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ORIGINAL ARTICLE

Relevance of *CYP2B6* and *CYP2D6* genotypes to methadone pharmacokinetics and response in the OPAL study

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Aims: Our study aimed to evaluate the impacts of the cytochrome P450 (*CYP*) *2B6-G516T* and *CYP2D6* genetic polymorphisms on pharmacokinetic and clinical parameters in patients receiving methadone maintenance treatment.

Methods: Opioid PhArmacoLogy (OPAL) was a clinical survey of the sociodemographic characteristics, history and consequences of pathology associated with methadone maintenance treatment response and current addictive comorbidities. A subgroup of 72 methadone patients was genotyped.

Results: When comparing the three *CYP2B6* genotype groups, the methadone *(R)*- and *(S)*-methadone enantiomer concentrations/doses (concentrations relative to doses) were different ($P = .029$, $P = .0019$). The CYP2D6 phenotypes did not seem to be relevant with regard to methadone levels. On multivariate analysis, neither the *CYP2B6* genotype nor the CYP2D6 phenotype explained the *(R)*-methadone concentration/dose values ($P = .92$; $P = .86$); the *(S)*-methadone concentration/dose values ($P = .052$; $P = .95$ [although there was a difference between the TT group and GT and GG groups {$P = .019$}]); or opiate cessation ($P = .12$; $P = .90$).

Conclusion: The genotyping of *CYP2B6 G516T* could be an interesting tool to explore methadone intervariability.

KEYWORDS

CYP2B6, CYP2D6, methadone, pharmacokinetic, response to treatment

1 | INTRODUCTION

In France, methadone, a pure mu agonist, is approved as a maintenance treatment for opiate addiction and is used in medical, social and psychological therapeutic management.[1-3] It is administered as a racemic mixture of *(R)*- and *(S)*-methadone. The *(R)*-enantiomer accounts for most of the opioid effect.[4,5] Elevated *(R)*-methadone may induce respiratory depression, whereas *(S)*-methadone more potently blocks the human voltage-gated potassium channel, which has a greater potential impact on long QT syndrome.[3,5,6] The range of prescribed methadone doses is broad, and physicians have to adjust the dose progressively for each patient according to the clinical response,[7-9] owing to interindividual variation in the methadone blood concentration following any given dosage, and because the half-life of elimination ranges from 5 to 130 hours, with an average

The authors confirm that the PI for this paper is Professor Marie Grall-Bronnec and that she had direct clinical responsibility for patients.

of 22 hours.[3,4] Some clinical factors are associated with higher methadone dose requirements, and the dose varies during the course of treatment.[10]

Methadone is intensively metabolized by the liver and intestines. Various in vitro and in vivo studies have shown the involvement of different cytochrome P450 (CYP) enzymes, particularly CYP2B6, in methadone metabolism,[3,4,11-13] associated with the *CYP2B6-G516T* genetic polymorphism[3] and, to a lesser extent, *CYP2D6*,[14,15] *CYP3A4*,[15,16] and the gene encoding ATP Binding Cassette Subfamily B Member 1 (*ABCB1*, the permeability glycoprotein [P-gp] transporter).[15,17,18] The influence of genetic polymorphisms on pharmacodynamic properties and treatment response has been less explored, and is not supported by much evidence.[4,14,19-26] Moreover, the impact of genetic variations could be compounded by interactions between many environmental and individual factors.[3,26,27]

The results of pharmacogenomics studies in the field of methadone maintenance treatment (MMT) have been described in terms of dose magnitude, plasma or dose-adjusted plasma concentrations, responders *vs* nonresponders, and adverse effects. In these previous studies, the response to treatment was defined by the dose requirement, continued opioid use[26] or composite criteria, including the nonconsumption of heroin and cocaine, the absence of complaints of withdrawal symptoms, the steady and regular attendance at the therapy programme,[4,12,15,19,20,23] dropout rate and mean dose.[25]

Our study aimed to evaluate the impacts of the *CYP2B6* polymorphism on methadone enantiomer levels and clinical parameters in patients receiving MMT.

What is already known about this subject

- Recent studies have highlighted the importance of the cytochrome P450 (*CYP*) *2B6-G516T* genetic polymorphism in methadone pharmacokinetics.
- To the best of our knowledge, no study has explored the clinical effects of the *CYP2B6 G516T* genetic polymorphism from an integrative perspective, combining biopsychosocial and clinical data related to the disorder, the response to treatment and the pharmacokinetics.

What this study adds

- We assessed the clinical impact of the *CYP2B6 G516T* genotype on opiate cessation.
- Currently, no pharmacogenetic test has been approved. Our results showed that the genotyping of *CYP2B6-G516T* could be an interesting tool to explore methadone intervariability from the perspective of personalized medicine.

2 | METHODS

OPAL (Clinical trial NCT01847729) was an observational cross-sectional, multicentre study involving 10 care centres in France. It was approved by the local Research Ethics Committee (GNEDS), the Advisory Committee on the Processing of Health Research Information (CCTIRS) and the Data Protection Commission (CNIL). The sample consisted of 263 patients aged 18 years or older receiving maintenance treatment for opioid addiction for at least 6 months. The primary objective was to determine the prevalence of addictive comorbidities.

An ancillary study comprising a prespecified pharmacogenetic and pharmacokinetic analysis was conducted solely on the patients receiving methadone. The present work reports the data obtained in the ancillary study.

2.1 | Study subjects

Among the OPAL study participants, only those receiving methadone were included in the ancillary study (n = 72).

The clinical assessment included a clinical structured interview carried out by a physician during a medical consultation with the patient, and a set of standardized self-report questionnaires. Blood samples were collected immediately before treatment administration from subjects who had been on MMT for at least 6 months, with no change in dosage in the 5 days prior to performing the ancillary study.

Sociodemographic data included opioid dependence, data relating to the MMT, and psychopathological data included the presence of attention deficit hyperactivity disorder,[28-30] and the profile and level of impulsivity.[31] Addictological data included substance use disorders (for substances other than opioids),[32-34] problem gambling[35] and the evolution of these disorders following the introduction of MMT.

2.2 | Genotyping

The patients were genotyped for different polymorphisms: *CYP2B6-G516T* (rs3745274) and *CYP2D6* (*CYP2D6**3 rs35742686, *4 rs3892097 and *6 rs5030655) using the TaqMan allelic discrimination assay. Complete deletion (*CYP2D6*5*) and gene duplication (*CYP2D6*2xN*) were detected by quantitative polymerase chain reaction using TaqMan allelic discrimination with the ABI Prism® 7900HT Sequence Detection System (Applied Biosystem, Courtaboeuf, France). The observed genotype frequencies were in Hardy–Weinberg equilibrium.

Plasma concentrations of methadone and its *(R)* and *(S)* enantiomers were measured by liquid chromatography coupled with mass spectrometry.[36] The analysis combined straightforward sample preparation, consisting of protein precipitation with acetonitrile and an online enrichment by a flush/back-flush cycle before the second-dimension chromatography. Using D3-deuterated internal standards enables the significant relative matrix effect to be overcome. This

method was linear up to 2000 ng/mL. This simple sample preparation provides sensitive (limit of quantitation 25 ng/mL for *(R,S)*-methadone) analyte detection. The concentration results by patient were dose adjusted (ng/ml/mg).

The characteristics of patients were compared according to the three *CYP2B6-G516T* genotype groups, using a chi-square, Fisher's exact (categorical variables) or Kruskal-Wallis test (continuous variables), and the three different CYP2D6 phenotype groups.

Analyses of variance were performed to explain *(R)*- and *(S)*-methadone concentration/dose by taking into account, at the same time, the *CYP2B6* genotype and the CYP2D6 phenotype. Similarly, logistic regression was used to explain opiate cessation (The number of patients quitting opioid use) – again, by taking into account the *CYP2B6* genotype and the CYP2D6 phenotype. All analyses were performed using Stata 15 software.

2.3 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org,[37] the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16.[38]

3 | RESULTS

3.1 | Patient characteristics

The patients had taken opioids for the first time at a mean age of 20 years. They were predominantly nasal **heroin** users. Most patients reported damage related to opioid dependence. Almost 80% of the patients were men, with an average age of 34 years at the time of the evaluation and relatively good socio-professional integration (Table 1).

At the time of the evaluation, the average dose of methadone taken was 50 mg per day, and the patients reported co-occurring substance use, mainly tobacco (*n* = 67, 93%), alcohol (*n* = 60, 83.3%), cannabis (*n* = 58, 80.6%), **cocaine** (*n* = 47, 65.3%), **amphetamine**/ecstasy (*n* = 30, 41.7%), **lysergic acid diethylamide**/new psychoactive substances (*n* = 28, 38.9%) and benzodiazepines (*n* = 30, 41.7%). Moreover, one in two patients reported risky consumption of alcohol and/or cannabis. The prevalence of gambling was high (*n* = 33, 45.8%).

All subjects were Caucasians, with the exception of two Africans.

3.2 | Relevance of genotype to methadone levels and clinical response

Regarding the *CYP2B6* (rs3745274) genotype frequencies, nine patients (12.5%) were TT, 24 patients (33.3%) were GT and 39 patients (54.2%) were GG.

TABLE 1 Description of the population

Characteristic	Patients *N* = 72
Number of men	56 (78%)
Age	33.8 ± 5.7
Number participating in graduate studies	29 (40%)
Number who were married	33 (46%)
Number who had dependent children	21 (29%)
Number in stable housing	61 (85%)
Number employed in professional jobs	33 (46%)
Debt	29 (40%)
Consumption in the patient's entourage or family	59 (82%)
Age at first intake	19.8 ± 4.5
Age at onset of dependence	22.4 ± 5.2
Age at the first attempt to stop	25.3 ± 5.7
Heroine as the principal drug	67 (93%)
Number using the nasal route	42 (58%)
Number using other psychotropic drugs	60 (83%)
Damage related to opioid dependence:	
- psychiatric	59 (82%)
- somatic	25 (35%)
- professional	43 (60%)
- socio-emotional	58 (81%)
- legal	41 (57%)
- financial	50 (69%)

When comparing the three groups, methadone enantiomer concentrations/doses were different. The cessation of opioid use between the three groups was not significant (Table 2). Methadone dose, *(R)*- and *(S)*-methadone concentration/dose and cessation of opiates were compared according to GG, GT and TT groups. Only the following differences between individual groups were statistically significant:

- between GG and GT groups: *(R)*- and *(S)*-methadone concentration/dose (*P* = .028 and *P* = .014) and cessation of opiates (*P* = .032)
- between GG and TT groups: *(R)*- and *(S)*-methadone concentration/dose (*P* = .046 and *P* = .002).

There was no difference between the groups in terms of withdrawal symptoms, a worsening or improvement in the consumption of non-opioid substances, gambling disorders, sociodemographic characteristics, history or severity of the addictive disorder, impulsivity, comorbidity or current substance use.

Regarding the *CYP2D6* polymorphism, 10 patients (13.9%; 95% confidence interval 6.9, 24.1) were considered to be poor metabolizers (PM), 60 patients (83.3%) were considered to be extensive metabolizers (EM),and two patients (2.8%) were considered to be ultrarapid metabolizers (UM).

In our study, the CYP2D6 phenotypes did not seem to be relevant with regard to either methadone levels or opiate cessation (Table 3).

TABLE 2 Influence of *CYP2B6 G516T* genetic polymorphism

Characteristics N	All patients (*N* = 72)	GG 39	GT 24	TT 9	Test value (ddl)	*P* value
Methadone dose (mg/day)	53 ± 35	47 ± 29	65 ± 45	48 ± 22	3.25 (2)	.20
(R)-methadone concentration/dose (ng/ml/mg)	2.93 ± 2.51	2.80 ± 3.20	3.04 ± 1.36	3.21 ± 1.31	7.05 (2)	.029
(S)-methadone concentration/dose (ng/ml/mg)	3.01 ± 2.06	2.54 ± 2.15	3.26 ± 1.54	4.37 ± 2.34	12.53 (2)	.0019
Cessation of opiates	48 (67%)	22 (56%)	20 (83%)	6 (67%)	NA	.088

Comparison using Kruskal-Wallis test for continuous variables and Fischer exact test for opiate cessation.

CYP = cytochrome P450; NA = not available.

TABLE 3 *CYP2D6 ph*enotype and methadone levels or clinical response

Characteristics	All patients (*N* = 72)	PM 10	EM 60	UM 2	Test value (df)	*P* value
Methadone dose (mg/day)	53 ± 35	49 ± 27	54 ± 37	45 ± 7	0.16 (2)	0.92
(R)-methadone concentration/dose (ng/ml/mg)	2.93 ± 2.51	2.75 ± 0.99	2.99 ± 2.72	1.95 ± 0.27	1.50 (2)	0.47
(S)-methadone concentration/dose (ng/ml/mg)	3.01 ± 2.06	2.86 ± 1.29	3.06 ± 2.19	2.16 ± 0.86	0.48 (2)	0.79
Cessation of opiates	48 (67%)	6 (60%)	41 (68%)	1 (50%)	NA	0.64

Comparison using Kruskal-Wallis test for continuous variables and Fischer exact test for opiate cessation.

CYP = cytochrome P450; ; EM = extensive metabolizers; NA = not available; PM = poor metabolizers; UM = ultrarapid metabolizers.

In multivariate analysis, neither the *CYP2B6* genotype (F = .09, 2.67 df; *P* = .92) nor the CYP2D6 phenotype (F = 0.15, 2.67 df; *P* = .86) explained the *(R)*-methadone concentration/dose values. Neither the *CYP2B6* genotype (F = 3.09, 2.67 df; *P* = .052) nor the CYP2D6 phenotype (F = 0.05, 2.67 df; *P* = .95) explained *(S)*-methadone concentration/dose values. Nevertheless, there was a difference between the *CYP2B6* TT group and GT and GG groups (*t* = 2.39, 67 ddl; *P* = .019). Neither the *CYP2B6* genotype (chi-square value = 4.30, 2 df; *P* = .12) nor the CYP2D6 phenotype (chi-square value = .22, 2 df; *P* = .90) explained opiate cessation; nevertheless, there was a difference between the *CYP2B6* GT group and GG and TT groups (odds ratio = 3.79, z = 2.07; *P* = .038).

4 | DISCUSSION

In their 2018 review, Fonseca and Torrens[26] highlighted the influence of *CYP2B6*, and to some extent *CYP2D6* and *CYP2C19*, genetic variability on methadone pharmacokinetics.[4,17,19,39-44] Three studies described in that review[26] reported that the *CYP2B6* gene had no influence on the methadone response. Nevertheless, the differences in the published study methods may have played a role in the variability of the results, and, thus, the results should be interpreted cautiously.

Our study confirms the impact of the *CYP2B6* genotype on plasma methadone enantiomer concentrations, which was previously reported for *(S)*-methadone[19] and confirmed in a genome-wide association study (GWAS);[45] CYP2B6 displays stereoselectivity toward *(S)*-methadone.[46] It appears that activity at mu receptors is related to the concentration of *(R)*-methadone. In terms of the evaluation of the response to methadone, we focused on effects specifically linked to the mu receptor—namely, opioid consumption. Indeed, the expected improvement in the overall addictive situation, including social characteristics, cannot be directly and solely attributed to methadone, and should be considered more globally in terms of the overall care of the addiction. The modest difference in the concentration/dose of *(R)*-methadone, as well as the small number of subjects, could explain the modest effect of genotype on opiate cessation (only the GT group in multivariate analysis), although there was no difference in the criteria for increased use of other substances. Considering the sample size and *P* values, these results need to be confirmed by broader studies.

The lack of correlation observed between methadone dose and *CYP2D6* genetic polymorphism was not surprising as this enzyme may contribute only marginally to the methadone first-pass effects, as compared with *CYP2B6*.[27]

The methadone concentration relative to dose (concentration per milligram of methadone administered) ranged from 1.24 to 35.65 in our population. In a previous study, Eap et al found an up to 17-fold interindividual variation in the methadone blood concentration for any given dose.[9] This wide range of plasma concentrations is typical in drugs metabolized by polymorphic proteins. In addition, some patients took medication and cannabis, which may have influenced the methadone kinetics.[47]

In our study, the frequency of the *CYP2B6 516T* allele was 29%, which is almost identical to that reported by Crettol et al[4] or Mouly et al.[27] The frequency of CYP2D6 PMs was slightly higher than the expected 5–10% but was within expected population variation regarding Confidence interval.[48] It has already been reported that CYP2D6 PM status has no influence on methadone plasma level.[19]

Few genome-wide pharmacogenomics studies have searched for genes involving the regulatory mechanisms of methadone dose,

pharmacokinetics, plasma *(R)*- and *(S)*-enantiomer concentrations, or pharmacodynamic associations with various single nucleotide polymorphisms.[45] However, GWAS that allow identification of new genes associated with methadone dose[45] need a large number of subjects, which is rarely the case in pharmacogenetics studies (Clinical Pharmacogenetics Implementation Consortium, https://cpicpgx.org).

We selected patients who had had no dose change in the past 5 days. We assumed that this corresponded to the steady state for patients for whom the methadone half-life is about 24 hours. In fact, as MMT is prescribed in our group of patients for a mean of 46 months (from 1 to 89 months), regardless of the half-life, all patients should have reached steady state.

Patients in the GG group should receive higher doses to achieve the same plasma concentration, as they have a more extensive metabolism. The dose should be adjusted by the physician in consideration of the clinical efficacy generally, without having to factor in the plasma level. In our study, we did not observe this clinical adjustment; we observed that the TT group had a lower dose administered, and the GT group a higher dose administered. Surprisingly, similar results were reported in the Mouly et al study.[27] However, both studies included a small number of subjects, and these results need to be confirmed in a larger cohort.

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CONTRIBUTORS

C.V.-V. wrote the manuscript; M.G.-B., G.C.-B., J.L. and R.B. designed the research; M.G.-B., C.D., B.L.G., R.B., C.V. and E.J.L. performed the research; J.B.H. performed the statistical analysis; and C.V. and C.V.-V. analysed the data.

COMPETING INTERESTS

There are no competing interests to declare.

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