Equivalent Blood Pressure Reduction and Tolerability with Controlled-Release Metoprolol 50mg Once Daily and Conventional Metoprolol 50mg Twice Daily
A Double-Blind 8-Week Comparison in Hypertensive Patients

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Summary

In a prospective, multicentre, double-blind, parallel group study, the blood pressure-lowering effects of an oral 50mg once-daily dosage of metoprolol CR/ZOK (controlled-release/zero-order kinetics), an agent with 24-hour activity, were compared with those of conventional oral metoprolol 50mg twice daily in patients with mild to moderate hypertension. After a 2-week placebo washout phase, 54 patients were treated with metoprolol CR/ZOK and 55 patients received conventional metoprolol for 8 weeks. The target variables of blood pressure and heart rate were measured in the supine and standing positions at rest, under standardised conditions, in the morning and evening after 4 weeks’ treatment and at the end of the 8-week treatment phase. After 8 weeks, blood pressure and heart rate at the end of the respective dosage intervals were significantly reduced from baseline in both treatment groups. Mean systolic and diastolic blood pressures measured in the morning, 12 hours after conventional metoprolol and 24 hours after metoprolol CR/ZOK, were 16.8/11.0mm Hg and 16.2/11.2mm Hg, respectively, lower than baseline values. Heart rate after 8 weeks’ treatment was reduced by 9.0 beats/min with metoprolol CR/ZOK and by 9.3 beats/min with conventional metoprolol. The small deviations in the 95% confidence intervals demonstrate the equal efficacy of the 2 preparations. Approximately the same number of patients in the 2 groups reported adverse events. Even though not significant, the total number of adverse events was 25% lower in metoprolol CR/ZOK recipients.

The results of this study confirm that once-daily oral metoprolol 50mg administered as a controlled-release formulation with 24-hour activity and zero-order kinetics constitutes an effective treatment for most patients with mild to moderate hypertension. In addition, antihypertensive efficacy with this formulation is achieved at half the dosage required with conventional metoprolol.
The WHO/International Society of Hypertension,11 the US Joint National Committee (JNC) on high blood pressure[2] and other national hypertension societies recommend that drug treatment for hypertension should, in principle, begin with monotherapy. Drug selection from the 5 basic classes of antihypertensive agents is made according to disease-specific (primary disease, concomitant diseases, and risk factors) and economic factors. The JNC recommendations are firmly directed towards first-line therapy with β-adrenoceptor antagonists or diuretics[2] since these classes of agents are the only ones that have so far been proved, in representative intervention trials, to reduce cardiovascular mortality and morbidity on a population scale.[3]

In view of the recognised problems of compliance among patients with hypertension, there is an increasing need for once-daily administration of antihypertensives with relatively uniform plasma concentrations over a 24-hour period and proven 24-hour activity.[4,5]. Such an agent would avoid high peak drug concentrations (which are often associated with more severe adverse events), loss of selectivity, or the induction of counter-regulative mechanisms by the body. It would also ensure the continuance of its cardiovascular protective properties, even in the so-called circadian ‘problem periods’ such as the early morning hours. Modern antihypertensive agents are also required to improve the quality of life, compliance and the prognosis of the hypertensive patient. A new pharmaceutical formulation of metoprolol seems to meet these requirements.

Metoprolol CR/ZOK (controlled-release/zero-order kinetics) provides controlled drug release from the gastrointestinal tract into the circulation at a slow, virtually constant rate.[6] This preparation is bound to succinate and is formulated as very small pellets. Metoprolol CR/ZOK exhibits effective 24-hour β-adrenoceptor antagonist activity.[7,9] Corresponding effects on blood pressure have been found by Scholz,[10] using 24-hour ambulatory blood pressure measurement (ABPM), and by other investigators who reported similar reductions at 12 and/or 24 hours after drug administration,[11-13] even with low dosages of 50 mg/day.[14-16]

It has previously been shown that 50mg once daily of the new metoprolol formulation is as effective as 100mg once daily of conventional metoprolol.[11] Furthermore, data on exercise heart rate suggest that while 12 hours postdose conventional 50mg tablets are as effective as metoprolol CR/ZOK 50mg (both given as a single dose), they are similar to placebo after 24 hours.[17]

Thus, the aim of the present study was to objectively compare the blood pressure-lowering effects and tolerability of metoprolol CR/ZOK 50mg once daily at 12 and 24 hours postdose with those of conventional metoprolol administered at double the dosage (50mg twice daily).

Patients and Methods

Patients

110 ambulant patients with mild to moderate essential hypertension who were aged between 18 and 70 years were recruited from 6 centres in Germany for participation in the study. Approximately half of the patients were on antihypertensive treatment until entering the washout/placebo period.

The exclusion criteria for participation in the study were pregnancy or lactation, secondary hypertension, severe heart failure (NYHA III and IV), atrioventricular-block grade II or III, sinoatrial-block, impaired hepatic or renal function, other serious illnesses causing a substantial reduction in quality of life, and alcohol or drug addiction. In addition, the recognised contraindications for β-adrenoceptor antagonist treatment were strictly observed.

Patients were informed about the study and gave their written consent. The study was carried out under strict observance of the Declaration of Helsinki, after approval had been given by the Ethics Committee of the Bavarian Chamber of Physicians.