The muscarinic M1-receptor-selective antagonist, telenzepine, had no bronchodilatory effects in COPD patients

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ABSTRACT: In a double-blind, placebo-controlled, randomized, cross-over trial, we studied the effects of the muscarinic M1-receptor-selective antagonist (±)-telenzepine (3 mg orally at 6 p.m. for 5 days) in 21 patients with chronic obstructive pulmonary disease (COPD). At enrolment all patients showed at least a 50% decrease in airway resistance (Raw) after inhalation of 400 µg fenoterol or 200 µg oxitropium bromide. Telenzepine did not have a significant effect on forced expiratory volume in one second (FEV1) or forced vital capacity (FVC). Also, no significant changes could be detected in daily spirometric profiles or Raw.

The results indicate that short-term treatment with the M1-selective antagonist, telenzepine, does not improve airway function in COPD patients, at least after administration by the oral route.

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In patients with chronic obstructive pulmonary disease (COPD), cholinergic tone is often the only reversible component [1-3]. Ipratropium bromide has been shown to be a potent bronchodilator in both chronic bronchitis and emphysema, being as effective as, or even superior to, β2-sympathomimetics in many patients [4].

There is now abundant evidence, that several muscarinic receptor subtypes exist [5, 6]. Although five receptor subtypes have been cloned [7, 8], only three subtypes can be differentiated pharmacologically [6, 9-12]. The differentiation of muscarinic receptor into subtypes may have clinical relevance, as the receptor subtypes will have different function, and the development of selective drugs may, therefore, be of clinical benefit in the treatment of airway disease [13]. Drugs such as atropine, ipratropium bromide, and oxitropium bromide are non-selective anticholinergic drugs, blocking M1-3 receptors with equal affinity.

It has been shown that vagally-mediated bronchconstriction in asthmatic patients can be inhibited by blockade of pirenzepine-sensitive muscarinic receptors, presumably localized in parasympathetic ganglia [14]. Another M1-receptor selective antagonist, telenzepine, has recently been considered for the treatment of peptic ulcers [15]. The selectivity of telenzepine for the different muscarinic receptor subtypes is comparable to that of pirenzepine, but it is at least 10 times more potent [16]. In guinea-pigs, telenzepine exerts potent bronchodilatory effects [17]. In patients with chronic obstructive bronchitis, administration of a single, oral dose of 5 mg telenzepine led to a substantial improvement in lung function [18]. The aim of the present study was to investigate the effect of five days of treatment, with 3 mg·day⁻¹ telenzepine, on airway function in patients with COPD.

Methods

Subjects

Three female and 18 male patients with the diagnosis of COPD (of at least 3 yrs duration) participated in the study. None of the patients had a history of asthma. All were ex-smokers. The protocol of the study was approved by the local Ethics Committee and written informed consent was obtained from all patients. The mean age of the patients was 63 yrs (range 46-74 yrs); the median body weight was 66 kg (range 53-89 kg); and the mean height was 167 cm (range 157-183 cm).

Only patients with at least 50% reduction in airflow resistance (Raw), either 15 min after inhalation of 400 µg fenoterol, or 60 min after inhalation of 200 µg oxitropium bromide were enrolled. Apart from the study medication, only inhaled β2-sympathomimetics were accepted for the treatment of airways obstruction, during the period of the study. Eight patients took either fenoterol (4×400 µg·day⁻¹) or salbutamol (4×200 µg·day⁻¹) administered by metered dose inhaler.
From a total of 53 patients with COPD, 21 patients showed at least a 50% decrease in Raw after inhalation of either fenoterol or oxitropium bromide and were enrolled in the study. Fourteen patients showed at least a 50% decrease in Raw after inhalation of fenoterol, 11 patients after inhalation of oxitropium bromide, and 7 patients showed this response after inhalation of either drug. The median decrease of Raw in all patients was 50% after inhalation of both fenoterol (range -17 to -75%) and oxitropium (range -62 to 36%). The median increase in forced expiratory volume in one second (FEV1) was 14% (range -21 to 113%) after administration of fenoterol, and 15% (range -5 to 26%) after administration of oxitropium (individual data not shown).

### Design

The study was conducted as a placebo-controlled, double-blind, randomized, cross-over trial. After a 3 day prestudy period, the 21 patients received either (±) telenzepine (3 mg of the racemic mixture) or placebo, for 5 days. The treatment periods were separated by at least 3 days of wash-out. Drugs were supplied as film-coated tablets of identical appearance. One tablet was taken with 100 ml of water at 6 p.m. After drug intake on treatment day 5, spirometry was carried out at different time points during the following 24 h periods: 6 p.m., 8 p.m., 10 p.m., 6 a.m., 10 a.m., 2 p.m. and 6 p.m. At 8 a.m. on the first treatment day and at 8 a.m. on the day following the last treatment day (i.e., 14 h after the last drug intake) airway function was determined by whole body plethysmography (Siemens FD 90S). Resting electrocardiographic function (ECG) was recorded before and after each treatment period. Arterial blood pressure and heart rate were measured daily at 8 a.m. Standard hematological and clinical laboratory tests were performed to evaluate compound safety.

### Results

Table 1 summarizes the values for Raw. Ten patients took telenzepine in the first treatment period, and 11 patients in the second period. Again, telenzepine did not have any effect on Raw after 5 days of treatment (p>0.05).

Figure 1 shows the mean spirometric profile, obtained during the 24 h period following the last drug intake. As shown for FEV1 and PEF, the curves for telenzepine and placebo treatment were nearly superimposed upon each other. Statistical analysis of time-averaged values for FVC, FEV1, and PEF showed no significant difference between telenzepine and placebo treatment (p>0.05; data not shown). According to the cross-over analysis, no significant carry over or period effects were observed.

### Table 1. - Airway function in COPD patients (n=21)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before</th>
<th>After</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC l</td>
<td>2.64 (1.70-3.57)</td>
<td>2.97 (1.77-3.81)</td>
<td>3.04 (1.85-3.53)</td>
<td>2.79 (1.73-3.79)</td>
</tr>
<tr>
<td>% pred</td>
<td>62 (56-74)</td>
<td>72 (57-83)</td>
<td>70 (56-78)</td>
<td>69 (53-81)</td>
</tr>
<tr>
<td>FEV1 l</td>
<td>1.59 (1.16-2.08)</td>
<td>1.74 (1.25-2.20)</td>
<td>1.85 (1.13-2.14)</td>
<td>1.64 (1.06-2.20)</td>
</tr>
<tr>
<td>% pred</td>
<td>58 (34-73)</td>
<td>63 (48-71)</td>
<td>58 (37-73)</td>
<td>57 (38-70)</td>
</tr>
<tr>
<td>PEF l/s²</td>
<td>4.5 (3.3-6.8)</td>
<td>5.0 (3.4-7.0)</td>
<td>4.5 (3.5-6.7)</td>
<td>4.8 (3.4-6.2)</td>
</tr>
<tr>
<td>% pred</td>
<td>53 (35-76)</td>
<td>60 (42-76)</td>
<td>61 (40-75)</td>
<td>55 (41-71)</td>
</tr>
<tr>
<td>PEF 50 l/s</td>
<td>1.1 (0.6-1.5)</td>
<td>0.9 (0.5-1.4)</td>
<td>1.1 (0.6-1.5)</td>
<td>1.0 (0.6-1.4)</td>
</tr>
<tr>
<td>% pred</td>
<td>43 (25-73)</td>
<td>43 (21-64)</td>
<td>43 (32-67)</td>
<td>45 (25-65)</td>
</tr>
<tr>
<td>RV l</td>
<td>2.98 (2.54-4.69)</td>
<td>3.31 (2.21-4.36)</td>
<td>3.37 (2.29-4.21)</td>
<td>3.49 (2.51-4.41)</td>
</tr>
<tr>
<td>% pred</td>
<td>177 (162-223)</td>
<td>193 (138-235)</td>
<td>184 (152-229)</td>
<td>201 (155-233)</td>
</tr>
<tr>
<td>RV/TLC %</td>
<td>51 (45-62)</td>
<td>48 (44-60)</td>
<td>49 (44-59)</td>
<td>52 (44-62)</td>
</tr>
<tr>
<td>pred</td>
<td>30 (28-33)</td>
<td>30 (28-33)</td>
<td>30 (28-33)</td>
<td>30 (28-33)</td>
</tr>
</tbody>
</table>

Data are presented as median plus 68% range in parenthesis. FVC: forced vital capacity; FEV1: forced expiratory volume in one second; PEF: peak expiratory flow; PEF 50: forced expiratory flow at 50% vital capacity; RV: residual volume; TLC: total lung capacity; COPD: chronic obstructed pulmonary disease; % pred: percentage predicted.

### Statistical analysis

For the interference statistical analysis, FEV1, peak expiratory flow (PEF), forced expiratory flow at 50% vital capacity (FEF 50), forced vital capacity (FVC), and Raw were considered as key parameters of airway function. In case of FEV1, PEF, FEF 50 and FVC, the time-averaged values over 24 h (mesors) after drug intake were compared by means of the distribution-free, cross-over analysis [19]. In the case of Raw, the changes versus baseline were compared. Descriptive analysis included median and central 68% range. Due to the multiple testing of different airway function parameters, the significance level of α=0.01 (two-sided) was considered as relevant.
The only appreciable unwanted effect observed during the study was a dry mouth in 11 patients. In those patients taking telenzepine, the serum concentration was within the expected range (data not shown). In patients with ulcer/dyspepsia, treatment with 3 mg telenzepine, administered once daily in the evening, gave similar healing rates to pirenzepine or ranitidine [23-25]. Pharmacokinetic studies in man revealed a bioavailability of about 60% after oral administration and a steady-state elimination half time of 18 h for telenzepine, which allows, therefore, a once daily dosage regimen [25].

As recently shown by autoradiography in human lung sections, muscarinic M3 receptors are located in airway ganglia, submucosal glands and alveoli [26]. The M3 selective antagonist, pirenzepine, at a dose of 10 mg i.v. induces bronchodilatation of peripheral airways in healthy subjects [27]. Functional studies presented evidence that M3 receptors may also be present in human cholinergic nerves. In atopic volunteers, inhaled pirenzepine, at a low dose, did not inhibit bronchoconstriction due to methacholine, whereas ipratropium bromide was able to block this bronchoconstrictor effect [14]. However, the same dose of pirenzepine was as effective as ipratropium in blocking reflex bronchoconstriction induced by sulphur...
dioxide, suggesting an effect on some peripheral part of the cholinergic pathway, probably the parasympathetic ganglia [14]. In support of this possibility, pirenzepine has been shown to depress parasympathetic ganglionic neurotransmission in rabbit bronchi in vitro [25]. By reducing vagal tone, M₁ antagonists may have a therapeutic role in obstructive airways diseases.

Based on these considerations and the promising pharmacological properties, the effects of telenzepine on airways function in patients with COPD were of particular interest. The compound was administered orally to patients with COPD, at a 3 mg·day⁻¹ dose, which has been proven effective in patients with peptic ulcers. With a elimination half-life of about 18 h, steady-state pharmacokinetics are thought to be reached after five repeated administrations. As shown in the present placebo-controlled, cross-over study, telenzepine did not have any beneficial effect on airway function in patients with COPD, in whom the bronchial obstruction was at least partially reversible after inhalation of a β₂-sympathomimetic or of the anticholinergic oxitropium bromide. Obviously, telenzepine did have antimuscarinic effects in these patients, since the typical symptom "dry mouth" was observed to a considerable extent. On the other hand, the unchanged cardiac parameters indicate no significant interaction of telenzepine with cardiac M₂ receptors.

After this study had been completed, a study was published presenting a remarkable improvement of airway function in COPD patients after administration of telenzepine [18]. After intake of a single dose of 5 mg telenzepine in the morning, 18 patients showed an increase (time average over 6 h) in FEV₁, from 1.46 to 1.67 l (p<0.01), and in PEF from 3.58 to 3.88 l.s⁻¹ (p<0.01) [18]. There may be two possibilities to explain the observed differences between these two studies. Firstly, the patients in the study of CAZZOLA et al. [18] showed a higher degree of reversibility in airways obstruction after inhalation of salbutamol. The median improvement of FEV₁ 15 min after inhalation of 200 μg salbutamol was 20% (range 15–74%). Secondly, CAZZOLA et al. [18] used a higher dose of telenzepine in the morning than the one used in the present study with intake in the evening. It seems likely that for blockade of vagal tone at night a higher dose of the anticholinergic is necessary. In addition, as discussed by CAZZOLA et al. [18], it is possible that telenzepine, at a dose of 5 mg, does have direct effects on muscarinic M₁ receptors on smooth muscle. However, based on the experiences in the present study and in earlier studies in patients with ulcer/dyspepsia, with respect to adverse events, 3 mg telenzepine appears to be the maximally tolerable daily dose.

Possible explanations for the missing effects of telenzepine in the present study are: firstly, that blockade of M₁ receptors on human cholinergic nerves is insufficient to reduce vagal tone; and secondly, that at a dose of 3 mg telenzepine·day⁻¹, a sufficient M₁ blockade in the airways of patients was not achieved. The physiological role of M₁ receptors in autonomic ganglia is still uncertain.

However, since inhaled pirenzepine, which shows a similar degree of receptor subtype selectivity to telenzepine, showed a distinct bronchodilatory effect after SO₂-provocation in atopic volunteers [14], the main cause for the negative results in the present study may indeed be due to an insufficient effect of orally-administered telenzepine in human airways in vivo.

From the present study, one can thus draw conclusions for further drug development. Since the (+)-enantiomer of telenzepine is responsible for the pharmacological effects of the drug [17, 22], only this isomer and not the racemic mixture should be evaluated in further studies. In order to achieve higher concentrations in the bronchial system, the inhalative administration of the drug would be of advantage.

References

19. Koch GG. — The use of nonparametric methods in the