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Genotyping of patients treated with selective serotonin reuptake inhibitors

ORIGINAL ARTICLE

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BACKGROUND

Selective serotonin reuptake inhibitors (SSRIs) are used by over 180,000 people in Norway. The enzymes CYP2D6 and CYP2C19 are key in the metabolism of SSRI antidepressants. The serotonin transporter coded by *SLC6A4* may be significant for the efficacy of the drugs.

MATERIAL AND METHOD

All patients who had undergone genotyping for *CYP2D6*, *CYP2C19* and *SLC6A4* at the Centre for Psychopharmacology in 2020 were included, irrespective of indication. For those patients where data were available, *CYP2C19* genotype was linked to serum concentration measurement of escitalopram, which is the most commonly used SSRI drug.

RESULTS

Out of 3,492 patients, 432 (12.4 %) had a combination of genotypes of *CYP2D6*, *CYP2C19* and *SLC6A4* considered to lead to the most favourable metabolism and efficacy of SSRI antidepressants. The dose requirement in patients with poor CYP2C19 metabolism was more than halved to achieve the same concentration of escitalopram compared to patients with normal metabolism.

INTERPRETATION

Our findings demonstrate the low prevalence of the most favourable genotype combination for response to SSRIs. Genotype combinations probably contribute to the wide variation between individuals in the efficacy of these drugs and the fact that treatment does not produce the desired outcome in many patients.

MAIN FINDINGS

Out of more than 3,000 patients, approximately one in seven had a combination of genotypes of *CYP2D6*, *CYP2C19* and *SLC6A4* considered to lead to the most favourable metabolism and efficacy of treatment with selective serotonin reuptake inhibitors.

In patients with poor CYP2C19 metabolism, the median serum escitalopram concentration was above the upper limit of the reference range presumed to have a beneficial effect.

In 2020, more than 180,000 people in Norway used a selective serotonin reuptake inhibitor (SSRI), and the majority of these used escitalopram (1). SSRI drugs work by inhibiting the reuptake of serotonin in serotonergic synaptic clefts and entail a lower risk of toxic reactions and adverse effects than tricyclic antidepressants (TCA) (2). Escitalopram also has fewer anticholinergic effects than tricyclic antidepressants, making it suitable for older patients. The widespread use of SSRIs can also be attributed to the fact that the drugs are indicated for anxiety (3) and other mental health disorders.

However, the effects associated with the use of SSRIs are not all favourable. Sexual dysfunction is common in both women and men (4), and high doses of citalopram and escitalopram are contraindicated due to the risk of arrhythmias (5). There are also concerns

about an initial increase in attempted suicide (3), although some studies indicate the opposite (6). Adverse effects are generally associated with high serum concentrations. Patients with impaired elimination and resulting high serum concentrations of escitalopram switch to other antidepressant treatment to a much greater extent than patients with normal metabolism (7). SSRIs are eliminated via metabolism in the liver, by enzymes in the CYP450 system, with CYP2D6 and/or CYP2C19 being key for all SSRIs (Table 1). There are several different alleles (variants) of the genes that code for these CYP enzymes. Various combinations of CYP alleles determine the genotype, which in turn can be categorised by enzyme activity and thus effect on drug metabolism and serum concentrations of SSRIs. This activity is the phenotype and is classified as normal, ultra-rapid, intermediate or poor metabolism. Similarly to the dosage of the SSRIs, a patient's phenotype will have consequences for serum concentrations (7).

Table 1

Active substance, trade name, metabolic pathway and reference range for serum concentrations of different SSRIs.

Active substance	Best known trade name	Metabolic pathway	Reference range
Escitalopram	Cipralex	CYP2C19 (CYP2D6 and CYP3A4 are involved to a lesser extent)	20–120 nmol/L
Citalopram	Cipramil	CYP2C19 (CYP2D6 and CYP3A4 are involved to a lesser extent)	70–350 nmol/L
Sertraline	Zoloft	CYP2C19 (CYP3A4, CYP2B6, CYP2C9 and CYP2D6 as well as UGT are involved to a lesser extent)	20–250 nmol/L
Paroxetine	Seroxat	CYP2D6	40–400 nmol/L
Fluoxetine	Fontex	Partly CYP2D6 and CYP2C9 (CYP3A4 and CYP2C19 are involved to a lesser extent)	400–2,500 nmol/L
Fluvoxamine	Fevarin	Partly CYP2D6 and CYP1A2	60–900 nmol/L

Even with normal metabolism of SSRIs, it is not guaranteed that the patient will have the anticipated effect from treatment. Since these drugs work by inhibiting reuptake of serotonin in the synapses, the amount of target protein (serotonin transporter) will be significant for efficacy. The gene *SLC6A4* codes for the serotonin transporter. The regulatory region 5-HTTLPR in this gene can be present as a short (S) or long (L) variant, which influences levels of serotonin transporter. Two alleles of the short variant (S/S) cause low levels and an increased risk of lack of efficacy of SSRIs compared to the allele combinations causing high (L/L) or intermediate (S/L) levels of serotonin transporter (8–10). The L/L genotype will produce the most favourable effect, while the S/L genotype is considered to lead to an adequate effect of SSRIs. In addition, the S/L genotype is most common in most populations, and therefore documentation about efficacy and recommended dosage is largely based on this subgroup.

In order to optimise treatment with an SSRI, it would be useful to have phenotype information for both CYP enzymes and the serotonin transporter. The objective of this study was to investigate the proportion of our patient population that has the most favourable phenotype combination of CYP2D6, CYP2C19 and serotonin transporter, as well as to investigate the relationship between phenotype and serum concentration of the most commonly used SSRI drug, escitalopram.

Material and method

This retrospective cross-sectional study was conducted in the Centre for Psychopharmacology at Diakonhjemmet Hospital in Oslo following approval from the hospital's data protection officer. Data about serum concentration measurements and pharmacogenetic analyses were obtained from an internal drug monitoring database for patients who had undergone *CYP2D6*, *CYP2C19* and *SLC6A4* genotyping from 1 January 2020 to 31 December 2020. The indication for pharmacogenetic analysis included lack of efficacy or adverse effects with various medications (mainly psychotropic drugs) and wish for genotyping before the start of treatment to investigate which medications would be most suitable for the patient. There was a lack of information about the indication in the request for a large proportion of the tests.

We wanted to investigate escitalopram metabolism in the genotyped patients. Therefore, we identified escitalopram concentrations in the included patients measured in the period 1 January 2019 to 31 December 2020. The data were linked and then anonymised, and the linking key and personal data were deleted on publication. The genotyping methods have been described in detail previously (7). After genotyping of the most relevant variant alleles for *CYP2D6* and *CYP2C19,* the patients were classified into various phenotypes according to normal, ultra-rapid, intermediate or poor metabolism (often referred to with the abbreviations NM, UM, IM and PM respectively) based on standard analysis practice in our laboratory (see www.pharmgkb.org for updated list). Together with genotype of the gene that codes for the serotonin transporter (L/L, S/L or S/S) and measured serum concentrations, this forms the basis of the feedback given to the requesting doctor.

For each test result, the requesting doctor was informed in writing about whether the serum concentration was as expected based on the dosage and, if applicable, given advice about changes to the treatment regimen. Serum concentrations within the reference range are expected to produce a clinical effect since the reference values have been drawn up based on use of therapeutic doses in the normal population. In the event of extremely high levels, the requesting doctor was alerted by telephone and advised to reduce the dose, discontinue treatment or monitor the patient closely, depending on the drug, comorbidities and other circumstances. Intoxication tests were excluded from this material. We have no information about the consequences of the test results or whether the patients were being treated with medications that may have caused interactions with escitalopram.

A total of 6,069 patients over the age of 16 years underwent genotyping for both *CYP2D6* and *CYP2C19*, while 3,492 also underwent genotyping for *SLC6A4*, which codes for the serotonin transporter. The data were linked with serum escitalopram concentration measurements. The time of the last dose and sampling time had to be listed, and only samples taken 12–24 hours after the last dose of escitalopram were included. Null values and presumed intoxication tests (> 250 nmol/L), as well as samples where the stated dose was over 60 mg or not stated, were excluded. Our material thus contained 287 patients with measured concentrations of escitalopram. In cases where there were several available serum concentration measurements from the same patient, one random concentration was chosen from each patient.

Escitalopram is predominantly metabolised by the enzyme CYP2C19. The relationship between serum concentration and dose (C/D ratio) was calculated to work out which dosage should be recommended for the individual patient according to CYP2C19 phenotype.

STATISTICS

The data were examined with the Shapiro-Wilks test, which showed that they were not normally distributed. Comparisons of serum concentration, dosage and predicted dose requirement in escitalopram patients with various CYP2C19 phenotypes were therefore performed with a nonparametric test (Kruskal-Wallis test), with Dunn's method as post-hoc analysis.

Results

The 6,069 *CYP2D6* analyses performed revealed that 3,325 patients (54.8 %) had normal metabolism, 2,232 (36.8 %) had intermediate metabolism, 365 (6.0 %) had poor metabolism and 147 (2.4 %) had ultra-rapid metabolism. Corresponding figures for *CYP2C19* were 3,974 (65.5 %), 1,643 (27.1 %), 196 (3.2 %) and 256 (4.2 %). The analyses of *SLC6A4* revealed that 1,683 (48.2 %) patients had intermediate levels of the serotonin transporter (S/L genotype), while 1,152 (33.0 %) had high levels (L/L genotype) and 657 (18.8 %) low levels (S/S genotype).

The phenotype for normal metabolism for both CYP2D6 and CYP2C19 as well as high levels of serotonin transporter (L/L genotype) was found in 442 patients (12.4 %) (Figure 1).

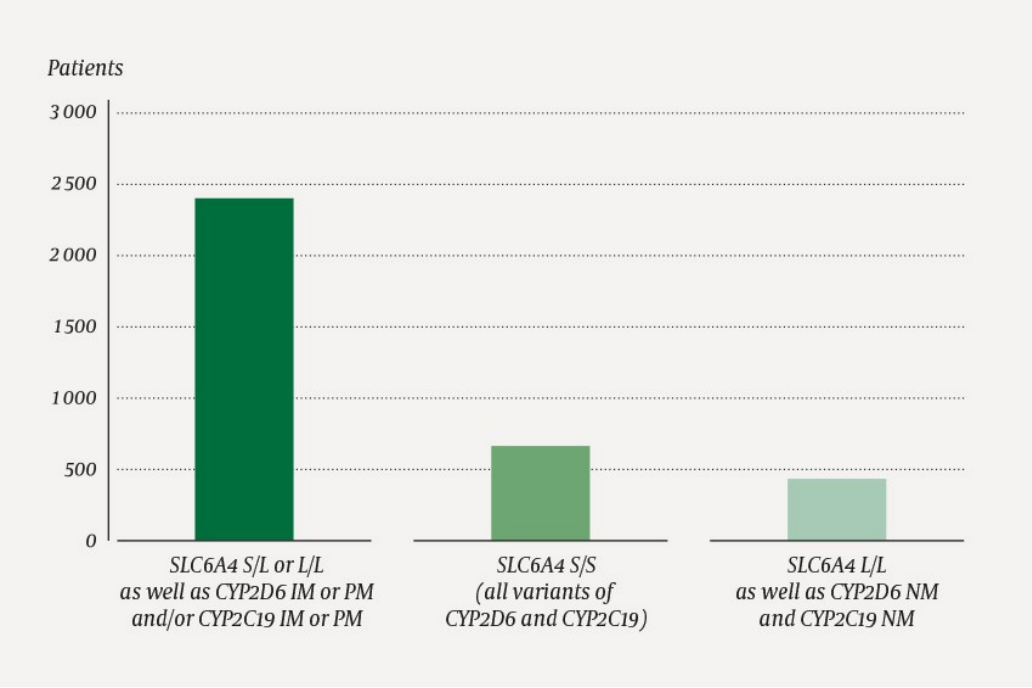

Figure 1 Linked data for CYP2D6, CYP2C19 and SLC6A4. 657 patients (18.8 %) had the S/S genotype of SLC6A4 and thus a low expected effect from SSRIs. 2,403 patients (68.8 %) had intermediate or poor metabolism via CYP2D6 and/or CYP2C19. 432 patients (12.4 %) had the L/L genotype of SLC6A4 and normal metabolism via both CYP2D6 and CYP2C19. IM = intermediate metabolism, NM = normal metabolism, PM = poor metabolism.

A total of 3,174 patients (87.6 %) had one or more phenotypes of CYP2D6, CYP2C19 and/or the serotonin transporter indicative of an effect to a greater or lesser extent on the efficacy and/or metabolism of some or all SSRIs. In all, 56 patients (1.6 % of patients genotyped for *CYP2D6*, *CYP2C19* and *SLC6A4*) had low levels of the serotonin transporter and a phenotype for poor metabolism via CYP2D6 and/or CYP2C19. Among the 2,744 patients with poor, intermediate or ultra-rapid CYP2D6 enzyme activity, 1,802 (29.7 % of the 6,069 patients tested) had normal CYP2C19 enzyme activity. Among patients with poor, intermediate or ultra-rapid CYP2C19 enzyme activity, 1,153 (19.0 % of the 6,069 patients tested) had normal CYP2D6 enzyme activity.

The median serum concentration of escitalopram was 47.0 nmol/L in patients with the phenotype normal metabolism for CYP2C19 ($n = 202$), 66.0 nmol/L in patients with intermediate metabolism ($n = 64$), and 133 nmol/L in patients with poor metabolism ($n = 7$) (Figure 2). The mean concentration (SD) was 60.7 nmol/L (50.9), 75.2 nmol/L (47.4) and 142 nmol/L (65.7) respectively. There was a statistically significantly difference in the distribution of serum concentration values in the groups with intermediate and poor metabolism respectively compared to the distribution in the group with normal metabolism (p-value of 0.013 and <0.001 respectively). There was no significant difference between the group with normal metabolism and the group with ultra-rapid metabolism. There were no differences in daily dose between the groups.

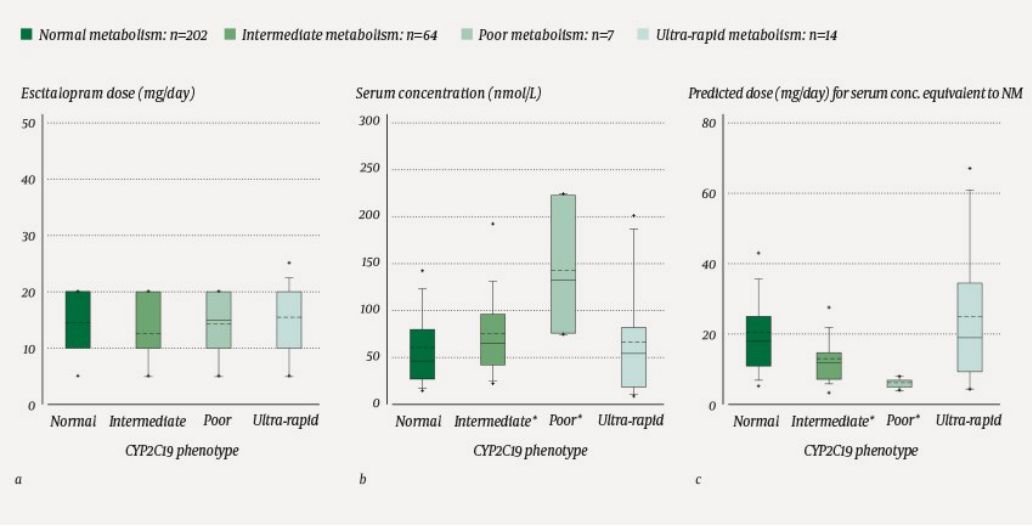

Figure 2 Dosage (a), serum concentration (b) and predicted dose requirement (c) of escitalopram for the various CYP2C19 phenotypes. The figure shows median values (solid horizontal line), mean values (dotted horizontal line), interquartile range (box height), 10th and 90th percentiles (error bars) and 5th and 95th percentiles (plus sign). Median values and 10th and 90th percentiles coincide in some cases with 25th or 75th percentiles. Asterisk (*) indicates statistically significant difference ($p < 0.05$) from normal metabolism. NM = normal metabolism. Note different y-axis scales in Figures a, b and c.

Based on estimates of median C/D ratio in patients in the different groups, we were able to calculate the dose required to achieve the same serum concentrations as the group with normal enzyme activity (Table 2). The predictions indicated that the groups with intermediate and poor metabolism had significantly lower dose requirements than the group with normal metabolism. There was no significant difference between the groups with normal and ultra-rapid metabolism. All the patients with poor metabolism via CYP2C19 whose escitalopram concentrations had been measured either had intermediate or normal metabolism via CYP2D6. There was no difference in age between the phenotype groups.

Table 2

CYP2C19 phenotype and dosage of escitalopram. Calculated dose of escitalopram to achieve the same serum concentrations as the normal metabolism group for various phenotypes of CYP2C19, based on the findings in this study.

CYP2C19 phenotype	Concentration/dose ratio, median (nmol/mg)	Change in required dose from normal phenotype (%)	Equivalent to 5 mg for normal phenotype (mg)	Equivalent to 10 mg for normal phenotype (mg)	Equivalent to 20 mg for normal phenotype (mg)
Normal metabolism	3.4	0	5.0	10.0	20.0
Intermediate metabolism	5.1	−34	3.3	6.6	13.2
Poor metabolism	9.2	−63	1.8	3.7	7.3
Ultra-rapid metabolism	3.2	+5	5.3	10.6	21.1

Discussion

In this study, we found that a patient with an assessed need for genotyping in connection with drug treatment is most likely to have normal metabolism via CYP2D6 or CYP2C19, which are the primary enzymes in the metabolism of serotonin reuptake inhibitors. One-third of patients also have high levels of serotonin transporter in the synapses. Only 12.4 % of patients in our study had the phenotype for normal enzyme activity for both the CYP enzymes as well as high levels of serotonin transporter.

More than two-thirds of patients in our study had a phenotype that suggests intermediate or poor metabolism via CYP2D6 or CYP2C19, as well as high or intermediate levels of serotonin transporter. In this group of patients, genotyping would be able to provide useful information because the majority of these patients had normal activity for the other key SSRI-metabolising CYP enzyme (CYP2D6/CYP2C19). Therefore, it is possible that a patient with adverse effects or therapeutic failure with, for instance, escitalopram (CYP2C19) and functional serotonin transporter may benefit from switching to an SSRI primarily metabolised by the CYP2D6 enzyme. Therefore, genotyping may be a useful supplement to serum concentration measurements in order to personalise treatment and reduce the risk of adverse effects and therapeutic failure.

Use of the Hamilton depression scale has shown an increased response rate to treatment with escitalopram when there are high serotonin transporter levels compared to intermediate and very low levels (11). Therefore, it could be assumed at the start of treatment with an SSRI that the L/L genotype of *SLC6A4* in combination with normal metabolism of the relevant drug by CYP2C19/CYP2D6 is most favourable. However, as our study shows, most patients have intermediate serotonin transporter levels, and this is still considered to lead to an adequate clinical effect from SSRIs. Therefore, the clinical benefit of genotyping *SLC6A4* is not entirely clear since the S/S genotype does not cause a complete lack of serotonin transporter either. Consequently, an analysis result revealing the S/S genotype does not rule out efficacy for all SSRIs (12) and must never override clinical assessment of treatment response, despite several meta-analyses and review articles demonstrating that patients with *SLC6A4* genotype S/S have less favourable treatment outcomes (8–10).

Rationally, other types of antidepressants should nonetheless be considered in preference to SSRIs if it is known that the patient has the S/S genotype of *SLC6A4*. The small group of patients who have the phenotype for poor CYP2D6 and/or CYP2C19 metabolism in addition to low serotonin transporter levels (S/S) are likely to be particularly susceptible to adverse effects. In total, only 8.2 % ($n = 56$) of patients with the S/S genotype of *SLC6A4* in our study were in this category. Contrary to the case for use of SSRIs such as escitalopram (7, 9), no association was found in one study between decreased serotonin transporter levels and efficacy of treatment with the SNRI (serotonin and noradrenaline reuptake inhibitor) duloxetine (13). Depending on the indication and clinical presentation, other antidepressants that do not exclusively work via the serotonin transporter, e.g. vortioxetine, venlafaxine, bupropion, mirtazapine and mianserin, may also be appropriate alternatives.

Due to QT prolongation and the risk of serious arrhythmias (5, 14–16), the maximum recommended daily dose of escitalopram is 20 mg. It is natural to assume that patients in the group with poor metabolism have a much higher risk of these adverse effects, since at any given dose they will have serum escitalopram concentrations almost three times higher than concentrations in patients in the group with normal metabolism. Some studies suggest that the difference between the groups with poor and normal metabolism is even greater (17). Given the risk of ventricular arrhythmias and sudden cardiac death (15), it is important to prevent serum concentrations reaching toxic levels, even with the use of normal doses. Therefore, it is advisable to adjust escitalopram dosage based on CYP2C19 phenotype (Table 2) and to monitor with serum concentration measurements. In this way,

the risk of serious adverse effects can be reduced. Patients with a phenotype that suggests ultra-rapid or normal metabolism often require higher doses than patients with intermediate or poor metabolism (17).

Another serious and very common adverse effect of SSRIs is sexual dysfunction. There may be an effect on arousal, libido, orgasm and ejaculation, with an overall prevalence of between 25 % and 73 % of patients. These adverse effects can lead to decreased adherence to treatment, and many patients are reluctant to talk to their doctor about sexual adverse effects (18). Since these adverse effects can be dose-related (19), patients with intermediate or poor CYP2D6 and/or CYP2C19 metabolism will probably be at increased risk if they are being treated with an SSRI metabolised by the relevant enzyme. These patients would benefit from adjustment of their SSRI treatment to the CYP phenotype.

As well as there being a clear difference in serum concentrations of escitalopram between the phenotypes with normal, intermediate and poor CYP2C19 metabolism, there is wide variation within the groups. In our study, this is particularly apparent in the group with increased enzyme activity, in which two patients had unexpectedly high serum concentrations of over 150 nmol/L. On one hand, this shows that the phenotypes include a heterogeneous range of genotypes, and that hitherto unknown variants may exist which cause different enzyme activity than is currently known about and which are reflected in serum concentrations. On the other hand, it shows that genotyping alone cannot predict serum concentrations (and thus efficacy of treatment) or the risk of adverse effects in patients, which is demonstrated, for instance, by the fact that the number of SSRI serum concentration measurements above the upper limit of the reference range are two-fold higher in patients aged 60 years or older compared with patients younger than 60 years (20).

It is possible that our patient material consists of patients who have an abnormal effect from escitalopram, and therefore it has a different distribution of genotypes than the average population. However, frequency studies with European patients demonstrate figures consistent with the data in our study (21, 22). Nevertheless, this may change over time because migration may change the prevalence of various CYP genotypes (23). Our material from genotyped patients originates from a group with far wider indications for genetic testing than treatment with SSRIs because these tests may be appropriate during treatment or before initiating treatment with a wide variety of drugs. Therefore, the selection is as relevant as it is possible to get in a retrospective study from normal clinical practice. Nevertheless, genotyping alone cannot be used to predict efficacy of treatment of SSRIs, and in our material this particularly applies to patients with ultra-rapid metabolism. To be able to give accurate recommendations about dosage of SSRIs, we require more information about other factors that can affect the bioavailability and elimination of drugs from the body. In addition to metabolising enzymes and age, serum concentrations are also affected by weight, sex, renal function, hepatic function, bowel disease, interactions with other drugs and a number of other factors. Several SSRIs can also inhibit the metabolism of other drugs. Therefore, systematised clinical information may improve patient treatment and lead to a decrease in the number of drug-related hospital admissions. This is important because this patient group accounts for up to 20 % of all admissions to Norwegian emergency departments (24).

CONCLUSION

A small proportion of patients in the study had the phenotype combination of the enzymes CYP2D6 and CYP2C19 and the serotonin transporter coded by *SLC6A4* that is most favourable for treatment with the six SSRI drugs on the market in Norway. Knowing the individual patient's phenotypes offers the potential to optimise treatment and reduce the risk of adverse effects when SSRIs are prescribed.

The article has been peer-reviewed.

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