Substantial rise in sparteine metabolic ratio during haloperidol treatment

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A sparteine test was carried out in 14 patients suffering from acute schizophrenic psychoses before and 1–2 times during oral haloperidol treatment in doses of 10–40 mg day⁻¹. In patients classified as extensive metabolisers (sparteine MR < 20 before treatment), haloperidol treatment resulted in a rise in sparteine MR that correlated with the serum-haloperidol concentration both within and between patients. At the highest serum haloperidol concentrations (60–80 nM) an increase in sparteine MR by a factor 15–50 was seen, but no patients were transformed into phenotypically poor metabolisers. The steady state concentration of haloperidol on the initial standard dose of 10 mg day⁻¹ was the same in one patient classified as a sparteine poor metaboliser (MR = 112) as in eleven patients classified as extensive metabolisers (MR:0.22–1.47).

Keywords sparteine oxidation haloperidol drug interaction genetic polymorphism

Introduction

The genetic polymorphism related to the oxidation of sparteine and debrisoquine has been established as an important factor in pharmacokinetic variation of several drugs, including all the classical tricyclic antidepressants (Bertilsson *et al.*, 1980; Brøsen *et al.*, 1986a). Another aspect of the sparteine/debrisoquine oxygenase is its role in drug-drug interactions. An *in vitro* screening test has been developed in which the ability of a given compound to competitively inhibit the oxidation of sparteine or debrisoquine in microsomal preparations from human liver is examined (Otton *et al.*, 1983; Boobis *et al.*, 1983; Inaba *et al.*, 1985). Quinidine is a very potent *in vitro* (Otton *et al.*, 1984) and *in vivo* inhibitor of sparteine and debrisoquine oxidation (Brinn *et al.*, 1986; Speirs *et al.*, 1986; Brøsen *et al.*, 1987), but *in vitro*, panel, and clinical studies indicate that its elimination via the sparteine

oxygenase is limited (Mikus *et al.*, 1986; Otton *et al.*, 1988; Brinn *et al.*, 1986; Gram & Brøsen, 1988). Several neuroleptics, among them haloperidol, are also potent *in vitro* inhibitors of the sparteine oxygenase (Inaba *et al.*, 1985), and are clinically potent inhibitors of the metabolism of tricyclic antidepressants (Gram & Overø, 1972; Gram 1975; Gram *et al.*, 1984; Gram & Brøsen, *in press*). The aim of this study was to examine if therapeutic doses of haloperidol inhibit the oxidation of sparteine, an effect that may explain the previously observed interactions with tricyclic antidepressants.

Methods

The subjects of the study were in-patients (Centre Psychiatrique Esquirol), suffering from acute

schizophrenic or schizopreniform psychoses. In total 17 patients were recruited initially, but three were excluded due to lack of motivation and cooperation. Thus, 14 patients (eight women and six men, age: 23–48 years) were studied. Haloperidol treatment was given as an oral solution. All patients were started with a loading dose of 10 mg in the evening followed by 5 mg twice daily at 12 h intervals for 7–9 days. After 8–10 days the dose was increased by a factor 2–4. Blood for assay of serum-haloperidol concentrations was drawn in the morning before the first dose each day during the first week and then at 1–3 day intervals for the following 2–3 weeks. Additional medication was restricted to the occasional use of antiparkinsonian drugs, largely benzhexol (Artane®). A sparteine test was carried out immediately before treatment, at the end of the initial week on 10 mg haloperidol per day, and again after 10–14 days on the final dose. Owing to compliance problems seven patients missed one or two tests. In one patient (number 2) the drug-free test was carried out on a later occasion. The sparteine test involved the ingestion of sparteine, 100 mg (Depasan®) in the evening, collection of urine for the following 12 h, and measurement of sparteine and oxidized metabolites in urine.

Haloperidol in serum was assayed by gas chromatography as described in detail elsewhere (Forsman *et al.*, 1974; Moulin *et al.*, 1982). The lower level of detection was 1–2 nM and the reproducibility was about 5–10% (coefficient of variation, day-to-day assay). Sparteine and its

metabolic products, 2- and 5-dehydrosparteine, were assayed in urine by gas chromatography (Vinks *et al.*, 1982). The lower limit of detection for 2- and 5-dehydrosparteine was about 0.25 nM. The results were expressed in terms of the metabolic ratio (MR):

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

In samples with undetectable dehydrosparteines the assay detection limit was used for the calculation of MR.

Statistical testing was carried out using the Wilcoxon test for pair differences and the Spearman rank correlation test.

Patients consented to participate on the basis of verbal information, and the study was approved by an internal ethics review committee.

Results

On the initial dose relatively stable haloperidol concentrations were attained within 2–3 days. Steady state concentrations were calculated on the basis of 2–6 measurements obtained on consecutive days from the 4th day of medication onwards. The inpatient variation was 10–20% (coefficient of variation) and a three-fold variation between patients of mean steady state concentrations was found (Table 1). Among the 12

Table 1 Haloperidol concentrations and sparteine metabolic ratio in the patients studied

Subject	Sex	Age (years)	Initial steady state serum concentration haloperidol (nM)*	before treatment	Sparteine-MR during treatment	
					initial dose	final dose
1	F	48	11.6	—	—	5.9
2	F	36	23.9	1.47	—	7.9
5	F	25	15.6	112	—	24
7	F	23	26.5	—	—	3.9
8	M	29	11.3	0.27	0.46	4.3
9	M	36	8.2	0.21	0.28	12.7
10	M	43	11.8	1.16	—	—
11	F	32	16.2	0.50	0.71	4.52
12	F	27	11.0	0.78	0.51	1.51
13	F	28	8.6	0.73	0.70	—
14	F	34	12.6	1.12	1.62	5.7
15	M	31	12.0	0.47	1.23	14.2
16	M	32	9.0	0.28	0.43	0.76
17	M	32	7.6	0.22	0.54	—

* Dose 10 mg day⁻¹ in all patients

— No sparteine test

patients that were sparteine-tested whilst not being treated, one was classified as a poor metaboliser (PM: MR > 20) and the others were extensive metabolisers (EM, Table 1). On the initial haloperidol dose seven of nine EM-patients had a MR higher than that measured by the control test ($P < 0.10$). On the final dose seven of seven EM-patients (with pre-drug MR recorded) showed an increase in MR ($P < 0.02$; Table 1). As shown in Figure 1 there was a relationship between serum-haloperidol (measured in the morning 12 h before or at the end of the sparteine test) and the relative increase in MR from the control period ($r_s = 0.85$, $n = 17$, $P < 0.001$). At usual therapeutic concentrations (15–40 nM) the MR increased by a factor of 1.5 to 9 and in three patients who achieved higher haloperidol concentrations (60–80 nM) an increase by a factor 15–50 was seen.

Amongst the twelve patients who had a pre-treatment sparteine test, the PM patient had a haloperidol steady state concentration on the initial fixed dose (10 mg day⁻¹) similar to those observed in the eleven EM subjects.

Discussion

This study shows that in therapeutic doses haloperidol causes a marked increase in sparteine

Figure 1 Relationship between serum haloperidol concentrations measured immediately before or after the sparteine test and the corresponding relative increase in sparteine MR from before (MR_C) to during haloperidol treatment (MR_D). The lines connect two measurements in the same patient.

MR. The most likely explanation of this is an inhibition of the sparteine oxygenase.

Haloperidol and neuroleptics of the phenothiazine type have been shown to be potent *in vitro* inhibitors of sparteine oxidation (Inaba *et al.*, 1985). In accordance with this Syvälahti *et al.* (1986) found very high debrisoquine MR in patients treated with thioridazine or levomepromazine with about 40% being phenotypical PMs.

The present findings provide an explanation of the much earlier clinical observations that neuroleptics are potent inhibitors of the metabolism of tricyclic antidepressants (Gram & Overø, 1972; Gram, 1975). This interaction is clinically important (Gram *et al.*, 1984), and the site of this interaction is most likely the sparteine oxygenase as also inferred from *in vitro* studies (von Bahr *et al.*, 1985). For imipramine, inhibition by neuroleptics appears to show the same selectivity for 2-hydroxylation relative to demethylation (Gram, 1975; Brøsen *et al.*, 1986b) as that demonstrated with regard to the genetic polymorphism related to the sparteine oxidation (Brøsen *et al.*, 1986a).

The main route of elimination of haloperidol is considered to be oxidative dealkylation (Jørgensen, 1986), probably via a cytochrome P450-mediated oxidation. The similar haloperidol concentration achieved in the one PM patient compared with those in the eleven EM patients suggests that the elimination of haloperidol is not to any major extent mediated via the sparteine oxygenase. Some *in vitro* inhibitors of the sparteine/debrisoquine oxygenase such as propranolol and quinidine are largely eliminated via other pathways and this may also apply to haloperidol. On the other hand, recent data suggest that two other neuroleptics, thioridazine and perphenazine, are largely metabolised via the sparteine/debrisoquine oxygenase (von Bahr *et al.*, 1988; Dahl-Puustinen *et al.*, 1988).

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The results described in this publication represent a contribution to the aims of COST-B1.

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