Inhibition of antipyrene elimination by disulfiram and cimetidine: the effect of concomitant administration

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We investigated the effect of concomitantly administered disulfiram and cimetidine on antipyrene elimination. On day 1, 2, 4 and 6 of two periods of 6 days one sample antipyrene saliva clearance (APC) was measured in nine healthy volunteers. From day 2 to 6 of period I disulfiram 400 mg day\(^{-1}\) was administered and on day 5 and 6 cimetidine 1000 mg day\(^{-1}\) was added. In period II only cimetidine was given (on days 5 and 6). On day 4 of period II APC was increased 1.3 fold, probably due to self-induction by repeated antipyrene administration. Taking this into account disulfiram and cimetidine separately decreased APC 0.64 and 0.70 times, respectively. When both inhibitors were given APC was reduced 0.52 times. The results suggest that the effects of cimetidine and disulfiram on antipyrene elimination are additive.

Keywords disulfiram cimetidine antipyrene inhibition of drug metabolism

Introduction

It is well established that many xenobiotics can alter hepatic drug metabolism to a clinically important extent either through a stimulating or an inhibiting effect on microsomal enzymes. To date, most of these studies have considered the effect of a single substance on hepatic drug metabolism. Frequently, however, man is exposed to several environmental factors or drugs capable of modifying microsomal enzyme activity and the combined effect may be difficult to predict.

We have investigated the effect of two concomitantly administered inhibitors of hepatic drug metabolism, disulfiram and cimetidine, on antipyrene elimination.

Methods

Nine healthy volunteers, five women and four men, participated in the study after giving informed consent (age: 32 ± 4 years; weight: 63 ± 13 kg; height: 174 ± 8; mean ± s.d.). The study was approved by the local ethics committee. The subjects consumed alcohol socially and one of the women was a smoker. No drugs were taken during the month preceding the investigations. The trial consisted of two periods, each of 6 days, separated by some months. On day 1, 2, 4 and 6 during both periods the subjects ingested antipyrene 1 g and clearance was estimated by the one sample method (Døssing et al., 1982). Disulfiram 400 mg once a day was administered, simultaneously with antipyrene when appropriate, from day 2 to 6 during the first period. Cimetidine 1000 mg day\(^{-1}\) was given on day 5 and 6 of both periods. In a third 6 day study period five subjects (nos 1, 4, 7, 8 and 9) repeated the four antipyrene tests without any concomitant drug administration. Salivary concentrations of antipyrene were measured by h.p.l.c. (Sonne et al., 1985). When antipyrene clearance was calculated for day 2, residual antipyrene from the antecedent administration on day 1 (salivary...
concentration before ingestion times the estimated volume of distribution) was included in the dose.

During period I 2 h aminopyrine breath tests after ingestion of 5 µg, 2 µCi [14C]-aminopyrine were performed simultaneously with the antipyrine clearance measurements. However, due to technical difficulties this part of the data was excluded from the analysis.

The time course of antipyrene clearance during the two first and the third study periods was analysed by two-factorial analysis of variance. Differences between means were tested with multiple t-tests according to the method of Bonferroni (Wallenstein et al., 1980). P values less than 0.05 were considered statistically significant.

Results

Results of the one sample antipyrene clearance (APC) during the two periods are given in Table 1. The residual s.d. was 17% of the grand mean.

APC was reduced on the first day of disulfiram treatment and further reduced on the third day of administration to 0.84 times the initial value of period I. Additional cimetidine treatment caused a further decrease of APC to 0.68 times the initial value of period I.

Antipyrene was administered repeatedly in a dose capable of inducing its own metabolism (Ohnhaus & Park, 1979). The extent of this self-

induction was assessed in period II (and III) of the experiment and amounted to 1.28 times the initial value of period II after three 1 g doses of antipyrene given over 4 days. From this level additional cimetidine treatment decreased APC to 0.89 times the initial value of period II. In the third study period with five subjects APC was 55.6 ± 12.0 ml min⁻¹ on day 1 and increased 1.22 ± 0.13, 1.29 ± 0.12 and 1.27 ± 0.04 fold on day 2, 4 and 6, respectively ($P < 0.05$).

In order to compensate for the antipyrene mediated enzyme induction, period II may serve as base line for period I. Thus, on the first and third day of disulfiram treatment APC was decreased to 0.79 and 0.64 times the respective base line values of day 2 and 4, period II, whereas the decrease due to disulfiram was 0.75 fold, when administration was concomitant with cimetidine.

The effect of cimetidine is apparent when APC measurements of days 4 and 6 of each period are compared. Thus, the effect of cimetidine alone and on top of disulfiram was a 0.70 and 0.81 fold decrease in APC, respectively. The effect of the combined inhibiting treatment was a 0.52 fold decrease in APC from day 4, period II, to day 6 of period I.

Discussion

We investigated the effect of two concomitantly administered inhibitors of hepatic drug metabolism in a design consisting of two 6 days periods.

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<td>Mean</td>
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<td>39.5†</td>
<td>32.0‡</td>
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<td>14.6</td>
<td>16.1</td>
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<td>21.2</td>
<td>18.0</td>
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† denotes $P < 0.05$ vs parallel value of opposite period;  
* $P < 0.05$ vs value of day 1 of same period;  
‡ $P < 0.05$ vs value of preceding measurement of same period.
Enzyme inhibition was assessed by antipyrine clearance determined by a one sample method with little intrindividual variation and resistance to changes in apparent volume of distribution (Dössing et al., 1983; Pilsgaard & Poulsen, 1984). Period I permitted investigation of the time course of the inhibiting effect of disulfiram, which has previously been shown to be maximal within 4 days of administration (Vesell et al., 1975). In the present setting antipyrine clearance was depressed further after 3 than after 1 day of disulfiram treatment. This delayed effect is in contrast to the immediate effect cimetidine exerts on hepatic drug metabolism (Dössing et al., 1983; Feely et al., 1984). The second and the third study period were undertaken because antipyrine is capable of stimulating microsomal drug metabolism per se in the doses used (Ohnhaus & Park, 1979), amounting to a 1.28 fold increase reached on day 4 in the present design.

Assuming that the effects of disulfiram and cimetidine are exerted independently of the antipyrine mediated enzyme stimulation, the clearance measurements during period II (no disulfiram) can be considered as base line for the effect of disulfiram. However, cimetidine mediated enzyme inhibition is relatively larger during administration of the inducer, rifampicin (Feely et al., 1984). On the other hand cimetidine decreased clearance 0.70 fold during antipyrine induction in period II, which is what would have been expected during cimetidine treatment of non-induced subjects (Dössing et al., 1983). Moreover, the effect of disulfiram administration for 3 days was a decrease in antipyrine clearance amounting to 0.64 times, in agreement with Vesell et al. (1975). Accordingly, it appears that the slight enhancement of antipyrine elimination did not significantly affect the relative inhibiting effect of disulfiram and cimetidine in the present setting.

The effect on antipyrine clearance of each of disulfiram and cimetidine was a 0.64 and 0.70 fold decrease, respectively, whereas the combined treatment caused a 0.52 fold reduction. This suggests that the effects of these two inhibitors are additive, although not in a strict arithmetical sense, which also appears consistent with the observation that cimetidine inhibits hepatic drug metabolism in a dose dependent way, but less so with increasing dose (Bartle et al., 1983; Feely et al., 1984).

In conclusion this study suggests that therapeutic doses of disulfiram and cimetidine inhibit antipyrine elimination additively. If this applies to other microsomal oxidized drugs, the risk of drug accumulation must be considered particularly when several drugs with inhibiting properties are coadministered.

References


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