Osmotic Release Oral Drug Delivery System of Metoprolol in Hypertensive Asthmatic Patients
Pharmacodynamic Effects on \( \beta_2 \)-Adrenergic Receptors

Karin Bauer, Gerhard Kaik, Brigitte Kaik

Abstract This study investigated the effects of an osmotic release oral drug delivery system of metoprolol on the changes induced by cumulative doses of inhaled salbutamol on bronchomotor tone, skeletal muscle, and the circulatory system after single (day 1) and multiple (day 7) dosing in 18 hypertensive asthmatic patients (forced expiratory volume in 1 second >50% predicted; diastolic blood pressure >90 mm Hg). The patients were given 14/190 mg metoprolol, 100 mg atenolol, and placebo once daily for a 7-day period each in a randomized, double-blind, crossover design. At the estimated time of peak plasma concentrations, cumulative doses of salbutamol (12.5, 37.5, 112.5, 412.5, 812.5, and 1612.5 \( \mu \)g) were applied every 20 minutes. Specific airway conductance, finger tremor amplitude, heart rate, and blood pressure were registered at baseline and at each dose increment. The slopes of the salbutamol dose-response curves of specific airway conductance did not differ on day 1 (P>.05). On day 7, atenolol caused a shift of the dose-response curves of specific airway conductance to the right (P<.05), whereas metoprolol was indistinguishable from placebo (P>.05). The median cumulative salbutamol concentrations causing a 50% increase in specific airway conductance were 416 and 384 \( \mu \)g (days 1 and 7, respectively) for placebo, 594 and 444 \( \mu \)g for metoprolol, and 562 and 1419 \( \mu \)g for atenolol. The median cumulative salbutamol concentrations causing a 35% increase in tremor were 732 and 706 \( \mu \)g for placebo, 812 and 1213 \( \mu \)g for metoprolol, and 797 and 1323 \( \mu \)g for atenolol. These results demonstrate that single doses of metoprolol and atenolol showed no differences in their effects on the \( \beta_2 \)-adrenergic receptors of bronchial and skeletal muscle compared with placebo. Multiple doses of metoprolol caused no measurable bronchial \( \beta_2 \)-adrenergic receptor antagonism in contrast to atenolol. Multiple doses of both \( \beta \)-adrenergic receptor antagonists caused a measurable blockade of \( \beta_2 \)-adrenergic receptors of skeletal muscle. (Hypertension. 1994;24:339-346.)

Key Words: metoprolol • receptors, adrenergic, \( \beta \) • muscle, smooth, skeletal • albuterol • asthma

Metoprolol, introduced in 1975, has been described as an effective, well-tolerated, cardioselective \( \beta \)-adrenergic receptor antagonist without significant partial agonist activity used extensively in the treatment of hypertension and angina pectoris. Its efficacy in the secondary prevention of myocardial infarction and reduction of the incidence of ventricular fibrillation, reinfarction, and sudden death has suggested cardioprotective properties.

The oral osmotic (oros) release drug delivery system of metoprolol (Alza Corp) consists of an osmotically active core, made up mainly of active drug, surrounded by a semipermeable membrane. A small hole is drilled through this membrane with a high-speed laser beam. Osmotic pressure causes the passage of water into the drug reservoir, resulting in a slow, continuous release of active material. The oros system is designed to release the drug at a constant hourly rate until 80% has been released and then at a slower rate for the remaining 20% to provide relatively consistent release over a 24-hour period, avoiding unnecessary high peaks in plasma concentrations.

Clinical studies in healthy volunteers and asthmatic patients showed that metoprolol oros produced less bronchial \( \beta_2 \)-adrenergic receptor antagonism than equivalent doses of atenolol and sustained-release metoprolol probably because of the relatively low, sustained plasma concentrations provided by the oros formulation. However, no comparative data on the effects of single and multiple doses of metoprolol oros on \( \beta_2 \)-receptors have been published in hypertensive patients with concomitant asthma. Various pathophysiological mechanisms causing asthma as well as influences of regular therapy are absent in healthy subjects. Therefore, our respective data on bronchomotor tone in healthy subjects cannot be suggested without restriction to be identical with those in asthmatic hypertensive patients.

The aim of this study was to compare the effects of single and multiple doses of metoprolol oros on the changes induced by cumulative doses of inhaled salbutamol on bronchial smooth muscle and skeletal muscle and the circulatory system in hypertensive patients with concomitant asthma. Atenolol and placebo were used for comparison. The assessments were made after a single dose on day 1 and after multiple dosing on day 7 of the respective treatment periods.
TABLE 1. Demographic Data, Pretrial Medication, and Bronchial Reversibility of 18 Hypertensive Asthmatic Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/ Smoking Habits</th>
<th>Age, y</th>
<th>Height, m</th>
<th>Weight, kg</th>
<th>Duration Asthma/Hypertension, y</th>
<th>Therapy Before Trial</th>
<th>Blood Pressure, mm Hg</th>
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FEV₁ indicates forced expiratory volume in 1 second; sGaw, specific airway conductance; NS, never smoker; ES, exsmoker (>5 years); B, beclomethasone dipropionate (B-1, 1200 μg/d; B-2, 1500 μg/d); BU, budesonide (400 μg/d); F, fenoterol (pm); I, isopropylbromide (pm); F-I, combination metered dose inhaler (pm); S, salbutamol (pm); and T, terbutaline (pm).

*30 Minutes after inhalation of 400 μg salbutamol (4 puffs) from a metered dose inhaler.

Methods

Full written informed consent was obtained from all patients after approval of the local hospital ethics committee.

Patients

Twenty-eight stable asthmatic patients (outpatients, whites) with concomitant essential hypertension but no other important disorders were recruited (Tables 1 and 2). Inclusion criteria were an actual forced expiratory volume in 1 second (FEV₁) greater than 50% of the predicted value, a rise in FEV₁ of at least 15% after inhalation of 400 μg salbutamol applied by a metered dose inhaler, and a diastolic blood pressure greater than 90 mm Hg. Each patient had a normal electrocardiogram (ECG, 12-lead), a Holter ECG monitoring Lown Grade 0-1, and a normal chest radiograph. Sixteen patients met the criteria of mild hypertension defined by the 1993 guidelines for the management of mild hypertension with a diastolic blood pressure between 95 and 105 mm Hg (Tables 1 and 2). Eleven patients showed a higher diastolic blood pressure values up to 115 mm Hg; patient 4 showed a diastolic blood pressure of 125 mm Hg at the screening visit only. Exclusion criteria were FEV₁ less than 50% of the predicted value, angina pectoris, second- and third-degree heart block, heart failure, bradycardia less than 50 beats per minute, impaired renal or hepatic function, diabetes mellitus, pregnancy, lactation, or any known severe adverse reactions to β-adrenergic receptor antagonists. Patients were excluded if they had had an acute illness or an exacerbation of airflow obstruction within 6 weeks before the start of the study. None of the patients had a history of extrinsic asthma. Regular medication consisted of bronchodilator therapy and regular inhaled corticosteroids (1200 to 1500 μg beclomethasone dipropionate daily or 800 μg budesonide daily) (Tables 1 and 2). None of the patients was taking antihypertensive medications before the start of the study. All patients had to be in the use of all the equipment and inhalation techniques.

Techniques

FEV₁ (best of three measurements) and specific airway conductance (sGaw) were measured by a constant-volume technique.
body plethysmograph (Jaeger Co). \( s_{\text{Gaw}} \) is the reciprocal of airway resistance corrected for thoracic gas volume, and the mean of five reproducible traces was used for analysis. All values were corrected for body temperature, pressure, and saturation. Finger tremor was measured by a previously validated method using a piezoelectric accelerometer (Zak Co) taped to the terminal phalanx of the right middle finger with the forearm supported and the hand outstretched. Tremor amplitude was assessed as the sum of the integrated signals over a period of 10 seconds; a mean value was calculated from four consecutive measurements. Heart rate was assessed by Holter ECG monitoring (Hewlett-Packard Co). Continuous ambulatory readings of the ECG were made during the assessment of the salbutamol dose response on days 1 and 7, respectively. Blood pressure was measured with a standard mercury sphygmomanometer, taking the first and the fifth Korotkoff sounds as the systolic and diastolic values, respectively.

### Study Design

The study was carried out in a randomized, double-blind (investigator blinded), three-period, crossover, placebo-controlled design with at least 7 days washout phase between treatment periods. To maintain investigator blinding, medication was dispensed by a study coordinator, and patients were instructed not to discuss their study medication with the investigator conducting the clinical evaluations.

### Drugs

Patients were given single daily doses of 14/190 mg metoprolol oros, 100 mg atenolol, or placebo over a 7-day treatment period. The oros system is identified by two numbers: the second represents the total milligram content of the drug in the tablet. The 14/190 mg metoprolol oros tablet contains 190 mg metoprolol fumarate (equivalent to 200 mg metoprolol tartrate) released at a rate of 14 mg metoprolol fumarate hourly. The preparations supplied for oral administration were of identical appearance and taste and were provided by CIBA-GEIGY Ltd. Salbutamol was administered by specially prepared metered dose aerosols delivering 12.5 and 25 \( \mu g \) per puff (Aerosol Services AG) and by a commercially available metered dose aerosol delivering 100 \( \mu g \) per puff (Glaxo Operations).

### General Procedure

Assessments were performed on days 1 and 7 of each treatment period at the same time of day. The salbutamol dose response started at the estimated time of peak plasma concentrations, that is, 12 hours after the dose for metoprolol oros, 3 hours for atenolol, and 3 hours for placebo. During the complete trial, inhaled \( \beta \)-adrenergic receptor agonists were allowed if necessary. No additional oral bronchodilators or antihypertensive drugs were permitted. The dose of inhaled steroids was kept constant throughout the study. The morning dose was applied between 7 and 8 AM and the evening dose between 8 and 9 PM. On study days the evening dose was given after salbutamol dosing at 9 PM. All patients had to abstain from inhaled \( \beta \)-adrenergic receptor agonists 12 hours before each study day.

When the patients arrived, an ECG (12-lead) was recorded and an ambulatory ECG monitor was attached. After 30 minutes of rest, postmedication baseline measurements of all parameters were made. Dose-response curves were then constructed using six increasing doses of inhaled salbutamol as follows: 12.5, 25, 75, 300, 400, and 800 \( \mu g \), resulting in cumulative doses of 12.5, 37.5, 112.5, 412.5, 812.5, and 1612.5 \( \mu g \). Dose increments were made every 20 minutes. A 5-minute period was scheduled for recording all parameters, and the order of recording was \( s_{\text{Gaw}} \), tremor, heart rate, and blood pressure. Subjective effects were documented on all days of each treatment period as well as at each dose increment of the salbutamol dose response on days 1 and 7 as either spontaneously reported or reported after direct questioning, and these

### Table 2. Demographic Data, Pretrial Medication, and Bronchial Reversibility of 10 Study Dropouts

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Mean: 51.20 ± 2.08 | 75.20 ± 0.03 | 3.59/1.67 ± 0.15 | 2.79 ± 0.03 | 3.06 ± 0.10 | 10.16 ± 0.03

Definitions are as in Table 1.

*30 Minutes after Inhalation of 400 \( \mu g \) salbutamol (4 puffs) from a metered dose inhaler.
were graded as mild, moderate, or severe in nature. Routine laboratory profiles were made before the patient entered the trial and on day 7 of each treatment period. At the conclusion of the study, a physical examination, ECG (12-lead), and routine laboratory profile were repeated.

### Statistical Evaluation

Data are presented as mean±SEM. The area under the curve (AUC) was determined for sGaw, tremor amplitude, heart rate, and blood pressure using the log trapezoidal rule method. The data were analyzed with an ANOVA model for a three-period crossover design. Standard SPSS routines were used to analyze data for normality of distribution and homogeneity of variances. To exclude carryover effects, tests for treatment period interactions were performed. Dose-response curves were constructed for each patient by plotting the cumulative concentration (CC) of salbutamol against sGaw and tremor amplitude. The cumulative concentration of salbutamol producing a 50% increase in sGaw (CC50sGaw) and a 35% increase in tremor (CC35tremor) from postmedication baseline was calculated by linear interpolation from the dose-response curves for each patient and each treatment. As salbutamol caused insufficient change from postmedication baseline in some patients, the respective CC was set equal to 1613 μg (greater than the maximal CC of salbutamol) in these cases. Because of a violation of the normality of distribution and the variance homogeneity assumption of the CC data, a nonparametric analysis (Wilcoxon rank sum test) with a Bonferroni α-adjustment was performed on the ranks of the CC data. Holter ECG recordings were analyzed for heart rate, ventricular ectopic beats, and supraventricular premature beats. Values were considered to be significantly different at a value of P<.05. Results were assessed by the SPSS+ software package (SPSS Inc).

### Results

The data of 18 patients could be subjected to analysis, and the data of 10 patients had to be excluded (Tables 1 and 2). Six patients (patients 2, 3, 14, 15, 20, and 22) discontinued prematurely for personal reasons not related to the trial medication but because of the time-consuming study design. One patient (patient 11) acquired an upper respiratory tract infection during the placebo treatment period. One patient (patient 6) experienced finger tremor and palpitations of moderate degree during the salbutamol dose response on placebo (day 1) and refused to continue. Two patients showed an impairment of asthma during the washout period: patient 10 after having finished the placebo and metoprolol treatment period and patient 13 after the metoprolol and atenolol phase. Patient 13 needed systemic corticosteroids and oral β2-adrenergic receptor agonists as additional treatment. Statistics on pretrial baseline characteristics comparing the patients who completed the study with those who dropped out revealed no statistically significant differences between the groups (P>.05) (Tables 1 and 2).

### Effect of β-Adrenergic Receptor Antagonists on Postmedication Baseline

Table 3 shows postmedication baseline values for each of the treatment periods. ANOVA showed no difference between treatments for sGaw on day 1 (P>.05) and day 7 (P>.05) and for tremor on day 1 (P>.05). On day 7 mean postmedication baseline tremor amplitude showed significantly lower values during both active drugs compared with placebo (P<.01). On days 1 and 7 the active drugs showed significantly lower postmedication baseline values compared with placebo for heart rate (P<.001, P<.0001) and for diastolic blood pressure (P<.01, P<.01), respectively. For systolic blood pressure no significant differences could be found (P>.05, P>.05).

### Dose Response With Inhaled Salbutamol

There were highly significant linear dose-response relations for sGaw (P<.0001) and tremor (P<.0001) on days 1 and 7, respectively (Figs 1 through 3).

### Specific Airway Conductance

The slopes of the salbutamol dose-response curves did not differ on day 1 (P>.05), whereas on day 7 atenolol caused a marked shift of the dose-response curve to the right (P<.05) (Fig 1). Analysis of AUCsGaw revealed no significant difference between any of the treatments on day 1 (P>.05). On day 7 the differences between atenolol and placebo (P<.05) and those between atenolol and metoprolol (P<.05) were significant. The difference between placebo and metoprolol was not significant (P>.05). The comparison of AUCsGaw between days 1 and 7 of each treatment period resulted in significant differences for atenolol only (P<.01) (Fig 2).

### CC50sGaw

Table 4 presents individual values of CC50sGaw. The median was 416 and 384 μg (days 1 and 7, respectively) for placebo, 594 and 444 μg for metoprolol, and 562 and 1419 μg for atenolol. Statistical analysis on the ranks of CC50sGaw revealed no significant differences between the drugs on day 1 (P>.05); on day 7 atenolol differed...
The line graphs (Fig 1 and Fig 2) show specific airway conductance ($sGaw$) response to cumulative concentrations of inhaled salbutamol after pretreatment with 14/190 mg metoprolol oros (stars), 100 mg atenolol (triangles), and placebo (circles) in 18 hypertensive asthmatic patients.

Significantly from placebo ($P<.05$) and metoprolol ($P<.05$).

**Tremor Amplitude**

Both active drugs caused a shift of the salbutamol dose-response curve to the right, which was more clearly and statistically significant on day 7 ($P<.05$) (Fig 3). Analysis of $AUC_{tremor}$ revealed no significant differences between treatments on day 1 ($P>.05$). On day 7 the difference between placebo and both $\beta$-adrenergic receptor antagonists was significant ($P<.0001$), whereas the active drugs did not differ from each other ($P>.05$). The comparison of $AUC_{tremor}$ between days 1 and 7 of each treatment period resulted in significant differences for atenolol ($P<.05$).

**$sGaw$**

The median values of $CC_{tremor}$ were 732 and 706 $\mu g$ for placebo, 812 and 1213 $\mu g$ for metoprolol, and 797 and 1323 $\mu g$ for atenolol (Table 4). Statistical analysis on the ranks of $CC_{tremor}$ showed no significant differences between the drugs on day 1 ($P>.05$). On day 7 the difference between placebo and atenolol ($P<.05$) and that between placebo and metoprolol ($P<.05$) were significant. No significant difference was observed between metoprolol and atenolol ($P>.05$).

**Heart Rate and Systolic and Diastolic Blood Pressures**

A $CC_{heart}$ rate causing an increase in heart rate of 25 beats per minute could not be calculated because of insufficient change from postmedication baseline within our salbutamol dose range. No salbutamol dose-response relation could be obtained for systolic and diastolic blood pressures.

**Holter ECG Monitoring**

There was no rise in supraventricular or ventricular ectopic beats, and no important arrhythmias occurred during the salbutamol dose response.
Fra 3. Line graphs show tremor response to cumulative concentrations of inhaled salbutamol after pretreatment with 14/190 mg metoprolol oros (stars), 100 mg atenolol (triangles), and placebo (circles) in 18 hypertensive asthmatic patients.

Side Effects

No serious adverse effects were reported. Some patients reported fatigue, headache, heartburn, nervousness, and mild agitation during the treatment periods. Salbutamol-related adverse effects of mild to moderate degree were restlessness, tremor, palpitations, and headache.

Overall Tolerability and Drug Safety

No other clinical, electrocardiographic, or laboratory adverse experiences were found.

Discussion

The results of the present study demonstrate that single doses of metoprolol oros showed no measurable influence on \( \beta_2 \)-adrenergic receptors of bronchial smooth muscle and skeletal muscle in our hypertensive asthmatic patients. Multiple doses of metoprolol oros caused no measurable bronchial \( \beta_2 \)-adrenergic receptor antagonism but did cause a measurable blockade on \( \beta_2 \)-adrenergic receptors of skeletal muscle.

Effects on \( \beta_2 \)-Adrenergic Receptors of Bronchial Smooth Muscle

Single doses of both 14/190 mg metoprolol oros and 100 mg atenolol had no measurable influence on bronchial \( \beta_2 \)-adrenergic receptors in our hypertensive asthmatic patients. Neither metoprolol oros nor atenolol caused a difference in postmedication baseline lung function before salbutamol inhalation, and the salbutamol dose-response curves were indistinguishable from those with placebo. Another single-dose study in 12 asthmatic patients showed similar results in postmedication baseline sGaw after 14/190 mg metoprolol oros, whereas after 100 mg atenolol postmedication baseline sGaw was significantly lower than after placebo. 12 In that study single doses of both metoprolol oros and atenolol blunted the salbutamol-induced AUC\(_{\text{area}}\) values, with no significant difference between the drugs. 12 These conflicting results on the bronchial effects of single doses of cardioselective \( \beta \)-adrenergic receptor antagonists indicate a different sensitivity to \( \beta \)-adrenergic receptor antagonism in different groups of mild to moderate asthmatic patients. 11,12,18-20 Therefore, in the treatment of hypertensive asthmatic patients, it would seem sensible to avoid \( \beta \)-adrenergic receptor antagonists, as alternative forms of antihypertensive therapy are likely to be as effective and at least as well tolerated. 13,21

Therapeutically used, \( \beta \)-adrenergic receptor antagonists are mainly administered over a prolonged period of time, so we compared the effects of metoprolol oros on \( \beta_2 \)-receptors after a single dose on day 1 with those after repeated doses on day 7. Multiple doses of \( \beta_2 \)-adrenergic receptor antagonists caused no measurable bronchial \( \beta_2 \)-adrenergic receptor antagonism but did cause a measurable blockade on \( \beta_2 \)-adrenergic receptors of skeletal muscle.

Effects on \( \beta_2 \)-Adrenergic Receptors of Skeletal Muscle

To assess \( \beta_2 \)-adrenergic receptor antagonism on \( \beta_2 \)-receptors of skeletal muscle, we investigated the changes on finger tremor amplitude. After single doses of metoprolol and atenolol, postmedication baseline tremor values and tremor response to salbutamol showed no differences compared with placebo. Multiple doses of both \( \beta_2 \)-adrenergic receptor antagonists shifted the tremor dose-response curve to the right. These results clearly demonstrate a separation of the \( \beta_2 \)-adrenergic receptor antagonism of metoprolol oros on \( \beta_2 \)-receptors of different tissues, with the effect on bronchial smooth muscle being less than that for skeletal muscle.

Quantification of \( \beta_2 \)-Adrenergic Receptor Antagonism

Evaluation of the CC of inhaled salbutamol causing a certain relevant change in sGaw and tremor amplitude demonstrates a quantitative approach to \( \beta_2 \)-adrenergic receptor antagonism on \( \beta_2 \)-receptors of different tissues, although the interindividual variation was relatively high. 15,22 After pretreatment with placebo, the median
TABLE 4. Individual Cumulative Salbutamol Concentrations Causing a 50% Increase in sGaw and 35% Increase In Tremor Amplitude

<table>
<thead>
<tr>
<th>Patient</th>
<th>Placebo</th>
<th>Metoprolol oros, 14/190 mg</th>
<th>Atenolol, 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sGaw</td>
<td>Tremor</td>
<td>sGaw</td>
</tr>
<tr>
<td>Day 1</td>
<td>Day 1</td>
<td>Day 1</td>
<td>Day 7</td>
</tr>
<tr>
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<td>101</td>
<td>897</td>
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<tr>
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<td>377</td>
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<td>927</td>
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<tr>
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<td>543</td>
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<td>934</td>
</tr>
<tr>
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<td>189</td>
<td>724</td>
</tr>
<tr>
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<td>533.66</td>
<td>732.61</td>
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<tr>
<td>±SEM</td>
<td>80.01</td>
<td>103.71</td>
<td>75.10</td>
</tr>
</tbody>
</table>

sGaw indicates specific airway conductance. Salbutamol concentrations are in micrograms.

Salbutamol CC inducing a 50% increase in sGaw was about half the CC inducing a 35% increase in tremor amplitude. These results are in keeping with previous findings that a plateau level of the inhaled salbutamol dose-response curve for sGaw occurred with lower concentrations of inhaled salbutamol than for systemic effects such as tremor and heart rate because of exposure of airways β-adrenergic receptors to high local concentrations of inhaled salbutamol compared with the low plasma salbutamol levels in the periphery.15,23

After pretreatment with multiple doses of both active drugs, β2-adrenergic receptor antagonist on skeletal muscle resulted in significantly higher CC values of salbutamol compared with those after placebo or the respective single doses. These findings may be due to the fact that β2-adrenergic receptor sensitivity may be changed after prolonged exposure to β2-adrenergic receptor antagonists.

After pretreatment with single and multiple doses of metoprolol oros, CC50sGaw was comparable to that after placebo. In contrast, multiple doses of atenolol resulted in remarkably higher salbutamol concentrations for CC50sGaw. These results may be explained by the fact that the most crucial parameter for the negative effect of β2-adrenergic receptor antagonists on the airways is the peak plasma concentration.10,18 Therefore, the consistent drug delivery of the oros system, which avoids high peak plasma concentrations and provides smooth plasma concentrations, may be an advantage in the pharmacodynamic effects of β-adrenergic receptor antagonists.

β-Adrenergic receptor antagonists without any cardioselectivity are contraindicated in asthmatic patients because of their bronchoconstrictive effect.24-26 Selective β1-adrenergic receptor antagonists have been shown to cause less pronounced bronchoconstriction27-35 and were thought to be less dangerous in patients with concomitant asthma.26 Especially those β-adrenergic receptor antagonists with enhanced β1-selectivity such as bisoprolol19 and those with partial β1-agonist activity such as dilevalolol37 or celiprolol38 were considered to have advantages over conventional β-blockers such as atenolol in some patients with concomitant asthma.21

Conclusions

Although metoprolol oros had no measurable influence on bronchomotor tone in our asthmatic hypertensive patients, the presence of systemic effects on β2-receptors of skeletal muscle could be demonstrated. As sensitivity to β-adrenergic receptor antagonists differs from asthmatic to asthmatic dependent on the balance of various pathophysiological mechanisms, the lack of a measurable bronchial β2-antagonism of metoprolol oros...
obtained in our stable asthmatic patients should not be interpreted as a relevant aspect of drug safety applicable to all asthmatic hypertensive patients. As there are several other groups of antihypertensive agents from which to choose, it must be concluded that both cardio-selective $\beta$-adrenergic receptor antagonists, atenolol and metoprolol oros as well; are contraindicated for antihypertensive treatment in patients with concomitant asthma.

Acknowledgment
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