

Effect of concomitant administration of cimetidine and phenobarbital on antipyrine elimination and metabolite formation

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Abstract. Cimetidine 1000 mg/day and phenobarbital 100 mg/day were given to five healthy volunteers for 13 days in order to investigate the combined effect and time course of inhibition and induction on hepatic drug metabolism. The one-sample antipyrine saliva clearance (APC) and urinary metabolite profile were measured weekly, once before, two times during and four times after drug administration. On the second day of drug treatment APC was 0.7 fold and the formation clearance of the 3 oxidized metabolites 0.6 fold decreased owing to an early inhibition by cimetidine ($p < 0.05$). After 8 days of concomitant drug administration, i.e. when the drug mediated inhibition and induction are supposed to be at maximum, mean APC was 0.85 times the initial value ($p > 0.05$), whereas the formation clearances of nor- and 3-hydroxymethylantipyrine were still significantly depressed. Four and 11 days after drug withdrawal, when phenobarbital, but not cimetidine could be demonstrated in plasma, APC was 1.2 times the initial value ($p < 0.05$). The results suggest, that the respective effects of cimetidine and phenobarbital on antipyrine elimination are additive, when given concomitantly, but that cimetidine exerts a relatively greater inhibition in the phenobarbital induced state.

Key words: cimetidine - phenobarbital - antipyrine - inhibition - induction - hepatic drug metabolism

Introduction

Drug associated inhibition and induction of hepatic drug metabolism may have great implications. In clinical practice several drugs are often administered concomitantly thus producing a potential for both inhibition and induction. The combined effect of two inducing agents on hepatic drug metabolism seems, in most cases, to be greater than the effect of either agent alone [Ohnhaus et al. 1979], although it may occasionally be less than the sum. It is also suggested, that two inhibitors exert their effects in an additive way [Loft et al. 1986].

This study was designed to follow the time course of changes in the rate of antipyrine elimination and metabolite formation during the concomitant administration of an inhibiting (cimetidine) and an inducing (phenobarbital) agent.

Methods

Five healthy non-smokers, four men and one woman aged 26-36 years, participated in the study after giving informed consent. The study was approved by the local ethical committee. The subjects only consumed alcohol socially and received no drugs during the preceding month. The subjects ingested 1 g of antipyrine once a week, before, two times during, and four times after a 13-day treatment period with cimetidine 1000 mg/day and phenobarbital 100 mg/day. The clearance of antipyrine was estimated by the one-sample method [Døssing et al. 1982]. Salivary concentrations of antipyrine [Sonne et al. 1985] and concentrations of metabolites in 48 hour urine [Pilsgaard and Poulsen 1984] were measured by h.p.l.c. The formation clearance of each of the antipyrine metabolites was calculated as the fraction of dose excreted times the total clearance.

Cimetidine and phenobarbital in plasma were determined before, two times during, and three times after drug administration, using h.p.l.c. [Larsen et al. 1979], and respective spectrophotometry [Roberts et al. 1971].

Table 1 One-sample antipyrine clearance in ml/min in 5 subjects before, during and after concomitant administration of cimetidine (CIM) and phenobarbital (PHEN).

Week No.	CIM + PHEN						
	1	2	3	4	5	6	7
Subject No.							
1	79	47	65	94	95	94	83
2	95	58	75	76	84	93	91
3	34	24	35	59	50	40	40
4	80	66	59	110	96	95	78
5	54	42	56	79	75	58	54
mean	68	47*	58	84*	80*	76	69
SD	24	16	15	19	19	25	21

* denotes $p < 0.05$ vs initial value

The data were investigated statistically by two-way analysis of variance and Dunçan's multiple range test. P-values less than 0.05 were considered statistically significant.

Results

The time related changes in the total antipyrine clearance (APC) are given in Table I. The residual SD was 13% of the grand mean. After one day of combined cimetidine and phenobarbital administration the mean APC was reduced to 0.7 times the initial value ($p < 0.05$) and the formation clearances of all 3 oxidative metabolites were decreased 0.6 fold ($p < 0.05$; Table 2). Following eight days of drug treatment, the mean APC was 0.85 times the initial value ($p > 0.05$), whereas the formation clearance of both nor- and 3-hydroxyantipyrine was still significantly depressed.

Four and 11 days after cessation of cimetidine and phenobarbital the mean APC increased to 1.2 times the initial value ($p < 0.05$; Table 1). The formation clearances of nor- and 3-hydroxymethylan-

tipyrine were significantly increased 11 days after drug withdrawal (Table 2). At the last measurements the APC and metabolite profile had returned to the preexposure level. Phenobarbital was found in plasma during the first three weeks after drug administration, whereas cimetidine was only detectable during the two weeks of drug treatment.

Discussion

The effect of concomitant administration of an inhibitor and an inducer of hepatic drug metabolism was investigated by means of one of the most widely used probes, antipyrine [Vesell 1979]. Provided, that the sampling time is ideal and accurately recorded and a sensitive antipyrine analysis is employed, a two-digit number of samples is required to exceed the precision of the one-sample method we used for the clearance determination [Døssing et al. 1982, Døssing et al. 1983a]. Moreover, a computer simulation study has shown that changes in or errors in estimation of the volume of distribution have negligible effect on the results [Pilsgaard and Poulsen 1984]. Accordingly, the random variation was small in the present as well as in previous drug interaction studies, where the one-sample antipyrine clearance has been used [Døssing et al. 1983b, Loft et al. 1986, Sonne et al. 1985].

The measurement of the urinary antipyrine metabolite profile allows detection of differential alterations in the metabolic pathways [Danhof et al. 1982].

On the second day of concomitant cimetidine and phenobarbital administration, the total antipyrine clearance was uniformly decreased to mean 0.7 times the initial value and the formation clearance of all 3 oxidized metabolites was 0.6 fold depressed. This extent of inhibition of antipyrine metabolism is similar to the effect of cimetidine given alone [Døssing et al. 1983b]. In agreement, the inhibitory effect of cimetidine is exerted within 24 hours after administration, whereas 7 to 10 days are required for the

Table 2 The formation clearance of 4-hydroxyantipyrine (4-OH), norantipyrine (NOR) and 3-hydroxymethylantipyrine (3-OH-M) and renal clearance of unchanged antipyrine (AP) in 5 subjects before, during and after concomitant administration of cimetidine (CIM) and phenobarbital (PHEN). Values are in ml/min and given as mean \pm SD.

Week No.	CIM + PHEN						
	1	2	3	4	5	6	s ²
4-OH	26.0 \pm 13.9	14.3 \pm 7.2*	20.6 \pm 8.4	28.7 \pm 13.1	26.9 \pm 14.7	26.7 \pm 14.6	22.0
NOR	13.8 \pm 4.6	7.8 \pm 4.1*	9.0 \pm 3.1*	16.5 \pm 4.1	17.6 \pm 4.4*	14.4 \pm 5.6	8.23
3-OH-M	12.9 \pm 3.1	7.7 \pm 2.8*	8.6 \pm 2.1*	14.7 \pm 5.5	17.4 \pm 5.3*	13.2 \pm 1.8	4.92
AP	1.7 \pm 0.8	1.2 \pm 1.1	1.1 \pm 0.4	1.7 \pm 0.8	1.3 \pm 0.5	1.8 \pm 0.7	0.25

* denotes $p < 0.05$ vs initial value and s² is the residual variance

maximal phenobarbital mediated induction [Døssing et al. 1983b, Feely et al. 1984, Roberts et al. 1971].

After eight days of combined drug administration, i.e. when cimetidine and phenobarbital are supposed to exert their respective effects fully, the total clearance of antipyrine was still depressed in 3 subjects, but had returned to the preexposure level in 2, rendering the mean effect statistically insignificant. On the other hand, the formation clearance of nor- and 3-hydroxymethylantipyrine was still significantly reduced. The effect of phenobarbital treatment alone for 8 to 10 days is usually a 1.6 fold or so increase in total antipyrine clearance with a greater enhancement of the formation of norantipyrine than of the other metabolites [Danhof et al. 1982, Døssing et al. 1983b].

Accordingly, if their effects were strictly additive one would expect phenobarbital at least to balance the cimetidine mediated inhibition of the total antipyrine clearance and in particular of the formation rate of norantipyrine. Our findings therefore, suggest that a partly additive effect of concomitant cimetidine and phenobarbital on the hepatic metabolism of antipyrine and the effect of cimetidine are relatively stronger in a phenobarbital induced state.

Recently, others have demonstrated that the cimetidine mediated inhibition of the total antipyrine elimination rate is more pronounced in rifampicin [Feely et al. 1984] and phenytoin induced subjects [Neuvonen et al. 1981]. On the other hand, the inhibition and induction of the total antipyrine clearance by cimetidine and carbamazepine seem to counterbalance one another [MacPhee et al. 1984].

Four and 11 days after withdrawal of cimetidine and phenobarbital the total clearance of antipyrine and after 11 days the formation clearance of nor- and 3-hydroxymethylantipyrine as well, were significantly increased as compared with the initial values. Thus, the inhibitory effect of cimetidine was rapidly lost due to its short elimination half-life, allowing the slowly eliminated phenobarbital to exert the enhancing effect for the long period it was present in plasma.

Other combinations of inhibitors and inducers have been investigated. It has been found that the effect of two inducers is generally greater than the effect of each of them, and that the final result cannot be predicted quantitatively. Accordingly, the combination of antipyrine and phenobarbital have a smaller while antipyrine and rifampicin have a greater effect than the sum total of the drugs in question [Ohnhaus et al. 1979]. The effect of two inhibitors on hepatic drug metabolism is to some degree additive too [Loft et al. 1986].

The present study suggests that the effect of concomitant inhibition and induction of hepatic drug metabolism, using therapeutic doses of cimetidine and

phenobarbital, is additive and that enzyme induction may increase the relative effect of an inhibiting agent.

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