Sotalol and Metoprolol Comparison of Their Anti-Hypertensive Effect

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Summary. 28 patients, aged 35–62 years, with uncomplicated hypertension, entered a double-blind, crossover study, in which the effects of single daily doses of sotalol and metoprolol were compared. Both drugs exerted a clinically useful anti-hypertensive effect as monotherapy, or in combination with a thiazide diuretic. No significant difference in hypotensive effects was noted between the two beta-blocking agents, when the dose was titrated to an optimal clinical effect. Treatment with sotalol and metoprolol was associated with a clinically insignificant increase in serum uric acid concentration. The side-effects observed were few, and in only two cases was therapy discontinued. We regard both sotalol and metoprolol as useful anti-hypertensive drugs.

Key words: hypertension, metoprolol, sotalol; comparison, plasma levels, serum uric acid

Metoprolol is a cardioselective beta-adrenergic blocking agent devoid of any ancillary pharmacological properties (Skinner et al., 1976). Although completely absorbed, its first pass metabolism limits bioavailability to 40–60%, and considerable inter-individual variability in blood levels is observed. The plasma half-life is 3–4 h (Regárdh 1975). Metoprolol is excreted in the form of inactive metabolites. Its anti-hypertensive properties are well documented (Bengtsson et al. 1975; Bengtsson 1976; Collste et al. 1976). It can be administered once daily, but less consistent control of exercise tachycardia is observed with this regimen (Reybrouck et al. 1978). It has recently been suggested that metoprolol possesses superior antihypertensive activity to alprenolol and oxprenolol in equipotent beta-receptor blocking doses (Tuomilehto and Nissinen 1979). Alprenolol and oxprenolol are noncardioselective beta-blockers, which also possess intrinsic stimulating activity (ISA).

We have compared the antihypertensive effects of metoprolol with another non-cardioselective beta-adrenergic blocking agent, sotalol, which does not possess ISA (Levy and Richards 1965). Sotalol has an attractive pharmacokinetic profile: its bioavailability is almost complete, it is not metabolised and it is not bound to serum proteins (Anttila et al. 1976; Johnsson and Regårdh 1976). Sotalol has no active metabolites and it is excreted via the kidneys (Schnelle and Garrett 1973; Anttila et al. 1976). The terminal plasma half-life of sotalol is approximately 17 hours, and the duration of its pharmacological effects permits once daily dosage (Anttila et al. 1976).

The objectives of the present study were to compare metoprolol and sotalol with regard to their antihypertensive effects and tolerability.

Materials and Methods

Patients

28 patients, 6 women and 22 men, mean age 52 years (range 35–62 years), were included in the study. They all had essential hypertension and a standing blood pressure more than 140/90 mmHg. The diagnosis was made after routine examination in our Hypertension Clinic (Andersson et al. 1978). 10 of the patients were classified as WHO Stage 1 and the others as WHO Stage 2. The 10 patients with mild hypertension had not previously been treated, and antihypertensive medication had already been instituted in the others. Seven of the latter were taking beta-adrenoceptor blocking agents, which were
discontinued four weeks prior to the trial. Nine patients were receiving other anti-hypertensive medication, which was kept unchanged throughout the study. Beta-blockers were added to their treatment regimen, because of inadequate blood pressure control.

Methods

The study was carried out in a double-blind crossover fashion, with an initial placebo period (4 weeks) and a second placebo period (four weeks) between the two active drug treatment periods. The patients were randomly allocated to start either with sotalol or metoprolol. During the treatment periods, each of 16 weeks, the dose was increased every fourth week until acceptable blood pressure control (diastolic blood pressure < 95 mm) was achieved. Sotalol was begun with a dose of 160 mg per day, which was increased if necessary by 160 mg monthly. The maximum daily dose of sotalol was 640 mg, given as a single oral dose. Metoprolol therapy was initiated with 100 mg daily, and was, if necessary, increased monthly by 100 mg/day, up to a maximum of 400 mg/day. The doses of both drugs were chosen according to the recommendations of the manufacturers. Both drugs were given as one dose in the morning, and blood pressure was recorded 24 h after the last dose.

Blood pressure was always measured by the same nurse at the out-patient clinic. It was measured in the supine position after 5 min rest, and after one minute in the standing position, using a mercury manometer and stethoscope. The inflation cuff was 12 cm wide and 35 cm long. The measurements, performed in the right arm, were recorded to the nearest 2 mmHg. Diastolic blood pressure was taken as Phase 5 (disappearance). The heart rate was determined by palpation of the radial pulse immediately before the blood pressure measurement in the supine position.

Laboratory tests were done during the two placebo periods and at the end of each active treatment period. The tests included blood chemistry (haemoglobin, haematocrit, serum creatinine, bilirubin, SGOT, uric acid, cholesterol and triglycerides) and urinalysis (microscopy, protein and glucose). Spontaneously reported side-effects were recorded, and they were judged as possibly or definitely drug related.

Sotalol and Metoprolol Blood Levels

The plasma concentrations of sotalol and metoprolol were determined on the last visit, approximately 24 h after taking the last dose. All blood samples were centrifuged and plasma was separated and frozen at −20 °C until analysis. Plasma sotalol was determined by a spectrofluorometric method (Garrett and Schnelle 1971). Plasma metoprolol was determined with a new spectrofluorometric method: plasma 1 ml was added to two drops of HClO4 70% v/v, shaken to precipitate the protein, and the sample was then centrifuged for 5 min at 3000 rpm. The clear supernatant was adjusted to pH 13 with NaOH 6.25 N and extracted with an (4:1,v/v) ether-chloroform mixture 5 ml. After shaking for 30 min on an automatic shaker, and separating by allowing the samples to stand for 30 min, the organic phase was decanted over a phase-separating filter and 0.1 N HCl 3 ml was added. This was again shaken for 30 min and allowed to separate. The organic phase was discarded. The acid samples were then analysed in a spectrofluorimeter (Jobin-Yvon JY-3) at 275 nm excitation and 300 nm fluorescence. Standards of 150, 225, 300, 450 and 600 ng/ml, equivalent to 50, 75, 100, 150 and 200 ng/ml in the measured acid media, were added to control plasma and were run simultaneously with each set of samples. The lower limit of detection was 10 ng/ml plasma.

Statistical Analysis

For comparison of the effects of each of the beta-adrenoceptor blockers and placebo on blood pressure and laboratory tests, a two-tailed paired t-test was used. The anti-hypertensive effects of metoprolol and sotalol were compared by two-way analysis of variance (ANOVA), using the general linear model procedure (GLM) of the SAS Institute. Differences were regarded as statistically significant if p < 0.05.

Results

Blood Pressure and Heart Rate

Details of the 26 patients completing the study are given in Table 1. The effects of sotalol and metoprolol on blood pressure during the course of the study are shown in Figs. 1 and 2. The greatest drop was seen during the first month of therapy, with little change in the subsequent months of therapy, despite the increasing doses given to the majority of patients. The effects on blood pressure and heart rate at the end of therapy were summarised in Table 2. Blood pressure and pulse rate returned to pre-treatment levels during the second placebo period and were averaged.