Beta-Adrenoceptor Blockers and Terbutaline in Patients with Chronic Obstructive Lung Disease*

Effects and Interaction After Oral Administration

J. Wunderlich, M.D.; H. N. Macha, M.D.; H. Wudicke, M.D.; and H. Huckauf, M.D.

We studied the effects of a combined treatment with $\beta_2$-stimulating and $\beta$-blocking drugs in 35 patients suffering from chronic obstructive lung disease (COLD) and ischemic heart disease, and/or arterial hypertension. The drugs used were equipotent repeated oral doses of metoprolol (100 mg twice daily [bid]), propranolol (80 mg bid), and a matching placebo for $\beta$-adrenoceptor blockade given in a double-blind and crossover fashion. The intake period of each $\beta$-blocker was two days with consecutive two-day-washout period; 2.5 mg terbutaline and $\beta$-stimulator placebo, respectively, were given throughout the whole trial three times daily (tid). Propranolol alone caused severe deterioration of lung function. After 18 patients had been studied, this drug had to be excluded from the trial. When compared with placebo, metoprolol provoked increasing obstruction, too, but to a significantly lesser degree than propranolol. These negative effects on FEV$_1$ and FRC were completely equalized by terbutaline. Predictive factors for the tolerability of $\beta$-blockers in patients with COLD could not be found. Therefore, careful observations in the initial phase of the treatment with $\beta$-selective blockers are necessary.

The pharmacologic action of $\beta$-blocking agents, ie increasing bronchial resistance, limits their use in patients with chronic obstructive lung disease (COLD). According to the classification of $\beta$-adrenoceptors by Lands et al, selective blockers have been developed which might also provoke increasing obstruction, but in most cases, to a far lesser degree than nonselective blockers. On the basis of this theoretical model, $\beta$-stimulators were given concomitantly with $\beta$-blockers in order to minimize the bronchial response to the blocking therapy. But all the studies performed to test the clinical relevance of this dealt with a small number of patients, or modes of drug administration which are not used clinically, and the designs of these studies were not completely double-blind.

One aim of our study was to compare the effects of two $\beta$-blockers, metoprolol and propranolol, and a placebo blocker, on lung function and cardiovascular factors given with and without an underlying treatment of a $\beta$-stimulator, terbutaline. Another objective was to use repeated clinical oral doses of the blockers since selectivity of a $\beta$-receptor blocker

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*From Medizinische Klinik und Poliklinik, Abteilung Cardiopneumologie, Klinikum Steglitz der Freien Universität, Berlin, Germany.

Manuscript received June 12; revision accepted January 29. Reprint requests: Dr. Wunderlich, Helgoldamer Ufer 6, 1000 Berlin 21, West Germany

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group II-III, WHO 1962) for more than three years. Eleven patients suffered from coronary heart disease and essential hypertension. One patient had recurrent chest pain and tachycardias based on hypertrophic obstructive cardiomyopathy (HOCM). In all patients, treatment with drugs such as steroids, digitalis, diuretics, antihypertensives, and organic nitrates was not changed during the trial. Treatment with bronchodilators (β-stimulators and aminophylline) was withdrawn before the trial was started. Patients were thus advised to use them in case of emergency after contacting the investigators.

**Measurements and Ratings**

All the measurements were performed two to three hours after intake of regular medication and test medication. Conventional lung function tests were performed in the sitting position, spirometry first (wet spirometer, Pulmotest [Gordard] linear displacement recorded with an accuracy of 1 percent full-scale deflection, time as 2 percent) and thereafter, body plethysmography (volume constant body plethysmograph, spontaneous breathing [Jaeger]). Predicted normal values were taken from Goldmann and Becklake.11 Best values of three lung-functional maneuvers performed were taken, and statistical analyses were performed. Thereafter, the ECG was registered and blood pressure measurements were performed by the same observer with the subject in the horizontal position. After this procedure, patients were interviewed by another observer as to interim history and drugs taken within the past 48 hours. Subjective declarations of breathlessness were classified as mild (no therapeutic interventions needed), moderate (injection of 0.24 g aminophylline and β-stimulator inhalation), and severe (injection of 0.24 g aminophylline, 50 mg cortisone and inhalation of β-stimulators). Compliance control was performed by pill-count.

**Statistics**

(a) Lung functional data of functional residual capacity (FRC) were calculated in percentage of predicted normal. Forced expiratory volume in one second (FEV₁), systolic arterial blood pressure (BP₁), diastolic arterial blood pressure (BP₂), heart rate (HR), and airway resistance (Raw) were calculated as absolute values. We calculated mean values and the standard deviations (SD).

(b) The Wilcoxon-Mann-Whitney test for two independent samples, two-tailed, was used for statistical evaluation between the groups with and without β-stimulator.

**Figure 1.** Design of study.

**Figure 2.** Effect of propranolol and metoprolol in patients on and off terbutaline therapy; mean values (±) and standard deviations (SD) of positive and negative differences (Δ%) of FRC, Raw and FEV₁-values measured before and after a two-day-treatment period with terbutaline/placebo. Histograms: asterisks-marked values are significantly different (p<0.05); positive sign of Δ% = increase in FEV₁, Raw, FRC; negative sign of Δ% = decrease in FEV₁, Raw, FRC; terbutaline/placebo; --- = propranolol; ----- = β-blocker placebo; --- = metoprolol.

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**Beta Blockers and Terbutaline in Cold**

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Table 1—Pre-study Characteristics in the Placebo and Terbutaline Groups

<table>
<thead>
<tr>
<th></th>
<th>Terbutaline (n = 18)</th>
<th>Placebo (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>61.9 ± 8.4</td>
<td>61.0 ± 7.5</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>170.1 ± 6.0</td>
<td>164.8 ± 9.3</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>73.9 ± 8.7</td>
<td>70.5 ± 15.3</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Functional residual capacity (% pred)</strong></td>
<td>183.4 ± 37.0</td>
<td>167.3 ± 42.3</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Residual volume (% pred)</strong></td>
<td>216.2 ± 55.1</td>
<td>192.3 ± 42.8</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Forced expiratory volume in L sec</strong></td>
<td>1.29 ± 0.70</td>
<td>1.22 ± 0.63</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Airway resistance (cm H2O/L/sec)</strong></td>
<td>5.58 ± 2.26</td>
<td>7.31 ± 4.49</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Heart rate (min⁻¹)</strong></td>
<td>85 ± 15</td>
<td>85 ± 15</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>156 ± 17</td>
<td>157 ± 17</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
<td>95 ± 12</td>
<td>87 ± 9</td>
<td>ns</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>Terbutaline</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women</strong></td>
<td>5</td>
<td>6</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>13</td>
<td>11</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Smoking history</strong></td>
<td>14</td>
<td>13</td>
<td>ns</td>
</tr>
</tbody>
</table>

(d) The Friedman test for several related samples was used to test the differences between three drugs: placebo, metoprolol and propranolol.

(e) Positive and negative differences were calculated and expressed as percentage of the value measured before a new period of drug intervention (baseline value E = 0 percent). Comparison was uniformly performed at a level which was previously fixed at 5 percent.

RESULTS

General

After 18 patients had been studied (10 with terbutaline, 8 without), the decision was taken to exclude propranolol from the trial because 12 of these patients had developed moderate to severe bronchospasm with subsequent interruption of the propranolol intake (Fig 2). Six of these patients had terbutaline, and six had terbutaline placebo treatment. In five patients, a bronchospastic attack occurred after intake of one tablet of propranolol. Four patients developed bronchospasm after taking two tablets of propranolol. Three patients reported breathlessness after the whole propranolol intake period. In all these patients, objective evaluation using lung function tests confirmed these subjective declarations.

Because of this break in the study, when 18 patients had been investigated, two groups were formed for comparison: group 1 (n = 35) which had placebo β-blocker and metoprolol with (n = 8) and without terbutaline (n = 17); and group 2 (n = 18) which had placebo β-blocker, metoprolol and propranolol with (n = 10) and without (n = 8) terbutaline.

Patient Characteristics

As can be seen from Table 1 (patients without propranolol treatment) and Table 2 (patients with propranolol treatment), respiratory and cardiovascular measurements in both groups (terbutaline and placebo) yielded no significant differences when tested with Wilcoxon-Mann-Whitney, at a 5 percent level. Group 2 has been proven a representative sample of group 1. The distribution of history data (angina pectoris, myocardial infarction), drugs, findings of chest roentgenograms and ECG at rest were similar in both groups. The patients’ compliance was nearly 100 percent in both groups.

Subjective Statements

There were no differences in respect to reported attacks of angina pectoris, subjective feeling of tachycardia, and use of nitrates in both groups (with or without terbutaline).

Comparison of Two Groups (n=10 with, and n=8 without Terbutaline) in Respect to Effects of β-Blocker Placebo, Metoprolol, and Propranolol

Figure 2 presents means and standard deviations of positive or negative differences in percentage of baseline values measured after a two-day treatment with terbutaline, and thereafter a two-day treatment with either β-blocker placebo, metoprolol, or pro-
pranolol. The FRC is not decreased significantly by terbutaline (−5.1 ± 8.1 percent) as compared to placebo terbutaline (+0.4 ± 4.9 percent). Terbutaline increased FEV₁ (+21.7 ± 29.6 percent, P < 0.05) and decreased Raw (−17.0 ± 23.6 percent, p < 0.05) significantly when compared to β-stimulator placebo (FEV₁ −3.5 ± 13.5 percent, Raw + 8. ± 28.1 percent).

When β-blocker placebo was given, there was nearly no influence on FEV₁, FRC, and Raw. These effects were nearly identical in both groups. Metoprolol treatment with terbutaline simultaneously caused an increase of FRC (+7.1 ± 7.9 percent) and of Raw (+44.5 ± 43.4 percent), and a decrease of FEV₁ (−19.0 ± 17.9 percent). These deteriorations of lung function were not significantly different when metoprolol was given without terbutaline: FRC (+6.2 ± 7.8 percent), Raw (+51.5 ± 75.0 percent), and FEV₁ (−14.4 ± 20.3 percent). Propranolol caused severe deteriorations of FRC (+24.9 ± 49.6 percent), FEV₁ (−31.0 ± 11.5 percent), and Raw (+105.1 ± 65.7 percent) in the terbutaline group as well as in the β-stimulator placebo group: FRC (+42.5 ± 39.0 percent), FEV₁ (−36.0 ± 13.6 percent), and Raw (+110.5 ± 65.0 percent).

As Figure 2 points out, the negative effects of propranolol on FEV₁, Raw, and FRC are not essentially different in both groups, whereas terbutaline reduced the negative effects of metoprolol in a remarkable degree, the impression is warranted that both drugs produced nearly a 0 result.

In respect to the variables FEV₁, Raw, and FRC in the groups with and without terbutaline, separate statistical analysis was performed by use of the formula according to Friedman (see "statistics") in order to differentiate between three drugs: β-blocker placebo, metoprolol, and propranolol. With or without terbutaline, placebo caused the lowest and propranolol the highest deterioration of FEV₁, Raw, and FRC. The differences between these three drugs were statistically significant.

Comparison of Two Groups, Terbutaline (n = 18) and Placebo (n = 17) in Respect to Effects of β-blocker Placebo and Metoprolol Treatment

Effects of FEV₁, FRC, Raw: As presented in Figure 3, the effects of terbutaline on FRC (−5.5 ± 9.9 percent) and Raw (−12.8 ± 20.8 percent) are not significantly different from those of β-stimulator placebo: FRC (+2.4 ± 13.4 percent) and Raw (+16.5 ± 59.8 percent), whereas FEV₁ is increased by terbutaline to a remarkable degree when compared to placebo (+21.3 ± 25.8 percent) vs (+3.9 ± 20.1 percent, P ≤ 0.05).

In both groups, placebo β-blocker did not influence FRC, Raw, or FEV₁ in a different degree.

As expected, FRC increased during the metoprolol treatment period, but differences between the two groups are not seen (+5.4 ± 10.9 percent with terbutaline vs +8.8 ± 28.0 percent without terbutaline, ns. Neither the reductions of FEV₁ (−19.3 ± 14.6 percent with terbutaline vs −16.1 ± 19.7...
percent without terbutaline), nor the increase of Raw (+ 48.4 ± 45.4 percent with terbutaline vs + 52.4 ± 66.2 percent without terbutaline) caused by metoprolol are statistically significant as far as the differences are considered. Since FEV₁ was increased significantly by terbutaline when compared with placebo (Fig 3) and the decrease of FEV₁ by metoprolol was of the same degree in both groups consistently, the final absolute values between both groups are statistically different as well.

When comparison was made between improvements caused by terbutaline on FEV₁ (+ 21.3 ± 25.8 percent) and on FRC (- 5.5 ± 9.9 percent), and deteriorations caused by metoprolol on FEV₁ (- 19.3 ± 14.5 percent) and on FRC (+ 5.4 ± 10.9), we achieved a “so-called” O result, ie, the effects of β-blockade are neutralized. Such a result is not to be seen when Raw is chosen for comparison. These values are over the preterbutaline values, but the differences are not significantly different due to wide standard deviations.

With or without terbutaline simultaneously, metoprolol caused a distinct reduction of FEV₁ and an increase of Raw when compared to the effects of β-blocker placebo. These results were significant on a level of 5 percent.

**Effects on Heart Rate and Blood Pressure.** As presented in Figure 4, terbutaline induced an increase of heart rate (+ 7.8 ± 17.3 percent vs - 1.2 ± 7.5 percent, P ≤ 0.05) and a decrease of diastolic blood pressure (- 6.8 ± 11.2 percent vs, + 5.8 ± 10.9 percent, P≤0.05), when compared with terbutaline placebo, whereas the effects of both drugs on systolic blood pressure were not significantly different.

In respect to heart rate, systolic and diastolic blood pressure, placebo β-blocker had no effects on these variables, neither with nor without terbutaline.

When metoprolol was given, the reduction of heart rate in the terbutaline-treated group was significantly different when compared with β-stimulator placebo (- 22.0 ± 16.3 percent vs - 10.3 ±
The present study demonstrated that oral administration of β₂-stimulator (terbutaline, 7.5 mg daily) improved ventilatory function in patients with COLD in comparison to placebo. The cardiovascular result of the effects of terbutaline in our study is an increased amplitude of arterial blood pressure (BP, unchanged, HR increased, and BPd decreased). The increase of the heart rate and of the amplitude of arterial blood pressure may be due to stimulation of cardiac and vascular β₂-receptors. Therefore, according to Ablad et al.² and Carlsson et al.,¹² cardiac output might be increased and vascular resistance reduced.

In our study, propranolol caused severe deteriorations of ventilatory function (Fig 2). Like Johnsson et al.,¹⁷ and Tivenius,¹₈ we found that these effects were not inhibited significantly by oral administration of terbutaline. Therefore, propranolol was omitted, and the effects of this β-blocker on heart rate and blood pressure are not given and discussed because the comparison between metoprolol and propranolol is reported by several other authors.¹₄,¹₈ Our data suggest that the administration of propranolol cannot at all be recommended in COLD. Nevertheless, we found in two cases no subjective complaints with respect to breathlessness during the propranolol treatment period. Both patients suffered from irreversible COLD. Their values of lung function were little influenced when propranolol was compared to placebo.

Because five of 17 patients (without terbutaline) tolerated metoprolol without subjective breathlessness and objective deteriorations of ventilatory function, and in 11 of 18 patients with terbutaline, metoprolol did not change the improvements of terbutaline, we looked for individual prestudy characteristics, history of chronic bronchitis, and differential hemograms with respect to eosinophilia in all these cases. No predictive factor could be found indicating why these patients tolerated β-blockade better than the others. In our study, we found that the improvement of ventilatory function caused by terbutaline is prevented by the application of metoprolol. These observations are in accordance with Formgren,⁶ but not with other authors.⁸,¹³ Some of them¹² used 100 mg metoprolol daily and performed measurements before and after inhalation of isoprenaline, while others⁶ had used single doses of metoprolol, 100 mg, and isoprenaline infusions. They found that the isoprenaline-mediated increase in FEV₁ and FVC was not significantly altered after metoprolol compared with placebo. This shows that metoprolol had not minimized the pharmacologic effects of isoprenaline on the bronchial system. The different results of our study might be explained by the greater β₁-effects of isoprenaline in comparison with terbutaline because there are β₁-adrenoceptors in the bronchi too, and/or a dose-dependent deterioration⁸,⁹ of lung function values—we used 100 mg metoprolol twice a day.

With regard to the increased heart rate caused by terbutaline, the reduction of this measurement after

**FIGURE 4. Effect of metoprolol in patients on and off terbutaline therapy; mean values ( staffers) and standard deviations (SD) of positive and negative differences (Δ%) of heart rate (HR), systolic blood pressure (BPₜ), and diastolic blood pressure (BPₜ) measured before and after a two-day treatment period with terbutaline/terbutaline placebo and metoprolol, β-blocker placebo respectively. Positive sign of Δ% = increase of HR, BPₜ, BPₜ; negative sign of Δ% = decrease of HR, BPₜ, BPₜ.**
metoprolol is of a greater magnitude than that which has been registered by metoprolol alone. The comparison of the effects of metoprolol with and without terbutaline is quantitatively of the same degree. The reduction of systolic and diastolic blood pressure is nearly identical in both groups. The impression is warranted that the reduction of diastolic blood pressure caused by terbutaline is reinforced by metoprolol. Our observations corresponded with the findings of Formgren. From our results, we came to the following conclusions: according to the supposition that terbutaline is a relatively selective \( \beta_2 \)-stimulating drug, and that metoprolol is a relatively selective \( \beta_1 \)-adrenoceptor blocker, the effects of 200 mg metoprolol and 7.5 mg terbutaline daily on the bronchial system may be explained by blockade of \( \beta_1 \)-receptors equipotent to the \( \beta_2 \)-stimulation. Because these dosages of terbutaline and metoprolol produced, in combination, a decrease of heart rate, the distribution pattern of \( \beta_1: \beta_2 \)-adrenoceptors in the heart must not only be inverse to that in the bronchi, but also be more greatly in favor to \( \beta_1 \)-adrenoceptors. Therefore, it is nearly impossible that any drug would have absolute selectivity with respect to organ systems, neither \( \beta \)-stimulators nor \( \beta \)-adrenoceptor blockers at the present state of knowledge of \( \beta \)-receptor mechanisms.

Because a total of 15 (5 of 17 without and 11 of 18 with terbutaline) out of 35 patients tolerated (ie, neither subjective declarations of breathlessness nor deteriorations of ventilatory function) metoprolol, this blocker may be given in individual dosage in patients who suffer from coronary artery disease and/or hypertension in combination with COLD. Careful observations in the initial phase of the treatment are necessary, because selectivity depends on individual response of the bronchial system and/or dosage. We do not agree with other authors who recommended an \( a \) \( \text{priori} \) regular basal \( \beta_2 \)-adrenoceptor stimulation in optimal dosage (oral and inhalation) when \( \beta_1 \)-receptor blockers were given to patients with COLD. However, in individual cases, depending on symptoms and/or effects, terbutaline might be added, and in some patients, even larger doses than we used in this study might be necessary.

References