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Oral administration of carvedilol and prazosin inhibits the prostaglandin $F_{2\alpha}$- and noradrenaline-induced contraction of human hand veins in vivo

C. Beermann[1], J. Schloos[2], and G.G. Belz[1]

[1] Zentrum für Kardiovaskuläre Pharmakologie, ZeKaPha GmbH, Mainz-Wiesbaden

[2] Zentrum der Pharmakologie, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt/Main

Summary. Carvedilol is a β-blocker with additional vasodilating activity. This study was performed in order to determine whether the vasodilator action of orally administered carvedilol in man is based upon an α-adrenoceptor antagonism exclusively or if evidence for an additional mechanism could be confirmed. The influence of carvedilol (50 mg p.o.) and prazosin (2 mg p.o.) upon the vasoconstrictor effect of noradrenaline and prostaglandin $F_{2\alpha}$, infused into superficial hand veins, was established in 8 healthy male volunteers. Increasing dosages of the vasoconstrictors below their threshold of systemic activity were employed in order to obtain dose-response curves of the hand veins congested at a venous occlusion pressure of 40 mmHg. These dose-response curves were repeated 1 and 3.5 h after oral administration of either carvedilol, prazosin, or placebo. The ex vivo, in vitro α_1-receptor occupancy in plasma was measured before and after each vasoconstrictor dose-response curve, using an α_1-radioreceptor binding assay. Washout periods of 48 h were kept between study days, investigating the influence of one orally administered drug upon one of the local vasoconstrictor dose-response curves at a time. In the α_1-radioreceptor assay, plasma concentrations from 0.9- to 1.7-fold the equilibrium dissociation constant (K_i) of carvedilol could be evaluated 1 as well as 3.5 h after medication, corresponding with a receptor occupancy of 44%–63%. After prazosin, 9–13 times the K_i values were determined, which amounts to an α_1-adrenoceptor occupation of about 90%–93%. Consequently, the dose-response curves to noradrenaline of the hand veins were attenuated to a greater extent after oral prazosin compared with carvedilol. In contrast, no statistically significant differences between the effects of carvedilol and prazosin could be found as regards the vasoconstriction induced by prostaglandin $F_{2\alpha}$. An oral placebo did not affect the reproducibility of either vasoconstrictor dose-response curve. We conclude that the relatively weak occupancy at α_1-receptors by carvedilol cannot fully explain the effectivity of carvedilol (50 mg p.o.) in inhibiting prostaglandin $F_{2\alpha}$-induced vasoconstriction when compared with prazosin (2 mg p.o.). An additional mechanism of vasodilation could be responsible for this phenomenon.

Key words: Carvedilol – Prazosin – Hand vein – Receptor binding – Vasoconstriction

Carvedilol was developed in the early 1980s as a β-blocking compound with vasodilatory properties [22]. Human as well as animal studies suggest that carvedilol exerts vasodilation through a blockade of α-adrenoceptors [14]. The clinical importance of an additional mechanism of the vasodilative action of carvedilol has been the subject of conflicting reports [8, 15]. In the present study, two different approaches were chosen to gain further insight into the mechanism of action of carvedilol:

1. Investigations by radioreceptor assays (RRA) have proven to be a valuable tool in the determination of receptor-specific actions of drugs. The effects of the parent drug along with active metabolites may be detected by this method, thus providing a link between plasma concentration kinetics and effect time course [23].
2. An elegant method for investigating the action of vasoactive drugs in man was developed by Robinson et al. [20] and Aellig [1]. It provides an opportunity to derive dose-effect curves of vasoconstrictors on human hand veins in vivo. Systemically active doses need not be used, since the vasoactive compound may be infused locally. This renders the possibility of investigating the influence of vasodilatatory drugs on these dose-effect

curves in vivo [6]. Vasodilators may be administered locally or systemically, thus opening a field for evaluating the mechanisms of action of these compounds in man [4].

The present study combines both methods in order to investigate the vasodilating mechanism of carvedilol. An α_1-specific RRA was employed in order to quantify the receptor-specific actions of carvedilol and its metabolites [Schloos et al. unpublished data]. Noradrenaline and prostaglandin $F_{2\alpha}$ were used to constrict human hand veins. The effects of carvedilol on these vasoconstrictor actions were evaluated. Noradrenaline serves as an α-adrenoceptor agonist, whereas prostaglandin $F_{2\alpha}$ exerts a vasoconstriction which is not dependent upon adrenergic mechanisms [3, 10, 21]. Prazosin, an α_1-adrenoceptor antagonist [11], was employed in order to serve as a positive control to carvedilol.

The aim of the present study was to gain further insight into the vasodilating action of carvedilol by comparing the effects of orally administered carvedilol and prazosin.

Methods

Two independent studies of similar design were performed in order to evaluate the influence of carvedilol and prazosin on human hand veins in situ. Eight healthy male volunteers were enrolled in each study after their fully informed, written consent had been obtained. The studies were performed according to the modified declarations of Helsinki and Tokyo.

Study 1, investigating the influence of carvedilol, followed a single-blind, four-way, randomized, crossover design (Fig. 1). On each study day, the volunteers (aged 23–30 years, weighing 72–84 kg) received a single oral dose of 50 mg carvedilol or alternately an oral placebo in combination with one of the i.v. vasoconstrictors. Between study days, washout periods of 48 h were adhered to.

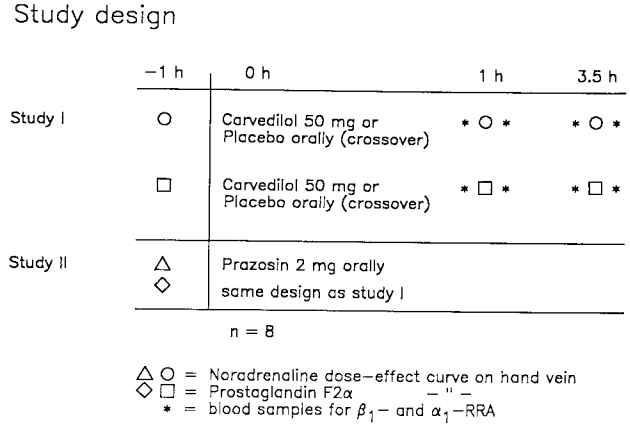


Fig. 1. Design of the studies. RRA, radioreceptor assays

Study 2, employing prazosin, followed a single-blind, two-way, randomized, crossover design (Fig. 1). With one exception, the same volunteers as in study 1 (aged 23–35 years, weighing 72–84 kg) could be recruited. On each study day, they were administered a single oral dose of 2 mg prazosin. Again, washout periods of 48 h were kept between experiment days.

Noradrenaline (Arterenol 1 mg/ml; Hoechst, FRG) was diluted with sterile saline to a concentration of 120 ng/ml. Vitamin C 4 mg/ml (Cebion forte 100 mg/ml; Merck, FRG) was added as an antioxidant. The solution was infused continuously into a superficial hand vein by an infusion pump (Perfusor ED 2; Braun, FRG). Dosages of 6, 18, 54, 162, and 486 ng/min were administered by increasing the rate of infusion from 0.05 to 4.05 ml/min by a factor of 3. Each dosage was given for a period of 4 min.

Prostaglandin $F_{2\alpha}$ (Minprostin $F_{2\alpha}$; Upjohn, FRG) was diluted to a concentration of 4 µg/ml in the same manner as noradrenaline, but no vitamin C was added. The dosages administered were 200, 600, 1800, and 5400 ng/min by increasing infusion rates from 0.05 to 1.35 ml/min by a factor of 3. Again, each dose was infused over a period of 4 min.

Protocol

The volunteers reported to the laboratory after an overnight fast and remained fasting until the completion of each study day. With the subject remaining supine, one hand was elevated above the heart level. A superficial hand vein showing no crossings with other veins was punctured using a butterfly needle (25G). To prevent an occlusion of this needle, a continuous infusion of saline solution (0.9%) was started. Except for the periods during which vasoconstrictors were administered, an infusion rate of 0.33 ml/min was kept.

At 1.5 cm downstream from the tip of the needle, a transducer (LVDT MC025MHR: Schaevitz Engineering, USA) was mounted on the skin above the zenith of the hand vein under investigation. An oscillator/amplifier (Venograph; Boucke, Tübingen, FRG) was used to obtain a chart recording of the transducer signal.

A blood pressure cuff, connected to a regulator (DR 88; Boucke, Tübingen, FRG), was placed around the upper arm. During the last 2 min of the 4-min infusion period for each dose, it was inflated to a pressure of 40 mmHg. The automatic

regulator allowed the maintenance of this venous occlusion pressure precisely. At the end of this 2-min registration period, the diameter of the dilated hand vein was determined. Thereafter, the cuff was deflated, allowing the hand vein to return to its state of rest.

One hour after the baseline vasoconstrictor dose-effect curves had been obtained, the volunteers received the oral medication together with 100 ml of water. Another hour and 3.5 h after drug intake, the vasoconstrictor dose-effect curves were repeated. Before oral medication and at the beginning and after completion of each dose-effect curve, blood was withdrawn for RRA (Fig. 1).

α_1-Radioreceptor assay (α_1-RRA)

Receptor binding studies were carried out with membranes prepared from rat liver as the source of α_1-adrenoceptors using tritiated prazosin as a radioligand. A 200-µl sample of the native plasma was added to 50 µl of the membrane suspension, 30 µl of the radioligand (2 nmol/l, final assay concentration), and 20 µl of 310 mosm/l sodium phosphate buffer (pH 7.4). This mixture was incubated for 2 h at 25° C. The incubation was terminated by rapid filtration under reduced pressure over a glass-fibre filter (Whatman GF/C) for separation of the radioligand bound to the membranes from the unbound fraction. The filters were washed with 10 ml of ice-cold buffer to reduce nonspecific binding. Thereafter, the radioactivity retained on the filters was determined by liquid scintillation counting.

The plasma concentrations of carvedilol and prazosin were calculated in terms of effect equivalents (i.e., multifold of the K_i value) according to the following equation:

$$n \cdot K_i = ((B_{max} \cdot L/(B - nsb \cdot L)) - L) \cdot 1/K_D - 1$$

where B denotes the amount of radioligand bound at the concentration of L, B_{max} is the maximal binding capacity, and K_D the equilibrium dissociation constant of the radioligand; nsb refers to the nonspecific binding of the radioligand, and K_i is the equilibrium dissociation constant of the inhibitor.

Vasoconstrictor dose-effect curves

In the present study, the dosage of the vasoconstrictor was increased by altering the infusion rate rather than changing the concentration of the solution as described by Aellig [1]. Thus, a continuous infusion of noradrenaline or prostaglandin $F_{2\alpha}$ could be obtained. Preceding each dose-effect curve, the infusion rate of saline was increased in the range from 0.05 to 1.6 ml/min in order to exclude an influence of the infused volumes upon the measurement. The registered hand vein diameter, which remained uninfluenced by the infusion rate, served as a baseline value (100%) for the following experiment employing vasoconstrictors.

The diameter of the hand vein was evaluated as follows. Two minutes after the infusion rate of the saline or vasoconstrictor solution had been altered, the cuff was inflated to 40 mmHg. The response of the hand vein to this venous occlusion pressure, reached after another 2-min period, was registered. According to the principles of Robinson et al. [20] and Aellig [1], the change of the skin level above the vein caused by venous occlusion is referred to as the 'diameter' of the hand vein.

Data evaluation

The hand vein diameters thus obtained were calculated and are presented in percentage of the baseline value preceding each experiment. Unless otherwise stated, all values in the figures are presented as means ± SEM.

In order to compare the results in a semiquantitative way, the areas under each dose-effect curve (AUC) were evaluated individually for every experiment. The AUC calculated from the control experiment preceding oral medication was then subtracted from the AUC of either dose-effect curve obtained after oral medication later the same day, thus obtaining ΔAUC. A resulting positive ΔAUC would correspond to a diminished response to the vasoconstrictor after oral medication. The results, depicted as median ± 1st and 3rd quartile, were subjected to a nonparametric testing by the Mann-Whitney U-test.

Results

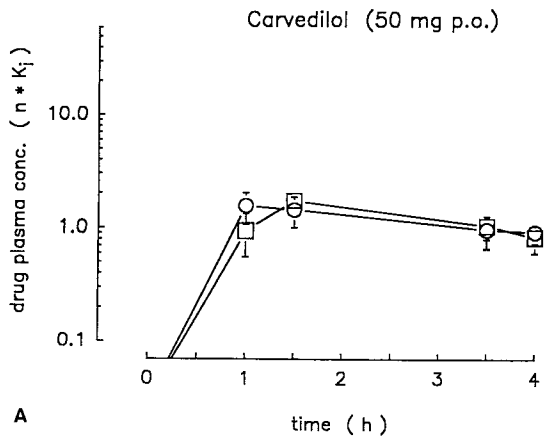
In Table 1 the mean diameters (in mm) of the hand veins before infusion of vasoconstrictors are listed. Neither placebo nor carvedilol or prazosin significantly changed the hand vein diameter under infusion of saline.

Plasma concentrations from α_1-RRA

The α_1-adrenoceptor blocking activities after oral administration of carvedilol and prazosin were determined by an in vitro method using plasma specimens drawn before and after infusion of noradrenaline and prostaglandin $F_{2\alpha}$ (Fig. 1). The resulting

Table 1. Diameter of the hand veins (mm) at 40 mm Hg occlusion of the upper arm during infusion of saline and before administration of vasoconstrictors (mean ± SEM; $n = 8$)

	Placebo		Carvedilol (50 mg p.o.)		Prazosin (2 mg p.o.)	
	Noradrenaline	$PGF_{2\alpha}$	Noradrenaline	$PGF_{2\alpha}$	Noradrenaline	$PGF_{2\alpha}$
Before medication	1.30 ± 0.12	1.34 ± 0.10	1.34 ± 0.08	1.33 ± 0.07	1.35 ± 0.13	1.19 ± 0.13
Medication + 1 h	1.27 ± 0.11	1.32 ± 0.10	1.29 ± 0.09	1.25 ± 0.06	1.25 ± 0.12	1.15 ± 0.11
Medication + 3.5 h	1.28 ± 0.11	1.27 ± 0.10	1.30 ± 0.09	1.27 ± 0.06	1.20 ± 0.12	1.14 ± 0.09



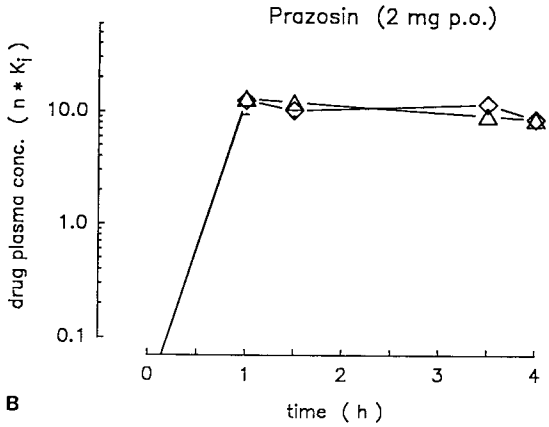
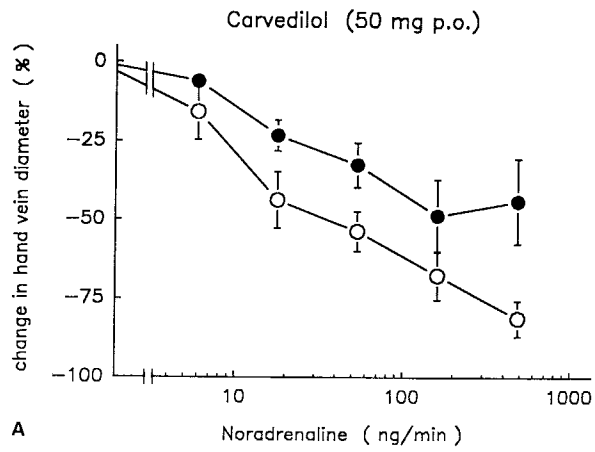


Fig. 2A, B. Time course of plasma concentrations after oral administration of 50 mg carvedilol (**A**) and 2 mg prazosin (**B**). The plasma concentrations are expressed as multiples of the K_i value of the respective drug as determined using the α_1-RRA (mean ± SEM). Blood samples were taken before (1 h, 3 h) and after (1.5 h, 3.5 h) the dose-effect curves of noradrenaline (○, △) and prostaglandin $F_{2\alpha}$ (□, ◇) were derived



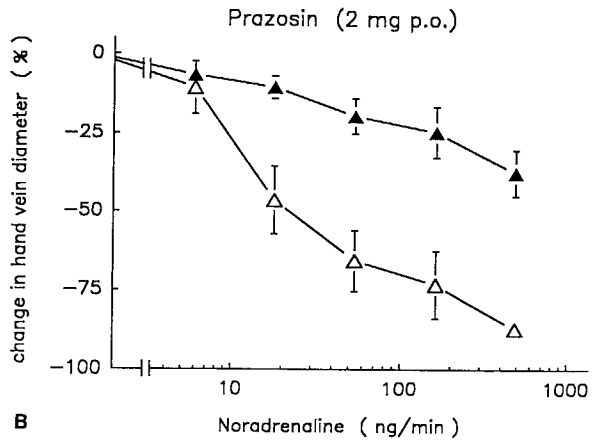


Fig. 3A, B. Dose-effect curves for noradrenaline-induced venoconstriction before (*open symbols*) and 1 h after (*closed symbols*) oral administration of 50 mg carvedilol (**A**) and 2 mg prazosin (**B**). Changes in hand vein diameter were measured at a cuff pressure of 40 mmHg and are given as percentage of the control value before infusion of noradrenaline (mean ± SEM; $n = 8$)

plasma concentrations, expressed in multiples of the equilibrium dissociation constant (K_i) of carvedilol and prazosin, were calculated from the inhibition of receptor binding and are depicted in Fig. 2.

After administration of 50 mg carvedilol p.o., plasma concentrations reached levels of 0.9–1.7 · K_i at 1–1.5 h, with a small decline to 0.8–1.0 · K_i at 3.5–4 h (Fig. 2A). The receptor occupancy due to the free concentration of the antagonist present in the plasma sample thus amounted to 44%–63% during this study period.

After 2 mg prazosin p.o., plasma concentrations were higher compared with carvedilol, reaching 10–13 · K_i after 1–1.5 h and 9–11 · K_i after 3.5–

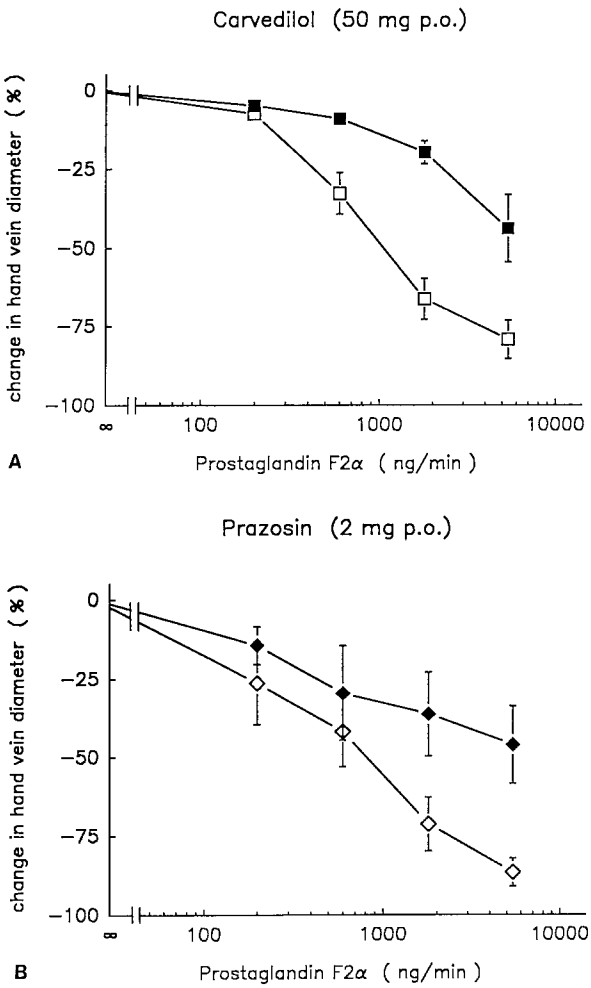


Fig. 4 A, B. Dose-effect curves for venoconstriction induced by prostaglandin $F_{2\alpha}$ before (*open symbols*) and 1 h after (*closed symbols*) oral administration of 50 mg carvedilol (**A**) and 2 mg prazosin (**B**). Changes in hand vein diameter were measured at a cuff pressure of 40 mmHg and are given as percentage of the control value before infusion of prostaglandin $F_{2\alpha}$ (mean ± SEM; $n = 8$)

4 h following oral medication (Fig. 2B). This corresponds to a receptor occupancy of 90%–93%. Only small variations occurred with respect to the plasma concentrations of carvedilol and prazosin when given repeatedly on different study days.

Noradrenaline dose response of human hand veins in situ

The dose-effect curves of noradrenaline-induced venoconstriction before and 1 h after administration of 50 mg carvedilol p.o. are depicted in Fig. 3A. A significant attenuation of the response of the hand vein to locally infused noradrenaline could be observed as compared with placebo.

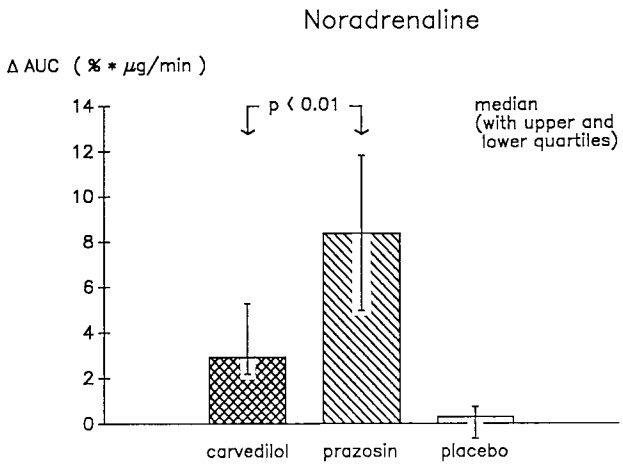


Fig. 5. Difference between the area under the dose effect curves (ΔAUC) determined by infusion of noradrenaline before and 1 h after oral administration of 50 mg carvedilol p.o., 2 mg prazosin p.o., or placebo (median ± 1st and 3rd quartile; $n = 8$)

From the calculated ΔAUC, this could be verified at the 5% significance level. The median ΔAUC is shown in Fig. 5. Similar results were obtained 3.5 h after carvedilol (not depicted).

Oral administration of 2 mg prazosin leads to a greater attenuation of the local venoconstrictive effect of noradrenaline than 50 mg carvedilol. This result, depicted in Fig. 3B for the dose-effect curve, obtained 1 h after administration of the oral medication was also confirmed at 3.5 h (not shown). From the calculation of the ΔAUC as shown in Fig. 5, this difference between carvedilol and prazosin effects could also be verified at the 1% significance level.

Prostaglandin $F_{2\alpha}$ dose response of human hand veins in situ

Prostaglandin $F_{2\alpha}$ possesses a lower venoconstrictive potency as compared with noradrenaline since higher dosages were required to reach a comparable venoconstrictor effect. No significant alteration of the local effect of prostaglandin $F_{2\alpha}$ could be observed during the placebo experiment. Similar to noradrenaline, the dose-dependent venoconstriction caused by locally infused prostaglandin $F_{2\alpha}$ was attenuated 1 h after carvedilol p.o. (Fig. 4A). This is obvious from the calculation of the ΔAUC as depicted in Fig. 6 and could also be verified at the 5% significance level.

Similar to carvedilol, the venoconstriction induced by locally infused prostaglandin $F_{2\alpha}$, was attenuated 1 h after 2 mg prazosin p.o. Figure 4B compares the results of these experiments with

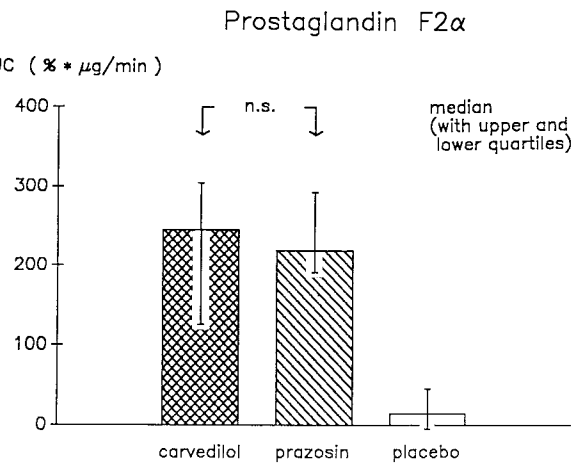


Fig. 6. Difference between the area under the dose effect curves (ΔAUC) determined by infusion of prostaglandin $F_{2\alpha}$ before and 1 h after oral administration of 50 mg carvedilol p.o., 2 mg prazosin p.o., or placebo (median $\pm$ 1st and 3rd quartile; $n=8$)

those after carvedilol p.o. In contrast to the local effect of noradrenaline, no statistically significant differences could be observed between the ΔAUCs, evaluated after administration of carvedilol or prazosin (Fig. 6). Similar results were obtained 3.5 h after oral medication (not depicted).

Discussion

This study in man clearly confirms that carvedilol administered in a single oral dose of 50 mg possesses α_1-antagonistic properties. As compared with carvedilol (50 mg p.o.), prazosin (2 mg p.o.) resulted in a considerably higher α_1-adrenoceptor binding activity. The evaluation of the RRA suggests that carvedilol led to an about 50% occupation of the α-adrenoceptors, whereas in the experiments employing prazosin an at least 90% blockade of α-adrenoceptors could be observed. The α-blockade exerted by both drugs was not significantly altered throughout the course of the experiments (i.e., up to 4 h) as expected from investigations on the pharmacokinetics for both drugs [16, 18].

As described by Collier et al., administration of vasodilating substances do not affect the resting hand vein diameter [6]. Since vasodilation must be interpreted as anti-vasoconstriction rather than active dilatation [5], this observation leads to the conclusion that the adrenergic tone of the resting hand vein must be very low. Hence, a preconstriction of the hand vein is necessary in order to evaluate vasodilating effects [19].

Aellig's method provides a unique opportunity for establishing nearly complete dose-effect curves of vasoconstrictors on human hand veins in vivo. The results from the placebo experiments as well as reports from other authors show that these dose-effect curves are reproducible even from day to day, although a great interindividual variety may be observed [3, 12, 13]. Consequently, a quantitative analysis of the data obtained from these experiments is permissible.

The calculation of the ED_{50} of vasoconstrictors (agonists) and the evaluation of rightward shifts by antagonists as originally described by Arunlakshana and Schild [2] form a frequently used method for quantitative drug analysis. Since the evaluation by Schild plots applies only to competitive receptor antagonism, another approach had to be chosen in order to avoid assumptions about the vasodilating mechanism of carvedilol. A semiquantitative analysis of the AUC was performed in order to compare the effects of oral placebo, carvedilol, and prazosin on the dose-effect curves of noradrenaline and prostaglandin $F_{2\alpha}$.

In order to obtain a coarse measure for the attenuation of venoconstrictor effects, the AUC of the control experiment was subtracted from the AUC evaluated after administration of medication. After placebo no resulting ΔAUC, i.e., a good reproducibility of the local vasoconstrictor actions, could be observed. The effect of prostaglandin $F_{2\alpha}$ was attenuated to the same extent after 50 mg carvedilol p.o. as after 2 mg prazosin p.o. The resulting ΔAUC for prostaglandin $F_{2\alpha}$ showed no statistically relevant difference between both orally administered drugs. We conclude from this that the dosages of carvedilol and prazosin used in these experiments are about equieffective as regards the nonadrenoceptor-dependent vasoconstrictor action of prostaglandin $F_{2\alpha}$ [9].

In contrast to prostaglandin $F_{2\alpha}$, a statistically significant difference between the AUCs for noradrenaline obtained before and after carvedilol or prazosin could be seen. The adrenoceptor-mediated venoconstrictor effect of noradrenaline was attenuated to a greater extent after oral administration of the α-blocker prazosin than after carvedilol. The rightward shift of the noradrenaline dose-effect curves in vivo was paralleled by the degree of ex vivo, in vitro inhibition of α_1-receptor binding after carvedilol and prazosin p.o.

If carvedilol like prazosin were to exert vasodilation mainly via α-adrenoceptor blockade, no difference between the ΔAUCs for noradrenaline would be expected as regards the results of the experiments with prostaglandin $F_{2\alpha}$. However, noradrenaline is not an exclusive α_1-adrenoceptor

agonist. It also mediates β-adrenoceptor-induced venodilation, which could be attenuated by β-adrenoceptor antagonists [24]. It might be argued that the abolition of this β-adrenoceptor-induced venodilation by noradrenaline after medication with the β-blocking agent carvedilol could be responsible for the less pronounced attenuation of the vasoconstrictor effect of noradrenaline as compared with prazosin. However, the relevance of this mechanism is deemed small [7, 17], and our investigations of carvedilol and prazosin by RRA clearly demonstrated a difference in occupation of α_1-receptors. Therefore, we believe that even a possible attenuation of β-adrenoceptor-mediated vasodilation could not fully explain the results observed following carvedilol administration.

We conclude that the relatively weak occupancy of α_1-receptors by carvedilol cannot fully explain the effectivity of carvedilol (50 mg p.o.) in inhibiting prostaglandin $F_{2\alpha}$-induced vasoconstriction when compared with prazosin (2 mg p.o.). An additional mechanism of vasodilation could be responsible for this phenomenon. Although the antihypertensive effect of carvedilol is located mainly on the arterial side of circulation, no fundamental differences in the response to vasoconstrictors can be expected between arteries and veins [19]. Since the present results were derived from human blood vessels in vivo, we may also conclude that another vasodilative mechanism of carvedilol besides α-adrenoceptor blockade could play a role in the therapeutic effects of this new drug.

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Prof. Dr. med. G.G. Belz
Alwinenstrasse 16
W-6200 Wiesbaden, FRG

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Pharmacological profile of β-adrenoceptor blockers with vasodilating properties, especially carvedilol – rationale for clinical use

G. Sponer, W. Bartsch, and K. Strein
Boehringer Mannheim GmbH, Cardiovascular Pharmacology

Summary. The rationale for the combined use of β-adrenoceptor antagonists and vasodilators is to improve the efficacy of the antihypertensive therapy and to reduce the incidence of side effects. If suitable coagents are selected and used at appropriate doses, the disadvantages of each separate component (compromised blood flow to individual organs, increase in total peripheral resistance, unfavorable lipid profile for β-blockers; stimulation of counter-regulatory mechanisms, retention of water and electrolytes for vasodilators) can be balanced. In addition, the favorable effects of each (reduction in cardiovascular morbidity and mortality for β-blockers, and favorable hemodynamic profile for vasodilators) may be used to advantage. Such a treatment rationale can be accomplished by a free combination or by using a dual-acting drug. From the practical point of view, the latter may be preferable. The basic requirement for such a drug is that the two effects are evoked in the same dose range. Carvedilol is a dual-acting drug designed to produce β-blockade and vasodilatation in the same dose range. The vasodilatation is mediated predominantly by specific α_1-adrenoceptor blockade; at markedly higher concentrations additional vasodilating actions can be observed. These effects resemble those of Ca^{2+}-antagonistic properties. However, they do not contribute to the acute blood-pressure-lowering activity, but may be responsible for the increased blood flow to some organs. At β-blocking doses, carvedilol reduces the total peripheral resistance, and blood flow to the kidneys is preserved. Cardioprotection has been demonstrated in a variety of experimental investigations.

Key words: Carvedilol – β-adrenoceptor blockade – Vasodilatation – Hemodynamics – Mode of action

Rationale for the use of β-blockers with additional vasodilating properties

The main hemodynamic disorder underlying arterial hypertension is the abnormally high peripheral vascular resistance. The most rational goal of any drug therapy should therefore be to restore normal hemodynamic conditions at rest and under physical or emotional stress, while reducing blood pressure to normotensive levels. Consequently, any strategy for the treatment of established hypertension should include vasodilating compounds. For this reason, drugs which decrease the blood pressure via reduction of total vascular resistance, such as dihydropyridines, ACE-inhibitors, K^+-channel openers, and selective α_1-adrenoceptor antagonists have drawn increasing attention in recent years. However, therapy with only a variety of vasodilators may not be reasonable in some cases, because they also induce activation of such counterregulatory mechanisms as reflex tachycardia and stimulation of the renin-angiotensin-aldosterone system. These compensatory responses may limit the antihypertensive activity of the drugs. On the other hand, long-term treatment with most β-adrenergic receptor blockers does not reduce the vascular peripheral resistance in hypertensive patients and, therefore, does not correct abnormal hemodynamics, particularly during exercise [13]. Moreover, the blood pressure of some hypertensive patients treated with β-blockers cannot be controlled because of adrenergic vasoconstriction [2].

Thus, the blood pressure of many hypertensive patients cannot be adequately controlled by monotherapy. This may be due to either a limited efficacy of the agent used or the occurrence of side effects. A combination of drugs provides a higher efficacy and, therefore, a greater response rate, because of the combined blood-pressure-lowering activities of agents with different mechanisms. Addi-