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Article type : Original Article

The effect of perazine on the CYP2D6- and CYP2C19-phenotypes as measured by the dextromethorphan and mephenytoin tests in psychiatric patients

by

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Short title:

Perazine: Effect on CYP2D6 and CYP2C19

(Received 22 October 2019; Accepted 26 November 2019)

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Revised Manuscript submitted to the
Basic and Clinical Pharmacology and Toxicology
25 November, 2019

Abstract

There is evidence that the antipsychotic drug perazine is an inhibitor of CYP2D6. This study aimed at evaluating its effect on CYP2D6- and CYP2C19 activities in submitting psychiatric patients to phenotyping with dextromethorphan and mephenytoin, respectively, substrates of these enzymes, - before and during a treatment with perazine. 31 patients were phenotyped with dextromethorphan (CYP2D6) and mephenytoin (CYP2C19) before and after a 2-week treatment with 450 ± 51 mg/day (mean ± sd) perazine. At baseline, 5 patients appeared to be poor metabolisers (PM) of dextromethorphan and 2 patients of mephenytoin. The metabolic ratio (MR) of dextromethorphan/dextrorphan as determined in collected urine increased significantly (Wilcoxon; $P < 0.0001$) from baseline (0.39 ± 1.38 (mean ± sd)) till day 14 (1.46 ± 2.22). In 19 out

of 26 extensive metabolisers (EM) of dextromethorphan, the phenotype changed from EM to PM. This suggests an almost complete inhibition of CYP2D6 by perazine and/or its metabolites. On the other hand, perazine (or some of its metabolites) did seemingly not inhibit CYP2C19. In conclusion, this study suggests that in patients treated with perazine and co-medicated with CYP2D6 substrates, there could be an increased risk of adverse effects as a consequence of a pharmacokinetic interaction.

Key words : Perazine – pharmacokinetic interaction – CYP2D6 – CYP2C19 – pharmacogenetics – psychiatric patients

Introduction

Perazine, a typical antipsychotic drug of the phenothiazine type (1), is mainly metabolised by CYP1A2, CYP3A4, CYP2C9 and CYP2C19 to various metabolites in human liver microsomes, while CYP2D6 as well as other forms of cytochrome P-450 play a less important role (2, 3). Relatively few studies have dealt with its cytochrome P-450-inhibiting properties (3). Recently, it was demonstrated in risperidone-treated schizophrenic patients that in plasma, the concentrations of risperidone and its dose-corrected concentrations (C/D), as well as those of the active moiety (risperidone and 9-OH-risperidone) were higher in patients co-medicated with perazine than in those without this co-medication (4). The metabolic ratio (9-OH-risperidone/risperidone) appeared to be higher in the latter subjects. This was interpreted as an inhibition of CYP2D6 and CYP3A4 by perazine. Actually, CYP2D6, and to a lesser extent CYP3A4, hydroxylate risperidone to 9-OH-risperidone (i.e. paliperidone). In addition, both compounds are dealkylated by CYP3A4 (5).

The genetically polymorphic CYP2D6 is implicated in the metabolism of numerous psychotropic drugs (6). Dextromethorphan is often used as a phenotyping probe for CYP2D6, as it is a substrate of this enzyme, but also to a minor degree of CYP3A4 (7). After the administration of 25 mg dextromethorphan hydrobromide to subjects, urine or plasma can be collected for the analysis of the parent compound and its metabolite dextrorphan, formed by CYP2D6 (8). The ratio of the concentrations of dextromethorphan / dextrorphan (MR-dex) helps determine the phenotype of the patients with regard to CYP2D6: a MR-dex > 0.3 (the antimode) classifies patients as poor (PM), and a lower value as extensive (EM) metabolizers. However, this test is sensitive to co-medications which inhibit CYP2D6, and may yield a phenoconversion from an EM- to a PM-phenotype. Dextromethorphan may be considered as the preferred probe for *in vitro* and *in vivo* drug-drug interaction studies, due to its highest sensitivity to CYP2D6 inhibition (9). Similarly, for the genetically polymorphic CYP2C19, mephenytoin represents a phenotyping probe (8) (10). After the oral administration of 100 mg of this racemic compound, the enantiomers S- and R-mephenytoin are measured in urine samples. The ratio S-/R-mephenytoin (S-/R-meph) allows to separate PM (with a ratio > 0.8) from EM (< 0.8).

As only very few studies are available on the inhibition of CYP2D6 and CYP2C19 by perazine, the purpose of our study was to obtain further information on this property in submitting patients to the combined dextromethorphan – mephenytoin test, before and during their treatment with perazine.

Materials and Methods

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies (11). In a 5-week clinical study, the efficacy of the antidepressant trimipramine was compared to that of perazine in the treatment of schizophrenic patients (12). Patients who were treated with antipsychotic drugs before the commencement of the study underwent a washout period of 2 - 3 days. This washout period was not less than 1.5 times the interval between injections in patients medicated with antipsychotic drugs administered as depot preparations. The study medication perazine was then installed gradually over a period of 4 days to reach a daily dose of not less than 450 mg/day, but in case of poor response, the maximal, allowed dose was 600 mg/day. 50 patients were treated with 459 ± 62 mg/day (mean ± sd; median dose: 450 mg/day) perazine during the maintenance treatment period. As co-medications during the first 14 days, only lorazepam, diazepam or oxazepam could be administered. In particular, no CYP2D6 and CYP2C19 inhibitors were allowed. With the aim to evaluate the CYP2D6-inhibiting properties of perazine, the dextromethorphan and mephenytoin tests were carried out twice in the patients, before and 2 weeks after commencement of treatment with trimipramine or perazine. The compounds measured for the phenotyping (dextromethorphan, dextrorphan, S- and R-mephenytoin) of the patients were assayed as previously described (8, 13).

The statistical analysis was carried out using IBM-SPSS (version 25; SPSS Inc., Chicago, IL, USA): descriptive statistics, the non-parametric Wilcoxon matched-pair test for the comparison of the metabolic ratios before and during perazine treatment (significance level: 0.05).

Results

In the perazine-treated group, there were 31 patients (14 male, age: 38 ± 13 y (range: 19 – 61 y)) for whom the results of both pharmacogenetic tests carried out before and during the antipsychotic treatment were available (Figure 1). The smoking status of many patients was not available and therefore not reported here. On the day of the second phenotyping (day 14), the dose of perazine was 450 mg/day in 28 out of 31 patients (450 mg ± 51 mg/day). The MR-dex increased significantly (Wilcoxon; $P < 0.0001$) from baseline (0.39 ± 1.38 (mean ± sd)) till day 14 (1.46 ± 2.22), while the S-/R-meph ratios remained constant (ns) (0.19 ± 0.25 and 0.19 ± 0.27, respectively). At baseline, 5 patients appeared to be PM of dextromethorphan and 2 patients PM

of mephenytoin. During the treatment with perazine, MR-dex increased considerably in all but one (a PM) patients. In 19 out of 26 EM-dex, the phenotype changed from EM to PM, which suggests an almost complete inhibition of CYP2D6 by perazine and/or its metabolites. On the other hand, perazine did not significantly modify the S-/R-meph ratios and no phenoconversion regarding CYP2C19 was observed.

Discussion

Using a similar design as in the present study, amitriptyline (14) and risperidone (15) appeared to be relatively weak CYP2D6 inhibitors, due to the low rate of phenoconversion which occurred when the dextromethorphan test was carried out before and during a treatment with one of these psychotropic drugs. Thioridazine is considered as a strong CYP2D6 inhibitor and indeed, phenoconversion was observed in a high proportion of patients treated with 200 or 400 mg/day thioridazine, using the repeated dextromethorphan schedule (14). However, in the present study, perazine appeared to be a particularly strong CYP2D6 inhibitor as illustrated by the high phenotype conversion rate from EM to PM in dextromethorphan phenotyped patients (Figure 1).

Despite perazine was a frequently prescribed antipsychotic drug and is still available in some countries, most of the scarce information on its metabolism and pharmacokinetics in clinical conditions was published in the seventies and eighties of the last century, when the individual properties of the different cytochrome P-450 isoforms and their role in the biotransformation of psychotropic drugs were not yet fully characterized.

The *in vitro* hydroxylation of imipramine, clomipramine and amitriptyline was inhibited in liver microsomes of rats pretreated during 10 days with perazine, in comparison with untreated animals (16). CYP2D6 plays an important role in the metabolism of these tricylic antidepressants (17, 18). A preliminary study reported an elimination T1/2 = 34.8 h for perazine (value actually calculated from the excretion in urine of total radioactive products after administration of radioactively labelled perazine to 4 healthy volunteers) and a T1/2 = 22.2.h for desmethylperazine, but the methodology used strongly suggests that further studies are needed (19). In a single dose study with 10 psychotic patients, a mean plasma T1/2 = 10 h (7.5h - 16h) was measured for perazine. As graphically shown (20), the elimination of demethlyperazine appeared to be slower than that of the parent compound. Indeed, in schizophrenic patients treated with perazine in clinical conditions, steady-state plasma concentrations of desmethylperazine concentrations were constantly higher than those of perazine (21). From these data, it can be concluded that in the present study, steady-state concentrations of perazine

and its metabolite desmethylperazine were most probably reached on day 14, when the patients were again phenotyped while treated with a stable perazine dose since at least 10 days. Consequently, phenotyping was carried out at a period where already a maximum inhibition of cytochrome P-450, if any, had occurred.

While this study confirms the inhibition of CYP2D6 by perazine in *in vitro* (3) and *in vivo* (4) studies, there was no evidence that this drug inhibits CYP2C19, as the pretreatment with perazine treatment did not significantly modify the S/R-meph ratio in mephenytoin-phenotyped patients (Figure 1). This seems to be in contradiction with an *in vitro* study in human liver microsomes, where perazine strongly inhibited S-(+)-mephenytoin-hydroxylation (3). No explanation can be forwarded for this discrepancy.

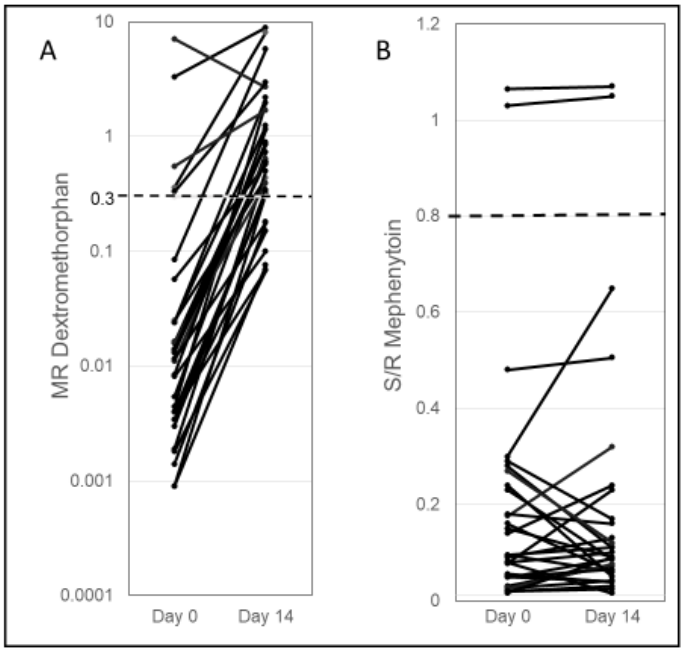
There are several limitations in this study which need to be listed. This investigation confirms the CYP2D6-inhibiting property of perazine in clinical conditions as already reported earlier (4). Both studies share also the fact that patients were not genotyped for CYP2D6 (and CYP2C19), and that plasma concentrations of perazine and of its metabolites were not monitored. In the present study, drug monitoring in plasma could have allowed to show a possible relationship between the change in the metabolic ratios of the test probes and the pharmacokinetics of perazine. As the metabolism of perazine partly depends on CYP1A2 activity (2), it would have been interesting to analyse the effect of perazine on the metabolism of the test probes in function of the smoking status of the patients. Unfortunately, such data were only available from a minority of the patients. It must, however, be mentioned that smoking does not influence neither CYP2D6 nor CYP2C19 activities.

In conclusion and in line with a previous study on risperidone and perazine (4), the combination of perazine with other drugs metabolized by CYP2D6 should be carried out with caution, and therapeutic drug monitoring of the victim drug may help avoid unwanted drug effects. Finally, in future versions of TDM guidelines, such as that of the AGNP-TDM group, perazine should be added in the list of CYP2D6 inhibitors (18).

Acknowledgements: We are grateful to Mrs Marlyse Brawand-Amey and Michèle Jonzier-Perrey for their technical contribution. There was no conflict of interest in relationship with this study. The study was partly financed by Rhone-Poulenc-Rorer/Germany

Figure 1. CYP2D6- and CYP2C19-phenotypes in 31 patients phenotyped with dextromethorphan (A) and mephenytoin (B), before and after a 14-day treatment with perazine.

The horizontal lines indicate the antimodes (MR-dex: 0.3; S-/R-meph: 0.8).



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