Variation in the *CYP2D6* gene is associated with a lower serum sodium concentration in patients on antidepressants

Sonja Kwadijk-de Gijssel,¹ Monique J. Bijl,^{1,2} Loes E. Visser,^{1,2}
Ron H. N. van Schaik,³ Albert Hofman,² Arnold G. Vulto,¹
Teun van Gelder^{1,4} & Bruno H. Ch. Stricker^{2,4,5}

¹Department of Hospital Pharmacy, ²Department of Epidemiology, ³Department of Clinical Chemistry and ⁴Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, and ⁵Drug Safety Unit, Inspectorate for Health Care, The Hague, the Netherlands

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Several antidepressants are metabolized by the polymorphic enzyme cytochrome P450 2D6 (*CYP2D6*).
- The variant allele *CYP2D6**4 is the main polymorphism resulting in decreased enzyme activity in Caucasians.
- Decreased *CYP2D6* enzyme activity potentially leads to higher plasma concentrations of antidepressants.
- Consequently, patients carrying the *4 allele are more likely to suffer from adverse drug reactions such as hyponatraemia.

WHAT THIS STUDY ADDS

- The association between *CYP2D6* genotype and serum sodium concentration in users of antidepressants has not been examined thoroughly, and most studies suffer from small numbers of poor metabolizers (PMs) of *CYP2D6*.
- This study shows that serum sodium concentrations in users of tricyclic antidepressive drugs are lower in *CYP2D6* PMs than in extensive metabolizers.

Correspondence

Dr Professor Bruno H. Ch. Stricker, Med PhD, Erasmus MC, Department of Epidemiology, PO Box 2040, 3000 CA, Rotterdam, the Netherlands.
Tel: + 31 70 340 6793
Fax: + 31 70 340 6707
E-mail: b.stricker@erasmusmc.nl

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AIM

To study the effect of the *CYP2D6**4 polymorphism on serum sodium concentration in users of antidepressants [selective serotonin reuptake inhibitors and tricyclic antidepressants (TCAs)].

METHODS

In this population-based cohort study, all subjects in the Rotterdam Study were included who used an antidepressant at baseline and from whom a blood sample was available in which *CYP2D6* genotype and serum sodium concentration could be determined ($n = 76$). Multivariate linear regression was used to study the association between *CYP2D6**4 and serum sodium concentration.

RESULTS

CYP2D6 poor metabolizers (PMs) (*4/*4) had a significantly lower mean serum sodium concentration in comparison with *CYP2D6* extensive metabolizers (EMs) (*1/*1) [difference -3.9 mmol l^{-1} ; 95% confidence interval (CI) $-0.86, -7.03$; $P = 0.013$]. In *CYP2D6**4 heterozygotes (*1/*4) serum sodium concentration was 1.7 mmol l^{-1} (95% CI $-3.48, 0.18$) lower compared with *CYP2D6* EMs, but this difference was not statistically significant ($P = 0.077$).

CONCLUSIONS

The serum sodium concentration in PMs was lower in users of an antidepressant, especially in TCA users. Therefore *CYP2D6* PMs might be at increased risk of developing symptoms of hyponatraemia.

Introduction

Hyponatraemia is the most common electrolyte disorder in ambulatory outpatients, especially in the elderly [1]. Hyponatraemia can be defined as a serum sodium concentration of $<136 \text{ mmol l}^{-1}$ and the prevalence is estimated to vary between 5 and 10% in a healthy elderly population to 30% in patients admitted to a hospital [1, 2]. Predisposing factors for hyponatraemia are increasing age, female gender, usage of diuretics (especially thiazides), recent history of pneumonia, low body mass index (BMI) and impaired renal function [3].

The use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) has also been reported as a cause of hyponatraemia [3–10]. Although the precise mechanism is not known, antidepressants are thought to cause the syndrome of inappropriate antidiuretic hormone release (SIADH) by direct or indirect stimulation of vasopressin release from the posterior pituitary gland. SIADH can lead to retention of water and to hyponatraemia [4]. The occurrence of SIADH in patients using antidepressants (TCAs and SSRIs) has been previously described in several case reports and a case series and is estimated to occur in five on every 1000 patients treated per year [1, 5, 7, 11, 12].

Most antidepressants are metabolized by the hepatic enzyme cytochrome P450 2D6 (CYP2D6), which is highly polymorphic with >60 variant alleles (<http://www.cypalleles.ki.se>). Individuals carrying two functional CYP2D6 alleles (*1, *2) have 'normal' enzyme activity and are classified as extensive metabolizers (EMs). However, 5–10% of the population lack enzyme activity due to inheritance of two nonfunctional alleles (*3, *4, *5, *6) and form the so-called poor metabolizers (PMs). Heterozygous carriers of nonfunctional alleles exhibit decreased enzyme activity and are usually classified as intermediate metabolizers (IMs). CYP2D6*4 is the most common variant allele in Caucasians (allele frequency of 20%) [13].

PMs have higher plasma concentrations of antidepressants metabolized by CYP2D6 and are therefore more likely to suffer from adverse drug events [14]. Hyponatraemia or low serum sodium concentration may be one of these adverse events. In one study, it was found that SSRI-related hyponatraemia is not related to CYP2D6 genotype, or excessive drug concentrations, but the study population was small ($n = 20$) and concerned only severe cases of hyponatraemia ($<130 \text{ mmol l}^{-1}$) [15]. It is unknown whether CYP2D6 genotype influences serum sodium concentration in users of antidepressants, especially in TCA users.

Therefore, the objective of this population-based cohort study was to examine the influence of the CYP2D6*4 polymorphism on serum sodium concentration in patients treated with a TCA or SSRI.

Methods

Setting

This study is part of the Rotterdam Study, a prospective population-based cohort study among inhabitants of Ommoord, a suburb of Rotterdam. Between 1990 and 1993, all 10 275 persons aged ≥ 55 years were invited to participate. The aims of the Rotterdam Study are to investigate incidence of, and risk factors for cardiovascular, neurodegenerative, locomotor and ophthalmological diseases in the elderly [16, 17]. The Medical Ethics Committee of the Erasmus Medical Centre approved the study and written informed consent was obtained from all participants. All drug prescriptions dispensed to participants were made available in computerized form as of January 1991.

The study population consisted of all subjects in the Rotterdam Study who used an antidepressant (TCA or SSRI) at baseline ($n = 139$) and from whom a blood sample was available in which CYP2D6 genotype and serum sodium concentration could be determined ($n = 76$).

Genotyping

At the baseline examination of the Rotterdam Study, blood was obtained from which DNA was isolated. Genotyping for the CYP2D6*4 polymorphism (1846G $\rightarrow$ A) was performed using Taqman allelic discrimination assays as described earlier [14].

Exposure and outcome definition

Use of antidepressants was defined as current use of an antidepressant (N06AA/AC or N06AB/AE) at the time of blood sampling for DNA genotyping and determination of the serum sodium levels.

Serum sodium concentration in mmol l^{-1} was considered as the outcome of interest.

Statistical analysis

Genotype frequency was tested for deviation from Hardy-Weinberg equilibrium (HWE) using a χ^2 test. A multivariate linear regression model was used to assess the effect of the CYP2D6*4 polymorphism on serum sodium concentration. The model was adjusted for age and gender and additionally for covariates that changed the point estimate by $>10\%$. The following covariates were considered as potential confounders: age, gender, use of diuretics, BMI in kg m^{-2} , antidepressant dose and renal function [14].

Analyses were performed in the total cohort of antidepressant users and separately in TCA and SSRI users. All analyses were performed with SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA).

Results

The study population characteristics are shown in Table 1. Information on CYP2D6 genotype and serum sodium concentration was available in 76 antidepressant users.

The allele frequency of the *CYP2D6**4 allele in our study population was 18.4%. The genotype distribution was in HWE.

No association was demonstrated between *CYP2D6* genotype and serum sodium concentration among non-antidepressant users in the Rotterdam Study ($P = 0.146$). The association between *CYP2D6* genotype and serum sodium concentration in antidepressant users is given in Table 2. *CYP2D6* PMs (*4/*4) had a significantly lower mean serum sodium concentration in comparison with *CYP2D6*

EMs (*1/*1) [difference -3.9 mmol l^{-1} ; 95% confidence interval (CI) $-0.86, -7.03$; $P = 0.013$]. In *CYP2D6**4 heterozygotes (*1/*4) serum sodium concentration was 1.7 mmol l^{-1} (95% CI $-3.48, 0.18$) lower compared with *CYP2D6* EMs, but this difference was not statistically significant ($P = 0.077$).

The analysis was repeated separately for participants using a TCA or SSRI. The association between *CYP2D6* and serum sodium concentration in the subgroup analysis of TCA users was similar to the difference found in all antidepressant users and is given in Table 2. The results of the analysis for SSRIs showed no statistically significant difference in serum sodium concentration between the different *CYP2D6* genotypes (Table 2).

Table 1

Patient characteristics

Variable	Number of patients (%)
Mean age, years (SD) ($n = 76$)	69.7 (8.5)
Gender	
Female	57 (75%)
Male	19 (25%)
<i>CYP2D6</i> genotype*	
* 1/ *1 (EM)	53 (69.7%)
* 1/*4 (IM)	18 (23.7%)
* 4/*4 (PM)	5 (6.6%)
Antidepressant use	
SSRI	12 (15.8%)
TCA	64 (84.2%)
Mean dose in DDD (SD)	
AD	0.8 (0.5)
SSRI	1.1 (0.7)
TCA	0.5 (0.4)
Co-administration	
Diuretic use	14 (18.4%)
Mean level of albumin (g l^{-1})	42.8 (2.4)
Body mass index, kg m^{-2} (SD)	26.6 (3.6)
Glomerular filtration rate, ml min^{-1} (SD)	69 (18.6)

*Hardy–Weinberg equilibrium, $\chi^2 = 3.42$ ($P = 0.06$). EM, extensive metabolizer; PM, poor metabolizer; IM, intermediate metabolizer; AD, antidepressant; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; DDD, defined daily dose equivalents.

Discussion

The main finding of this study is that antidepressant users homozygous for the *CYP2D6**4 allele had a significantly lower serum sodium concentration than antidepressant users with the wild-type genotype. When the analyses were performed separately for TCAs and SSRIs, this association was still observed in users of TCAs, but not in SSRI users. The last observation may be explained by the small number of SSRI users ($n = 12$) and the observation that there was only one PM in this group. In addition, the amount of drug metabolized by *CYP2D6* might explain the absence of association in SSRI users, since TCA metabolism seems more dependent on *CYP2D6* enzyme activity than that of SSRIs [14, 18].

Although the clinical relevance of severe hyponatraemia ($\text{Na} < 118 \text{ mmol l}^{-1}$) is well recognized and leads to serious symptoms such as confusion, unconsciousness, grand mal seizures and even death, mild hyponatraemia may cause important symptoms, with instability, delayed

Table 2

Association between *CYP2D6* genotype and serum sodium concentration in users of antidepressants

<i>CYP2D6</i> genotype	Patients ($n = 76$)	Mean serum sodium concentration, mmol l^{-1} *	Mean dif serum sodium concentration (95% CI), mmol l^{-1} *
All antidepressants (TCA or SSRI)			
* 1/ *1 (EM)	53	140.3	Ref
* 1/ *4 (IM)	18	138.6	-1.65 ($-3.48, 0.18$)
* 4/ *4 (PM)	5	136.4	-3.94 ($-0.86, -7.03$)
TCA			
* 1/ *1 (EM)	44	140.4	Ref
* 1/ *4 (IM)	16	138.9	-1.37 ($-3.39, 0.64$)
* 4/ *4 (PM)	4	136.0	-4.32 ($-7.85, -0.79$)
SSRI			
* 1/ *1 (EM)	9	140.0	ref
* 1/ *4 (IM)	2	136.0	5.38 ($-11.76, 1.00$)
* 4/ *4 (PM)	1	138.0	1.07 ($-9.57, 7.42$)

Ref, reference group. *Adjusted for age and gender. EM, extensive metabolizer; PM, poor metabolizer; IM, intermediate metabolizer; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.

reaction time and more mental errors in patients with a normal serum sodium concentration [19].

In this study, serum sodium concentration was examined as a continuous variable. The number of patients with a serum sodium concentration ≤ 136 mmol L⁻¹ in our cohort was too small to assess the effect of *CYP2D6* genotype on hyponatraemia.

Besides SIADH as a cause of hyponatraemia, excess of water intake or dietary sodium deficiency could also result in hyponatraemia. The lower serum sodium concentration of the PMs was probably not caused by excess water intake due to a dry mouth, compulsive water drinking or primary polydipsia because albumin concentrations in these subjects were within the normal range, which suggests that the lower serum sodium is not a dilution of body water.

Observational studies are prone to selection, information and confounding bias. Selection bias is unlikely since missing blood samples and/or genotypes were not expected to be specifically related to *CYP2D6* genotype. Information bias also seems unlikely as both *CYP2D6* genotype and serum sodium concentration measurements were performed prior to formulation of the research question. In this study, only the *CYP2D6**4 polymorphism was determined, since this is the most common polymorphism among PMs. The frequency of the *4 allele (18.5%) corresponded to the literature, and the population was in HWE, although borderline significant ($P = 0.06$) [13].

The genotyping assay was validated by DNA sequencing, but the assay was unable to deal with the gene deletion (*5). *4/*5 were classified as *CYP2D6* *4/*4, which may have led to overestimation of *4/*4 individuals in HWE. This did not affect a subject's phenotype, because both *4/*4 and *4/*5 were classified as *CYP2D6* PM. However, some misclassification of PMs, IMs and ultrarapid metabolizers in the reference group (EM) might have occurred. These misclassifications, however, will lead to an underestimation of the association rather than an overestimation.

Potential confounding by age, gender, BMI, glomerular filtration rate, antidepressant dose and use of diuretics was dealt with in the multivariate analyses. Bijl et al. found an association between *CYP2D6* genotype and TCA maintenance dose [14]. In our study, antidepressant dose was not of any influence.

In conclusion, the data in this study show that among users of antidepressants, *CYP2D6* PMs have a lower serum sodium concentration than EMs.

Competing interests

None to declare.

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