Bisoprolol: A New Cardioselective Beta Blocker In Hypertensive Patients

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Summary:

Bisoprolol, a cardioselective beta adrenergic receptor blocking drug, was given to 25 outdoor patients for six weeks after two weeks on placebo period. Mean age was 49±1 years, mean weight was 69.1±2 Kg, mean height was 156±2 Cm and mean duration of hypertension was 5.4±0.6 years. Mean supine systolic pressure decreased from 161±4 mmHg to 136.6±3.2 mmHg (P<.001) while standing pressure dropped from 159±5 mmHg to 137±3 mmHg (P<0.001). Mean supine diastolic pressure fell from 104±1 mmHg to 90.6±1.2 mmHg (P<0.001), while erect diastolic pressure fell from 105.9±1.4 mmHg to 93±1.3 mmHg (P<.001). Mean supine arterial pressure decreased from 123 mmHg to 106 mmHg while standing mean arterial pressure decreased from 123 mmHg to 107 mmHg. Supine pulse rate decreased from 94.7±2.1 /min to 78±2 beats/min (P<.001) while standing pulse rate decreased from 101±3 beats/min to 81±1.6 beats/min (P<.001). Bisoprolol found effective and well tolerated in most of the patients with mild to moderate hypertension.

Introduction:

During sixth decade of this century Beta adrenoceptor antagonists were developed for the treatment of cardiac arrhythmias and angina pectoris. It was discovered later on that long term treatment with beta blockers caused decrease in arterial blood pressure. Two years later it was proved that beta adrenoceptor blocking drugs can be used as antihypertensive agents[1].

All beta adrenoceptor blocking drugs are competitive inhibitors (antagonists) at the beta adrenergic receptors. Increase in concentration of the stimulating drug (agonist) will overcome the blockade. The net effect of the drug on the receptors is proportional to the local concentration of agonists and antagonists[2].

Cardioselectivity is not an absolute property but is a dose dependent one. At low doses metoprolol, atenolol etc. are cardioselective beta blocking drugs and are 50 to 100 times more active in inhibiting the effect of isoproterenol in the heart then they are inhibiting these in the bronchial tree and peripheral blood vessels. However at high doses beta 2 antagonism appears and cardioselectivity is lost[2]. Cardioselective beta blockers may aggravate bronchospasm in certain patients. Poor penetration of Bisoprolol in the central nervous system would appear to be desirable in patients with renal or hepatic disease as this drug will be cleared independently of the diseased organ or its clearance will not be effected by moderate alteration in organ function.

Beta adrenergic blocking drugs can be characterized by their pharmacokinetic properties. One property is lipophilic or hydrophilic. Bisoprolol takes an intermediate position between lipophilic and hydrophilic properties of beta blockers. It is readily and virtually completely absorbed (>90%) orally and has small hepatic first pass metabolism[3]. It is cleared partially by liver and partially by the kidneys, i.e., it has balanced clearance. Bisoprolol has long plasma elimination half life with particularly Betal selectivity and is the beta blocker which is suitable for single daily administration half life[5]. Betal selective drugs should be used in diabetic patients[6].

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Bisoprolol does not have intrinsic symptomimetic activity or membrane stabilising activity.

Patients:

Twentyfive patients (20 females and 5 males) with essential hypertension were included in this study. All patients were on antihypertensive treatment on which either they were not controlled or were taking medicines irregularly. All the antihypertensive treatments were stopped at least one week before starting treatment with placebo.

TABLE NO. 1

STUDY DESIGN

Wash Out Period	One week
Placebo Period	Two weeks
On Active Treatment	Six weeks
On 5 Mg	Two weeks + Four weeks
If not controlled dose increased to 10 Mg	Four weeks
At the end of Six weeks	
On 5 Mg	14 Patients
On 10 Mg	07 Patients

Study Schedule:

Each patient at the time of entry was evaluated by physical examination, blood pressure, electrocardiography, laboratory data and chest radiography. All patients received placebo treatment for two weeks. Patients visited the hypertension clinic weekly during placebo period and first two weeks on active drug treatment then fortnightly for one month. After placebo treatment, 5 mg of active drug was given and if blood pressure was not controlled then the dose was increased to 10 mg daily.

The study was done as an open uncontrolled blind study. Detailed clinical evaluation before starting treatment did not show any secondary cause for the hypertension or any other concomitant disorder.

Arterial pressure was measured with a standard mercury sphygnomanometer by the same observer and was expressed as the average of three readings obtained after the patient had been in supine position for supine blood pressure at least for 10 minutes and for 2 minutes in erect position for standing blood pressure. Systolic pressure was recorded at Korotkoff phase I and the diastolic pressure at phase V. Mean arterial pressure was calculated from the sum of 1/3rd systolic and 2/3rd diastolic pressure. Heart rate was taken before taking the blood pressure. Informed consent was obtained before the study.

All patients were advised to come empty stomach between 8.00 A.M. to 11.00 A.M. Written consent of the patients was taken. Electrocardiographic evaluation included the 12 standard leads. Blood and urine samples (at week 0,8) were taken after the blood pressure and pulse rate has been determined to avoid the influence of stress of withdrawing the samples.

All adverse events were recorded whether spontaneous or patient told after direct questioning.

Statistical Evaluation:

Statistical evaluation was performed on the patients who completed the trial. A paired t test was used for assessing the significance of the differences between mean values. All tests used were two tailed and $P \leq .05$ was considered as the upper limit of the significance. Results are expressed as means and standard error of means.

Inclusion Criteria:

Male or female patients above 20 years, diastolic pressure between 95 to 115 mmHg.

Patients with established essential hypertension.

Newly diagnosed patient.

Patients with unsatisfactory treatment.

TABLE NO. 2

GENERAL INFORMATION:

Mean Weight	69.1±2.10Kg
Mean Height	156±2.3Cm
Mean Age	48.9±1.98 Years
Mean duration of Hypertension	5.4±0.64 Years
Total No. of Patients Enrolled:	25
Withdrawn due to side effects:	2
Normalized during Placebo Period:	2
Completed the Trial	21

Exclusion Criteria:

Patients with severe hypertension and all forms of secondary hypertension.

Patients with uncompensated heart failure.

Patients with recent (less than 3 months) cardiac infarction or shock.

Patients with the heart block or bradycardia (less than 50 beats/min.) before the start of treatment.

Patients with Asthma or COPD.

Patients with late stage of peripheral arterial disease. Patients with severe organic disease.

Patients with severe renal impairment.

Patients known to be alcoholic or drug abusers.

Pregnant women or nursing mothers.

Patients receiving concomitently other antihypertensive medications.

TABLE NO. 3

SITTING BLOOD PRESSURE

	Before Treatment	After Treatment
Systolic	161±3.5	137±3.7* mmHg
Diastolic	104±1.4	91±1.4* mmHg
MAP	123	106 mmHg
Pulse Rate	94±2.1	78±1.7*/min

P Value *=<.001)

STANDING BLOOD PRESSURE

Systolic	159±3.4	136±3.14* mmHg
Diastolic	105±1.4	91±1.5* mmHg
MAP	126	109 mmHg
Pulse Rate	101±2.1	82±1.7*/min

P Value *=<.001)

Drop Out Criteria:

Onset of any exclusion criteria.

Serious side-effects due to active drug.

Request for withdrawal from the study by the patient.

Results:

Twentyfive patients, 20 (80%) females and 5 (20%) males were admitted for this study. Mean weight before treatment was 69.1±2 Kg (range 50-90 Kg) and after treatment it was 68.6±2 Kg. Mean height was 156.7±2 Cm (range 140-190 Cm) and mean duration of hypertension was 5.4±.6 years (Range two years to 13 years) and mean age was 48.9±2 years (Range 35-69 years).

Twentyone (84%) patients completed the trial. 2 (8%) patients were withdrawn from the study because they did not tolerate the drug. Blood pressure of 2 (8%) patients was normalized during placebo period so were excluded from the study. None of these patients was smoker.

Mean supine systolic pressure before treatment was 161±4 mmHg and after treatment of six weeks blood pressure decreased to 136.6±3.2 mmHg while supine diastolic pressure before treatment was 104.4±1 mmHg and after six weeks it was dropped to 90.6±1.2 mmHg. Mean standing systolic pressure decreased from 159.2±3 mmHg to 137.3±3 mmHg and mean diastolic pressure fell from 105.9±1.45 mmHg to 92.28±2 mmHg.

Mean arterial pressure in supine position dropped from 123.3 mmHg to 106 mmHg while standing mean arterial pressure decreased from 123.6 mmHg to 107 mmHg. (See Tab. No. 3).

Mean pulse rate in supine position dropped from 94.7±2/min to 78.4±1.5/min while drop in mean standing pulse rate was from 101±2/min to 81±1.6/min. (See Tab. No. 3).

At the end of six weeks14 (66%) patients were on 5 mg Bisoprolol and 7 (33%) patients were on 10 mg.

Laboratory Results:

No statistically significant difference for haemotological and biochemical results were observed after six weeks therapy with Bisoprolol except serum cholesterol level which was decreased from 209 mg. to 189 mg. P(<.05) while HDL was decreased but the decrease was not significant statistically. (See Tab. No. 4).

TABLE NO. 4

LABORATORY RESULTS

	Before Treatment	After Treatment
RBCs	5.8±1.7	4.4±.6
TLC	7.5±.4	7.2+.5
Blood Sugar	111±10	111±12
S. Creatinine	.9±.8	.9±.07
SGPT	27.4±2.6	26.9±2.33
HDL	37.3±1	34.4±0.9
LDL	128±4.6	114±6.3
Cholesterol	209±6	189±4**
Triglycrides	224±21	229±26

P Value **=<.05)

X-Ray chest did not show any abnormality. Urine complete examination did not reveal any significant abnormality after completion of trial. ECG before treatment and after treatment was similar except decrease in heart rate.

Side Effects:

Diziness, nausea, sleep disturbance, weakness, cold extremities has been observed by others[7]. Two patients were excluded from the study. One developed urticaria after taking the first dose while the second patient had severe headache, palpitation and cold extremities so was also excluded from the study. Lethargy, headache and polyuria were the main complaints of the patients.

The unwanted effects reported by the patients are summarised in Table No. 5.

Adverse effects were mostly mild to moderate and only two patients discontinued the treatment because of untoward effects. In rest of the patients complaints were transient and most of these disappeared during therapy.

Discussion:

The aim of our study was to observe the effectiveness of Bisoprolol in lowering the blood pressure both in supine and standing position in hypertensive patients, to see the tolerance by the patients and to monitor the side effects within six weeks of initiation of treatment. This drug was also compared with placebo.

Antihypertensive agents should be prescribed in simplified regimens whenever possible for improvement of patient compliance during chronic therapy. Patients non compliance with antihypertensive therapy is a major obstacle to achieve an effective control of blood pressure.

Achieving maximum benefits of therapy is especially important in light of epidemiological evidence that long term well controlled blood pressure reduction can decrease mortality and morbidity even in the population of patients who have mildly elevated blood pressure.

In the present study of patients with mild to moderate hypertension, supine and standing blood pressure decreased slowly and effectively during six weeks time. Fall in supine and standing systolic and diastolic pressure was significant. Fall in pulse rate was also significant both in supine as well as in standing position.

TABLE NO. 5

On Placebo Treatment	Side Effects
Nausea	2
Pain Abdomen	2
Loose Motion	1
Total Patients	3
On Active Treatment	
Polyurea	2
Cramps Legs	1
Headache	2
Rashes (Allergy)	1
Cold Extremities	1
Uneasiness	1
Lethargy	2
Dyspnoea	1
Dry Mouth	1
Total Patients	6

Bisoprolol was well tolerated by all patients except two. Considerable attention has been given to observe metabolic adverse effects of it. Bisoprolol

had not produced any haemotological or biochemical deterioration except serum cholesterol level which was decreased significantly.

Fall in supine systolic pressure was 15% while in fall in supine diastolic pressure was 12%, 13% heart rate was decreased. Similarly 15% standing systolic pressure, 13% standing diastolic pressure and 13% standing heart rate was decreased.

Conclusion:

This placebo controlled single blind study of drug monotherapy for patients with uncomplicated mild to moderate essential hypertension demonstrates that Bisoprolol is an effective, well tolerated and safe means of achieving blood pressure in patients with mild to moderate hypertension who have tolerated the drug well with a dose range of 5 to 10 mg. Adverse effects were mostly mild and discontinuation of Bisoprolol therapy was necessary in only 2 (10%) of patients. Patients had good compliance of drug therapy because of single drug regimen.

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