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Comparison of the effect of oxitropium bromide and of slow-release theophylline on nocturnal asthma

V. Bellia, G. Ferrara, F. Cibella, G. Cuttitta, A. Visconti, G. Insalaco, M. Mirto and G. Peralta

Istituto di Pneumologia dell'Università, Istituto di Fisiopatologia Respiratoria del C.N.R., Palermo, Italy.

Summary: The effects of a new inhaled antimuscarinic drug, oxitropium bromide, and of a slow-release theophylline preparation upon nocturnal asthma were compared in a placebo-controlled double-blind study. Two samples were studied: 12 patients received oxitropium at 600 μg (6 subjects) or at 400 μg t.i.d. (6 subjects) whereas 11 received theophylline at 300 mg b.i.d. Morning dipping, assessed by the fall in peak flow overnight, was significantly reduced in the periods when either active drug was taken, whereas no difference was noticed during the placebo administration. No significant difference was noticed between results obtained with either active drug, as well as with either dosage of oxitropium. No subject reported side effects of oxitropium, as compared to three subjects reporting nausea, vomiting and tremors after theophylline.

Oxitropium proves to be a valuable alternative to theophylline in nocturnal asthma, since it is equally potent, safer and does not require the titration of dosage.

Introduction

Nocturnal recurrence of attacks is a very common phenomenon among asthmatic subjects:[1] its importance is related both to the resulting respiratory distress and to the possible unfavourable prognostic implications.[2,3] The treatment of nocturnal asthma is mainly based upon slow-release theophylline preparations;[4] however, there is some concern about the narrow therapeutic index of these drugs and the effects of physiological variables upon their kinetics: therefore a careful titration of the dosage is highly advisable in each patient.

Based upon some evidence of the role of vagal activity in producing nocturnal bronchoconstriction,[5,6] some investigations have been recently carried out in order to evaluate the protective effect of antimuscarinic inhaled agents: both ipratropium bromide[7] and a longer acting derivative, oxitropium bromide,[8] proved effective in protecting at least some 'responsive' patients.

The present investigation was aimed at comparing oxitropium bromide with the more conventional slow-release theophylline. In addition, since the effect of the antimuscarinic agent has been found to be dose-related,[8] we evaluated also whether definitely high doses might be more effective than those used in this investigation.[8]

Correspondence: Professor V. Bellia M.D., Istituto di Pneumologia, Via Trabucco 180, 90146 Palermo, Italy.
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Materials and methods

Patients

Twenty-four asthmatic out-patients (13 males, 11 females) aged 18–60 years were selected on the basis of the following criteria: history of bronchial asthma as defined by the ACCP-ATS Joint Committee on Pulmonary Nomenclature;[9] recent history of nocturnal asthma, defined as recurrent awakening with wheezing and breathlessness at night;[10] early morning falls (morning dips) of peak expiratory flow (PEF) greater than 20% of the highest maximum daily value for at least 7 consecutive days preceding the study. Exclusion criteria were cardiovascular, ocular, genitourinary disease and a history of intolerance to theophylline or antimuscarinic agents.

Beta-stimulant drugs and corticosteroids were not administered throughout the study, whereas sodium cromoglycate was allowed, provided that no change in the administration regimen was introduced from the cited 7-day screening period till the end of the study.

Treatments

The following pharmaceutical preparations were used: (1) oxitropium bromide by metered aerosol

delivering 100 μg per puff; (2) placebo of oxitropium by metered aerosol; (3) slow-release anhydrous theophylline in 300 mg tablets; (4) placebo of theophylline in tablets.

Protocol

After the early run-in period, given the informed consent, subjects were randomly allocated to one of four treatment groups (Figure 1) so that on a double-blind basis everyone was tested with a single drug: in fact each subject alternated one of the active drugs (oral or inhaled) for one week and the relevant placebo for the other week, whereas the placebo of the other type of drug was administered throughout the whole 2-week period. The standard regimen for all the series was one tablet b.i.d. for the oral preparations; for the inhaled preparations, in order to allow a comparison between a medium and a high dosage, 12 randomly selected patients were instructed to inhale 4 puffs t.i.d., whereas the remaining 12 inhaled 6 puffs t.i.d.; in all cases the last daily dose was taken at bedtime, after performing the evening measurement of PEF (see below).

All subjects were recommended to keep a regular daily schedule of diurnal activity and nocturnal rest. They were instructed to record PEF four times daily (on waking, at lunch time, in the afternoon and at bedtime): on each occasion they made the measurement in triplicate and recorded the highest value on a diary chart. On the same chart they reported respiratory symptoms occurring at night or in the early morning (chest tightness, cough and wheeze), as well as any untoward effect possibly related to treatments.

At the end of each week of treatment, patients were submitted to clinical and functional assessment (forced expiratory volume in one second, FEV_1), as well as to the measurement of the trough theophylline concentration (nephelometry, ICS, Beckman).

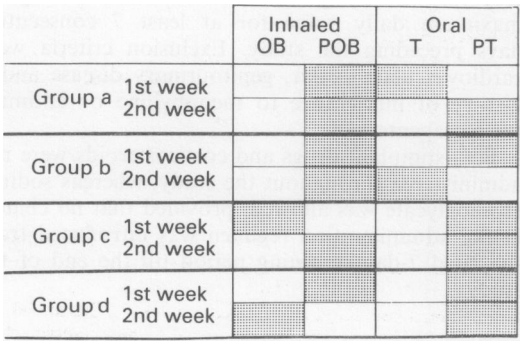

Figure 1 Schematic diagram of the protocol of administration of drugs. OB: oxitropium bromide; POB: placebo of oxitropium bromide; T: theophylline; PT: placebo of theophylline.

Evaluation of results

The effects of treatments were evaluated by measuring the morning to maximum PEF ratio of the last 5 days of each week of treatment, since the early 2 days were assumed as accounting for the wash-in/wash-out period for any treatment. Statistical analysis was performed by Student's '*t*' test for paired or unpaired data as applicable to various circumstances.

Results

Since one patient of Group b withdrew because of nausea and vomiting, the results of 23 patients were examined: 12 had been submitted to administration of oxitropium (6 at 400 μg t.i.d. and 6 at 600 μg t.i.d.), whereas 11 had been on theophylline. In the latter patients, trough theophylline concentrations were within the therapeutic range (9.9 to 13.7 mg/l). No significant difference was recorded for FEV_1 between the two samples at the beginning of the study (81.1% predicted ±18.7 for oxitropium and 81.7% predicted ±12.1 for theophylline) and the mean morning dip of PEF over the run-in period (respectively 35.7% predicted ±12.1 and 37.3% predicted ±16.4).

After both treatments (Figure 2) a significant decrease in morning dip was recorded in all patients; in fact in 9/12 of the oxitropium group (4 in the 600 μg subgroup and 5 in that submitted to the lower dose regimen) and 8/11 of the theophylline group the index fell below the 20% threshold. Similar results were obtained for FEV_1 (Figure 3).

No significant difference between results obtained with either active drug, as well as with either

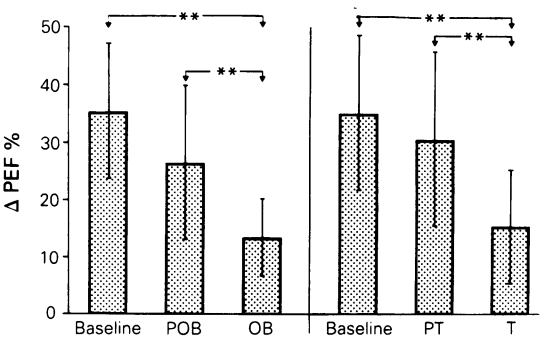

Figure 2 Effects of different treatments upon morning dip of PEF (ΔPEF). For abbreviations see **Figure 1**. $^{**}P<0.01$.

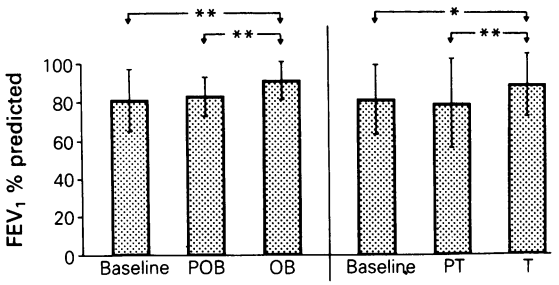

Figure 3 Effects of different treatments upon FEV_1. For abbreviations see **Figure 1**. $*P<0.05$; $**P<0.01$.

dosage of oxitropium was noticed. Finally, no significant difference between baseline values and the results of both placebos was found.

All subjects reported a subjective improvement when submitted to the active drug, as expressed by a reduction of events of nocturnal awakening with symptoms and by the disappearance of chest tightness in the early morning.

No significant side effects from oxitropium were recorded, whereas in three cases submitted to theophylline, nausea, vomiting and tremors were noticed.

Discussion

Oxitropium bromide has been demonstrated to be a long-acting antimuscarinic bronchodilator: in fact its effects have been reported as still significant 10 hours after inhalation.[11,12] The results of the present investigation suggest that because of this characteristic it proves as effective as theophylline in preventing nocturnal asthma but with fewer side effects and without any need for titrating the dose in each patient.

The high therapeutic ratio of the antimuscarinic agent is further confirmed by the use of a definitely high dose (i.e., 600 μg), which proves to be as safe as the 400 μg one: the comparable effects of the two dosages upon morning dip, if analysed along with the results of Coe and Barnes,[8] concerning the use of 200 and 400 μg, allow one to conclude that 400 μg may be regarded as the optimal dose in the specific setting of nocturnal asthma and that further increases in dosage, though apparently safe, are not warranted by any further gain in therapeutic effect.

Unlike the previous investigation,[8] no patient was found to be a non-responder to therapy, since the decrease in morning dip was significant in all patients, including those 3/12 in whom the index did not fall below the 20% threshold, commonly considered as associated with nocturnal asthma. Anyway a comparable proportion of subjects on theophylline showed a similar behaviour, thus once more confirming the similar spectrum of the two drugs.

Since no apparent difference in clinical characteristics of samples may be pointed out, this difference with respect to the previous investigation[8] may be interpreted as due to the fact that in the previous study patients were given a single dose at night, whereas in our investigation they were submitted to regular administration throughout the day: on this basis it is possible that a more effective control of vagal activity was obtained, decreasing the baseline vagal tone and thus further reducing the effects of variations in vagal drive or in vagal efferent activities occurring during the night.

Though grounded on physiological as well as on experimental evidence, the use of inhaled anticholinergic drugs has not yet gained a wide acceptance, probably because of prejudice derived from the early experiences with atropine compounds. The results of the present investigation warrant a preliminary therapeutic challenge with these drugs in all patients affected by nocturnal asthma. With the exception of definite contraindications, the use of oxitropium bromide may prove safer than that of theophylline and at least equally effective.

Acknowledgement

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