

Aerosol salbutamol administration by IPPB: lowest effective dose

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Ruffin, R E, Obminski, G, and Newhouse, M T (1978). *Thorax*, 33, 689–693. Aerosol salbutamol administration by IPPB: lowest effective dose. This study was conducted to determine whether small doses of salbutamol solution, aerosolised and delivered by intermittent positive-pressure breathing (IPPB), would be as effective as the 5 to 10 mg dose usually recommended for inhalational use. In nine asthmatic subjects we found that there was no significant difference between the peak bronchodilator effect of 1.0, 2.5, and 5.0 mg of salbutamol solution as assessed by FEV₁ ($p > 0.05$). The 5 mg dose of salbutamol solution caused a significantly longer duration of effect than the 1.0 mg and smaller doses of salbutamol, but it also caused four of the nine subjects to complain of unwanted effects. In addition, a radiotracer technique in four normal subjects showed that an inverse relationship exists between the amount of aerosol deposited in the lungs and the tidal volume of IPPB. The maximum dose deposited in the lungs was about 10% of that initially present in the nebuliser.

Intermittent positive-pressure breathing (IPPB) is a mode of administering aerosolised drugs to asthmatic patients (Petty, 1974). It has been argued that IPPB offers no advantage over quiet breathing as an aerosol administration mode, and recent work by Dolovich *et al* (1977) supports this contention. Advocates of IPPB do exist, however, and in Canada salbutamol solution has been released only for use in IPPB apparatus.

There is a 25- to 50-fold discrepancy in the usual doses of salbutamol advocated for administration by IPPB (5–10 mg) compared with the usual metered dose inhaler (MDI) dose of 200 μ g (Shenfield *et al*, 1973). Despite the relative safety of the more selective β_2 -adrenergic agonists, such as salbutamol, with respect to unwanted β_1 cardiac effects, it is important to avoid large doses of these drugs. This is because in patients with severe airways obstruction and hypoxemia who may have associated coronary artery disease there may be a considerably lower threshold at which β_2 -adrenergic agonists cause arrhythmias. This study compared placebo and five doses of salbutamol aerosol administered in a double-blind fashion by IPPB in a group of nine asthmatic subjects. In addition a

radiotracer technique assessed the dose and distribution of aerosol delivered to four normal subjects.

Materials and methods

CLINICAL STUDY IN ASTHMATICS

Nine subjects with mild to moderately severe asthma who had previously shown an improvement of greater than 20% in FEV₁ within 15 minutes of inhaled salbutamol (200 μ g) were selected. There were five men and four women, aged from 20 to 56 years. The subjects' mean baseline FEV₁ ranged from 29 to 76% of the predicted value. Eight subjects were regularly using inhaled salbutamol and beclomethasone dipropionate aerosols; two of them were also taking regular oral theophylline. Each subject was familiar with the use of the IPPB apparatus (Bird Mark 10 respirator). All study days were started after a 15-minute rest period, at the same time of day for each subject. When possible studies were conducted on consecutive days, provided that the baseline FEV₁ was within $\pm 15\%$ of the first day's value. No subject received inhaled bronchodilator for eight hours before each study day, the two taking oral theophylline omitted this drug for

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24 hours before each study day, but those taking inhaled beclomethasone dipropionate continued this medication in the usual dose. None was exposed to a relevant allergen, other than house-dust, for at least four weeks before the study.

Ventilatory function was determined by measuring FEV₁, mean forced expiratory flow rate over the middle half of the forced vital capacity (FEV_{25-75%}), and forced vital capacity (FVC) from the best of three spirograms recorded on a bellows spirometer (Vitalograph). All volumes were measured at BTPS. Ventilatory function, pulse rate, and blood pressure were measured just before drug administration and at 30, 60, 90, 120, 180, and 240 minutes after.

After baseline measurements the subjects received an aerosol produced from 5 ml of saline containing either 0, 0.25, 0.50, 1.0, 2.5, or 5 mg of salbutamol in a double-blind fashion with randomised order of administration.

An ultrasonic generator (Monaghan 670B) was used to produce aerosol particles of 3.9 μ m aerodynamic mass median diameter (\bar{g} 1.6). The same Bird Mark 10 respirator driven by 50 pounds per square inch pressure (344.7 kPa) of compressed air was used to deliver the aerosol to each subject (fig 1). The dead space between the subject's mouth and the generator was 25 ml. The same respirator settings were used for each subject. On average it took 10 (range 9 to 12.5) minutes for the ultrasonic generator to cease producing visible aerosol. When no further aerosol was being produced this was called zero time. The range of expiratory volumes, measured with a Wright respirometer, was 1.0 to 2.7 l, and the breathing frequency ranged between 11 and 17 breaths a minute.

RADIOTRACER STUDY IN NORMALS

We used the radiotracer method described by

Ruffin *et al* (1978a) to measure the amount of aerosol deposited in the airways, stomach, and oropharynx of four healthy subjects—two men and two women (age range 22–33). Their baseline FEV₁ ranged from 98 to 112% of the predicted value. The aerosols for inhalation were produced by an ultrasonic generator and a Bird nebuliser and delivered under the same conditions as in the first method. To enable sufficient data points to be obtained each subject inhaled the aerosol at varying tidal volumes between 1.0 and 4.0 l in separate experiments. The radioactivity deposited in each subject was calculated as described by Ruffin *et al*, (1978a). ^{99m}Tc HSA was used as the radiotracer, so that absorption of the radioactivity in the 10-minute breathing period was not significant in contrast to ^{99m}Tc pertechnetate which has an effective lung half-life of about 15 minutes (Ruffin *et al*, 1978a). On the basis of clearance studies in normal subjects, the amount removed from the lungs during the 10-minute inhalation period is less than 1% of the total airway dose (Ruffin *et al*, 1978b).

Statistical analysis was performed by two-way analysis of variance with a multiple range comparison test (Sokal and Rohlf, 1969) and linear regression analysis by the method of least squares (Snedecor and Cochran, 1956).

Written informed consent was obtained from each subject, and the project was approved by the ethics committee.

Results

CLINICAL STUDY IN ASTHMATICS

There was no significant difference ($P > 0.05$) between the salbutamol study days and the placebo day for baseline FEV₁ (range 1.78–1.86 l). Similarly, differences in the baseline FEV_{25-75%} and FVC were small and insignificant ($P > 0.05$).

The 5 mg dose of salbutamol produced an im-

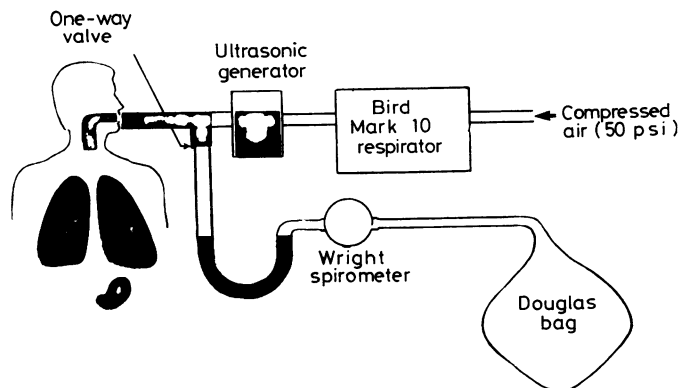


Fig 1 Schematic representation of intermittent positive-pressure apparatus for the study. Included are scintigraphs illustrating distribution of radioactivity at completion of an inhalation with most of radioactivity residing in mouthpiece, tubing, and aerosol generator.

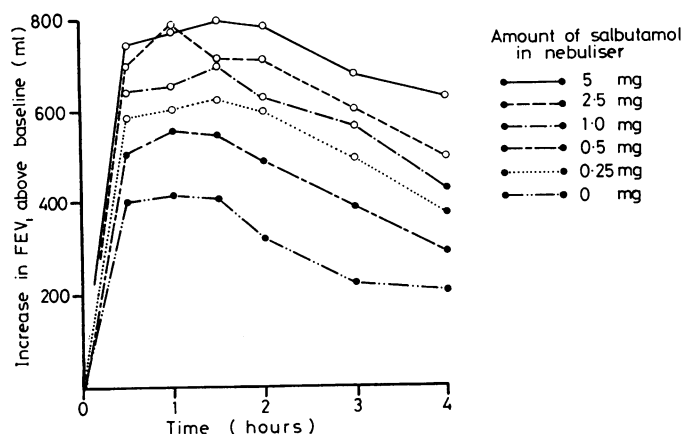


Fig 2 Mean increases in FEV_1 above baseline values after drug administration for the nine asthmatics. Open circles = significantly greater than placebo, $P < 0.05$.

provement in FEV_1 compared with placebo for the four hours after drug administration, as did the 2.5 mg dose ($P < 0.05$) (fig 2). The 1 mg and 0.25 mg doses produced significant improvement in FEV_1 compared with placebo, but not for the entire four-hour study. The response to 0.5 mg of salbutamol did not reach statistical significance ($P > 0.05$). There was no significant difference between the FEV_1 increase produced by the 5 mg, 2.5 mg, and 1 mg doses of salbutamol until the 240 minute reading when the FEV_1 increase produced by the 5 mg dose was greater than that by the 1 mg dose ($P > 0.05$) (fig 2).

Similar trends were observed with the increases in $FEV_{25-75\%}$ and FVC. The only significant change in blood pressure or pulse rate occurred at 30 minutes when 5 mg of salbutamol caused a mean 8.2 mmHg increase in systolic blood pressure ($P < 0.05$). Three subjects complained of tremor and one felt apprehensive after the 5 mg salbutamol dose, one of these subjects also had tremor after the 2.5 mg salbutamol dose, while another complained of transient facial paresthesiae after each salbutamol dose except the 0.5 mg dose.

RADIOTRACER STUDY IN NORMAL SUBJECTS

The study with four normal subjects showed an inverse relationship between the percentage of the nebuliser dose being deposited in the lungs and the depth of breathing (fig 3). The correlation coefficient was -0.73 for the Monaghan nebuliser ($P < 0.05$) and -0.51 for the Bird micronebuliser ($P < 0.2$) for the relation between tidal volume and percentage deposition in the lungs.

Figure 1 shows a composite set of scintiphotos demonstrating the distribution of radioactivity after the generator was no longer producing visible aerosol. For the Monaghan nebuliser studies the

mean (\pm SE) recovery rate of radioactivity was 88.5% (± 2.9) and for the Bird micronebuliser studies 87.7% (± 3.1).

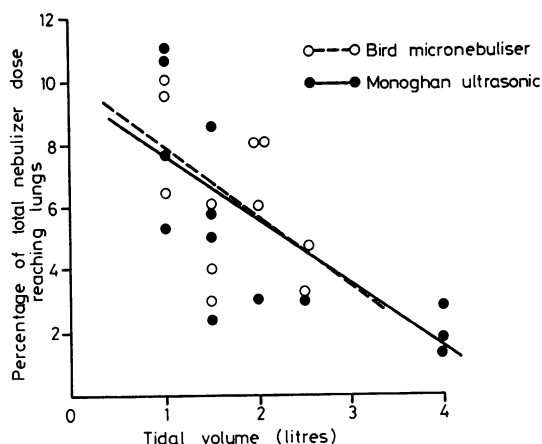


Fig 3 Relation between percentage of solution deposited in lungs and tidal volume of IPPB for Monaghan nebuliser and Bird micronebuliser. Each point represents a value from one of four normal subjects. Lines represent derived relationship for each aerosol generator.

Discussion

This study showed that peak bronchodilator effectiveness assessed by the FEV_1 was similar for the conventional dose of salbutamol respirator solution (5 mg) and for two- and five-fold smaller doses in this group of asthmatics with mild to moderately severe airways obstruction. In addition a radiotracer technique showed that less than 10%

or as little as 2% of the starting nebuliser dose may reach the lungs, and that the larger the breath the smaller the amount of aerosol deposited in the lungs in normal subjects when aerosols are delivered by IPPB.

An assumption made in the clinical study was that equivalent amounts of aerosol were delivered to each subject—that is, each subject was assumed to have received the same proportion of the starting solution on each study day. This assumption is made in most bronchodilator studies except where indirect (Shenfield *et al*, 1973; 1974) measurements of bronchodilator dose by radiotracer techniques have been made. The 95% confidence limits for the relationship between tidal volume and percentage lung deposition in normal subjects (fig 3) for the Monaghan nebuliser were, at 1 l tidal volume, a range of 5.2 to 9.8% lung deposition. Although increasing the number of subjects is likely to decrease the 95% confidence range limits, our experimental evidence contradicts the assumption of equivalent aerosol dose delivered to subjects via IPPB, as has been suggested by Choo-Kang *et al* (1970).

Previous studies of the bronchodilator effect of salbutamol administered by IPPB have: (1) examined doses of salbutamol greater than 5 mg (Choo-Kang *et al*, 1970); (2) compared IPPB salbutamol (10 mg) and 200 µg salbutamol by metered dose inhaler (Choo-Kang and Grant, 1975); and (3) used different groups of patients to compare 5 mg and 2.5 mg of salbutamol by IPPB (Spitzer *et al*, 1972).

With the possible variation in effective bronchodilator dose (or airway bronchodilator dose) in mind, the present study has shown that using a 5 mg dose of salbutamol in the generator achieves a longer period of bronchodilatation than the 1 mg dose. The longer duration of effect is to be expected with a large dose, since the local drug concentration will be at effective levels for a longer period than with a smaller dose. It is important to note that a dose-related increase in FEV₁ was observed in this study. The lack of statistical significance of this trend is probably due to the small number of subjects. The larger dose is accompanied by an increasing incidence of side effects, however, and for most purposes in mild to moderate asthma the smaller dose would appear to be more appropriate.

The data obtained with the radiotracer technique suggests that the percentage lung dose is similar when using either a Monaghan ultrasonic nebuliser or a Bird micronebuliser. Asmundsson *et al* (1973) used a similar radiotracer technique to measure the absolute deposition of saline in the lungs and found no significant difference between an ultra-

sonic nebuliser (1%) and the Bird micronebuliser with IPPB (2%). In their four subjects studied with IPPB Asmundsson *et al* (1973) noted that the amount of deposition of saline in the lungs was inversely proportional to the tidal volume (range 1.2–3.1 l). Shenfield *et al* (1973) found that the total dose of tritiated salbutamol via IPPB received by five subjects was 15–20% of the nebuliser dose, but tidal volume during the IPPB breathing was not measured. Thus there is some discrepancy between the results of Asmundsson *et al* (1973) and Shenfield *et al* (1973). Our results were similar to those of Shenfield *et al* (1973), with the total (lung, throat, and stomach) dose to subjects with the Bird micronebuliser being 9.5% for 2.5 l tidal volume and up to 23.8% for 1 l tidal volume. Nevertheless, we did observe a similar inverse relation between tidal volume and lung deposition to that noted by Asmundsson *et al* (1973), which is not unexpected, because keeping the inspiratory time constant on the respirator and increasing tidal volume increases the flow rate and so leads to greater impaction of the aerosol particles in the delivery system and upper airway. Pavia *et al* (1977) have shown that the depth of aerosol penetration into the lungs is inversely related to the inspiratory flow rate, and directly related to tidal volume and FEV₁ for spontaneous respiration of a monodisperse particle.

It is of interest to compare the lung aerosol deposition efficiency using IPPB versus metered dose inhaler. If a 10% lung deposition efficiency is assumed for MDI (Davies, 1975) then about 20 µg of salbutamol in the lung from two puffs of an MDI gives near maximum bronchodilatation (Minette, 1971). If, as our data suggests, we assume a 5% lung aerosol deposition as an average IPPB efficiency then 20 µg in the lungs should be achieved with a starting dose of 0.4 mg of salbutamol in the generator. Thus, from both a theoretical aspect and the experimental data obtained from this study, a rational approach for the use of salbutamol aerosol from IPPB apparatus is to use a starting generator dose of 1 mg rather than the usual 5–10 mg dose. An indication for altering the dose would be very high inspiratory flow rates when the efficiency of lung aerosol deposition with IPPB may fall considerably. These data apply to moderately severe asthma and may not apply in extremely severe asthma.

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