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Efficacy and dose finding of Metoprolol inThai Patients : A Placebo-controlled,Single-Blind, Randomized, Crossover Study

C. Ongcharit

N. Chujamsai

นิพนธ์ต้นฉบับ

Efficacy and dose finding of Metoprolol in Thai Patients : A Placebo-controlled, Single-Blind, Randomized, Crossover Study.

Chompunoot Ongcharit*
Noravee Chuajamsai*

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Twenty Thai patients with essential hypertension in WHO stage I and II classification, were studied in a single-blind crossover type with metoprolol in the dosage of 100 mg. and 50 mg. twice daily, divided to group A and B for the period of 4 weeks, then the crossover of the dosage was taken for another 4 weeks. Statistically significant reduction in both systolic and diastolic blood pressures in the supine and standing positions, and also in the heart rate were found in both groups. It could also be suggested from this study that metoprolol in the dosage of 50 mg. twice daily is sufficient for treating most of hypertensive Thai patients with negligible unwanted side effects.

ชมพูนุท อ่องจริต, นรวีร์ จั่วแจ่มใส. ประสิทธิภาพ และขนาดของ Metoprolol ในผู้ป่วยไทย. จุฬาลงกรณ์เวชสาร 2529 กุมภาพันธ์; 30 (2) : 145-151

การศึกษาประสิทธิภาพของ Metoprolol ในการรักษาโรคความดันโลหิตสูงชนิดไม่ทราบสาเหตุได้ทำในผู้ป่วยไทย 20 ราย การศึกษานี้เป็นแบบ single blind randomized crossover โดยแบ่งผู้ป่วยออกเป็น 2 พวก พวกแรก ให้ยา metoprolol ในขนาด 200 มก. ต่อวัน เป็นเวลา 1 เดือนแล้วจึงลดขนาดของยาเป็น 100 มก. ต่อวัน เป็นเวลาอีก 1 เดือน ส่วนพวกที่ 2 นั้น ให้ยาในขนาด 100 มก.ต่อวัน 1 เดือนแล้วจึงเพิ่มขนาดของยาเป็น 200 มก. ต่อวันอีก 1 เดือน ผลที่ได้นั้นพบว่ายานี้ในขนาด 100 มก.ต่อวัน ก็ทำให้มีการลดความดันโลหิตลงได้อย่างดีในผู้ป่วยที่เป็นชนิดอ่อนและชนิดปานกลาง ผลข้างเคียงของยานี้มีน้อยมาก และจะเกิดเพียงชั่วคราว จึงทำให้ผู้ป่วยทนต่อยาได้ดีมาก

* Department of Medicine, Faculty of Medicine, Chulalongkorn University.

It has been accepted that beta-adrenergic blocking agents have a definite and significant role in the management of hypertension for more than 10 years[1,2,3,4,5,6] Given either alone or in combination with other anti-hypertensive drugs, they are effective and provide a smooth control of blood pressure.[7,8,9,10] Side effects are minimal, well tolerated and often diminish with time.[11,12] Further advantages are gained by some patients with the use of selective beta-1 adrenergic blocking drugs, because of being cardioselective it reduces unwanted effects of beta-2 blocking activity and it can be administered with caution in patients with medical conditions aggravated by beta-2 blockage such as chronic obstructive pulmonary disease, diabetes mellitus and Raynaud's disease. Metoprolol, one of such agents, has been proved similarly useful in recent years.[13,14,15,16,17] Despite a uniform satisfactory response, however, the dosage and frequency of administration vary only slightly in different reports most of which came from studies in the western part of the world.

This study was designed as a single blind crossover type to determine the efficacy and effective dosages as well as unwanted effects of metoprolol, a cardioselective adrenergic beta receptor antagonist without intrinsic stimulating activity.

Material

Twenty patients selected for this trial were fully informed for consent. They were those of either sex, from the cardiac division, who were newly diagnosed as having essential hypertension with 3 consecutive weekly readings of diastolic blood pressure greater than 100 mm. of mercury or those already receiving antihypertension drugs but discontinued the treatment two weeks before the trial began. The age of the patients ranged from 32 to 62 years average 48.75 years and were in either WHO stage I or II classification. The full clinical assessment including complete blood count, blood chemistry, electrolytes, urinalysis, ECG, chest X-ray and intravenous pyelography was performed to exclude secondary hypertension. Patients were excluded also if they had a resting heart rate below 50 beats/minute or myocardial infarction or they were suffering from renal, hepatic or hematological diseases.

Method

All the twenty patients were randomly allocated into group A or B, ten for each group and were given placebo during the 2 weeks of run-in period. Then the patients in group A were started on the treatment with metoprolol 100 mg. twice daily and in group B with 50 mg. twice daily (Figure I). After 4 weeks of treatment (week 4) the patients treated on 100 mg. twice daily were switched over to 50 mg. twice daily and vice versa for group B for another 4 weeks (week 8).

At each visit week 0,2,4 and 8 blood pressure and heart rate were assessed after 10 minutes in the supine position and after 2 minutes in the standing position. Diastolic blood pressure recorded was Korotkoff phase V by using a mercury sphygmomanometer. The value of blood pressure and heart rate during the whole trial period was the mean figure from three consecutive blood pressure and heart rate measurement both in supine and standing positions. Blood pressure, heart rate, all other clinical examinations and the questioning of unwanted side effects were carried out by

DESIGN OF THE TRIAL

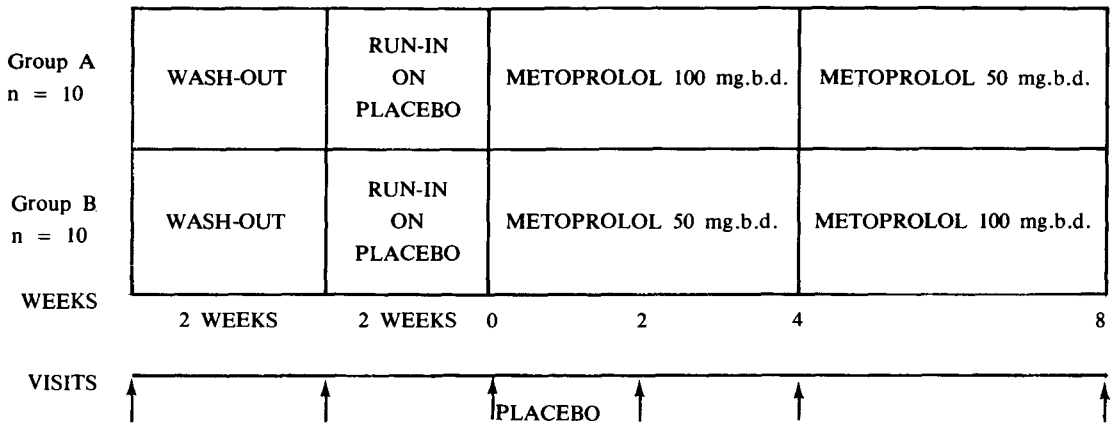

Figure 1

the same observer (by C.O.). The severity of unwanted side effects was assessed into mild (score 1), moderate (score 2) and severe (score 3).

Statistical methods : mean values of the assessment during placebo and metoprolol periods were calculated and the significant difference between sample means was estimated by Student's t-test for the mean differences between paired observation. In this way each patient acted as his or her own control throughout the trial. Statistical significance was defined as a P value of less than 0.05.

Results

Effects on arterial blood pressure

1. In both groups with metoprolol 100 mg. twice daily and 50 mg. twice daily, the systolic and diastolic blood pressures were reduced considerably after two weeks of treatment and has statistical significance both in supine and standing positions except the systolic blood pressure of the supine position in group A which was reduced from 175.4 to 160.6 mm.Hg. without statistical significance.

2. After four weeks of treatment in the two groups both systolic and diastolic blood pressures in both supine and standing positions were all lowered with highly statistical significance in the majority of mean value ($p < 0.01$) as shown in Table I & II.

3. After the dosage was lowered by half in group A both systolic and diastolic blood pressures in both supine and standing positions went up but only the systolic pressure in the supine position with the lower dosage was increased significantly ($p < 0.05$). The diastolic blood pressure in both positions seemed to increase only slightly and non-significantly.

In group B after increasing the dosage to 100 mg. twice daily for one month the systolic blood pressures in both positions increased slightly without statistical significance (from 141.0 ± 4.75 to 142.9 ± 8.07 mm.Hg. in supine position and 146.0 ± 5.75 to 148.2 ± 8.00 mm.Hg. in standing position) but the diastolic blood pressure in both positions was further lowered but without significance (from 91.8 ± 3.80 to 89.6 ± 3.78 and 94.0 ± 3.04 to 92.4 ± 4.33 mm.Hg.).

Table 1 Mean value ± sem of blood pressure & heart rate before & after treatment with metoprolol in group A

	Placebo	METOPROLOL 100 mg. b.d.		METOPROLOL 50 mg. b.d. Week 8
		Week 2	Week 4	
SYSTOLIC BP				
– Supine	175.4 ± 5.44	160.6 ± 6.06	159.2* ± 5.35	166.4* ± 6.88
– Standing	176.4 ± 5.26	157.0* ± 7.47	154.6** ± 4.33	166.0 ± 7.81
DIASTOLIC BP				
– Supine	118.8 ± 2.70	105.6** ± 4.60	104.2** ± 3.89	106.8 ± 5.43
– Standing	122.4 ± 2.27	102.0** ± 4.67	103.0** ± 3.00	109.8 ± 4.41
HR (beats/min)				
– Supine	75.8 ± 3.76	68.8* ± 4.18	61.8** ± 2.80	66.9 ± 3.89
– Standing	80.0 ± 4.09	68.4** ± 4.60	61.6** ± 3.61	69.7 ± 5.17

Differences from placebo $^{*}p < 0.05$
$^{**}p < 0.01$

Tabel 2 Mean value ± sem of blood pressure & heart rate before & after treatment with metoprolol in group B

	Placebo	METOPROLOL 50 mg. b.d.		METOPROLOL 100 mg. b.d. Week 8
		Week 2	Week 4	
SYSTOLIC BP				
– Supine	166.6 ± 3.13	145.6** ± 5.96	141.0** ± 4.75	142.9 ± 8.07
– Standing	171.6 ± 1.93	145.0** ± 6.20	146.0** ± 5.75	148.2 ± 8.00
DIASTOLIC BP				
– Supine	112.4 ± 1.33	96.8** ± 3.74	91.8** ± 3.80	89.6 ± 3.78
– Standing	114.6 ± 2.31	99.6** ± 4.44	94.0** ± 3.04	92.4 ± 4.33
HR (beats/min)				
– Supine	87.8 ± 2.67	67.6** ± 2.38	72.4** ± 4.10	67.6* ± 3.56
– Standing	89.7 ± 1.80	69.6** ± 2.58	75.3** ± 5.02	66.4* ± 3.91

Differences from placebo $^{*}p < 0.05$
$^{**}p < 0.01$

Effects on heart rate

Administration of metoprolol of either 100 mg. or 50 mg. twice daily caused a significant reduction in heart rate in both supine and standing positions ($p < 0.01$) except the patients in group A in supine position at the end of second week of treatment with $p < 0.05$ (Table I). One patient had the heart rate below 50 beats per minute after the whole period of treatment with either low or moderate dosage.

After the crossover of the dosage the heart rate of the patients in group A rose up in both positions but without statistical significance while in group B it was lower significantly.

Effects on body weight

The average body weight before and after the treatment was 67.72 and 67.94 Kg. so there was no significant change in body weight of the patients before and after the administration of metoprolol.

Effects on subjective symptoms and side effects

The symptoms caused by hypertension in some patients such as headache and palpitation disappeared within two weeks after treatment of metoprolol.

There was one case who complained of mild dizziness after the first week of treatment with metoprolol 100 mg. twice daily in group A. He was 62 years old, the oldest in this trial population. He suffered this symptom in the first week and it disappeared on the second week of treatment with the same dosage continued. Apart from this case, none of the patients had any kind of unwanted side effects.

Discussion

In most studies the initial hypotensive effect of metoprolol was between two to four weeks. The fall of the arterial blood pressure in our study is of the same order of magnitude. The reduction of systolic and diastolic blood pressures could be obtained by ordinary or less than ordinary recommended dosage that is 50 mg. twice daily, though we are well aware of the usual recommended dosage of 200 mg. of metoprolol or even larger between 300-400 mg. recommended by many authorities.[16,18]

It is note worthy that direct comparison between the result of treatment in group A and B at the end of 4 weeks of treatment gave no significant difference by statistical analysis so the lower dose level of metoprolol 50 mg. twice daily can be recommended.

This lower dose level was not related to body weight in our study because the average weight of the trial subjects was 67.72 Kg.

If we regard diastolic blood pressure of 95 mm.Hg. as our target result of satisfactory reduction, it is noted that eight patients in group B had a good response while only three out of ten in group A had the same result though on bigger dosage of metoprolol. It could be explained by the fact that six patients in group B had mild hypertension (diastolic blood pressure 100-119 mm.Hg.), the remaining four had moderate hypertension (diastolic blood pressure 120-129 mm.Hg.) and none with diastolic blood pressure 130 mm.Hg. or more so monotherapy of metoprolol in this group was quite adequate. In group A, only two cases had mild hypertension, four moderate and four severe so the administration of metoprolol 200 mg. daily seemed to be inadequate for two cases of moderate and four cases of severe degree

in this group. This rather poor outcome is consistent with the result in other studies done mostly in the hypertensive caucasians which the combinations of beta adrenergic blocking agents and other anti-hypertensive drugs especially thiazide diuretics are generally recommended for such cases.[19]

Regarding side effects, dizziness and tiredness secondary to hypotension and bradycardia are well-known to be common when using betablockers.[20,21] These side effects including sleep disturbance and nightmares are generally not serious and usually vanish during long term therapy because all betablockers are known to penetrate the brain at different rates. Dizziness was noticed in one case. It occurred during the first week after administration of metoprolol and disappeared without changing the regime of the study.

No other side effects such as sexual disturbances and cold feet were noted during the whole trial.

In conclusion the smaller dosage of metoprolol 50 mg. twice daily seemed to be adequate in the treatment of mild to moderate degree for essential hypertension in Thai patients at Chulalongkorn Hospital and Medical School. All the patients can tolerate the drug very well without any side effects except one case with dizziness who was 62 years old man.

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References

1. Prichard BNC, Gillam PMS. Use of propranolol (inderal) in the treatment of hypertension, Br Med J 1964 Sep 19 ; 2 (5411) : 725-727
2. Richards FA. Propranolol in hypertension. Am J Cardiol 1966 Sep ; 18 (3) : 384-386
3. Paterson JW, Dollery CT. Effect of propranolol in mild hypertension. Lancet 1966 Nov 26 ; 2 (7474) : 1148-1150
4. Shanks RG. The pharmacology of beta sympathetic blockade. Am J Cardiol 1966 Sep ; 18 (3) : 308-316
5. Humphries GS, Delvin DG. Treatment of hypertension with propranolol. Br Med J 1969 Feb 15 ; 1 (5641) : 445
6. Gill DG. Adrenergic blockade in hypertension. Lancet 1972 May 20 ; 1 (7760) : 1125
7. Tarazi RC, Dustan HP. Beta adrenergic blockade in hypertension : practical and theoretical implications of long-term haemodynamic variation. Am J Cardiol 1972 May ; 29 (5) : 633-640
8. Lewis PJ, Myers MG, Reid JL, Dollery CT. Mechanism of betablockade hypertension. N Engl J Med 1973 Mar 29 ; 288 (13) : 689
9. O'Brien ET, Mackinnon J. Propranolol and polythiazide in treatment of hypertension. Br Heart J 1972 Oct ; 34 (10) : 1042-1044
10. Ongcharit C, Tungsanga K. Propranolol and propranolol with thiazide in hypertensive Thai patients. J Med Assoc Thai 1977 Oct ; 60 (10) : 465-469
11. Dollery CT. Advances in the treatment of hypertension. Practitioner 1970 Oct ; 205 (1228) : 486-493

12. Lambert DM. The use of propranolol in the treatment of hypertension. Practitioner 1973 Feb ; 210 (1256): 277-282
13. Bengtsson C. Comparison between metoprolol and propranolol as antihypertensive agents : a double-blind cross over study. Acta Med Scand 1976; 199:71-74
14. Bengtsson C, Johnsson G, Regradh C.G. Plasma levels and effects of metoprolol on blood pressure and heart rate in hypertensive patients after and acute dose and between two doses during long-term treatment. Clin Pharmacol Ther 1975 Apr ; 17 (4) : 400-408
15. Bengtsson C, Johnsson G. Six years on beta-blockers : a six-year follow-up study of hypertensive women treated with alprenolol and metoprolol. In : Abstracts of papers from the Fourth Meeting of the International Society of Hypertension, Sydney, Australia. 1976, 133
16. Rosengard S. Antihypertensive effect and tolerability for metoprolol during long-term treatment : a multicentre study. J Int Med Res 1977 ; 5 (3) : 199-206
17. Sannerstedt R, Wasir H. Acute haemodynamic effects of metoprolol in hypertensive patients. Br J Clin Pharmacol 1977 Feb ; 4 (1) : 23-26
18. Bergstrand RH, Vedin JA, Wilhelmsson CE, Berglund G. Comparative study of metoprolol and alpha-methyldopa in untreated essential hypertension. Eur J Clin Pharmacol 1976 ; 10 (6) : 375-379
19. Brogden RN, Heel RC, Speight TM, Avery GS. Metoprolol : a review of its pharmacological properties and therapeutic efficacy in hypertension and angina pectoris. Drugs 1977; 14 : 321-348
20. Jaattela A, Pyorala K. A controlled study on the anti-hypertensive effect of a new beta-adrenoreceptor-blocking drug, metoprolol in combination with chlorthalidone. Clin Sci Mol Med 1976 Dec; 51 Suppl 3 : 521S-523S.
21. Bengtsson C. The effect of metoprolol-a new selective adrenergic beta-receptor blocking agent-in mild hypertension. Acta Med Scand 1976; 199 : 65-70

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