CYP2D6 and CYP2C19 genotypes of patients with terodiline cardiotoxicity identified through the yellow card system

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Aims Terodiline has concentration dependent QT prolonging effects and thus the potential for cardiotoxicity. Pharmacogenetic variation in terodiline metabolism could be responsible for cardiotoxicity. We sought to determine whether CYP2D6 (debrisoquine hydroxylase) or CYP2C19 (S-mephenytoin hydroxylase) status is a risk factor for terodiline cardiotoxicity.

Methods Using the UK Yellow Card scheme to identify patients, blood samples were obtained from eight patients who survived ventricular tachycardia or torsades de pointes suspected to be due to terodiline, for determination of CYP2D6 and CYP2C19 genotypes. Genotype prevalence was compared with that in published general population groups.

Results One patient was a CYP2D6 poor metaboliser (*CYP2D6*4* homozygous) and a second was heterozygous for *CYP2D6*4,* a slightly lower frequency for these genotypes compared with the general population ($P=0.31$). In the case of CYP2C19, one patient was a poor metaboliser and four were heterozygous for the variant *CYP2C19*2* allele, compared with general population frequencies of 2% and 23%, respectively ($P=0.035$).

Conclusions These findings suggest that debrisoquine poor metaboliser status is not primarily responsible for terodiline cardiotoxicity. However, possession of the *CYP2C19*2* allele appears to contribute to adverse cardiac reactions to terodiline. The present study demonstrates the feasibility of using spontaneous adverse drug reaction reporting schemes to determine the contribution of genotype for metabolizing enzymes to uncommon adverse drug reactions.

Keywords: terodiline, CYP2D6, CYP2C19, pharmacovigilance

Introduction

Terodiline is an anticholinergic drug used to treat urinary incontinence due to detrusor instability. It has QT prolonging effects in man producing serious cardiac adverse drug reactions, notably ventricular tachycardia and torsades de pointes [1, 2]. This led to withdrawal of the drug from the market in 1991. We have previously demonstrated concentration-dependent QTc prolongation in patients receiving terodiline [3]. The metabolic pathways of elimination of terodiline in man remain uncertain. In particular, the P450 enzymes responsible for elimination of the drug have not been characterized. In the rat, the major pathways are aromatic *p*-hydroxylation and benzylic oxidation with participation of multiple cytochrome P450 enzymes [4]. In man, the main metabolites are *p*-hydroxyterodiline, *p*-hydroxy-*m*-methoxyterodiline and hydroxy-tertbutyl-*m*-methoxyterodiline [5]. In one study, the single poor metaboliser of debrisoquine from a group of eight healthy volunteers exhibited a three-fold decrease in clearance and increase in half-life of (+)–terodiline relative to the extensive metabolisers [6].

Given the close relationship between QT prolongation and terodiline plasma concentration, we hypothesized that pharmacogenetic variation in the terodiline metabolic

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**died 30 September 1998.*

Received 24 September 1999, accepted 19 April 2000.

pathway of hydroxylation, could be responsible or contribute to cardiotoxicity. To determine whether CYP2D6 or CYP2C19 genotype is a risk factor for terodiline cardiotoxicity, we determined genotypic status of patients with terodiline cardiotoxicity reported through the UK 'yellow card' spontaneous adverse drug reaction reporting system.

Methods

Subjects and protocol

Blood samples were sought from patients with suspected terodiline cardiotoxicity reported through the yellow card system. Twenty-eight patients with reported ventricular tachycardia or torsades de pointes were identified by the Medicines Control Agency (MCA). Reporting general practitioners were sent a letter in 1994 requesting they approach the patient for a blood sample. A patient identification sheet and consent form was sent to the general practitioner, along with an EDTA blood tube and padded stamped addressed envelope. Where the original report had been made by a hospital doctor, the name of the patient's general practitioner was requested. Samples, identifiable by a patient code number, were sent directly to the Department of Pharmacological Sciences at Newcastle. To preserve confidentiality, patient names and addresses were held by the MCA. Anonymised clinical details (patient age, sex and details of terodiline toxicity) were sent to the Newcastle investigators. Studies were approved by the Newcastle Joint Ethics Committee.

Genotyping for CYP2D6 and CYP2C19 polymorphisms

Leukocyte genomic DNA was prepared from 10 ml blood samples (7). Genotyping for the *CYP2D6*3* and *CYP2D6*4* alleles and *CYP2C19*2* and *CYP2C19*3* alleles was carried out by PCR as described previously [8–10].

Data analysis

Fisher's exact test was used to determine whether the incidence of alleles was significantly different from the general population.

Results

Blood samples were obtained from eight patients; six via the MCA and two through direct contact with the two hospital doctors who had published seven cases of terodiline induced cardiotoxicity, all known to the MCA. Of the 26 contacts made to general practitioners by the MCA, two patients were reported to have died (not reported to be due to terodiline), six patients were reported to be lost to follow up because they moved to another practice unknown to the original general practitioner. No reply was received from 12 GPs. The eight patients (6F) were aged 65–87 years. Six were reported to have experienced torsades de pointes and two ventricular tachycardia. It was not possible to obtain electrocardiographic confirmation of the dysrhythmia, and as for all 'yellow card' reports this was reliant on the accuracy of the reporting doctor. Details of concomitant medication were available in six patients. Possible drugs that could have contributed to QT prolongation and ventricular dysrhythmias were frusemide (through hypokalaemia, although the patient was also taking potassium supplements) and quinine (possible QT prolonging effects) in one patient, and indapamide in a further patient.

The genotype data is summarized in Table 1. The CYP2D6 genotype and allele frequencies were not significantly different to those previously reported with one subject homozygous for *CYP2D6*4* and one heterozygote. The two subjects taking concomittant medication that could have contributed to QT prolongation were both homozygous wild type. The combined frequency of the homozygous mutant and the heterozygote was therefore 25%, which was lower than the previous observed frequency of 45% reported for a large British control group, but not significantly different ($P = 0.31$ with the odds ratio of 0.40: 95% confdence interval 0.08–2.03) [11]. Screening for *CYP2D6*3* and **4* results in detection of at least 90% of CYP2D6 poor metabolisers [12]. In the case of CYP2C19, where *CYP2C19*2* is the predominant variant allele among Caucasians [13], one subject was homozygous mutant for *CYP2C19*2* with four others being heterozygous for this allele, resulting in 62.5% of the group being positive for at least one *CYP2C19*2* allele compared with 25% of a

Table 1 Genotype frequencies among patients showing terodiline cardiotoxicity compared with published control frequencies.

Polymorphism and genotype	*Terodiline cardiotoxicity*	*Control population*
CYP2D6		
	($n = 8$)	($n = 662$)*
Wt/wt	6 (0.75)	364 (0.55)
Mut/wt	1 (0.125)	267 (0.40)
Mut/Mut	1 (0.125)	31 (0.047)
CYP2C19		
	($n = 8$)	($n = 105$)
Wt/wt	3 (0.375)	79 (0.75)
Mut/wt	4 (0.50)	24 (0.23)
Mut/mut	1 (0.125)	2 (0.02)

* [12, **Reference 13.**

previously studied Caucasian group (13) ($P=0.035$ with an odds ratio of 5.1; 95% CI 1.1–22.7). Both subjects taking concomitant medication that could have contributed to QT prolongation were heterozygotes.

Discussion

The results of this study do not suggest that CYP2D6 poor metaboliser status is a major risk factor for terodiline cardiotoxicity, although given the limited number of samples we were able to obtain, a small contribution cannot be absolutely excluded. It is also possible that possession of a CYP2D6 gene duplication which leads to the 'ultrarapid metaboliser' phenotype, and was not screened for in this study, could be a risk factor because of high concentrations of a toxic metabolite that might be produced. However, two of the eight subjects were clearly not ultrarapid metabolisers, possessing one or two poor metaboliser alleles. Furthermore a study of QT interval prolongation in healthy volunteers has suggested that it was most likely to be parent drug related [14]. The increased incidence of patients homozygous or heterozygous for the *CYP2C19*2* allele is interesting, although the relevance is unclear. Further study is required to establish whether either of the terodiline enantiomers undergo metabolism by CYP2C19. Since the number of patients studied is small, the observed statistical significance should be treated with caution. Several studies of CYP2C19 phenotype-genotype relationships have reported that heterozygotes show on average slower metabolism than homozygous wild-type subjects, which would be consistent with the present findings [15]. It is unlikely that the heterozygotes were positive for other variant *CYP2C19* alleles as these are very rare [16]. In view of the fact that cardiotoxicity with terodiline appears to have been a relatively rare complication, it seems likely that low activity in metabolizing enzymes other than CYP2C19 and CYP2D6 may also be important.

A limitation of the study was the 3 to 4 years delay between reporting of cases to the Committee on Safety of Medicines and the request to general practitioners. In many instances, the patient had died or moved to another practice. If requests for blood samples were made to doctors with acknowledgement of receipt of a report, it is likely that response rates would be higher than in our study. The use of buccal brush samples could also be considered if venepuncture reduces patient participation. Another limitation is the lack of information on patient ethnicity which is not recorded on 'yellow cards'. Such information could be collected in future studies but this might reduce response rates from doctors and patients. Alternatively, data on ethnicity could be collected through spontaneous adverse drug reaction reporting mechanisms. Ideally sex-and age-matched controls from the same general practices should have been used as a control population. However, it is not feasible in a study using individual general practitioners across the UK to obtain blood samples from controls. In this context, the use of population study data is the most appropriate comparison. However, it is possible that bias from an unknown ethnicity mismatch may have occurred. Inevitably there is also a selection bias against more severe fatal adverse drug reactions. This would be expected to weaken the power of studies to detect pharmacogenetic contributions to adverse drug reactions. Of 1117 yellow cards received relating to terodiline, 31 had a fatal outcome of which 28 were cardiovascular disorders, including 12 reports of sudden death (Dr P. Waller, Medicines' Control Agency, personal communication).

We have demonstrated that it is feasible to use spontaneous adverse drug reaction reporting mechanisms such as the UK 'yellow card' system to obtain blood samples from patients with uncommon adverse drug reactions. For such reactions this provides a potential mechanism to study an adequate number of affected individuals. Patient anonymity and doctor confidentiality were preserved, consistent with the legislative framework that the Medicines Control Agency operates under. Given the delay in approach to general practitioners, a reasonable response rate was obtained. Were the system to be used prospectively, or shortly following the reporting of an adverse reaction, a much higher response rate might be expected, enabling greater sample sizes to be obtained. Consideration should be given by regulatory authorities and investigators to using the above method prospectively to investigate the contribution of genotype to uncommon adverse drug reactions.

We are grateful to Professor Sir Michael Rawlins, Wolfson Unit of Clinical Pharmacology, Newcastle upon Tyne for his contribution in facilitating the study. We thank Dr James McBlane, Dr John Price and Dr Patrick Waller of the Medicines Control Agency for assistance in the study. We thank Dr Martin Connolly and Dr Penny Astridge, University of Leeds, Dr Grahame Macphee, Southern General Hospital, Glasgow and the general practitioners who provided patient samples for this study.

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