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Different Beta-Blocking Effects of Carvedilol and Bisoprolol in Humans

G. Koshucharova, R. Zweiker, R. Maier, P. Lercher, V. Stepan, W. Klein, K. Stoschitzky

Bisoprolol is a β_1 -selective beta-adrenergic antagonist while carvedilol is a non-selective beta-blocker with additional blockade of α_1 -adrenoceptors. Administration of bisoprolol has been shown to cause up-regulation of β -adrenoceptor density and to decrease nocturnal melatonin release, whereas carvedilol lacks these typical effects of beta-blocking drugs. The objective of the present study was to investigate beta-blocking effects of bisoprolol and carvedilol in healthy subjects.

We compared the effects of single oral doses of clinically recommended amounts of bisoprolol (2.5, 5 and 10 mg) and carvedilol (25, 50 and 100 mg) to those of placebo in a randomised, double-blind, cross-over study in 12 healthy male volunteers. Three hours after oral administration of the drugs heart rate and blood pressure were measured at rest, after 10 min. of exercise, and after 15 min. of recovery.

Bisoprolol tended to decrease heart rate during exercise (–17 %, –21 % and –25 %) to a slightly greater extent than carvedilol (–17 %, –18 % and –21 %) although the differences between the two drugs were not significant. At rest, increasing doses of bisoprolol further decreased heart rates (63, 61 and 53 beats/min) whereas increasing doses of carvedilol resulted in increasing heart rates (63, 63 and 68 beats/min), with 100 mg carvedilol failing to differ significantly from placebo (71 beats/min).

We conclude that clinically recommended doses of carvedilol cause clinically relevant beta-blockade in healthy humans predominantly during exercise where it appears to be slightly less effective than bisoprolol. On the other hand, the effects of carvedilol on heart rate at rest appear to be weak or non-existent, particularly in subjects with a low sympathetic tone, whereas bisoprolol is a potent beta-blocker both at rest and during exercise. The weak clinical consequences of beta-blocking effects of carvedilol might possibly be caused by a reflex increase in sympathetic drive due to a decrease in blood pressure resulting from the α -blocking effects of the drug. *J Clin Basic Cardiol* 2001; 4: 53–56.

Key words: carvedilol, bisoprolol, beta-blockers, heart failure

Bisoprolol is a selective antagonist of adrenergic β_1 -receptors [1] whereas carvedilol is a non-selective β -blocker with additional α_1 -blocking and antioxidant effects [2]. In recent years, β -blockers have been shown to be highly effective in the treatment of congestive heart failure (CHF). Carvedilol decreased mortality in large randomised placebo-controlled studies by 65 % (although not as the primary end point) [3], whereas bisoprolol did so by 34 % [4]. However, it is not known whether or not carvedilol is better than bisoprolol since the beneficial effects of the two substances in patients suffering from heart failure have never been investigated in one prospective, randomised, clinical trial. In addition, it is unclear whether or not there are clinically relevant differences between the β -blocking effects of carvedilol and bisoprolol. Therefore, it appears important to directly compare β -blocking effects of carvedilol and bisoprolol in humans.

Nearly all β -blockers currently used in research and clinical practice are racemates consisting of (R)- and (S)-enantiomers in a fixed 1:1 ratio, and all β -blocking potency resides exclusively in the (S)-enantiomers whereas the (R)-forms do not contribute to the β -blocking effect of the racemic drugs [5]. Chronic administration of β -blockers produces reactive up-regulation of β -receptor density [6]. In addition, β -blockers reduce nocturnal melatonin production [7]. However, carvedilol has been shown neither to cause up-regulation of β -receptor density in some cases [8] nor to influence nocturnal melatonin production [7]. The lack of these typical effects of β -blockers in (R,S)-carvedilol is currently unexplained. However, there are several hypotheses as to which mechanisms might possibly account for these properties in carvedilol: Firstly, an insufficient β -blockade by (R,S)-carvedilol in clinical practice; secondly, intrinsic sym-

pathomimetic activity (ISA) of (R,S)-carvedilol; thirdly, reflex activation of sympathetic tone caused by vasodilation due to α -blockade of both (R)- and (S)-carvedilol. However, ISA was not described with (R,S)-carvedilol [9]. On the other hand, in a recent study in healthy subjects who received single oral doses of (R)-, (S)- and (R,S)-carvedilol, the racemate failed to significantly decrease heart rate, whereas optically pure (R)-carvedilol even slightly increased heart rate under resting conditions [10], thus supporting our third hypothesis mentioned above.

In order to address these unsolved issues, we performed a randomised, double-blind, placebo-controlled, cross-over study in 12 healthy volunteers using three doses of (R,S)-carvedilol (25 mg, 50 mg, 100 mg) and (R,S)-bisoprolol (2.5 mg, 5 mg, 10 mg), respectively, which represent the upper range of dosages recommended for these drugs in clinical practice as well as those used in the US carvedilol trial [1] and in the CIBIS-II trial [2] to determine clinically relevant β -blocking effects of (R,S)-carvedilol and (R,S)-bisoprolol in humans.

Throughout the following text, whenever bisoprolol and carvedilol are mentioned without specific reference to the (R)- and (S)-enantiomers, the commercially available racemic (R,S)-mixtures were used.

Methods

Study protocol

Twelve healthy male volunteers, age 25–42 years, received single oral doses of 25 mg, 50 mg and 100 mg (R,S)-carvedilol, 2.5 mg, 5 mg and 10 mg (R,S)-bisoprolol, and placebo at intervals between 3 and 7 days according to a randomised, double-blind, placebo-controlled, cross-over protocol. Prior

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to inclusion in the study subjects gave written informed consent and underwent a short physical examination, ECG, and determination of routine laboratory parameters to ensure current health. In particular, subjects with obstructive pulmonary disease, diabetes mellitus, peripheral arterial disease, AV-block, bradycardia (resting heart rate < 50/min) or hypotension (blood pressure < 100/70 mmHg) were excluded.

On each day of the study, subjects entered the laboratory between 7 and 9 a.m. following an overnight fast. The blinded study medication was swallowed with 50–100 ml of water. Three hours later, exercise was performed for 10 min. on a bicycle ergometer at 70 % of mean individual work load. Heart rate and blood pressure were measured at rest immediately before the onset of exercise, during the last minute of exercise, and at rest after 15 min. of recovery. Continuous ECG monitoring and cuff sphygmomanometry were used to record heart rate and blood pressure. The investigation conforms with the principles outlined in the Declaration of Helsinki (Br Med J 1964; II: 177) and was approved by the Ethics Committee of the Faculty of Medicine, Karl Franzens University, Graz, Austria.

Materials

(R,S)-bisoprolol and (R,S)-carvedilol were taken from formulations commercially available in Austria (Concor® and Dilatrend®, respectively). The blinded pharmaceutical formulations (hard gelatine capsules) containing 25 mg (R,S)-carvedilol, 50 mg (R,S)-carvedilol, 100 mg (R,S)-carvedilol, 2.5 mg (R,S)-bisoprolol, 5 mg (R,S)-bisoprolol, 10 mg (R,S)-bisoprolol, or placebo together with mannitol and carbosil as auxiliary materials, were prepared according to the specifications of the European Pharmacopoeia at the Institute of Pharmaceutical Technology, Karl Franzens University, Graz, Austria.

Statistical analysis

Results are given as arithmetic means \pm 1 SD unless otherwise indicated. Significances of differences within groups were calculated using Repeated Measures ANOVA (Friedman's Repeated Measures ANOVA on Ranks when applicable) and Student-Newman-Keuls test for *post-hoc* testing. A p-value < 0.05 was considered statistically significant.

Results

Subjects were 33 ± 5 years of age, were 181 ± 8 cm in height and weighed 74 ± 7 kg, and performed at 156 ± 13 Watts over 10 min. on the bicycle ergometer.

Haemodynamic results are summarised in Table 1. At rest before exercise, increasing doses of bisoprolol caused a progressive decrease in heart rate (63, 61 and 53 beats/min) which was significantly different from placebo in all cases, whereas increasing doses of carvedilol caused increasing heart rates (63, 63 and 68 beats/min) with the result obtained with 100 mg carvedilol failing to reach statistical significance from placebo (Fig. 1); furthermore, 10 mg bisoprolol were significantly more effective than 100 mg carvedilol ($p < 0.05$). Similar trends were observed at rest after 15 min. of recovery (Fig. 2); again, 10 mg bisoprolol were significantly more effective than 100 mg carvedilol ($p < 0.05$). During exercise, both carvedilol and bisoprolol significantly decreased heart rate compared to placebo (–17 %, –18 %, –21 % and –17 %, –21 %, –25 %, respectively) (Fig. 3); bisoprolol appeared slightly more effective than carvedilol; however, the differences between the effects of carvedilol and bisoprolol did not reach statistical significance.

Table 1. Heart rate (beats/min) and systolic and diastolic blood pressure (mmHg) obtained 3 hours after oral single dose administration of carvedilol (25, 50 and 100 mg), bisoprolol (2.5, 5 and 10 mg) and placebo at rest, after 10 min. of exercise, and after 15 min. of recovery. Significances of differences within groups by Repeated Measures ANOVA (Friedman's Repeated Measures ANOVA on Ranks when applicable) and *post-hoc* analyses from placebo by Student-Newman-Keuls test; n = 12; n.s., not significant

	Placebo	25 mg Carvedilol	50 mg Carvedilol	100 mg Carvedilol	2.5 mg Bisoprolol	5 mg Bisoprolol	10 mg Bisoprolol
Heart rate Rest ($p < 0.001$)	72 ± 6	63 ± 7 –13 % $p < 0.05$	63 ± 7 –12 % $p < 0.05$	68 ± 9 –3 % n.s.	63 ± 9 –13 % $p < 0.05$	61 ± 8 –15 % $p < 0.05$	53 ± 8 –18 % $p < 0.05$
Systolic BP Rest ($p < 0.001$)	120 ± 9	111 ± 10 –7 % n.s.	105 ± 11 –12 % $p < 0.05$	101 ± 8 –16 % $p < 0.05$	117 ± 9 –2 % n.s.	110 ± 10 –8 % n.s.	107 ± 8 –10 % $p < 0.05$
Diastolic BP Rest ($p = 0.01$)	70 ± 3	70 ± 6 ± 0 % n.s.	68 ± 7 –4 % n.s.	63 ± 5 –11 % $p < 0.05$	70 ± 6 ± 0 % n.s.	68 ± 5 –4 % n.s.	70 ± 5 ± 0 % n.s.
Heart rate Exercise ($p < 0.001$)	157 ± 16	131 ± 13 –17 % $p < 0.05$	128 ± 10 –18 % $p < 0.05$	124 ± 9 –21 % $p < 0.05$	131 ± 15 –17 % $p < 0.05$	124 ± 12 –21 % $p < 0.05$	117 ± 10 –25 % $p < 0.05$
Systolic BP Exercise ($p = 0.002$)	174 ± 11	157 ± 17 –10 % $p < 0.05$	150 ± 20 –14 % $p < 0.05$	144 ± 20 –17 % $p < 0.05$	161 ± 17 –8 % n.s.	153 ± 19 –12 % $p < 0.05$	148 ± 17 –15 % $p < 0.05$
Diastolic BP Exercise (n.s.)	66 ± 5	63 ± 5 –5 % n.s.	62 ± 6 –6 % n.s.	61 ± 6 –8 % n.s.	66 ± 8 ± 0 % n.s.	63 ± 8 –5 % n.s.	66 ± 6 ± 0 % n.s.
Heart rate Recovery ($p < 0.001$)	75 ± 6	66 ± 8 –12 % $p < 0.05$	67 ± 6 –10 % $p < 0.05$	70 ± 8 –6 % n.s.	66 ± 7 –12 % $p < 0.05$	64 ± 9 –14 % $p < 0.05$	59 ± 8 –21 % $p < 0.05$
Systolic BP Recovery ($p = 0.004$)	116 ± 9	110 ± 9 –5 % n.s.	105 ± 9 –9 % $p < 0.05$	101 ± 8 –13 % $p < 0.05$	110 ± 8 –5 % n.s.	109 ± 9 –6 % n.s.	107 ± 10 –8 % n.s.
Diastolic BP Recovery (n.s.)	68 ± 4	64 ± 7 –7 % n.s.	62 ± 6 –10 % n.s.	60 ± 5 –13 % n.s.	67 ± 7 –2 % n.s.	63 ± 7 –8 % n.s.	65 ± 5 –5 % n.s.

Systolic blood pressure was significantly decreased by 5 and 10 mg bisoprolol during exercise, whereas bisoprolol had no significant effect on systolic blood pressure at rest before exercise and after 15 min. of recovery. 50 and 100 mg carvedilol decreased systolic blood pressure at rest, during exercise and during recovery, whereas 25 mg bisoprolol had a significant effect on systolic blood pressure only at exercise and during recovery. 50 and 100 mg carvedilol were significantly more effective in decreasing systolic blood pressure at rest before exercise than 2.5 mg bisoprolol ($p < 0.05$). However, there were no further significant differences between the effects of either of the drugs on systolic blood pressure.

100 mg Carvedilol significantly decreased diastolic blood pressure at rest before exercise (-11% , $p < 0.05$). However, there were no further significant effects of any of the drugs on diastolic blood pressure in this study with oral single-dose administration.

Discussion

The present data show that clinically recommended doses of carvedilol and bisoprolol exert different β -blocking effects: Heart rate during exercise, one of the most relevant parameters to determine clinically effective β -blockade, was decreased by both carvedilol and bisoprolol. The effects of 2.5, 5 and 10 mg bisoprolol (-17% , -21% and -25%) appeared more pronounced than those of 25, 50 and 100 mg carvedilol (-17% , -18% and -21%) (Fig. 3). However, there were no statistically significant differences between the effects of carvedilol and bisoprolol.

On the other hand, both at rest before exercise as well as after 15 min. of recovery, bisoprolol decreased heart rate, but to a lesser extent than during exercise. As predicted, increasing doses of bisoprolol caused decreasing heart rates (Fig. 1, 2). In contrast, 100 mg carvedilol failed to exert significant effects on heart rate under these resting conditions. Unexpectedly, increasing doses of carvedilol caused increasing heart rates (63, 63 and 68 beats/min. at rest before exercise, Fig. 1, and 66, 67 and 70 beats/min. at rest during recovery, Fig. 2), a finding opposite to what would be expected with a β -blocker.

These findings obtained with carvedilol might possibly be explained by a decrease in blood pressure caused by the α -blocking effects of the drug. The decrease in blood pressure may be expected to cause a compensatory increase in sym-

thetic tone: On the one hand, the increase in sympathetic tone might diminish the effect of the drug on blood pressure – actually, carvedilol had no significant effect on diastolic blood pressure (except 100 mg at rest before exercise), and 25 mg carvedilol also failed to decrease systolic blood pressure at rest both before exercise and after 15 min. of recovery. On the other hand, this increase in sympathetic tone might diminish or nearly abolish the β -blocking effects of carvedilol – indeed, under conditions with a physiologically low sympathetic tone, ie, at rest before exercise and during recovery, 100 mg carvedilol failed to significantly decrease heart rate, whereas bisoprolol, which lacks α -blocking effects, significantly decreased heart rate both at rest and during recovery.

These data suggest that carvedilol is rather weak as a β -adrenergic antagonist, exerting clinically relevant β -blocking effects predominantly under conditions with an elevated sympathetic tone, ie, during exercise in the present study, but lacking β -blockade when sympathetic tone is low, ie, at rest, in higher doses. This might be one reason why carvedilol appears to exert less side effects resulting from β -blockade than other (“pure”) β -blockers [11]. In addition, the nearly complete lack of clinical consequences of β -blocking effects of carvedilol at rest might explain why – in contrast to other (“pure”) β -blockers – it does not decrease nocturnal mela-

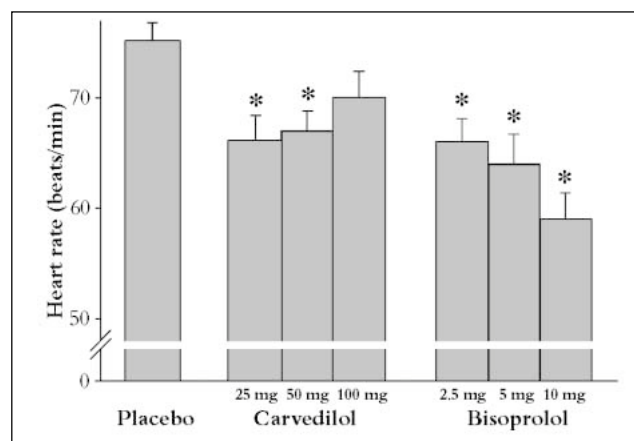


Figure 2. Effects of single oral doses of placebo, 25, 50, and 100 mg carvedilol, and 2.5 mg, 5 mg, and 10 mg bisoprolol on heart rate at rest after 15 min. of recovery; 10 mg bisoprolol are significantly more effective than 100 mg carvedilol ($p < 0.05$). Means \pm SEM; $n = 12$; *, $p < 0.05$ (compared to placebo)

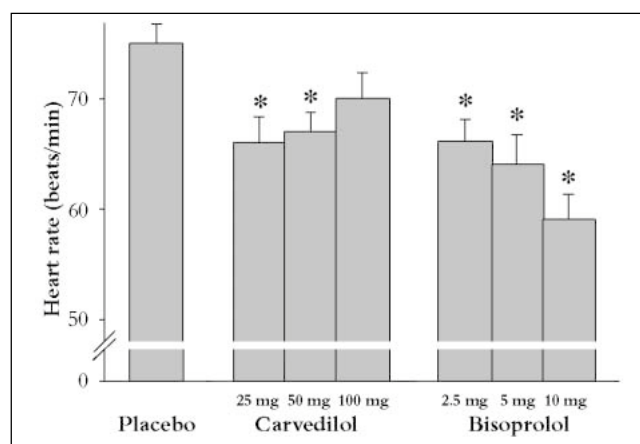


Figure 1. Effects of single oral doses of placebo, 25, 50, and 100 mg carvedilol, and 2.5, 5, and 10 mg bisoprolol on heart rate at rest before exercise; 10 mg bisoprolol are significantly more effective than 100 mg carvedilol ($p < 0.05$). Means \pm SEM; $n = 12$; *, $p < 0.05$ (compared to placebo)

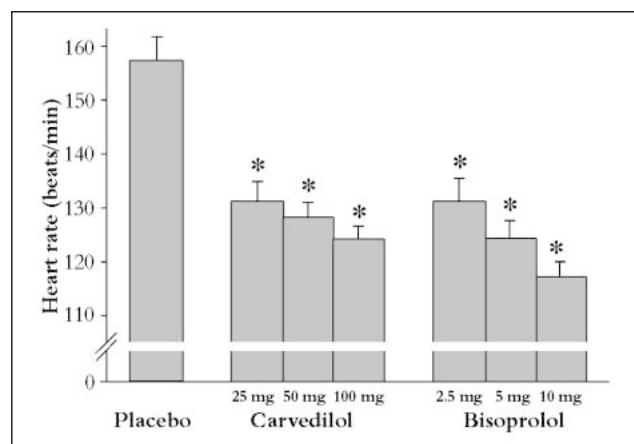


Figure 3. Effects of single oral doses of placebo, 25, 50, and 100 mg carvedilol, and 2.5 mg, 5 mg, and 10 mg bisoprolol on heart rate during exercise; 10 mg bisoprolol appear to be slightly, although not significantly, more effective than 100 mg carvedilol. Means \pm SEM; $n = 12$; *, $p < 0.05$ (compared to placebo)

tonin release as shown in a previous study [7] since nocturnal sleep is doubtless one of the most distinct resting conditions. It might also be the reason why long-term therapy with carvedilol may fail to cause upregulation of β -receptor density which is a typical effect of β -blocking drugs [8]. A further reason for these different effects of bisoprolol and carvedilol on resting heart rate might be the fact that bisoprolol but not carvedilol exhibits pronounced inverse agonist activity on β_1 -adrenoceptors [12, 13].

The observed increase in heart rate with increasing doses of carvedilol at rest and during exercise might be explained by the fact that the affinity of carvedilol to β_1 -receptors is about 2-fold higher than that to α_1 -receptors [9, 14]. Therefore, β -blockade obtained with 25 mg carvedilol might be more complete than α -blockade, resulting in a greater increase in α - than in β -blockade with increasing doses of carvedilol producing a higher compensatory increase in sympathetic tone, thus decreasing the net β -blocking effect of the drug under resting conditions with increasing doses.

It has to be emphasised that the present study was performed in healthy males who usually have a low sympathetic tone at rest. Therefore, the net clinical β -blockade of carvedilol may be higher in patients with an increased sympathetic tone even under resting conditions such as those with CHF. Thus, it is not surprising that studies with carvedilol in patients with CHF yielded clear and significantly decreasing effects of the drug on heart rate at rest [15–19] which is in contrast to the results of the present single-dose study where carvedilol only had a slight or no effect on resting heart rate. However, this decrease in heart rate was obtained after long-term administration of carvedilol, and active metabolites have been described which might increase the β -blocking potency of the drug [20].

Our data further suggest that the potentially better effects of carvedilol on clinical outcomes in patients with CHF cannot be explained by higher β -blockading effects of carvedilol when clinically recommended doses of carvedilol (25–100 mg daily) or bisoprolol (2.5–10 mg daily) are administered. Furthermore, the α -blocking effect of carvedilol is also unlikely to account for a potential benefit of carvedilol over “pure” β -blockers since the doxazosin arm of the ALLHAT trial had to be finished prematurely due to a doubling of the risk of CHF caused by this α -adrenergic antagonist [21]. Therefore, the antioxidant and antineutrophil effects [22] and/or the prevention of contractile dysfunction induced by hydroxyl radicals [23] might be the ultimate potential benefits of carvedilol over bisoprolol known to date for patients with CHF.

We conclude that clinically recommended doses of carvedilol cause clinically relevant β -blockade in humans mainly during exercise although carvedilol appears to be slightly less effective than bisoprolol. On the other hand, the clinical consequences of the β -blocking effects of carvedilol under resting conditions appear to be rather weak, at least in subjects with low sympathetic tone, whereas bisoprolol exerts significant β -blockade even at rest. This lack of clinically effective β -blocking efficacy of carvedilol at rest might be a result of compensatory sympathetic stimulation due to a decrease in blood pressure resulting from the α -blocking effect of the drug. These results might explain why carvedilol, in contrast to bisoprolol, may fail to cause up-regulation of β -adrenoceptor density and does not decrease nocturnal melatonin release, two typical effects of “pure” β -blockers. In addition, the nearly complete lack of β -blocking efficacy under resting conditions might be the reason for the weak side effects of carvedilol resulting from β -blockade, particularly at rest. However, irrespective of its weak β -blocking effects, carvedilol is at least as effective as bisoprolol in reducing arte-

rial blood pressure, most likely due to its additional α -blocking effects, whereas bisoprolol appears to be somewhat more potent than carvedilol as a β -adrenergic antagonist.

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