

Salmeterol versus slow-release theophylline combined with ketotifen in nocturnal asthma: a multicentre trial

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Salmeterol versus slow-release theophylline combined with ketotifen in nocturnal asthma: a multicentre trial. J.F. Muir, L. Bertin, D. Georges, French Multicentre Study Group.

ABSTRACT: We wished to assess the efficacy of inhaled salmeterol (SML; 50 µg *b.i.d.*) compared to a combination of slow-release theophylline and ketotifen *p.o.* (TK; T 300 mg + K 1 mg *b.i.d.*) for the treatment of nocturnal asthma. Ninety six patients with nocturnal asthma, (forced expiratory volume in one second (FEV₁) 60–90% of predicted value, reversibility ≥15%, at least two nocturnal awakenings per week) were eligible for a multicentre, double-blind, double-dummy cross-over study (14-day run-in, two successive 28-day treatment periods). Efficacy was assessed as success/failure, success being defined as the complete disappearance of nocturnal symptoms/awakenings during the last week of each treatment period.

There was a statistically significant difference between SML and TK for this criterion: 46% and 39% success with SML during periods I (first 28-day period) and II (following the cross-over), compared to only 15% and 26% with TK, respectively ($p < 0.01$). SML was also significantly better for the other criteria (lung function, rescue salbutamol intake during day and night). Side-effects were five times less frequent in SML-treated patients ($p < 0.004$).

Efficacy and tolerance of SML were obviously far better than those of TK in patients with nocturnal asthma.

Eur Respir J, 1992, 5, 1197–1200.

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Keywords: ketotifen
nocturnal asthma
salmeterol
theophylline

Received: January 30 1992
Accepted after revision August 2 1992

Nocturnal asthma, *i.e.* awakening due to coughing, wheezing or breathlessness, is quite common, as more than 70% of asthmatic patients suffer from sleep disturbances related to this condition [1]. The period of greatest vulnerability is around 4 a.m. [2], which accounts for the lack of efficacy of conventional inhaled, short-acting bronchodilators in this indication. Sustained-release theophylline is currently used in patients with nocturnal asthma and some studies have shown that this drug could control nocturnal symptoms and improve airflow during the early hours of the morning [3–5]. However, quality of sleep, defined by electroencephalography, might be impaired by theophylline [6] and some trials have failed to show any improvement of sleep in patients treated with slow-release theophylline [7]. The bronchodilating action of theophylline is potentiated by ketotifen [8], whilst some papers indicate a mutual attenuation of the central nervous system (CNS) effects of ketotifen and theophylline at therapeutic doses [9]. Salmeterol is a new long-acting β_2 -agonist efficacy of which in nocturnal asthma, has been established in a placebo-controlled trial [10]. The present study was designed to assess the efficacy and tolerance of inhaled salmeterol compared to a combination of slow-release

theophylline with ketotifen for the treatment of nocturnal asthma and the improvement of sleep, in adult patients.

Patients and methods

Patients

One hundred and fifteen patients were screened and ninety six (47 males) were eligible for this multicentre (30 centres), double-blind, double dummy, cross-over study, with a 14-day run-in period and two successive 28 day treatment periods. The patients were aged 17–70 yrs (mean \pm SD: 42 \pm 13 yrs) and weighed 45–80 kg (mean: 65 \pm 10 kg). They were suffering from chronic asthma (forced expiratory volume in one second (FEV₁) 60–90% of predicted value, reversibility ≥15% after 200 µg inhaled salbutamol), with at least two nocturnal awakenings per week due to coughing, wheezing or breathlessness during the 2 week run-in period. Patients with respiratory tract infection, or hospitalization due to an exacerbation of asthma within 28 days prior to the study, or with serious

non-controlled systemic disorders, or clinically significant laboratory abnormalities were not eligible. Patients treated with ketotifen within a month prior to the study, or with β -blockers, or with more than 2 mg·day⁻¹ of inhaled steroids, or oral steroids at a dosage >20 mg·day⁻¹ of prednisolone, were also not eligible. All other treatments of asthma had to be discontinued at entry into the run-in period.

This study was approved by the Ethics Committee (Rouen University Hospital). Written informed consent was obtained from all patients, who were seen as out-patients.

considered as a wash-out period. This criterion was assessed as success or failure. Success was defined as the complete disappearance of nocturnal symptoms (recorded every morning in the patient's diary card) during the last week of each treatment period. The improvement of sleep was also expressed as the percentage of awakening-free nights.

Other criteria included: 1) daily morning and evening peak expiratory flow rate (PEFR) measurements, using a Mini-Wright peak flow meter (the best of 3 measures was recorded in the patient's diary card); 2) intakes of rescue salbutamol; and

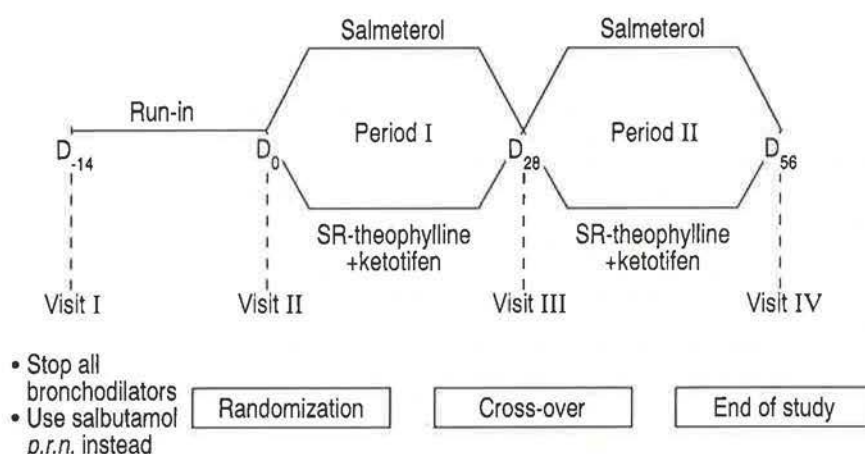


Fig. 1. — Study plan. D: day; SR: slow-release.

Treatments

The only bronchodilator treatment allowed during the 2-week run-in period was inhaled salbutamol 200 μ g *p.r.n.* Eligible patients were randomly allocated to receive, for 28 days, either salmeterol (50 μ g *b.i.d.* by metered-dose inhaler, $n=50$) and placebo tablets for slow-release theophylline and ketotifen, or slow-release theophylline (300 mg *b.i.d.*, $n=46$) combined with ketotifen (1 mg *b.i.d.*) as tablets and a placebo for salmeterol. At the end of this first period, they were crossed over to receive the other treatment for a further 28 days. The study plan is presented in figure 1. A rescue salbutamol metered-dose inhaler was provided for every patient, to be used *p.r.n.* throughout the study period. Patients were not allowed to take any other bronchodilating drugs, sodium cromoglycate or anti-histamine drugs. Exacerbations of asthma could be treated according to the investigator's choice.

Criteria of response

Efficacy was assessed in the clinic just before (D0) and at the end (D28) of each 28-day treatment period, on the improvement of sleep during the last week of each treatment period, the first 3 weeks being

3) evaluation of lung function (FEV_1 , forced vital capacity (FVC), forced mid-expiratory flow (FEF_{25-75}) on D0 and at the end of each treatment period.

Statistical methods

The sample size was determined for the main criterion with $\alpha=0.05$ and $\beta=0.20$, assuming that the frequency of successes would be 75 and 90% in the theophylline-ketotifen and salmeterol groups, respectively. The choice between a cross-over analysis or the use of an analysis appropriate for a parallel design on the first period data only, was based on the method of WILLAN and PATER [11, 12], which means that we chose the analysis with the larger corresponding test statistic. This method, recommended by JONES and KENWARD [13], keeps the risk $\alpha=5\%$ whatever the carry-over effect. Therefore, the results for the "improvement of sleep" defined as success/failure were analysed according to a cross-over design using a log-linear model for cross-over binary data [14], and the remaining criteria according to a parallel group design on the first period data. Tests for qualitative data were performed by means of the Chi-squared test. The quantitative data were compared using Student's *t*-test, if normally distributed according to Shapiro Wilk's test, and by using Wilcoxon rank-score test if

not. The significance levels of all statistical tests were corrected according to the method of WILLAN and PATER [11, 12].

Results

Comparability of treatment groups

At the time of inclusion (D0), there were no significant differences among the two groups (salmeterol first or slow-release theophylline-ketotifen first) as regards sex distribution, age, height, weight, concomitant illnesses, previous treatments and evaluation criteria. Seventy two percent of the patients were known to be atopic and 87% had positive skin tests to common allergens. A majority of patients (88%) were non-smokers. Mean (\pm SD) FEV₁ was 70 \pm 10% and 68 \pm 9% of predicted value in the salmeterol and slow-release theophylline-ketotifen groups, respectively. Sixty percent of the patients were using inhaled beclomethasone, at a mean (\pm SD) dosage of 1,000 \pm 400 μ g \cdot day⁻¹ and 9 patients were treated with oral steroids, at a mean dosage of 14 \pm 5 mg \cdot day⁻¹ of prednisolone. These treatments were continued at a constant dosage throughout the study.

Withdrawals

There were 15 withdrawals from the study during the first treatment period: 6 patients given salmeterol (3 adverse effects: bronchospasm, tachycardia, exacerbation; 2 intakes of steroids; 1 "persistence of symptoms"); and 9 on theophylline-ketotifen (5 adverse effects: 2 gastrointestinal disorders, dizziness, exacerbation, headache; 2 intakes of steroids; 1 "persistence of symptoms"; 1 lack of compliance); a diary card was missing for a patient given slow-release theophylline-ketotifen. There were 8 withdrawals during the second period: 4 patients treated with salmeterol (2 intakes of steroids; 1 exacerbation; 1 lost to follow-up); and 4 given slow-release theophylline-ketotifen (2 adverse effects: diarrhoea, drowsiness; 1 intake of steroids; 1 lost to follow-up). Therefore, the cross-over analysis was performed on the results obtained in 72 patients, and the parallel group analysis on the data from 80 patients (first treatment period).

Efficacy

The number of salmeterol and slow-release theophylline-ketotifen treated patients totally free of nocturnal symptoms during the last week of each treatment period was equal to 46 and 15% for the first period and to 39 and 26% for the second, respectively. The difference between treatment groups is highly significant ($p < 0.01$).

Salmeterol is better than slow-release theophylline-ketotifen as regards the percentage of symptom-free nights: 67 \pm 6% and 43 \pm 7% at the end of the first period for salmeterol and slow-release theophylline-ketotifen, respectively ($p < 0.025$). There is a statistically significant difference between treatment groups as regards rescue salbutamol intake during the night: 0.8 \pm 0.2 puffs \cdot night⁻¹ in the salmeterol-treated patients, compared to 1.3 \pm 0.2 puffs \cdot night⁻¹ in the slow-release theophylline-ketotifen group ($p < 0.025$, Wilcoxon rank test). Salbutamol use nearly halved during the daytime in the salmeterol group: 1.1 \pm 0.3 compared to 2.1 \pm 0.4 puffs \cdot day⁻¹ for slow-release theophylline-ketotifen treated patients ($p < 0.025$). At the end of the first treatment period, mean FEV₁ was significantly higher ($p < 0.05$) in the salmeterol group (83 \pm 3% of predicted value, that is to say a 13% increase in D0 value) than in the slow-release theophylline-ketotifen group (74 \pm 3% of predicted value, 6% increase in D0 value). At the end of the first period, the difference between treatment groups was not statistically significant for morning PEFR, FVC and FEV₂₅₋₇₅.

Tolerance

No drug-related, serious, adverse effects were reported. Twenty six drug-related, minor, adverse effects were reported: 4 (mainly tachycardia, and nervousness) in 3 salmeterol-treated patients and 22 (mainly gastrointestinal disorders, vomiting and headaches) in 15 slow-release theophylline-ketotifen treated patients. This difference between treatment groups is statistically significant ($p = 0.004$).

Discussion

It has already been established that inhaled salmeterol at a dosage of 50 μ g *b.i.d.* is an effective treatment for nocturnal asthma compared to placebo [10]. The next logical step was thus to compare salmeterol with a treatment recommended for patients with nocturnal asthma, namely slow-release theophylline combined to ketotifen, which is frequently prescribed in this indication as a twice daily dosage. The present study demonstrates the superiority of salmeterol compared to slow-release theophylline-ketotifen, using a more selective criterion than the usual "percentage of symptom-free nights". It should be noted, however, that salmeterol also gives significantly better results using this criterion.

Salmeterol was not only significantly better than the slow-release theophylline-ketotifen combination on sleep improvement, but it was also superior to the latter as regards bronchodilating effects (FEV₁) ($p < 0.05$), and the need for rescue salbutamol intakes during night and day ($p < 0.025$). The lack of significant difference between treatment groups as to morning PEFR is probably related to the fact that theophylline-

ketotifen-treated patients took more rescue salbutamol during the last part of the night, these patient's morning PEFR being thus "falsely" increased.

During recent years, inhaled steroids have been recommended as first-line treatment of moderate chronic asthma [15]. Sixty percent of the patients included were treated with inhaled steroids and kept on taking this treatment at a constant dosage throughout the study. It has been shown that inhaled steroids were as effective as slow-release oral β_2 -agonists in controlling nocturnal asthma and that the combination was better [16]. The present trial was not designed to compare steroid-treated patients with those who were not, but it could be advisable to associate salmeterol with inhaled steroids.

Salmeterol was significantly better tolerated ($p < 0.004$), with five times less drug-related adverse events than in the combination-treated patients. We chose not to adjust theophylline dosage to plasma levels, as this is not done in current medical practice and as a double-blind design would not have been possible. However, patients included had to weigh 45–80 kg and the mean dosage was $9.2 \text{ mg} \cdot \text{kg}^{-1}$ body weight per day. Considering the large difference observed between the two treatment groups, it is very unlikely that any adjustment to plasma levels would have changed the results, while the already high number of adverse events in the theophylline group could have increased.

We conclude that salmeterol is not only highly effective as a bronchodilator drug but is also the first treatment which really allows patients suffering from nocturnal asthma to sleep normally, with an excellent efficacy-safety ratio.

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