THE EFFECT OF DIFFERENT NEBULIZERS WITH AND WITHOUT INTERMITTENT POSITIVE PRESSURE BREATHING ON THE ABSORPTION AND METABOLISM OF SALBUTAMOL

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- 1 The absorption and metabolism of [^3H]-salbutamol have been studied to assess whether intermittent positive pressure breathing (IPPB) or a particular nebulizer have any advantages in delivering bronchodilator drugs to asthmatic patients.
- 2 [^3H]-salbutamol (10 mg) was given to asthmatic patients from either the Bird Mark 7 ventilator without intermittent positive pressure, the Bird micronebulizer attached to an electric air compressor, or the Wright's nebulizer attached to the same compressor.
- 3 All patients showed a high early plasma level of radioactivity due mainly to free salbutamol. This pattern suggests absorption from the lung and is similar to that seen after giving the drug from the Bird nebulizer using IPPB.
- 4 In all cases less than 20% of the original dose was absorbed by the patient.
- 5 Improvement in forced expiratory volume in one second (FEV_1) was seen with all three treatments.

Introduction

The selective β_2 -adrenergic receptor stimulant salbutamol (2-*i*-butylamino-1-[4-hydroxy-3-hydroxymethyl]phenylethanol) is now widely used in the treatment of asthma (Choo-Kang, Parker & Grant, 1970). Using a tritiated preparation we have studied its absorption and metabolism after various routes of administration. Put directly into the bronchi via a bronchoscope it appears in plasma in minutes and is not metabolized by the lung. There is a predominance of free (unconjugated) salbutamol for the first hour and only later does metabolite appear (Evans, Paterson & Shenfield, 1973). Taken orally, peak plasma levels of total radioactivity occur at 3-4 h but at all times there is a predominance of metabolite over free salbutamol (Walker, Evans, Richards & Paterson, 1972). The lung and the gastro-intestinal tract thus show very different patterns of both absorption and metabolism for salbutamol. Knowing these differences it has been possible to interpret the fate of salbutamol given by various forms of inhalation.

It is well known that a proportion of an 'inhaled' drug is deposited in the oropharynx and swallowed (Paterson, Conolly, Davies & Dollery, 1968). Salbutamol inhaled from a dry pressurized aerosol is mainly swallowed (80-90% of the dose)

with a late peak plasma level and a predominance of metabolite. The bronchodilating effect is produced by the smaller proportion (about 10-20%) of the inhaled dose that reaches the lungs directly (Evans, Paterson, Richards & Walker, 1971). None of the dose is breathed out in the breath expired after the use of the inhaler (Paterson, unpublished data). When given by wet nebulization and intermittent positive pressure breathing (IPPB) from the Bird Mark 7 ventilator (Shenfield, Evans, Walker & Paterson, 1973) only 10-20% of the original dose put into the nebulizer was retained by the patient: some remained in the apparatus and a significant proportion was recovered from the expired air. Even though less of the original dose is retained by the patient, much higher early plasma levels are seen with a predominance of free salbutamol. Only later does metabolite predominate with a second peak plasma level at 3-4 hours. This presumably represents the swallowed fraction of drug. On this evidence proportionately more of the retained drug reached the lungs when given by the Bird ventilator and IPPB than when given from a dry pressurized aerosol.

There could be several reasons for this: wet particles might have more optimal properties than dry particles, the IPPB might mechanically force

more drug into the lungs, or the Bird nebulizer might produce an aerosol of optimal particle size. A further possibility was that the pattern of rhythmic breathing over 10 min has advantages over a single quick inhalation. The present studies were designed to try to determine which of these factors was of most importance. As with all the other studies [^3H]-salbutamol was used.

Methods

Nine male asthmatic patients were studied. All were in-patients recovering from an acute exacerbation, receiving daily treatment with salbutamol (10 mg) given from a Bird Mark 7 ventilator using IPPB, and capable of increasing their FEV₁ by at least 20% after treatment with a bronchodilator. No bronchodilator drugs were given from 22.00 h on the night preceding the study.

On the morning of the study, baseline measurements were made of pulse, blood pressure, and FEV₁, an indwelling venous cannula was inserted, and a control blood sample was taken. Treatment was then given with one of three machines; a physiotherapist was present throughout, and patients all wore nose clips. Treatment was stopped when the nebulizers appeared to be empty, and the physiological measurements were repeated immediately and throughout the day. Blood samples were taken at 20, 30, 45 and 60 min, then half-hourly for 2 h, and hourly for 8 hours. Further specimens were taken at 24, 48, and 72 hours. Urine was collected for 72 hours. Three patients were allocated to each treatment. The machines used were as follows:

(1) Bird Mark 7 ventilator (Bird Corporation, Palm Springs, California) with the side arm of the breathing head assembly disconnected from the machine and the ventilator worked by hand, the patient triggering the magnet with the hand trigger. The sensitivity control was set at 7 as was the flow rate (inspiratory time). Thus the flow rate through the nebulizer was that normally used but the inspiratory pressure recorded on the dial never exceeded 2 cm of water.

(2) The Bird micronebulizer attached to an air compressor (Aerolyser Electric Inhaler CF1A, Aerosol Products Colchester Ltd., London) run off mains electricity.

(3) The Wright's nebulizer (Aerosol Products Colchester Ltd., London) attached to the electric air compressor.

In all cases the machines were adapted for use with a mouthpiece, and expiratory air was collected in a Douglas bag. With treatment (1) a bag containing oxygen was attached to the loose end of the breathing head assembly to provide an

inspiratory reservoir. For treatments (1) and (2), [^3H]-salbutamol (10 mg; 2 ml of 5% solution) was made up to 5 ml with 0.9% w/v NaCl. For treatment (3), 2 ml of solution was used to standardize the length of treatment since preliminary studies had shown that nebulization was slower with this machine.

The duration of the treatments was: (1) 15, 13, 14.5 min; (2) 13, 7, 8 min; (3) 12, 11, 8 minutes. For (2) and (3), nebulization was continuous and it was necessary to stop the machines at intervals to allow patients to cough.

The bags, nebulizers, and attached tubing were washed out with water and aliquots (1 ml) of the washings counted in Instagel (Packard) scintillation fluid (9 ml). Aliquots of plasma (0.5 ml) and aliquots of urine (1 ml) were mixed with 18 ml and 9 ml of scintillation fluid respectively. All measurements of radioactivity were made with a Packard Tri-Carb liquid scintillation spectrometer. Plasma and urine from all nine patients were further analysed for the presence of free salbutamol and its metabolite (Evans, Walker, Brittain & Paterson, 1973).

Results

The results from a previous study in which similar patients were treated with the Bird ventilator using IPPB are included for comparison (Shenfield *et al.*, 1973). Patient W.G. (treated with the Bird nebulizer, 2) noticed palpitations and his pulse rate rose by 28 beats/min during treatment and then returned to pre-treatment levels. He also experienced tremor. Patient W.A. also developed tremor with this treatment and salbutamol from the Wright's nebulizer caused tremor in two patients (J.S. and G.C.). There were no other side-effects. In all patients there was a marked rise in FEV₁ and no obvious difference in the time of the peak response (Table 1).

Fate of original dose

In each study a large proportion of the dose was recovered from the nebulizer, tubing and Douglas bag. With treatments (1) and (2) the 'expired air bag' also collected any of the dose that dribbled from the tubing. In all cases less than the estimated available dose was recovered from the patients' urine in 24 hours. Table 2 summarizes the fate of the administered dose of [^3H]-salbutamol.

Plasma levels

Table 1 gives the 30 min and peak plasma levels.

The 30 min plasma levels are within the same range for the three treatments in the present study and for treatment with the Bird using IPPB. Within each group the plasma picture was similar (Figures 1, 2 and 3). In all cases there was a rapid early rise of plasma radioactivity over 80% of which was free salbutamol. With treatments (1) and (2) there was a second, later peak at 3-4 h, the majority of which was metabolite. Following treatment with the Wright's nebulizer the total plasma level was sustained and metabolite predominated after 1 h but there was no obvious second peak (Figure 3). In all cases the metabolite was the same as that previously described after oral and aerosol administration (Evans *et al.*, 1973).

Urinary excretion

There was a trend for less of the available dose to be recovered in the urine following treatment with the Wright's nebulizer, although this was not statistically significant. In view of the small and variable proportion of the original dose recovered from the urine, the metabolite was expressed as a percentage of the total 24 h recovery for each patient (Table 2).

FEV₁ response

Baseline FEV₁ was markedly below predicted normal in all patients. The mean predicted normal

Table 1 Plasma radioactivity and FEV₁ response (means and ranges for each group of patients) after administration of [³H]-salbutamol (10 mg) by different nebulizers with and without intermittent positive pressure breathing (IPPB).

Treatment	**30 min plasma level (nmol/l)	**Peak plasma level (nmol/l)	Time of peak level (h)	Peak rise in FEV ₁ (litres)	Peak rise in FEV ₁ as % baseline	Time of peak FEV ₁ (h)
Bird with IPPB* (4 patients)	57.2 (27.5-118)	79.2 (51-118)	2.1 (0.5-4.0)	1.2 (0.5-1.8)	44.8 (23-67)	1.25 (0.75-2.0)
Bird without IPPB (3 patients)	40.0 (32-49)	67.9 (53-96.4)	3.0 (3-3)	1.1 (0.8-1.4)	154.7 (42-222)	1.4 (0.75-2.0)
Bird nebulizer (3 patients)	48.4 (42.2-58.7)	105.3 (62-160)	3.5 (1.5-4.5)	0.7 (0.5-1.1)	81.0 (66-111)	1.5 (0.3-2.5)
Wright's nebulizer (3 patients)	42.7 (38.9-48.5)	51.0 (46.5-57.6)	1.25 (0.75-2.0)	0.6 (0.3-0.8)	56.3 (35-84)	0.9 (0.75-1.0)

* Data from Shenfield *et al.*, 1973.

** Total tritium activity equivalent to nmol/l of original [³H]-salbutamol.

Table 2 Fate of original dose of [³H]-salbutamol and its urinary recovery in 24 h (means and ranges for each group of patients) after administration by different nebulizers with and without intermittent positive pressure breathing (IPPB).

Treatment	Original dose (mg)	Nebulizer and tubing (mg)	Expired air (mg)	Estimated dose (mg)	24 h urinary recovery Total (mg)	% as metabolite
Bird with IPPB* (4 patients)	9.8 (9.2-10.0)	3.3 (2.3-4.3)	3.9 (3.4-5.0)	2.4 (2.0-3.0)	1.2 (1.0-1.5)	51 (48-56)
Bird without IPPB (3 patients)	9.9 (9.8-9.9)	5.3 (4.9-5.6)	2.4 (1.7-2.9)	2.2 (1.9-2.6)	0.8 (0.6-0.9)	46 (44-47)
Bird nebulizer (3 patients)	9.8 (9.8-9.9)	3.3 (1.4-5.3)	3.3 (1.0-7.1)	3.2 (1.3-5.6)	1.3 (1.0-1.8)	49 (45-52)
Wright's nebulizer (3 patients)	9.6 (9.4-9.9)	4.7 (4.1-5.2)	1.3 (1.1-1.6)	3.7 (2.6-4.4)	0.6 (0.5-0.7)	41 (36-47)

* Data from Shenfield *et al.*, 1973.

Fig. 1 Patient D.H. FEV₁ response (○) and plasma drug levels: (■) free salbutamol; (▲) metabolite; (●) total radioactivity, after treatment (stippled area) with salbutamol using the Bird ventilator without intermittent positive pressure.

Fig. 2 Patient W.G. FEV₁ response (○) and plasma drug levels: (■) free salbutamol; (▲) metabolite; (●) total radioactivity, after treatment (stippled area) with salbutamol using the Bird nebulizer alone.

value was 3.3 litres (range 2.9–4.1 litres) and the mean baseline value was 1.0 litre (range 0.6–1.9 litres) or 31% of predicted (range 13–56%). The percentage rise in FEV₁ was greater than 15% in every patient. Figures 1, 2 and 3 show individual responses for one patient from each group. The numbers are too small to decide if there was any difference in FEV₁ response between nebulizers.

Discussion

The purpose of this study was to see whether IPPB or a particular form of wet nebulizer altered the pattern of absorption and metabolism of salbutamol in asthmatic patients. In all three groups reported the 30 min plasma levels were in the same range as in our previous study with the Bird ventilator and IPPB (Shenfield *et al.*, 1973). In all cases there was an early predominance of free salbutamol similar to that seen after bronchoscopic administration, and hence reflecting that proportion of the dose reaching the lungs (Evans *et al.*, 1973). With all the methods of administration proportionately more drug reaches the lung than is the case after inhalation from a

dry pressurized aerosol (Evans *et al.*, 1971). Thus neither IPPB nor the make of nebulizer are responsible for the previously reported difference. It may therefore be due to the different pattern of breathing. The dry aerosol is taken as a single puff and thus airstream velocity will be much greater than with continuous inhalation and inertial deposition will occur to a greater extent (Hatch & Gross, 1964). This would lead to a greater proportion of the dose being deposited in the oropharynx and swallowed. The wet aerosols are used for 10–15 min and bronchodilatation will occur during inhalation; thus a progressively greater fraction of the drug could reach the lung.

In our earlier study using the Bird ventilator with IPPB it was found that only a small amount of the dose placed in the nebulizer was available to the patient, the majority remaining in the apparatus or being expired (Shenfield *et al.*, 1973). These findings were repeated with the other methods studied here. However, the difference between the 'calculated' dose available to the patient and the urinary recovery is more marked than in our previous study. The 'missing' fraction is not absorbed by the patient for when tritiated salbutamol is given to asthmatics orally,

Fig. 3 Patient G.C. FEV₁ response (○) and plasma drug levels: (■) free salbutamol; (▲) metabolite; (●) total radioactivity, after treatment (stippled area) with salbutamol using the Wright's nebulizer.

intravenously, by pressurized aerosol or via a bronchoscope, over 80% of the dose is recovered from the urine in three days (Walker *et al.*, 1972; Evans *et al.*, 1973). Neither the bags nor the nebulizers absorb drug (Paterson, unpublished data) and the discrepancy may be due to the technique of administration. It was necessary to stop briefly after every 6-8 breaths when using treatments (2) and (3) and inevitably some drug was lost from the mouthpiece. In addition air was lost from the bags in taking them on and off the apparatus and in washing them out.

We are confident that the 24 h urinary recovery is an accurate reflection of the actual dose absorbed by the patients. Thus in all cases only 10-20% of the dose placed in the nebulizer was actually available to the patients. This contrasts with a pressurized aerosol where 100% of the dose is available to the patient although only 10-20% may be inhaled directly into the lung. This finding accounts for the observation of previous workers that, in terms of physiological response, isoprenaline given from a dry pressurized aerosol seems as effective as a tenfold larger dose from a wet nebulizer (Feinmann & Newell, 1963; Cohen & Hale, 1965; Chang & Levison, 1972).

There is no doubt that each of these wet nebulizers gets more drug to the lungs than do dry pressurized aerosols. However, the blood and urine

levels cannot tell us where in the lung the drug has been deposited and absorbed. It does not follow that bronchodilatation will be better or even as effective because more drug is absorbed from the lung. The effective fraction of the inhaled dose is that which is deposited locally in the appropriate part of the bronchial mucosa. This is not necessarily related to total absorption from the lung as reflected by a high plasma level of free drug.

All our patients showed marked improvement in their FEV₁ with all of the treatments and the average percentage rise in FEV₁ was similar with each type of device. However, due to differing baselines and the small number of patients these data could not be statistically analysed. We found no difference in improvement in FEV₁ produced by these different nebulizers in a separate study using unlabelled salbutamol and giving each of the three treatments to the same ten patients (Webber, Shenfield & Paterson, 1974).

Grant (personal communication) found that asthmatic patients with an FEV₁ of more than 50% of their predicted value showed as much improvement with a pressurized aerosol as with the same drug given by a Bennett ventilator. Patients with an FEV₁ of less than 50% of their predicted value showed a greater improvement with the Bennett. This concurs with our clinical impression that patients needing hospital admission benefit from the opportunity to inhale the drug over a longer period.

There is no definite advantage in achieving a high plasma level since the bronchodilating effect is produced by local deposition of the drug. Also higher plasma levels produce a higher incidence of side-effects. We used a dose of 10 mg although Choo-Kang *et al.*, (1970) showed that the same peak improvement in FEV₁ could be produced with salbutamol (5 mg) given from the Bennett ventilator. A still smaller dose might be adequate.

It remains possible that IPPB might have some additional advantage in patients in status asthmaticus. In all other instances the present results show that whereas wet nebulization of bronchodilator drugs can be valuable, neither IPPB nor a particular nebulizer confer any special advantage as judged by total drug absorbed from the lung.

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