A pharmacokinetic and pharmacodynamic interaction study between nebivolol and the H_2-receptor antagonists cimetidine and ranitidine

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Aims The study was designed to investigate the effects of the H_2-receptor antagonists, cimetidine and ranitidine on the pharmacokinetics and pharmacodynamics of nebivolol in healthy volunteers.

Methods Twelve healthy volunteers took part in a randomized placebo-controlled cross-over study. Each subject received on three separate occasions placebo, cimetidine (400 mg twice daily) or ranitidine (150 mg twice daily) for 24 h before and 48 h after a single oral dose of nebivolol (5 mg). Nebivolol and its individual (+) and (−) enantiomers were determined tby h.p.l.c.

Results Ranitidine had no significant effect on nebivolol pharmacokinetics. Cimetidine, however, resulted in a 21–23% increase in C_{max} of unchanged nebivolol and of each enantiomer plus its hydroxylated metabolites. Cimetidine significantly ($P<0.05$) increased the AUC [mean ± s.d. (95% C.I. of differences in mean)] for unchanged (±)-nebivolol [7.76 ± 3.07 ng ml^{-1}h with placebo; 11.50 ± 5.40 (1.75, 8.76) ng ml^{-1}h with cimetidine], (+)-nebivolol plus its hydroxylated metabolites [73.0 ± 18.0 ng ml^{-1}h with placebo; 91.5 ± 25.7 (1.0, 23.1) ng ml^{-1}h with cimetidine] and (−)-nebivolol plus its hydroxylated metabolites [101 ± 32 ng ml^{-1}h with placebo; 123 ± 38 (3.3, 27.0) ng ml^{-1}h with cimetidine]. Statistical analysis of the resting blood pressure and heart rate and exercise data did not suggest any consistent effects of ranitidine or cimetidine upon the pharmacodynamic effects of nebivolol.

Conclusions There was no interaction between ranitidine and nebivolol. Although cimetidine inhibited nebivolol metabolism, it did not have a significant influence on the pharmacodynamics of the drug.

Keywords: nebivolol, β-adrenoceptor antagonist, cimetidine, ranitidine, H_2-receptor antagonists

Introduction

Nebivolol is a selective β-adrenoceptor antagonist. It is a 50:50 racemic mixture of the enantiomeric pair (+)-nebivolol (+SRRR) and (−)-nebivolol (−RSSS) [1]. The (+)-enantiomer is one hundred fold more potent a β-adrenoceptor antagonist than the (−)-enantiomer [2]. Nebivolol is metabolized by the liver to a variety of metabolites, some of which have β-adrenergic blocking properties. Less than 0.5% of an oral dose of nebivolol is excreted in the urine unchanged [3]. The drug undergoes extensive first-pass metabolism, and is subject to debrisoquine type genetic polymorphism. The absolute oral bioavailability of nebivolol was 12% in EMs and 96% in PMs, [3].

The H_2-receptor antagonists, cimetidine and ranitidine are widely used for effective treatment of gastric and duodenal ulcers. Cimetidine is well known to inhibit the hepatic cytochrome P450 (CYP450) metabolism of a number of concurrently administered drugs. Ranitidine also exerts an inhibitory effect, but to a lesser degree than cimetidine. In addition to their CYP450 inhibitory activity, cimetidine and ranitidine have been shown to influence the bioavailability of a number of orally administered drugs by increasing the intragastric pH [4–6]. Cimetidine and ranitidine have also been shown to reduce the renal clearance of organic cations by competing for active tubular secretion in the proximal tubule of the kidney [7–11].

It is possible that concurrent administration of nebivolol with either cimetidine or ranitidine could affect nebivolol pharmacokinetics by alteration of its absorption and elimination. The present study investigated potential effects of the two H_2-receptor antagonists on the pharmacokinetics and pharmacodynamics of a single oral dose of nebivolol in a group of healthy volunteers.

Methods

Twelve healthy, non-smoking males aged 19–23 years (median 20 years) took part in a placebo-controlled randomized single-blind crossover study which was approved by the Newcastle Joint Ethics Committee. No subject had a history of alcohol or drug abuse, was taking any medication (other than simple analgesics if necessary) prior to or during the trial. All subjects underwent a general medical examination and a 12 lead electrocardiogram on entry.

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Haematology, serum biochemistry, full liver function and urinalysis tests were performed prior to and after each treatment phase. All subjects included in the study were phenotyped as extensive metabolizers of debrisoquine (metabolic ratio of debrisoquine: 4-hydroxydebrisoquine < 8) using a standard test [12].

Following an overnight fast, each subject received, on three separate occasions (phases I–III), placebo (twice daily), ranitidine (150 mg twice daily) or cimetidine (400 mg twice daily) for 24 h before and 48 h after a single oral dose of nebivolol (5 mg). Blood samples (10 ml) were collected at 0 (pre nebivolol dose), 0.25, 0.5, 1, 2, 4, 6, 8, 10, 24, 32 and 48 h post dose. There was a minimum of 10 days washout period between each treatment phase. Plasma samples were analysed for unchanged nebivolol and for each enantiomer plus its corresponding hydroxylated metabolites. Resting blood pressure and heart rate were measured at 0, 2, 4, 6, 8, 10, 24 and 48 h. Measurements were made after 5 min sitting and immediately on standing. Exercise heart rate and perceived exertion (using the Borg scale [13]) after a standardized 3 min exercise step test, using a 46 cm high box at a rate of 32 steps min^{-1} [14] were also determined at 0, 2, 4, 8 and 24 h during each treatment phase.

Plasma concentrations of (±)-nebivolol were determined by high performance liquid chromatography, with a limit of detection of 0.1 ng ml^{-1} [15]. The accuracy (R.E.) and precision (C.V.) of the assay was +6.2% and 9.5% at 0.421 ng ml^{-1}, −0.7% and 3.4% at 2.63 ng ml^{-1} and +5.0% and 3.8% at 13.2 ngml^{-1} respectively. Concentrations of each isomer (either (+) or (−)-nebivolol) plus their corresponding hydroxylated metabolites in plasma were determined by radioimmunoassay using enantioselective antibodies [16]. The detection limit of the r.i.a. method was 0.5 ng ml^{-1}. The accuracy (R.E.) and precision (C.V.) obtained from independently prepared quality control samples were +2.2% and 6.8% at 1.41 ng ml^{-1}, +4.0% and 3.6% at 5.25 ng ml^{-1} and +6.3% and 2.8% at 17.6 ng ml^{-1}, respectively for (−)-nebivolol and hydroxylated metabolites and +6.1% and 11.2% at 1.41 ng ml^{-1}, +4.8% and 5.0% at 5.25 ng ml^{-1} and +8.9% and 4.9% at 17.6 ng ml^{-1}, respectively for (+)-nebivolol.

Data analyses

The area under the plasma concentration-time curve (AUC) for unchanged nebivolol and of each enantiomer plus its corresponding hydroxylated metabolites were determined by the linear trapezoidal rule and extrapolated to infinity using the elimination rate constant (λ_z). The latter was determined by linear regression of the terminal points of the ln-linear concentration-time curve. The terminal half-life ($t_{1/2,z}$) was calculated as $0.693/\lambda_z$. The t_{max} and C_{max} values were determined by visual inspection of the data.

Statistical analysis

Pharmacokinetic parameters, except t_{max}, were analysed using analysis of variance (ANOVA). Differences in t_{max} were evaluated by the Wilcoxon matched-pairs signed ranks test. The 95% confidence intervals for the percentage ratios of C_{max} and AUC were calculated using the mean square error from the ANOVA. A general linear model which included factors of sequence, subjects (nested in sequence), period and treatment was used. Descriptive statistics were used to calculate resting systolic and diastolic blood pressure and heart rate. A crossover analysis of variance technique was employed to compare the pre-dose measurements with those of 2, 4, 6, 8, 10, 24 and 48 h after nebivolol administration in both sitting and standing positions. Descriptive statistics were also used for the Borg scores and the heart rate measurements after 3 min exercise. A crossover ANOVA technique was employed to compare the heart rate measurements, with a paired *t*-test for further pairwise comparisons of the data. Values are given as the mean ± s.d. (95% C.I.).

Results

Pharmacokinetics

Pharmacokinetic parameters of unchanged nebivolol are shown in Table 1. Cotreatment with ranitidine had no significant effect on nebivolol pharmacokinetics. The C_{max}

Table 1 Pharmacokinetic parameters [mean ± s.d. (95% C.I. differences in mean values)] of nebivolol (N), (+)-nebivolol plus hydroxylated metabolites (+N+OHM) and (−)-nebivolol plus hydroxylated metabolites ((−)N+OHM) after pretreatment with placebo (P), ranitidine (R) and cimetidine (C).

	C_{max} *(ng ml^{-1})*	t_{max} *(h)*†	$t_{1/2,z}$ *(h)*	*AUC (ng ml^{-1} h)*
N+P	1.48 ± 0.45	1.0	11.2 ± 7.8	7.76 ± 3.07
N+R	1.50 ± 0.54 (0.12, 0.77)	1.0 (−0.5, 0.4)	11.9 ± 8.0 (−2.8, 1.9)	8.27 ± 3.55 (−2.15, 4.05)
N+C	1.82 ± 0.55 (−0.98, 0.78)	1.0 (−0.3, 0.5)	10.3 ± 4.1 (−7.5, 5.7)	*11.50 ± 5.40 (1.75, 8.76)
(+)dN+OHM+P	6.04 ± 1.13	3.9	14.0 ± 4.3	73.0 ± 18.0
(+)dN+OHM+R	6.22 ± 1.35 (−0.30, 1.03)	3.0 (−0.8, 0.5)	16.6 ± 7.0 (−4.4, 5.7)	71.3 ± 23.5 (−14.7, 16.5)
(+)dN+OHM+C	*7.28 ± 2.05 (0.26, 2.28)	4.0 (−0.22, 1.3)	19.0 ± 7.8 (−3.2, 9.1)	*91.5 ± 25.7 (1.0, 23.1)
(−)1N+OHM+P	10.5 ± 2.5	3.0	17.8 ± 8.6	101 ± 32
(−)1N+OHM+R	10.2 ± 2.3 (−1.56, 0.62)	3.9 (−0.7, 1.0)	16.6 ± 9.9 (−7.3, 7.0)	117 ± 31 (−4.44, 19.71)
(−)1N+OHM+C	*12.7 ± 3.8 (0.8, 3.6)	4.0 (−2.3, 1.3)	15.4 ± 8.9 (−7.4, 4.0)	*123 ± 38 (3.3, 27.0)

*$P < 0.05$. †Median.

and AUC percentage ratio on coadministration with ranitidine relative to placebo was 101% (95% C.I. 74–129%) and 107% (95% C.I. 63–150%) respectively. The C_{max} and AUC percentage ratio on coadministration with cimetidine relative to placebo was 123% (95% C.I. 96–150%) and 148% (95% C.I. 105–191%) respectively. Nebivolol t_{max} was not significantly altered by cimetidine cotreatment (Table 1).

Pharmacokinetic parameters of (+)- and (−)-nebivolol enantiomers plus their corresponding hydroxylated metabolites on cotreatment with ranitidine were not significantly different from those after intake of nebivolol with placebo (Table 1). The C_{max} and AUC percentage ratios for each nebivolol enantiomer plus its hydroxylated metabolites on coadministration with ranitidine relative to placebo were 103% (95% C.I. 87–119%) and 97% (95% C.I. 80–115%) respectively for (+) nebivolol plus its hydroxylated metabolites and 97% (95% C.I. 86–108%) and 116% (95% C.I. 98–134%) respectively for (−)-nebivolol plus its hydroxylated metabolites.

The C_{max} and AUC percentage ratios for each enantiomer plus its hydroxylated metabolites on coadministration with cimetidine relative to placebo were 121% (95% C.I. 105–136%) and 125% (95% C.I. 108–143%) respectively for (+)-nebivolol plus its hydroxylated metabolites and 121% (95% C.I. 110–132%) and 122% (95% C.I. 104–140%) respectively for (−)-nebivolol plus its hydroxylated metabolites. The t_{max} for each of (+)- and (−)-nebivolol plus their hydroxylated metabolites were not changed significantly (Table 1).

Pharmacodynamics

Exercise data There were consistent decreases in mean heart rate from baseline for all treatment groups (Figure 1). The mean decreases were greater 4 and 8 h after nebivolol administration (in the order of 20 beats min^{-1}) than after 2 h (in the order of 10 beats min^{-1}). There was an overall treatment by period interaction, however, at both 4 h ($P=0.022$) and 8 h ($P=0.046$) compared with baseline. There was also a statistically significant overall period effect at 8 h compared with baseline ($P=0.007$). There were greater decreases in exercise heart rate during phase I ($P=0.026$) and phase III ($P=0.013$) than during phase II. However, there were no statistically significant differences in mean AUC(0,8 h) and AUC (0,24 h) exercise heart rate between the three treatments (data not shown).

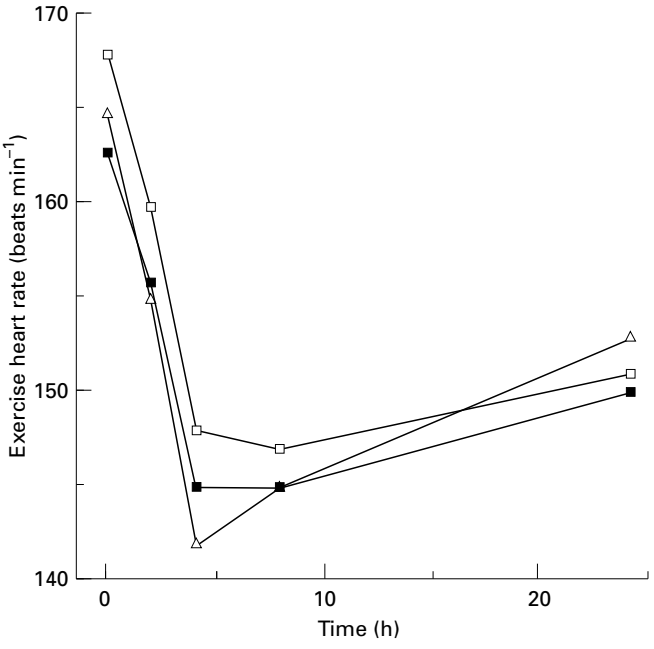

Figure 1 Mean exercise heart rate after co-treatment of nebivolol with placebo (□), ranitidine (■) and cimetidine (△).

There were no statistically significant treatment, period or treatment by period interactions for Borg scores.

Resting blood pressure and heart rate There were generally mean decreases from baseline in resting diastolic and systolic blood pressures in the order of 5–10 mmHg. These mean decreases were consistent for all three treatment groups. There were no consistent mean differences from baseline in heart rate (data not shown).

Discussion

The present study showed that cotreatment with ranitidine did not influence the pharmacokinetics of a single oral dose of nebivolol. Cimetidine on the other hand increased the bioavailability of unchanged nebivolol and of its individual (+)- and (−)-enantiomers plus their corresponding hydroxylated metabolites, most likely as a result of inhibition of nebivolol first-pass metabolism.

The increase in nebivolol bioavailability on cotreatment with cimetidine, however, is unlikely to be due to increased nebivolol absorption by alteration of intagastric pH, since nebivolol bioavailability was unaltered by cotreatment with ranitidine. It is also unlikely that the significantly higher plasma concentrations of nebivolol enantiomers plus their hydroxylated metabolites could have resulted from inhibition of their renal excretion by cimetidine, as urinary excretion of nebivolol and its unconjugated hydroxylated metabolites account for less than 5% of the administered dose [3].

Nebivolol metabolism in man is complex and is subject to debrisoquine type genetic polymorphism. *N*-dealkylation mainly in combination with hydroxylation, acyclic monooxidation and aromatic hydroxylation, followed by glucuronidation and glucuronidation of unchanged nebivolol are the major metabolic pathways in subjects phenotyped as extensive debrisoquine hydroxylators [3]. *N*-dealkylation of nebivolol is probably mediated through CYP3A4, and the metabolism of a number of compounds via this pathway has been shown to be inhibited by cimetidine [17]. It is possible that the increase in nebivolol bioavailability observed in the present study is due to inhibition of nebivolol metabolism via the *N*-dealkylation step.

Despite its effects on nebivolol pharmacokinetics, statistical analysis of the resting vital signs and exercise data did not suggest any consistent effects of cimetidine upon nebivolol pharmacodynamics. However, there were statistically significant period interactions for sitting systolic blood pressure and exercise heart rate and treatment by period interactions for exercise heart rate, which may have masked any subtle changes in the cardiovascular measurements.

In summary, cotreatment with ranitidine had no significant effect on the pharmacokinetics and pharmacodynamics of

nebivolol. Although cimetidine inhibited nebivolol metabolism, it did not have a significant influence on the pharmacodynamic effects of the drug. However, in the present study pretreatment with cimetidine was for one day only and nebivolol was administered as a single dose. Therefore a significant pharmacodynamic interaction between nebivolol and cimetidine cannot be ruled out under steady state conditions and in patients who may receive both drugs chronically.

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