

Slow-release oral salbutamol and aminophylline in nocturnal asthma: relation of overnight changes in lung function and plasma drug levels

A J FAIRFAX, W R McNABB, H J DAVIES, AND S G SPIRO

From the Department of Medicine, Brompton Hospital, London, and Glaxo Group Research, Ware, Hertfordshire

ABSTRACT In a double-blind controlled trial 14 chronic asthmatic patients with regular nocturnal exacerbations took 16 mg slow-release oral salbutamol (two Ventolin spandets), 450 mg slow-release aminophylline (two Phyllocontin Continus tablets), or placebo at midnight. Mean peak expiratory flow rates on waking were significantly higher on the active drugs than on placebo ($p < 0.01$ for salbutamol; $p < 0.05$ for aminophylline) but neither drug abolished the overnight fall in PEFR. Plasma drug levels at 0600 hr were 17.3 ng/ml (± 5.3 ng/ml SD) for salbutamol, and 7.1 $\mu\text{g/ml}$ (± 3.1 $\mu\text{g/ml}$ SD) for theophylline. Steady-state data derived from plasma levels of salbutamol during intravenous infusion indicated that the morning salbutamol levels were probably in a therapeutic range for asthma. The morning theophylline levels, however, were suboptimal when aminophylline was given only at night.

Early morning wheezing is a common symptom of asthma for which sustained release bronchodilator tablets are frequently prescribed. In normal people a diurnal variation of peak expiratory flow (PEFR) of up to 10% has been observed.¹ However, in asthma much larger variations frequently occur, and may sometimes pass unnoticed by the patient.² These overnight falls in PEFR may continue apparently harmlessly for many years or may be associated with deterioration in the overall control of the subject's asthma.^{3, 4}

Although slow-release bronchodilator preparations are widely prescribed to prevent nocturnal symptoms of asthma, there are few data to suggest the correct dose based on measurement of drug plasma levels. Information is available on the therapeutically effective range of plasma levels of theophylline for acute and chronic asthma, but there is no such information for salbutamol. This study was undertaken to investigate the plasma levels of salbutamol and theophylline produced by slow-release oral preparations, and to relate these to the degree of control achieved in chronic nocturnal asthma and

known effective drug levels where possible.

Methods

SUBJECTS

Fourteen patients with chronic asthma gave informed consent to the study which was approved by the hospital ethical committee. They comprised eight men and six women aged 14–71 years (mean 41 years). All had a history of nocturnal wheezing or chest tightness and regular falls in PEFR of $\geq 15\%$ overnight during a run-in period of seven days. Six had one or more positive skin prick tests to common allergens. Six patients were smokers. Their usual maintenance therapy was not changed during the study: 13 subjects took regular salbutamol by metered dose aerosol, dose 300–2000 $\mu\text{g/day}$ (mean 900 μg), 11 took beclomethasone, dose 400–1000 $\mu\text{g/day}$ (mean 500 $\mu\text{g/day}$), and three took disodium cromoglycate. Seven were sufficiently severely affected to require daily oral prednisolone (5–20 mg/day; mean 11 mg/day). Eight subjects had previous hospital admissions for asthma but none in the three months before the study. None was taking oral β -adrenergic stimulants or any theophylline compounds.

Address for reprint requests: Dr A J Fairfax, Department of Medicine, Brompton Hospital, Fulham Road, London SW3 6HP.

STUDY DESIGN

The subjects, who were all outpatients, were taught to measure and record PEFR at or near midnight, and on waking in the morning using a miniature Wright's peak flow meter.⁵ The best of three values was used for analysis.

The trial lasted for four weeks during which the subjects took two tablets before going to sleep after recording their evening PEFR values. Each period of treatment lasted one week and these were randomised on a latin-square design ensuring a placebo week between the two active drug weeks. Treatment comprised one week on 16 mg slow-release salbutamol; one week on an identical salbutamol placebo; one week on 450 mg slow-release aminophylline; and one week on an identical aminophylline placebo. The subjects kept a diary during the four weeks to record any side effects. Each morning they scored subjectively the severity of their nocturnal symptoms as follows: 0=none; 1=slight—woke once during night; 2=moderate—woke several times during night; 3=severe—awake most of the night with asthma. These were used to produce a cumulative weekly score from 0–21 for each subject. Those on maintenance salbutamol by aerosol were asked to take 200 µg after the initial morning PEFR and then repeat the PEFR measurement again after 15 minutes.

On the last night of each week on active drug the patients were admitted to hospital overnight. Peak flow measurements were continued in hospital and vitalograph records of FEV₁/FVC made at the same time. A blood sample was taken at midnight before the tablets were given, and at 0600 hr. The plasma was separated immediately and deep frozen. Plasma salbutamol was measured by solvent extraction and gas chromatographic analysis.⁶ Plasma theophylline was estimated by enzyme immunoassay which is specific for theophylline.⁷

Seven of the 14 patients agreed to a further study involving overnight infusion of salbutamol. This was repeated on a subsequent night in five subjects. Salbutamol was given intravenously in 5% dextrose at a constant rate of 8 µg/kg/hour by infusion pump over 15 hours. Heart rate was recorded hourly and plasma samples taken to obtain steady-state levels. In four subjects sampling was continued throughout the following day to determine the half-life of the drug.

Results

All 14 subjects completed the four-week study. There was good patient compliance in taking

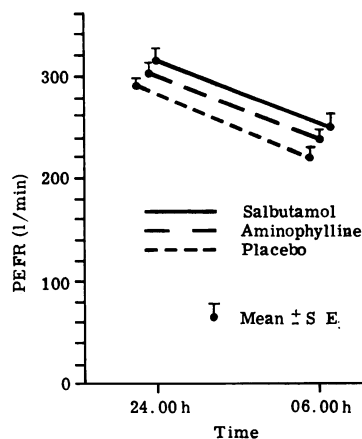


Fig 1 Mean peak expiratory flow rates of 14 subjects taking salbutamol, aminophylline, and placebo tablets at midnight.

medication and completing the diary cards.

The mean peak flow results of all 14 subjects during the study are shown in fig 1. The two control weeks, which did not differ significantly, were pooled for analysis. Morning mean PEFR was significantly higher ($p < 0.002$) during the fortnight on active treatment ($245 \text{ l/min} \pm 7.0 \text{ l/min SE}$) than in the fortnight on placebo ($218 \text{ l/min} \pm 7.2 \text{ l/min SE}$). When analysed separately mean morning PEFR was 251 l/min on salbutamol and 240 l/min on aminophylline ($p < 0.01$ and < 0.05 respectively) compared with placebo by Kruskal-Wallis analysis of variance followed by Mann-Whitney U test for pairs. The evening PEFR values were also slightly higher during the fortnight on active drugs (311 l/min) compared with the control period (292 l/min) but this difference was not statistically significant. The overnight fall in mean PEFR expressed as a percentage of the evening value was 25.5% on placebo, 20.9% on salbutamol, and 21.5% on aminophylline. During the seventh night on active treatment in hospital the mean FEV₁ and FVC fell by 17% and 18% of the evening values respectively on salbutamol, and by 16% and 21% on aminophylline.

The mean symptom scores for the group were 7.0/week on placebo, 6.5/week on salbutamol, and 5.8/week on aminophylline. Four patients complained of side effects on therapy; three noted hand tremor on salbutamol and one had headaches and wakefulness on aminophylline. As a result one patient halved the dose of salbutamol tablets and one halved the dose of both drugs. One person complained of tiredness on placebo.

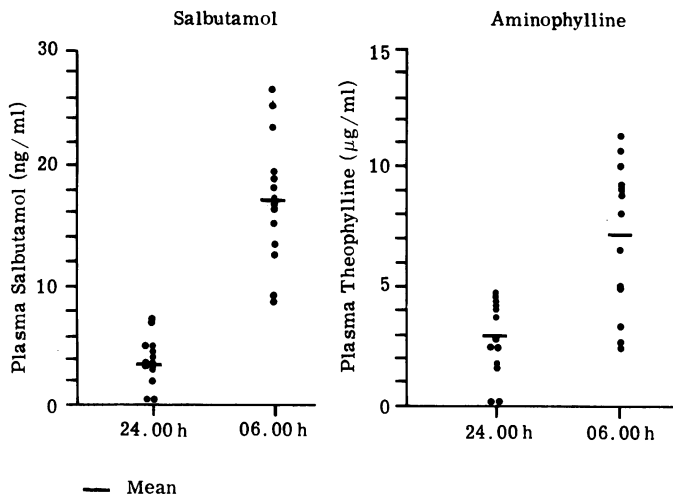


Fig 2 Plasma levels of salbutamol and theophylline at midnight and at 0600 hr on the last day of each treatment week.

The drug plasma levels for all subjects at midnight and 0600 hr on the seventh day of therapy are shown in fig 2. For salbutamol the mean midnight level was 3.7 ng/ml (± 2.1 ng/ml SD) and the 0600 hr level was 17.3 ng/ml (± 5.3 ng/ml SD). Similarly for theophylline the midnight and 0600 hr values were 2.9 μ g/ml (± 1.7 μ g/ml SD) and 7.1 μ g/ml (± 3.1 μ g/ml SD) respectively.

In the seven subjects who received a 15-hour intravenous salbutamol infusion on completion of the four-week study, the plasma levels reached a plateau by six hours and this was maintained until the end of the infusion (fig 3). At 15 hours the plasma level was 20.3 ng/ml (± 3.2 ng/ml

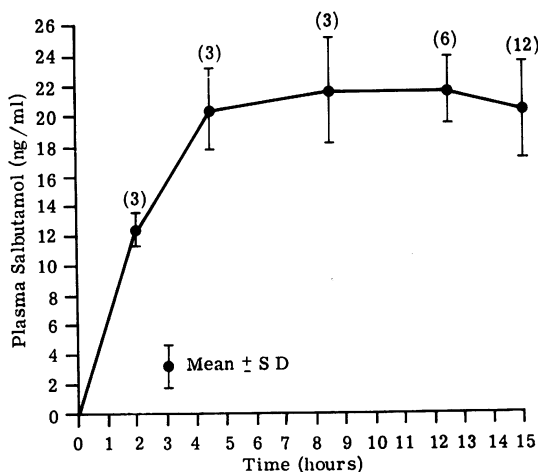


Fig 3 Plasma salbutamol during constant rate infusion using 8 μ g/kg/hr. Figures in parentheses = number of subjects at each time.

SD). The mean heart rate during the infusions was 97.4 beats/minute (± 10.7 SD). Two patients complained of shaking of the hands and one of palpitation. One person was observed to be mildly euphoric. In four subjects decay curves were determined after stopping intravenous infusion. The data best fitted single exponential curves from which the plasma half-life of salbutamol was found to be 6.0 hours (± 0.1 hours SD).

An analysis of variance was made of each individual patient's PEFR results comparing the morning PEFR values on each drug to those on placebo. At the 5% level of significance two patients responded to salbutamol, three to aminophylline, two to both drugs, and seven to neither. With salbutamol, the plasma levels at 0600 hr in the 10 non-responders were very similar (mean 17.1 ng/ml) to those of the four

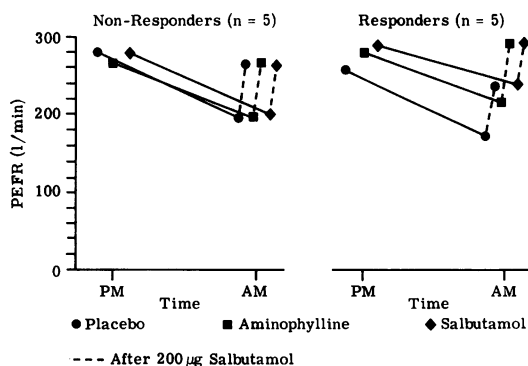


Fig 4 Morning peak expiratory flow rates before and after inhaled salbutamol in responders and non-responders to oral salbutamol and aminophylline.

responders and there was no apparent relationship between the drug plasma level and change in overnight PEFR. With aminophylline, the 0600 hr plasma levels of theophylline were low in the nine non-responders (mean 6.3 µg/ml) and five had levels ≤ 5 µg/ml as a possible cause of treatment failure.

Ten of the 14 subjects repeated their morning PEFR measurements after inhaled salbutamol. Five of the 10 were judged responders to one or both oral bronchodilator drugs and five were non-responders. All, however, improved their PEFR values after 200 µg of inhaled salbutamol (fig 4).

Discussion

Nocturnal asthma is a common symptom and the patients studied were representative of many asthmatics seen in clinical practice. They were selected, however, on the basis of having repeated nocturnal falls in PEFR of at least 15% of the evening value, in the absence of an exacerbation of asthma. Studies of nocturnal asthma have shown that physiological measurements such as PEFR, FEV₁, vital capacity, and airways resistance all fall overnight in a manner similar to an acute asthma attack,² and these measurements are more sensitive assessors than subjective symptom scores.

The spontaneous variability in nocturnal asthma over any period in excess of one week makes clinical documentation of therapeutic intervention difficult. Nevertheless, it is a common symptom and large quantities of medication are prescribed to control it. The administration of slow-release bronchodilator preparations to prevent these symptoms seems logical, yet very little information is available on the drug plasma levels that can be achieved. Although earlier reports that slow-release sympathomimetics such as salbutamol and spandets are helpful in nocturnal asthma,³ there is no information as to the dose of drug required to produce a plasma level that may be considered adequate. Therefore, in addition to measuring plasma levels of salbutamol and theophylline at the end of a week of sustained-release bronchodilator therapy we have compared them to plasma levels achieved during a salbutamol infusion and to known therapeutic levels of theophylline. We chose a salbutamol infusion rate of 8 µg/kg/hr, a dose which has been shown in chronic asthmatics to produce near maximal bronchodilatation with minimal cardiovascular side effects.⁸ The plasma levels measured were similar to those achieved with 16 mg of slow-release oral salbu-

tamol and this would therefore appear to be a dose producing plasma drug levels within the therapeutic range. The long half-life of salbutamol and the presence of detectable salbutamol 24 hours after the last oral dose suggest that therapeutic levels of salbutamol are maintained for longer than just six hours. Nevertheless, there was only a partial protection from nocturnal decreases in PEFR in our patients and there was no correlation between the decrease in PEFR from evening to morning and the plasma salbutamol levels.

Although the circadian pattern of nocturnal asthma has been observed to coincide with a nadir of endogenous catecholamine secretion,⁹ it would appear that a lack of endogenous β -stimulation is unlikely to be a major cause of nocturnal asthma as overnight falls in PEFR were still seen in the seven subjects receiving the intravenous infusion of salbutamol which was sufficient to maintain a mean resting heart rate of over 90 beats per minute and to produce noticeable muscle tremor.

It is generally recognised that a therapeutic effect of theophylline compounds is detectable at plasma levels of >5 µg/ml but that maximal improvement only occurs with theophylline levels between 10–20 µg/ml.¹⁰ In our subjects the theophylline levels at 0600 hr showed a wide scatter and were in the lower therapeutic range with a mean level of 7 µg/ml. Twice daily therapy with 450 mg slow-release aminophylline has been shown to produce levels between 15–20 µg/ml at between four and six hours after the last oral dose.¹¹ This may, therefore, be a more effective regimen although the plasma half-life of theophylline is known to be variable.¹⁰ In addition, the preliminary results of a study using this dose regimen has shown that the overnight falls in PEFR continue and with the higher dose there is an appreciable incidence of side effects.¹²

In conclusion, oral slow-release salbutamol and aminophylline have been shown to produce objective improvement of PEFR on waking in half the patients studied in this trial. The changes produced were relatively small, however, and the diurnal pattern of asthma was not abolished despite apparent therapeutic levels of bronchodilator drugs in the early morning. Those patients unresponsive to either salbutamol or aminophylline by mouth all showed rapid increases in PEFR after a standard 200 µg inhaled dose of salbutamol on waking, as did those subjects who were judged to have responded to the tablet therapy. The measurement of plasma levels of salbutamol and theophylline may be useful to

exclude inadequate dosage as a cause for failure to respond to oral therapy. This study has also shown that 16 mg of slow-release salbutamol is likely to produce potentially efficacious drug levels, while 450 mg of slow-release aminophylline may produce suboptimal levels in some subjects. However, the simple administration of adequate doses of a sustained release bronchodilator is unlikely to help more than 50% of patients suffering from nocturnal asthma.

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