (0.20 to 1.07)
P value	NS	NS	< 0.01
Normal range (Farrell & Zaluzny, 1984)	0.51–0.74	6.5–16	0.34–1.02

V = volume of distribution; $t_{½}$ = half-life; AP CL = antipyrine clearance.
Values are expressed as median (range).

P-450 (Singh & Renton, 1984). It has also been demonstrated that only those interferons with antiviral activity depress cytochrome P-450 (Renton *et al.*, 1984). It is possible that the biochemical pathways that mediate the antiviral and antitumour effects of interferons also mediate the depressive effect on hepatic cytochrome P-450 metabolism and that these effects are inseparable (Renton *et al.*, 1984). However, the very early effect (less than 24 h) of interferon in the present study may indicate a more immediate effect. Furthermore, the effect of interferon on antipyrine clearance does not appear to be cumulative; antipyrine clearance after nine interferon injections was not significantly different from antipyrine clearance following a single injection of interferon (data not shown). Studies *in vitro* are required to ascertain whether interferon competitively inhibits, destroys or suppresses synthesis of cytochrome P-450.

With the growing interest in the value of interferon treatment in hepatitis B (Omata *et al.*, 1985) as well as for some malignancies (Gutterman *et al.*, 1980; Quesada *et al.*, 1984), it is important that clinicians are aware of potentially toxic drug interactions that may result from the inhibition of hepatic mixed function oxidases by interferon.

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