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DOUBLE-BLIND TRIAL WITH STANDARD DOSES OF FENOTEROL AND SALBUTAMOL IN ASTHMATIC CHILDREN

By

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In recent years therapeutic resources for the treatment of asthma bronchiale have been supplemented with selective β_2 -receptor stimulators (5). This has increased our means of dealing with conditions of bronchial obstruction with greater accuracy and less risk of side-effects. These drugs have already proved to have a wide therapeutic range with only very slight side-effects, such as muscular tremor and increased heart rate, when given in normal dosages with dose-aerosol. When the drug is administered orally or parenterally (13) the risk of these side-effects grows considerably.

The first drugs with selective β_2 -receptor stimulating properties to be introduced on the market were salbutamol (Ventoline®) and terbutalin (Bricanyl®), both possessing well-documented bronchodilating properties. Another drug with the same characteristics has now been introduced, viz. fenoterol (Berotec®). It represents a further development of orciprenaline (Alupent®), though lacking its cardiotropic properties. Comprehensive pharmacological documentation is available regarding β_2 -selectivity, pharmacokinetics, and metabolism (2, 4, 10, 12). Clinical investigations of the effect of fenoterol on the lung function of adult asthmatic patients indicate its favourable therapeutic properties (1, 3, 6, 7, 8, 9, 11). As regards children, the bronchodilating properties of the drug

have only been studied with respect to its capacity for preventing exercise-induced asthma (14). The aim of the present investigation is to compare the bronchodilating effect of the drug and its action, if any, on the circulation of a number of asthmatic children with the already well-known substance, salbutamol (Ventoline®), in standard dosages.

MATERIAL AND METHOD

The investigation comprises 16 children, i.e. 15 boys and 1 girl, suffering from chronic asthma and aged 7–13 years ($M = 10.4$ years). Bronchial obstruction was manifest in all of these patients (Table 1). They were all outpatients at the Paediatric Clinic, Huddinge Hospital.

TABLE 1

Dynamic Lung Function in 16 Asthmatic Children 7–13 Years Old, Calculated and Initial Values. SD = Standard Deviation.

		M_1	SD
Calculated	FEV _{1.0}	2.14	0.41
Basal	FEV _{1.0}	1.51	0.55
Calculated	VC	2.52	0.56
Basal	VC	1.90	0.50

All had positive reactions to skin tests and bronchial provocation. X-ray controls of the lungs showed normal conditions in all cases. One of the patients was on continuous steroid therapy in aerosol form (Becotide®). At the time of the investigation all patients were free from clinical symptoms and infection.

Bronchodilating substances were administered to the patients by means of the conventional masked aerosols containing identical propellant gases and in the following dosages:

Fenoterol (Berotec®)	1 inhalation (200 µg)
Salbutamol (Ventoline®)	1 inhalation (100 µg)

Dynamic spirometry, forced expiratory volume during the first second (FEV_{1.0}) and vital capacity (VC), were carried out with a Vicatest dry spirometer (Mijnhardt–Holland). The best value of three trials was noted. The heart rate (HR) was determined manually, by palpation of the radial artery. The study was performed on 3 consecutive days. All symptomatic treatment, including steroid therapy for one of the children, was suspended at least 12 h before the trials.

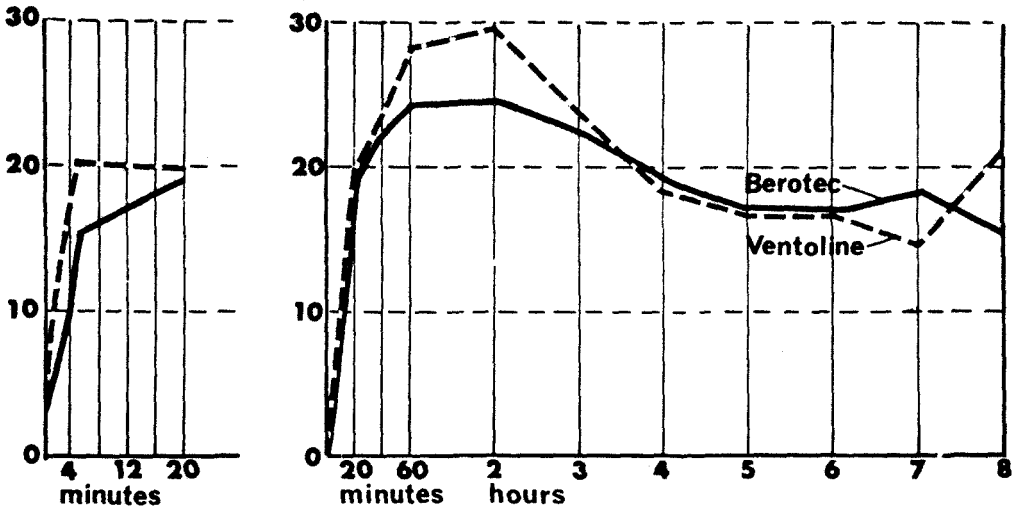
Per cent change in FEV_{1,0}

Fig. 1.

Changes in mean-values of FEV_{1,0} after inhalation of Berotec (200 µg) and Ventoline (100 µg) as compared with the initial values ($M = 1.51$ l) in 16 asthmatic children.

On the first day the patients were trained in maximal expiration with the Vicatest spirometer, and in inhalation technique with a placebo aerosol.

On the second and third day the trials were performed with the double-blind technique, cross-over comparison and randomized order. The initial values of FEV_{1,0} and VC were determined at 8 a.m. The patients then inhaled the active substance, after which FEV_{1,0}, VC and HR were recorded after 1, 3, 5, 20, 40 and 60 min, and then every hour for 7 h.

The initial values of FEV_{1,0} and VC in the fenoterol and salbutamol groups were compared (Student's t-test for two independent groups). No significant differences were found. Nor was there any significant difference between the initial value of FEV_{1,0} and VC on the second and third day (Student's t-test for paired observations). It is therefore likely that the patients' initial values were identical, irrespective of the order of treatment. Any carry-over effect should be regarded as negligible.

RESULTS

Fig. 1 shows that a rapid increase of FEV_{1,0} occurred after the inhalation of salbutamol and fenoterol. The deviation from the initial value is significant after 5 min (Student's t-test with a 95 per cent confidence interval), reaching its maximum

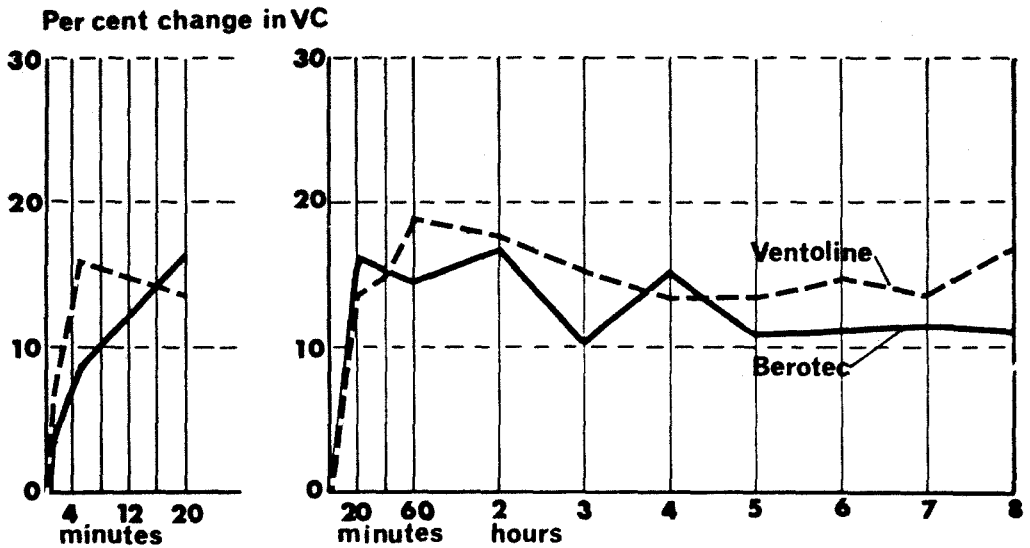


Fig. 2.

Changes in mean-values of VC after inhalation of Berotec (200 mcg) and Ventoline (100 mcg) as compared with the initial values ($M = 1.90$ l) in 16 asthmatic children.

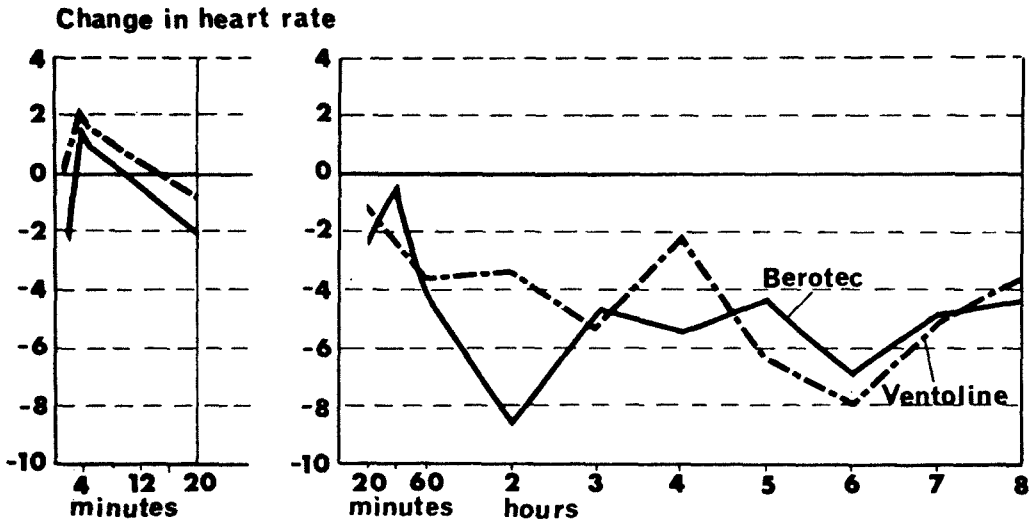


Fig. 3.

Mean heart rate changes in 16 asthmatic children after inhalation of bronchodilator drugs, Berotec (200 mcg) or Ventoline (100 mcg).

after 120 min. After 7–8 h, there is no longer any statistically significant difference between the values obtained and the O-value. The same applies to the change in VC, though the maximum value was obtained after approximately 60 min

(Fig. 2). A complete return to initial values was still not in evidence 8 h after inhalation of the active substances.

There was no significant difference between salbutamol and fenoterol as regards time of response to the drugs, maximal effect, and duration of the dosages administered. Nor did the same dosages cause any increase in the heart rate (Fig. 3). None of the patients felt any subjective discomfort whatsoever after inhaling the active substance.

DISCUSSION

It may be inferred from the present study that the children with bronchial asthma in the age-group 7–13 years were well able to tolerate fenoterol in the normal, specified dosage of 200 μg . Fenoterol has a rapid bronchodilating effect and the duration seems satisfactory. This has previously been confirmed in clinical trials with adults (3, 9). There was no significant difference between salbutamol and fenoterol as regards the bronchodilating effect. Five minutes after inhalation, the two drugs produced a significant increase in FEV_{1.0} and VC, attaining a maximal value after 120 and 60 min, respectively. However, salbutamol had a more rapid increase and also a somewhat higher maximal value than fenoterol, none of the differences were significant (Student's t-test for paired observations).

A number of studies are available concerning comparisons between the response time, maximal effect and duration in different β_2 -receptor stimulators (1, 6, 7, 8, 11). Different results have been obtained, depending on whether the trials were made with doses defined as equipotent, or the same number of inhalations of the substances used. In one particular study (8) two inhalations of fenoterol (400 μg), salbutamol (200 μg), terbutalin (500 μg) and orciprenaline (1500 μg) were compared and fenoterol was found to give the most rapid and most conspicuous increase of FEV_{1.0}. Another trial with fenoterol and salbutamol in a dosage of two inhalations each gave the same result. However,

the difference was not significant with one inhalation of either drug, nor when one inhalation of fenoterol was compared with two inhalations of salbutamol. In another comparative study (6), using what is defined as equipotent doses of fenoterol (400 μg), salbutamol (400 μg) and terbutalin (500 μg), the difference between these three drugs was not established as significant until after 6 h. It was then found that the remaining effect of fenoterol on $\text{FEV}_{1.0}$ was more pronounced than with the other two drugs. It is difficult to find in the available literature any dose-response curves of the three β_2 -receptor stimulators which were compared in this study, nor is there any definition as to what signifies equipotent doses. In all probability, the differences in response time, maximal effect and duration of the respective drugs are contingent to dosage. As only single doses of fenoterol and salbutamol were administered in the present study, it is impossible to draw any conclusions concerning the therapeutic range of fenoterol. The aim of this study was not to determine the dose-response curves but, simply, to compare the broncho-relaxing and possible cardiotropic effects of the drugs in recommended standard doses in routine clinical treatment.

Inhalation therapy in broncho-obstructive conditions with drugs stimulating both the β_1 -receptors and β_2 -receptors (isoprenalin and orciprenalin) involves an added risk of cardiac side-effects. Besides, these drugs have a short duration, which often necessitates frequent inhalation in acute cases with the ensuing risk of overdosage and side-effects. The recommended restricted use of these drugs must be considered as justified. Since the introduction of modern selective β_2 -receptor stimulators on the market, the therapeutic situation has improved. They provide a better therapeutic effect and, at the same time, prevent undesirable side-effects such as muscular tremor and tachycardia. Thus, modern β_2 -receptor stimulators in aerosol form are especially appropriate for the treatment of acute broncho-obstructive conditions. Fenoterol (Berotec®) seems to defend its position in the therapeutic arsenal used in pediatric allergological routine treatment.

SUMMARY

The broncho-dilating effect of fenoterol in aerosol form was studied in 16 children with asthma. The drug was compared with salbutamol in standard doses in a double-blind trial. Dynamic spirometric tests ($FEV_{1.0}$ and VC) were performed before and up to 8 h after inhalation. There was a significant increase in the expiratory flow 5 min after inhalation of the two drugs. Maximal values were reached in 60–120 min. After 7–8 hours the increase was no longer significant. There were no significant differences between the two drugs tested. As no cardio-vascular side-effects or subjective discomfort was noted, fenoterol will be of great value in the routine treatment of children with asthma bronchiale.

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