The influence of CYP2D6 phenotype on the clinical response of nebivolol in patients with essential hypertension

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What is already known about this subject

- The variability in drug metabolism has been recognized as an important factor in the occurrence of adverse effects or lack of therapeutic efficacy.
- The metabolism of the third-generation β_1 -receptor antagonist nebivolol has been shown to be highly dependent on cytochrome P450 2D6 enzymatic activity in preclinical studies.

What this study adds

- This paper assesses the role of a cytochrome P450 2D6 gene defect on the antihypertensive response to nebivolol in a clinical setting.
- Despite significant differences in drug disposition, the chronic administration of nebivolol produced similar efficacy and tolerability in hypertensive patients either characterized as poor or extensive metabolizers of the drug.
- The study offers insight into the relative contribution of nebivolol enantiomers in systemic blood pressure control.

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Aims

Nebivolol is a β_1 -adrenergic receptor antagonist with vasodilating properties used in the treatment of hypertension. It is administered as a racemic mixture (D- and L-nebivolol) and is highly metabolized by the cytochrome P-450 2D6 (CYP2D6). The purpose of this study was to determine the role of CYP2D6 phenotypes on the efficacy and tolerability of nebivolol during chronic administration to patients with essential hypertension.

Methods

Two hundred and eighteen patients were genotyped and phenotyped for CYP2D6 activity, allowing to find and match 14 poor metabolizers (PMs) with 23 extensive metabolizers (EMs). Patients took rac-nebivolol 5 mg daily for 12 weeks. Blood pressure (BP), heart rate, adverse events, plasma levels of the two enantiomers D- and L-nebivolol and their corresponding hydroxymetabolites were assessed.

Results

The metabolic disposition of nebivolol was enantioselective and highly influenced by CYP2D6 phenotypes. Mean steady-state plasma concentrations of D- and L-nebivolol were 10- and 15-fold greater in PMs than in EMs, respectively ($P < 0.0001$). Despite these differences in the pharmacokinetics of nebivolol, EMs and PMs displayed similar BP responses. Mean reductions in sitting systolic and diastolic BPs were $-11/-10 \pm 9/4$ mmHg in EMs and $-11/-9 \pm 10/5$ mmHg in PMs. Side-effects were mild to moderate and not different between groups.

Conclusion

Polymorphisms in the gene encoding CYP2D6 significantly influenced the metabolism of nebivolol, but not its antihypertensive efficacy and tolerability. The similar clinical response between EMs and PMs could be explained by the contribution of active hydroxylated metabolites of nebivolol to its antihypertensive actions in EMs.

Introduction

Nebivolol is a selective β_1 -adrenoreceptor antagonist approved for the treatment of essential hypertension [1]. It is clinically administered as a racemic mixture of D- and L-nebivolol. Although the β -blocking activity has been attributed mainly to D-nebivolol, there is evidence to suggest that part of the drug efficacy results from the action of the L-enantiomer in a vasodilatory non- β_1 -adrenergic pathway. Indeed, both animal and human studies have demonstrated that nebivolol as the racemate induced arterial relaxation through the release of endothelium-derived nitric oxide in a dose-dependent manner [2, 3]. Additionally, experiments in spontaneous hypertensive rats have shown that the blood pressure (BP) reduction was acute and immediate following peritoneal administration of racemic nebivolol but not of D-nebivolol [4]. Although biochemical mechanisms whereby nebivolol evokes vasodilation are to be fully elucidated, the drug appears to be distinct from other β -adrenergic antagonists with a similar property such as carvedilol (α_1 -antagonism; antioxidant) and bucindolol (α_1 -antagonism) [5]. The extent to which the antihypertensive effect of nebivolol is mediated by vasodilation remains to be clarified in the clinical setting [6, 7].

In a previous study conducted in patients with essential hypertension, we compared the 24-h ambulatory BP-lowering effect of racemic nebivolol with that of D-nebivolol [8]. The analysis of BP patterns indicated that a similar antihypertensive response was induced by the two treatments, thus failing to confirm experiments in spontaneously hypertensive rats. However, our study design did not eliminate the possibility that vasodilation can account for an additional BP-lowering effect when there is a relatively high concentration of the L-enantiomer in circulation. Nebivolol is extensively metabolized in the liver through CYP2D6-dependent aromatic hydroxylation [9]. Polymorphic variants of CYP2D6 responsible for the poor metabolizer (PM) phenotype markedly alter the metabolic disposition of the drug compared with the normal enzymatic activity found in extensive metabolizer (EM) patients. Indeed, the absolute bioavailability of a single 5-mg dose of racemic nebivolol administered to a group of healthy young men was reported to rise from 12% in EMs to 96% in PMs [10]. Since the enantiomers of nebivolol show differences in pharmacological activity, the therapeutic outcome can be different in individuals who exhibit a large variability in drug metabolism. The aim of the present study was to evaluate the clinical implication of CYP2D6 phenotype on the efficacy and tolerability of nebivolol during chronic administration to patients with essential hypertension.

Methods

Study population

Study subjects were recruited at the Hypertension Research Unit, Laval University Medical Research Center, Québec, Canada. Outpatients with uncomplicated essential hypertension as confirmed by a sitting diastolic BP ≥ 90 and ≤ 114 mmHg or a sitting systolic BP ≥ 140 and ≤ 180 mmHg on three different occasions over a 3-month period were eligible for the study. All patients had normal cardiac, respiratory, hepatic and renal function. Women of childbearing potential without an effective method of birth control and patients having any contraindication for the administration of a β -blocker were excluded. Concomitant administration of drugs affecting BP or substrates of CYP2D6 was not allowed.

At screening, CYP2D6 phenotype was determined in 218 consecutive eligible subjects following informed consent. PM status was found in 15 individuals. Except for one subject who withdrew consent prior to inclusion in the placebo phase, all of the PMs participated in the study. Twenty-three CYP2D6 EMs were recruited as controls. EMs were selected for the study if they matched with PMs with respect to gender, weight ($\pm 10\%$) and age (± 5 years). Selection was made by an independent party located at the hospital pharmacy department where patients' demographic data and CYP2D6 phenotype results were centralized. Because the PM phenotype was expected to be infrequent in the population [11], 1.5 times as many EMs as PMs were enrolled in the study. Thus, half of the PMs were randomly assigned to match with two EMs. Patients and investigators were informed of CYP2D6 phenotype results after study completion only. The study was approved by the Ethics Review Board of Laval University Medical Research Center.

Study protocol and clinical assessments

This was a prospective, open-label study. Participants underwent a single-blind placebo run-in period for 4 weeks followed by a 12-week open treatment period with nebivolol 5 mg (Janssen-Ortho, Toronto, ON, Canada) given once daily in the morning.

Clinic BP readings were obtained after a 15-min rest period using a standard mercury sphygmomanometer with cuff size to fit the patient's arm. Systolic BP was noted when the first Korotkoff (Phase I) sound was heard, and diastolic BP at the point of disappearance of the fifth Korotkoff (Phase V) sound. Each measurement represented the average of three readings taken 2 min apart in the sitting position. BP and heart rate measurements were obtained between 07.00 h and 10.00 h in the

morning immediately before the dose intake (trough), every 2 weeks during the placebo run-in period and at weeks 0 (baseline), 2, 4, 8 and 12 of the active treatment period. Evaluations were also performed 3 h postdose (peak) at weeks 0, 4 and 12.

Drug tolerability was monitored at each visit by the recording of patients' spontaneous complaints and by direct questioning about side-effects [12]. All adverse events were evaluated qualitatively and quantitatively [13]. Special attention was paid to symptoms associated with a decrement in BP, such as dizziness, vertigo, light-headedness, visual disturbance and general weakness. Physical examination, electrocardiogram, biochemical and haematological laboratory tests and the presence of orthostatic hypotension were also assessed at weeks 0, 4 and 12.

CYP2D6 phenotyping and genotyping

All subjects eligible for the study were both phenotyped and genotyped for CYP2D6. Phenotyping was performed based on a method previously reported by Chen *et al.* using dextromethorphan as a probe drug [14]. The oxidative capacity of CYP2D6 was expressed as the metabolic ratio of urinary unchanged dextromethorphan to dextrophan. Patients were categorized as PM for CYP2D6 when the metabolic ratio was ≥ 0.3 .

CYP2D6 genotyping allowed for unequivocal confirmation of PMs. CYP2D6 alleles were determined from genomic DNA isolated from leucocytes using a long distance and multiplex polymerase chain reaction (PCR) [15]. The method consists of the amplification of a 4666-bp fragment containing the entire CYP2D6 gene. The fragment serves as a template for a multiplex allele-specific PCR assay to identify simultaneously five non-functional CYP2D6 alleles: *3, *4, *6, *7 and *8. The CYP2D6*5 allele with deletion of the entire CYP2D6 gene was detected in a separate PCR assay [16]. All samples were further analysed by long-PCR for duplicated CYP2D6 gene. Alleles were classified as CYP2D6*1 alleles when they were not CYP2D6*3, *4, *5, *6, *7 or *8.

Drug assays

Plasma samples for the determination of D- and L-nebivolol and their corresponding hydroxylated metabolites were drawn from an antecubital vein 24 h postdose (trough) and 3 h after drug intake (peak) at baseline and after 4 and 12 weeks of treatment. Blood samples were collected in heparinized tubes and centrifuged for 15 min at 1300 g. Plasma was aspirated and immediately stored in plastic tube at -20°C for 30 days. Plasma concentrations of the unchanged

D-nebivolol and L-nebivolol were determined by extraction and stereospecific radioimmunoassay (RIA) [17]. The cross-reactivity between both isomers has been evaluated to be $<2.0\%$ [18]. The concentrations of each enantiomer plus its corresponding hydroxylated metabolite were measured by RIA without extraction. The enantioselective antibodies cross-react with aromatic and alicyclic hydroxylated metabolites of D-nebivolol that have an *in vitro* β_1 -adrenergic receptor binding affinity comparable to D-nebivolol [9]. The detection limit of the RIA procedure was 0.1 ng ml^{-1} [18].

Statistical analysis

The primary efficacy parameter was the change in trough diastolic BP from baseline to end-point. Changes in trough systolic BP, peak systolic and diastolic BP and heart rate were also analysed. Within-group comparisons to detect changes from baseline were made using a paired two-sided Student's *t*-test or Wilcoxon signed rank test in the case of non-normality. Between-group comparisons of continuous data were performed using analysis of variance (ANOVA) with CYP2D6 metabolizer group as a factor in the model. Fisher's exact test was used to compare the proportion of adverse events. A *P*-value of ≤ 0.05 was considered to be statistically significant. With 35 patients completing the study, there was a 85% chance to detect as clinically and statistically significant a 4-mmHg difference between EMs and PMs in the mean diastolic BP change from baseline, with an assumed standard deviation of 6 mmHg at the two-sided 5% level. To cope with potential drop-outs, three additional patients (one PM and two EMs) were enrolled. Statistical analysis was performed using SPSS for Windows Release 11.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as means $\pm$ SD unless otherwise specified.

Results

Table 1 shows the baseline characteristics of the 37 patients studied. There were no differences in age, gender, body weight, serum creatinine levels, sitting systolic and diastolic BP or heart rate between the two metabolizer groups. The genotyping was found to predict the phenotypic status in all subjects.

Blood pressure and heart rate

Effects of nebivolol on BP and heart rate at trough are presented in Figure 1. Changes from baseline values are displayed in Table 2. In both EMs and PMs, the drug significantly reduced the BP throughout the active treatment period. Comparison of the changes in systolic and diastolic BP at any time point of the active treatment

Table 1

Demographic and baseline characteristics of hypertensive patients characterized as extensive (EMs) and poor (PMs) metabolizers of CYP2D6 (means $\pm$ SD)

	EMs, <i>n</i> = 23	PMs, <i>n</i> = 14
Age, years (range)	56.2 $\pm$ 7.6 (45–64)	54.6 $\pm$ 8.3 (36–70)
Sex, male/female	12/11	8/6
Body weight, kg	79.1 $\pm$ 13.8	82.1 $\pm$ 13.6
Dextromethorphan to dextrorphan ratio	0.0020–0.1818	0.3333–6.6667
Genotype frequencies	13 CYP2D6*1/*4 9 CYP2D6*1/*1 1 CYP2D6*1/*5	5 CYP2D6*4/*4 3 CYP2D6*4/*3 3 CYP2D6*4/*5 2 CYP2D6*5/*5 1 CYP2D6*4/*6
Serum creatinine, $\mu\text{mol l}^{-1}$	79.4 $\pm$ 14.1	76.9 $\pm$ 15.8
Sitting systolic BP, mmHg	157.7 $\pm$ 16.6	154.8 $\pm$ 17.4
Sitting diastolic BP, mmHg	101.3 $\pm$ 5.1	103.3 $\pm$ 4.2
Sitting heart rate, beats min $^{-1}$	71.7 $\pm$ 6.6	70.6 $\pm$ 5.6

BP, Blood pressure.

Figure 1

Trough (24-h postdose) sitting systolic (top of bars) and diastolic (bottom of bars) blood pressure and heart rate (lines) during 12 weeks of treatment with racemic nebivolol in hypertensive patients characterized as either extensive (EMs; ■) or poor (PMs; □) metabolizers of CYP2D6. Means $\pm$ SEM. * P < 0.05; ** P < 0.01; *** P < 0.0001 vs. baseline; † P < 0.05 EMs vs. PMs

period indicated that the BP response was similar between the two study groups. At the end of the 12-week treatment, mean decreases in trough BP were -10.8 ± 9.3 mmHg in EMs and -10.5 ± 10.3 mmHg in

PMs for systolic BP and -10.2 ± 4.0 mmHg in EMs and -9.3 ± 5.2 mmHg in PMs for diastolic BP. There was no difference among groups with respect to the proportion of treatment responders, as defined by a decrease in sitting diastolic BP of at least 10 mmHg from baseline or a decrease of ≤ 90 mmHg (57% in EMs vs. 70% in PMs; $P = 0.47$). With respect to the effect measured 3 h postdose, nebivolol induced similar BP changes in both groups. At 12 weeks, systolic/diastolic BP reductions were $-7.8 \pm 7.9/-6.2 \pm 6.6$ mmHg in EMs and $-9.3 \pm 9.0/-8.0 \pm 5.1$ mmHg in PMs.

There was a trend for smaller heart rate reductions in PMs during the study (Table 2). At 12 weeks, the heart rate at trough decreased 9.2 ± 6.5 beats min $^{-1}$ in EMs and 5.0 ± 4.6 beats min $^{-1}$ in PMs [difference of 4.2 beats min $^{-1}$ between EMs and PMs; 95% confidence interval (CI) 0.2, 8.2; $P < 0.05$]. At peak, the decrease was 5.1 ± 6.1 beats min $^{-1}$ in EMs compared with 1.6 ± 6.1 beats min $^{-1}$ in PMs (difference of 3.4 beats min $^{-1}$ between EMs and PMs; 95% CI -0.8 , 7.7; $P = 0.099$).

Nebivolol plasma concentrations

Table 3 summarizes mean plasma concentrations of unchanged D- and L-nebivolol, plus their corresponding hydroxylated metabolites, after acute dosing and during chronic administration of the racemate. Data indicate that the metabolic disposition of nebivolol varies considerably due to CYP2D6 capacity. Whereas EMs were able to transform most of the drug into hydroxylated

Table 2

Changes from baseline in blood pressure (BP) and heart rate in extensive (EMs) and poor (PMs) metabolizers of CYP2D6 treated with nebivolol 5 mg (means; 95% CI)

	Week	EMs	PMs	P (EMs vs. PMs)
<i>Trough effect</i>				
Systolic BP (mmHg)	2	-9.9 (-15.9, -3.8)**	-11.6 (-18.9, -3.0)*	0.736
	4	-11.7 (-15.5, -8.0)***	-11.0 (-18.8, -3.2)*	0.840
	8	-13.3 (-17.2, -9.4)***	-10.7 (-17.6, -5.9)**	0.520
	12	-10.8 (-14.1, -7.0)***	-10.5 (-18.1, -6.8)**	0.931
Diastolic BP (mmHg)	2	-9.6 (-12.2, -7.0)***	-8.4 (-12.1, -4.8)***	0.578
	4	-10.3 (-11.9, -8.7)***	-9.1 (-11.1, -5.6)***	0.333
	8	-11.8 (-13.6, -10.0)***	-10.8 (-14.1, -7.6)***	0.555
	12	-10.2 (-11.9, -8.5)***	-9.3 (-6.3, -12.3)***	0.542
Heart rate (beats min ⁻¹)	2	-7.3 (-9.5, -5.1)***	-2.1 (-6.6, 2.4)	0.019
	4	-8.9 (-12.9, -5.5)***	-5.7 (-8.3, -3.2)***	0.180
	8	-9.0 (-11.9, -6.2)***	-5.8 (-9.3, -2.3)**	0.149
	12	-9.2 (-12.0, -6.7)***	-5.0 (-7.4, -2.3)***	0.041
<i>Peak effect</i>				
Systolic BP (mmHg)	4	-9.1 (-13.9, -4.3)***	-8.4 (-12.8, -4.8)***	0.848
	12	-7.8 (-12.9, -4.8)***	-9.3 (-14.8, -5.9)***	0.707
Diastolic BP (mmHg)	4	-6.2 (-9.1, -2.5)**	-6.2 (-9.3, -3.2)**	0.999
	12	-6.2 (-8.9, -3.5)***	-8.0 (-11.0, -5.0)***	0.374
Heart rate (beats min ⁻¹)	4	-7.6 (-12.3, -2.9)*	-2.4 (-6.7, 1.9)	0.121
	12	-5.1 (-8.1, -2.0)**	-1.6 (-4.1, 1.7)	0.099

*P < 0.05; **P < 0.01; ***P < 0.0001 from baseline.

Table 3

Peak and trough plasma concentrations of unchanged D- and L-nebivolol, alone plus their corresponding hydroxylated metabolites, after a first dose of racemic nebivolol 5 mg and following 4 and 12 weeks of daily administration to hypertensive patients either characterized as poor (PMs) or extensive (EMs) metabolizers of CYP2D6

	Plasma concentrations, ng ml ⁻¹ means (±SD)					
	EMs	PMs	P	EMs	PMs	P
<i>First dose</i>						
D-nebivolol	0.57 (0.39)	1.97 (0.75)	<0.0001			
L-nebivolol	0.48 (0.30)	1.76 (0.77)	<0.0001			
D-nebivolol + hydroxylated D-nebivolol	7.48 (4.29)	4.91 (2.30)	NS			
L-nebivolol + hydroxylated L-nebivolol	11.59 (4.31)	3.38 (2.65)	<0.0001			
<i>Week 4</i>						
D-nebivolol	0.74 (0.62)	3.76 (1.76)	<0.0001	0.19 (0.20)	1.87 (1.31)	<0.0001
L-nebivolol	0.66 (0.58)	10.16 (4.56)	<0.0001	0.64 (0.45)	6.49 (3.71)	<0.0001
D-nebivolol + hydroxylated D-nebivolol	10.63 (3.30)	8.86 (3.07)	NS	2.52 (2.61)	3.79 (2.39)	NS
L-nebivolol + hydroxylated L-nebivolol	18.49 (5.94)	19.81 (6.43)	NS	3.17 (2.61)	12.16 (5.05)	<0.0001
<i>Week 12</i>						
D-nebivolol	0.85 (0.73)	4.17 (1.52)	<0.0001	0.18 (0.20)	1.92 (1.16)	<0.0001
L-nebivolol	0.67 (0.77)	10.92 (4.27)	<0.0001	0.40 (0.29)	9.03 (4.15)	<0.0001
D-nebivolol + hydroxylated D-nebivolol	11.91 (5.12)	8.96 (4.52)	NS	2.60 (2.40)	4.12 (3.41)	NS
L-nebivolol + hydroxylated L-nebivolol	19.74 (5.68)	22.02 (6.85)	NS	3.28 (2.56)	13.99 (6.30)	<0.0001

Table 4

Symptoms and adverse effects reported by extensive (EMs) and poor (PMs) metabolizers during 12 weeks' treatment with racemic nebivolol 5 mg

	EMs (n = 23) n (%)	PMs (n = 14) n (%)
Heart rate and rhythm disorders		
Bradycardia	2 (8%)	0
Circulation		
Peripheral oedema	1 (4%)	1 (7%)
Respiratory system		
Cough	2 (8%)	1 (7%)
Dyspnea	1 (4%)	1 (7%)
Sinusitis	0	2 (15%)
Upper tract infection	4 (16%)	0
Gastrointestinal system		
Dyspepsia	0	1 (7%)
Nausea	1 (4%)	1 (7%)
Urinary system		
Cystitis	0	1 (7%)
Musculoskeletal system		
Back pain	3 (13%)	1 (7%)
Leg pain	1 (4%)	1 (7%)
Nervous system		
Dizziness	1 (4%)	1 (7%)
Headache	2 (8%)	3 (21%)
Hyperkinesia	0	1 (7%)
Hypoaesthesia	1 (4%)	1 (7%)
General weakness	2 (8%)	0
Head/eyes		
External otitis	0	1 (7%)

metabolites, PMs presented high plasma concentrations of the unchanged drug at any time point of the treatment period. Metabolic ratios of the total hydroxylated metabolites/parent nebivolol concentrations in EMs were 14- and 21-fold higher than those of PMs at trough (9.8 in EMs vs. 0.70 in PMs) and at peak (23.2 in EMs vs. 1.12 in PMs), respectively. Average steady-state plasma concentrations of D- and L-nebivolol at trough were about 10- and 15-fold higher in PMs than in EMs, respectively (all $P < 0.0001$ between groups). Analyses performed on the summed plasma concentrations of the unchanged enantiomers plus their respective metabolites at trough showed no difference between groups with respect to D-nebivolol but a fourfold higher concentration of L-nebivolol derivatives in PMs after either 4 or 12 weeks of treatment ($P < 0.0001$ compared with EMs).

Adverse events

Table 4 displays adverse reactions and symptoms that occurred during therapy with nebivolol. A total of 21

events were experienced by the EMs vs. 17 events by the PMs. All events were of mild to moderate intensity and not clinically different between groups. Two EMs but no PM developed asymptomatic bradycardia (<55 beats min^{-1}) during the active treatment period. The events were considered as very likely to be related to nebivolol as they resolved when nebivolol was discontinued. The two patients completed the study with no change in therapy. With respect to haematology and clinical chemistry, no significant abnormality was observed in any metabolizer group. None of the participants experienced symptoms or signs of orthostatic hypotension.

Discussion

In the present study, the chronic administration of a standard 5-mg dose of nebivolol reduced significantly the BP of hypertensive subjects characterized either as poor or extensive metabolizers for CYP2D6. Despite major differences in drug disposition, the BP response was similar between the two groups of patients, in the order of 10 mmHg for both systolic and diastolic BP. Patient tolerability in terms of the nature and frequency of side-effects was not influenced by the CYP2D6 phenotype. None of the study subjects experienced a severe adverse event in relation to the drug therapy. Results reported herein are comparable to previous data published on the antihypertensive effect of nebivolol in a general population of White origin [19, 20]. Our study indicates that the use of nebivolol in hypertensive patients with a genetically impaired CYP2D6 metabolism appears to be as safe and efficacious as in those with a normal metabolic capacity.

A defective CYP2D6 capacity has been reported to alter markedly the metabolic disposition of nebivolol in healthy male volunteers [10]. We hypothesized that hypertensive patients with a lack of CYP2D6 activity might present a pronounced BP response to nebivolol due to elevated concentrations of the parent drug in circulation. Although the effects of β -blockers are merely correlated with plasma concentrations, drug accumulation arising from CYP2D6 phenotype can significantly impact on the efficacy and tolerability of these drugs [21]. In addition, β -blockers that decrease peripheral resistance, such as carvedilol, have been associated with frequent orthostatic symptoms due to prominent vasodilation [22]. The vasodilatory action of nebivolol has been demonstrated in various settings, including isolated blood vessels of treated animals [2, 23, 24] and human forearm vasculature after either direct infusion [3, 25, 26] or oral administration [27, 28]. This vasodilatory effect has been attributed mainly to the presence of the L-enantiomer in the racemate [2] and described as

being dose dependent [3, 24]. In the present study, hypertensive patients with the PM phenotype had plasma levels of L-nebivolol up to 15-fold higher than those of EMs. Such an excess in plasma was associated neither with an acute or pronounced fall in blood pressure nor with particular toxicity over 12 weeks of treatment.

β -Blockade appears to be the predominant mechanism of action by which racemic nebivolol reduces BP, irrespective of the patient's CYP2D6 capacity. The β -blocking activity of nebivolol, which has been ascribed mainly to the D-enantiomer, was found equipotent between the parent drug and the metabolite [10]. In individuals with a genetic CYP2D6 defect, the accumulation of the parent drug in plasma is likely to compensate for the low formation of active hydroxylated metabolites.

The conduct of the study in individuals having or not an impaired CYP2D6 capacity helped to characterize further the ancillary properties of nebivolol in hypertension. Thus, we could determine the clinical consequences of (i) a substantial increase in drug bioavailability and (ii) the relative accumulation of the vasodilatory L-enantiomer to occur from stereoselective metabolism. All of the study patients equally received nebivolol 5 mg once daily, the recommended dosage beyond which monotherapy offers little benefit in terms of BP control [19]. The drug was given over a 12-week period to take into account the potential variability in the bioavailability and haemodynamic effects reported with β -blockers during prolonged administration [29]. Since normotensive individuals may respond differently to β -blockade [30], only patients with uncomplicated essential hypertension were included in the study. To minimize the heterogeneity of the study population, patients were matched for age, gender and body weight. Metabolic status was ascertained both genotypically and phenotypically. Of interest, a similar degree of BP control was achieved in the two study groups with less β -blockade in PMs. Indeed, heart rate reductions were smaller in PMs than in EMs, and consistent with the fact that two EMs but no PMs experienced bradycardia during the study. Such a difference in cardiac effects between PMs and EMs is intriguing, as PMs were expected to carry the extensive risk associated with the treatment. A possible explanation for this finding is that the negative chronotropic effect of the D-enantiomer in PMs was attenuated by an enhanced adrenergic counter-regulation against the vasodilatory properties of the L-enantiomer. Additional investigations are warranted to assess more specifically the contribution of the L- and D-enantiomers to the haemodynamic effects of nebivolol.

In conclusion, the results of the present study indicate that the antihypertensive effects of nebivolol are not importantly influenced by the significant variability in pharmacokinetics between PMs and EMs. A standard 5-mg dose regimen of nebivolol can be efficaciously and safely used to treat patients with essential hypertension regardless of their CYP2D6 genotype.

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