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A trial of clenbuterol in bronchial asthma

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Anderson, G. and Wilkins, E. (1977). *Thorax*, **32**, 717–719. **A trial of clenbuterol in bronchial asthma.** Clenbuterol is a β_2-sympathomimetic bronchodilator. In a double-blind cross-over trial in 19 asthmatic patients with reversible airways obstruction, oral administration of both clenbuterol (40 μg) and salbutamol (4 mg) caused significantly greater increases in peak expiratory flow rate (PEFR) than placebo, that of clenbuterol lasting longer. The patients' subjective assessment also suggested the relief of their symptoms by the active drugs. Side-effects were minimal.

Clenbuterol is a recently synthesised sympathomimetic agent with a specific affinity for the β_2-adrenergic receptors in the bronchial musculature. Animal studies have shown that its bronchodilator action is more prolonged than that of orciprenaline and salbutamol (Engelhardt, 1976). The purpose of this study was to compare in a double-blind cross-over manner the effects of clenbuterol, salbutamol, and placebo in patients with bronchial asthma.

Patients and methods

Nineteen patients with bronchial asthma were studied. All showed an improvement in peak expiratory flow rate (PEFR) exceeding 15% five minutes after inhaling 2 puffs (0·16 mg) of isoprenaline. The characteristics of the patients are shown in Table 1. All bronchodilator drugs were stopped at least 10 hours before the trial, but patients taking corticosteroids and sodium cromoglycate continued to do so.

After giving informed consent patients were trained to record PEFR following the method of Lal *et al.* (1974). On a practice day before the trial they were instructed on rising to make three technically acceptable readings of PEFR at 10-minute intervals until two consecutive readings were within 10 l/min. The higher reading was accepted as a basal value (time 0). Three PEFRs were recorded 10, 20, and 30 minutes and 1, 2, 3, 4, 6, 8, and 10 hours after the basal value. Values were recorded on a standard form together with a record of any side-effects and the time of their occurrence.

Table 1 *Details of patients studied*

Total no. of patients	19	
Males	10	
Age, years (mean and range)	50	(18–71)
Positive skin tests	13	
Blood eosinophilia ($>0{\cdot}5\times10^9$/l)	4	
Steroid treatment during trial	12	
Cromoglycate treatment during trial	6	

Patients recorded a subjective impression of their breathing during the test day. This was compared to that on the day before the trial and scored as 1, worse; 2, no change; 3, a little better; 4, much better; 5, very much better. Patients were told to contact the physician if any difficulties were experienced during the trial period.

After completing the practice day patients were studied over three consecutive days and were given sealed packets each containing three tablets, two white and one coloured. Each patient was given in random order the following drugs: placebo day, two white tablets (placebo) and one blue tablet (placebo); salbutamol day, two white tablets (placebo) and one pink tablet (4 mg salbutamol); clenbuterol day, two white tablets (2×20 μg clenbuterol) and one yellow tablet (placebo). It has been shown that salbutamol, 4 mg, gives a bronchodilatation effect equivalent to clenbuterol, 40 μg (Kamburoff *et al.*, 1977). The tablets were taken between 0800 and 0900 hours, immediately after obtaining basal values for PEFR. PEFR was then recorded at the same intervals as on the practice day and similar recordings were made of side-effects and breathing scores. Patients were studied as outpatients and were interviewed after the practice day to ensure that they were able to cope with the methods of the trial.

Analysis of variance was carried out at each time-point on the patients' PEFR readings, and Duncan's multiple range test was used to investigate further any differences between treatments. Subjective assessments of breathing were analysed by a Friedman two-way analysis of variance (Siegel, 1956).

Results

The results of mean PEFR in 19 patients are shown in Table 2. During the placebo day there was a slow rise in PEFR until four hours after recording the basal values, when a plateau was reached. These increases were significant ($P<0.05$) at 10 minutes and from one to eight hours.

Table 2 *Mean PEFR in 19 patients*

Time after ingestion of tablets (min)	*Mean % change (± 1 SE)*		
	Clenbuterol	*Salbutamol*	*Placebo*
10	5·4 ± 2·5	7·3 ±3·7	4·8 ±2·3
20	9·8 ± 3·2	14·5 ±4·5	2·9 ±3·3
30	17·4 ab± 5·0	20·5 a ±4·6	4·9 b ±3·6
60	27·9 ab± 4·8	33·6 a* ±6·8	8·8 b* ±3·9
120	40·0 a* ±10·7	40·3 a* ±7·5	12·7 b* ±4·5
180	44·8 a ±13·5	39·9 a* ±7·8	17·8 b* ±5·5
240	51·5 a ±16·8	35·9 a ±8·0	17·7 b ±4·8
360	48·7 a* ±13·8	34·5 a* ±7·9	12·2 b* ±4·6
480	53·8 a* ±18·8	34·0 a ±9·7	15·9 b* ±4·5
600	41·8 a* ±10·9	26·6 ab ±8·7	11·3 b* ±6·1

If any two treatments at the same time point do not have a common letter they are significantly different ($P < 0.05$).
*$P < 0.01$.

With salbutamol there was a significant ($P<0.05$) increase above the baseline values from 20 minutes onwards, the increase being highly significant ($P<0.01$) from 30 minutes to eight hours. Clenbuterol showed a significant increase at every time-point, the increase being highly significant ($P<0.01$) from 20 minutes to 10 hours.

With both salbutamol and clenbuterol there were significant ($P<0.05$) differences from placebo values from two to eight hours. For clenbuterol alone this difference was significant ($P<0.01$) at 10 hours, and for salbutamol alone significant differences were seen at 30 minutes ($P<0.05$) and one hour ($P<0.01$). The differences between the effects of clenbuterol and salbutamol were not quite significant, but were almost so at eight hours.

The results of the breathing scores are shown in Table 3. Eighteen patients produced satisfactory records. While there is an apparent improvement with the active drugs this was not significant. The incidence and nature of side-effects is shown in Table 4. The differences between the number of side-effects with placebo (6), salbutamol (5), and clenbuterol (10) were not quite significant.

Table 3 *Results of breathing scores*

Result		*Clenbuterol*	*Salbutamol*	*Placebo*
Very much better	(5)	1	1	0
Much better	(4)	6	7	4
A little better	(3)	8	6	3
No change	(2)	3	4	10
Worse	(1)	0	0	1

Table 4 *Side-effects in 19 patients*

Side-effect	*Clenbuterol*	*Salbutamol*	*Placebo*
Tremor	4	3	1
Headache	2	0	2
Dizziness	1	0	1
Feeling of warmth	2	1	0
Cough	1	0	1
Nasal discharge	0	1	0
Chest pain	0	0	1

Discussion

Oral administration of clenbuterol and salbutamol produced a significantly better bronchodilatation than did placebo. This effect was present for up to eight hours with salbutamol and for up to 10 hours with clenbuterol, suggesting a longer duration of action of the latter. The prolonged effect of clenbuterol accords with the results of pharmacokinetic studies in man, where a plasma half-life of about 35 hours has been demonstrated (Zimmer, 1976). Clenbuterol is not subject to the action of catechol-o-methyl transferase and this partly explains its prolonged action, which may also be a function of its firm binding at the β-receptor (Engelhardt, 1976). The long plasma half-life and consequent cumulative effect may allow small doses to be given two or three times daily to produce an effect equivalent to the single doses of 40 μg in this study.

The increase in PEFR with placebo treatment was also noted by Salorinne *et al.* (1975), who attributed it to a combination of the normal diurnal variation of PEFR in asthma and placebo effect. With both salbutamol and clenbuterol the side-effects were minor.

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