Bisoprolol
A Preliminary Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Hypertension and Angina Pectoris

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**Summary**

**Synopsis**

Bisoprolol is a β₁-adrenoceptor antagonist with no partial agonist (intrinsic sympathomimetic) activity or membrane stabilising (local anaesthetic) activity. The oral bioavailability of bisoprolol is high (90%) and the drug has a long elimination half-life which allows once-daily administration; in addition, it is hepatically and renally cleared in equal proportions. In non-comparative studies, and comparative trials, bisoprolol proved effective, and as efficacious as atenolol, low doses of metoprolol, diuretics and nifedipine SR in hypertension, and atenolol and verapamil in stable angina pectoris. Bisoprolol has been well tolerated in most patients.

Thus, bisoprolol is an effective alternative to other β-adrenoceptor antagonists in patients with mild to moderate essential hypertension or stable angina pectoris. Furthermore, its unique pharmacokinetic properties may offer advantages in selected patients. However, the results of further comparative studies with established agents in the treatment of hypertension and angina pectoris are still awaited so that a final assessment of the relative place in therapy of bisoprolol in these disease states may be made.

**Pharmacodynamic Studies**

Bisoprolol is a β₁-adrenoceptor antagonist which has been shown to be devoid of partial agonist or membrane-stabilising activity. Animal studies have shown that bisoprolol is a more potent antagonist of β₁-adrenoceptors than atenolol or metoprolol, but the drug appears to be less potent than propranolol and betaxolol in this regard. Bisoprolol possesses a long duration of action, with significant reductions in exercise tachycardia (about 20%) being observed in subjects with stable angina pectoris 24 hours after oral administration of 5 and 10mg. Both systolic and diastolic blood pressures are reduced by bisoprolol (by up to about 20%, respectively, in healthy subjects and in patients with mild to moderate essential hypertension) as well as myocardial oxygen demand (by up to 34%).

Respiratory function in healthy subjects was not affected by bisoprolol 20 and 40mg orally, but in asthmatic patients oral bisoprolol 10 and 20mg and metoprolol 100mg significantly reduced peak expiratory flow rate (p < 0.01 vs placebo), while bisoprolol 10mg also significantly decreased vital capacity and forced expiratory volume in 1 second (p < 0.01 vs placebo). The patients remained asymptomatic and all of these changes in ventilatory parameters were rapidly reversed by inhaled terbutaline.

In non-diabetic healthy subjects bisoprolol did not significantly affect insulin-induced hypoglycaemia or the compensatory rise in serum lactate concentration after insulin. In hypertensive non-insulin-dependent diabetics bisoprolol had no effect on carbohydrate metabolism.
Statistically significant increases in serum triglycerides (p < 0.05) and reductions in high density lipoprotein (HDL)-cholesterol (bisoprolol, p < 0.01; atenolol, p < 0.05) were reported in a 3-month comparison of oral bisoprolol 10 and 20 mg/day and atenolol 50 and 100 mg/day in patients with mild to moderate essential hypertension. However, the overall effects of bisoprolol on lipid metabolism are as yet still unclear and further studies in this area are required.

Pharmacokinetic Studies

Bisoprolol, possessing both lipophilic and hydrophilic properties, has been shown to have a bioavailability ~ 90% after oral administration. Peak plasma concentrations are reached within 3 hours of a single 10mg dose in healthy subjects, with maximum plasma concentrations of between 36 and 78 μg/L being achieved after the same dose in healthy subjects and patients with varying degrees of renal and hepatic insufficiency. Animal studies indicate that bisoprolol is rapidly and widely distributed, but little placental transfer occurs and the drug only penetrates the blood-brain-barrier to a small degree in comparison to metoprolol and propranolol. Bisoprolol binds to human plasma proteins to the extent of about 30%. Approximately 50% of a dose of bisoprolol is hepatically metabolised to 3 inactive metabolites while the rest is renally excreted unchanged; in addition, < 10% of the drug undergoes ‘first-pass’ metabolism. The elimination half-life of unchanged bisoprolol in healthy subjects is 9 to 12 hours and is increased to about 18 hours in patients with renal impairment or to about 13 hours in patients with hepatic cirrhosis.

Therapeutic Trials

Several short and long term non-comparative studies have indicated that the optimum oral dose range of bisoprolol in patients with mild to moderate essential hypertension is 5 to 20mg once daily. Systolic and diastolic blood pressures were well controlled with a single daily dose of bisoprolol (15 to 20% reductions from baseline), and in long term non-comparative studies reductions in diastolic blood pressure to ≤ 90mm Hg were achieved in 70 to 95% of patients. In comparative studies bisoprolol 5 to 20mg once daily was as effective as atenolol 50 to 100 mg/day, metoprolol 100 mg/day and nifedipine SR 40 to 80 mg/day, and more effective than daily treatment with hydrochlorothiazide 50mg plus amiloride 5mg in reducing blood pressure in patients with mild to moderate essential hypertension.

Non-comparative clinical trials in patients with stable angina pectoris have confirmed the efficacy of bisoprolol in short term studies. During a 12-month study approximately 50% of the patients were completely free from anginal attacks, with 27%, 55% and 18% of the patients receiving bisoprolol 5mg, 10mg and 20mg daily, respectively. In comparative studies bisoprolol 5 to 10mg once daily and atenolol 100mg once daily produced similar increases in exercise duration, time to onset of exercise-induced ischaemia and reductions in the frequency of anginal attacks, glyceryl trinitrate (nitroglycerin) consumption and myocardial oxygen demand. In addition, in combination therapy with isosorbide dinitrate 20mg twice daily, bisoprolol 10 to 20mg once daily or verapamil 240 to 360 mg/day produced comparable improvements in exercise duration, myocardial ischaemia and oxygen demand, frequency of anginal attacks and glyceryl trinitrate consumption. However, these comparative studies involved only small numbers of patients, and further comparative studies in larger patient groups are required to confirm their findings.

Side Effects

Bisoprolol has been well tolerated by most patients in long term trials (6 to 24 months duration). ‘Giddiness’, headache and tiredness were the most commonly reported adverse reactions. In long term trials, side effects necessitated discontinuation of treatment in about 2.7% of patients. In comparative trials the tolerability of bisoprolol 5 to 20 mg/day appeared to be comparable to atenolol 50 to 100 mg/day, metoprolol 100 mg/day and verapamil 240 to 360 mg/day, and superior to nifedipine SR 40 to 80 mg/day or hydrochlorothiazide 50 mg/day plus amiloride 5 mg/day. Adverse reactions tend to occur...
more frequently during the first few weeks of bisoprolol treatment and then subside with continued therapy.

**Dosage and Administration**

The usual oral dose of bisoprolol in mild to moderate essential hypertension or stable angina pectoris is 10mg once daily with a maximum recommended dose of 20 mg/day. In some patients 5 mg/day may be adequate. However, in end-stage renal or hepatic insufficiency, dosage should not exceed 10mg once daily.

### 1. Pharmacodynamic Studies

Bisoprolol (fig. 1) is a new, relatively cardioselective β-adrenoceptor blocking agent. It possesses both hydrophilic and lipophilic properties and is devoid of partial agonist or membrane-stabilising activity.

#### 1.1 β-Adrenoceptor Blocking Activity

#### 1.1.1 Relative Potency

**Animal Studies**

Bisoprolol was shown to be a less potent inhibitor than propranolol of the positive chronotropic effect of isoprenaline (isoproterenol) on spontaneously beating guinea-pig atria (Harting et al. 1986). The negative logarithms of the molar concentrations of β-adrenoceptor antagonist which halved the potency of isoprenaline (pA₂ values) were 7.45 and 8.44 for bisoprolol and propranolol, respectively, indicating that in these in vitro experiments the potency of bisoprolol was approximately one-tenth that of propranolol. Schliep et al. (1986) investigated the inhibitory potency of intravenous bisoprolol, atenolol and propranolol on the positive chronotropic effects of intravenous isoprenaline (0.2 μg/kg) in reserpine-treated anaesthetised cats in vivo. The mean doses which inhibited the effects of isoprenaline on the heart by 50% (ID₅₀) for propranolol, bisoprolol and atenolol were 0.07, 0.58 and 1.42 μmol/kg, respectively. Thus, bisoprolol was a less potent β₁-adrenoceptor antagonist than propranolol, but was more potent than atenolol in this model, results which have similarly been reported in conscious pigs (Duncker et al. 1987).

In rat cardiac ventricular membrane preparations in vitro, the binding affinity of bisoprolol (Ki value 36.9 nmol/L) to β₁-adrenoceptors was considerably greater than that of atenolol (Ki value 1640 nmol/L), but less than those of propranolol and betaxolol (Ki values 2.89 and 25.7 nmol/L, respectively) [Klockow et al. 1986]. Similarly, Manalan et al. (1981) found that the affinity of bisoprolol for canine myocardial β₁-adrenoceptors was greater than those of metoprolol and atenolol (Ki values of 81.4, 500 and 3400 nmol/L, respectively), but less than that of propranolol (Ki value 5.8 nmol/L). These values for the affinity of bisoprolol for β₁-adrenoceptors are in general agreement with those obtained by Wang et al. (1985) who found that bisoprolol inhibited the binding of ¹²⁵I-iodo-

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**Fig. 1.** Structural formulae of bisoprolol and propranolol.
Bisoprolol: A Preliminary Review

cyanopindolol (ICYP) to rabbit lung β-adrenoceptors (Ki value 26.9 nmol/L) in vitro. In addition, in isolated tissue and binding studies using kitten and guinea-pig heart preparations. Kaumann and Lemoine (1985) found an affinity constant for bisoprolol on β1-adrenoceptors ranging from 1.4 to 11 nmol/L. Furthermore, in a preparation of rat salivary gland in vitro, Wellstein et al. (1986a) showed that propranolol, bisoprolol and betaxolol had similar affinities for β1-adrenoceptors (Ki values 25, 25 and 23 nmol/L, respectively) while the Ki value for atenolol was 270 nmol/L in the same preparation.

It should be remembered, however, that statements as to the affinity of bisoprolol and other β-blockers for β1-adrenoceptors as a measure for their potency may be misleading in light of the fact that most experiments have been primarily designed to study the relative affinity for β1- versus β2-adrenoceptors, i.e., the β1/β2-selectivity ratio of various β-blockers (section 1.1.2). In addition, in humans the doses of the various β-blockers used in therapy may differ considerably in their potency ratios, if compared with animal data, due to differences in their bioavailability.

Studies in Humans

In man resting heart rate is controlled primarily by parasympathetic activity, and only to a minor extent by sympathetic activity. Thus, changes in resting heart rate are of little value in assessing cardiac β-blocking activity. However, moderate to strenuous exercise leads to increased activity of the sympathetic nervous system, and reduction in exercise-induced tachycardia has been widely used to assess the relative potency of β-adrenoceptor antagonists (Beresford & Heel 1986).

The relative β1-adrenoceptor antagonist potency of bisoprolol was assessed by Kramer et al. (1986) in healthy subjects using measurements of the workload ratio after/before β-blockade for an exercise-induced heart rate of 120 beats/min (WR120). A single intravenous dose of bisoprolol 0.07 mg/kg produced a comparable WR120 to propranolol 0.2 mg/kg (1.38 and 1.39, respectively) and at this dose the effect on exercise tachycardia was significantly greater than that of acebutolol 0.8 mg/kg, metoprolol 0.2 mg/kg or penbutolol 0.04 mg/kg (p < 0.01).

Single oral doses of bisoprolol 2.5 to 40 mg produced a dose-dependent reduction in exercise-induced tachycardia (13 to 26%) in healthy subjects although the difference between 20 mg and 40 mg was only small (Leopold et al. 1986b). The maximum reduction in exercise-induced tachycardia in healthy subjects following a single oral dose of bisoprolol 10 mg was comparable to that produced by propranolol 40 mg, atenolol 50 mg and metoprolol 100 mg (fig. 2). Furthermore, a very high dose of bisoprolol did not cause any greater reduction in exercise tachycardia in a double-blind, placebo-controlled study in healthy subjects conducted by Wellstein et al. (1987). However, this study was designed to investigate the time course of the relative β1-selectivity of various β-blockers by means
of $\beta_1$- and $\beta_2$-adrenoceptor occupancy in specific tissues. Bisoprolol 100mg, atenolol 200mg and propranolol 240mg were administered as a single oral dose to groups of 6 subjects, who exercised on bicycle ergometers at 75% of their maximum work capacity; only because low $\beta_2$-occupancies were expected, even at high drug concentrations of the $\beta_1$-selective compounds, were these very high 'pharmacological' doses used. Thus, although the maximum reductions in exercise tachycardia caused by bisoprolol, atenolol and propranolol were 17%, 21% and 19%, respectively, these results (the ratios of the potencies between the $\beta$-blockers tested) should be interpreted with caution.

The results of these studies of the dose-dependent effects of bisoprolol and of standard $\beta$-adrenoceptor antagonists have indicated that the therapeutic oral dose range for bisoprolol is 5 to 20mg once daily (Leopold et al. 1986b).

1.1.2 Cardioselectivity

$\beta_1$-Adrenoceptors are found mainly in the heart, kidney and adipose tissue, whereas $\beta_2$-adrenoceptors occur mainly in the respiratory system, peripheral blood vessels, uterus, liver and pancreas. The term 'cardioselective' $\beta$-adrenoceptor antagonists refers to those agents which selectively block $\beta_1$-adrenoceptors with relatively little blocking action on $\beta_2$-adrenoceptors (Cruickshank 1980; McDevitt 1983).

Animal Studies

The affinity of an antagonist for different types of receptors can be assessed by the $pA_2$ values for $\beta_1$- and $\beta_2$-adrenoceptors in various isolated tissues. The $pA_2$ value of bisoprolol against the positive chronotropic effect of isoprenaline in isolated guinea-pig atria in vitro ($\beta_1$-adrenoceptor subtype) was 7.45. However, compared to propranolol ($pA_2$ value 8.92), bisoprolol ($pA_2$ value 6.41) was only a weak antagonist of isoprenaline-induced relaxation of guinea-pig tracheal strips, contracted with histamine, in vitro. Since the $pA_2$ value is a logarithmic measurement, these values indicate that the affinity of bisoprolol for the cardiac $\beta_1$-adrenoceptors was about 11 times greater than its affinity for $\beta_2$-adrenoceptors in the trachea. In contrast, propranolol showed a 3-fold selectivity for $\beta_2$-adrenoceptors in this preparation (Harting et al. 1986).

In other in vitro studies using preparations from kitten heart (Kaumann & Lemoine 1985), rat heart and lung membranes (Klockow et al. 1986), canine heart and lung (Manalan et al. 1981), rabbit lung membranes (Wang et al. 1985), and rat salivary gland and reticulocyte membranes (Wellstein et al. 1987), bisoprolol showed a 23- to 100-fold $\beta_1$-adrenoceptor selectivity. In comparison, atenolol, betaxolol and metoprolol were 4- to 35-fold, 12- to 35-fold, and 4- to 20-fold $\beta_1$-selective, respectively. Propranolol was 2- to 5-fold $\beta_2$-selective in these studies.

In anaesthetised, vagotomised dogs Schliep and Harting (1984) found that the concentrations of bisoprolol required to prevent the isoprenaline-induced reduction in diastolic blood pressure (mediated by $\beta_2$-adrenoceptors) were much higher (147-fold $\beta_1/\beta_2$ selectivity) than those required to prevent the positive chronotropic effects of isoprenaline (mediated by $\beta_1$-adrenoceptors). In contrast, the comparable apparent $\beta_1/\beta_2$ selectivity ratios obtained for practolol, betaxolol, acebutolol/atenolol/metoprolol, mepindolol, and propranolol, respectively, were > 17, 6 to 15, 1.1 to 3.2, 0.6 to 1, and 0.2 (propranolol had a 5-fold $\beta_2$-selectivity). Schliep et al. (1986) also found similar results when the $\beta_1/\beta_2$-adrenoceptor selectivity of bisoprolol was compared with that of atenolol and propranolol in the antagonism of isoprenaline-induced tachycardia and reduction in diastolic blood pressure, in anaesthetised cats ($\beta_1/\beta_2$ selectivity ratios 10 to 20, 1 to 7.5 and 0.3 to 1.6, respectively).

Studies in Humans

In healthy subjects Krämer et al. (1986) compared the $\beta_1/\beta_2$ selectivity ratio of intravenous bisoprolol with that of acebutolol, metoprolol, penbutolol and propranolol in a randomised, crossover study (section 1.1.1). The $\beta_1/\beta_2$ selectivity ratio, derived from the WR120 and the isoprenaline dose ratio for a fall in diastolic blood pressure of 25mm Hg, was taken to be 1 for propranolol and the relative ratios for bisoprolol, metoprolol, acebutolol
and penbutolol were calculated to be 12.2, 9.0, 6.2 and 0.6, respectively.

Wellstein et al. (1987) investigated the $\beta_1/\beta_2$ selectivity ratios of bisoprolol 100mg, atenolol 200mg and propranolol 240mg, administered orally, by using plasma samples drawn from healthy subjects to determine the \textit{in vitro} occupancy of $\beta_1$- and $\beta_2$-adrenoceptors in rat salivary gland ($\beta_1$) and rat reticulocytes ($\beta_2$). After the very high dose of bisoprolol, exercise-induced tachycardia was significantly inhibited for at least 60 hours, in parallel with the course of the $\beta_1$-adrenoceptor occupancy, whereas $\beta_2$-adrenoceptor occupancy was undetectable after 24 hours. It was concluded that a single daily dose of bisoprolol 5 to 10mg should allow 24-hour $\beta_1$-adrenoceptor antagonism without significant blockade of $\beta_2$-adrenoceptors.

In addition, the cardioselectivity of bisoprolol and atenolol was compared in 5 patients with untreated mild to moderate essential hypertension by Bolli et al. (1986), who measured cardiac $\beta_1$-adrenoceptor blockade by defining the intravenous doses of isoprenaline which increased the resting heart rate by 25 beats/min (chronotropic dose$^{25}$, CD$^{25}$), while vascular $\beta_2$-adrenoceptor blockade was assessed by measuring the increases in forearm blood flow in response to intravenous isoprenaline. Two patients received oral bisoprolol 10mg and atenolol 50mg for 7 days, and 3 patients received bisoprolol 20mg and atenolol 100mg daily for 7 days, in this randomised crossover study. The effects of bisoprolol and atenolol on heart rate, as shown by isoprenaline CD$^{25}$ values, were comparable at both dosage levels. At the lower doses of bisoprolol and atenolol the increases in forearm blood flow with isoprenaline were similar and amounted to approximately 65% of the placebo value. At the higher dose level the mean increase in forearm blood flow relative to placebo was 79% with bisoprolol and 45% with atenolol, demonstrating that atenolol 100mg daily blocked vascular $\beta$-adrenoceptors to a greater extent than bisoprolol 20mg daily.

The $\beta_1$-adrenoceptor selectivity of bisoprolol has also been investigated in healthy volunteers by Brodde et al. (1986), who compared the effects of bisoprolol, propranolol and pindolol on lymphocyte $\beta_2$-adrenoceptor density. Propranolol (a non-selective $\beta$-adrenoceptor antagonist without partial agonist activity) 160mg daily produced a 30 to 35% increase in the number of lymphocyte $\beta_2$-adrenoceptors after 2 days, while pindolol (a non-selective $\beta$-adrenoceptor antagonist with partial agonist activity) 10mg daily produced a statistically significant decrease ($p < 0.05$) in lymphocyte $\beta_2$-adrenoceptor density after 3 days. In contrast, bisoprolol 10 mg/day did not affect lymphocyte $\beta_2$-adrenoceptor density indicating that drug-induced changes in lymphocyte $\beta$-adrenoceptors are regulated by the $\beta_2$-adrenoceptor subtype and that bisoprolol is selective for $\beta_1$-adrenoceptors. In addition, the cardioselectivity of bisoprolol in man has been demonstrated via its effects on ventilatory function (section 1.4) and carbohydrate metabolism (section 1.6.1).

1.1.3 Duration of $\beta$-Adrenoceptor Blocking Activity

The duration of the reduction in exercise-induced tachycardia and blood pressure after a single dose of bisoprolol is relatively long compared with other $\beta$-adrenoceptor antagonists. Thus, 24 hours after administration of single oral doses of bisoprolol 5 and 10mg in 10 healthy subjects, exercise tachycardia, in comparison to placebo, was still reduced by 7% and 10%, respectively, although the corresponding values for atenolol 50 and 100mg were 6% and 14%, respectively (Leopold et al. 1986b). In 10 patients with essential hypertension Esper et al. (1986) reported that single oral doses of bisoprolol 10, 20 and 40mg significantly reduced systolic and diastolic blood pressures and heart rates from baseline values ($p < 0.05$) for up to 24 hours – with the exception of blood pressure 24 hours after the 10mg dose.

Non-invasive 24-hour ambulatory blood pressure monitoring was employed by Asmar et al. (1987) to investigate the duration of the antihypertensive effect of the last 10mg dose of bisoprolol, at the end of a 4-week study in 11 patients (who received 10mg daily for the duration of the study) with mild to moderate essential hypertension. Sys-
tolic and diastolic blood pressures, as well as heart rate, were significantly reduced \((p < 0.001 \text{ vs baseline placebo run-in values})\) until the fortieth hour after treatment with bisoprolol was stopped.

Single oral doses of bisoprolol 5 or 10mg have produced improvements in exercise capacity and reductions in rate-pressure product (heart rate \(\times\) systolic blood pressure) in patients with stable angina pectoris which have been maintained for 24 hours (de Muinck et al. 1987; Wagner 1986). In a summary of bisoprolol trials in coronary heart disease, Wagner (1986) also reported how bisoprolol 5 and 10mg, in 12 patients, reduced rate-pressure product values by about 19% and 44%, respectively, in comparison to placebo 12 hours after administration; these results were sustained for an additional 12 hours. However, in other studies reviewed by Wagner (1986), compared to bisoprolol 5mg the 10mg dose did not produce greater reductions in exercise tachycardia and rate-pressure product over 24 hours.

### 1.2 Partial Agonist and Local Anaesthetic Activity

Bisoprolol appears to have no partial agonist (intrinsic sympathomimetic) activity. \textit{In vivo} studies showed that bisoprolol, unlike pindolol or practolol, had no effect on heart rate in anaesthetised, reserpinised rats (Brodde et al. 1986; Harting et al. 1986).

Studies using rabbit corneal and guinea-pig skin reflex tests have revealed that a local anaesthetic effect of bisoprolol occurs only at high concentrations (1 to 3% solutions) [Harting et al. 1986].

### 1.3 Cardiovascular Effects

#### 1.3.1 Electrophysiological Effects

The acute electrophysiological effects of single intravenous doses of bisoprolol 5 to 10mg have been investigated in patients with cardiac arrhythmias or syncope of unknown origin (Neuss et al. 1986; Proclemer et al. 1987). In these studies bisoprolol produced significant increases in the sinus rhythm cycle length (17 to 19%; \(p < 0.05\)) and the sinus node recovery time (20 to 80%; \(p < 0.05\)), and prolonged the refractory parameters of the atrioventricular node [functional (\(p < 0.05\)) and effective refractory period (\(p < 0.05\)) and advancement of the Wenckebach point (\(p < 0.05\))]. The efficacy of oral bisoprolol 2.5 to 20 mg/day in 31 patients with premature ventricular contractions (\(n = 16\)), premature atrial contractions (\(n = 8\)), or sinus tachycardia (\(n = 7\)), was also investigated in a preliminary study by Sugimoto et al. (1986). The premature ventricular contraction frequency was reduced by more than 50% in 7 out of 16 patients. The premature atrial contraction frequency was decreased (40 to 98%) in 50% of the patients, and sinus tachycardia was reduced by 32 to 46% in all 7 patients with this condition. The patient response was judged to be comparable to that with propranolol.

#### 1.3.2 Haemodynamic Effects

**Animal Studies**

As might be expected from a \(\beta\)-adrenoceptor antagonist, the intravenous injection of single doses of bisoprolol produced dose-dependent reductions in heart rate, and in cardiac output with higher doses in anaesthetised dogs (Harting et al. 1986) and pigs (Verdouw et al. 1987). In consequence of the reduction in cardiac output, dose-dependent decreases in regional blood flows in stomach, skeletal muscle, liver and spleen were produced. However, blood flow to the small intestine and cerebral blood flow were only slightly affected (Verdouw et al. 1987). The clinical significance of the above haemodynamic effects in animals as applied to humans is as yet unclear, and additional clinical investigations in patients and volunteers are required to clarify this area of study.

**Studies in Humans**

The haemodynamic effects of single oral doses of bisoprolol 5 to 100mg and intravenous bisoprolol 10mg have been investigated in healthy subjects and patients with angina pectoris or essential hypertension (table 1).

In healthy subjects oral bisoprolol 5, 10, 20, 40
Table I. Summary of some single-dose haemodynamic studies of oral bisoprolol in volunteers and patients with cardiovascular disease

<table>
<thead>
<tr>
<th>References</th>
<th>Patient population [no. of subjects]</th>
<th>Dose (mg)</th>
<th>Patient status</th>
<th>Maximal percentage changes from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MBP SBP DBP HR CI TPR SVI PCP EDVI RPP</td>
</tr>
<tr>
<td>Bolli et al. (1986)(^a)</td>
<td>EH [5]</td>
<td>10</td>
<td>Rest</td>
<td>-12 -11 -14</td>
</tr>
<tr>
<td>Burkart et al. (1986)</td>
<td>Chronic [16] IHD</td>
<td>5</td>
<td>Rest ± ± ± ±</td>
<td>16 ± -26 +31 ± ± -18</td>
</tr>
<tr>
<td>Chatterjee (1986)</td>
<td>EH [12]</td>
<td>10</td>
<td>Rest ± ± ± ±</td>
<td>-16</td>
</tr>
<tr>
<td>Leopold et al. (1986b)</td>
<td>Vols [10]</td>
<td>5</td>
<td>Exercise ± ±</td>
<td>-17 -17 -17</td>
</tr>
<tr>
<td>Schnellbacher et al. (1986)(^a)</td>
<td>Stable AP [12] 10</td>
<td>Exercise</td>
<td>-18 ± ± ± ±</td>
<td>-31</td>
</tr>
<tr>
<td>Unpublished data on file, E. Merck</td>
<td>Stable AP [12](^a)</td>
<td>5</td>
<td>Rest ± ± ± ±</td>
<td>-11</td>
</tr>
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<td></td>
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<td></td>
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<td>10</td>
<td>Exercise ± ±</td>
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</tr>
</tbody>
</table>

\(^a\) Percentage changes in comparison to placebo.
\(^b\) Intravenous administration.

Abbreviations: MBP = mean blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; CI = cardiac index; TPR = total peripheral resistance; SVI = stroke volume index; PCP = pulmonary capillary wedge pressure; EDVI = end diastolic volume index; RPP = rate pressure product; Vols = healthy subjects; EH = essential hypertension; AP = angina pectoris; IHD = ischaemic heart disease; ± = no change from baseline value.
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and 100mg produced reductions in resting and exercise heart rate and systolic blood pressure of about 20% within 2 to 4 hours after administration [fig. 2] (Bailliart et al. 1987; Leopold et al. 1986b; Tattersfield et al. 1984; Wellstein et al. 1987). Bolli et al. (1986) reported that oral bisoprolol 10 and 20mg produced reductions in resting heart rate and systolic and diastolic blood pressure of about 11 to 17%, in comparison to placebo, in 5 patients with essential hypertension. In addition, oral bisoprolol 20 and 40mg reduced exercise tachycardia by 23 to 26%, systolic blood pressure by 15 to 19%, and diastolic blood pressure by 11 to 18% (all values p < 0.05 vs placebo), without affecting left ventricular contractility, in 10 patients with mild to moderate essential hypertension (Esper et al. 1986).

In comparison with baseline or placebo, in patients with angina pectoris or chronic ischaemic heart disease, single oral doses of bisoprolol 5, 10 and 20mg at rest and during exercise decreased heart rate, cardiac index and rate-pressure product (Bonelli & Staribacher 1986; Schnellbacher et al. 1986; Wagner 1986) and also elicited increases in total peripheral resistance (Burkart et al. 1986). These results reflect the expected counter-regulation to acute decreases in cardiac output observed after single doses of almost all β-blockers.

Comparisons of the actions of oral bisoprolol 10 and 20mg with atenolol 50 and 100mg on isoprenaline- and adrenaline (epinephrine)-induced changes in forearm blood flow, have been conducted in patients with essential hypertension by Bolli et al. (1986) [section 1.1.2]. In addition, in a randomised placebo-controlled double-blind crossover study, Bailliart et al. (1987) compared the effects of single oral doses of bisoprolol 10mg and propranolol 40mg, which had similar negative chronotropic and hypotensive effects on brachial and femoral artery flow rates and vascular resistances in 9 healthy subjects. At room temperature (25°C), bisoprolol and propranolol induced similar falls in brachial flow rate (26% and 35%, respectively), which were not significantly different from placebo and which were probably due to reductions of cardiac output. Unlike propranolol, bisoprolol did not increase brachial resistances, but both β-adrenoceptor antagonists induced increases in unimpeded femoral resistances (p < 0.001 and p < 0.01 vs placebo, respectively), although the increases after bisoprolol were less than those produced by propranolol (p < 0.01).

1.3.3 Effects on Myocardial Oxygen Consumption

Following bisoprolol administration myocardial oxygen demand, estimated from the rate-pressure product (heart rate × systolic blood pressure), was markedly reduced in healthy subjects and patients with angina pectoris (table 1).

The influence of single oral doses of bisoprolol 5 to 40mg on exercise-induced myocardial ischaemia (as shown by ST-segment depression), have been investigated in patients with stable angina pectoris by Bonelli and Staribacher (1986), Schnellbacher et al. (1986) and Prager et al. (1987). In patients in randomised double-blind placebo-controlled studies, bisoprolol 5, 10 and 20mg reduced exercise-induced ST-segment depression by 39 to 70% (p < 0.01 vs placebo) [Schnellbacher et al. (1986); Prager et al. (1987)]. In addition, in 7 patients with stable angina pectoris Bonelli and Staribacher (1986) reported that bisoprolol 40mg reduced ST-segment depression during exercise by 57% in comparison to baseline. However, in a randomised double-blind parallel study in 24 patients bisoprolol 5 and 10mg both caused reductions in peak exercise-induced ST-segment depression, and increased exercise tolerance by 53 to 55% and 36 to 41% at 4 and 24 hours after dosing, respectively. Furthermore, rate-pressure product decreased with both the 5 and 10mg doses by 26 to 27% and 21 to 22% at these same time intervals, respectively (Prager et al. 1987).

1.4 Effects on Respiratory Function

The respiratory function of 8 healthy subjects was not adversely affected by oral bisoprolol 20 and 40mg (Tattersfield et al. 1984).

In 16 patients with angina pectoris and co-existing chronic obstructive bronchitis who were treated with single oral doses of bisoprolol 5, 10,
15, 20, 30 and 40mg, a dose-dependent reduction in heart rate and systolic blood pressure was obtained (Dorow 1986). However, only bisoprolol 30 and 40mg produced an increase in airways resistance and forced expiratory volume in 1 second (FEV₁). None of the patients studied noticed any change in their pulmonary function.

The respiratory effects of single doses of bisoprolol 10 and 20mg have been compared with atenolol 100mg and placebo in 12 hypertensive asthmatic patients (Chatterjee 1986) and 12 patients with angina pectoris and chronic obstructive lung disease (Dorow et al. 1986). In these studies none of the active treatments produced any statistically significant reductions in FEV₁, peak expiratory flow rate (PEFR), vital capacity or intrathoracic gas volume. However, atenolol 100mg significantly increased airways resistance in comparison to bisoprolol 10 and 20mg and placebo (p < 0.05). In 8 asthmatic patients both bisoprolol 10 and 20mg and metoprolol 100mg increased bronchoconstriction (indicated by reductions in PEFR from about 350 to 300 L/min and 358 to 291 L/min, respectively, 2 hours after drug intake; both p < 0.01 vs baseline values), and bisoprolol 10mg also significantly decreased vital capacity and FEV₁ (from 4.04 to 3.78L and 2.43 to 2.1L, respectively; both p < 0.01 vs baseline values). The patients remained asymptomatic and all of these changes in ventilatory parameters were rapidly reversed by inhalation of terbutaline, but it was concluded that both bisoprolol and metoprolol should be used with caution in asthmatics, and then only when a β₂-adrenoceptor agonist is used concomitantly (Lammers et al. 1986).

1.5 Effects on Renal Function

The acute effects of intravenous bisoprolol 10mg on renal function have been investigated in 6 patients with essential hypertension and normal renal function (Glück & Reubi 1986). Bisoprolol reduced heart rate by 23%, glomerular filtration rate (GFR) by 14%, effective renal plasma flow (ERPF; or para-amino-hippuric acid clearance, \(\text{CL}_{\text{PAH}}\)) by 23%, and plasma renin activity by 25%. However, mean blood pressure remained unchanged due to increased systemic vascular resistance, and reductions in urine volume and sodium clearance were not statistically significant. Significant correlations were observed between the reduction in heart rate and the reductions in GFR or ERPF (\(r = 0.56, p < 0.01\) and \(r = 0.51, p < 0.01\), respectively) as well as between the reductions in GFR and ERPF (\(r = 0.52, p < 0.01\)). It was concluded that the acute changes in kidney function produced by bisoprolol were similar to those observed after intravenous administration of propranolol, pindolol, atenolol, metoprolol and acebutolol.

1.6 Metabolic Effects

1.6.1 Carbohydrate Metabolism

Cardioselective β₁-adrenoceptor antagonists are less likely to affect glucose metabolism than propranolol as most of the effects of catecholamines on carbohydrate metabolism are mediated by β₂-adrenoceptors (Janka et al. 1986). They are also less likely to delay recovery from hypoglycaemia than non-selective β-adrenoceptor antagonists (for review see Verschoor et al. 1986).

Insulin-Induced Hypoglycaemia

Blood glucose concentrations are markedly reduced following a bolus injection of insulin. Single-dose oral administration of propranolol 40mg to 10 healthy subjects delayed the rise of the serum glucose concentration in the recovery phase (0.5 to 2 hours after intravenous administration of insulin), whereas bisoprolol 10mg or metoprolol 50mg only slightly delayed the recovery from hypoglycaemia. In addition, under control conditions, hypoglycaemia led to compensatory glycogenolysis with a consequent rise in serum lactate concentrations that was strongly reduced by propranolol but not by bisoprolol or metoprolol (Leopold et al. 1986b).

As these compensatory metabolic processes, after insulin-induced hypoglycaemia, are mediated by β₂-adrenoceptors it would again appear that bisoprolol and metoprolol act as relatively selective β₁-adrenoceptor antagonists.
Table II. Pharmacokinetic properties of bisoprolol and some β-adrenoceptor antagonists (after Simpson 1987; Bühring et al. 1986; Haeusler et al. 1986; Kirch et al. 1986, 1987; Leopold 1986; Leopold et al. 1986a)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral bio-availabilitya (%)</th>
<th>First-pass hepatic metabolism</th>
<th>Elimination half-life (h)</th>
<th>Predominant route of eliminationb</th>
<th>Active metabolites of potential clinical importance</th>
<th>Protein binding (%)</th>
<th>Volume of distribution (L/kg)</th>
<th>Relative lipid solubilityc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>90</td>
<td>≈10%</td>
<td>≈11 (PO)</td>
<td>Hepatic metabolism and renal excretion (≈50% unchanged)</td>
<td>No</td>
<td>≈30</td>
<td>≈2.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>20-60</td>
<td>Yesd</td>
<td>7 (PO)</td>
<td>Renal excretion (≈15% unchanged; ≈28% active metabolite) and hepatic metabolism</td>
<td>Yes</td>
<td>≈20</td>
<td>1.2</td>
<td>Low</td>
</tr>
<tr>
<td>Alprenolol</td>
<td>10-60</td>
<td>Yesd</td>
<td>2-3 (IV, PO)</td>
<td>Hepatic metabolism</td>
<td>Yes</td>
<td>76-85</td>
<td>1.1</td>
<td>High</td>
</tr>
<tr>
<td>Atenolol</td>
<td>50-60</td>
<td>No</td>
<td>6-9 (PO)</td>
<td>Renal excretion (mostly unchanged)</td>
<td>No</td>
<td>&lt;5</td>
<td>1.1</td>
<td>Very low</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>80-89</td>
<td>No</td>
<td>14-22 (IV, PO)</td>
<td>Hepatic metabolism and renal excretion (≈16% unchanged)</td>
<td>No</td>
<td>55</td>
<td>5-9</td>
<td>Moderate/ high</td>
</tr>
<tr>
<td>Bevantolol</td>
<td>60</td>
<td>Yesf</td>
<td>1-3 (PO)</td>
<td>Hepatic metabolism</td>
<td>No</td>
<td>95-98</td>
<td>1.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>30-70</td>
<td>Yesf</td>
<td>4-5 (PO)</td>
<td>Renal excretion</td>
<td>No</td>
<td>≈25</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Esmolol</td>
<td>10-80</td>
<td>Yesd</td>
<td>3-5 (IV, PO)</td>
<td>Blood esterase hydrolysis</td>
<td>No</td>
<td>56</td>
<td>3.4</td>
<td>Low</td>
</tr>
<tr>
<td>Labetalol</td>
<td>40-50</td>
<td>Yesd</td>
<td>3-4 (IV, PO)</td>
<td>Hepatic metabolism</td>
<td>No</td>
<td>≈50</td>
<td>5-9</td>
<td>Moderate/ high</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>40-50</td>
<td>Yesd</td>
<td>14-24 (PO)</td>
<td>Renal excretion (all unchanged)</td>
<td>No</td>
<td>8-12</td>
<td>5.5</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nadolol</td>
<td>30-60</td>
<td>No</td>
<td>2-6 (PO)</td>
<td>Hepatic metabolism</td>
<td>No</td>
<td>≈30</td>
<td>1.9</td>
<td>Very low</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>25-60</td>
<td>Yesg</td>
<td>2 (PO)</td>
<td>Hepatic metabolism</td>
<td>Probably not</td>
<td>92</td>
<td>1.3</td>
<td>Moderate</td>
</tr>
<tr>
<td>Penbutolol</td>
<td>100</td>
<td>No</td>
<td>26</td>
<td>Hepatic metabolism</td>
<td>&gt;95</td>
<td>?</td>
<td>?</td>
<td>High</td>
</tr>
<tr>
<td>Pindolol</td>
<td>100</td>
<td>No</td>
<td>3-4 (IV)</td>
<td>Renal excretion (≈40% unchanged) and hepatic metabolism</td>
<td>No</td>
<td>50</td>
<td>1.2</td>
<td>Low</td>
</tr>
<tr>
<td>Propranolol</td>
<td>30</td>
<td>Yes</td>
<td>2-4 (IV)</td>
<td>Hepatic metabolism</td>
<td>Yes</td>
<td>93</td>
<td>2.8</td>
<td>High</td>
</tr>
<tr>
<td>Sotalol</td>
<td>60-100</td>
<td>No</td>
<td>5-13 (PO)</td>
<td>Renal excretion (≈75% unchanged)</td>
<td>No</td>
<td>&lt;1</td>
<td>1.3</td>
<td>Very low</td>
</tr>
<tr>
<td>Timolol</td>
<td>75</td>
<td>No</td>
<td>4-5 (PO)</td>
<td>Hepatic metabolism and renal excretion (≈20% unchanged)</td>
<td>?f</td>
<td>60</td>
<td>1.7</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

a Percentage of dose reaching systemic circulation as unchanged drug after oral administration.
b Renal disease: Compounds eliminated primarily by renal excretion accumulate in renal failure, necessitating modification of dosage. Bioavailability of propranolol increases in renal failure due to decreased hepatic first-pass metabolism. Bioavailability of pindolol is decreased in renal failure but is compensated by decreased renal clearance. Percentages are those of the given dose.
c Cirrhosis: Bioavailability of compounds subjected to significant first-pass metabolism increases due to reduced hepatic extraction. This will be particularly marked if there is significant portal systemic shunting.
d Based on the partition coefficient octanol/water.
e The total body clearance of these drugs approaches the hepatic blood flow, indicating that they are extensively removed from the blood during their first passage through the liver.
f Metabolites with possible pharmacological activity have been identified but their clinical importance has not been clearly established.

Abbreviations: PO = oral administration; IV = intravenous administration.
Effects in Hypertensive Diabetics

The effects of 2 weeks' treatment with oral bisoprolol 10 mg/day were investigated in a double-blind placebo-controlled crossover study in 20 patients with mild to moderate essential hypertension and coexisting non-insulin-dependent diabetes mellitus. Patients had been stabilised on diet (n = 2) or sulphonylureas (n = 18). In comparison to placebo, bisoprolol did not change blood glucose concentrations, haemoglobin A1 concentrations or the amount of glucosuria. Furthermore, no episodes of hypoglycaemia were observed in the patients receiving bisoprolol. The authors concluded that bisoprolol had no influence on carbohydrate and lipid metabolism in non-insulin-dependent diabetic patients (Janka et al. 1986).

1.6.2 Lipid Metabolism

Hypertension is just one of several factors which contribute to the development of atherosclerosis; abnormal plasma concentrations of lipids and lipoproteins are another. Ideally, an agent used to treat hypertension should not produce potentially harmful changes in plasma lipid concentrations. Undesirable effects here would include high concentrations of total cholesterol, low density lipoprotein (LDL)- and very low density lipoprotein (VLDL)-cholesterol, serum triglycerides or VLDL-triglycerides and apoprotein B1 or low concentrations of high density lipoprotein (HDL)-cholesterol or apoprotein A1.

The effects of daily oral bisoprolol 2.5 to 40mg, for 2 to 3 months (Bühler et al. 1986; Frithz & Weiner 1987; Lithell et al. 1986) or up to 12 months (Frithz & Weiner 1986; Weiner & Frithz 1986b), on serum lipids have been investigated in patients with mild to moderate essential hypertension. No significant changes in total cholesterol and LDL-cholesterol were observed. However, in two comparative studies of treatment with oral bisoprolol 10 to 20 mg/day and atenolol 50 to 100 mg/day both treatments produced small but statistically significant increases in serum triglycerides (p < 0.05) [Bühler et al. 1986; Lithell et al. 1986].

The effects of treatment with bisoprolol on HDL-cholesterol concentrations are also unclear. Although slight, but statistically significant, reductions in HDL-cholesterol were observed after 3 months' treatment with bisoprolol 10 and 20 mg/day (p < 0.01) and atenolol 50 and 100 mg/day (p < 0.05) [Lithell et al. 1986], the HDL-cholesterol concentration was unchanged during bisoprolol treatment (2.5 to 40 mg/day) in two 12-month studies (Frithz & Weiner 1986; Weiner & Frithz 1986b). Thus, the effects of bisoprolol on lipid metabolism are equivocal and further studies in this area are required.

2. Pharmacokinetic Studies (Table II)

The balanced pharmacokinetic properties that bisoprolol exhibits in humans may be attributed to its 'balanced in vitro partition behaviour' (partition coefficient of 1.09 at pH 7.0 in an n-octanol-Davies-Universal buffer of 37°C; Prichard 1987) [Leopold 1986]: the drug is as soluble in water as it is in organic solvents and hence possesses equal lipophilicity and hydrophilicity.

The pharmacokinetics of bisoprolol have been investigated in small numbers of healthy subjects and patients with renal or hepatic impairment (table III), but further studies are required in patients with hypertension or ischaemic heart disease.

Plasma concentrations of bisoprolol in pharmacokinetic studies have been measured by a specific high pressure liquid chromatography method with a sensitivity of 1 to 2 μg/L in plasma and 10 μg/L in urine (Bühring & Garbe 1986).

2.1 Absorption

Bisoprolol is extensively absorbed from the gastrointestinal tract following oral administration (> 90%) [Leopold et al. 1986a]. Mean peak plasma concentrations of 36 and 445 μg/L, respectively, were reached within 3 hours of a single 10mg oral dose in 12 healthy subjects (Leopold 1986; fig. 3) and a single 100mg oral dose (an extremely high dose which is well above the therapeutic dose range) in 6 healthy subjects (Wellstein et al. 1986b). Similarly, mean maximum steady-state plasma concentrations of 52 to 56 μg/L were reported in 6 and
8 healthy subjects treated with oral bisoprolol 10mg once daily for 7 days (Kirch et al. 1986, 1987), respectively. Administration of bisoprolol with food did not affect the rate or extent of its absorption (Leopold et al. 1986a).

The mean time to reach peak plasma concentrations after the oral administration of bisoprolol 10mg has been reported to be in the region of 1.7 to 3.0 hours (Kirch et al. 1986; Leopold 1986). Values for the area under the plasma-concentration time curve (AUC_{0-\infty}) for oral bisoprolol 10mg are in the range 597 to 661 \(\mu g/L \cdot h\) (Kirch et al. 1986, 1987; Leopold et al. 1986a) in comparison to a value of 672 \(\mu g/L \cdot h\) reported after the intravenous administration of bisoprolol 10mg (Leopold et al. 1986a). Leopold et al. (1982) administered bisoprolol 10, 20 and 40mg to healthy subjects and showed that the magnitude of the AUC for bisoprolol was dose related (AUC values 574, 1024, 2195 \(\mu g/L \cdot h\), respectively). Later studies further substantiated the fact that bisoprolol exhibits linear pharmacokinetics over a wide dose range (fig. 4, Leopold 1986; Takeuchi et al. 1985).

2.2 Distribution

Animal studies using rats have shown that bisoprolol is rapidly and widely distributed. Five minutes after the intravenous administration of \(^{14}\text{C}\)-bisoprolol, the highest concentrations of radioactivity were found in lung, kidneys and liver. One hour after oral administration, the highest concentrations of radioactivity were located in the liver and kidneys, and concentrations higher than in the plasma were present also in the lung, spleen and adrenals. After 4 and 8 hours radioactivity was only apparent in the liver, kidney and gastrointestinal tract. Repeated oral administration did not affect the pattern of distribution and no accumulation of bisoprolol or its metabolites was observed (Bühring et al. 1986).

In rats, bisoprolol penetrated the blood-brain barrier to a greater extent than atenolol, and to a lesser extent than metoprolol and propranolol (brain/plasma concentration ratios: 2, < 0.1, 8 and 40, respectively). In addition, little placental transfer of bisoprolol occurred in rats (Bühring et al. 1986).

Bisoprolol is not extensively bound to plasma proteins: 26 to 33% of the drug was reported to be
bound in human serum and the in vitro binding was independent of the plasma bisoprolol concentration (range 10 to 5000 µg/L) [Bühring et al. 1986].

The volume of distribution for bisoprolol 10mg in healthy subjects was 235L (Leopold 1986) or 2.93 L/kg (Kirch et al. 1987) after oral administration, and was reported to be 226 and 269L after intravenous administration and after the administration of an oral 20mg solution, respectively (Leopold 1986).

2.3 Metabolism

The hepatic metabolism of bisoprolol was similar in animals (rats, dogs, monkeys) and humans and consisted of O-dealkylation followed by oxidation to 3 carboxylic acid metabolites (Bühring et al. 1986) [fig. 5]; direct pharmacological testing and indirect subtype selective β-adrenoceptor assays have shown that the 3 metabolites are devoid of β-adrenoceptor antagonistic activity in man (Bühring et al. 1986; Wellstein et al. 1986b). The drug is also not stereoselectively metabolised in man (Leopold 1986; Wellstein et al. 1986b) and is not subject to genetic oxidation polymorphism of the debrisoquine type. In man, approximately 50% of a dose of bisoprolol is excreted in the urine unchanged and an equal proportion is metabolised in the liver; in addition, as bisoprolol is not a high hepatic clearance drug, it exhibits only a moderate hepatic ‘first-pass’ effect (≤ 10%) after oral administration (Bühring et al. 1986; Leopold 1986).

2.4 Excretion

Bisoprolol and its metabolites are excreted in the urine; approximately 50% of the dose is excreted unchanged (Leopold 1986) and the elimination half-life of the unchanged drug was 9 to 12 hours after administration of oral bisoprolol 10mg in tablet form, or 20mg as an oral solution, in healthy subjects (Hayes et al. 1987; Kirch et al. 1986, 1987; Leopold 1986; Payton et al. 1987). After intravenous injection of bisoprolol 10mg the mean elimination half-life of unchanged bisoprolol was 10.3 hours (Leopold 1986). Total and renal clearance values for single and repeated oral doses of bisoprolol 10mg were 14 to 16 L/h and 7.3 to 8.4 L/h, respectively, and for bisoprolol 20mg, as an oral solution, were 18.2 and 8.9 L/h, respectively (Kirch et al. 1986, 1987; Leopold 1986).

2.5 Effects of Renal or Hepatic Disease on Pharmacokinetics

Bisoprolol is removed from the plasma via 2 equally effective routes of elimination: half of the dose is hepatically metabolised and the other half is renally excreted unchanged. This phenomenon is known as ‘balanced clearance’ (sections 2.3 and 2.4).

The effects of hepatic and renal impairment on the pharmacokinetics of bisoprolol have been studied after the administration of single 10mg oral doses (Hayes et al. 1987; Payton et al. 1987) and during repeated treatment (10mg daily) for 7 days (Kirch et al. 1987; table III). Accumulation of unchanged bisoprolol by a factor of more than 2 (in excess of the normally observed interindividual variation of pharmacokinetic parameters) did not occur in patients with renal or hepatic impairment with repeated administration, indicating that the concept of balanced clearance was effective in patients with insufficiency of different degrees of one of the main clearance organs. However, in some patients with renal or hepatic disease the elimination half-life of the drug was prolonged to 27.6 and 21.1 hours, respectively, and in view of this, the daily dosage of bisoprolol should not exceed 10mg in those patients who have end-stage renal or hepatic failure (Kirch et al. 1987). The treatment of patients on long term intermittent haemodialysis or on continuous ambulatory peritoneal dialysis should be monitored by observing the clinical effect (Payton et al. 1987).

2.6 Effect of Hyperthyroidism on Pharmacokinetics

Nine hyperthyroid patients were treated with
oral bisoprolol 10mg once daily for 7 days (Pfannenstiel et al. 1986). The values for maximum and minimum plasma bisoprolol concentrations and the steady-state plasma elimination half-life of bisoprolol were similar to those observed in healthy subjects. No significant changes in serum thyroid hormones were observed during bisoprolol treatment.

2.7 Relationship of Plasma Concentration to Pharmacodynamic Effect

The haemodynamic effects of various bisoprolol plasma concentrations were investigated in 13 patients with ischaemic heart disease (Bonelli and Staribacher 1986); no appreciably greater reduc-
Table III. Mean pharmacokinetic parameters of oral bisoprolol 10mg in healthy subjects and patients with kidney or liver diseases

<table>
<thead>
<tr>
<th></th>
<th>Single-dose</th>
<th></th>
<th>Multiple-dose (daily for 7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>Healthy renal impairment, CL_{cr} (ml/min)</td>
<td>Healthy liver disease</td>
<td>Healthy renal impairment, liver disease</td>
</tr>
<tr>
<td></td>
<td>30-60</td>
<td>10-29</td>
<td>&lt; 10</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>C_{max} (µg/L)</td>
<td>51.4</td>
<td>55.3</td>
<td>60.2</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>69.5</td>
<td>37</td>
</tr>
<tr>
<td>C_{max} (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{min} (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (µg/L * h)</td>
<td>881</td>
<td>1124</td>
<td>1711</td>
</tr>
<tr>
<td></td>
<td>682</td>
<td>1341</td>
<td>688</td>
</tr>
<tr>
<td>AUC_{ss} (µg/L * h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL_{o} (L/h)</td>
<td>13.9</td>
<td>11.3</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>8.3</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>CL_{ren} (L/h)</td>
<td>14.2 *</td>
<td>7.8 *</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>7.3</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>t_{1/2} (h)</td>
<td>12.1</td>
<td>17.7</td>
<td>19.6</td>
</tr>
<tr>
<td></td>
<td>8.7</td>
<td>16.7 **</td>
<td></td>
</tr>
<tr>
<td>t_{max} (h)</td>
<td>2.5</td>
<td>2</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>6.0 **</td>
<td></td>
</tr>
<tr>
<td>U_{0-24h} (% dose)</td>
<td>52.1</td>
<td>33.5</td>
<td></td>
</tr>
<tr>
<td>Vd (L)</td>
<td>243</td>
<td>289</td>
<td>178</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>170</td>
<td>323</td>
</tr>
<tr>
<td>CL_{cr} (ml/min)</td>
<td>93</td>
<td>46</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>CL_{antipyr} (ml/min)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Factor of accumulation</td>
<td>1</td>
<td>1.46</td>
<td>1.62</td>
</tr>
</tbody>
</table>

a  Systemic clearance, CL, with F = 0.88.
b  Pugh modification of Child’s scoring system (Pugh et al. 1973).

Abbreviations: C_{max} = maximum plasma concentration; C_{max}^{ss} = steady-state C_{max}; C_{min}^{ss} = steady-state minimum plasma concentration; AUC = area under the plasma concentration-time curve; AUC_{ss} = AUC during dosing interval (t) at steady-state; CL_{o} = oral clearance; CL_{ren} = renal clearance; t_{1/2} = elimination half-life, t_{max} = time required to reach C_{max}; U_{0-24h} = amount of drug recovered in urine after 24 hours; Vd = volume of distribution; CL_{cr} = creatinine clearance; CL_{antipyr} = antipyrine clearance.

Significantly different from control values: * = p < 0.05; ** = p < 0.01.
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Fig. 6. Relationship between bisoprolol plasma concentrations and reduction in cardiac index at submaximal exercise, in comparison to baseline, in 13 patients with ischaemic heart disease treated with single oral doses of bisoprolol 10 or 40mg (after Bonelli & Staribacher 1986).

...tions in cardiac index were reported with bisoprolol plasma concentrations greater than 60 μg/L (fig. 6).

Wellstein et al. (1986b, 1987), however, investigated the relationship between the plasma concentration of bisoprolol and its β-adrenoceptor antagonistic effect (reduction in exercise tachycardia) in man, including also the β-adrenoceptor occupancy rate of the drug (fig. 7). Reduction in bisoprolol plasma concentration was paralleled by reduction in receptor occupancy, and reduction of an inhibiting effect on exercise tachycardia. This latter correlation of plasma concentration and heart rate has also been reported elsewhere (Arnold et al. 1986). Since the usual therapeutic dosage of oral bisoprolol (10mg daily) produces plasma concentrations of 11 to 78 μg/L (table III), it may be inferred that in the therapeutic dose range (5 to 10mg) bisoprolol does not occupy β2-adrenoceptors.

3. Therapeutic Trials

3.1 Studies in Mild to Moderate Essential Hypertension

Bisoprolol 5 to 20mg once daily has been compared with atenolol, nifedipine, hydrochlorothiazide plus amiloride, and low dose metoprolol (100 mg/day). In addition, it has also been evaluated in long term non-comparative studies (12 to 24 months duration) in patients with mild to moderate essential hypertension. All of the comparative trials have been randomised and double-blind...
with an adequate placebo run-in period, and most have also been parallel in design. Blood pressure readings were taken about 24 hours post-dose and in some studies particular emphasis has been put on evaluating the effect of bisoprolol on exercise blood pressure (Haasis & Bethge 1987; Kirsten et al. 1986; Weiner & Frithz 1986a,b; data on file, E. Merck). The patient numbers have been small in some trials and further comparative studies against the above drugs, propranolol, diuretics and calcium antagonists are still required.

3.1.1 Non-Comparative Studies

In short term (~3 months duration) randomised dose-finding studies with parallel groups for comparing the antihypertensive effect of bisoprolol 5, 10 and 20mg, significant dose-dependent reductions in resting and exercise blood pressure and heart rate and in responder rates 24 hours post-dose have been demonstrated by Weiner and Frithz (1986a) and Kirsten et al. (1986). However, in a randomised crossover study including 12 patients with essential hypertension the effect of 4 weeks treatment with bisoprolol 20mg on diastolic blood pressure was not superior to that of bisoprolol 10mg (Cardona et al. 1986) [table IV].

In non-comparative dose-titration studies normalisation of systolic and diastolic blood pressure and significant reductions in heart rate were apparent after 2 to 6 weeks’ treatment with daily oral bisoprolol 2.5 to 40mg (Frithz & Weiner 1986, 1987; Gießecke & Englert 1986; Ikeda et al. 1986; Weiner & Frithz 1986a; unpublished data on file, E. Merck; fig. 8).

During long term treatment studies (12 to 24 months duration) a dose range of bisoprolol from 5 to 20mg has been shown to be adequate for optimal blood pressure control in the majority of patients with mild to moderate essential hypertension (table V). Since supine and standing blood pressures and heart rates were reduced to the same extent (15 to 20%), orthostatic regulation was unaffected by bisoprolol (Amabile & Serradimigni 1987; Cardona et al. 1986; Frithz & Weiner 1986, 1987; Gießecke & Englert 1986; Lithell et al. 1986, 1987).

Bisoprolol has also produced clear reductions in exercise-induced elevations of systolic and diastolic blood pressure and heart rate 24 hours post-dose (Haasis & Bethge 1987; Kirsten et al. 1986; Weiner & Frithz 1986a,b; unpublished data on file, E. Merck).

| Reference                        | Study design | No. of patients | Duration of placebo run-in (weeks) | Daily dose of bisoprolol (mg) | Duration of treatment (weeks) | Reduction of blood pressure (%) | Reduction of heart rate (%) | Patient response (%) |
|----------------------------------|--------------|-----------------|-----------------------------------|------------------------------|-----------------------------|------------------------------|--------------------------|---------------------|---------------------|
| Weiner & Frithz (1986b)          | pri, r, db, p| 16              | 3                                 | 5                            | 8                           | 12/12                       | 13/11                     | 18                  | 15                  | 75<sup>a</sup>     |
| Kirsten et al. (1986)            | pri, r, db, p| 15              | 2                                 | 5                            | 12                          | 8/10                        | 11                        | 17                  | 21                  | 75<sup>b</sup>     |
| Cardona et al. (1986)            | db, r, co    | 12              | 4                                 | 10                           | 4                           | 13/14                       | 25                        | 100<sup>b</sup>    | 75                  |

<sup>a</sup> Reduction in 24-hour supine diastolic blood pressure to < 90mm Hg or by ≥ 10mm Hg.

<sup>b</sup> Reduction in 24-hour supine diastolic blood pressure to < 90mm Hg.

Abbreviations: pri = placebo run-in; <sup>a</sup>r = randomised; db = double-blind; co = crossover; p = parallel groups.
3.1.2 Comparisons with Other β-Adrenoceptor Antagonists

The antihypertensive efficacy of bisoprolol 5 to 20mg once daily has been compared with that of atenolol 50 to 100mg once daily in randomised double-blind studies in patients with mild to moderate essential hypertension (Frances et al 1987; table VI). Six months’ treatment with oral bisoprolol 5 to 20mg once daily produced reductions in supine and standing blood pressures and heart rates 24 hours after drug intake that were statistically significant in comparison to baseline placebo values (p < 0.001), indicating that daily doses of bisoprolol 5 and 10mg were equivalent to atenolol 50 and 100mg in the reduction of elevated blood pressures (Lithell et al. 1986, 1987). The responder rate as defined by a reduction of diastolic blood pressure to ≤ 90mm Hg 24 hours after administration was highest (57%) in the group receiving bisoprolol 10mg daily (Lithell et al. 1987; table VI), indicating both dose dependency of bisoprolol treatment and a higher potency of bisoprolol 10mg versus atenolol 50mg. However, even bisoprolol 5mg exhibited optimal 24-hour antihypertensive activity in about half of the patients with mild to moderate hypertension which increased even more when the dose was doubled to 10mg daily (Lithell et al. 1987).

Similarly, in other double-blind crossover studies, with bisoprolol (10 or 20mg once daily) and atenolol (50 or 100mg once daily), there were slightly, but significantly, greater falls in blood pressure with bisoprolol (p ≤ 0.05: table VI) and bisoprolol reduced heart rate by 21%, and atenolol by 18% (p ≤ 0.05), while a target diastolic blood pressure of ≤ 95mm Hg was attained in 68 vs 56% of patients after administration of bisoprolol vs atenolol, respectively (p ≤ 0.05) [Buhler et al. 1986]. The subset of patients who were regular cigarette smokers (n = 25) had a higher antihypertensive response rate on bisoprolol (80%) than on atenolol (52%; p ≤ 0.05).

In another study, the residual effects of bisoprolol 10mg once daily on exercise systolic blood
pressure, heart rate and rate-pressure product, 24 hours after administration, were compared with those of a low dose of metoprolol (100mg once daily) in a 4-week randomised double-blind trial in 87 patients with mild to moderate essential hypertension (Haasis & Bethge 1987; table VI). After 4 weeks' treatment, exercise testing showed that bisoprolol 10mg 24 hours after administration elicited significantly greater effects on exercise systolic blood pressure, heart rate and rate-pressure product than metoprolol 100mg (p < 0.01). Three hours after administration the effects of the drugs on reducing exercise blood pressure, heart rate and rate-pressure product were similar (about 16%, 16% and 30%, respectively). Under resting conditions the difference in the percentage of patients responding to treatment (resting diastolic blood pressure ≤ 95mm Hg at 24 hours) was not statistically significant (86% and 70% for bisoprolol- and metoprolol-treated patients, respectively; p = 0.0526). The above results suggest that if once daily treatment of essential hypertension is desired, a β-blocker with a longer plasma elimination half-life such as bisoprolol would more reliably guarantee 24-hour antihypertensive efficacy, particularly with regard to the exercise-induced increases in blood pressure, than an agent with a shorter plasma elimination half-life.

### 3.1.3 Comparison with Hydrochlorothiazide Plus Amiloride

In a randomised, double-blind, parallel study Honoré (1987) compared the antihypertensive efficacy of bisoprolol 10mg once daily with that of a combination of hydrochlorothiazide 50mg plus amiloride 5mg once daily in 34 patients with mild to moderate essential hypertension. After 4 weeks' treatment mean percentage reductions in standing systolic and diastolic blood pressures in comparison to baseline placebo values 24 hours after drug intake in patients treated with bisoprolol or hydrochlorothiazide plus amiloride, were 13/17 and 9/
Table VI. Studies comparing bisoprolol (B) with atenolol (A) and metoprolol (M) in mild to moderate essential hypertension

<table>
<thead>
<tr>
<th>References</th>
<th>Study design</th>
<th>No. of patients*</th>
<th>Treatment dose (mg/day)</th>
<th>Duration (weeks)</th>
<th>Reduction of blood pressure (%)b supine</th>
<th>Reduction of heart rate (%)b supine</th>
<th>Patient response (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bühler et al.</td>
<td>pri, r, db, co, mc 94 B10-20 A50-100</td>
<td>8</td>
<td>14*/16*d</td>
<td>21*d</td>
<td>68c</td>
<td>73 vs 63% of patients &lt; 60 yrs responded to B vs A; while 56 vs 41% of patients &gt; 60 yrs responded to B vs A, respectively</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1986)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haasis &amp; Bethge</td>
<td>pri, r, db, p, mc 44 B10</td>
<td>4</td>
<td>15/15*d</td>
<td>20*d</td>
<td>86c</td>
<td>Blood pressure and heart rate increments during exercise 24 hours post-dose were significantly more reduced by B than by M (p &lt; 0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1987)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewis et al.</td>
<td>pri, db, co 14 B10</td>
<td>6</td>
<td>22*/16*d,g</td>
<td>23*/16*g</td>
<td>49-64*e</td>
<td>No significant differences for reducing heart rate between the 2 treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1988)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithell et al.</td>
<td>pri, r, db, p 21 B10</td>
<td>24'</td>
<td>10/11</td>
<td>10/10</td>
<td>16</td>
<td>Supine and standing blood pressures and heart rates were significantly reduced with both treatments (p &lt; 0.001 vs baseline placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1986)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithell et al.</td>
<td>pri, r, db, p, mc 97 B5, B10</td>
<td>26</td>
<td>8/12</td>
<td>9/9</td>
<td>16</td>
<td>Supine and standing blood pressures and heart rates were significantly reduced with both treatments (p &lt; 0.001 vs baseline placebo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1987)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Number evaluated for efficacy.
b Percentage reductions in blood pressure and heart rates between end of placebo run-in and end of treatment.
c Patients with diastolic blood pressure ≤ 95mm Hg.
d Sitting blood pressures and heart rates.
e Reduction in diastolic blood pressure to ≤ 90mm Hg or by ≥ 10mm Hg, or mean BP reduction ≥ 10mm Hg.
f Treatment was given for 12 weeks at each dose level.
g Reduction in blood pressure (mm Hg).

Abbreviations: pri = placebo run-in; r = randomised; db = double-blind; co = crossover; mc = multicentre; p = parallel groups; * = p < 0.05 between treatment groups.
Table VII. Some clinical trials involving the use of bisoprolol (B) in patients with chronic stable angina pectoris

<table>
<thead>
<tr>
<th>References</th>
<th>No. of patients*</th>
<th>Study design</th>
<th>Dosage (mg/day)</th>
<th>Study duration</th>
<th>Results (percentage change from control or placebo values)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>total exercise time (min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(time)</td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Englert &amp; Döring (1987)</td>
<td>20</td>
<td>pri, o</td>
<td>B5-20</td>
<td>12m</td>
<td>+77</td>
</tr>
<tr>
<td>Kato et al. (1986)</td>
<td>10</td>
<td>pri, sb</td>
<td>B5-10</td>
<td>4w</td>
<td>+57*</td>
</tr>
<tr>
<td>Prager et al. (1988)</td>
<td>64</td>
<td>o, mc</td>
<td>B5-20</td>
<td>12m</td>
<td>+38f</td>
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<td>Comparisons with other antianginal agents</td>
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<tr>
<td>De Divitiis et al. (1987)</td>
<td>11</td>
<td>pri, db, r, p</td>
<td>B10-20</td>
<td>8w</td>
<td>+28***</td>
</tr>
<tr>
<td>Kohli et al. (1986)</td>
<td>19</td>
<td>pri, db, r, co</td>
<td>B10</td>
<td>3w</td>
<td>+20**</td>
</tr>
<tr>
<td>Maltz et al. (1987)</td>
<td>19</td>
<td>pri, db, r, co</td>
<td>B5-10</td>
<td>6w</td>
<td>±</td>
</tr>
<tr>
<td>Maltz et al. (1987)</td>
<td>19</td>
<td>pri, db, r, co</td>
<td>A100</td>
<td>6w</td>
<td>±</td>
</tr>
</tbody>
</table>

a Number evaluated for efficacy.
b Time to angina increased by 3 minutes in the bisoprolol 5 and 10mg groups.
c About 42% and 57% of patients were free from angina attacks after 6 weeks and 12 months, respectively.
d ISDN 20mg twice daily was administered concomitantly to all patients.
e Atenolol caused a significantly greater increase than bisoprolol (p < 0.02).
f Results after 6 weeks' dose titration.
g Significant increase (p < 0.01) with bisoprolol and atenolol.
h Significant increase (p < 0.05) with bisoprolol and atenolol.
i Significant reduction (p < 0.001) with bisoprolol and atenolol.

Abbreviations: GTN = glyceryl trinitrate; RPP = rate-pressure product; pri = placebo run-in; o = open; sb = single blind; mc = multicentre; db = double blind; r = randomised; p = parallel; co = crossover; V = verapamil; ISDN =isosorbide dinitrate; A = atenolol; m = months; w = weeks; ± = quantitative value not significantly different from placebo.

Significantly different from control or placebo values: * = p < 0.05; ** = p < 0.02; *** = p < 0.01; **** = p < 0.001.
8, respectively, with bisoprolol producing a statistically significantly greater reduction in supine and standing diastolic blood pressure than hydrochlorothiazide plus amiloride (p < 0.002). Diastolic blood pressure was normalised (reduced to ≤ 90mm Hg) in 15/17 patients (89%) treated with bisoprolol and in only 4/17 patients (24%) treated with hydrochlorothiazide plus amiloride (p < 0.001). Those patients whose diastolic blood pressure remained over 90mm Hg (n = 12) received single-blind therapy with once daily administration of bisoprolol 10mg in combination with hydrochlorothiazide 50mg plus amiloride 5mg for a further 4 weeks. At the end of this period combination therapy had resulted in statistically significant reductions (p < 0.001) in supine and standing systolic blood pressures (8 to 10%), diastolic blood pressures (10 to 11%), and supine heart rate (17%); supine diastolic blood pressure was normalised in 4/12 (33%) of these patients.

3.1.4 Comparison with Nifedipine
Amabile and Serradimigni (1987) conducted a randomised double-blind parallel group trial of bisoprolol 10mg once daily and sustained-release (SR) nifedipine 20mg twice daily in 56 patients over the age of 60 years with mild to moderate essential hypertension. Blood pressure readings were taken about 24 hours after bisoprolol and 12 hours after the evening dose of nifedipine SR. After 4 weeks' treatment systolic and diastolic blood pressures in both the bisoprolol and the nifedipine groups were significantly reduced in comparison to baseline placebo values (p < 0.001). At the end of this phase of the study supine diastolic blood pressure was normalised in 22/28 patients (79%) in the bisoprolol group and in 24/28 (86%) of the nifedipine-treated patients who then continued to receive their initial treatment for a further 4 weeks. The doses of bisoprolol and sustained-release nifedipine were doubled in the patients whose diastolic blood pressure remained > 90mm Hg. After 8 weeks, further reductions in systolic and diastolic blood pressure, in comparison to baseline placebo values, were achieved both in the patients now receiving bisoprolol 10 to 20mg once daily (16% and 19%, respectively) and those receiving nifedipine SR 20 to 40mg twice daily (17% and 20%, respectively). However, bisoprolol, unlike nifedipine SR, caused statistically significant reductions in heart rate (10 to 13%; p < 0.001 vs baseline). Episodes of bradycardia were not reported. It was concluded that once-daily bisoprolol 10 to 20mg effectively reduced elevated blood pressure for 24 hours in elderly hypertensive patients and that this treatment effect was comparable to that produced by sustained-release nifedipine 20 to 40mg administered twice daily.

3.2 Studies in Chronic Stable Angina Pectoris

Once-daily treatment with bisoprolol 5 to 20mg in patients with stable angina pectoris has been investigated in non-comparative dose-titration studies and comparisons with atenolol and verapamil, for periods of up to 12 months (table VII). The studies have included an adequate run-in period, with bicycle ergometry or treadmill exercise testing used in the evaluation of the patient's symptoms. However, most studies have been carried out in relatively small groups of patients and, although short term human pharmacological investigations have revealed a sustained anti-ischaemic effect of once daily oral bisoprolol 5 to 10mg for 24 hours, further long term comparative studies involving greater numbers of patients and comparisons with propranolol and other β-blockers, nitrates and calcium antagonists are needed before the role of bisoprolol in the treatment of angina pectoris can be specifically defined.

3.2.1 Non-Comparative Studies
Non-comparative dose-titration studies of the antianginal efficacy of bisoprolol 5 to 20mg once daily were carried out by de Muinck et al. (1987), Englert and Döring (1987), Kato et al. (1986) and Prager et al. (1988). These studies showed that within 2 weeks bisoprolol 5mg produced clinically significant increases in exercise duration and tolerance, indicated by the delayed appearance of electrocardiographic signs of myocardial ischaemia (ST-segment depression) and reduced myocardial
oxygen consumption (rate-pressure product) during exercise. The symptoms of exercise-induced angina were also improved, as shown by a reduction of the frequency of anginal attacks and glyceryl trinitrate (nitroglycerin) consumption. During a 12-month study, in which the antianginal efficacy of bisoprolol was assessed in 64 patients, approximately 50% of the subjects were completely free from anginal attacks, and at the end of this period the daily dose distribution of bisoprolol was as follows: 5mg, 27% of patients; 10mg, 55% and 20mg, 18% (Prager et al. 1988). Doubling the dose of bisoprolol from 5mg to 10mg daily resulted in a therapeutic enhancement in those patients who could not sufficiently be treated with bisoprolol 5mg. However, a further increase to bisoprolol 20mg did not produce any clinically significant improvement of angina pectoris symptomatology both during exercise and as evaluated by the frequency of anginal attacks.

3.2.2 Comparisons with Atenolol

The efficacy of 3 to 6 weeks' treatment with bisoprolol 5 and 10mg once daily was compared with that of atenolol 100mg once daily in double-blind placebo-controlled randomised crossover trials in a total of 38 patients, using treadmill exercise testing 22 to 24 hours after the last drug dose (Kohli et al. 1986; Maltz et al. 1987; table VII). In comparison to baseline placebo values, bisoprolol and atenolol produced significant increases in exercise time (20% and 32%, respectively) and time to 1mm ST-segment depression (12% and 19%, respectively); in addition, both drugs produced significant reductions in rate-pressure product during exercise (17% and 15%, respectively), frequency of anginal attacks (both approximately 50%) and consumption of glyceryl trinitrate tablets (34 and 40%, respectively) [table VII]. In one study, the increase in exercise duration with atenolol 100 mg/day was significantly greater than with bisoprolol 10mg/day (p < 0.02 intratreatment) [Kohli et al. 1986], although comparable statistically significant reductions in mean resting (p < 0.025 vs placebo; Kohli et al. 1986; Maltz et al. 1987) and maximum exercise (p < 0.001 vs placebo; Kohli et al. 1986) heart rates were reported with both treatments. Although these studies indicate that bisoprolol 5 and 10mg once daily are as effective as atenolol 100mg in controlling the symptoms of angina, further long term comparative studies in larger patient populations should be conducted to confirm this.

3.2.3 Comparison with Verapamil

Bisoprolol 10mg once daily and verapamil 80mg 3 times daily were compared for 4 weeks in 21 patients with stable or spontaneous angina who continued to receive isosorbide dinitrate 20mg twice daily. Subsequently doses were increased to bisoprolol 20mg once daily and verapamil 120mg 3 times daily for a further 4-week period (De Divitiis et al. 1987; table VII). Significant reductions in ischaemic ST-segment depression, frequency of anginal attacks, glyceryl trinitrate consumption and rate-pressure product as well as significant increases in exercise duration (p < 0.01 vs baseline placebo) were reported with both treatments by the end of the study. Bisoprolol appeared to produce a slightly, but not significantly, greater reduction in myocardial oxygen demand than verapamil (33% and 25%, respectively), which may have been due to a greater negative chronotropic effect with bisoprolol.

4. Side Effects

Since bisoprolol is a β-adrenoceptor antagonist, it is no surprise that side effects resulting from its use resemble those known from other β-adrenoceptor antagonists and consist primarily of symptoms (subjective and objective) which reflect exaggerated pharmacodynamic effects of the drug. However, as most of the long term studies of bisoprolol in essential hypertension and angina pectoris have been non-comparative in nature, the results of further long term comparisons with placebo are awaited in order to confirm the side effect profile of the drug.

The most frequently reported adverse effects reported to be due to bisoprolol were giddiness, headache, fatigue and bradycardia (Englert & Döring 1987; Giesecke & Englert 1986; Lithell et al.
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Evidence from long term studies suggests that the majority of side effects occur during the first few weeks of bisoprolol therapy and then subside with continued therapy. Moreover, in a randomised double-blind crossover study comparing bisoprolol 10 to 20mg and atenolol 50 to 100mg, the incidence of complaints such as headache, nervousness, sleep disturbances and cold extremities present before treatment decreased during treatment with both β-adrenoceptor antagonists (Bühler et al. 1986).

Bisoprolol appears to have been well tolerated to date in long term studies (6 to 24 months duration) in oral dosages of 2.5 to 40mg once daily and the number of patients withdrawn from bisoprolol treatment because of adverse effects was low (approximately 2.7% of patients treated in long term trials). In addition, the incidence of side effects has not increased in the elderly or in patients with renal or hepatic impairment (Grevel et al. 1987).

Few adverse laboratory effects have been reported, although in some studies statistically significant elevations of serum triglycerides, and reductions in HDL-cholesterol have been observed (section 1.6.2). In 6-month randomised double-blind comparative studies (Lithell et al. 1986, 1987) in patients with mild to moderate essential hypertension, and short term studies (3 to 8 weeks duration) in patients with mild to moderate essential hypertension (Bühler et al. 1986) or stable angina pectoris (Kohli et al. 1986; Maltz et al. 1987), bisoprolol 5 to 20mg once daily and atenolol 50 to 100mg/day were both well tolerated. Similarly, in a 4-week randomised double-blind study in 87 patients with mild to moderate essential hypertension, side effects (nausea, headache, dizziness) were reported in approximately 30% of patients treated with bisoprolol 10mg or metoprolol 100mg once daily (Haasis & Bethge 1987).

A 4-week randomised double-blind study in 40 patients with mild to moderate hypertension comparing bisoprolol 10mg versus hydrochlorothiazide 50mg plus amiloride 5mg also observed side effects with bisoprolol treatment including drowsiness, cold extremities, muscle cramps and skin symptoms in 30% of patients while asthenia, dizziness, nightmares, muscle cramps and skin rash occurred in 35% of the patients receiving the diuretic. There was also a trend for elevated serum uric acid and decreased serum potassium concentrations in the diuretic-treated patients which did not occur in those patients treated with bisoprolol alone (Honoré 1987).

In short term comparisons (2 months duration) with the calcium antagonist nifedipine SR 40 to 80mg/day in mild to moderate essential hypertension and verapamil 240 to 360mg/day in patients with angina pectoris, bisoprolol 10 to 20mg once daily was considered to be better tolerated than nifedipine SR (p < 0.05) [Amabile & Serradimigni 1987] and comparable to verapamil (De Divitiis et al. 1987). Furthermore, in a 14-day study in human volunteers comparing the effects of bisoprolol 10mg once daily versus pindolol 10mg twice daily on the central nervous system, both β-adrenoceptor antagonists did not affect mood, vigilance, tremor or reaction times; however, with bisoprolol no negative effect on sleep quality or ‘feeling refreshed’ after sleep was found. With pindolol, on the other hand, significant impairment of sleep quality was observed after the first dose and a decrease in ‘feeling refreshed’ after sleep continuing up to day 14 of treatment was also reported (Görtelmeyer & Klingmann 1985).

### 5. Drug Interactions

In 18 hypertensive diabetic patients stabilised on sulphonylureas, 2 weeks’ treatment with bisoprolol 10mg once daily had no effect on carbohydrate metabolism in a double-blind placebo-controlled crossover study (Janka et al. 1986; section 1.6.1).
Since β-blockers are metabolised by the same liver microsomal enzymes which metabolise many other drugs, pharmacokinetic interactions may occur with these other drugs or with inhibitors or inducers of microsomal enzymes. Cimetidine, for example, inhibits both microsomal enzymes and renal proximal tubular secretion of organic cations, and significantly increases plasma concentrations of metoprolol or propranolol (Somogyi & Muirhead 1987). However, only a slight tendency towards this interaction was found when bisoprolol and cimetidine were given to healthy subjects (Kirch et al. 1986). Concomitant administration of the potent microsomal enzyme inducer rifampicin produced statistically significant reductions in the plasma concentrations (p < 0.01), AUC (p < 0.01) and elimination half-life (p < 0.05) of bisoprolol as well as an increase in total body clearance of the drug (p < 0.05) [Kirch et al. 1986]. The pharmacokinetics of bisoprolol and trichlormethiazide have been shown not to be altered when both drugs are administered concomitantly (Leopold et al. 1988).

6. Dosage and Administration

The usual oral dose of bisoprolol in mild to moderate essential hypertension or stable angina pectoris is 10mg once daily with a maximum recommended dose of 20 mg/day. In some patients 5 mg/day may be adequate. Dosage adjustment of the drug is not normally required for elderly patients. However, in patients with severely impaired renal function (creatinine clearance < 20 > 5 ml/min/1.73m²), and/or patients with advanced hepatic insufficiency, the daily dose of bisoprolol should not exceed 10mg.

7. The Place of Bisoprolol in Therapy

Bisoprolol is a β₁-adrenoceptor antagonist which effectively lowers blood pressure in patients with mild to moderate essential hypertension and increases exercise tolerance in patients with angina pectoris. In trials in patients with mild to moderate hypertension the drug has shown a comparable antihypertensive efficacy to atenolol, low dose metoprolol, diuretics and nifedipine; similarly, in patients with stable angina pectoris bisoprolol has been shown to be as effective as atenolol and verapamil.

Although bisoprolol is relatively cardioselective, as with all β-adrenoceptor antagonists it should be used with caution in patients in whom a reduction in cardiac output might precipitate heart failure, and in those with chronic obstructive pulmonary disease, a history of frequent hypoglycaemic episodes, longstanding diabetes mellitus, diabetes secondary to pancreatectomy, and in patients requiring strict normoglycaemic control.

Bisoprolol possesses a long elimination half-life, enabling the drug to be given on a once daily basis. This, and the fact that the drug is cleared in equal proportions heptically and renally, may offer advantages both in terms of compliance and pharmacokinetic considerations in selected patients with hypertension and angina pectoris.

Most patients respond to bisoprolol 5 to 20mg once daily but the dosage should not exceed 10 mg/day in patients with end-stage renal or hepatic impairment. Bisoprolol has also been well tolerated in long term trials although the drug’s effects on plasma lipid and lipoprotein concentrations are equivocal.

Thus, there is no doubt that bisoprolol is an effective and well tolerated β₁-adrenoceptor antagonist that should be considered when β-blocker drug treatment in patients with mild to moderate essential hypertension and/or chronic stable angina pectoris is required. However, the results of further studies in large patient populations evaluating the long term safety and efficacy of the drug in relation to placebo or commonly used standard treatment regimens for hypertension and angina pectoris are still awaited so that an adequate and accurate assessment of the relative place in therapy of bisoprolol in these disease states can be ascertained.

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Bisoprolol: A Preliminary Review


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