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Pharmacodynamic profile of bisoprolol, a new β_1-selective adrenoceptor antagonist

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1 The pharmacodynamic profile of bisoprolol, a new β_1-selective adrenoceptor antagonist, was investigated in four independent studies including 36 healthy male volunteers.
2 Using the model of exercise-induced tachycardia (ET) the β-adrenoceptor blocking properties of bisoprolol (2.5–40 mg) were examined in comparison to metoprolol (50 and 100 mg), propranolol (40 and 80 mg) and atenolol (50 and 100 mg). The maximal reduction of ET was achieved between 1 and 4 h following single oral administration.
3 The dose-response relationship using individual maximal reduction of ET showed, on a molar basis, that bisoprolol is about 5, 7 and 10 times more effective than propranolol, atenolol and metoprolol, respectively.
4 In the model of insulin-induced hypoglycaemia bisoprolol behaved as a β_1-selective adrenoceptor antagonist.
5 There was a good correlation ($r = 0.94$) between the log bisoprolol concentration and the reduction in exercise-induced tachycardia.
6 Bisoprolol is a potent new cardioselective β-adrenoceptor antagonist with a competitive action at β_1-adrenoceptors.

Keywords bisoprolol β_1-adrenoceptor antagonist pharmacodynamics

Introduction

Bisoprolol fumarate (2:1), (±)-1-((α-(2-isopropoxyethoxy-*p*-tolyl)oxy)-3-(isopropylamino)-2-propanol-fumarate (2:1), (in this paper termed bisoprolol), has been characterized in animal studies as a β-adrenoceptor antagonist with exceptionally high β_1-adrenoceptor selectivity, without intrinsic sympathomimetic activity and practically no membrane stabilizing activity (Brodde *et al.*, 1985; Manalan *et al.*, 1982; Schliep & Harting, 1984). The plasma elimination half-life of bisoprolol in healthy volunteers is 10–12 h, which should permit a once-a-day dose regimen in man. Another favourable pharmacokinetic feature is the high bioavailability of 90% (Leopold, 1986; Leopold *et al.*, 1982, 1986). In order to assess the basic pharmacodynamic profile of bisoprolol in man its β-adrenoceptor antagonistic potency, the β_1-adrenoceptor selectivity and concentration–effect relationships were investigated in four independent studies in healthy volunteers.

Methods

Subjects

Thirty-six healthy male volunteers aged between 19 and 43 years were involved in the studies. The subjects took no medication and their physical examination as well as clinical laboratory checks did not indicate any pathological changes. The body weight was within the range of ± 10% of normal (Table 1).

The studies were performed in accordance with the legal provisions of the Federal Republic of Germany and the revised Declaration of Helsinki including review by the local ethical review committee GGEM (Gutachtergremium Experimentelle Medizin) and written informed consent was obtained.

Study protocols

Studies 1 and 2 The β-adrenoceptor blocking properties of bisoprolol were examined using

the model of exercise-induced tachycardia (McDevitt, 1977) in comparison to the non-selective β-adrenoceptor antagonist propranolol and the β_1-selective adrenoceptor antagonists metoprolol and atenolol.

The following doses were ingested by the subjects after an overnight fast together with a light standard breakfast at intervals of 1 week: In study 1 (single-blind cross-over design): bisoprolol (2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg), metoprolol (50 mg, 100 mg), propranolol (40 mg, 80 mg) and placebo as tablets. In study 2 (double-blind, randomized, cross-over design): bisoprolol (5 mg, 10 mg), atenolol (50 mg, 100 mg), and placebo as capsules.

The β-adrenoceptor antagonistic effect was assessed by measuring pulse rate (PR), systolic blood pressure (SBP) (Korotkoff's phase I) and diastolic blood pressure (DBP) (phase V).

Measurement: Pulse rate was taken manually (15 s) before and prior to the end of 5 min of exercise. Blood pressure was measured indirectly using calibrated sphygmomanometers (Boso) in supine position before and immediately after the end of 5 min of exercise.

Since the values in the control test showed only minimal circadian variation, the changes during active drug treatment were related to the individual pre-drug value. Additionally the rate-pressure product (RPP = SBP × PR) was calculated (Robinson, 1967).

The physical workload on a bicycle ergometer (Dynavit Conditronic 30, Keiper) was individually adjusted to produce a pulse rate of 150 beats min^{-1} within 5 min of exercise.

Times of measurement: Study 1: measurements were made pre-drug and at hourly intervals up to 8 h post administration (p.a.) before and after exercise. Study 2: measurements were made pre-drug, at hourly intervals up to 10 h and at 24 h p.a. before and after exercise.

In both studies the relative β-adrenoceptor antagonistic efficacy of the different drugs was calculated utilizing the model of parallel dose-effect relationship after log transformation of the molar doses. The target variable was the maximal reduction in pulse rate relative to the pre-drug value. In study 2 the 95% confidence interval was also calculated (Cavalli-Sforza, 1972).

Study 3: The β_1-adrenoceptor selectivity of bisoprolol was investigated using the model of insulin-induced hypoglycaemia (Newman, 1976, 1977) in comparison to metoprolol and propranolol, in a single-blind cross-over study with a preliminary placebo phase. After an overnight fast the subjects ingested as single doses bisoprolol 10 mg, metoprolol 50 mg and propranolol 40 mg at an interval of 7 days. Three hours after medication 0.1 i.u. insulin kg^{-1} bodyweight was injected intravenously. The cardiovascular parameters heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were automatically recorded (Dinamap, Critikon) before medication, directly before the administration of insulin and then for 2 h at 15 min intervals. The influence on carbohydrate metabolism was studied by measuring serum glucose and serum lactate concentrations directly before the administration of insulin and then for 2 h at 15 min intervals.

Heart rate, serum glucose and serum lactate concentrations were subjected to statistical evaluation. The variation of these variables as a function of time was expressed as: i, maximum change (Δ max) between 0.5 and 2 h compared to the 0 h (pre-insulin) value, negative values represent a decrease compared to the value at 0.5 h (post-insuliin) and positive values in increase; and ii, area from the 0 h (pre-insulin) level and the course of the measurements between 0.5 and 2 h (post-insulin). Positive values represent areas below the initial level and negative values areas above the initial level. The target variables were evaluated in separate two-factorial analyses of variance with the factors 'medication' and 'volunteers'. Significant effects of medication ($P < 0.05$) were subsequently checked with Tukey's test to identify differences between treatments.

Study 4: The relationship between plasma concentration of bisoprolol and pharmacologic effect (inhibition of exercise-induced tachycardia) was studied in a placebo controlled double-blind randomized cross-over study following intravenous injection of 10 mg bisoprolol (in 20 ml).

Measurements were made at: 0, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h after medication.

Bisoprolol plasma concentrations were determined using a specific h.p.l.c. method (Bühring

Table 1 Anthropometric data of the volunteers (mean, s.d.)

	Study 1	*Study 2*	*Study 3*	*Study 4*
Number	$n = 6$	$n = 10$	$n = 10$	$n = 10$
Age (years)	31 ± 8	33.1 ± 6.7	33.0 ± 6	31.0 ± 9
Body weight (kg)	83 ± 7	77.4 ± 6.6	77.5 ± 9.6	82.6 ± 8.8
Height (cm)	181 ± 2	177.6 ± 4.2	175 ± 7	181 ± 6

Table 2 β-adrenoceptor antagonistic properties of bisoprolol, metoprolol and propranolol in the model of exercise-induced tachycardia. (n = 6, single-blind, cross over)

Substance	*Oral dose* (*mg*)	*Mean changes in % of the pre-drug value at respective time of maximal effect (taken from the mean curves for PR, see Figure 1) (mean (s.d.))*			
		PR	*SBP*	*DBP*	*RPP*
Bisoprolol	2.5	−13 (2)	−16 (4)	−4 (4)	−27 (3)
	5	−15 (4)	−21 (4)	−2 (5)	−33 (5)
	10	−18 (4)	−28 (5)	−7 (7)	−41 (5)
	20	−24 (7)	−25 (4)	−4 (6)	−43 (7)
	40	−26 (8)	−29 (3)	−8 (8)	−47 (2)
Metoprolol	50	−16 (5)	−23 (3)	−17 (4)	−35 (5)
	100	−19 (7)	−23 (4)	−15 (1)	−38 (7)
Propranolol	40	−19 (5)	−25 (3)	−7 (6)	−39 (6)
	80	−22 (2)	−32 (2)	−10 (5)	−47 (2)
Placebo		+4 (2)	−3 (6)	−10 (9)	−5 (4)

PR = pulse rate
SBP = systolic blood pressure
DBP = diastolic blood pressure
RPP = rate pressure product

& Garbe, 1986) with a lower limit of detection of 1–2 ng ml^{-1}. The plasma concentration effect relationship was assessed in a semilogarithmic plot of bisoprolol plasma concentrations *vs* reduction of exercise-induced tachycardia observed at the corresponding time plots. Bicycle ergometry was as described for studies 1 and 2.

Results

Studies 1 and 2

Bisoprolol caused a dose-dependent reduction in exercise-induced tachycardia (Table 2 and 3, Figures 1 and 2). Also propranolol and metoprolol in study 1 and atenolol in study 2 (Figure 2 and Table 3) resulted in a dose-dependent reduction in exercise-induced tachycardia. The maximum effect was observed between 1 and 4 h after administration. In study 2, where the 24 h p.a. values were measured, there was a clear reduction in exercise-induced tachycardia present after oral administration of 5 and 10 mg bisoprolol as well as with 50 and 100 mg atenolol (Figure 2 and Table 3).

Bisoprolol also reduced the exercise-induced increase in systolic blood pressure (Table 2) and the rate-pressure product (Table 2). There were no differences in diastolic blood pressure in comparison to placebo (Table 2 and 3).

Figure 3 shows the dose effect relationships resulting from study 1 and 2. It is justified to combine these results because the values for 5 and 10 mg bisoprolol have been reproduced in the second study under a double-blind, randomized situation.

On a molar basis, bisoprolol was about 5, 7

Table 3 β-adrenoceptor antagonistic properties of bisoprolol and atenolol in the model of exercise-induced tachycardia.
(n = 10, double-blind, cross over, randomized)

Substance	*Oral dose* (*mg*)	*Mean changes in % related to the pre-drug value at the time of maximal effect (mean (s.d.))*				*% residual effect 24 h p.a. related to the maximal value = 100%*
		PR	*SBP*	*DBP*	*RPP*	*PR*
Bisoprolol	5	−17 (3)	−17 (4)	+3 (3)	−31 (3)	42
	10	−19 (3)	−18 (4)	−4 (8)	−34 (5)	54
Atenolol	50	−19 (3)	−20 (5)	−3 (8)	−36 (6)	32
	100	−21 (5)	−22 (6)	+2 (4)	−38 (8)	65
Placebo		+3 (3)	+3 (3)	+8 (8)	+6 (5)	

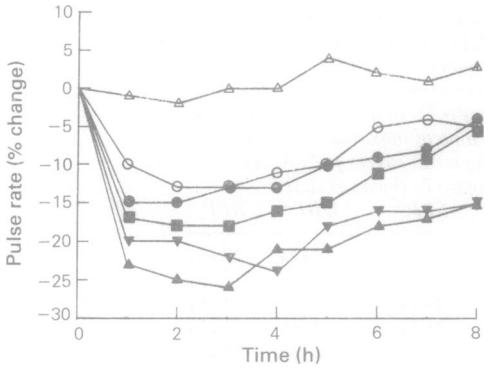

Figure 1 Mean reduction of exercise-induced tachycardia in six volunteers following single oral doses of bisoprolol (○ 2.5 mg, ● 5 mg, ■ 10 mg, ▼ 20 mg, ▲ 40 mg) and placebo (△).

and 10 times more potent than propranolol, atenolol and metoprolol, respectively. The 95% confidence interval for factor 7 in study 2 (bisoprolol *vs* atenolol) is 3.75–13.17.

Study 3

Compared to the control values the resting heart rate was slightly but similarly reduced under the influence of all three β-adrenoceptor antagonists until the time point of i.v. administration of insulin (Figure 4b). The tachycardia observed in the placebo experiment as a result of the hypoglycaemia was virtually eliminated by propranolol, whereas this reaction was only damped by bisoprolol and metoprolol.

Under the influence of all four treatments on average a nadir of the glucose concentration of about 1 mmol l^{-1} was reached 30 min after i.v. administration of insulin (Figure 4a).

The rise of the serum glucose concentration in the recovery phase (= 30 min to 2 h after the i.v. administration of insulin) was delayed by propranolol whereas under the influence of bisoprolol and metoprolol the recovery from hypoglycaemia was only slightly delayed.

Under control conditions hypoglycaemia led to a rise of the serum lactate concentration, which was strongly reduced by propranolol but not by bisoprolol or metoprolol (Figure 4c).

Statistically significant differences due to the medication ($P < 0.05$) were found for the variables: HR (Δ max, area) serum glucose (area) and serum lactate (Δ max). No differences could be found between bisoprolol and metoprolol by the pairwise comparisons in the Tukey's test. Significant differences ($P < 0.05$) were found in comparison with propranolol.

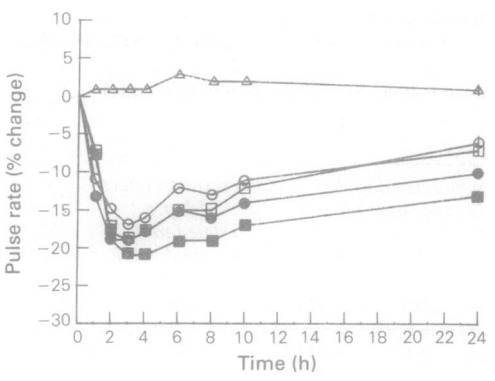

Figure 2 Mean reduction of exercise-induced tachycardia in 10 volunteers following single oral doses of bisoprolol (○ 5 mg, ● 10 mg), atenolol (□ 50 mg, ■ 100 mg) and placebo (△).

Study 4

The plasma concentrations of bisoprolol after i.v. administration of 10 mg decreased from an average of 43.1 ng ml^{-1} (1 h p.a.) to 8.0 ng ml^{-1} (24 p.a.). The mean half-life of bisoprolol was about 10 h (mean, s.d.: 9.7 h ± 1.9 h).

There was a close correlation ($r = 0.94$) between the log plasma concentration of bisoprolol and the corresponding pulse rate reductions (Figure 5).

All doses of bisoprolol tested in the four studies were tolerated by the volunteers without symptoms and laboratory parameters remained normal.

Discussion

In the model of exercise-induced tachycardia bisoprolol clearly shows β-adrenoceptor antagonistic activity of high potency in comparison to propranolol, metoprolol and atenolol (Figure 3). The maximal effects after propranolol, metoprolol and atenolol were nearly identical to published data (Johnsson *et al.*, 1975a,b; Harry, 1977, respectively), confirming that this model was working properly. Propranolol, metoprolol and atenolol were used in this model in therapeutic doses and as the results observed are similar to published data, we would expect the possible therapeutic dose range for bisoprolol to be 5–20 mg. This suggestion was substantiated by clinical studies in hypertension and in angina pectoris (Frithz & Weiner, 1985; Hauger-Klevene, 1984; Janka *et al.*, 1986; Kohli *et al.*, 1985; Prager & Wagner, 1984; Weiner & Frithz, 1986). Information about the duration of action of bisoprolol over 24 h was given by study 2 (Table 3 and Figure 2). Twenty-four hours after the oral administration of 5 and 10 mg

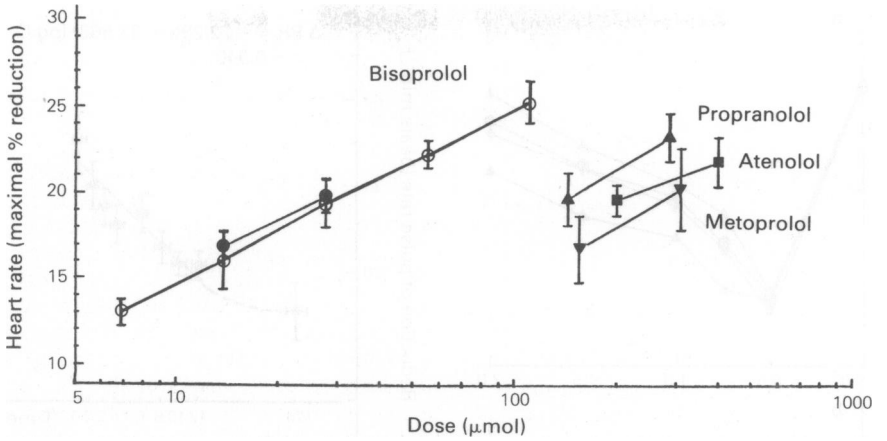

Figure 3 Synopsis of dose-effect-relations of bisoprolol (2.5, 5, 10, 20, 40 mg), propranolol (40 and 80 mg), atenolol (50 and 100 mg) and metoprolol (50 and 100 mg) as single oral doses in the model of exercise-induced tachycardia (individual maximum reductions in pulse rate).
Study 1: bisoprolol (○) propranolol (▲) and metoprolol (▼).
Study 2: bisoprolol (●) and atenolol (■).

bisoprolol residual effects of 42 and 54%, respectively were found, relative to the maximal reduction in exercise-induced tachycardia. This and the plasma elimination half-life of 10–12 h for bisoprolol should allow a once-a-day dosage regimen. This has been confirmed in clinical studies in hypertension (Weiner & Frithz, 1986) and in patients with stable angina pectoris (Wagner, 1986). The values for atenolol are virtually identical with published data (Harry, 1977).

Insulin-induced hypoglycaemia produces a sympathetic stimulus mainly through endogenous adrenaline release and is a valid model for determining the β_1-adrenoceptor selectivity of a β-adrenoceptor antagonist (McDevitt, 1983). The observed degree of hypoglycaemia was sufficient to distinguish between β_1-selective and non-selective β-adrenoceptor antagonists on the basis of the duration of the hypoglycaemic phase (Lager, 1983). The expected reactions to i.v. administration of insulin occurred under control conditions (Figure 4).

The glucose concentration in the serum was reduced, reaching minimum values 30 min after the administration of insulin with subsequent gradual recovery by glucogenolysis in the muscles and in the liver and by hepatic gluconeogenesis. These compensatory metabolic processes are preferentially or at least partly mediated by β_2-adrenoceptors (Weiner & Taylor, 1985). The lactate concentration in the serum rose steeply early in the recovery phase as a manifestation of compensatory muscle glycogenolysis. This response is preferentially mediated by β_2-adrenoceptors and thereafter falls off slowly. This mechanism not only generates glucose directly but also makes lactate available as a substrate for hepatic gluconeogenesis (Lager, 1983). The hypoglycaemia is accompanied by a tachycardia due to an increased release of catecholamines, especially adrenaline (Armitstead *et al.*, 1983; McDevitt, 1983).

After pretreatment with 40 mg propranolol the recovery from hypoglycaemia was delayed and the hypoglycaemia-induced tachycardia was virtually eliminated. These parameters were differently affected after pretreatment with 10 mg bisoprolol or 50 mg metoprolol. In comparison with the situation after propranolol the restoration of normal serum glucose concentrations in the recovery phase was delayed to a significantly smaller extent (Figure 4a). This response is typical for treatment with β_1-selective adrenoceptor antagonists (Deacon & Barnett, 1976; McDevitt, 1977). Under the influence of β_1-selective blockade, especially early in the recovery phase, glycogenolysis and also gluconeogenesis in the liver is (due to maintained responsiveness of the β_2-adrenoceptors) less impeded than following nonselective β-adrenoceptor blockade.

The rise of the serum lactate concentration observed under the influence of pretreatment with bisoprolol and metoprolol is a further indication of the β_1-adrenoceptor selectivity of the two substances, because glycogenolysis, especially in the muscles, is mediated via β_2-adrenoceptors (Lager, 1983). This explains the significantly smaller rise of the serum lactate concentrations under the influence of the β_1/β_2-adrenoceptor antagonist propranolol. The pre-insulin heart rate was lowered by bisoprolol somewhat more than by propranolol and metoprolol (Figure 4b).

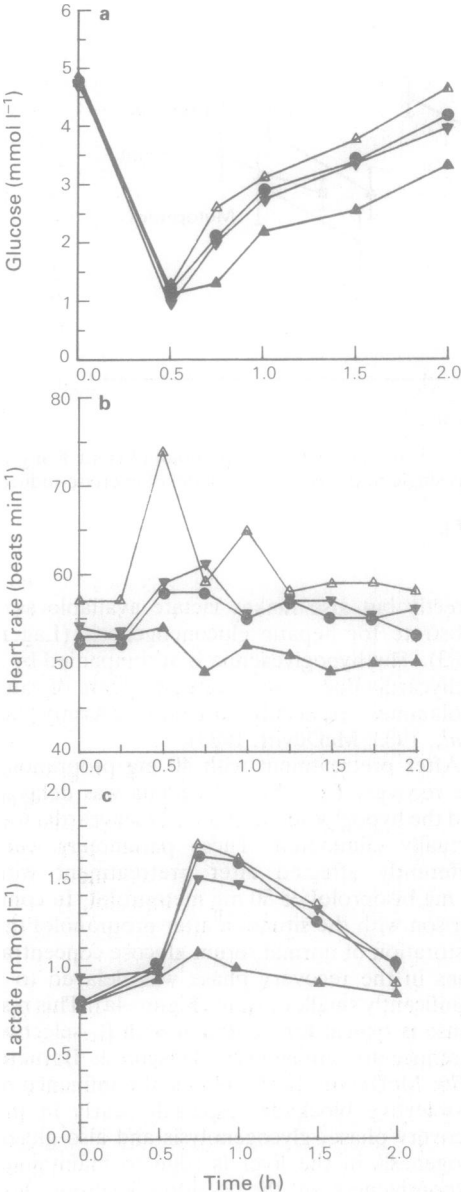

Figure 4 Mean serum glucose concentrations (a), mean heart rates (b) and mean serum lactate concentrations (c), after 0.1 i.u. insulin/kg i.v. (0.0 h) and 3 h after oral administration (−3 h) of placebo (△) and 10 mg bisoprolol (●), 50 mg metoprolol (▼) and 40 mg propranolol (▲).

The explanation (based on the dose effect relationship for exercise-induced tachycardia) is, that the dose of bisoprolol in this study was relatively higher than that of propranolol and especially that of metoprolol. This does not effect the conclusions on the cardioselectivity of bisoprolol

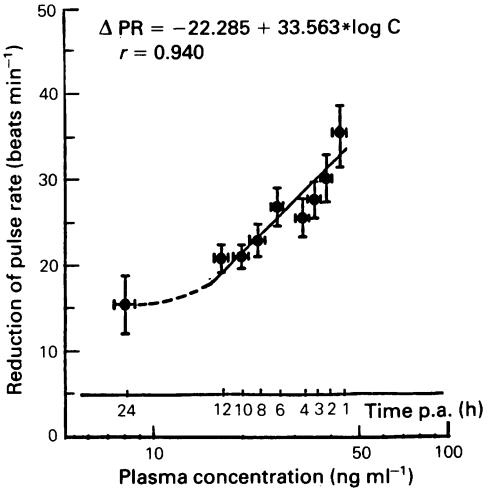

Figure 5 Relationship (mean ± s.e. mean) between plasma concentration of bisoprolol and reduction of pulse rate in the model of exercise-induced tachycardia after 10 mg bisoprolol i.v. Linear regression without the 24 h p.a. value.

compared to propranolol and may even underestimate this property compared to metoprolol.

The inhibition of the hypoglycaemia-induced tachycardia is weaker under the influence of pretreatment with β_1-selective adrenoceptor antagonists than under propranolol. Whereas after pretreatment with β_1-selective adrenoceptor antagonists a tachycardic reaction is maintained during the hypoglycaemic phase (even though at a lower level as compared to the control situation) under the influence of propranolol a further fall in the heart rate was observed. This is the consequence of a hypertensive reaction occurring during hypoglycaemia under the influence of therapy with non-selective β-adrenoceptor antagonists (Östman, 1983). After pretreatment with propranolol the sequence of events is as follows: Intravenous insulin leads to hypoglycaemia which triggers the release of adrenaline. Then, unopposed α-adrenoceptor stimulation from adrenaline release results in a marked diastolic pressor effect, which triggers a bradycardia via the baroreceptors (Davidson *et al.*, 1976).

Thus bisoprolol behaves as a β_1-selective adrenoceptor antagonist in the model of the insulin-induced hypoglycaemia. Clear β_1-adrenoceptor selectivity of bisoprolol was also observed while studying its effect on the ventilatory function in volunteers as well as in patients with chronic obstructive bronchitis or with asthma (Tattersfield *et al.*, 1984; Dorow & Tönnesmann, 1984; Lammers *et al.*, 1984). Since the hypoglycaemia-induced tachycardia is caused primarily

by the release of adrenaline it is of interest to discuss results from Brown, J. E. *et al.* (1983) who studied the effect of a specific β_2-adrenoceptor antagonist (ICI II8551) on adrenaline infusion in man. As in the case of the nonselective β-adrenoceptor blocking propranolol in hypoglycaemia-induced tachycardia, the β_2-adrenoceptor antagonism of ICI 118551 not only prevented the adrenaline-induced tachycardia but also resulted in a slight bradycardia. In both cases, while peripheral β_2-adrenoceptors are antagonized, adrenaline's pressure action probably activates the baroreceptors leading to increased vagal drive and explains (in both situations) the lack of tachycardia or even the bradycardia. Besides this mechanism an antagonistic action on β_2-adrenoceptors in the sinus node may play a role (Brown M. J. *et al.*, 1983; McDevitt, 1983).

Like other β-adrenoceptor antagonists bisoprolol shows a close relationship between plasma concentrations and effect on exercise-induced tachycardia. The curve in Figure 5 may represent the middle and lower segment of a sigmoidal concentration–effect curve, while the upper portion of this curve is not attained after 10 mg bisoprolol.

We conclude that bisoprolol is a β-adrenoceptor antagonist of high potency which exhibits clear β_1-adrenoceptor selectivity throughout the dose range of 5–20 mg. A long elimination half-life of 10–12 h should permit a reliable once-a-day regimen in hypertension as well as in stable angina pectoris.

References

Armitstead, J. G., Lightman, S. L., Brown, M. J., Cauron, R. C. & Vaughan, N. J. A. (1983). The effect of selective and nonselective β-adrenoceptor blockade, and of naloxone infusion, on the hormonal mechanisms of recovery from insulin-induced hypoglycaemia in man. *Br. J. clin. Pharmac.*, **16**, 718–721.

Brodde, O. E., Daul, A. & Bock, K. D. (1985). The intrinsic sympathomimetic activity of β-adrenoceptor antagonists is not β-adrenoceptor-subtype selective. *Naunyn-Schmiedeberg's Arch. Pharmac.*, **326**, Suppl., R 81.

Brown, M. J., Brown, D. C. & Murphy, M. B. (1983). Hypokalemia from beta$_2$-receptor stimulation by circulating epinephrine. *New Engl. J. Med.*, **309**, 1414–1419.

Brown, J. E., McLeod, A. A., Shand, D. G. (1983). Evidence for cardiac β_2-adrenoceptors in man. *Clin. Pharmac. Ther.*, **33**, 424–428.

Bühring, K. U. & Garbe, A. (1986). Determination of bisoprolol, metoprolol, atenolol, and propranolol in plasma and urine. *J. Chromatogr.* (in press).

Cavalli-Sforza, L. (1972). *Biometrie. Grundzüge biologisch-medizinischer Statistik.* 3. Aufl. Stuttgart: G. Fischer Verlag.

Davidson, N. McD., Corrall, R. J. M., Shaw, T. R. D., French, E. B. (1976). Observations in man of hypoglycaemia during selective and non-selective beta-blockade. *Scot. med. J.*, **22**, 69–72.

Deacon, S. P. & Barnett, D. (1976). Comparison of atenolol and propranolol during insulin-induced hypoglycaemia. *Br. med. J.*, **2**, 272–273.

Dorow, P. & Tönnesmann, U. (1984). Dose-response relationship of the beta-adrenoceptor antagonist bisoprolol in patients with coronary heart disease and chronic obstructive bronchitis. *Eur. J. clin. Pharmac.*, **27**, 135–139.

Frithz, G. & Weiner, L. (1985). Effects of bisoprolol administered once daily to patients with essential hypertension. A dose titration study with special reference to the lipoprotein pattern in serum. Abstr. No. 292, *Abstr. Comm. Cardiovascular Pharmacotherapy International Symposium*, Geneva.

Harry, J. D. (1977). The demonstration of atenolol as a beta-adrenoceptor blocking drug in man. *Postgrad. med. J.*, **53**, Suppl. 3, 65–69.

Hauger-Klevene, J. H. (1984). Effect of a new cardioselective beta-blocker in patients with mild and moderate essential hypertension. Bisoprolol (EMD 33 512) Abstr. No. 431, *Abstr. Comm. 10th Scientific Meeting, International Society of Hypertension*, Interlaken, Switzerland.

Janka, H. V., Disselhoff, G., Ziegler, A. G. & Mehnert, H. (1986). Einfluß von Bisoprolol auf den Kohlenhydratstoffwechsel von Typ-II-Diabetikern. *Münch. Med. Wschr.* (in press).

Johnsson, G., Nyberg, G. & Sölvell, L. (1975). Influence of metoprolol and propranolol on hemodynamic effects induced by physical work and isoprenoline. *Acta pharmac. tox.*, **36**, Suppl. V, 69–75.

Johnsson, G., Regardh, C. G. & Sölvell, L. (1975). Combined pharmacokinetic and pharmacodynamic studies in man of the adrenergic β_1-receptor antagonist metoprolol. *Acta pharmac. tox.*, **36**, Suppl. V, 31–44.

Kohli, R. S., Khurmi, N. S., Kardash, M. M., Hughes, L. O., Lahiri, A. & Raftery, E. B. (1985). Efficacy of once daily bisoprolol in stable angina pectoris: an objective comparison with atenolol and long-term follow-up. *Eur. Heart J.*, **6**, 845–850.

Lager, I. (1983). Adrenergic blockade and hypoglycaemia. *Acta med. Scand.*, Suppl., **672**, 63–67.

Lammers, J. W. J., Folgering, H. Th. M. & von Herwaarden, C. L. A. (1984). Ventilatory effects of β_1-receptor selective blockade with bisoprolol and metoprolol in asthmatic patients. *Eur. J. clin. Pharmac.*, **27**, 141–145.

Leopold, G. (1986). Balanced pharmacokinetics and metabolism of bisoprolol. *J. cardiovasc. Pharmac.*, (in press).

Leopold, G., Pabst, J., Ungethüm, W. & Bühring, K. U. (1982). Phase I studies on EMD 33 512, a new β_1-selective adrenoceptor blocking agent. *Clin. Pharmac. Ther.*, **31**, 243.

Leopold, G., Pabst, J., Ungethüm, W. & Bühring,

K. U. (1986). Basic pharmacokinetics of bisoprolol, a new highly β_1-selective adrenoceptor antagonist. *J. clin. Pharmac.* (in press).

Manalan, A. S., Besch, H. R. & Watanabe, A. M. (1982). Characterization of 3H (±) carazol binding to β-adrenergic receptors. *Circ. Res.*, **49**, 326–336.

McDevitt, D. G. (1977). The assessment of β-adrenoceptor blocking drug in man. *Br. J. clin. Pharmac.*, **4**, 413–425.

McDevitt, D. B. (1983). Clinical significance of cardioselectivity. State-of-the art. *Drugs*, **25**, Suppl. 2, 219–226.

Newman, R. J. (1976). Comparison of propranolol, metoprolol and acebutolol on insulin-induced hypoglycaemia. *Br. med. J.*, **2**, 447–449.

Newman, R. J. (1977). Comparison of the antilipolytic effect of metoprolol, acebutolol, and propranolol in man. *Br. med. J.*, **2**, 601–603.

Östman, J. (1983). β-Adrenergic blockade and diabetes mellitus. A review. *Acta med. Scand.*, Suppl. 672, 69–77.

Prager, G. & Wagner, G. (1984). Wirkung von Bisoprolol bei koronarer Herzkrankheit. Einfluß auf Herz-Kreislauf-Parameter und ischämische ST-Streckensenkung: Untersuchung zur Wirkungsdauer. *Dtsch. med. Wschr.*, **109**, 1914–1917.

Robinson, B. F. (1967). Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation*, **35**, 1073–1083.

Schliep, H. J. & Harting, J. (1984). β_1-selectivity of bisoprolol, a new β-adrenoceptor antagonist, in anaesthetized dogs and guinea pigs. *J. cardiovasc. Pharmac.*, **6**,1156–1160.

Tattersfield, A. E., Cragy, D. J., Bacon, R. J. (1984). Assessment of β-adrenoceptor selectivity of a new β-adrenoceptor antagonist, bisoprolol, in man. *Br. J. clin. Pharmac.*, **18**, 343–347.

Wagner, G. (1986). Summary of short- and long-term studies with bisoprolol in coronary heart disease. *J. cardiovasc. Pharmac.* (in press).

Weiner, L. & Frithz, G. (1986). Antihypertensive effects of bisoprolol during once daily administration in patients with essential hypertension. A dose-ranging study with parallel groups. *Eur. J. clin. Pharmac.*, **29**, 517–521.

Weiner, N. & Tayler, P. (1985). Neurohumoral Transmission: The Autonomic and Somatic Motor Nervous Systems. In *The Pharmacological Basis of Therapeutics*, 7th Edn, eds Goodman Gilman, A., Goodman, L. S. & Gilman, A. New York: Macmillan Publishing Company.

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