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Sparteine oxidation is practically abolished in quinidine-treated patients

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In eight patients a sparteine-test was carried out immediately before and after 1 week of treatment with quinidine 600–800 mg day^{-1}. Before treatment one patient was classified as a poor metaboliser (metabolic ratio: ≥ 20), and seven patients as extensive metabolisers. During quinidine treatment, the formation of sparteine metabolites (2- and 5-dehydrosparteine) was practically abolished. Patients initially classified as extensive metabolisers thus exhibited the phenotype of poor metabolisers during quinidine treatment.

Keywords genetic polymorphism sparteine quinidine oxidation phenotype

Introduction

The genetic polymorphism affecting the oxidation of debrisoquine and sparteine has been studied extensively in recent years, and the frequency of so called 'poor metabolisers' has been determined to be 7–10 per cent in several studies in various Caucasian populations (Evans *et al.*, 1980; Eichelbaum & Woolhouse, 1985; Küpfer & Preisig, 1984; Wedlund *et al.*, 1984; Brøsen *et al.*, 1985). The oxidation of several drugs in clinical use such as β-adrenoceptor antagonists and tricyclic antidepressants has also been shown to be affected by this polymorphism (Clark, 1985).

An *in vitro* approach to screen for drugs which may undergo oxidative metabolite reactions subject to this genetic variation has recently been proposed. This technique is based on studies of the influence of various drugs on the formation of oxidized metabolites of debrisoquine (Boobis *et al.*, 1983), sparteine (Otton *et al.*, 1983) or desipramine (von Bahr *et al.*, 1985) in microsomal preparations from human liver. Drugs which competitively inhibit these reactions are capable of binding to the active site of the cytochrome P-450 isozyme involved, thereby raising the possibility that they themselves may be oxidized by this isozyme showing genetic variations. Among more than 200 compounds submitted to such *in vitro* testing, quinidine was the most potent inhibitor, as indicated by inhibitor constant values (K_i) as low as 60 nM for the inhibition of sparteine oxidation (Otton *et al.*, 1984).

The present study was undertaken to determine whether the potent *in vitro* inhibition by quinidine of sparteine oxidation is also apparent in patients on therapeutic doses of quinidine.

Methods

Eight patients, all Caucasians (five male, three female, age 33–84 years, Table 1) with supraventricular arrhythmias were studied. In each patient a sparteine-test was carried out immediately before and after 1 week of treatment with quinidine sulphate (200 mg × 3–4 as tablets). The patients showed no signs of cardiac incompetance, liver or renal disease (serum-creatinine < 150 μM), and were not receiving β-adrenoceptor antagonists, tricyclic antidepressants, neuroleptics or cimetidine. Treatment with other drugs (Table 1) was continued at the same doses throughout the study. Patients consented to participate on the basis of verbal and written infor-

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Table 1 The results of the study

Subject No.	Sex	Age (years)	Quinidine dose (mg day^{-1})	Plasma concentration (μM) Quinidine	3-OH-quinidine	Sparteine-test 12 h urinary excretion (% of dose) sparteine	dehydro-sparteines*	total	MR	Concurrent medication‡ (dose per day)
1	F	73	0	—	—	36.5	1.3†	37.8	28	digoxin (187.5 μg)
			800	5.3	0.5	32.0	0.2†	32.2	160	
2	M	58	0	—	—	8.8	14.7	24.4	0.60	tolbutamide (1500 mg)
			800	3.8	2.0	34.3	1.6†	35.9	21	
3	M	69	0	—	—	23.1	3.3	26.7	6.4	digoxin (62.5 μg)
			800	6.7	1.4	33.9	1.0	35.5	21	
4	M	66	0	—	—	31.5	11.7	43.3	2.7	digoxin (125 μg)
			800	3.4	0.5	21.2	0.1†	21.3	210	
5	M	33	0	—	—	30.0	26.0	56.0	1.2	—
			800	4.8	0.5	38.0	1.2	39.2	32	
6	F	84	0	—	—	13.0	38.0	51.0	0.34	
			600	1.9	0.6	30.6	0.2†	30.8	150	—
7	M	80	0	—	—	31.7	8.1	39.7	1.3	frusemide (40 mg)
			800	4.5	1.0	28.2	0.9	29.1	31	phenobarbitone (100 mg)
8	F	63	0	—	—	35.2	27.4	62.5	3.9	digoxin (125 μg)
			600	2.2	0.3	48.6	0.1†	48.6	490	

* 2-DHS plus 5-DHS
† no detectable metabolites. Detection limit-value (0.25 μM) used for calculation of % excretion.
‡ constant during the two tests

mation and the protocol was approved by the regional ethics committee.

The sparteine test involved the oral administration of 100 mg sparteine sulphate (Depasan®, Giulini) followed by collection of urine for 12 h.

Sparteine (SP) and the two metabolic products 2- and 5-dehydrosparteine (DHS) in urine were assayed by gas chromatography according to Vinks *et al.* (1982). The lower limit of detection for 2- and 5-DHS was 0.25 μM. Excretion of SP, 2-DHS and 5-DHS was expressed as per cent of dose in 12-h-urine and the metabolic ratio (MR) was calculated from:

$$MR = \frac{\text{12-h excretion of SP}}{\text{12-h excretion of 2-DHS + 5-DHS}}$$

According to an earlier population study (Brøsen *et al.*, 1985) poor metabolizers were defined as subjects with MR $\geqslant$ 20. In samples with undetectable dehydrosparteines, the assay detection limit was used for calculation of percentage excretion and MR.

Quinidine and its primary metabolite, 3-OH-quinidine, in plasma were assayed by quantitative thin-layer chromatography, developed in our laboratory, using a Zeiss Chromatogram Scanner. The lower limit of detection was about 0.1 μM (both compounds) and the reproducibility of the assay was 5–7%. All samples were run in duplicate.

Results

As shown in Table 1, all patients had therapeutic plasma concentrations of quinidine and 3-OH-quinidine on the given dose.

According to the results of the pre-quinidine sparteine test one patient was classified as a poor metaboliser (MR = 28) and seven patients were phenotyped as extensive metabolisers (MR = 0.34–6.4).

The formation of dehydrosparteines in the extensive metabolisers was almost totally abolished during quinidine treatment. The excretion of unchanged sparteine increased accordingly. The only exception to this was patient no. 4 who probably provided an incomplete urine collection during the second sparteine test (total excretion was only 22%). However, the MR value, being relatively independent of urine collection compliance, indicated a clear inhibition of the oxidative metabolism of sparteine. All patients initially classified as extensive metabolisers thus exhibited the phenotype of poor metabolisers during quinidine treatment.

Discussion

Our study has shown that the marked inhibitory properties of quinidine on the microsomal oxidation of sparteine *in vitro* are also reflected by *in vivo* findings.

Several clinically important drugs are metabolised by the same isozyme as sparteine. Thus studies in sparteine/debrisoquine phenotyped subjects have indicated that the overall elimination of metoprolol (Lennar *et al.*, 1982), timolol (Lewis *et al.*, 1985) and bufuralol (Dayer *et al.*, 1982) is associated largely with this isozyme, whereas the oxidation of propranolol is only partially affected (Lennard *et al.*, 1984; Raghuram *et al.*, 1984). Therefore, the present findings suggest that quinidine may also inhibit the oxidative metabolism of these drugs, and a recent study on metoprolol confirms this (Leeman *et al.*, 1986). In general the significance of an inhibitory effect of quinidine on the oxidation of a given drug will depend on the presence of alternative routes of elimination other than the oxidation through the 'sparteine/debrisoquine isozyme'. Thus, drugs like metoprolol will be particularly affected. Interaction studies are needed to determine the clinical significance of these possible interactions.

For future pharmacogenetic research our findings serve as a strong reminder that exogenous factors, *in casu* xenobiotics, may cause changes in metabolism sufficient to obscure genetic factors. Clinical studies with nortriptyline (Nordin *et al.*, 1985) and imipramine (Brøsen *et al.*, in preparation) have shown that both compounds cause moderate inhibition of the oxidation of debrisoquine and sparteine. This weaker effect compared with that of quinidine is in good agreement with their lower *in vitro* potency as inhibitors.

A further question raised by the findings is whether the elimination of quinidine is under the same genetic control as the sparteine/debrisoquine oxidation. Pronounced interindividual variation in the elimination of quinidine is well documented (Ochs *et al.*, 1980), but any relationship to the sparteine/debrisoquine oxidation remains to be studied.

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