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Terbutaline sulphate Turbuhaler: effect of inhaled flow rate on drug deposition and efficacy

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Summary

The deposition and efficacy of 0.5 mg terbutaline sulphate from Turbuhaler (Astra Pharmaceuticals), a multi-dose powder inhaler, have been measured simultaneously in 10 asthmatic subjects at two inhaled flow rates (fast, mean 57 l/min and slow, mean 28 l/min). At the fast flow rate, a mean (SEM) 16.8 (2.6)% of the dose was deposited in the lungs, compared with 9.1 (1.5)% of the dose at the slow flow rate ($P < 0.01$). At either flow rate, the majority of the dose was deposited in the oropharynx, and this quantity was significantly higher with slow inhalation ($P < 0.01$). There was a trend towards a reduced bronchodilator response at the lower flow rate, but this did not reach statistical significance. It is concluded that Turbuhaler works optimally at a fast inhaled flow rate, but functions adequately at a lower flow rate which some patients may find easier to attain.

Introduction

Dry powder inhalers have been developed as an alternative to pressurised metered dose inhalers (MDIs), since many patients cannot use MDIs correctly. The major errors in inhaler technique are either poor coordination or failure to continue inhaling when the propellant spray reaches the back of the throat (Crompton, 1982; Pedersen et al., 1986). Chlorofluorocarbon (CFC) propellants in pressurised MDIs also cause environmental damage (Newman, 1990). Dry powder inhalers are breath-actuated, the patient's inspiratory effort being used to disperse the drug particles in the inhaled air stream, and hence do not use propellants. Turbuhaler (Astra Pharmaceuticals) contains 200 doses of 0.5 mg terbutaline sulphate as a dry powder (Wetterlin, 1988) but with no additives; since it is small, portable and multi-dose, it maintains the useful practical advantages of the pressurised MDI. Turbuhaler has proved easy to use and patients often prefer it to a conventional pressurised aerosol (Engel et al., 1989). Particle deposition (Newman et al., 1989) and clinical efficacy (Persson et al., 1988; Engel et al., 1989) are similar to those from pressurised devices. The efficacy of Turbuhaler depends upon delivering an adequate mass of drug in 'respirable' particles (Persson and Wirén,

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1989), and this mass will vary according to the flow rate of air through the device (Jaegfeldt et al., 1987). The objective of the present study was thus to assess the aerosol deposition and bronchodilator efficacy of radiolabelled terbutaline sulphate using two different inhaled flow rates in a group of asthmatic subjects.

Materials and Methods

Turbuhaler was labelled with the radionuclide Tc99m (physical half-life 6 h, gamma ray energy 140 KeV), using the technique of Newman et al. (1989). Briefly, Tc99m was extracted out of the aqueous phase in chloroform and was added to 50 mg spheronised terbutaline sulphate in a small heated beaker. Following the almost immediate evaporation of the chloroform, the powder was added to an empty inhaler. A mouthpiece was attached, and the inhaler was primed by extracting 10 doses into a filter by a vacuum pump. Tests with a multistage liquid impinger had shown previously that the distributions within the impinger stages of untreated drug, drug treated with chloroform/Tc99m and radiolabel were similar, suggesting that the radiolabel would act as a marker for the presence of the drug in vivo (Newman et al., 1989).

Studies were performed on 10 patients with a clinical diagnosis of asthma. Five were male and 5 female, and their ages ranged from 22 to 78 years. Each patient had previously demonstrated an increase in forced expiratory volume in 1 s (FEV1) exceeding 15% following inhalation of a bronchodilator aerosol. Patients gave informed consent in writing, and the study was approved both by the Administration of Radioactive Substances Advisory Committee in the U.K. (ARSAC) and by the Ethical Practices Sub-Committee of the Royal Free Hospital.

Patients each performed 2 radioaerosol studies, in a randomised order, at least 48 h apart, with targeted peak inhaled flow rates (PIFRs) of 60 (fast) and 30 (slow) l/min. Prior to each test, patients withheld the use of inhaled beta-agonists for 12 h, inhaled ipratropium bromide for 24 h and oral methyl-xanthines for 48 h. On arrival at the laboratory, lung function tests (FEV1, peak expiratory flow rate (PEFR) and maximum mid-expiratory flow rate (MMFR)) were first measured by Vitalograph Compact spirometer (Vitalograph; Buckingham), the best of three attempts being taken as the true measure of lung function. Baseline FEV1 did not vary by more than 15% between the study days.

Having practiced inhalation through a dummy inhaler, patients were then administered a single 0.5 mg dose of labelled terbutaline sulphate from Turbuhaler, which was connected in series with a Vitalograph Compact modified for inhalation. This instrument gave a record of inhaled volume, PIFR, time to reach peak flow and breath-holding pause. Data were accepted only if the PIFR was between 50 and 70 l/min when the targeted value was 60 l/min, and between 20 and 40 l/min when the targeted value was 30 l/min. Breath was held for 10 s and exhalation was then performed via a filter to trap exhaled particles.

Immediately following inhalation, a single posterior–anterior view of the chest and stomach, and a single lateral view of the oropharynx were taken by an Ohio 110 gamma camera connected on-line to a Nodecrest data processing system (Newman et al., 1988, 1989). Counts were corrected for tissue attenuation during their passage to the detector. Pulmonary function tests were repeated 15, 30 and 60 min after inhalation.

A calibration dose was taken from Turbuhaler into a filter by a vacuum pump, and the percentages of the dose on the inhaler mouthpiece and on the exhalation filter were determined by comparing the radioactive count rates of these items with that of the calibration filter. Radioaerosol that was not recovered on the mouthpiece or on the exhalation filter was assumed to be in the patient, and was divided into lung and oropharyngeal fractions according to the attenuation-corrected counts recorded over each site.

Results

One of the 10 patients did not complete both radioaerosol studies, but did inhale terbutaline sulphate at both flow rates. The fractionation of

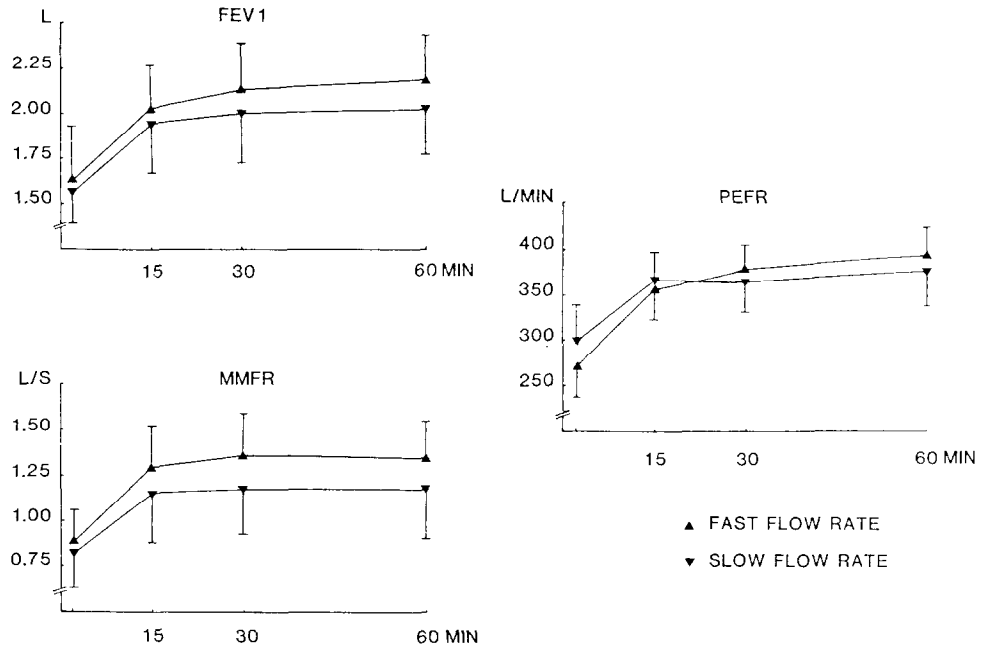

Fig. 1. Mean (+SE) values of FEV1, PEFR and MMFR immediately prior to inhalation of 0.5 mg terbutaline sulphate via Turbuhaler, and then 15, 30 and 60 min later, for fast (approx. 60 l/min) and slow (approx. 30 l/min) inhalations through Turbuhaler.

the drug dose for fast and slow inhalations is shown in Table 1 for the 9 patients who inhaled radioaerosol at both flow rates. Inhalation at the faster flow rate resulted in a significant increase in deposition in the lungs ($P < 0.01$, multivariate analysis of variance), which was almost exactly matched by a significant decrease in deposition in the oropharynx ($P < 0.01$). The percentages of the dose on the mouthpiece and in the exhaled air were similar for the 2 study days.

TABLE 1

Mean (SE) percentages of the dose deposited at various sites after inhalation from Turbuhaler at fast (approx. 60 l/min) and slow (approx. 30 l/min) inhaled flow rates

% deposited in	Fast flow	Slow flow	*P*
Lungs	16.8 (2.6)	9.1 (1.5)	< 0.01
Oropharynx	69.8 (2.3)	79.2 (2.4)	< 0.01
Mouthpiece	12.8 (1.0)	11.2 (1.3)	n.s.
Exhaled air filter	0.5 (0.2)	0.4 (0.1)	n.s.

TABLE 2

Mean (SE) baseline lung function values, and inhalation details for studies at fast (approx. 60 l/min) and slow (approx. 30 l/min) inhaled flow rates

	Fast flow	Slow flow	*P*
Baseline FEV1 (l)	1.61 (0.26)	1.59 (0.26)	n.s.
Baseline PEFR (l/min)	270 (32)	296 (34)	n.s.
Baseline MMFR (l/s)	0.86 (0.20)	0.84 (0.18)	n.s.
PIFR (l/min)	56.6 (1.7)	27.9 (0.8)	< 0.01
Inhaled volume (l)	2.17 (0.24)	2.26 (0.32)	n.s.
Time to reach peak flow (s)	0.6 (0.1)	1.0 (0.3)	n.s.
Breath-holding pause (s)	9.0 (0.3)	8.6 (0.4)	n.s.

Changes in FEV1, PEFR and MMFR are shown in Fig. 1. There was a trend towards greater response with fast inhalation, but the areas under the bronchodilator response curves for the 2 study days were not significantly different.

The baseline lung function values and details of the inhalation manoeuvres are shown on Table 2. PIFR was significantly higher on the fast flow day ($P < 0.01$), but there were no differences between the study days in baseline FEV1, baseline PEFR, baseline MMFR, inhaled volume, time to reach peak inhaled flow or breath-holding pause.

Discussion

The finding of reduced oropharyneal deposition, and consequent enhanced lung deposition, at the faster inhaled flow rate is an apparent paradox in terms of classical aerosol physics. Both theory (Agnew, 1984) and experiment (Lippmann and Albert, 1969; Heyder et al., 1986) predict that for any given aerosol size, deposition in the oropharynx is enhanced with fast inhalation. However, particle size from Turbuhaler is modified by the speed of inhalation. Rapid inhalation de-aggregates particles of drug, mainly in the spiral channels in the inhaler mouthpiece, and doubling the flow rate through Turbuhaler approximately doubles the mass of drug contained in 'respirable' particles equal to or smaller than 5 μm diameter (Jaegfeldt et al., 1987). Since the probability of impaction is proportional to the square of particle size but is only directly proportional to inhaled flow rate, the reduction in particle size has an effect greater than that of increasing the flow per se. Hence the net effect of increasing the flow rate through Turbuhaler is that of reducing particle impaction in the oropharynx and increasing drug delivery to the lungs. The percentage of the dose delivered to the lungs from Turbuhaler was similar to that observed for other powder inhalers (Vidgren et al., 1988, 1990).

Our findings indicate that inhalation through Turbuhaler should be fast for optimal particle deposition in the respiratory tract. At a lower flow rate (30 l/min), drug delivery to the lungs was significantly reduced, although there was not a significant reduction in the efficacy of a standard dose of 0.5 mg terbutaline sulphate. This indicates that the lower amount of drug delivered to the lungs at a PIFR of about 30 l/min is sufficient to give a virtually full bronchodilator response to 0.5 mg terbutaline sulphate in adult asthmatic patients. The distribution patterns of radioaerosol within the lungs may have differed between the two inhaled flow rates, but we did not attempt to quantify this since Kr81m scans, used to define the lung edges, were not obtained in these patients.

Other studies have compared the efficacy of terbutaline sulphate Turbuhaler by different inhalation modes, although no previous study has assessed the effect of inhalation mode on drug deposition. In asthmatic children, Pedersen et al. (1990) found that inhalations at 60 and 31 l/min were equally efficacious, although with reduced efficacy at 22 and 13 l/min. In adults, Dolovich et al. (1988) found that inhalations at 60 and 30 l/min produced similar changes in FEV1, but that changes in indices of small airways function were reduced at the lower flow rate. In our study, changes in MMFR (also an index of small airways function) were not significantly different between the two flow rates. The additions to the basic inhalation manoeuvre of breath-holding, head tilting to make a straighter path for the aerosol and exhalation to residual volume prior to inhalation, did not further enhance the response in asthmatic children (Hansen and Pedersen, 1989). Hence a simple inhalation technique is possible, which should enhance patient compliance. Preliminary exhalation *through the device* should be avoided as this may blow some of the drug powder out of the dosing disk (Engel et al., 1990b).

Although the performance of other currently available powder inhalers is dependent upon the inhaled flow rate (Groth and Dirksen, 1983; Pedersen, 1986; Auty et al., 1987), there is probably a minimum flow rate for each device at which full drug efficacy is maintained. The results of this and other studies (Dolovich et al., 1988; Engel et al., 1990b; Pedersen et al., 1990) suggest that for Turbuhaler this flow rate is approximately 30

l/min. Measurement of PIFR in large groups of children (Pedersen et al., 1990) and adults (Engel et al., 1990a) have suggested that virtually any adult asthmatic and most asthmatic children over 6 years of age can attain this flow rate through Turbuhaler, although not all wheezy children younger than 6 years of age will be able to do so.

In conclusion, drug delivery from the terbutaline sulphate Turbuhaler is optimised at an inhaled flow rate of 60 l/min, although the device virtually retains its efficacy at a lower flow rate of 30 l/min which some patients may find easier to attain. The importance of a breath-holding pause in adult subjects, and the effect of inhaled flow rate upon the delivery of the non-water soluble drug budesonide from Turbuhaler, remain to be determined in further studies.

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