Comparison of the effects of nadolol and bisoprolol on noradrenaline-evoked venoconstriction in man *in vivo*

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Aims In an attempt to explore the possible involvement of venodilator β-adrenoceptors in the constrictor response of the human dorsal hand vein to noradrenaline, we examined the ability of nadolol, a non-selective β_1/β_2-adrenoceptor antagonist, and bisoprolol a selective β_1-adrenoceptor antagonist, to potentiate the response.

Methods Twelve healthy male volunteers participated in three weekly sessions. In each session nadolol (40 mg), bisoprolol (5 mg) or placebo was ingested, and (-) noradrenaline acid tartrate (0.33–33.33 ng min^{-1}) was infused locally into the dorsal hand vein 2 h after the ingestion of the drugs. Changes in vein diameter were monitored with the dorsal hand vein compliance technique. Subjects were allocated to treatments and sessions according to a double-blind balanced cross-over design. Systolic and diastolic blood pressure, and heart rate were also measured.

Results Noradrenaline produced dose-dependent venoconstriction which was antagonized by bisoprolol but remained unaffected by nadolol (ANOVA with repeated measures: $F(2,22)=5.07$, $P<0.025$; Dunnett's test: placebo *vs* nadolol; $t=0.35$, df$=22$, $k=3$, NS; placebo *vs* bisoprolol; $t=2.83$, df$=22$, $k=3$, $P<0.01$). Mean ($\pm$s.e. mean) log ED_{50}s (ng min^{-1}) were 0.44 ± 0.15 (placebo), 0.73 ± 0.11 (bisoprolol) and 0.50 ± 0.21 (nadolol); mean (95% CI) differences were 0.29 (-0.005, 0.58) for placebo *vs* bisoprolol and 0.06 (-0.35, 0.46) for placebo *vs* nadolol. Both active drugs significantly (compared with placebo, $P<0.05$) decreased (mean change from pretreatment $\pm$s.e. mean) heart rate (bisoprolol -16.08 ± 2.01; nadolol -11.67 ± 2.06) and systolic blood pressure (bisoprolol -15.0 ± 0.80; nadolol -9.47 ± 0.18).

Conclusions The failure of nadolol and bisoprolol to potentiate noradrenaline-evoked venoconstriction argues against the involvement of masked venodilator β-adrenoceptors in the response. The mechanism underlying the antagonism of noradrenaline-evoked venoconstriction by bisoprolol remains to be elucidated.

Keywords: nadolol, bisoprolol, noradrenaline, dorsal hand vein, β-adrenoceptors

Introduction

The human dorsal hand vein contains both α- and β-adrenoceptors [1–3]. There is good evidence for the existence of both venoconstrictor α_1- and α_2-adrenoceptors [3–6], and venodilator β_2-adrenoceptors [7–8]. Although it is generally acknowledged that venodilator β-adrenoceptors are of the β_2 subtype, the possible involvement of β_1-adrenoceptors has not been excluded [9–12].

The physiological sympathomimetic amine noradrenaline has affinity for both α- and β-adrenoceptors [9]. Although noradrenaline is a powerful constrictor of the human dorsal hand vein [13–14], it is possible that the constrictor response is attenuated by the activation of masked venodilator β-adrenoceptors. The possible involvement of these masked receptors could be revealed by the use of β-adrenoceptor antagonists: the blockade of the masked venodilator receptors is expected to result in the potentiation of the constrictor response [15]. Indeed, some early work indicates that non-selective β-adrenoceptor antagonists are able to potentiate the venoconstrictor response to adrenaline [16] and noradrenaline [1, 17].

In the present study we compared the effects of pharmacodynamically active small single oral doses [18] of the non-selective β_1/β_2-adrenoceptor antagonist, nadolol and the selective β_1-adrenoceptor antagonist, bisoprolol on noradrenaline-evoked venoconstriction in man, using the dorsal hand vein compliance technique. Our prediction was that if the venoconstrictor response to noradrenaline is attenuated by masked β_2-adrenoceptors, but not by β_1-adrenoceptors, nadolol would potentiate the response but bisoprolol would be without any effect. On the other hand, if both β_2- and β_1-adrenoceptors are involved both antagonists would cause potentiation of the response.

Some of these results have been presented to the British Pharmacological Society [19].

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Methods

Subjects

Twelve healthy male volunteers aged 19–31 years (mean ± s.e. mean, 22.9 ± 4.3) and weighing 60–105 kg (mean ± s.e. mean, 80.3 ± 6.0) participated. Each subject completed a brief medical history and underwent a complete physical examination. The study was approved by the University of Nottingham Medical School Ethics Committee. All volunteers gave their written informed consent.

Drugs

(-)Noradrenaline acid tartrate (Levophed®) was obtained from Sanofi-Winthrop, Guildford, Surrey, UK, bisoprolol fumarate (Monocor*5®) from Lic. E. Merck, Darmstadt, Germany, nadolol (Corgard®) from Squibb, Bristol-Myers, UK. The sterile solutions of noradrenaline acid tartrate were administered locally into the vein at a constant rate of 0.3 ml min^{-1} in the dose range: 0.33–33.33 ng min^{-1}. Bisoprolol 5 mg, nadolol 40 mg, and lactose placebo were prepared in identical capsules for double-blind administration.

Tests

The dorsal hand vein compliance technique The dorsal hand vein compliance technique, as modified by Aellig [13], was used as described by Pan *et al*. [2]. Our detailed methods are described elsewhere [20]. In brief, the subject lay supine at room temperature (22–24° C). One arm was placed on a padded support sloping upwards at an angle of 30° from the horizontal to ensure complete emptying of the superficial hand veins. A 27-gauge butterfly needle was inserted into a suitable dorsal hand vein and a continuous infusion of 5% dextrose saline was started at a rate of 0.3 ml min^{-1}. The linear variable differential transformer (LVDT: Schaevitz Engineering, Pennsauken, NJ, USA; model 100 MHR) was then mounted onto the back of the hand over the summit of the vein under investigation. After insertion of the needle, recordings of the position of the core situated over the top of the vein were made both before and after inflation of a sphygmomanometer cuff on the ipsilateral upper arm to 45 mm Hg, until two equal readings were obtained. This baseline venodilatation during saline infusion with the cuff inflated was taken as '100% relaxation' (or '0% constriction'); the recording obtained with the cuff deflated (and the vein emptied) was taken as '100% constriction'. The difference between the two positions of the core gave a measure of the diameter changes of the vein under the congestion pressure of 45 mmHg. Each drug-infusion period lasted for 5–7 min; the cuff was inflated at the end of the third minute for at least 2 min (i.e. a sufficient period of time to ensure that the signal from the LVDT had plateaued). Increasing concentrations of the agonist were given at a constant infusion rate (0.3 ml min^{-1}) by switching to a separate infusion pump. Blood pressure and pulse rate were monitored (see below) at frequent intervals on the contralateral arm.

Cardiovascular measures Systolic and diastolic blood pressure were measured using a mercury sphygmomanometer, and heart rate by feeling the pulse of the radial artery at the wrist for 1 min. Measurements were taken on the arm opposite to the one used for the pharmacological testing, before and after treatment with the systemically administered and locally infused drugs; the pre-post treatment change was taken as the effect of the drug.

Experimental design

Subjects were allocated to treatments and sessions according to a double-blind balanced cross-over design. Each volunteer participated in three experimental sessions at weekly intervals, each session being associated with one of the following treatments: bisoprolol (5 mg), nadolol (40 mg), or placebo. At the beginning of each session the subjects rested for 30 min and then the pre-treatment tests were carried out (heart rate, systolic and diastolic blood pressure). The subject then took the capsules; 120 min later, the recording of baseline venous diameter started for a period of about 30 min, after which the local infusion of five doses of noradrenaline commenced; each dose was applied for 5–7 min. Heart rate, and systolic and diastolic blood pressure measurements were carried out on four occasions in each session: before and 2 h after the ingestion of the capsule, before the infusion of noradrenaline and after the infusion of the highest dose of noradrenaline. The timing of the start of local infusion and post-treatment tests was based on the single-dose pharmacokinetics of bisoprolol and nadolol; it has been reported that peak plasma concentration is attained 2–4 h after oral administration of a single dose of bisoprolol [21–22], and nadolol [23–24].

Data analysis

Dorsal hand vein responses The raw data were analyzed with two-way analysis of variance (dose of agonist; systemic drug treatment) with repeated measures on both factors. When a significant overall main effect of drug treatment was identified, individual comparisons were made between placebo *vs* bisoprolol and placebo *vs* nadolol with Dunnett's test. The individual dose-response curves obtained in each subject were also analysed by fitting a rectangular hyperbolic function to the data using a computer programme based on Wilkinson's method [25]. This analysis yields estimates of the maximal response (E_{max}) and the dose producing the half-maximal response (ED_{50}). The analysis also provides the index of determination (p^2) for each curve; p^2 expresses the proportion of the data variance accounted for by the fitted function [26]. The distribution of the ED_{50} values was normalized by logarithmic transformation. Student's *t*-test for paired comparisons was used to compare the effects of bisoprolol *vs* placebo, and nadolol *vs* placebo on E_{max} and log ED_{50}. In addition, the geometric mean ED_{50} was calculated for each of the three dose-response curves. The degree of antagonism of the responses by bisoprolol and nadolol was expressed in two ways: by calculating the

percentage change in geometric mean ED_{50} in the presence of bisoprolol and nadolol, and by calculating the dose-ratio [20].

Cardiovascular measures Analysis of variance (repeated measures) and Dunnett's test were used to compare the effects of bisoprolol and nadolol on cardiovascular measures.

A probability level of $P<0.05$ was adopted as the threshold for significance for all statistical tests.

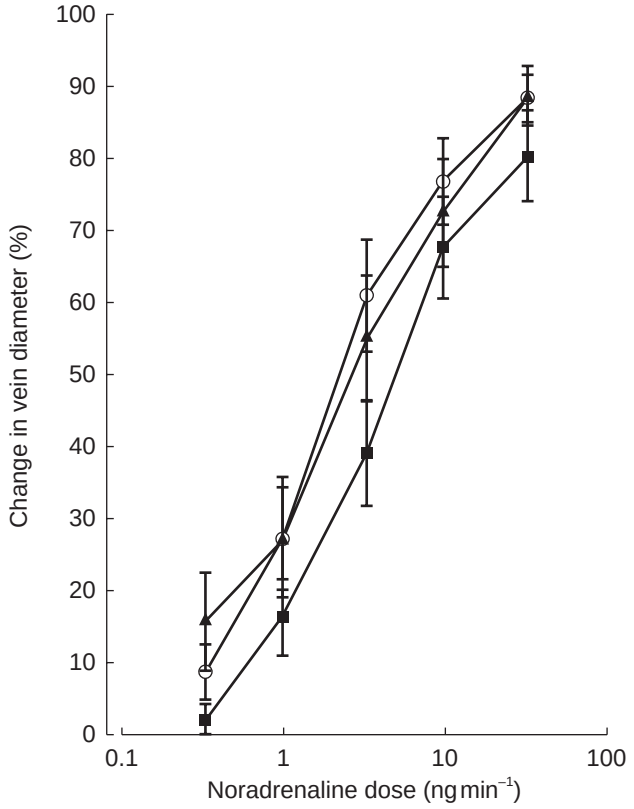

Figure 1 Dose-response curves for the venoconstrictor effect of noradrenaline during local infusion into the superficial dorsal hand vein (cuff pressure 45 mm Hg) 2 h after ingestion of placebo (○), bisoprolol 5 mg (■), and nadolol 40 mg (▲); mean ± s.e. mean $n=12$. 100% response was defined as abolition of the venodilatation produced by the inflation of the cuff.

Results

Dorsal hand vein responses

Venous diameter (at an occlusion pressure of 45 mm Hg) was recorded prior to the application of noradrenaline and compared between the placebo, bisoprolol and nadolol sessions. The venous diameters (mm; mean ± s.e. mean, n = 12) were: 0.74 ± 0.10 (placebo), 0.78 ± 0.12 (bisoprolol), and 0.87 ± 0.09 (nadolol). There was no significant difference between the venous diameter recorded after treatment with placebo, bisoprolol, and nadolol (ANOVA with repeated measures; $F(2,22)=0.96$, NS). The mean differences (95% CI) between the effects of placebo and active treatments were: placebo *vs* bisoprolol: 0.04 (−0.18, 0.26); placebo *vs* nadolol: 0.13 (−0.10, 0.35); bisoprolol *vs* nadolol −0.09 (−0.25, 0.08).

The effects of systemic drug treatments on the dose-response curves to noradrenaline are shown in Figure 1. Noradrenaline evoked dose-dependent venoconstrictor responses (ANOVA with repeated measures: $F(4,44)=72.52$, $P<0.0001$), which were antagonized by bisoprolol and remained unaffected by nadolol (ANOVA with repeated measures: $F(2,22)=5.07$, $P<0.025$; Dunnett's test: placebo *vs* nadolol; $t=0.35$, df = 22, $k=3$, NS; placebo *vs* bisoprolol; $t=2.83$, df = 22, $k=3$, $P<0.01$). In the case of the individually fitted curves ($n=12$) the value of p^2 ranged from 0.84 to 0.99 (median 0.92) in the presence of placebo, from 0.87 to 0.99 (median 0.97) in the presence of bisoprolol, and from 0.54 to 0.99 (median 0.96) in the presence of nadolol. The estimated parameters of the dose-response curves ($n=12$) are shown in Figure 2. Although the mean log ED_{50} increased in the presence of bisoprolol, this did not reach statistical significance (Student's *t*-test: placebo *vs* bisoprolol; $t=2.16$, df = 11, $P=0.054$; placebo *vs* nadolol; $t=0.30$, df = 11, NS). Mean E_{max} did not differ between the three treatment conditions. The geometric mean ED_{50} increased by approximately 95% in the presence of bisoprolol, and by approximately 15% in the presence of nadolol, and the dose ratios were: placebo *vs* bisoprolol 1.94, and placebo *vs* nadolol 1.14. The differences (95% CI)

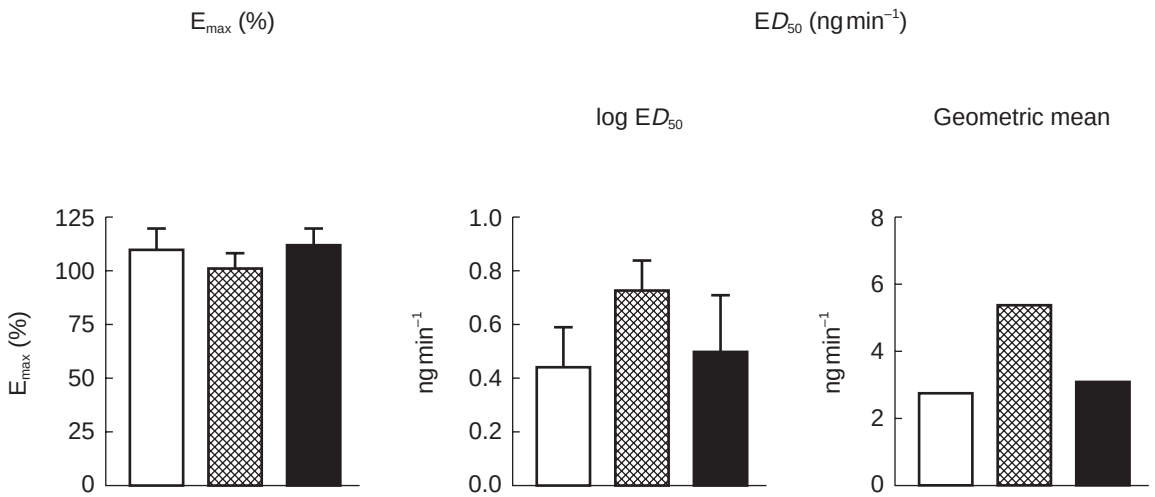

Figure 2 Parameters of the dose-response curves to noradrenaline (mean ± s.e. mean; $n=12$), calculated from individual subject data, 2 h after ingestion of placebo (open), bisoprolol 5 mg (hatched), and nadolol 40 mg (closed).

Table 1 Parameters of dose-response curves: differences (mean, 95% CI) between placebo (Pl), bisoprolol 5 mg (BIS5), and nadolol 40 mg (NAD40), $n=12$.

	Log ED_{50} (ng min^{-1})	*E_{max} (%)*
Pl/BIS5	0.29 (−0.01, 0.58)	−8.75 (−35.12, 17.62)
Pl/NAD40	0.06 (−0.35, 0.46)	2.30 (−8.48, 13.09)
BIS5/NAD40	0.23 (−0.05, 0.52)	−11.05 (−33.92, 11.81)

between the effects of the treatments on the parameters of the dose-response curve to noradrenaline are shown in Table 1.

Cardiovascular measures

The effects of bisoprolol, nadolol, and placebo on cardiovascular measures are shown in Figure 3. Both bisoprolol and nadolol decreased heart rate (ANOVA with repeated measures: $F(2,22)=23.18$, $P<0.0001$; Dunnett's test: placebo *vs* bisoprolol; $t=6.73$, df=22, $k=3$, $P<0.0001$; placebo *vs* nadolol; $t=4.31$, df=22, $k=3$, $P<0.001$), and systolic blood pressure (ANOVA with repeated measures: $F(2,22)=9.98$, $P<0.005$; Dunnett's test: placebo *vs* bisoprolol; $t=5.00$, df=22, $k=3$, $P<0.0001$; placebo *vs* nadolol; $t=3.14$, df=22, $k=3$, $P<0.01$). There was no statistically significant effect of bisoprolol and nadolol on diastolic blood pressure (ANOVA with repeated measures: $F(2,22)=1.73$, NS). The differences (95% CI) between the effects of placebo and the active treatments on the three cardiovascular measures are shown in Table 1.

Discussion

In the present study, we compared single oral doses of bisoprolol and nadolol on noradrenaline-evoked venoconstriction in man. The doses of the two β-adrenoceptor antagonists were selected on the basis of published reports on the effectiveness of these drugs in man. Both 5 mg bisoprolol and 40 mg nadolol have been shown to produce considerable antagonism (16.8 and 22.9%, respectively) of exercise-induced tachycardia, a β_1-adrenoceptor mediated response [18], and it is documented that bisoprolol 5 mg does not block β_2-adrenoceptors in man [27]. Furthermore,

Table 2 Cardiovascular measures; Heart rate (HR: beats min^{-1}), systolic blood pressure (SBP: mm Hg), and diastolic blood pressure (DBP: mm Hg), difference (mean, 95% CI, $n=12$) between placebo (Pl), and active drug treatments: bisoprolol 5 mg (BIS5), and nadolol 40 mg (NAD40).

	HR (beats min^{-1})	*SBP (mm Hg)*	*DBP (mm Hg)*
Pl *vs* BIS5	−12.25 (−16.36, −8.14)	−15 (−23.35, −6.65)	−3.42 (−7.17, 0.33)
Pl *vs* NAD40	−7.83 (−11.55, −4.12)	−9.42 (−14.43, −4.4)	−1.5 (−5.81, 2.81)
BIS5 *vs* NAD40	−4.42 (−8.61, −0.22)	−5.58 (−11.22, 2.56)	−2.33 (−6.20, 1.53)

nadolol, in doses of 20 to 80 mg, also effectively antagonizes β_1-adrenoceptor-mediated responses [28].

The results show, in agreement with a number of previous reports [3, 20, 29], that noradrenaline constricts the dorsal hand vein in a reproducible dose-dependent manner. A single oral dose (5 mg) of bisoprolol could antagonize the venoconstrictor responses to noradrenaline leading to a rightward shift in the dose-response curves of noradrenaline, whereas a single oral dose (40 mg) of nadolol [18] was without effect. Both nadolol and bisoprolol reduced heart rate and blood pressure, in agreement with previous reports [30–32] and consistent with the well-documented effects of these drugs on cardiovascular β-adrenoceptors.

The present results do not support our prediction that the non-selective β_1/β_2-adrenoceptor antagonist nadolol would potentiate the venoconstrictor response to noradrenaline. The lack of effect of nadolol on the response to noradrenaline is unlikely to be due to inadequate absorption of the drug since, in agreement with previous reports [18], 40 mg nadolol had significant pharmacodynamic effects in the cardiovascular system. As the predicted potentiation of noradrenaline-evoked venoconstriction by a non-selective β-adrenoceptor antagonist reflects agonist/antagonist interaction, the lack of potentiation may be due to the pharmacological properties of the agonist, antagonist, or both. Two previous reports may have bearing on these possibilities. First, it has been observed that the non-selective β-adrenoceptor antagonist nifenalol (INPEA) can potentiate the venoconstrictor response to adrenaline but not to

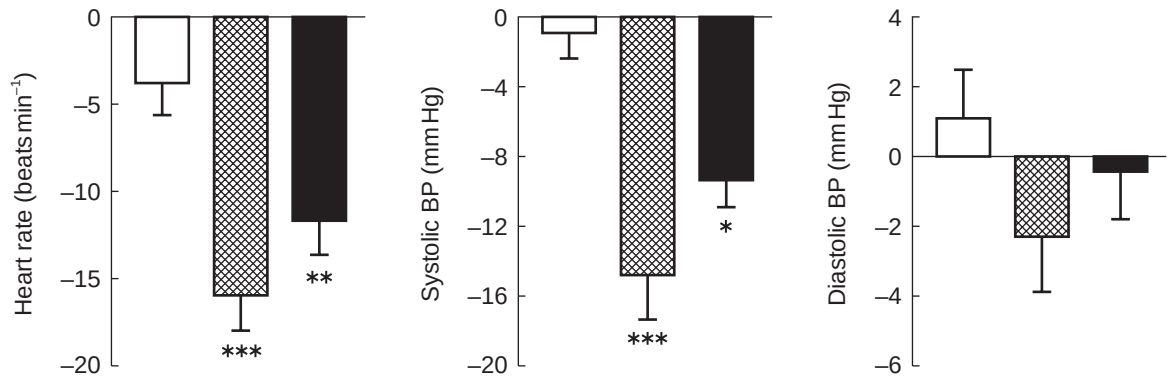

Figure 3 Cardiovascular measures (mean differences; mean ± s.e.mean), before and after placebo (open) and bisoprolol 5 mg (hatched), and nadolol 40 mg (closed). ***$P<0.0001$; **$P<0.001$; *$P<0.01$.

noradrenaline [16], and it is known that adrenaline has a much higher affinity for β_2-adrenoceptors, which may mediate the venodilatation, than noradrenaline [9]. Therefore, it is possible that, in our experiment, β_2-adrenoceptor activation did not attenuate the constrictor response to noradrenaline sufficiently to be revealed by β_2-adrenoceptor blockade. Secondly, it has been reported that another non-selective β-adrenoceptor antagonist, propranolol, can potentiate the venoconstrictor response to noradrenaline [1, 17], suggesting a possible pharmacological difference between nadolol and propranolol. Indeed, it has been proposed, on the basis of forearm plethysmography, that nadolol may have a partial agonistic activity at β-adrenoceptors [33]. If this is the case, venodilatation resulting from the agonistic effect of nadolol at β_2-adrenoceptors may counteract the potentiation of the constrictor response to noradrenaline resulting from the antagonism of the β_2-adrenoceptors. However, it should be noted that the partial agonistic activity of nadolol at β-adrenoceptors is not supported by observation in other test systems [34].

Finally it should be considered whether the mode of administration of the antagonists may have any bearing on our results, since we have administered nadolol systemically whereas O'Grady *et al.* [17] infused propranolol locally into the vein under study. However, there is evidence that single doses of systemically administered β-adrenoceptor antagonists can modify venoconstrictor responses to noradrenaline [35, 36]. Furthermore, it has been shown that venoconstrictor responses to noradrenaline can be potentiated by both locally infused and systemically administered propranolol [1].

It was predicted that bisoprolol, a highly selective β_1-adrenoceptor antagonist [37–38], would either potentiate or not affect the constrictor response to noradrenaline, depending on the contribution of venodilator β_1-adrenoceptors to the response. Since noradrenaline has a high affinity and intrinsic activity at β_1-adrenoceptors [9], any pharmacologically significant β_1-adrenoceptor activation in the dorsal hand vein should have been detected by blocking these receptors with bisoprolol. Indeed, bisoprolol reduced heart rate and systolic blood pressure consistent with effective β_1-adrenoceptor blockade. Contrary to our prediction of potentiation or no effect, bisoprolol antagonized the response. It is possible, theoretically, that the observed antagonism may have masked the potentiation of the response resulting from β_1-adrenoceptor blockade since it has been reported earlier that another β_1-adrenoceptor antagonist, practolol, can enhance noradrenaline-evoked venoconstriction [1], consistent with the presence of venodilator β_1-adrenoceptors in the dorsal hand vein. The possible involvement of β_2-adrenoceptors in the effect of practolol, however, cannot be excluded, since this drug loses its selectivity for β_1-adrenoceptors at higher dosage levels [34].

In a separate study we could confirm that bisoprolol, in a dose dependent fashion, antagonizes both noradrenaline- and phenylephrine-evoked venoconstriction [36]. At present there is no obvious explanation for these observations since bisoprolol is a highly selective β_1-adrenoceptor antagonist with no affinity for venoconstrictor α_1- and α_2-adrenoceptors [37–38]. Furthermore, bisoprolol is devoid of any partial agonistic activity [37–38] which could have resulted in venodilatation and consequent attenuation of the constrictor response to noradrenaline or phenylephrine. Finally, bisoprolol does not possess any direct vascular smooth muscle relaxing effect [39] which again could have resulted in the reduction in noradrenaline- and phenylephrine-evoked venoconstriction. As it has been shown that the β_1-adrenoceptor antagonist nebivolol can antagonize phenylephrine-evoked venoconstriction via the release of nitric oxide from the vascular endothelium [40–41], we have suggested [36] that a similar mechanism may also operate in the case of bisoprolol.

In conclusion, the present experiment using nadolol and bisoprolol, two modern tools recommended for the characterization of β-adrenoceptors [18, 37], failed to produce evidence for a possible role of β-adrenoceptors in attenuating the constrictor response of the dorsal hand vein to noradrenaline.

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