

Comparison of the Effect of the β_1 -Blocking Drugs Atenolol and Metoprolol on Bronchial Asthma

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Twenty patients with severe or medium severe asthma were given atenolol (Atenol® ICI-Pharma) and/or metoprolol (Seloken® Hässle) for tachycardia, hyperkinetic tremor, arterial hypertension or symptoms of angina pectoris. These cardioselective β -blocking drugs caused only a very slight decrease in PF values. There was no difference between atenolol and metoprolol as regards the PF values. A 24 hourly dose of 100 mg atenolol caused a distinct fall in diastolic pressure as compared with the same amount of metoprolol. Both these two β_1 -blockers moderated the tachycardia which occurs in asthma; atenolol in this dose had a slightly stronger action.

The subjective condition of five patients with severe or medium severe asthma was considerably relieved by atenolol and/or metoprolol. The relief manifested as a lessening of dyspnoea and improvement of the general status. No essential change was observed in the PF values despite the subjective effects. The most noteworthy change was the amelioration of tachycardia which had continued longer than expected in these patients. The heart rate dropped from 140-120/min to 90-70/min and dyspnoea was relieved at the same time.

Key words: asthma; atenolol/metoprolol.

Propranolol, the first non-selective β -blocking agent to acquire widespread clinical use, was observed to interfere with the respiration of asthmatics. The aggravation of bronchoconstriction through the action of propranolol proved to be such a regular occurrence in bronchial asthma that propranolol-induced bronchoconstriction has been considered a diagnostic criterion of asthma. Practolol was the only one out of the numerous β -blockers developed after propranolol that could be given to persons with bronchial asthma without untoward effects. However, the side effects in connection with the long-term use of practolol have resulted in the almost complete discontinuance of this drug. This has meant difficulties for asthmatics needing β -blocking drugs.

Two new β -blockers for clinical use have now been introduced almost simultaneously. They have for the most part, a β_1 -selective blocking action only and consequently do not enhance bronchoconstriction in

asthmatics (1, 5, 8, 9, 11, 12). These new β_1 -blockers are: atenolol (Atenol® ICI-Pharma) and metoprolol (Seloken® Hässle). As the incidence of arterial hypertension in bronchial asthmatics is almost as high as in the normal population (6), and as various cardiac arrhythmias as well as myocardial hypoxia in association with coronary stenosis are known to accompany attacks of asthma (2, 4, 10) the use of cardioselective β -blocking drugs is frequently indicated for asthmatics also. Information about the clinical suitability of these new β_1 -blockers in bronchial asthma is important. After using metoprolol in individual cases of bronchial asthma for approximately 1 year at the Hospital for Allergic Diseases, Helsinki University Central Hospital, we regard the results to be satisfactory. Therefore, we felt it was justified to perform a comparative study of the suitability of atenolol and metoprolol for patients with bronchial asthma.

MATERIAL AND METHOD

Patient material

Twenty patients undergoing treatment in our Medical Department for a severe or medium severe asthma syndrome were selected for the study. Initially, nine of these cases had required intensive asthma therapy (intravenous administration of infusion fluids, intravenous administration of cortisone, IPPB respirator, etc.). Peroral cortisone was imperative in 19 cases. All the patients received various β -sympathomimetic preparations (e.g. ephedrine, salbutamol).

Administration of the β -blockers in question to the selected patients was necessary for the following reasons: tachycardia in 10 cases, more than usually severe hyperkinetic tremor in 10 cases (partly the reason for sympathomimetic medication), arterial hypertension in three cases, prolonged chest pain associated with coronary heart disease in one case.

The asthma syndrome of all these patients was still active when administration of the β -blocking drug was commenced. Four patients were undergoing intravenous fluid therapy at the start of the trial.

Twelve of the asthmatics were women and eight men. Their mean age was 47, range 24–65 years.

Arrangement of the study

Atenolol and metoprolol were administered according to the following schedule (Fig 1). An equipotent single 100 mg dose of both drugs was given in the morning at 0800 hours (3). The dose for atenolol corresponds to the recommended 24-hour dose

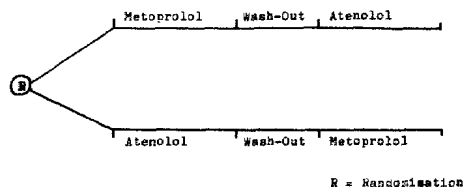


Fig. 1. The atenolol and metoprolol schedule.

in the treatment of hypertension (ICI-Pharma). On account of its shorter half-life, the effect of metoprolol will decrease considerably (almost disappear) during the latter half of the 24-hour period. Therefore metoprolol is administered twice a day in the treatment of hypertension (Hässel).

The patients' clinical status was followed with special care throughout the investigation. The number and nature of sputa were noted, likewise the clinical condition of the bronchi and the patient's subjective condition. Peak flow measurement was performed on each patient every second hour during the period from 0700 to 2100 hours. Tremor of the hands was evaluated by Bender's test. (The patient connects up a line of points of a certain shape. All points left outside the line are scored as minus.) Bender's test was also performed every second hour in the period 0700–2100 hours. Blood pressure was measured daily, approximately 1 hour after taking the medicine. Heart rate was recorded every morning and evening.

RESULTS

Peak flow

The daily PF mean of each patient was calculated from the recorded values. In addition, means were calculated for both the atenolol and metoprolol cycle and also for the wash-out cycle. The PF means for the days of atenolol and metoprolol administration and those for the wash-out days are summarized in Fig. 2. Both atenolol and metoprolol had a somewhat lowering effect on the PF values. This lowering effect of both drugs on the PF values was so similar that there was no statistical difference.

Tremor

Although administration of the β_1 -blocker reduced hand tremor considerably in some individual cases, the change does not emerge in the mean of the total material. No difference between the atenolol and metoprolol cycles and the control period was

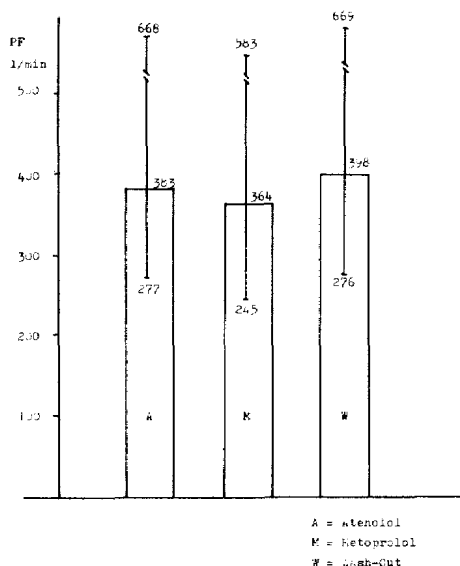


Fig. 2. Effect of atenolol and metoprolol on the peak flow values.

demonstrable in this study, the mean Bender's test minus score for each cycle being three (11).

Blood pressure

Three of the 20 patients had a previously diagnosed arterial hypertension. It must also be noted that the pharmaceuticals, fluids, etc. that the patient has to take can effect blood pressure markedly during a severe episode of asthma. Moreover, severe asthma in itself tends to influence the measurement of blood pressure values (7). The systolic blood pressure was about the same level in each group during the atenolol, metoprolol and wash-out cycles (Fig 3). The only distinct difference was that the diastolic blood pressure value during the atenolol cycle was clearly lower than during the metoprolol and wash-out cycles (3).

Heart rate

The effect of atenolol and metoprolol on the heart rate of patients with asthma is

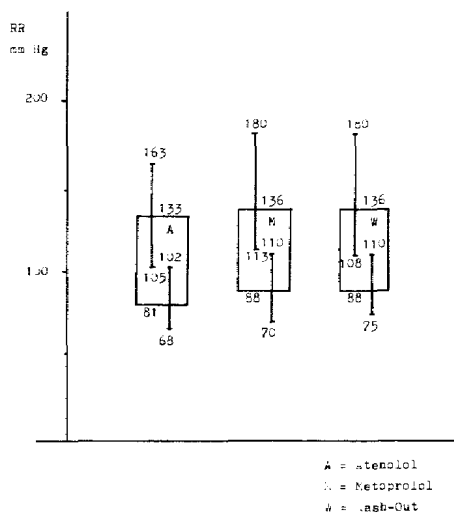


Fig. 3. Effect of atenolol and metoprolol on the blood pressure.

presented in Fig. 4. Both drugs distinctly slowed the heart rate compared with the wash-out cycle. Due to its longer half-life atenolol in the dosage applied here exerted an even more pronounced lowering effect on the heart rate than metoprolol (the mean of

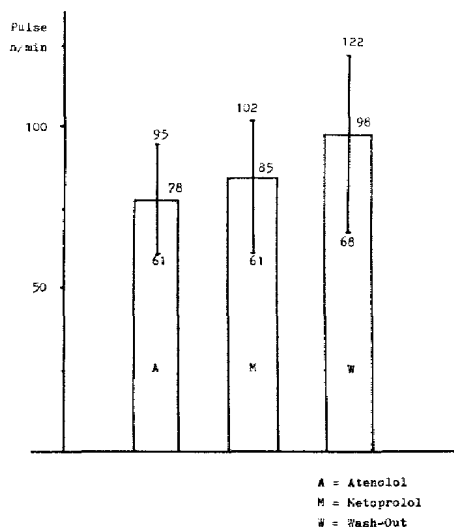


Fig. 4. Effect of atenolol and metoprolol on the heart rate.

the morning and evening rate was used in the experiments (3).

Clinical course of the disease

All 20 patients had severe or medium severe symptoms of asthma when the investigation commenced and were therefore given strong asthma medication. Four patients were receiving 160–250 mg/24 h of methylprednisolone intravenously. Nineteen patients were on peroral fluoxyprednisolone. All 20 patients received sympathomimetic medication. Asthmatic symptoms were reduced in all cases. In 15 cases easing of the asthma appeared to continue evenly also during β_1 -blocker medication.

Five patients appeared to have considerable relief immediately after atenolol or metoprolol medication was begun. All five had an abnormally long period of tachycardia following the asthma syndrome. Institution of medication reduced the heart rate by an average of 42 beats/min from the level of 140–120 beats/min. The heart rate rose again during the wash-out days and the patient's subjective condition and dyspnoea were aggravated on these days, and eased again when the second β_1 -blocker cycle began. Subjective easing of the patient's respiration was not confirmed in the PF values. This favourable effect emerged more clearly in connection with the metoprolol cycle in three cases and the atenolol cycle in two. These patients were aged 24, 28, 45, 50 and 59 years. Three cases involved "extrinsic" and two "intrinsic" asthma. All the patients had allergic rhinitis as well, and two had nasal polyps. All had eosinophilia ($370\text{--}980/\text{mm}^3$). The IgE was elevated in four of the patients ($380\text{--}2050\text{ U/ml}$).

DISCUSSION

The results indicate that the β_1 -blocking drugs, atenolol and metoprolol, in 24-hour doses of 100 mg have only a very slight

lowering effect on the PF values, even when administered to patients in a severe or medium severe phase of asthma. It must be borne in mind, however, that all these patients were receiving concurrent sympathomimetic medication and cortisone preparations. The small decreases in PF values that were observed probably corroborate the observation that there are small amounts of β_1 -receptors also in the bronchi (5). This must be considered when planning the strength of the β_1 -blocker dose for a bronchial asthma patient.

Amelioration of asthma symptoms seemed to continue normally in 15 out of the 20 patients examined, in spite of the atenolol and metoprolol medication. No aggravation of the asthma symptoms during the β_1 -blockade was perceived in the present material (5).

In some cases a distinct lessening of tremor in the hands was seen during the β_1 -blockade, but there was no statistically significant change in the total material. Earlier studies have shown that a non-selective but not a cardioselective β -blocker is capable of influencing muscle tremor. The tremor-alleviating effect is thus dependent on β_2 -receptors (11).

It is therefore apparent that the tremor-alleviating effect of atenolol and metoprolol in some cases is due chiefly to the tranquillizing effect of the drugs on the patient's general condition. Furthermore, it must be remembered that hand tremor, sometimes intensive, and common in connection with e.g. salbutamol medication, may be spontaneously relieved as the treatment continues.

On the whole, β_1 -blocking agents did not have a distinct lowering effect on the systolic blood pressure. This was probably because only three of the patients were known previously to have elevated blood pressure. The result may also be confused by the concomitant potent medication given to the asthmatics and the severe asthmatic episode in itself.

Atenolol distinctly reduced the diastolic

pressure. This effect was not observed with metoprolol. However, the metoprolol medication in this study did not follow the dose recommended by the drug manufacturer for the treatment of blood pressure.

The group of five patients in which subjective relief of dyspnoea and improved general status were observed during atenolol and/or metoprolol medication was interesting. According to the PF values, nothing dramatic occurred in these cases. Amelioration of the asthma symptoms appeared objectively to continue normally. The reason for the easing of dyspnoea and improvement of the general condition must therefore be sought elsewhere. As mentioned, all these patients had tachycardia of unusually long duration, albeit only 140–120/min. The β -blocker lowered the heart rate to 70–90/min. It is possible that the improvement in cardiac rhythm meant that the pumping capacity of the heart was intensified, thus relieving the dyspnoea. Another possible explanation is that administration of the β_1 -blocker reduced the "feeling of panic" that is often associated with β_2 -sympathomimetic medication. Improved perfusion of the pulmonary circulation by the β_1 -blockade may also be involved.

A fuller explanation of, for example, the possible easing of the pulmonary circulation requires further study. The present work has provided evidence that administration of atenolol and/or metoprolol may even be beneficial for asthmatics, especially in the cases in which tachycardia is disproportionately strong and continues longer than expected even after the most severe asthmatic obstruction has been relieved.

According to this study, atenolol and metoprolol may be given with normal indications, even during a severe asthmatic episode, if bronchodilator sympathomimetic medication is used concurrently.

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