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Relationship between plasma desipramine levels, CYP2D6 phenotype and clinical response to desipramine: a prospective study

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Abstract *Objective*: The clinical relevance of the CYP2D6 oxidation polymorphism in the treatment of depression with desipramine (DMI) was studied prospectively in depressed outpatients.
Methods: After CYP2D6 phenotype determination with dextromethorphan, 31 patients were treated with oral DMI at a dosage of 100 mg per day for 3 weeks. At the end of the 3rd week of treatment, severity of depressive symptoms was assessed by the Hamilton Depression Rating Scale and steady-state plasma concentrations of DMI and its metabolite 2-hydroxydesipramine (2-OH-DMI) were measured by high-performance liquid chromatography (HPLC).
Results: Plasma DMI levels were significantly correlated with dextromethorphan metabolic ratio. The two patients with the poor metabolizer phenotype showed the highest plasma concentrations of DMI and complained of severe adverse effects, requiring dosage reduction. No significant correlation was found between plasma levels of either DMI or DMI plus 2-OH-DMI and antidepressant effect.
Conclusion: These findings indicate that the dextromethorphan metabolic ratio has a great impact on steady-state plasma levels of DMI in depressed patients and may identify subjects at risk for severe concentration-dependent adverse effects. On the other hand, this index of CYP2D6 activity does not seem to predict the degree of clinical amelioration.

Key words CYP2D6, phenotyping, Desipramine, Dextromethorphan

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Introduction

In vivo and in vitro studies have demonstrated that the hydroxylation of tricyclic antidepressants is catalyzed by a specific cytochrome P-450 isoenzyme, called CYP2D6, which is the target of the debrisoquine/sparteine genetic polymorphism [1, 2]. Since hydroxylation is a rate-limiting step in the elimination of tricyclics and their effects are considered to be concentration dependent, pharmacokinetic differences resulting from genetically determined variability in the expression of CYP2D6 have potentially important clinical implications [3]. Depressed patients with the poor metabolizer phenotype may achieve high plasma drug concentrations when treated with conventional doses and may develop side effects. Conversely, patients with a high rate of drug metabolism may not reach optimal plasma levels, with consequent therapeutic failure. In previous studies, indirect indices of CYP2D6 activity were found to be good predictors of plasma concentrations of desipramine (DMI) and nortriptyline in depressed patients [4–7]. Therefore, determination of a patient's metabolic capacity by using a phenotyping or genotyping test may be of value in selecting initially the optimal dose of a tricyclic compound. However, despite theoretical considerations, demonstration of the clinical relevance of the CYP2D6 polymorphism has been limited so far to a few reports in patients with extremely high or low rates of drug oxidation [8–10]. Moreover, in a large retrospective survey of patients taking imipramine, no correlation was found between debrisoquine oxidation ability and frequency or severity of side effects [11].

In this prospective study we evaluated the influence of the CYP2D6 oxidation polymorphism on plasma drug levels and clinical response in patients treated with DMI, a tricyclic antidepressant whose major metabolic route, 2-hydroxylation, is primarily determined by CYP2D6 activity [12].

Patients and methods

Patients attending the outpatient clinic of the Centers of Mental Health, Azienda USL 5, Messina, were included in the study if they met the following criteria: (1) diagnosis of depressive disorder according to DSM-IV; (2) a baseline score >20 on the 21-item Hamilton Depression Rating Scale (HDRS) [13]; (3) no drug treatment for at least 1 week; (4) absence of associated renal or hepatic disease, or of any condition contraindicating use of a tricyclic antidepressant; and (5) willingness to provide informed consent. The study was approved by local Ethics Committee. Patients were phenotyped for CYP2D6 by means of the dextromethorphan test [14]. After an overnight fast, each patient received a single oral dose of 30 mg dextromethorphan hydrobromide. Urine was collected for 8 h after dosing and, after recording the total volume, an aliquot was frozen at −20 °C until assay. After the phenotyping procedure, oral treatment with DMI was started with an initial daily dosage of 50 mg, which was increased to 100 mg daily within 3 days. This DMI dosage was kept constant until the end of the 3rd week unless a reduction was required by the appearance of side effects. No other drugs were allowed as additional treatment except for benzodiazepines, which are known not to affect plasma concentrations of tricyclic antidepressants [15]. The severity of depressive symptoms was evaluated at baseline and at the end of week 3 by using the HDRS. Adverse effects were assessed by interviewing (by specific questions) and examining the patients at the end of weeks 1, 2, and 3. After 3 weeks, DMI dosage could be modified according to clinical response. Responders were defined as patients with a greater than 50% decrease from baseline in the HDRS score, partial responders those with a 20–50% decrease and non-responders those with less than a 20% reduction in HDRS score. Blood samples were drawn on two consecutive days at the end of the 3rd week of treatment and plasma levels of DMI and unconjugated 2-hydroxydesipramine (2-OH-DMI) were analysed by high-performance liquid chromatography (HPLC) [16]. The sensitivity limits of the assay were 15 nmol/l for DMI and 25 nmol/l for 2-OH-DMI. For the CYP2D6 phenotyping test, urinary concentrations of dextromethorphan and its oxidized metabolite dextrorphan were determined by HPLC as previously specified [14]. The assays for both phenotype determination and plasma DMI levels were performed after completion of the clinical part of the study. Spearsman's rank correlation test was used for statistical analysis.

Results

Thirty-five patients, 23 females and 12 males, aged between 26 and 57 years, were included in the study. Twenty-six patients were affected by major depression and nine by dysthymia. Thirty-one patients completed the 3-week trial, while four patients dropped out, three because of lack of compliance and one because of a respiratory infection, presumably unrelated to the treatment. The dextromethorphan metabolic ratio (MR) ranged from 0.002 to 1.562 and two patients were classified as poor metabolizers (PMs) (MR > 0.3), the remaining patients being classified as extensive metabolizers (EMs) (MR < 0.3). Within the group of EMs, using an MR cut-off of 0.01 [14], there were 11 rapid and 18 slow EMs. Steady-state plasma DMI levels ranged from 130 to 984 nmol/l, while levels of 2-OH-DMI ranged from 25 to 268 nmol/l. In four patients, 2-OH-DMI concentrations were below the limit of detection. Plasma DMI levels were correlated significantly with the dextromethorphan MR (r_s = 0.74; n = 31; P < 0.01) (Fig. 1). There was also a weak, albeit significant, inverse correlation between dextromethorphan MR and plasma concentration of 2-OH-DMI (r_s = −0.44; n = 31; P < 0.05). No severe adverse effects were reported except for three patients who complained of slight confusion with marked sedation (two cases) and orthostatic hypotension (one case), all of whom required a reduction in DMI dosage to 50 mg per day after 5, 7 and 10 days, respectively. Two were PMs and showed the highest plasma levels of DMI in spite of the reduced dosage. As shown in Fig. 2, no correlation was found

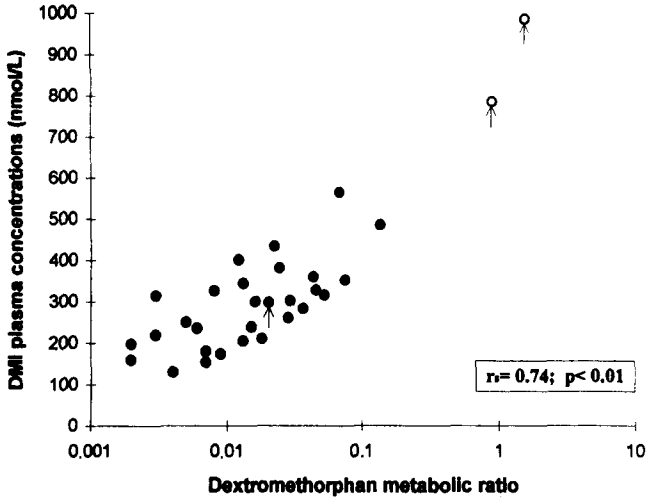

Fig. 1 Relationship between dextromethorphan metabolic ratio and steady-state plasma desipramine (*DMI*) concentrations in 31 depressed patients during treatment with DMI, 100 mg daily for 3 weeks. The two patients with a poor CYP2D6 metabolizer phenotype are indicated by *open symbols*. *Arrows* indicate three patients in whom DMI dosage had to be reduced to 50 mg daily after 5–10 days because of severe adverse effects

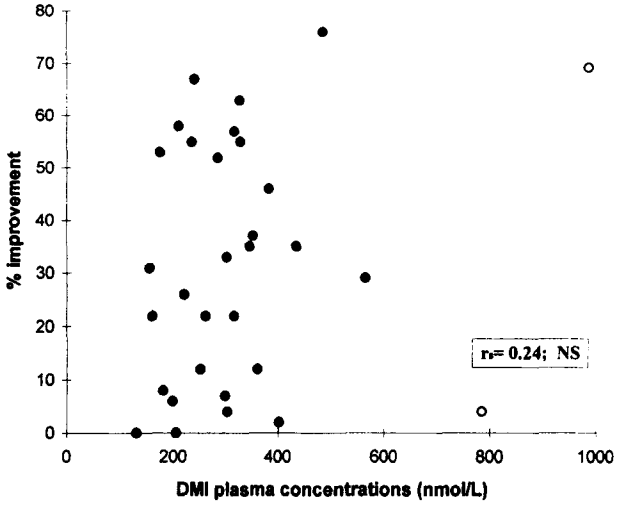

Fig. 2 Relationship between plasma desipramine (*DMI*) concentrations and antidepressant effect, expressed as percentage improvement in Hamilton Depression Rating Scale score after 3 weeks of treatment (vs baseline) in the patients included in the study. The two patients with a poor CYP2D6 metabolizer phenotype are indicated by *open symbols*

between plasma DMI levels and therapeutic outcome (r_s = 0.24; n = 31; NS). Similarly, plasma concentrations of DMI plus 2-OH-DMI were not correlated with antidepressant effect (r_s = 0.18; n = 31; NS). Moreover, no significant correlation was found between dextromethorphan MR and clinical improvement (r_s = 0.33; n = 31; NS). With regard to therapeutic outcome, in the subgroup of rapid EMs three patients were responders, four partial responders and four non-responders; in the subgroup of slow EMs six patients were responders, seven partial responders and five non-responders; one PM patient was a responder while the other did not respond. After 3 weeks, DMI dosage was increased to 150 mg per day in six out of the ten non-responders and after 2 weeks only three of them became partial responders.

Discussion

The results of this prospective study indicate that the dextromethorphan MR, like other indices of CYP2D6 activity, is a relatively good predictor of steady-state plasma concentrations of DMI [4, 6, 7], and may identify patients at risk for severe concentration-dependent adverse effects.

In agreement with observations made in a previous retrospective study [11], the index of CYP2D6 activity could not reliably predict the degree of clinical amelioration, and there was no clear-cut relationship between plasma DMI levels and antidepressant effect as assessed by the HDRS. Different possibilities must be considered to explain these findings. First, the relative weakness of the concentration-effect relationship may be partially accounted for by the heterogenicity and severity of the disease. In fact, a stronger relationship between plasma tricyclic levels and clinical outcome has been suggested in endogenously rather than non-endogenously depressed patients [17]. Admittedly, our study was performed in outpatients and also included some patients suffering from dysthymia. Moreover, while the concentration-response relationship has been clearly documented for imipramine and nortriptyline [17–19], studies with DMI have reported controversial results [20, 21]. Our findings may have additional explanations, such as the possible contribution of hydroxylated DMI metabolites to the overall pharmacological effect [22] and blurring of concentration-response relationship resulting from recruitment of placebo-responders as well as patients non-responsive to treatment, possibly related to the use of a relatively low initial dosage for a relatively short treatment time. With respect to the latter point, it is of interest that only three of six patients who did not respond after 3 weeks showed a partial response when DMI dosage was increased.

In conclusion, despite interpretative limitations related to the relatively small sample size, this study indicated no value of CYP2D6 phenotyping in predicting therapeutic response to DMI in patients with depression. However, out findings reinforce previous evidence that defective CYP2D6 metabolizers, as identified by the phenotyping test, are at risk of developing severe adverse effects when prescribed standard dosages of therapeutic antidepressants. Overall, the clinical implications of the CYP2D6 polymorphism appear to be most pronounced in patients at the extremes of the metabolizing capacity spectrum. In this respect, CYP2D6 genotyping may offer advantages over phenotyping because it allows identification not only of poor metabolizers, but also of ultra-rapid metabolizers who may require megadoses of tricyclic antidepressant to achieve an adequate response [23].

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