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The muscarinic M_1-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 M_1-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 (FEV_1) 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 M_1-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, β_2-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 M_{1-3} receptors with equal affinity.

It has been shown that vagally-mediated bronchoconstriction in asthmatic patients can be inhibited by blockade of pirenzepine-sensitive muscarinic receptors, presumably localized in parasympathetic ganglia [14]. Another M_1-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 $mg \cdot day^{-1}$ 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 airway 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 β_2-sympathomimetics were accepted for the treatment of airways obstruction, during the period of the study. Eight patients took either fenoterol (4×400 $\mu g \cdot day^{-1}$) or salbutamol (4×200 $\mu g \cdot day^{-1}$) 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 (FEV_1) 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 electro- cardiographic function (ECG) was recorded before and after each treatment period. Arterial blood pressure and heart rate were measured daily at 8 a.m. Standard haematological and clinical laboratory tests were performed to evaluate compound safety.

Statistical analysis

For the interference statistical analysis, FEV_1, 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 FEV_1, 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.

Results

Median values of airway function after treatment with telenzepine and placebo, are summarized in table 1. Treatment with 3 mg telenzepine for 5 days did not cause any significant change of any parameter ($p>0.05$), nor was a significant difference between telenzepine and placebo observed ($p>0.05$).

Table 2 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 FEV_1 and PEF, the curves for telenzepine and placebo treatment were nearly superimposed upon each other. Statistical analysis of time-averaged values for FVC, FEV_1, and FEF_{50} did not reveal any 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)

	Telenzepine		Placebo	
Parameter	Before	After	Before	After
FVC *l*	2.64 (1.70–3.57)	2.97 (1.77–3.81)	3.04 (1.85–3.53)	2.79 (1.73–3.79)
% pred	62 (56–74)	72 (57–83)	70 (56–78)	69 (53–81)
FEV_1 *l*	1.59 (1.16–2.08)	1.74 (1.25–2.20)	1.85 (1.13–2.14)	1.64 (1.06–2.20)
% pred	58 (34–73)	63 (48–71)	58 (37–73)	57 (38–70)
PEF $l \cdot s^{-1}$	4.5 (3.3–6.8)	5.0 (3.4–7.0)	4.5 (3.5–6.7)	4.8 (3.4–6.2)
% pred	53 (35–76)	60 (42–76)	61 (40–75)	55 (41–71)
FEF_{50} $l \cdot s^{-1}$	1.1 (0.6–1.5)	0.9 (0.5–1.4)	1.1 (0.6–1.5)	1.0 (0.6–1.4)
% pred	43 (25–73)	43 (21–64)	43 (32–67)	45 (25–65)
RV *l*	2.98 (2.54–4.69)	3.31 (2.21–4.36)	3.37 (2.29–4.21)	3.49 (2.51–4.41)
% pred	177 (162–223)	193 (138–235)	184 (152–229)	201 (155–233)
RV/TLC %	51 (45–62)	48 (44–60)	49 (44–59)	52 (44–62)
pred	30 (28–33)	30 (28–33)		

Data are presented as median plus 68% range in parenthesis. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow; FEF_{50}: forced expiratory flow at 50% vital capacity; RV: residual volume; TLC: total lung capacity; COPD: chronic obstructed pulmonary disease; % pred: percentage predicted.

Table 2. – Airway resistance (kPa·l $^{-1}$·s) during telenzepine and placebo periods

Sequence	Pts n	1st period Run-in	1st period Treatment	2nd period Wash-out	2nd period Treatment
Tel/Pla	10	0.39±0.12	0.39±0.08	0.38±0.08	0.41±0.13
Pla/Tel	11	0.47±0.25	0.45±0.18	0.49±0.19	0.49±0.20

Data are presented as mean±SD. Tel: telenzepine; Pla: placebo.

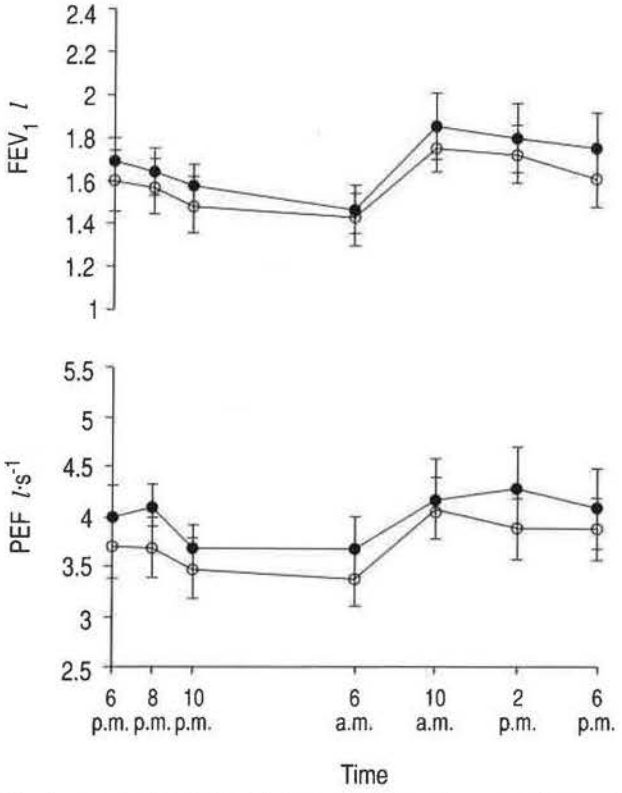

Fig. 1. – Patients' (n=21) data are presented as mean±SEM of spirometric profiles on day 5/6, after repeated dosing of either 3 mg telenzepine (●), or placebo (○), at 6 p.m. Telenzepine had no significant effect on either PEF or FEV_1. Note that ordinate axis does not extend to zero. PEF: peak expiratory flow; FEV_1: forced expiratory volume in one second.

Further explorative subgroup analysis showed that even in those patients in whom FEV_1 increased more than 10% after administration of either fenoterol or oxitropium bromide, telenzepine did not have any bronchodilatory effect (data not shown). In order to study the compliance of the patients, on day 6 blood was taken for drug monitoring in 10 patients. In those patients taking telenzepine, the serum concentration was within the expected range (data not shown).

The only appreciable unwanted effect observed during the study was a dry mouth in 11 patients. In nine cases, this symptom could be related to telenzepine intake, whereas in two cases it was observed during placebo intake. The adverse effect appeared within 2–3 h after drug intake, its degree was mild, except in one case, and it persisted during the whole treatment period. The symptom disappeared within 24 h after the last administration. One patient in the telenzepine-treated group and one patient in the placebo-treated group complained about transient headache. Otherwise, telenzepine proved to be well-tolerated and safe. There was no change in any of the standard laboratory parameters studied (data not shown). Telenzepine did not affect arterial blood pressure, heart rate, or ECG (data not shown).

Discussion

Telenzepine is a competitive muscarinic receptor antagonist. It exists as a mixture of two enantiomers. As shown in animal experiments, the affinity (pA_2) of (±)telenzepine for ganglionic-like M_1 receptors of rabbit vas deferens is 8.86, for M_2 receptors of rat left atrium 7.32, and for M_3 receptors of guinea-pig tracheal smooth muscle 7.77 [17]. In animals, the affinity of the compound for M_1 receptors is, therefore, approximately 10 times higher than that for M_3 receptors, and approximately 20 times higher than that for M_2 receptors. Due to its potency and selectivity, telenzepine in its tritiated form proved to be a suitable radioligand for M_1 receptors [20]. As shown in radioligand binding studies with brain cortex membranes from calf, telenzepine dissociates much slower (half time ($t_{1/2}$) 35 min at 37°C) from M_1 receptors than pirenzepine ($t_{1/2}$ 2.3 min) [21]. This difference has been confirmed in functional studies [22]. Due to the slow binding kinetics, telenzepine may be particularly effective in reducing vagal tone for a prolonged period.

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 M_1 receptors are located in airway ganglia, submucosal glands and alveoli [26]. The M_1 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 M_1 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* [28]. By reducing vagal tone, M_1 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 β_2-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 M_2 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 FEV_1 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 FEV_1 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 M_3 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 M_1 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 M_1 blockade in the airways of patients was not achieved. The physiological role of M_1 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 SO_2 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.

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