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European Journal of Pharmacology 445 (2002) 151–152

www.elsevier.com/locate/ejphar

Rapid communication

Variants of the CYP11B2 gene predict response to therapy with candesartan

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Received 1 May 2002; accepted 6 May 2002

Abstract

In a prospective trial, patients with an elevated diastolic blood pressure (above 95 mm Hg) received high-dose (16 mg) or low-dose (8 mg) candesartan in addition to standardised medication. A positive response to treatment was defined as a diastolic blood pressure <85 mm Hg at follow-up. Genotyping for two candidate genes was performed in 116 patients. Genotypes of the CYP11B2 promotor polymorphism significantly predicted a positive response to treatment (CC: 67%; TC: 34%; TT: 21%; $p=0.005$).

Keywords: Angiotensin-converting enzyme; CYP11B2; Pharmacogenetic

The renin–angiotensin–aldosterone system has been implicated in the modulation of blood pressure. Genetic variation in the genes encoding products of the renin–angiotensin–aldosterone system has the potential to influence the therapeutic responsiveness to angiotensin II type 1 receptor antagonists. The influences of genetic variation in the angiotensin-converting enzyme (DCP1) gene and AGTR1 gene on pharmacological therapy with angiotensin AT_1 receptor antagonists and β-adrenoceptor antagonist have been demonstrated earlier (McNamara et al., 2001; Kurland et al., 2001). Among well-described polymorphisms of the genes encoding products of the renin–angiotensin–aldosterone system, the angiotensin-converting enzyme (DCP1) I/D polymorphism is associated with an elevated gene product and arterial hypertension (Tiret et al., 1992), whereas the −344 T/C polymorphism of the CYP11B2 gene is associated with altered aldosterone levels (Brand et al., 1998). Of patients participating in a large prospective phase III trial (candesartan in patients with severe arterial hypertension, $n=627$), 116 gave their written informed consent for genetic diagnostics and formed the study population. In this prospective study, patients with a diastolic blood pressure above 95 mm Hg despite pre-treatment were included. In a first study phase, patients received standardised medication (12.5 mg hydrochlorthiazide plus 50 mg metroprolol if pre-treated with a β-adrenoceptor antagonist, 12.5 mg hydrochlorthiazide plus 5 mg amlodipine if pre-treated with a Ca^{2+}-channel blocker, 12.5 mg hydrochlorthiazid plus 5 mg ramipril if pre-treated with an angiotensin-converting enzyme inhibitor) for 2 weeks. Blood pressure was measured (pre-treatment blood pressure). Patients were randomised to study medication arms: 58 patients received 8 mg candesartan plus their standardised medication (12.5 mg hydrochlorthiazide plus 50 mg metroprolol or 5 mg amlodipine or 5 mg ramipril) and 56 patients received 16 mg candesartan plus 12.5 mg hydrochlothiazide. Two patients were lost to follow up. After 4 weeks of treatment with candesartan, the diastolic blood pressure was re-measured. In the study protocol, a positive response to therapy was defined as a diastolic blood pressure below 85 mm Hg. From all 116 patients genomic DNA was available. Analysis was performed for the I/D polymorphism of the angiotensin-converting enzyme gene, and for the −344 T/C polymorphism within the promotor region of the CYP11B2 gene (aldosterone synthase) (Tiret et

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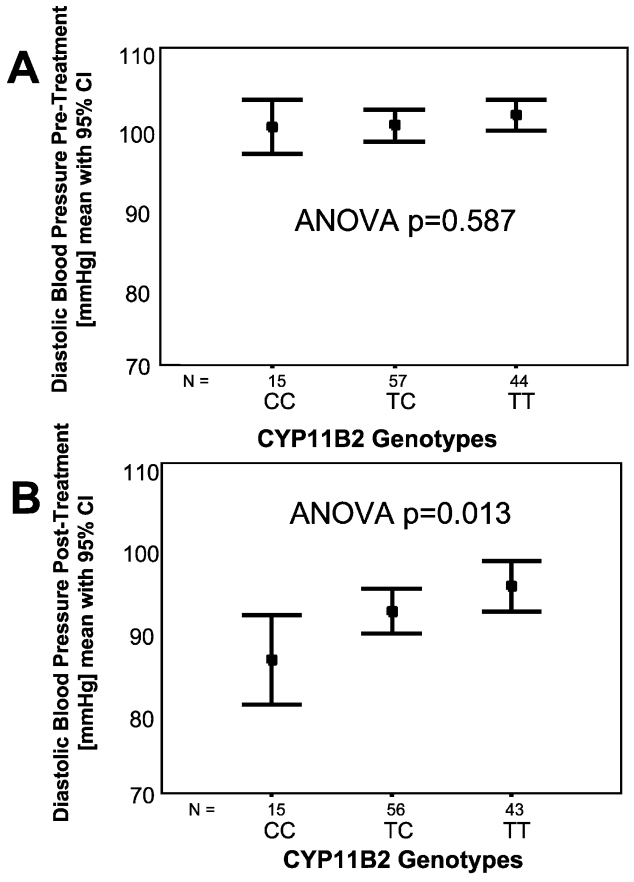
0014-2999/02/$ - see front matter
PII: S0014-2999(02)01766-1



C

CYP11B2	CC	TC	TT
N	15	56	43
Responder	67%	34%	21%
Nonresponder	33%	65%	81%

CHISQUARE p=0.005

Fig. 1. Relation of the genotype of the CYP11B2 gene with diastolic blood pressure before treatment (A) and after treatment with candesartan (B). The difference in the response rate to candesartan therapy is expressed in cross tables (C).

al., 1992; Brand et al., 1998; Hautanena et al., 1998). The study was approved by the ethics committee.

The mean age of included patients was 56 ± 11 years, with a mean body mass index of 28.4 ± 4.1 kg/m^2; 59% of the patients were men. Of the 116 patients, two were lost to follow up and 114 were included in the final analysis. Of the 114 patients 38 (33%) were responders to therapy. There was no difference between the two candesartan dosages (19 out of 58 responders vs. 19 out of 56 responders; $p = 0.53$). The candesartan dosages were statistically not different between the ACE and CYP11B2 genotypes. The genotype frequencies were not different from the Hardy–Weinberg equilibrium (ACE: DD = 30; ID = 66; II = 20/CYP11B2: CC = 15; TC = 57; TT = 44). Homozygosity for the C allele of the CYP11B2 gene was significantly associated with a better response to therapy (Fig. 1). Correspondingly, the diastolic blood pressure after treatment was significantly different: CYP11B2 CC 86 ± 10 mm Hg, TC 93 ± 10 mm Hg, TT 95 ± 10 mm Hg, $p = 0.017$. For the angiotensin-converting enzyme genotype, there was a trend toward higher response rates in patients with the D allele (ACE 13/29 DD (45%); 22/66 ID (33%); 3/19 II (16%); $p = 0.113$).

In a prospective phase III trial with the angiotensin AT_1 receptor antagonist candesartan the genotype of the aldosterone synthase gene (CYP11B2) predicted the response to therapy. We conclude that genetically determined differences in genes encoding proteins downstream of the AT_1 receptor-like CYP11B2 (Brand et al., 1998; Hautanena et al., 1998) are responsible for the different response of individuals to therapy. We are aware that this study has limitations. Because of the relatively small sample size, it is essential that the results are duplicated in larger studies. However, the data highlight the potential of individualised therapy based on genetic data. Such an approach has the potential to reduce the numbers needed to treat and therefore will hopefully reduce the harmful effects of pharmacological treatment. Pharmacological trials should not be initiated without considering pharmacogenetic analysis.

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