Furthermore, secondary prevention in HIV infected injecting drug misusers aims at another aspect: socially reintegrated patients or those enrolled in a drug treatment programme are more likely to attend educational programmes, which may limit the further spread of HIV infection.^{4 6 17}

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Salmeterol in nocturnal asthma: a double blind, placebo controlled trial of a long acting inhaled β_2 agonist

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Abstract

Objective—To determine whether inhaled salmeterol, a new long acting inhaled β adrenergic agonist, reduces nocturnal bronchoconstriction and improves sleep quality in patients with nocturnal asthma.

Design—Randomised, double blind, placebo controlled crossover study.

Setting—Hospital outpatient clinics in Edinburgh.

Subjects—Twenty clinically stable patients (13 women, seven men) with nocturnal asthma, median age 39 (range 18-60) years.

Interventions—Salmeterol 50 μ g and 100 μ g and placebo taken each morning and evening by metered dose inhaler. Rescue salbutamol inhalers were provided throughout the run in and study periods.

Main outcome measures—Improvement in nocturnal asthma as measured by peak expiratory flow rates and change in sleep quality as measured by electroencephalography.

Results—Salmeterol improved the lowest overnight peak flow rate at both 50 μ g (difference in median values (95% confidence interval for difference in medians) 69 (18 to 88) l/min) and 100 μ g (72 (23 to 61) l/min) doses twice daily. While taking salmeterol 50 μ g twice daily patients had an objective improvement in sleep quality, spending less time awake or in light sleep (−9 (−4 to −44) min) and more time in stage 4 sleep (26 (6-34) min).

Conclusions—Salmeterol is an effective long acting inhaled bronchodilator for patients with nocturnal asthma and at a dose of 50 μ g twice daily improves objective sleep quality.

Introduction

Three quarters of all asthmatic patients are woken from time to time by coughing, wheezing, and breathlessness.^{1,2} This nocturnal asthma is associated with significant sleep disturbance and increased nocturnal awakenings,^{3,5} and often these symptoms form the patient's main complaint. Hitherto no treatment has been shown to improve sleep quality in patients with nocturnal asthma.

Treatment of nocturnal bronchoconstriction has been limited by the short duration of action of conventional inhaled bronchodilators so that the bedtime dose does not produce effective bronchodilatation at the end of the night, when bronchoconstriction is usually at its most severe.⁶ Many asthmatic patients cannot tolerate therapeutically effective doses of sustained release oral β agonists^{7,8} or theophylline⁹ which, although effective in reducing nocturnal bronchoconstriction in patients with asthma,⁷⁻¹¹ do not produce any objective improvement in their sleep quality.^{12,13}

Salmeterol, a new inhaled β agonist, differs from conventional β agonists in that it produces effective bronchodilatation for 12 hours after a single inhaled dose.¹⁴ The object of our study was to evaluate both subjectively and objectively the effect of inhaled salmeterol on nocturnal bronchoconstriction and sleep quality in patients with nocturnal asthma.

Methods

Twenty patients with nocturnal asthma were entered into a randomised, double blind, crossover study (mean age 39 (range 18-60) years; seven men) to

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compare three inhaled treatments: 50 µg and 100 µg inhaled salmeterol aerosol twice daily and placebo aerosol twice daily. Nocturnal asthma was defined as an average overnight fall in peak expiratory flow rate of at least 15% in association with at least two nocturnal awakenings a week due to wheezing, coughing, or breathlessness over a two week run in period in a patient with known asthma. The mean percentage predicted peak expiratory flow rate of the patients during the run in period was 63% (SD 16%). All β_2 agonists were withdrawn during the study, apart from the study doses and a rescue salbutamol metered dose inhaler that was provided. All other maintenance asthma treatment for each patient was continued at constant dosage throughout the study period (oral steroid, six patients; inhaled steroid, 19; oral aminophylline, 11; inhaled ipratropium, six; inhaled cromoglycate, three). Patients were requested to abstain from beverages containing caffeine during the study; decaffeinated coffee was supplied.

Patients kept a diary record of triplicate peak expiratory flow rates taken four times during each day and at each nocturnal awakening with a mini-Wright peak flow meter. The best of the three recorded measurements at each time was used for analysis. Morning and evening peak expiratory flow rates were recorded immediately before patients took the study inhaler. Patients recorded, each morning, the number of nocturnal wakenings caused by asthma. Morning asthma symptoms, daytime asthma symptoms, and subjective sleep quality were scored on a worsening scale from 0 to 5. Data from the first five days of each limb of the study were not analysed to exclude possible carry over effects.

At the end of each two week study period patients spent two consecutive nights in a sleep laboratory where electroencephalography, electro-oculography, and electromyography were carried out with our standard electrode placement¹⁵ and recorded on a polygraph (Neuroscribe 18, Specialised Laboratory Equipment, Croydon) at a paper speed of 15 mm/s. The standard criteria¹⁶ were used for sleep staging. Only data from the second night on each occasion were analysed, the first night serving for acclimatisation. Each patient spent the same time in bed on all three study limbs (median 402 min).

The significance of observed changes was assessed by Wilcoxon signed ranks testing with application of the Bonferroni correction for multiple comparisons.

Results

TOXICITY

One patient was withdrawn on day 1 because of palpitation caused by sinus tachycardia while taking salmeterol 100 µg twice daily. Another patient withdrew from the study for social reasons. One patient who required maintenance oral prednisolone (5 mg per day) died in status asthmaticus in another hospital after

inhaling a perfume while taking salmeterol 100 µg twice daily. His salmeterol had been stopped on admission to hospital, seven hours before death. He had not received a booster dose of oral or intravenous steroid on admission. No patients reported any other side effects from taking salmeterol in either dose, despite being specifically asked about possible side effects at the end of each limb of the study.

DATA ANALYSIS

Data from 17 patients who completed all three limbs of the study and data from the first two limbs of the study in the case of the patient who died during the third limb of the study were used for analysis. Both doses of salmeterol produced significant improvements in morning and daytime asthma symptoms with fewer night time awakenings from asthma (table I). Peak flow readings at all recorded times, including the lowest recorded peak flow overnight, were significantly improved by the drug in either dose (fig 1) except for the value recorded at 10 pm, for which the improvement on the smaller dose of salmeterol did not reach significance. Overnight peak flow drop (calculated as 10 pm peak expiratory flow rate minus lowest overnight peak expiratory flow rate and expressed as a percentage of the 10 pm peak expiratory flow rate) was reduced by both salmeterol doses. The patients reported significant improvements in both morning and daytime asthma symptoms while taking salmeterol in either dose. There was a non-significant trend towards improve-

FIG 1—Mean (SE) peak expiratory flow rate in 18 asthmatic patients receiving placebo (●) or salmeterol 50 µg (□) or 100 µg (○) twice daily

TABLE 1—Variables recorded on diary cards by 18 asthmatic patients. Numbers are medians (ranges) unless stated otherwise*

	Placebo	Salmeterol		Salmeterol 50 µg v placebo	Salmeterol 100 µg v placebo	Salmeterol 50 µg minus placebo*	Salmeterol 100 µg minus placebo*
		50 µg	100 µg				
No of nocturnal awakenings caused by asthma	0.7 (0.2-6)	0.1 (0.0-9)	0.1 (0.1-4)	p<0.01	p<0.01	-0.3 (-0.7 to -0.1)	-0.3 (-0.7 to -0.2)
Subjective sleep quality†	1.7 (0.6-2.9)	1 (0.3-5)	1.1 (0.3-1)	p>0.05	p>0.05	-0.3 (-0.6 to 0.1)	-0.5 (-0.6 to 0)
No of morning symptoms	1.8 (1-3)	1 (0-3)	0.8 (0-3)	p<0.01	p<0.05	-0.8 (-1.2 to -0.4)	-0.7 (-0.9 to -0.2)
No of daytime symptoms	2.1 (1.3-7)	1.9 (0.3-3)	1.4 (0-4)	p<0.03	p<0.03	-0.7 (-1.1 to -0.2)	-0.3 (-0.9 to -0.1)
Overnight peak flow drop (l/min) (% of peak flow at 10 pm)	21 (0-48)	9 (0-42)	7 (0-50)	p<0.05	p<0.03	-13 (-18 to -2)	-8 (-15 to -2)
Lowest overnight peak flow (l/min)	221 (120-485)	290 (159-454)	293 (109-471)	p<0.02	p<0.01	47 (18 to 88)	36 (23 to 61)
No of puffs of rescue salbutamol in 24 hours	6.0 (0.20-0)	1.5 (0.16-0)	1 (0.14-0)	p<0.01	p<0.01	-1.7 (-5.3 to -1.2)	-2.2 (-5.3 to -1.2)

* Medians of pair differences (95% confidence intervals).

† On a worsening scale of 0 to 5.

TABLE II—Objective sleep measurements in 18 asthmatic patients. Numbers are medians (ranges) unless stated otherwise*

Sleep variable	Placebo	Salmeterol 50 µg	Salmeterol 100 µg	Salmeterol 50 µg v placebo	Salmeterol 100 µg v placebo	Salmeterol 50 µg minus placebo	Salmeterol 100 µg minus placebo
Total time spent awake at night (min)	53 (8-165)	40 (8-162)	37 (4-196)	0.06	NS	−14 (−37 to −2)	−10 (−36 to 9)
Total wakefulness after sleep onset (min)	45 (1-153)	25 (0-140)	18 (2-183)	<0.04	NS	−11 (−36 to −3)	−6 (−31 to 7)
Total time (min):							
Awake or stage 1 sleep	83 (18-218)	67 (22-187)	58 (19-223)	<0.04	NS	−26 (−44 to −4)	−14 (−36 to 7)
Stage 2 sleep	143 (88-196)	146 (52-184)	138 (57-214)	NS	NS	−6 (−31 to 20)	−8 (−22 to 11)
Stage 3 sleep	27 (4-45)	33 (20-50)	35 (17-66)	NS	NS	3 (−2 to 10)	10 (−3 to 15)
Stage 4 sleep	60 (19-111)	85 (41-114)	56 (26-111)	<0.02	NS	19 (6 to 34)	4 (−15 to 10)
REM sleep	67 (25-120)	77 (12-122)	80 (18-114)	NS	NS	5 (−7 to 16)	12 (−7 to 25)
Sleep efficiency (%)	86 (63-98)	91 (58-98)	90 (48-99)	NS	NS	3 (0 to 9)	3 (−3 to 9)

NS = not significant; REM = rapid eye movement.

*Medians of pair differences (95% confidence intervals).

FIG 2—Mean (SE) time spent in each sleep stage by 18 asthmatic patients receiving placebo or salmeterol 50 µg or 100 µg twice daily. REM sleep=rapid eye movement sleep

ment in subjective sleep quality. These improvements were achieved with a reduction in mean 24 hour rescue use of salbutamol by both 50 µg and 100 µg doses of salmeterol twice daily.

The objective sleep recordings showed an improvement in sleep architecture by salmeterol 50 µg twice daily, though there was no significant difference in sleep architecture between salmeterol 100 µg and placebo (table II). Specifically, use of salmeterol 50 µg twice daily was associated with more time spent in stage 4 (deep) sleep and a reduction in time spent awake or in stage 1 (light) sleep (fig 2).

Discussion

This study shows that inhaled salmeterol reduces overnight bronchoconstriction and also improves objective sleep quality in patients with nocturnal asthma. This is the first time that an agent used in the treatment of nocturnal asthma has been shown to improve objective sleep quality. The net effect of nocturnal asthma on patients' sleep is a reduction in slow wave sleep and an increase in the time spent in wakefulness and light sleep^{4,5} relative to normal subjects. Salmeterol 50 µg twice daily specifically improves these variables, thus tending to reverse the sleep disruption caused by nocturnal asthma. Other inhaled bronchodilators have been shown to reduce nocturnal bronchoconstriction in asthma¹⁷⁻¹⁹ but none has been shown to improve objective sleep quality. Salmeterol achieved a mean rise in the lowest recorded overnight peak expiratory flow rate of 21% as compared

with a 16% improvement by adding both salbutamol 800 µg and beclomethasone 200 µg four times daily¹⁷ in a group of patients with less severe asthma who were also taking less maintenance treatment than our patients. In addition, 16 of our 18 patients showed an improvement in lowest morning peak flow rate as compared with eight of 14 treated with salbutamol and beclomethasone and only nine of 18 patients treated with once nightly oxitropium.¹⁸ The fact that a small overnight drop in peak expiratory flow rates persisted during treatment with both doses of salmeterol is consistent with the belief that other, non-adrenergic, mechanisms are also involved in nocturnal asthma.²⁰

Oral bronchodilators, although effective in reducing nocturnal bronchoconstriction, have differing effects on sleep quality in asthma. Oral β agonists did not significantly change sleep architecture in patients with asthma,¹² whereas sustained release theophylline is associated with significant sleep disruption.^{13,21} This may prove to be an important consideration in treating nocturnal asthma as sleep deprivation impairs daytime cognitive performance,²²⁻²⁴ and we have recently shown that adults with nocturnal asthma have impaired daytime cognitive performance when compared with normal subjects matched for age and intellect.²⁵ Furthermore, theophylline has been shown to adversely affect learning, psychological performance, and behaviour in schoolchildren with asthma.²⁶⁻²⁹

Although salmeterol 100 µg twice daily was as effective a bronchodilator as salmeterol 50 µg in our study, it did not improve sleep quality whereas the lower dose did. We think that this is unlikely to be a chance finding as these results were consistent through several different sleep variables tested in each group. It seems likely that the higher dose of salmeterol may have caused some degree of central nervous system stimulation, which offset the potential benefit derived from its bronchodilator action. The lipophilic side chain of the compound may allow it to cross the blood-brain barrier; however, quantitative whole body autoradiography in rats suggests that only a small proportion of a salmeterol dose crosses this barrier (I Skidmore, personal communication).

Although salmeterol improved peak expiratory flow measurements; reduced asthma symptoms on waking and during the day; reduced the 24 hour requirement for rescue use of salbutamol; reduced the number of awakenings at night due to asthma; and improved objective sleep quality, there was no significant change in nocturnal use of salbutamol in patients taking 50 µg of the drug twice daily (p=0.15). This probably results from relatively low nocturnal use of salbutamol in the patients studied (see table II) as they had to be able to discontinue oral β agonists to qualify for admission and be well enough to manage for two weeks on placebo. However, a significant reduction in nocturnal use of salbutamol was noted with the higher dose of salmeterol (p<0.01).

Little is known about the mechanism by which salmeterol exerts its prolonged β₂ adrenergic agonist activity, but it is not through irreversible binding to β

adrenoreceptors as its action can readily be reversed with conventional β blockers. Utilisation of a lipophilic domain in the area around the β receptor may lead to exoreceptor binding, which would then localise the drug near β adrenoreceptors.³⁰

We conclude that inhaled salmeterol is an effective treatment for nocturnal asthma at both 50 and 100 μ g twice daily, and that the 50 μ g dose also significantly improves objective sleep quality. Comparison of the efficacies of salmeterol and theophylline in treating nocturnal asthma is an important next step in determining the optimal treatment for asthmatic patients.

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"Vanishing" of vertebra in a patient with sickle cell haemoglobinopathy

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Sickle cell haemoglobinopathy is common in Nigeria, affecting 2-3% of children.^{1,2} There have been extensive reviews of radiology in patients with sickle cell haemoglobinopathy in Nigeria.³ Common radiological features in the spine include osteoporosis, osteolytic foci, biconvexity of the intervertebral disc spaces, and flattening of the vertebral bodies. To our knowledge the "vanishing" of a vertebral body has not been reported before in such patients.

Case report

A 15 year old Nigerian boy presented in July 1990 with a two year history of a swelling in the lower back. He had had several episodes of recurring ill health consisting of fever, bone pains, and occasional jaundice. He had also felt a mass in the left upper quadrant for more than 10 years. Two years earlier he had developed a painful swelling in the lower back, which increased in size over several weeks. This was associated with constipation and total loss of power in both legs. He had received orthodox medical and traditional medical consultations and had been bedridden for three

months. After admission to hospital, and treatment with oral paracetamol, pethidine injections, oral haematinics, and topical massages with methyl salicylate and other antirheumatic liniments he had gradually recovered use of both legs. There was no history of contact with a patient with tuberculosis, and he had no other features referable to tuberculosis; he had never been treated with antituberculous drugs.

On physical examination at presentation the patient was pale and mildly jaundiced with prognathism and prominent maxillary bones. His anterior abdominal wall showed numerous scarification marks. There was hepatosplenomegaly. The spine showed prominent gibbous at L3 level, with a slight tilt to the right. At this level there was a non-tender bony mass of 5 cm $\times$ 3 cm in the midline. The overlying skin showed three healed pressure ulcers, the right leg was weak (power 4/5), and his gait indicated slight scoliosis to the right and a slight limp of the right foot. The result of the straight leg raising test was positive for the right leg at 60°. The right hamstring muscles were tender to palpation. Sensation to touch and pain was intact. There was a left lateral malleolar ulcer, which was healing with paper thin re-epithelialisation.

Laboratory investigations disclosed anaemia (haemoglobin 87 g/l), an erythrocyte sedimentation rate of 113 mm in the first hour, genotype SS, and a Mantoux test result of 10 mm. Results of liver function tests and serum electrolyte, urea, and creatinine concentrations were normal. Chest and skull radiographs were normal except for coarse trabeculation of the ribs. Plain abdominal radiographs showed multiple faceted gall stones. Spinal radiographs showed diffusely generalised osteoporosis, trabeculation, and pencil