Effects of the mixed phosphodiesterase III/IV inhibitor, zardaverine, on airway function in patients with chronic airflow obstruction

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Zardaverine is a selective inhibitor of phosphodiesterase (PDE) III and IV isozymes. It has been shown to exert potent bronchodilator effects in animals. In order to study the efficacy and safety in man, a phase II clinical trial in 10 patients with partially reversible chronic airflow obstruction was carried out. The trial was designed as a double-blind, randomized, five-period change-over study. Zardaverine (at single doses of 1.5 mg, 3.0 mg, or 6.0 mg), salbutamol (0.3 mg) and placebo were administered by metered dose inhaler on separate days. As evaluated by spirometry over a time period of 4 h, salbutamol induced a significant bronchodilatation. In contrast, zardaverine did not improve airway function in these patients. Unwanted effects of the study medication were not observed.

Introduction

Isozyme selective phosphodiesterase (PDE) inhibitors may represent a new class of drugs for the treatment of obstructive pulmonary disease such as asthma (1). Most evidence so far suggests that PDE III inhibitors, and possibly PDE IV and V inhibitors, possess bronchodilator activity. On the other hand, inhibitors of PDE IV may suppress the activity of inflammatory cells such as neutrophils or eosinophil leucocytes (1). Mixed PDE III/IV inhibitors may possess, therefore, both bronchodilatory and anti-inflammatory properties.

Zardaverine [6-(4-difluoromethoxy-3-methoxyphenyl)-3[2H]pyridazinone] has been characterized as a selective PDE III/IV inhibitor (2-4). In animals, zardaverine exhibits both bronchodilatory and anti-inflammatory activities (5). Very recently, it has been shown that inhaled zardaverine has a modest and short-lasting bronchodilatory effect in patients with asthma (6). The aim of the present phase II clinical study was to investigate the bronchodilatory activity of inhaled zardaverine in non-asthmatic patients with chronic airflow obstruction (CAO).

Methods

The protocol of the study was approved by an independent Ethics Committee and written informed consent was obtained from all patients. Ten male patients completed the study. None of the patients had a history of asthma or showed any symptoms typical for asthma at the time of the study. None of the patients had ever been treated with glucocorticosteroids. Baseline spirometry gave a vital capacity of 3.93 l [2.85-4.66, median and 68% central range; predicted 4.49 l (3.97-4.83), and a residual volume of 3.19 l (2.55-6.07; predicted 2.16 l (1.67-2.66)]. FEV1 was 66% (49-88%) of predicted value. The patients showed a >10% increase of FEV1 15 min after inhalation of 0.2 mg salbutamol, and also 30 min after inhalation of 6.0 mg zardaverine. The reversibility tests were performed on two separate days. In the case of salbutamol, FEV1 was 1.84 l (1.17-2.38, median and 68% central range) before drug inhalation and 2.26 l (1.50-2.69) after inhalation of the drug. In the case of zardaverine, FEV1 was 1.76 l (1.25-2.45) before and 2.01 l (1.38-2.85) after inhalation of the drug. In this pre-study screening, the response to placebo-inhalers was not studied. The mean age of the 10 patients was 62 years (range 50-74 years); mean body weight was 78 kg (range 59-910 kg) and mean height was 173 cm (157-190 cm) (individual data not shown). None of the patients received any concomitant anti-obstructive medication during the duration of the study.

Received 17 August 1994 and accepted in revised form 3 December 1994.

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The study was conducted as a placebo-controlled, double-blind, randomized five-period change-over study. One of the three doses of zardaverine, salbutamol or placebo was administered on five separate study days. The patients were randomly assigned to one of five treatment sequences occurring in a Latin square. The study medication was administered by three single puffs from a metered dose inhaler (MDI) using a spacer device (Volumatic®). Administered dosages were 1.5 mg, 3.0 mg and 6.0 mg zardaverine, and 0.3 mg salbutamol. The study medication for each treatment period was provided in MDIs of identical appearance. Before and after inhalation of the study medication, lung function was recorded at 10-min intervals during the first hour and at 30-min intervals during the next 3 h. Resting electrocardiographic function (ECG) was recorded and routine laboratory work up was carried out before and after the treatment period.

**STATISTICAL ANALYSIS**

The primary lung function parameter for the interference statistical analysis was FEV₁, time-averaged between 10–240 min after administration of the respective treatment. For each individual, the differences between verum and placebo were calculated for each time period. The time-averaged difference between verum and placebo over the 4-h dose interval was used to characterize the average effect over the dose interval. In addition, the respective values time-averaged over the first hour after drug inhalation were calculated. The ‘maximum effect’ within the interval of measurements was defined as the time-averaged value of three differences prior to, during and after the observed maximum difference. Duration and intensity of the ‘maximum effect’ were documented. The duration of action defined by a 10% increase in FEV₁ was evaluated throughout the interval, beginning with the first inhalation and ending 240 min later. ‘Maximum effect’ and duration of effect were considered as secondary characteristics with respect to FEV₁.

In order to test for a monotone dose–response relationship, the distribution-free Page test (6) was applied to the placebo dose and the three zardaverine doses in the case of the time-averaged FEV₁, and to the three zardaverine doses in the case of the placebo-adjusted ‘maximum effect’ and duration of effect. The significance level of 5% (one-sided) was considered as relevant. Descriptive analysis included median and 68% central range.

**Results**

Figure 1 shows the FEV₁ profile after administration of the study medication. Inhalation of salbutamol resulted in a clinically significant increase in FEV₁. In contrast, the FEV₁ values after inhalation of different doses of zardaverine were not statistically significant from the placebo response (P>0.05).

With respect to the time period of 10–240 min, the time-averaged FEV₁ difference between salbutamol and placebo was 0.29 1 (Table 1). The corresponding value for the first study hour was 0.33 1. In contrast, neither a statistically significant increase of FEV₁ (time-averaged 10–240 min and 10–60 min, respectively) after administration of zardaverine was observed (P>0.05), nor was a dose-dependency for zardaverine detected (P>0.05, Table 1).

The maximum increase in FEV₁ compared to placebo was observed after inhalation of 3.0 mg zardaverine, and amounted to 0.17 1 (Table 2). Again, this effect of zardaverine was not dose-related (P>0.05). In contrast, inhalation of 0.3 mg salbutamol resulted in a maximum increase in FEV₁ of 0.47 1 at 40 min. This effect of salbutamol lasted up to approximately 3 h. The duration of the non-significant increase in FEV₁ after administration of 1.5 mg, 3.0 mg or 6.0 mg zardaverine, respectively, was less than 1 h (Table 2).

Unwanted effects of zardaverine, for instance on the central nervous system, were not observed in this short-term study. There was neither a change in any of the standard laboratory parameters nor in the ECG (data not shown).

**Discussion**

Clinical experience with the use of isozyme selective phosphodiesterase inhibitors for the treatment of obstructive disease is limited. The results with the
Table 1 Mesors of differences in FEV₁ between active substance and placebo after inhalation of study medication

<table>
<thead>
<tr>
<th>Variable</th>
<th>FEV₁ (l) 10–240 min</th>
<th>FEV₁ (l) 10–60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg zardaverine</td>
<td>0.018 (-0.17-0.138)</td>
<td>0.041 (-0.145-0.334)</td>
</tr>
<tr>
<td>3.0 mg zardaverine</td>
<td>0.058 (-0.725-0.184)</td>
<td>0.074 (-0.161-0.169)</td>
</tr>
<tr>
<td>6.0 mg zardaverine</td>
<td>0.020 (-0.099-0.100)</td>
<td>-0.028 (-0.233-0.117)</td>
</tr>
<tr>
<td>0.3 mg salbutamol</td>
<td>0.285 (0.041-0.460)</td>
<td>0.329 (0.069-0.472)</td>
</tr>
</tbody>
</table>

Data are presented as median and 68% range in parentheses (n=10).

Table 2 Maximum increase in FEV₁ between active substance and placebo, time of occurrence and duration of increase by at least 10% compared to placebo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Maximum increase FEV₁ (l)</th>
<th>Time of occurrence (min)</th>
<th>Duration of increase (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mg zardaverine</td>
<td>0.138 (-0.085-0.440)</td>
<td>50 (20-210)</td>
<td>15 (0-101)</td>
</tr>
<tr>
<td>3.0 mg zardaverine</td>
<td>0.166 (-0.065-0.323)</td>
<td>150 (60-210)</td>
<td>58 (0-92)</td>
</tr>
<tr>
<td>6.0 mg zardaverine</td>
<td>0.090 (-0.025-0.213)</td>
<td>150 (60-210)</td>
<td>20 (0-102)</td>
</tr>
<tr>
<td>0.3 mg salbutamol</td>
<td>0.470 (0.163-0.673)</td>
<td>40 (30-150)</td>
<td>166 (48-230)</td>
</tr>
</tbody>
</table>

Data are presented as median and 68% range in parentheses (n=10).

PDE V inhibitor zaprinast, the PDE III inhibitor enoximone, and the PDE III/IV inhibitor AH 21-132 were at least partially equivocal (8-10).

Based on the IC₅₀ values (concentration required for half maximum inhibition) for inhibition of selective PDE isozymes, zardaverine shows more than 100-fold selectively for PDE III and PDE IV (3). Bronchodilation was demonstrated in vitro as well as in vivo in anaesthetized and conscious guinea pigs and in allergic sheep (3,4). Animal experiments suggest that, compared to theophylline, the bronchodilatory effect of zardaverine is more pronounced (11). In addition, an anti-inflammatory potential of zardaverine has been demonstrated in vivo by the inhibition of bronchial cell infiltration following allergen challenge in sensitized guinea pigs (5).

The aim of the present study was to investigate the bronchodilating efficacy of inhaled zardaverine in patients with chronic airflow obstruction, which was partially reversible after inhalation of a bronchodilator. The results of the study clearly demonstrated that inhaled zardaverine, at doses up to 6.0 mg, in the double-blind part of the trial did not have a significant bronchodilatory effect. This contrasts with the pre-study reversibility test, in which a significant increase in FEV₁, 30 min after inhalation of 6.0 mg zardaverine was observed. However, the time-averaged difference between the different doses of zardaverine and placebo over the 4-h study interval was neither clinically nor statistically significant. In contrast, inhaled salbutamol induced a significant bronchodilation in these patients. This emphasizes that to study the bronchodilating efficacy of a potentially weak bronchodilator, particularly in patients with only partially reversible airflow obstruction, it is necessary to look for time-averaged changes in lung function parameters rather than to concentrate on measurements at one single time point.

A more pronounced bronchodilatory effect of zardaverine was observed in patients with a higher degree of reversibility of their airflow obstruction, after inhalation of a β-sympathomimetic. For instance, in a study of allergic asthmatics, a modest and short-lasting bronchodilatation was observed after inhalation of 6.0 mg zardaverine (12). In another study, zardaverine significantly improved pulmonary function during the first hour of repeated inhalation (up to a total dose of 6.0 mg) (6). Again, the overall duration of bronchodilation was rather short and varied considerably between individual patients (6).

The results from the present study, together with those from the two studies in asthmatics, clearly indicate that zardaverine is, at most, a weak bronchodilator with a very limited duration of action. Obviously, the studies reported in man do not correlate with the promising findings in animal experiments. The most likely explanation for this
discrepancy is a very rapid clearance of inhaled zardaverine from the bronchial system (13). Another PDE III/IV inhibitor, the naphthyridine derivative B9004-70, has a much longer duration of action than zardaverine in animal experiments, and is currently under clinical investigation (13).

References