BISOPROLOL: PHARMACOKINETIC, PHARMACODYNAMIC, THERAPEUTIC USES, SIDE EFFECTS AND CONTRAINDICATIONS

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Abstract:
Bisoprolol exhibits a high absolute bioavailability (90%) because of its nearly complete absorption (greater than 90%) and small first-pass effect (10%). Bioavailability is independent of food intake. A long plasma-elimination half-life (10-11h) allows a once-a-day dose regimen. Because of the low plasma protein-binding (30%), kinetics are insensitive to protein-binding interactions. The balanced clearance (equieffective hepatic and renal clearance) renders the kinetics virtually insensitive to renal or hepatic insufficiency. Even in the case of complete failure of one clearance organ, the plasma elimination half-life of bisoprolol would only double. The metabolites that are inactive and do not accumulate are eliminated predominantly by the kidneys. There is no stereoselective metabolism. The metabolism of bisoprolol is insensitive to liver enzyme inhibition (cimetidine), and nearly insensitive to liver enzyme induction (rifampicin). The metabolism is independent of genetic oxidation-polymorphism (debrisoquine). The pharmacokinetics of bisoprolol are independent of the dose in the range from 2.5 to 100 mg. There is no age or sex dependency. Bisoprolol exhibits predictable pharmacokinetics with well-balanced properties leading to small intra- and interindividual variability of the plasma concentration time curves and pharmacokinetic parameters. Bisoprolol is the beta-blocker with LADME(liberation, absorption, distribution, metabolism, and elimination)-optimized pharmacokinetics. This is a prerequisite for therapeutic reliability.

Keywords: Bisoprolol**,** beta-blocker.

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Introduction:

Bisoprolol is a β1- adrenoceptor antagonist with no partial agonist activity or membrane stabilizing 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 **(1)**.

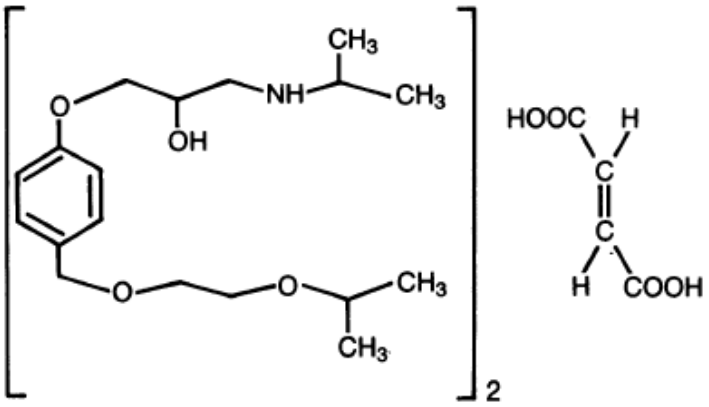

Figure (1): Chemical structure of bisoprolol**(2)**.

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 **(3)**.

Pharmacokinetic Studies:

Bisoprolol 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 hepaticallymetabolised 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**(3)**.

Bisoprolol is well absorbed following oral administration (bioavailability of approximately 90%). The drug has linear pharmacokinetics. Peak plasma bisoprolol concentrations (C_{max}) were 78% higher after repeated administration of bisoprolol 10 mg/day to patients with New York Heart Association (NYHA) grade III chronic heart failure than in healthy volunteers who received a single 10mg dose. The pharmacokinetics of bisoprololappear to be similar in the fed and fasting states. Bisoprolol is 30% plasma protein bound with an apparent volume of distribution of 3.5 L/kg.Bisoprolol is eliminated via renal excretion as unchanged drug (50%) and via hepatic metabolism as pharmacologically inactive metabolites (50%). The total clearance of bisoprolol is 15 L/h. The plasma elimination half-life (t½) of bisoprolol is prolonged in patients with chronic heart failure (17 hours) compared with in healthy volunteers (11 hours) **(4)**.

There are no pharmacokinetic data relating to the use of bisoprolol in patients with both chronic heart failure and either hepatic or renal dysfunction. However, minimal alteration in bisoprolol pharmacokinetics was seen in other patients with hepatic impairment or moderate renal impairment. Exposure to bisoprolol was increased approximately 2-fold in patients with severe renal

impairment or anuria. The pharmacokinetics of bisoprolol were similar in younger (aged ≤63 years) compared with older (aged ≥68 years) patients with hypertension **(5).**

Pharmacodynamic Studies:

Bisoprolol is a β1-adrenoceptor antagonist which has been shown to be devoid of partial agonist or membrane-stabilizing 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%) **(6)**.

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

Therapeutic uses:

Bisoprololis highly selective β_1-adrenoceptor antagonists, with clinical indications in many countries within the management of heart failure with reduced left ventricular ejection fraction (HFrEF), ischemic heart disease (IHD), and hypertension **(7)**.

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 **(8)**.

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 ischemia 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 ischemia 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 **(9)**.

Dosage and Administration:

Cardioselective agents are either administered orally or intravenously. Bisoprolol fumarate is administered only orally as 5 or 10 mg tablets once daily. The dose of bisoprolol fumarate should be tailored to the patient's individualized needs. The usual starting dose is 5 mg once daily. If the 5 mg dose does not produce a desired antihypertensive effect, the dose should be gradually increased to 10 mg and then, if needed, to 20 mg once daily **(10).**

Drug interaction:

Cimetidine and hydrochlorothiazide had no clinically relevant effects on the pharmacokinetics of bisoprolol. The reduction in bisoprolol steady-state Cmax and area under the plasma concentration-time curve with concomitant rifampicin were considered to be of little clinical relevance. Bisoprolol had no clinically relevant effects on the pharmacokinetics of digoxin, theophylline, hydrochlorothiazide or warfarin **(11).**

Side Effects:

A common side effect of cardiovascular blockers is bradycardia, decreasing heart rate and strength of contraction due to its negative chronotropic and inotropic effect. It also decreases cardiac output; therefore, it decreases exercise capacity. Blocking beta receptors on the SA and AV node always carries a risk of heart block. It correlates less

frequently with exacerbation of peripheral diseases such as the Raynaud phenomenon, bronchoconstriction, and hypoglycemia than non-selective beta-blockers **(10).'**

Other commonly encountered side effects include nausea, vomiting, and constipation. Hypoglycemia is a dangerous side effect that happens in people with diabetes mellitus using beta-blockers. The drug blocks the typical signs of hypoglycemia, such as tachycardia; therefore, it delays the body's normal response to hypoglycemia, which may lead to fear of complications. Among all adverse events, bradycardia, fatigue, asthenia, diarrhea, and sinusitis are dose-related **(12).**
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**(13)**.

Statistically significant increases in serum triglycerides 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**(6)**.

Contraindications:
Cardioselective beta-blockers are contraindicated in patients with marked sinus bradycardia, cardiogenic shock, complete heart block and should be monitored carefully in patients with second or third-degree heart block. In addition, patients with a history of recent fluid retention should not use beta-blockers without concomitant use of diuretics **(14).**

New studies suggest that cardioselective beta-blockers are contraindicated in patients with severe asthma or COPD, while it is entirely safe in patients with mild to moderate diseases **(10).**

In patients with diabetes mellitus, it may lead to masked hypoglycemia, so careful monitoring is necessary **(15).**
Bisoprolol should not be abruptly withdrawn as it can cause rebound hypertension and tachycardia. In addition, some patients have developed or exacerbated existing angina pectoris, myocardial infarction, or ventricular arrhythmia when therapy was abruptly stopped **(10).**

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