Association of CYP2D6 ultrarapid metabolizer genotype with deficient patient satisfaction regarding methadone maintenance treatment

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Abstract

Objective: The activity of cytochrome P-450 enzyme 2D6 (CYP2D6) could be related to heroin-dependent patient satisfaction with methadone maintenance treatment. We sought to compare satisfaction with the usual methadone treatment in patients who are ultrarapid, extensive or poor metabolizers, according to CYP2D6 genotyping.

Methods: Two hundred and five heroin-dependent patients filled out the Verona Service Satisfaction Scale for methadone maintenance treatment (VSSS-MT), before CYP2D6 genotyping.

Results: VSSS-MT overall scores were comparable in the poor metabolizer (N=9) and extensive metabolizer (N=185) groups, although they were higher in poor metabolizers and extensive metabolizers taken together than in the ultrarapid metabolizers (N=11) (p<0.003). Likewise, ultrarapid metabolizers scored higher than the rest of the sample on the VSSS-MT Basic Interventions subscale (p<0.001). Regarding this subscale, no poor metabolizers felt dissatisfied, and ultrarapid metabolizer males (N=7) reported lower satisfaction than ultrarapid metabolizer females (N=4) (p<0.022). Ultrarapid metabolizer genotype accounted for 4.2% of the variance on the VSSS-MT total scores, and 5.0% on the Basic Intervention scores.

Conclusion: Heroin-dependent patients who are CYP2D6 ultrarapid metabolizers according to genotyping present deficient satisfaction with methadone maintenance treatment.

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Keywords: Satisfaction with treatment; Methadone maintenance treatment; Genetics; Cytochrome P-450 CYP2D6; Heroin dependence

1. Introduction

Patients’ satisfaction with treatment is a global measure of treatment quality, reflecting patients’ evaluation of the care actually received, compared with their care expectations (Sitzia and Wood, 1997; Crow et al., 2002). Heroin-dependent patient satisfaction with methadone maintenance treatment (MT) can be assessed specifically and multi-dimensionally with the Verona Service Satisfaction Scale for MT (VSSS-MT) (Pérez de los Cobos et al., 2002). This scale assesses patient satisfaction with overall services received from MT centers, such as staff’s manner and skills and psychosocial interventions.

Two surveys performed using the VSSS-MT have shown that, overall, heroin-dependent patients reported slight satisfaction with MT, with approximately 15% of them feeling dissatisfied (Pérez de los Cobos et al., 2004, 2005). Contrary to our initial hypothesis, this outcome bore hardly any relation to aspects of the MT process on which the staff and the patients could easily disagree; for example, methadone dosage regulation or frequency of methadone take-home doses, and frequency of urinalysis. These unexpected results suggest that the reasons for patient dissatisfaction at our treatment centers are not the obvious ones, perhaps because the more evident causes of...
dissatisfaction tend to be neutralized through the patient–staff relationship.

Patient dissatisfaction could be related to pharmacological variables, which, although they are not assessed in usual clinical practice, could trigger a reduction of methadone’s effects in a particular group of patients. In this case, doctors would not identify affected patients and/or apply specific interventions to correct insufficient methadone effectiveness. Given such a scenario, patients with insufficient methadone effects could feel especially dissatisfied with staff skills and MT as a whole.

The activity of cytochrome P-450 enzyme 2D6 (CYP2D6) could be related to patient satisfaction with MT. Racemic methadone consists of a 50:50 mixture of the enantiomers (R)- and (S)-methadone. (R)-Methadone induces almost all of the opioid effects of racemic methadone (Kristensen et al., 1995). In the metabolism of racemic methadone, CYP2D6 plays a major role compared with CYP3A4 and CYP2B6 (Leavitt, 2005). However, CYP2D6 activity is key for MT, because in vivo it is particularly involved in clearance of the active R-enantiomer (Eap et al., 2001; Bégré et al., 2002). The CYP2D6 enzyme is mainly expressed in the liver. Notably, CYP2D6 activity also exists in brain zones that are crucial for treating addictive disorders, such as the nucleus accumbens (Miksys et al., 2002). Because the CYP2D6 gene is polymorphic, individuals may be grouped as poor metabolizers (PM), extensive metabolizers (EM), and ultrarapid metabolizers (UM), depending on the number of functional alleles they carry.

In a naturalistic study (Eap et al., 2001) which was performed using CYP2D6 genotyping, less UM than PM tended to be considered as having successful MT, measured in terms of absence of illicit opiates use and withdrawal complaints. The present study aimed to compare satisfaction with usual MT in heroin-dependent patients who are UM, EM or PM, according to their CYP2D6 genotypes. Our hypothesis was that a UM genotype is associated with a reduction in patient satisfaction with MT as a whole.

2. Method

2.1. Participants and controls

Participants were heroin-dependent patients who had received MT (DSM-IV: 304.02) at their respective centers for at least 5 months. All patients were unrelated, and all four of their grandparents were Spanish, of European, non-Roma origin. They were enrolled at four MT centers. All assessments were performed at Santa Creu i Sant Pau Hospital, one of the enrollment centers, in Barcelona, Spain. Staff from these centers had not previously assessed participants’ satisfaction with MT. Moreover, physicians had not changed the methadone dosages of these patients during the week prior to assessments. Written informed consent was obtained from all participants, who were paid for their participation in the study. The study procedure was approved by the Ethics Committee of Santa Creu i Sant Pau Hospital. Patients were enrolled in the study from September 2003 to September 2004.

Allelic and genotypic distributions of the patient group were compared with a control group of the same ethnic origin, as previously described (Menoyo et al., 2006). Briefly, the control group consisted of 105 unrelated volunteers who declared that they did not suffer from substance use disorders, with the exception of nicotine dependence. There were no statistically significant differences with regard to age or gender between the patients and the controls.

2.2. Measures

Patient satisfaction was assessed with the VSSS-MT (Pérez de los Cobos et al., 2002). This is a self-reported scale comprising four factors or subscales: Basic Interventions (15 items), Specific Interventions (8 items), Social Worker Skills (2 items), and Psychologist Skills (2 items). These factors have shown good to excellent internal reliabilities (Chronbach’s α: 0.91, 0.85, 0.87, and 0.92, respectively). At test–retest, intraclass correlation coefficients of VSSS-MT overall and factor scores have been fair to good (Pérez de los Cobos et al., 2002). Basic Interventions mainly assesses doctors’ and nurses’ skills, and the help received in improving social relationships and self-care. Specific Interventions only assesses psychosocial interventions. Each VSSS-MT item has a five-point Likert scale response option (1 = terrible, 2 = mostly dissatisfied, 3 = mixed, 4 = mostly satisfied, 5 = excellent). On items referring to professional manner or activities, participants also have the response option of ‘not applicable’. VSSS-MT scores are obtained by averaging applicable items; the range of scores on the VSSS-MT, both overall and subscales, is 1–5. VSSS-MT scores of ≥ 3 and ≤ 3 correspond to patient satisfaction and dissatisfaction, respectively. Patients also answered a questionnaire about substance use and MT history, and current treatment with medications that inhibit CYP2D6 activity (Ferrari et al., 2004; Leavitt, 2005; de Leon et al., 2006) and/or modify racemic methadone metabolism (Ferrari et al., 2004; Leavitt, 2005). Participants were instructed not to write their names on the self-report questionnaires in order to guarantee anonymity. Information on current MT was collected from the centers’ staff.

A 20 ml sample of venous blood was drawn from each patient before the intake of the daily methadone dose, in order to determine steady-state trough methadone plasma levels and CYP2D6 genotypes. DNA was isolated with a salting-out procedure (Miller et al., 1988). CYP2D6 genotyping was performed with a combination of long-PCR, direct sequencing, and allele-specific real-time PCR (Johansson et al., 1996; Sachse et al., 1997; Menoyo et al., 2006). Through this procedure, we assessed the presence of four functional alleles (*1, *2, *9, and *10), ten defective alleles (*3, *4, *5, *6, *7, *8, *12, *14, *15, and *21), and three alleles consisting of duplications of alleles *1 (*1 × 2), *2 (*2 × 2), and *4 (*4 × 2). Patients were grouped according to the number of functional alleles they carried: zero for PM, one or two for EM, and three or more for UM. Moreover, racemic methadone concentrations were measured with high-performance liquid chromatography using a 250 mm × 4.6 mm Lichrosorb Hobar SI-60 column (Merck KGaA, Darmstadt, Germany) (Queraltó et al., 1997). The method’s detection limit was 31 ng/mL, and the interassay precision (expressed as a coefficient of variation) was 7.9% at 195 ng/mL, and 5.4% at 381 ng/mL.

2.3. Data analysis

To test inter-group differences, χ²-tests were conducted for categorical variables, and ANOVAs or Mann–Whitney U-tests were used for continuous variables. All statistical tests were two-sided, and were considered significant at p < 0.05. Analyses were carried out using SPSS Version 11.5.2 (SPSS Inc., Chicago, IL).

3. Results

3.1. Characteristics of participants

The study sample included 205 patients, ranging in age from 21 to 56 years, with a mean of 36.8 (S.D. = 6.0) years. Males accounted for 71.7% of the sample. The frequency of CYP2D6 alleles detected in patients was as follows: *1, 37.6%; *2, 32.8%; *3, 1.0%; *4, 17.6%; *5, 2.9%; *6, 0.2%; *9, 2.7%; *10, 2.0%; *1 × 2, 1.0%; and *2 × 2, 2.2%. The other CYP2D6 alleles assessed were not detected. At genotypic level, 9 patients (4.4%) were found to be PM, 185 (90.2%) to be EM, and 11 (5.4%) to be UM. In the control group, the frequency of PM was 2.9%, with EM being 88.6%, and UM 8.6%. Patients and controls showed similar allelic and genotypic distribution.
Table 1

Features of methadone maintenance treatment of participants grouped according to CYP2D6 genotypes

<table>
<thead>
<tr>
<th>CYP2D6 genotype groups</th>
<th>PM (N=9)</th>
<th>EM (N=185)</th>
<th>UM (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current episode</td>
<td>59.6</td>
<td>36.2</td>
<td>45.5</td>
</tr>
<tr>
<td>Total</td>
<td>71.3</td>
<td>62.1</td>
<td>65.3</td>
</tr>
<tr>
<td>Daily dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (mg)</td>
<td>83.3</td>
<td>71.9</td>
<td>76.5</td>
</tr>
<tr>
<td>Weight-corrected (mg/kg)</td>
<td>1.2</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Concentrations (ng/mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncorrected</td>
<td>182.9</td>
<td>226.8</td>
<td>235.4</td>
</tr>
<tr>
<td>To dose-to-weight ratio (ng kg/mL mg)</td>
<td>213.9</td>
<td>255.6</td>
<td>232.6</td>
</tr>
</tbody>
</table>

Abbreviations: PM = poor metabolizers; EM = extensive metabolizers; UM = ultrarapid metabolizers.

* The 21 patients (2PM, 18EM and 1UM) who split their methadone daily doses were not compared.

Table 2

VSSS-MT scores of participants, grouped according to CYP2D6 genotypes

<table>
<thead>
<tr>
<th>PM (N=9)</th>
<th>EM (N=185)</th>
<th>UM (N=11)</th>
<th>PM/EM vs. UM* ANOVA-F</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSSS-MT, total (N=205)b</td>
<td>3.5</td>
<td>3.1</td>
<td>26.0, d.f. = 1, 203, P = 0.003</td>
</tr>
<tr>
<td>Basic Interventions (N=204)</td>
<td>3.7</td>
<td>3.1</td>
<td>10.57, d.f. = 1, 202, P = 0.001</td>
</tr>
<tr>
<td>Specific Interventions (N=174)</td>
<td>3.1</td>
<td>2.9</td>
<td>2.05, d.f. = 1, 172, P = 0.154</td>
</tr>
<tr>
<td>Social Worker Skills (N=185)</td>
<td>3.4</td>
<td>3.1</td>
<td>2.29, d.f. = 1, 183, P = 0.132</td>
</tr>
<tr>
<td>Psychologist Skills (N=127)</td>
<td>3.9</td>
<td>3.0</td>
<td>1.50, d.f. = 1, 125, P = 0.223</td>
</tr>
</tbody>
</table>

Abbreviations: VSSS-MT = Verona Service Satisfaction Scale for Methadone Treatment; PM = poor metabolizers; EM = extensive metabolizers; UM = ultrarapid metabolizers.

* UM were compared with the rest of the sample because PM and EM showed comparable total VSSS-MT scores.

Patients had used heroin for an average of 10.4 (S.D. = 6.3) years, most of them (69.8%) intravenously. Moreover, they frequently had histories of regular and/or maladaptive use pattern of alcohol (53.7%), benzodiazepines (38.5%), cannabis (86.3%), cocaine (71.2%), and tobacco (98.5%). Of the patients who received CYP2D6-inhibiting medications, 3 were PM, 51 were EM, and there were no UM. No differences were found amongst PM, EM, and UM for patient features or racemic methadone doses and plasma levels (Table 1), nor were differences found when we only compared the 136 patients who did not receive co-medications modifying racemic methadone plasma levels.

3.2. CYP2D6 genotypes and patient satisfaction

There were no differences in patient satisfaction by MT center. PM and EM showed comparable overall VSSS-MT scores (Table 2). Therefore, we compared UM versus the PM and EM groups taken together. UM scored lower than non-UM on the overall VSSS-MT and Basic Interventions subscale; there were no other statistically significant differences on the remaining VSSS-MT subscales (Table 2). The UM genotype accounted for 4.2% of overall VSSS-MT variance, and 5.0% of Basic Intervention variance.

Only one significant gender difference was found: UM males (N = 7) scored lower than UM females (N = 4) on the Basic Intervention subscale (2.8 [0.8] versus 3.7 [0.3]; U = 20.0; p = 0.022). Satisfaction of UM males and females was not compared separately by gender with the other participants’ satisfaction, due to the small size of the UM gender subgroups. Categorical analysis of the VSSS-MT scores showed that no PM reported dissatisfaction on the Basic Interventions section (Table 3). Lastly, patient dissatisfaction was more frequent regarding Specific Interven-

Table 3

Frequency of patients dissatisfied with methadone maintenance treatment in each CYP2D6 genotype group

<table>
<thead>
<tr>
<th>CYP2D6 genotype groups</th>
<th>PM N (%)</th>
<th>EM N (%)</th>
<th>UM N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSSS-MT, total</td>
<td>1 (11.1)</td>
<td>26 (14.1)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Basic Interventions</td>
<td>0</td>
<td>22 (12.0)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Specific Interventions</td>
<td>4 (50.0)</td>
<td>66 (42.3)</td>
<td>8 (80.0)</td>
</tr>
<tr>
<td>Social Worker Skills</td>
<td>4 (44.4)</td>
<td>74 (44.6)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Psychologist Skills</td>
<td>2 (28.6)</td>
<td>46 (40.4)</td>
<td>3 (50.0)</td>
</tr>
</tbody>
</table>

Abbreviations: VSSS-MT = Verona Service Satisfaction Scale for Methadone Treatment; PM = poor metabolizers; EM = extensive metabolizers; UM = ultrarapid metabolizers.

* Patient dissatisfaction is defined as VSSS-MT scores ≤3.
tions in UM than in non-UM (80% versus 42.7%; $\chi^2 = 5.31$, d.f. = 1, $p = 0.021$).

4. Discussion

The present study shows that heroin-dependent patients who are CYP2D6 UM report deficient satisfaction with their usual MT, whereas PM do not report dissatisfaction with the Basic Interventions aspect of their MT. As far as we are aware, this is the first time in the literature that patient satisfaction with treatment has been shown to be related to a biological variable. Given these results, it seems that assessment of patient satisfaction with MT and the individualization of pharmacological treatment for heroin dependence could prevent the undesired association found.

From our point of view, two conditions contributed decisively to this association. First, the projection of general patient satisfaction with medications onto the entire treatment experience (Shikiar and Rentz, 2004). This assumption is suggested by the fact that UM reported feeling particularly less satisfied with Basic Interventions, which is the VSSS-MT subscale most closely related with the pharmacological side of MT (Pérez de los Cobos et al., 2002); moreover, UM also reported dissatisfaction with the psychosocial interventions included on the Specific Interventions subscale. The second condition that could have contributed to the association detected was the persistence at phenotypic level of some CYP2D6 genotypic-related differences between UM and non-UM.

However, these differences disappeared between PM and EM. These groups were probably comparable in a clinical setting, because induction of CYP2D6 activity by xenobiotics remains controversial, whereas inhibition has achieved clinical significance (de Leon et al., 2006). The CYP2D6 enzyme is inhibited by methadone (Wu et al., 1993), other medications (de Leon et al., 2006), and cocaine (Tyndale et al., 1991; Ramamoorthy et al., 2002). We assume that, whereas the effect of these agents reduced CYP2D6 activity of EM to the level of PM (Shiran et al., 2003), it was not enough in the case of UM.

The present study’s results suggest that, in order to prevent deficient satisfaction, CYP2D6 genotype should be determined for all heroin-dependent patients who start MT. According to our findings, UM males should receive special attention, because they appear to be the main risk group. Our finding regarding the lower satisfaction of male UM, compared with female UM, backs up another study which reported that males undergoing MT have higher CYP2D6 activity than females (Shiran et al., 2003). UM patients having low satisfaction with MT could benefit from upward adjustment of their racemic methadone dose, aimed at increasing $R$-methadone bioavailability. In the present study, doctors did not perform such an adjustment. If low patient satisfaction persists after methadone dose adjustment, splitting of the daily methadone dose or treatment with opioids barely metabolized by CYP2D6 enzyme, such as morphine (Poulsen et al., 1996), should be assessed in the future with the aim of improving the deficient patient satisfaction found for UM.

The CYP2D6 UM genotype only accounted for 4.2% and 5% of the variance in VSSS-MT overall and Basic Interventions scores, respectively. However, two new developments could, in the near future, show a stronger association between CYP2D6 UM genotype and patient satisfaction than the one we detected on the present study. One of these is progress in genotyping methods, because it is currently only possible to detect 13–20% of real CYP2D6 UM (Dahl et al., 1995; Bathum et al., 1998; de Leon et al., 2006). The second is the development of a tool for assessing both specific and multidimensionally satisfaction with methadone as a medication, which is probably the aspect of patient satisfaction most closely related to CYP2D6 activity. VSSS-MT assesses it only partially (Pérez de los Cobos et al., 2005), but the aim of the present study was to assess patient satisfaction with MT as a whole.

Finally, limitations of the present study are: (1) The small size of UM gender subgroups made it impossible for us to clarify whether deficient satisfaction only affects UM males. (2) The non-assessment of R-methadone plasma levels reduced our capacity to explain the findings obtained (Hiltunen et al., 1999; Eap et al., 2000, 2001), since bioavailability of R-methadone was probably the link between UM genotype and deficient patient satisfaction. Nevertheless, plasma levels could not accurately reflect R-methadone bioavailability in the brain, since CYP2D6 enzyme is expressed in this organ (Miksys et al., 2002). (3) The findings of the present study may not be generalizable to other populations, given the genetic homogeneity of our study’s participants, and the particularities of methadone treatment management in Spain (Pérez de los Cobos et al., 2005).

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