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Omeprazole-induced acute interstitial nephritis is not related to CYP2C19 genotype or CYP2C19 phenotype

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Omeprazole-induced acute interstitial nephritis (OIAIN) is a rare adverse drug reaction. It is typically considered to be an idiosyncratic reaction affecting elderly patients. Omeprazole is a substrate for CYP2C19 and individuals who are homozygous variant for the null allele are poor metabolizers of this drug. These individuals have higher exposure to omeprazole. In the elderly metabolism of omeprazole is reported to be decreased despite a 'normal activity' genotype.

WHAT THIS PAPER ADDS

- The *CYP2C19* poor metabolizer genotype was not over represented in patients with OIAIN. However, almost a third of the patients appeared to have deficient CYP2C19 function.
- Metabolism of omeprazole may be compromised in the elderly and caution should be exercised when using this medication in this group of patients.

AIM

Omeprazole-induced acute interstitial nephritis (OIAIN) is a rare adverse event. It is unknown if this is an idiosyncratic immune mediated reaction or if it relates to direct drug toxicity. Individuals who are homozygous for the variant alleles of CYP2C19 are poor metabolizers of omeprazole and have a greater exposure to the drug. The aim of this study was to determine the prevalence of the CYP2C19 poor metabolizer genotype and phenotype in patients with OIAIN.

METHODS

Twenty patients were genotyped for the CYP2C19 variant alleles (*2, 681G>A and *3, 636G>A) by RFLP-PCR analysis and eighteen phenotyped for CYP2C19 metabolizer status.

RESULTS

The frequency of the CYP2C19*2 allelic variant was 12.5%, no *3 allelic variants were detected and no patient was a homozygous variant genotype. This was not different from the expected frequency. 33% of subjects were phenotypically CYP2C19 poor metabolizers.

CONCLUSIONS

There was discordance between CYP2C19 genotype and phenotype. However, up to 45% of healthy elderly subjects have a poor metabolizer phenotype. Thus neither CYP2C19 poor metabolizer genotype nor phenotype is a risk factor for OIAIN.

Introduction

The proton pump inhibitors (PPIs) are widely used and highly effective medications. Acute interstitial nephritis (AIN) is a rare but serious adverse reaction associated with the PPIs. In New Zealand, omeprazole, the most widely used PPI, was shown to be associated in AIN in older patients. Some individuals were exposed to the medication for up to 18 months prior to the onset of AIN and others developed AIN after a doubling in dose [1]. This raised the question of whether direct drug toxicity contributed to the development of interstitial inflammation.

Omeprazole undergoes hepatic clearance with CYP2C19 the major enzyme responsible [2]. CYP2C19 has two frequently inherited variant alleles, CYP2C19*2 and CYP2C19*3, which result in a loss of enzyme activity. Homozygous variant individuals are poor metabolizers (PM) of omeprazole [2]. Other factors influence the metabolic activity of CYP2C19. Co-morbidities such as liver disease or cancer alter the capacity of this enzyme, as do concurrent administration of drugs that are substrates for this enzyme. Another factor is advanced age, where omeprazole clearance is almost halved [3]. Thus the phenotype may be controlled by age, co-morbidities, other medications and CYP2C19 genotype.

The primary aim of this study was to determine the prevalence of CYP2C19 PM in a cohort of patients with OIAIN. Both the CYP2C19 genotype and functional activity were determined.

Methods

Subjects

This study was approved by the New Zealand Health and Disability Multi-Regional Ethics Committee. Patients with AIN attributed to PPI, from January 2000 to September 2008, were identified from the renal units in Auckland, Canterbury and Otago. Following informed written consent 20 subjects agreed to be participate.

Methodology

CYP2C19 activity status was determined using the probe drug proguanil (200 mg) [4]. The metabolic ratio was calculated from the plasma concentrations of proguanil and its metabolite cycloguanil by HPLC analysis of a 3 h blood sample. The assay had a lower limit of detection of 5 and 3 ng ml^{-1} and an inter- and intra- assay variability of <6% for proguanil and the metabolite cycloguanil, respectively. A proguanil : cycloguanil metabolic ratio of >10 corresponds to the PM phenotype [4].

DNA was extracted from whole blood using the PAXgene™ blood DNA kit (Qiagen, Hilden, Germany). Genotype was determined by PCR-RFLP analysis of CYP2C19*2 and CYP2C19*3 allelic variants as previously described [5].

In two patients (cases 5 and 13), who presented acutely the plasma concentrations of omeprazole and its 5′-hydroxy metabolite were determined using previously published methods [6]. The lower limits of detection were <10 ng ml^{-1} and inter- and intra- assay variability was <10%.

Clinical and laboratory data were extracted from the patients' medical records.

Expected genotype numbers were calculated using the Hardy–Weinberg equation. The chi-squared test was used to determine if the data were in agreement with the Hardy–Weinberg equilibrium. Predicted genotypes were compared with a reference population using the chi-square test, at a significance level of $\alpha = 0.05$ (two sided). Comparison of measured phenotype with genotype-predicted phenotype was assessed using Fisher's exact probability test at a significance level of $\alpha = 0.05$ (two sided).

Results

The demographics of the study population were typical of patients presenting with OIAIN. All subjects were Caucasian. The mean age of patients at presentation was 72.8 years (range 40–91 years) (Table 1).

The prevalence of the CYP2C19*2 allele was 12.5%, no CYP2C19*3 alleles were detected and no patients had a homozygous variant genotype. The distribution of the alleles was in agreement with the Hardy–Weinberg equilibrium and was not significantly different (chi-square = 2.27, 2 d.f., $P = 0.32$) from a reference population [7].

No omeprazole or metabolite were detectable in the two patients who presented acutely. Thus there was no evidence for prolonged exposure.

Case 18 had ongoing gastro-oesophageal reflux despite using H_2-receptor antagonists and restarted omeprazole. She was confirmed as a poor metabolizer of omeprazole (Table 1).

Seventeen patients were phenotyped for CYP2C19 activity using proguanil. Five patients had a metabolic ratio >10 indicative of a poor metabolizer status (Table 1).

The prevalence of phenotypic CYP2C19 poor metabolizers in patients was 33%, significantly higher than predicted by the CYP2C19 genotype ($P < 0.05$). This discordance between genotype-predicted and true phenotype occurred in both homozygous wild type and heterozygote carriers (Table 1).

Discussion

We did not observe an increased prevalence of the common variant CYP2C19 PM genotype. Individuals who are heterozygous carriers of CYP2C19*2 or *3 are intermediate metabolizers of omeprazole [2] and also do not

Table 1

Clinical characteristics and the CYP2C19 phenotype and genotype status of patients with omeprazole-induced acute interstitial nephritis

Case	Age (years)*	Gender	Baseline Cr† (μmol l^{-1})	Maximum Cr† (μmol l^{-1})	Current Cr† (μmol l^{-1})	Duration on PPI	Dose (mg)	Indication	CYP2C19 genotype	Metabolic ratio PG : CG‡	Actual metabolizer status
1	66	Female	69	290	138	4 months	10	GORD§	*1/*2	10.3	PM
2	73	Female	56	462	206	4 years	20	DU¶	*1/*1	1.3	EM
3	79	Female	99	375	174	2 months	20	GORD	*1/*1	0.8	EM
4	77	Female	68	156	93	12 weeks	40	On aspirin	*1/*1	15.2	PM
5	69	Female	87	338	109	4 months	20	Vomiting	*1/*1	1.1	EM
6	37	Female	70	570	110	19 months	20	Hiatus hernia	*1/*2	7.3	EM
7	81	Female	130	470	220	3 months	20	GORD	*1/*1	1.7	EM
8	62	Female	180	1400	250	1 week	20	Nausea	*1/*1	5.2	EM
9	78	Male	90	570	92	2 weeks	40	Dyspepsia	*1/*2	45.0	PM
10	79	Male	127	301	180	3 weeks	20	Gastritis	*1/*2	20.6	PM
11	56	Female	87	469	91	3 weeks	40	GORD	*1/*1	2.9	EM
12	65	Male	80	250	116	12 weeks	20	GORD	*1/*1	45.0	PM
13	91	Female	99	352	124	1 week	40	GORD	*1/*1	–	
14	78	Male	110	230	100	2 months	20	On aspirin	*1/*1	0.8	EM
15	76	Female	92	1010	100	8 months	20	Gastric ulcer	*1/*1	0.9	EM
16	77	Male	100	800	120	18 months	40	Hiatus hernia	*1/*1	1.0	EM
17	78	Female	110	260	159	14 months	20	On NSAIDs	*1/*2	–	
18	72	Female	86	124	90	40 months	40	GORD	*1/*1	HI>2**	PM
19	81	Male	114	564	136	18 months	40	Indigestion	*1/*1	1.6	EM
20	78	Female	78	585	138	8 years	20	GORD	*1/*1	2.0	EM

*Age at presentation with interstitial nephritis rounded down to the nearest year. †Cr: creatinine. ‡Proguanil : cycloguanil ratio in a 3 h post dose plasma sample. §GORD: Gastro-oesophageal reflux disease. ¶DU: Duodenal ulcer. **HI – hydroxylation index: log[omeprazole : 5′hydroxy omeprazole]. An omeprazole HI (log_{10} [omeprazole : 5′hydroxy omeprazole]) of <1 has been previously shown to correspond to an extensive metabolizer (EM) phenotype and an index >1 is a phenotypic poor metabolizer (PM). Patients 5 and 13 presented acutely, patient 5, when stable, was phenotyped with proguanil. Patient 13 declined to be phenotyped with proguanil. Patient 17 vomited after having the proguanil dose and hence was not phenotyped. Case 18 was retreated with omeprazole and a blood sample was obtained 2 h post dose (HI index >2; PM). All patients, except case 7, had biopsy proven AIN.

display increased prevalence. Recently, the CYP2C19*17 variant allele, associated with ultra-rapid metabolism and gain of function has been described [8]. Other rare allelic variants, associated with altered function exist (http://www.imm.ki.se/cypalleles/cyp2c19.htm). This study did not analyze these variants. Thus the role for CYP2C19 variant alleles is not entirely discounted and could be the target of future studies.

A third of the subjects, when tested retrospectively, had a PM phenotype. Compromised CYP2C19 activity results in prolonged and elevated concentrations of omeprazole. A retrospective test of phenotype may differ from the phenotype at the time of the adverse event, due to factors such as co-medications and liver disease which can result in CYP2C19 poor metabolizer 'phenocopies'. Patients' records were analyzed and no evidence for liver dysfunction or known medications that compromise CYP2C19 activity were identified.

A decreased CYP2C19 activity despite a 'normal activity' genotype has been observed previously in 45% of elderly wildtype patients [3] similar to the 33% incidence of CYP2C19 poor metabolizers observed our study. Thus the CYP2C19 poor metabolizer phenotype also is not a risk factor in omeprazole-induced AIN.

Some patients developed AIN only after an increase in the dose. Omeprazole has non-linear pharmacokinetics and a high dose (60 mg) in genotypic extensive metabolizers results in elevated plasma concentrations that mimic the concentrations observed in *CYP2C19* deficient subjects on a 40 mg dose [2, 9]. Elevated concentrations of omeprazole may predispose to AIN and could result in direct toxicity to the kidney via inhibition of the renal H^+K^+ATPase [10]. Alternatively, higher plasma concentrations of the drug may increase the chance of a hapten being presented to T lymphocytes resulting in an idiosyncratic immune mediated response.

Our primary hypothesis was that poor metabolizer genotype or phenotype may be an explanation for omeprazole-induced AIN. However, our data do not support this explanation. Nevertheless caution should be exercised in using omeprazole in the elderly.

Competing interests

This work was supported through a grant from the Department of Medicine, Faculty of Medical and Health Sciences, The University of Auckland. This manuscript is an original contribution previously unpublished (except as an abstract), and is not under consideration for publication elsewhere. The authors have participated in the study, in the writing of the paper and agree with submission of the paper for publication. There are no conflicts of interest to disclose.

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