

# THE USE OF METOPROLOL IN THE MANAGEMENT OF HYPERTENSION

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## SYNOPSIS

The hypotensive effect of Metoprolol was assessed in 15 previously untreated Asian patients with hypertension. Except for 1 patient who had secondary hypertension as a result of bilateral renal artery stenosis, all the rest had essential hypertension. There were 10 male and five female patients and their mean age was 37.4 years (range 17-55). In 13 patients, there was a four week run in period when placebo therapy was given. Oral Metoprolol was started initially at a dosage of 50 mg, twice a day (bd). This dosage was increased at fortnightly intervals until either a satisfactory blood pressure (BP) control was achieved or a total of 400 mgms of Metoprolol a day was given. 10 of the 14 patients whose BP was well controlled on a bd regime had their medication changed to once a day (om) at the same total dosage of Metoprolol.

The results of the blood pressure (BP) and heart rate (HR) measurements in 15 patients on a bd regime are as follows: Before treatment — Lying : BP  $166 \pm 3.9/107 \pm 2.0$  mmHg. HR  $85 \pm 2.5$  beats/min. Standing :  $165 \pm 5.4/110 \pm 2.5$  mmHg. HR  $92 \pm 4.8$  beats/min.

After treatment — Lying : BP  $136 \pm 6.5/87 \pm 1.7$  mmHg ( $p < 0.001$ ). HR  $70 \pm 3.5$  beats/min ( $p < 0.01$ ). Standing : BP  $132 \pm 4.9/89 \pm 2.3$  mmHg ( $p < 0.001$ ). HR  $75 \pm 3.4$  beats/min ( $p < 0.001$ ). A comparison of once and twice daily regime was made in 10 patients. BD Regime:— Lying : BP  $137 \pm 5.6/83 \pm 1.9$  mm Hg. Standing :  $132 \pm 4.9/89 \pm 2.3$  mm Hg. OM Regime — Lying : BP  $136 \pm 4.3/87 \pm 2.7$  mm HG (NS). Standing:  $136 \pm 4.3/87 \pm 2.7$  mm Hg (NS).

No significant side effects were encountered in any of the 15 patients and patient acceptability of treatment was excellent. We conclude that Metoprolol is a highly effective hypotensive agent for the treatment of hypertension in Asians, and can be given either as a twice daily or a once daily regime.

## INTRODUCTION

The place of beta adrenoreceptor blocking agents ("beta-blockers") in the management of all grades of hypertension is today well established. The many advantages which the beta-blockers offer in the treatment of hypertension compared with the other antihypertensive agents include a lack of postural and exercise induced hypotension, a relative absence of sexual difficulties in males, and a very high degree of patient acceptability. There are at present about ten beta-blockers in the market in Singapore, with a promise of more to come.

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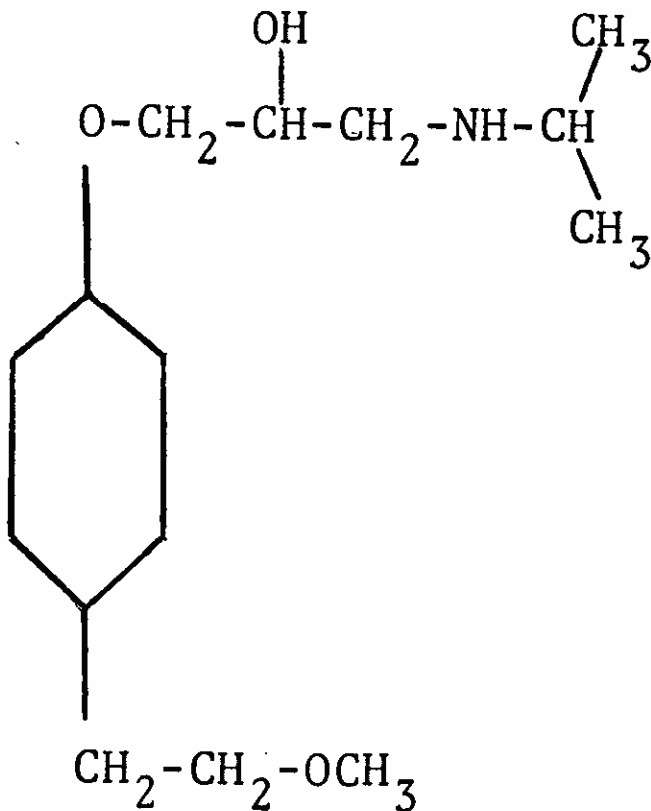


Fig. 1 Molecular Structure of Metoprolol

Metoprolol, with the molecular structure as shown in Fig. 1, is a relatively new beta-blocker in the Singapore scene. Although it has been shown by many studies elsewhere to be an effective hypotensive agent, Metoprolol has not been evaluated for the treatment of hypertension in our local context. Since the withdrawal of Practolol ("Eraldin"), because of its serious side-effects, the introduction of new cardio-selective beta-blockers such as Atenolol and Metoprolol has assumed importance, particularly for the treatment of cardiovascular disorders in patients with problems of obstructive lung disease.

**MATERIAL AND METHOD**

The objectives of our study were as follows: (1) To assess the efficacy of Metoprolol in the treatment of hypertension, (2) To determine the incidence of undesirable side-effects and the degree of patient acceptability, (3) To compare the response of a twice daily (bd) versus a once daily (om) regime.

Fifteen patients were started and all completed the open trial. There were 10 male and 5 female patients. Their ethnic groups comprised 13 Chinese, 1 Malay and 1 Sikh. The ages of the patients ranged from 17 to 55 with a mean of 37.4 years. All but 1 patient, a 17 year old Chinese girl with bilateral renal artery stenosis due to aorto-arteritis, were considered to suffer from essential hypertension. (Table 1).

**TABLE I PATIENT POPULATION (N = 15)**

- (1) SEX : M = 10, F = 5
- (2) RACE : CHINESE = 13, MALAY = 1, SIKH = 1
- (3) AGE : 17 TO 55 YRS. (MEAN = 37.4)
- (4) AETIOLOGY : ESSENTIAL = 14, BILAT. RENAL ARTERY STENOSIS = 1

Like most hypertensive populations, 13 of our 15 patients were asymptomatic. However, 2 complained of classical angina pectoris due to underlying coronary artery disease. Grade 1 fundal changes were seen in 1 and grade 2 changes in 2 of our patients. In the other 12 patients, the fundi were normal. Mild hypertension defined in this study as a diastolic blood pressure of less than 105 mm Hg, but greater than 95 mm Hg was seen in 4 patients, moderate hypertension defined as a diastolic blood pressure of 105 to 120 mm Hg was seen in 10, and severe hypertension defined as a diastolic blood pressure of more than 120 mm Hg was seen in 1 patient. None of our 15 patients was suffering from either congestive cardiac failure or bronchial asthma. (Tables II & III).

**TABLE II SYMPTOMS & SIGNS (N = 15)**

- = ASYMPTOMATIC — 13
- = ANGINA — 2
- = FUNDI — GD 0 — 12
- GD 1 — 1
- GD 2 — 2

**TABLE III SEVERITY OF HYPERTENSION (N = 15)**

- MILD DIAST. <105 mm Hg = 4
- MODERATE DIAST 105-120 mm Hg = 10
- SEVERE DIAST >120 mm Hg = 1

The resting electrocardiogram was normal in 11 patients, showed T-wave inversion consistent with coronary artery disease in 2, an infarction pattern in 1 and changes of left ventricular hypertrophy in a further 2 patients. Chest X-ray showed cardiomegaly in 2 patients. One patient was suffering from diabetes mellitus and another had hyperuricaemia with a blood uric acid level of 10.5 mg %. (Tables IV).

**TABLE IV INVESTIGATIONS (N = 15)**

- ECG : NORMAL — 11, T WAVE INVERSION — 2,
- INFARCT — 1, LVH — 2
- CXR : LVH — 2
- URINE : NORMAL FEME — 15, NORMAL VMA — 2,
- HAEMATOLOGICAL & BIOCHEMICAL PROFILE :
- DIABETES 1, HYPERURICAEMIA — 1

All patients had no previous treatment. In 13 patients, there was a run-in period when placebo therapy was given. Oral Metoprolol was then started initially at a dosage of 50 mg b.d. This dosage was increased at fortnightly intervals until either a satisfactory blood pressure (B.P.) control, defined here as a diastolic blood pressure of 90 mm Hg or less was achieved or a total of 400 mg of Metoprolol was given. Supine BP's were taken 3 times on each occasion after a 10-minute rest in bed followed by BP readings in the erect position. The average value of these 3 BP readings in each position was then recorded. The heart rate (HR) was also recorded in each position. At each visit, specific side-effects of beta-blocker therapy e.g. dreams, tiredness and symptoms suggesting congestive cardiac failure or bronchospasm, etc. were asked for. Ten of the 14 patients whose BP was well controlled on a b.d. regime had their medication changed to once a day at the same total dosage of Metoprolol. In this latter group of patients, the drug was taken every morning. However, on the morning of the patient's visit to the hospital for blood pressure measurements, Metoprolol was omitted until after the visit. Final assessment of the efficacy of once daily treatment was made after 8 weeks of therapy.

## RESULTS

Table V summarises the results of the 15 patients whilst on a b.d. regime. In the supine position, the mean systolic and diastolic BP and the mean HR were 166 mm Hg, 107 mmHg and 85 beats/min. respectively. These values fell to 136 mm Hg, 87 mm Hg and 70 beats/min. after therapy was commenced. In the standing position, the mean systolic and diastolic BP and the mean H.R. were 165 mm Hg, 110 mm Hg and 92 beats/min. respectively. With therapy, these values fell to 132 mm Hg, 89 mm Hg and 75 beats/min respectively.

The paired "T" tests between the systolic and diastolic BP and the HR in both the supine and erect positions before and after treatment showed highly significant p values of <0.001.

In 14 patients, satisfactory control of BP with a diastolic BP of 90 mm Hg or less was achieved. In the

remaining 1 patient whose initial pre-treatment BP was 180/110, no fall in BP was seen even with 400 mgs of Metoprolol daily. The average total dosage of Metoprolol required was 200 mg daily, with 4 patients needing 100 mgs, 8 patients 200 mgs, and 3 patients 400 mgs/day. The average period of time required for effective BP control was 4 weeks.

Table VI shows the results of a bd vs an om regime at the same total dosage of Metoprolol. In the supine position, the mean systolic and diastolic BP was 137 mm Hg and 83 mm Hg on a bd regime. These values were 132 mm Hg and 87 mm Hg on an om regime. Likewise, in the erect position, the mean systolic and mean diastolic BP on a bd regime was 132 and 89 mm Hg. These values were 136 mm Hg and 87 mm Hg on an om regime. The paired "t" tests between the systolic and diastolic BP's in both the supine and erect positions on a bd regime and on an om regime showed p values which were not significant.

**TABLE V**  
**TWICE DAILY DOSAGE (N = 15)**

LYING			
	BEFORE TREATMENT	AFTER TREATMENT	
SYST.	166 ± 3.9 mm Hg	165 ± 5.4 mm Hg	(p < 0.001)
DIAST.	107 ± 1.0 mm Hg	110 ± 2.5 mm Hg	(p < 0.001)
HR	85 ± 2.5 BTS/MIN	92 ± 4.8 BTS/MIN	(p < 0.001)
STANDING			
	BEFORE TREATMENT	AFTER TREATMENT	
SYST.	136 ± 6.5 mm Hg	132 ± 4.9 mm Hg	(p < 0.001)
DIAST.	87 ± 1.7 mm Hg	89 ± 2.3 mm Hg	(p < 0.001)
HR	70 ± 3.5 BTS/MIN	75 ± 3.4 BTS/MIN	(p < 0.001)

**TABLE VI**  
**BD VS OM DOSAGE (N = 10)**

LYING			
	BD DOSAGE	OM DOSAGE	
SYST.	137 ± 5.6 mm Hg	132 ± 4.9 mm Hg	NS
DIAST.	83 ± 1.9 mm Hg	89 ± 2.3 mm Hg	NS
STANDING			
	BD DOSAGE	OM DOSAGE	
SYST.	136 ± 4.3 mm Hg	136 ± 4.3 mm Hg	NS
DIAST.	87 ± 2.7 mm Hg	87 ± 2.7 mm Hg	NS

Figures 2, 3 and 4 illustrate the above results in a graphic form.

No side effects due to the drug therapy was elicited even on specific questioning during each visit. Patient acceptability of treatment was excellent.

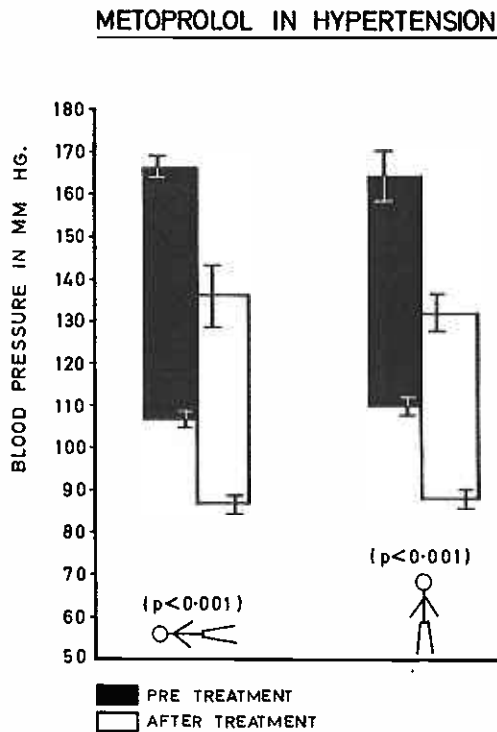


Fig. 2 Effect of Metoprolol on the supine and erect blood pressure when given as a twice daily regime (See text).

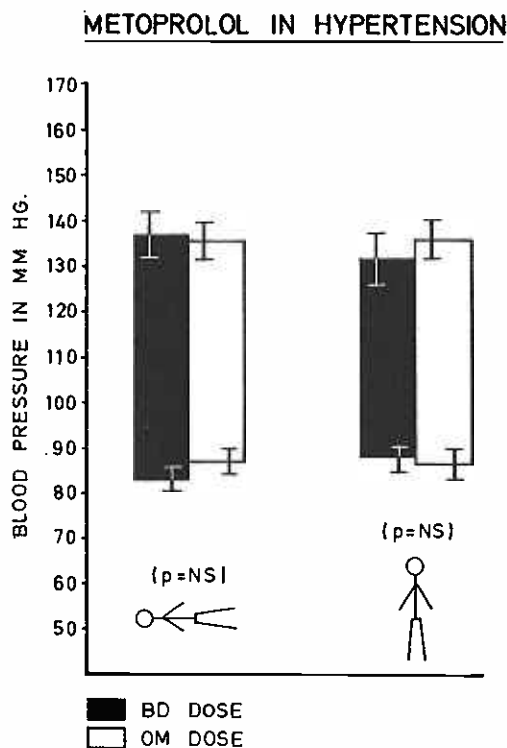


Fig. 3 Comparison of the erect and supine blood pressure when Metoprolol is given as a twice daily regime (bd) and as a once daily regime (om) at the same total daily dosage (see text).

### METOPROLOL IN HYPERTENSION

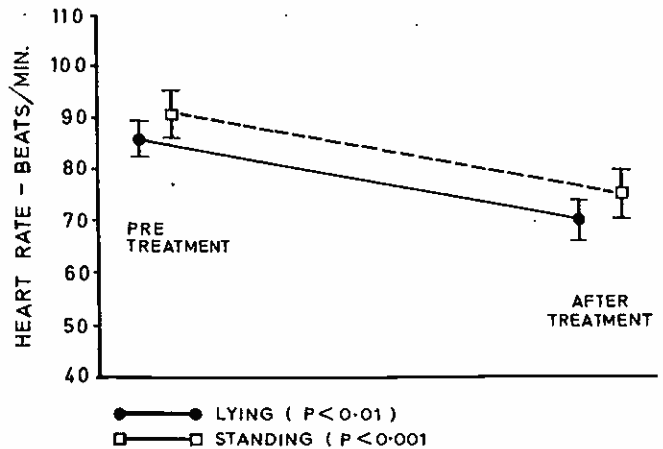


Fig. 4 Decrease in heart rate in both the erect and supine position with Metoprolol therapy given twice daily (see text).

### DISCUSSION

The introduction of beta blockers as effective hypotensive agents marks a milestone in the therapy of hypertension. Today, the place of beta blockers in the management of all grades of hypertension is well established. Beta blockers may be used either singly or in synergistic combination with other hypotensive agents particularly the diuretics and the vasodilators. The many advantages which the beta blockers offer in the treatment of hypertension compared to the other currently available antihypertensive agents include a lack of postural and exercise induced hypotension, excessive increase in blood pressure during physical and emotional stresses, a relative absence of sexual difficulties in males, and a very high degree of patient acceptability. Furthermore, there is evidence to suggest that hypertensive patients treated specifically with beta blockers may have a decrease in coronary events such as myocardial infarction and sudden death compared to those treated by other hypotensive agents.

Propranolol ("Inderal") was the first beta blocker which was shown to have a significant hypotensive effect. Since then many other beta blockers have been similarly appraised. In general, it can be said that all of the beta blockers available in the market today are equally effective as anti-hypertensive agents if used in equipotent doses. (Wilcox 1978).

Since the withdrawal of Practolol ("Eraldin") because of its serious side effects, the introduction of new cardio-selective beta blockers such as Atenolol and Metoprolol has assumed importance particularly for the treatment of cardiovascular disorders in patients with obstructive lung disease. Metoprolol ("Betaloc", "Lopressor") is a cardio selective beta blocker with no partial agonist activity. Although its plasma half life is only 3-4 hours, the duration of its beta blocking effects is considerably longer.

Metoprolol has been shown by many studies done elsewhere, particularly in the Scandinavian countries and in the United Kingdom, to be an effective and useful hypotensive agent. (Hansson et al 1977). However, this drug has not so far been evaluated for the treatment of hypertension in the local context. Furthermore, studies

specifically concerning whether Metoprolol could satisfactorily control the BP when given only once a day is rather scarce in the literature.

Data in this present study confirms the observations of other workers elsewhere that Metoprolol is indeed an effective pharmacological agent for the treatment of mild and moderate hypertension. Since only 1 patient had severe hypertension with a diastolic pressure of more than 120 mm Hg in this series, comments regarding the efficacy of Metoprolol in this situation is not possible. However, it is well recognised that in severe hypertension and sometimes even in moderate hypertension, beta blocker therapy when used alone may not be adequate, and other agents such as a diuretic and a vasodilator may be necessary. In this study, the average fall of systolic and diastolic blood pressures with Metoprolol treatment was around 30 mm Hg and 20 mm Hg respectively. There was also an average fall of heart rate by about 15 beats/min.

Like treatment with all other types of beta blockers, there was virtually no difference between the supine and erect blood pressure readings following Metoprolol therapy. No attempt was made in this study to assess the efficacy of this drug on the control of blood pressure during physical exercise.

This study also confirms the findings of a few previous workers who showed that Metoprolol could effectively control the blood pressure when given once a day. This observation has great importance in the management of hypertension since it has relevance to the problem of patient compliance which is today probably the single most important factor in the treatment of hypertension.

The less complicated the drug regime and the fewer the side effects of therapy, the better will be the compliance. In this respect, a drug which needs to be taken only once a day would contribute to better patient compliance compared to a drug which needs to be taken twice or three times a day.

In this study, none of the patients complained of any side effects due to the drug, although these were specifically enquired for during each visit to the clinic. Patient acceptability of treatment was excellent.

## CONCLUSION

It can be concluded from the above observations that Metoprolol is an effective agent for the treatment of hypertension. This drug is equally effective when given in a twice or once daily regime.

## REFERENCES

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