Br. J. clin. Pharmac. (1986), **21**, 75–77

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

S. LOFT,[1] J. SONNE,[1] H. PILSGAARD,[2] DØSSING[1] & ENGHUSEN POULSEN[2]
[1]Medical Department F, Gentofte University Hospital, DK-2900 Hellerup, Denmark and [2]Medical Department A, Division of Hepatology, Rigshospitalet, DK-2100 Copenhagen, Denmark

We investigated the effect of concomitantly administered disulfiram and cimetidine on antipyrine elimination. On day 1, 2, 4 and 6 of two periods of 6 days one sample antipyrine 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 antipyrine 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 antipyrine elimination are additive.

Keywords disulfiram cimetidine antipyrine 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 antipyrine 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 antipyrine 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 antipyrine 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 antipyrine tests without any concomitant drug administration. Salivary concentrations of antipyrine were measured by h.p.l.c. (Sonne *et al.*, 1985). When antipyrine clearance was calculated for day 2, residual antipyrine from the antecedent administration on day 1 (salivary

Correspondence: Dr S. Loft, Department of Clinical Chemistry, Gentofte University Hospital, DK-2900 Hellerup, Denmark

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 [^{14}C]-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 antipyrine 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 antipyrine 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.

Antipyrine 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 antipyrine 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 antipyrine 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.

Table 1 Antipyrine clearance (APC) in ml min^{-1} in nine subjects before and during administration of disulfiram (DS) and/or cimetidine (Cim) in two periods of 6 days.

	Period I				*Period II*			
Day	*1*	*2*	*4*	*(5) 6*	*1*	*2*	*4*	*(5) 6*
Treatment								
DS		×———	———	———×				
Cim				×———×				×———×
Subject								
1	44.4	29.5	32.2	28.5	45.1	47.0	55.7	32.2
2	38.1	35.2	40.1	21.3	40.8	42.5	38.2	33.6
3	50.5	41.9	35.2	24.1	58.6	53.2	57.3	48.9
4	28.3	53.9	40.3	41.3	39.6	48.5	55.4	41.5
5	39.6	29.7	18.9	16.0	51.1	41.1	46.7	46.1
6	29.5	37.3	28.4	21.0	31.4	35.4	54.4	30.5
7	83.4	72.5	60.5	69.3	58.4	104.6	99.2	52.2
8	37.1	31.9	38.3	32.5	38.8	47.0	75.0	51.8
9	71.6	54.5	62.2	34.6	67.7	71.0	71.0	49.5
Mean	47.0	42.9†	39.5*†	32.0*†§	47.9	54.5†	61.4*†	42.8*†§
s.d.	18.9	14.4	14.6	16.1	11.8	21.2	18.0	8.9

† 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 intraindividual variation and resistance to changes in apparent volume of distribution (Døssing *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 (Døssing *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 (Døssing *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 microsomally oxidized drugs, the risk of drug accumulation must be considered particularly when several drugs with inhibiting properties are coadministered.

References

Bartle, W. R., Walker, S. E. & Shapero, T. (1983). Dose dependent effect of cimetidine on phenytoin kinetics. *Clin. Pharmac. Ther.*, **33**, 649–655.

Døssing, M., Poulsen, H. E., Andreasen, P. B. & Tygstrup, N. (1982). A simple method for determination of antipyrine clearance. *Clin. Pharmac. Ther.*, **32**, 392–396.

Døssing, M., Pilsgaard, H., Rasmussen, B. & Poulsen, H. E. (1983). Time course of phenobarbital and cimetidine mediated changes in hepatic drug metabolism. *Eur. J. clin. Pharmac.*, **23**, 215–222.

Feely, J., Pereira, L., Guy, E. & Hockings, N. (1984). Factors affecting the response to inhibition of drug metabolism by cimetidine—dose-response and sensitivity of elderly and induced subjects. *Br. J. clin. Pharmac.*, **17**, 77–81.

Ohnhaus, E. E. & Park, B. K. (1979). Measurement of urinary 6β-hydroxycortisol excretion as an *in vivo* parameter in the clinical assessment of the microsomal enzyme-inducing capacity of antipyrine, phenobarbitone and rifampicin. *Eur. J. clin. Pharmac.*, **15**, 139–145.

Pilsgaard, H. & Poulsen, H. E. (1984). A one-sample method for antipyrine clearance determination in rats. *Pharmacology*, **29**, 110–116.

Sonne, J., Døssing, M., Loft, S. & Andreasen, P. B. (1985). Antipyrine clearance in pneumonia. *Clin. Pharmac. Ther.*, **37**, 701–704.

Vesell, E. S., Passanata, G. T. & Glenwright, P. A. (1975). Anomalous results of studies on drug interaction in man III. Disulfiram and antipyrine. *Pharmacology*, **13**, 481–491.

Wallenstein, S., Zucker, Z. L. & Fleiss, J. L. (1980). Some statistical methods useful in circulation research. *Circulation Res.*, **47**, 3–9.

(Received 26 April 1985, accepted 7 September 1985)