European Heart Journal (1987) **8**, (*Supplement M*), 103–113

Exercise blood pressure and heart rate reduction 24 and 3 hours after drug intake in hypertensive patients following 4 weeks of treatment with bisoprolol and metoprolol: A randomized multicentre double-blind study (BISOMET)

R. HAASIS* AND H. BETHGE†

**Medizinische Universitätsklinik Tübingen and † Städtische Kliniken, Medizinische Klinik, Darmstadt F.R.G.*

KEY WORDS: Hypertension, beta-adrenoceptor antagonists, metoprolol, bisoprolol, exercise test, duration of action, 24-h residual effects, beta$_1$selectivity

In a 4-week randomized, double-blind study, 87 patients with essential hypertension received either 10 mg bisoprolol (B) or 100 mg metoprolol (M) once daily (o.d.). The effects of the beta blockers on systolic blood pressure, heart rate and rate–pressure product during exercise, 24 h (E2) and 3 h (E3) after administration (p.a.) were compared with the values obtained in the baseline exercise test (E1). 24 hours p.a. the effects of B were significantly stronger than of M (E1–E2: B vs M; $P < 0.01$) whereas 3 h p.a. no significant differences were detectable between B and M. The residual effects 24 h p.a. in relation to the effects 3 h p.a. (E1–E2/E1–E3) were significantly greater with B (86–93%) than with M (53–66%).

In contrast to the findings with 100 mg M o.d., 10 mg bisoprolol o.d. guarantees a persistent reduction in exercise blood pressure and heart rate throughout the entire dosage interval of 24 h.

Introduction

Exercise heart rate is a generally acknowledged parameter for the assessment of the potency of beta blockers. To assess the extent of the beta receptor blockade and the blood pressure reduction at the end of a dosage interval of, for example 24 hours, it is necessary to know the effects that the beta blockers have in the period between the 1st and 4th hour following administration (p.a.). In this period the beta blockers reach their maximum concentration in the blood and also their maximum effect on exercise heart rate.

In only a few studies blood pressure and heart rate have been measured in patients with hypertension after several weeks' administration of beta blockers in the period between the 1st and 4th hour p.a. as well as 24 h p.a. at rest and also during exercise[1–8]. The aim of the present study was to compare the beta blockers bisoprolol (B) and metoprolol (M) with regard to the extent and duration of beta receptor blockade and blood pressure reduction after 4 weeks of treatment. From the relation between the findings 24 and 3 h p.a.—at 100 W during exercise—the residual effects at the end of the dosage interval were to be derived and evaluated in relation to the plasma elimination half-lives of the beta blockers.

Bisoprolol has a plasma elimination half-life of 10–12 h and a bioavailability of 90%[9–11]. The plasma elimination half-life of metoprolol is 3–4 h and its bioavailability is 50%[12]. Neither of the beta blockers shows an intrinsic sympathomimetic activity[12–14] and both are considered beta$_1$selective[12–17]. The beta$_1$selectivity of a beta blocker, however, is not an absolute property but rather a relative one that is dependent on the dose or respectively on the concentration in the blood[15,17,18].

Patients

A multicentre randomized double-blind study with verification of compliance (BISOMET study) was performed. Five centres for hypertensive diseases and 15 general practitioners took part. The study was approved by an ethical committee.

113 outpatients between 18 and 70 years of age

Address for correspondence: Prof. Dr. R. Haasis, Medizinische Universitätsklinik, Innere Medizin II, D-7400 Tübingen, F.R.G.

0195-668X/87/08M103 + 11 $02.00/0

with mild to moderate essential hypertension (WHO stages I and II) and a sitting diastolic blood pressure (at the end of a 2–4-week placebo phase) of >95 to ≤115 mmHg took part in the study.

The following patients were excluded from the study: patients with typical beta-blocker contraindications (congestive heart failure, bronchial asthma, bradycardia at rest (<50 beats min^{-1}), ECG conduction disturbances, refractory diabetes mellitus), patients with essential hypertension of stage III, patients who had had a myocardial infarction within the last 12 months, patients with secondary hypertension, intermittent claudication or angina pectoris (e.g. termination criterion in ergometry), alcoholism, drug abuse, concurrent impaired renal function (creatinine >1·7 mg dl^{-1}), bone marrow, liver, gastrointestinal tract or central nervous system diseases, and women of childbearing age. Concomitant intake of ovulation inhibitors, cimetidine, thyreostatics, antiarrhythmics and psychotropics (phenothiazine, MAO inhibitors, tricyclic antidepressants) was not allowed.

26 of the 113 patients could not be evaluated for efficacy: 6 patients dropped out in the placebo preliminary phase (5 of these on account of side-effects); 2 patients ended the beta-blocker therapy prematurely (see below); 8 patients (3 B, 5 M) showed inadequate compliance; and in the case of the 10 remaining patients (6 B, 4 M), the physicians had not compiled properly with the protocol.

The characteristics of the 87 evaluable patients (44 B, 43 M) are summarized in Table 1. There are no appreciable differences between the two treatment groups.

Study schedule (Fig. 1)

The randomized double-blind study was preceeded by a 2–4 week initial phase in which all patients received a placebo under single-blind conditions. Prior to the initial phase a clinical history was taken and a thorough medical examination was performed to check the inclusion and exclusion criteria. In addition, blood pressure, heart rate (sitting) and body weight were measured, an ECG was recorded and blood and urine samples were taken for laboratory tests. At least 2 weeks and at most 4 weeks after the start of the placebo treatment the randomized double-blind study began as soon as the 3rd diastolic pressure reading with the patient sitting quietly (three readings at 1-minute intervals) was in the range >95 and ≤115 mmHg. At this point, 24 h after the last placebo tablet, the following tests were

Table 1 Patient characteristics

	Bisoprolol	Metoprolol
Number	44	43
Men	30	26
Women	14	17
Age (years)	50·6 ± 9·7*	53·7 ± 7·0*
Weight (kg.)	80·2 ± 12·5*	77·3 ± 12·9*
Height (cm)	174 ± 9*	173 ± 7*
Smokers (no.)	11	12
Coronary heart disease (no.)	1	3
Concomitant therapy (no.) for		
Heart failure	1	2
Hyperuricaemia	4	7
Hyperlipidaemia	5	2
Previous treatment with		
beta blockers (no.)	15	17
Outcome:		
Very good	0	4
Good	6	9
Moderate	7	4
Poor	2	0

* Mean ± SD

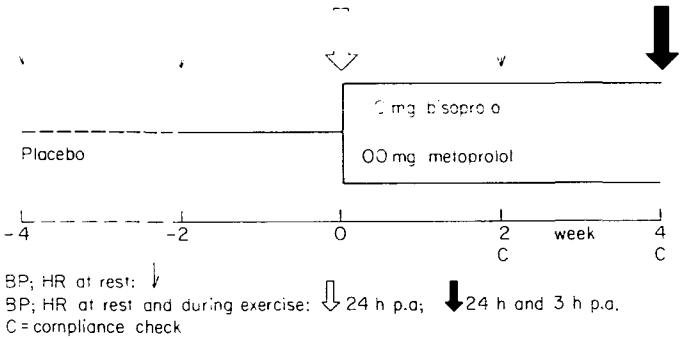

Figure 1 Study schedule (BP = blood pressure, HR = heart rate).

performed: blood pressure and pulse after 5 minutes sitting and during exercise (E1), ECG at rest, laboratory analyses, count of returned capsules, recording of spontaneously reported symptoms. The measurements of blood pressure and heart rate at rest and during exercise were repeated 3 h later. Since some of the patients had already taken the first active-substance capsule by this time, the relevant findings are not reported.

The patients were randomized into two treatment groups: one group received capsules containing 10 mg bisoprolol; the other received capsules of identical shape and color containing 100 mg metoprolol. Sufficient capsules for a 2-week period were issued. One capsule was swallowed with breakfast every morning. After 2 weeks of treatment the following readings were taken: blood pressure and pulse when seated, body weight, any adverse reactions, compliance check by counting the returned capsules and qualitative determination of the beta blocker in a urine sample. The patients were then given the capsules for the remaining 2 weeks. At the end of the 4-week treatment period the following tests were performed in the morning, 24 h after the last beta blocker capsule had been taken: blood pressure and pulse when seated and during exercise (E2), resting ECG, laboratory analyses, recording of any adverse reactions and compliance check. A further capsule was then swallowed in the presence of the doctor. Three hours later the cardiovascular measurements were repeated with the patient seated and during exercise (E3).

Methods of investigation

The blood pressure measurements were always made by the same doctor at the same time of day using a conventional sphygmomanometer. The systolic and diastolic blood pressure readings (SBP and DBP) coincided with the first faint Korotkoff sounds (phase I) and the disappearance of Korotkoff sounds (phase V), respectively. The cuff pressure was reduced by no more than 2–3 mm s^{-1} in the measurement range.

In accordance with the recommendations of Franz[19] the exercise test was performed on an electrically or mechanically braked, regularly calibrated bicycle ergometer operating at a speed of 50 rpm. The exercise began with 2 min at 50 W followed by 2 min at 75 W and 2 min at 100 W. Systolic blood pressure was measured during the last 20 s of each workload and heart rate was determined by means of a ECG recorded during the last 10 s. After the exercise test blood pressure and pulse were measured at 1 min intervals up to the 5th min of recovery, with the patient still seated on the ergometer. The ECGs were evaluated centrally.

Adverse reactions and symptoms reported spontaneously by the patients were recorded by the doctor, assessed according to severity, duration and frequency and evaluated for any possible connection with the beta blockers.

The beta blockers in a 2 ml urine sample were assayed by an HPLC method[20]. The urine samples were stored deep frozen at −20 °C until processed for analysis.

Evaluation

The main aim of the study was to compare the effects of the beta blockers on systolic blood pressure (SBP), heart rate (HR) and rate-pressure product (RPP) following a 4-week treatment period 24 h (E2) and 3 h (E3) p.a. during bicycle ergometry at the end of a 2-minute 100 W workload (confirmative statistics for the SBP differences E1–E2 and E2–E3).

In addition, the following findings were considered and checked for drug related differences in terms of descriptive statistics: HR- and RPP-differences E1–E2 and E2–E3, differences in SBP, HR and RPP at 100 W, differences in the areas (E1 to E2 and E1 to E3) between the ascending curves of SBP, HR and RPP during the entire 6-minute exercise, 24-hour residual effects during ergometry (at 100 W and during the entire exercise period): calculation of the ratios E1–E2/E1–E3 in percentages (the residual activity ratios given in the results were calculated from the differences in mean values and are thus only approximate values: this method of calculation was selected in order to facilitate comparisons with references in the discussion), blood pressure and heart rate at rest following 2 and 4 weeks treatment 24 h and 3 h p.a., and responder rates after 4 weeks treatment (responders were considered those patients whose resting diastolic blood pressure after sitting for 5 minutes was below 95 mmHg; the value that was taken for evaluation was in each case the 3rd of 3 readings taken at 1-minute intervals.)

The planned size of the random sample was 2×45 patients. The difference between the treatments was considered to be at least 10 mmHg (SBP) after 2 minutes exercise at 100 W 24 h p.a. The standard deviation (SD) was estimated to be between 5 and 10 mmHg (SD of the differences E2–E3). The Wilcoxon rank sum test was used for testing the differences. The type 1 error was set at $\alpha = 5\%$. Since two tests (SBP differences E1–E2 and E2–E3 at 100 W) were to be performed for the confirmative statistics at least one of the two tests had to reject the null hypothesis at the $\alpha = 2{\cdot}5\%$ level to achieve the aim of the study. If the other test led to a P-value less than $\alpha = 5\%$, both null hypotheses could be rejected at a type 1 error of $\alpha = 5\%$. This is true in accordance with the Holm–Bonferroni sequentially rejective multiple test procedure.

Results

SYSTOLIC BLOOD PRESSURE, HEART RATE AND RATE-PRESSURE PRODUCT DURING EXERCISE

During exercise 24 h p.a., lower values of SBP, HR and RPP were attained with B than with M at all measurement times (Fig. 2). Comparison of the results with B and M showed that the SBP-differences E1–E2 and E2–E3 at 100 W were significantly different ($P < 0{\cdot}01$ and $P < 0{\cdot}05$, respectively) (Table 2). Significant differences were also found between B and M for the respective HR- and RPP-differences at 100 W, the recorded values at 100 W (Table 2), and for the differences in area (Fig. 3; shaded areas). Three hours p.a. there were no significant differences in the effects of B and M on SBP, HR and RPP during exericse at 100 W (Table 2). This is also valid for the differences in area (not shown separately).

Whereas the 3-hour-effects of the two beta blockers on SBP, HR and RPP were comparable at 100 W and during the entire 6-min exercise period, the 24 h p.a. residual effects were significantly greater with B than with M (86–93% and 53–66% respectively) (Table 3; Fig. 3).

BLOOD PRESSURE AND HEART RATE AT REST

Whereas the SBP, DBP and HR values at the beginning and end of the 2–4-week initial placebo phase were comparable, a significantly greater reduction was observed in resting SBP ($P < 0{\cdot}05$), DBP ($P < 0{\cdot}01$) and HR ($P < 0{\cdot}05$) with B than with M, 24 h p.a., after only 2 weeks of treatment (Fig. 4). After 4 weeks the significantly stronger effect of B on DBP and on HR was still present, whereas the difference in SBP was no longer significant at this point. Three hours p.a. the resting values ($\bar{x} \pm SD$) were as follows in the patients treated with B or M: SBP 137 ± 19 and 141 ± 18 mmHg, respectively ($P < 0{\cdot}05$), DBP 82 ± 9 and 86 ± 8 mmHg, respectively ($P < 0{\cdot}05$), HR 63 ± 8 and 67 ± 10 beats min^{-1}, respectively (NS).

After 4 weeks of treatment the resting diastolic blood pressure 24 h p.a. was less than 95 mmHg in 86·4% of the bisoprolol patients and 69·8% of the metoprolol patients. This difference in responder rate was not significant ($P = 0{\cdot}0526$).

TOLERANCE

13 patients in each treatment group reported at least one adverse reaction during the beta blocker therapy. Symptoms reported by at least 3 patients in one or in both of the treatment groups are listed in Table 4. In the preliminary placebo phase headache and vertigo were reported by 7 and 3 patients, respectively. During the beta-blocker treatment the predominant symptoms were headache on metoprolol and nausea on bisoprolol. The symptoms were mostly assessed as mild/moderate and short/transient. One bisoprolol patient dropped out on account of nausea and vomiting after 1 week of treatment. One metoprolol patient

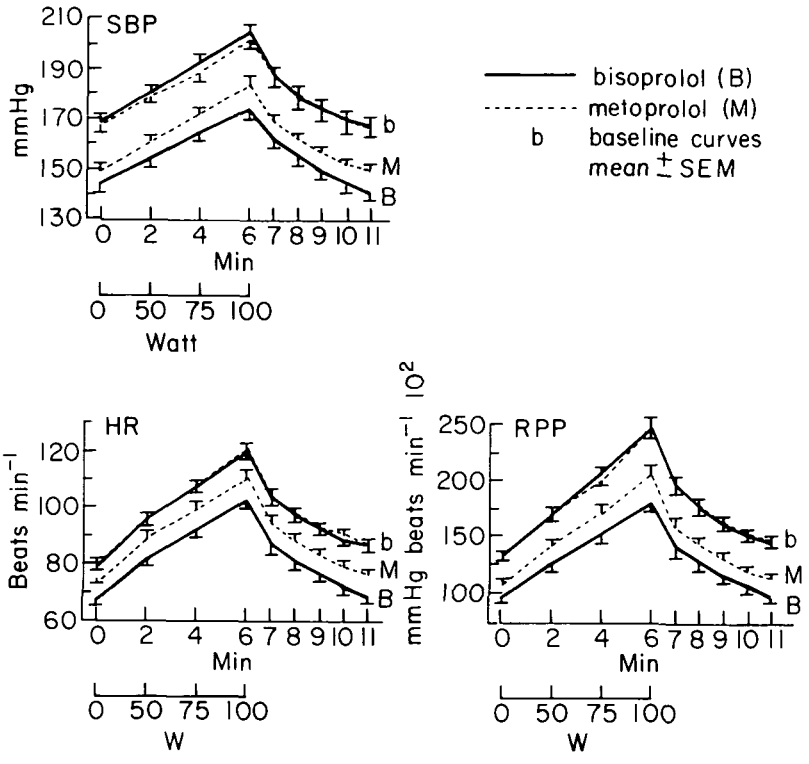

Figure 2 Comparison of the effects of bisoprolol (B) and metoprolol (M) on systolic blood pressure (SBP), heart rate (HR) and rate–pressure product (RPP) during and after ergometry before (b) and after 4 weeks of beta-blocker therapy 24 h p.a. Whereas before treatment the findings are similar in both groups, during exercise the curves are lower with B than with M indicating stronger effects of B.

experienced anginal symptoms during therapy; the final tests were not carried out. Apart from those that could be attributed to other diseases, no clinically significant laboratory changes occurred before or during the 4 weeks of beta-blocker therapy. Thus both beta blockers showed overall good tolerance.

Discussion

The present study showed that, measured in terms of the results of an exercise test up to 100 W with determination of SBP, HR and RPP in patients with hypertension, the action of 10 mg bisoprolol persists throughout the dosage interval of 24 h. The residual effects 24 h p.a. were 86–93% of the acute effects 3 h p.a.

Whereas bisoprolol and metoprolol showed comparable 3-hour effects on SBP, HR and RPP during exercise, the effects observed 24 h p.a. were significantly less with 100 mg metoprolol than with 10 mg bisoprolol. For metoprolol the residual effects 24 h p.a. were 53–66% of the acute effects 3 h p.a. In contrast to the findings with 10 mg bisoprolol, 100 mg metoprolol does not guarantee a persistant reduction in exercise blood pressure and heart rate throughout the entire 24-h dosage interval.

Our findings with metoprolol confirm the results of previous investigations in patients with hypertension in which exercise tests after several weeks of treatment with once-daily administration of 100–200 mg metoprolol revealed that the effects on blood pressure and heart rate were considerably less 24 h p.a. than 1–4 hours after administration[1–3,5–7]. The reference data regarding periods of treatment of 3–4 weeks are given in Figs 5 and 6. The values 1–4 h p.a. are distinctly lower than those 24 h p.a. and thus indicate incomplete beta receptor blockade and exercise blood pressure control at the end of the dosage interval.

Table 2 Systolic blood pressure (SBP), heart rate (HR) and rate–pressure product (RPP) at 100 W and differences between values at the three points of time

	SBP (mmHg)		HR (beats min^{-1})		RPP (mmHg × beats min^{-1})	
	B	M	B	M	B	M
Before therapy						
E1:						
mean	204·9	202·9	120·6	121·2	24 777	24 594
P value	NS		NS		NS	
After 4 weeks of treatment						
E2 (24 h p.a.)						
mean	174·5	184·5	102·4	110·5	17 996	20 574
P value	<0·01		<0·05		<0·01	
E3 (3 h p.a.)						
mean	170·2	172·6	100·1	101·7	17 175	17 769
P value	NS		NS		NS	
E1—E2:						
mean	30·4	18·4	18·2	10·7	6781	4020
P value	<0·01		<0·01		<0·01	
E2—E3:						
mean	4·3	11·9	2·3	8·8	821	2895
P value	<0·05		<0·01		<0·01	

B—bisoprolol, M—metoprolol.

The information from the literature on (50–) 100 mg atenolol once-a-day over a period of 3–4 weeks[1,3–7] is also shown in Figs 5 and 6. In five out of six studies in which 100 mg atenolol was compared with 100–200 mg metoprolol in conventional formulation, beta-receptor blockade was distinctly more persistent on atenolol than on metoprolol. Even with atenolol, however, lower values of SBP and HR during physical exercise were observed 1–4 h p.a. than 24 h p.a., indicating that once-daily 100 mg atenolol does not provide beta-receptor blockade that persists for the entire 24-h dosage interval either.

Even after once-a-day 200 mg metoprolol in slow or delayed release formulations for 2–4 weeks, the differences were usually relatively small between 0 and 24 h p.a. and distinct between 24 and 2–4 h p.a. (Figs 5 and 6)[4,6–8]. Thus even in sustained release formulations metoprolol does not induce a beta-receptor blockade and exercise blood pressure control that last convincingly throughout the 24-h dosage interval.

For the published studies in which the exercise heart rate was measured both 24 h p.a. and 1–4 h p.a., it is possible to calculate from the means of the respective maximum exercise heart rates quoted in the publications[1,3–5,7] the residual effect 24 h p.a. (see 'Evaluation'). The residual effect on exercise heart rate can be considered a measure of the degree of the beta-receptor blocking action 24 h p.a. The doses required are defined by the affinity of the beta blockers to the beta receptor, by the plasma elimination half-life—upon which the beta-blocker concentrations at the site of action depend—and also by the respective degree of sympathetic activity[2,18].

There seems to be a relationship between the residual effects of 100–200 mg metoprolol, (50–) 100 mg atenolol and 10 mg bisoprolol and the respective plasma elimination half-lives (Fig. 7). Bisoprolol has the longest plasma elimination half-life (10–12 h) of the three beta blockers under discussion and the strongest residual effect (about 90%) on exercise heart rate.

In the steady state after several days of treatment, plasma concentrations of between 8 and 10 ng ml^{-1} were recorded 24 h after the administration of 10 mg bisoprolol[10,21]. At this point in time—after the maximum bisoprolol plasma concentrations of 45–55 ng ml^{-1} 2–3 h p.a.[21]—about 21 hours and thus about two plasma elimination half-lives have elapsed. While the plasma concentration of bisoprolol have thus decreased to 20–25% of its maximum, the

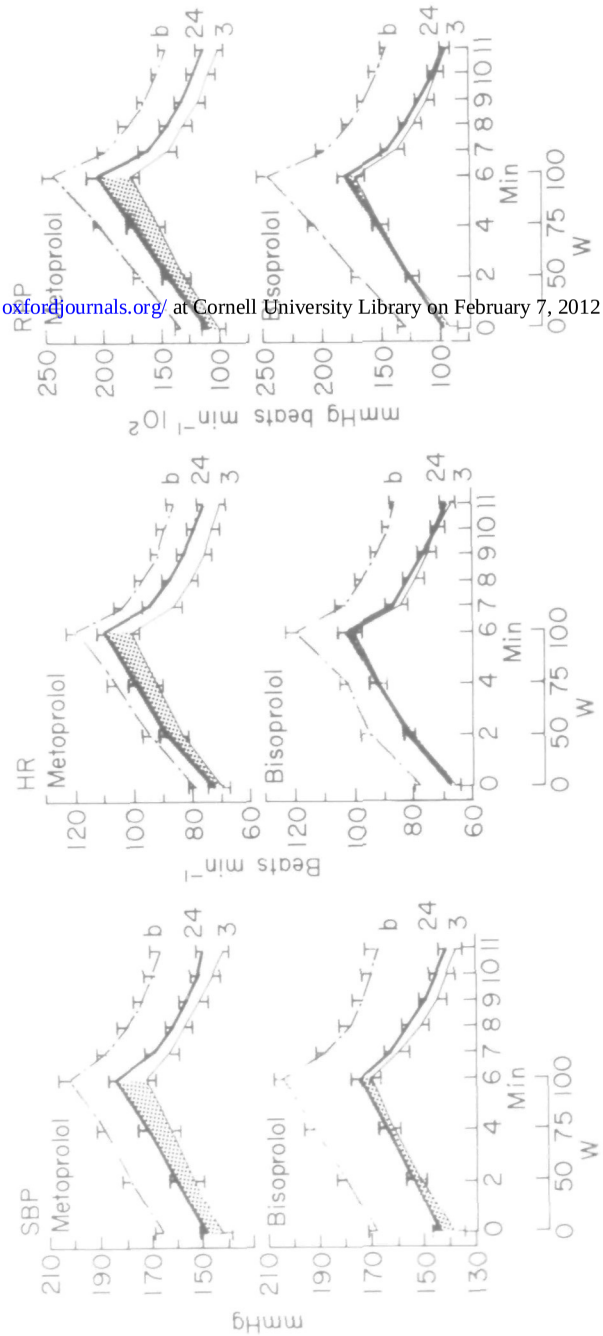

Figure 3 Effects of bisoprolol (B) and metoprolol (M) on systolic blood pressure (SBP), heart rate (HR) and rate–pressure product (RPP) during and after ergometry 24 and 3 h p.a., before (b) and after 4 weeks of beta-blocker therapy ($\bar{x} \pm$ SEM). For all three parameters the shaded areas between the baseline curves (b) and the 24 h p.a. curves are significantly ($P < 0{\cdot}01$) larger with B than with M, indicating stronger effects of B. The dark areas between the 24 h p.a. and 3 h p.a. curves provide a measure of the residual effects 24 h p.a.: the smaller these areas, the greater the residual effects. The residual effects are clearly larger with B than with M.

Table 3 24 h residual effects (as percentage of acute effect 3 h p.a.) at 100 W and calculated from area differences

	B	M	*P* value*
SBP: 100 W	86	63	0·02
Area	90	66	<0·02
HR: 100 W	90	53	0·001
Area	93	54	0·001
RPP: 100 W	89	58	<0·01
Area	92	60	<0·001

B—bisoprolol; M—metoprolol
* B *vs* M.

pharmacodynamic effect on exercise heart rate at 100 W was still 90% of the 3-hour value. The pharmacodynamic half-life of 10 mg bisoprolol under these conditions is thus obviously considerably longer than the kinetic half-life.

The more persistent pharmacodynamic effects of beta receptor blockers—when compared to the

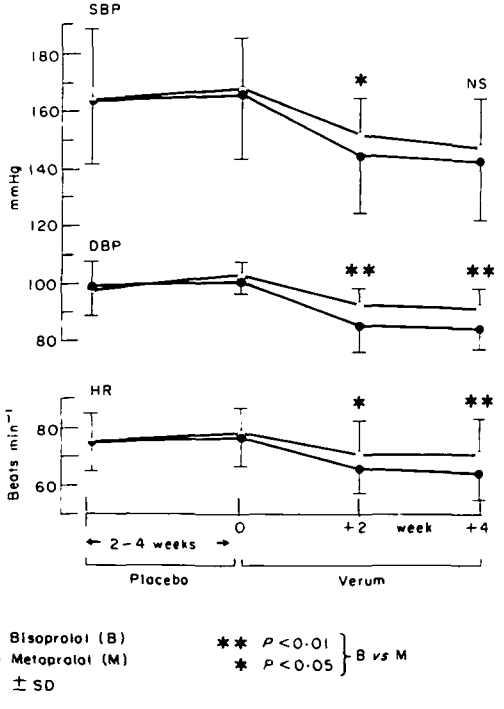

Figure 4 Systolic and diastolic blood pressure (SBP, DBP) and heart rate (HR) at rest, before and after a 2- to 4-week preliminary placebo phase and after 2 and 4 weeks of treatment with bisoprolol and metoprolol, 24 h p.a.

Table 4 Adverse reactions: symptoms reported by at least three patients (number of reports)

	Placebo	Bisoprolol	Metoprolol
Headache	7	1	5
Dizziness	3	4	4
Nausea	0	5	1

half-life of the elimination from the plasma—has frequently been attributed to deep compartments, active metabolites or to the persistent receptor binding due to a high affinity. In contrast to these auxilliary hypotheses, the concentration-effect relation analog to the law of mass action enables an explanation that is plausible because of its simplicity[22].

The relationship between the temporal course of the beta blocker concentrations in the blood on one hand and the duration of effect of beta blockers on the other as derived from the above explanation by Palm *et al.*[22], however, is completely valid from a quantitative point of view only after a single dose and in the case of the maximum possible competition of antagonist and agonist at the beta receptor, i.e. only in the case of maximum physical exertion with maximum sympathetic activity. In the case of the exercise load of 100 W (which corresponds to the daily physical exercise load) selected in the present study, the beta-receptor blockade still present 24 h after administration of 10 mg bisoprolol is—in hypertensive patients treated for 4 weeks—sufficient to guarantee 90% of the 3-hour effect. The respective value for 100 mg metoprolol was 53%.

In comparison with the clearly different effects of the two beta blockers on SBP, HR and RPP during exercise there were only relatively slight and inconsistent differences with regard to SBP and DBP at rest. This observation indicates that during treatment with beta blockers, blood pressure homeostasis under resting conditions, i.e. at a low sympathetic activity and after chronic treatment in hypertensive patients, displays little or no dependence on the prevailing agonist/antagonist situation at the beta receptors, but rathermore is regulated by other factors that are only indirectly connected with the more persistent blockade of the beta receptors. In other words: the plasma elimination half-life of a beta blocker seems to be of relatively little importance regarding the reduction of resting

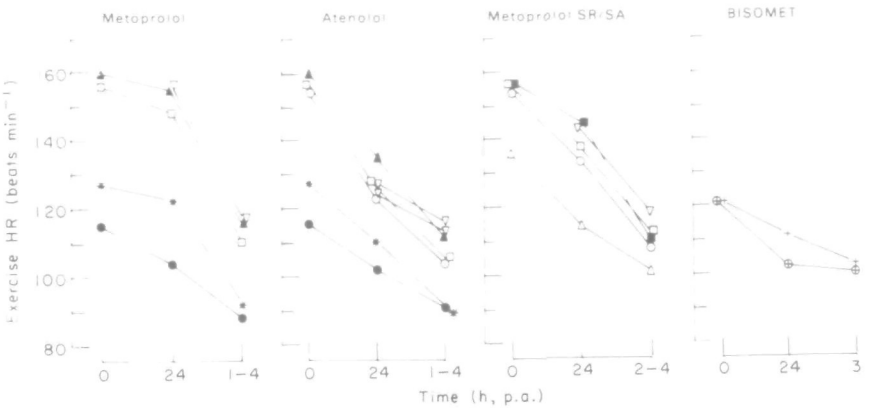

Figure 5 Exercise heart rate (HR) at the respective maximum workload before (0) and 24 and 1–4 h after administration of metoprolol (M), atenolol (A) and metoprolol in two sustained release formulations (SR, SA) (means of literature values). The symbols represent the following studies: ▲ ref. [5]: 100 mg M, 100 mg A; ▽ ref. [6]: 100 mg M, 50 and 100 mg A, 200 mg SR; ■ ref. [7]: 200 mg M, 100 mg A, 200 mg SA; □ ref. [7]: 200 mg SR; ★ ref. [1]: 100 mg M 100 mg A, ● ref. [3]: 200 mg M, 100 mg A, ○ ref. [4], 100 mg A, 200 mg SA; △ ref. [8]: 200 mg SA. The results of the present study (BISOMET) are given for comparison purposes: + 100 mg M, ⊕ 10 mg bisoprolol.

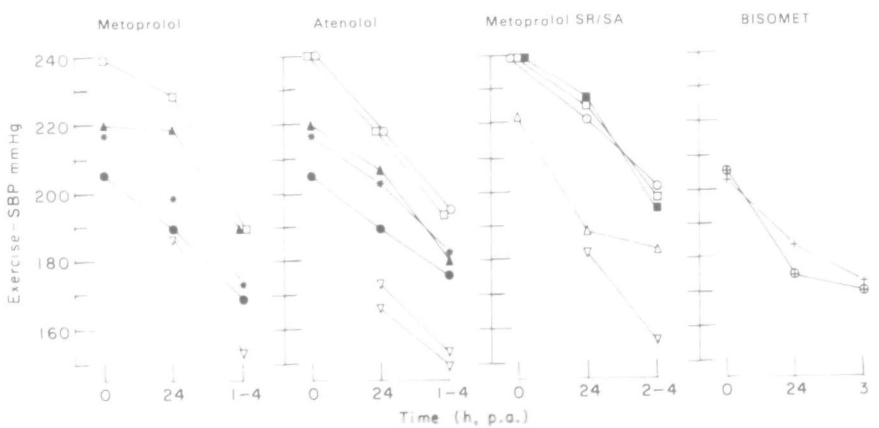

Figure 6 Systolic blood pressure (SBP) during exercise at the respective maximum workload, before (0) and 24 and 1–4 h after administration of metoprolol, atenolol and metoprolol in two sustained release formulations (means of literature values). See legend to Fig. 5 for further explanation.

blood pressure in long-term therapy of hypertensive patients. However, this conclusion should be qualified in the context of therapeutic recommendations, for the following reasons:

1. Patients with essential hypertension should lead a largely normal life. They are therefore exposed to numerous, often unforeseeable, physical and psychological situations that increase the release of endogenous catecholamines. The exercise level of 100 W chosen for this study corresponds to everyday physical exertion. Under these conditions the therapy of patients with hypertension should take into account the following three objectives:
(a) Increase in heart rate and blood pressure caused by exercise should be reduced as reliably and as evenly as possible throughout the entire dosage interval. (b) On account of the generally

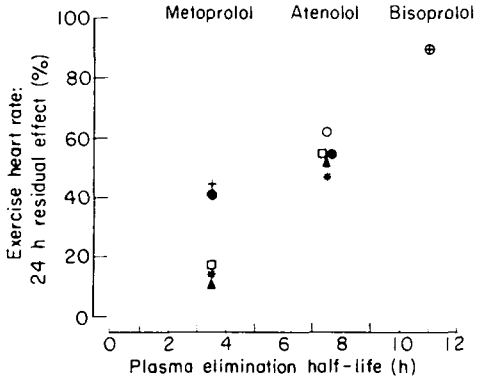

Figure 7 24 h residual effect of metoprolol, atenolol and bisoprolol on heart rate at the respective maximum workload versus the plasma elimination half-lives of the three beta blockers. See legend to Fig. 5 for explanation of symbols.

non-optimal compliance on the part of the hypertensive patient, which decreases further still as the number of tablets to be taken daily increases, the dosage interval should be 24 hours. (c) If a $beta_1$selective beta blocker is selected, its $beta_1$selectivity in the therapeutic dose range should be guaranteed also at the beginning of the dosage interval at relatively high plasma concentrations.

By analogy to the hypothesis that the duration of effects of beta blockers is defined by the concentration–(dose)–effect ratio, which in turn is based on the law of mass action, the first two therapeutic objectives should theoretically be achievable with any beta blocker, independent of its plasma elimination half-life, provided the dose is adequately high. However, dose increases in the once-daily administration of $beta_1$selective beta blockers with a short plasma elimination half-life with the aim of guaranteeing a constant beta-receptor blockade for 24 hours entail—apart from economic aspects—very high concentrations at the beginning of the dosage interval with the ensuant possiblility of dose-dependent side-effects and, particularly, of a decrease of the—concentration-dependent—$beta_1$selectivity[15,17,18].

When administered in single daily doses, the plasma concentrations of bisoprolol fluctuate by a factor of 4–5[9,10] during the dosage interval, whereas those of metoprolol fluctuate by a factor of 30–40[2,7]. The only beta blocker that is suitable for single daily administration with the objective of a beta-receptor blockade that persists to as great an extent as possible for 24 hours is one with a long plasma elimination half-life. Moreover, the only beta blocker that is able to guarantee plasma concentrations at which only the $beta_1$-receptors are blocked also at the start of such a dosage interval of 24 hours is one with a high $beta_1$selectivity. Bisoprolol combines a long plasma elimination half-life with a particularly distinct $beta_1$selectivity[13–17] and therefore appears to be particularly well suited for a once-daily beta-blocker therapy of essential hypertension.

2. Uniformly strong beta-receptor blockade is particularly desirable and necessary when coronary heart disease is present. Many hypertensive patients undoubtedly suffer additionally from symptomatic or asymptomatic coronary heart disease. In these patients the persistent reduction in rate–pressure product under exercise conditions is helpful in reducing angina pectoris attacks because such attacks invariably occur on reaching the same rate–pressure product, regardless of the type of exercise involved.

3. The blood pressure reduction to be produced by beta-blocker treatment is ultimately (irrespective of the mechanism) the direct or indirect consequence of the blockade of $beta_1$-receptors in various tissues. A $beta_1$-receptor blockade persisting throughout the dosage interval therefore probably guarantees more constant direct and indirect favourable effects on blood pressure than a beta-receptor blockade that varies considerably during the dosage interval. The significantly stronger effect on resting diastolic blood pressure with bisoprolol than with metoprolol that was observed in the present study can be interpreted in this sense. Not only the quantity but also the quality or constancy of the blood pressure control over the dosage interval might be of importance for regression of left-ventricular hypertrophy due to hypertension.

The biometric evaluation of this study was performed by the Department of Biometry of the Arzneimittelforschung Berlin GmbH (AFB).

The excellent help of our Medical Records Officer Ms. P. Pollert is gratefully acknowledged as are the contributions of the following investigators: G. G. Belz, R. G. Englert, H.-J. Giesecke, MD; S. Görlitz, MD; M. Heilmann, MD; B. Krönig, MD; H. Plum, R. Rost, G. V. Sabin, W. Walldorf, Ch. Watz, G. Weiss.

References

[1] Comerford MB, Besterman E. Dosing intervals in beta-blocker therapy. Lancet 1980; 4: 1196.

[2] Danielson M, Kjellberg J, Kuylenstierna J, Lundkvist L, Svensson O. Influence of time and physical activity on blood pressure and heart rate during treatment with β-blocking agents once daily. Acta Med Scand 1983; 214: 381–5.
[3] Franz IW. Ergometrie bei Hochdruckkranken. Springer: Berlin, 1982.
[4] Morley CA, Cavalcanti C, Perrins EJ, Sutton R. A comparison of once daily atenolol and metoprolol SA in mild to moderate hypertension. Br J Clin Pharmacol 1983; 15: 715–7.
[5] Nilsson OR, Atterhög JH, Castenfors J *et al.* A comparison of 100 mg atenolol and 100 mg metoprolol once a day at rest and during exercise in hypertensives. Acta Med Scand 1984; 215: 301–7.
[6] Scott AK, Rigby JW, Webster J, Hawksworth GM, Petrie JC, Lovell HG. Atenolol and metoprolol once daily in hypertension. Br Med J 1982; 284: 1514–6.
[7] Silas JH, Freestone S, Lennard MS, Ramsay LE. Comparison of two slow-release formulations of metoprolol with conventional metoprolol and atenolol in hypertensive patients. Br J Clin Pharmacol 1985; 20: 387–91.
[8] Witchitz S, Moisson P, Kolsky H. A comparative trial of ordinary metoprolol tablets and metoprolol sustained release tablets in hypertensive patients at rest and on exercise. Pharmatherapeutica 1984; 3: 566–72.
[9] Leopold G, Pabst J, Ungethüm W, Bühring KU. Basic pharmacokinetics of bisoprolol, a new highly beta$_1$-selective adrenoceptor antagonist. J Clin Pharmacol 1986; 26: 616–21.
[10] Leopold G. Balanced pharmacokinetics and metabolism of bisoprolol. J Cardiovasc Pharmacol 1986; 8 (Suppl 11): S16–20.
[11] Wellstein A, Palm D, Belz GG, Leopold G, Bühring KU, Pabst J. Concentration kinetics of propranolol, bisoprolol and atenolol in humans assessed with chemical detection and a subtype-selective β-adrenoceptor assay. J Cardiovasc Pharmacol 1986; 8 (Suppl 11): S41–5.
[12] Benfield P, Clissold SP, Brogden RN. Metoprolol: an updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy, in hypertension, ischaemic heart disease and related cardiovascular disorders. Drugs 1986; 31: 376–429.
[13] Brodde OE. Bisoprolol (EMD 33 512), a highly selective β_1-adrenoceptor antagonist: In vitro and in vivo studies. J Cardiovasc Pharmacol 1986; 8 (Suppl 11): S29–35.
[14] Haeusler G, Schliep HJ, Schelling P *et al.* High β_1-selectivity and favourable pharmacokinetics as the outstanding properties of bisoprolol. J Cardiovasc Pharmacol 1986; 8 (Suppl 11): S2–15.
[15] Krämer B, Balser J, Stubbig K, Krämer G, Kübler W. Comparison of bisoprolol with other β-adrenoceptor blocking drugs. J Cardiovasc Pharmacol 1986; 8 (Suppl 11): S46–57.
[16] Wang XL, Brinkmann M, Brodde OE. Selective labelling of β_1-adrenoceptors in rabbit lung membranes by $(-)^3$H bisoprolol. Eur J Pharmacol 1985; 114: 157–65.
[17] Wellstein A, Palm D, Belz GG. Affinity and selectivity of β-adrenoceptor antagonists in vitro. J Cardiovasc Pharmacol 1986; 8 (Suppl 11): S36–40.
[18] Borchard U. Pharmakologie der Beta-Rezeptorenblocker. Basel: Aesopus, 1983.
[19] Franz IW. Ergometrie zur Diagnostik bei der arteriellen Hypertonie. Therapiewoche 1984; 34: 5974–88.
[20] Bühring KU, Garbe A. Determination of the new β-blocker bisoprolol and of metoprolol, atenolol and propranolol in plasma and urine by high performance liquid chromatography. J Chromatogr 1986; 382: 215–24.
[21] Kirsten R, Neff J, Heintz B, Nemeth N, Rahlfs VW, Nelson K. Influence of different bisoprolol doses on haemodynamics, plasma catecholamines, platelet aggregation and α_2 and β-receptors in hypertensive patients. J Cardiovasc Pharmacol 1986; 8 (Suppl 11): S113–21.
[22] Palm D, Wellstein A, Jablonka B, Wiemer G. Rezeptor-Affinität, Kinetik der Plasmakonzentration und Dosis als bestimmende Größen für das Zeit-Wirkungsprofil von Beta-Rezeptorenblockern. Vergleichende Untersuchungen mit Propranolol und Carteolol. In: Palm D, ed. Therapie der koronaren Herzkrankheit mit Beta-Rezeptorenblockern. Pharmakodynamische und pharmakokinetische Aspekte. Erlangen: Perimed, 1984; 21–30.