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An economical method of comparing inhaled bronchodilators in reversible diffuse airways obstruction

With special reference to a β-2 stimulant—salmefamol

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Lal, S., Dash, C. H., and Gribben M. D. (1974). *Thorax*, **29**, 317–322. **An economical method of comparing inhaled bronchodilators in reversible diffuse airways obstruction: with special reference to a β-2 stimulant—salmefamol.** A method is described for comparing the bronchodilator effect of a large number of drugs. It involves self-recording of peak expiratory flow rate by patients at home. From the experience gained, the method was used to compare isoprenaline, orciprenaline, terbutaline, salbutamol, and salmefamol with an inert pressurized aerosol. The results of the comparison show that the method is simple and practical and that salmefamol would seem to have a more prolonged bronchodilator effect than the other drugs tested.

The usual method of comparing single doses of bronchodilators (for degree and duration of effect) requires each patient to attend the laboratory several times—one day for each drug to be tested plus a day for the control test. On each occasion the necessary measurements are repeated by the technician at fixed-time intervals before and after drug administration. This procedure is time-consuming for technicians in busy hospital research/service laboratories and also limits the number of patients to those who can take time off work or away from domestic commitments.

There is general acceptance that the more sophisticated measurements, such as airways resistance, have little or no advantage in clinical practice over simpler measurements such as forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEFR). Moreover, a readily portable instrument is available in the Wright peak flow meter (Wright and McKerrow, 1959), and the recordings made on this apparatus correlate well with FEV_1 (Lal, Ferguson, and Campbell, 1964). A reasonable method, therefore, would be to ask patients to record PEFR at fixed intervals without interrupting their usual daily duties. Such a method would be less arduous for both the patient and the technician. This aspect becomes more important as longer-acting drugs are developed. We describe here such a method and also the effect of a new long-acting bronchodilator, salmefamol (AH 3923) (Hartley, Jack, Lunts, and Ritchie, 1968; Kennedy and Dash, 1972), in comparison with other β-stimulants, salbutamol, terbutaline, orciprenaline, and isoprenaline, all given by metered aerosol.

MATERIALS AND METHODS

All patients selected for study suffered from reversible airways obstruction and were known to show at least 15% improvement in their FEV_1 with bronchodilators. The drugs, namely orciprenaline 1·5 mg, terbutaline 500 μg, isoprenaline 200 μg, salbutamol 200 μg, salmefamol 200 μg, and a placebo, were delivered by two inhalations from metered aerosols. The first three drugs were contained in commercially available canisters but none of the patients was familiar with these. The last three drugs were contained in three identical canisters which were not commercially available. All six canisters were given the same label. Each patient was supplied with a box containing 12 aerosols, two of each. The aerosols were labelled days 1–12. The code was such that each of the five active aerosols was used once in the first five days and for the second time in the second five days (distributed randomly) while the placebos were allocated to days 11 and 12. Thus, for practical purposes, the trial was double-blind

except for the last two days when the physician was aware that placebo was being used, but the patients were unaware of this.

Each patient was asked to start the procedure first thing in the morning and to keep to approximately the same time each day. The patient was instructed to record three technically acceptable PEFRs and to repeat this procedure at 10-minute intervals until two consecutive groups of readings were within 10 l/min, after which two inhalations were to be taken from the appropriate aerosol. Ten minutes later he was to record three PEFRs and then repeat the measurements at hourly intervals. Because we did not wish the patient to record PEFR unnecessarily, he was told to stop when any one of the following circumstances occurred:

1. PEFR returned to pre-drug levels, or
2. the need was felt to inhale from an openly labelled salbutamol aerosol, or
3. 10.00 pm arrived.

At the end of each day of the study the patient was asked to say whether he had felt 'very much worse', 'a little worse', 'the same', 'a little better' or 'very much better' than on the preceding day.

Patients had their usual oral bronchodilator withdrawn during the 12 days of the trial, but disodium cromoglycate and steroids were generally continued unchanged.

This type of study can be thought of as a 'steady-state' trial: the effects of the drugs are investigated while the clinical condition of each patient is reasonably static. Ideally for such a trial, when all the patients have been selected, a session is specially arranged for their instruction and the initiation of the trial. This was achieved in the present study. Twenty-three patients attended and they were divided into four groups of five or six. Each group was carefully instructed in the procedure to be adopted. All patients were experienced in the use of the flow meter and metered aerosols, but their ability to carry out the manoeuvres was reaffirmed at this session.

At the end of the study, two weeks later, the aerosols and record sheets were collected. The best of the three acceptable PEFRs at each interval was used in all the subsequent calculations. Analysis of variance and Duncan's test (Harter, 1960) were applied to the peak measurement of PEFR and the duration of the effect after each drug. The changes in PEFR were expressed as percentage improvement compared with the pre-drug baseline values. When the PEFR after the drug had returned to, or within 5 l/min. of, the pre-drug level, or the patient used an openly labelled salbutamol aerosol for relief of bronchospasm, or 10.00 pm arrived, the PEFR at subsequent intervals was recorded as showing zero change from baseline. Thus in no instance was a negative percentage change possible. A scoring system was allocated to the patient's subjective assessment and these data were then analysed by the χ^2 test.

RESULTS

Twenty patients (7 males and 13 females) satisfactorily completed the study; their ages ranged from 22 to 59 (mean 40) years and their predicted PEFRs (Cotes, 1968) from 430 to 630 (mean 520) l/min. The other three patients (1 male and 2 females) either did not fully understand the instructions given or were unable to complete the repeated recordings. The baseline PEFRs of the groups on the six kinds of aerosols did not differ significantly and the means of each group ranged from 35·7 to 38·8% of the predicted means.

It is now recognized that patients with diffuse airways obstruction have a low PEFR in the morning which gradually improves over the next few hours. This phenomenon is well illustrated following placebo aerosol in Fig. 1, which also shows the mean improvement in PEFR for the other five aerosols over a period of 12 hours. The curves return to the baseline when all the patients on that drug have satisfied one of the three aforementioned criteria (see Materials and Methods). By removing the diurnal changes in PEFR (as shown by the placebo response) from the changes observed after the test drugs, the effect of the bronchodilators can be compared more realistically (Fig. 2). As one would expect, isoprenaline shows an initial bronchodilatation which decreases rapidly. The other four more selective β-adrenoreceptor stimulants maintain the improvement for much longer periods.

The duration of effect varied widely between patients. The longest acting drug for each patient, based on the mean duration of the two treatment days for that drug, is shown in Table I.

TABLE I

NUMBER OF PATIENTS NOTING LONGEST IMPROVEMENT IN PEFR AGAINST PARTICULAR AEROSOLS

Drug	Dose (μg)	No. of Patients
Isoprenaline	200	2[1]
Orciprenaline	1,500	1
Salbutamol	200	2[1]
Salmefamol	200	12[1]
Terbutaline	500	4[1]
Placebo		2

[1]Indicates patients in whom there was no difference in duration of bronchodilatation between two drugs (in one patient salbutamol tied with isoprenaline and in another with terbutaline, salmefamol tied with terbutaline in one further patient).

Both the duration of bronchodilatation and the maximum effect obtained were calculated from the original data. Analysis of variance demon-

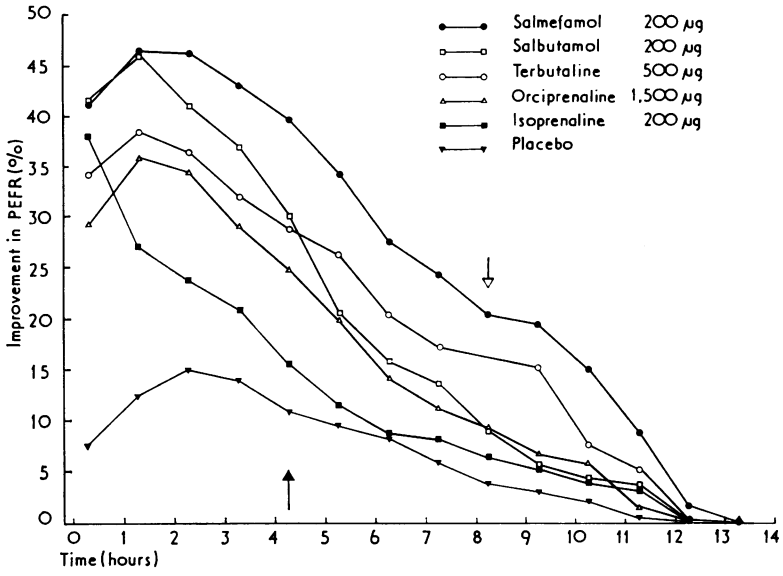

FIG. 1. *Mean improvement in peak expiratory flow rate as a percentage of baseline recordings. The arrows indicate when 50% of the records for isoprenaline (▲) and salmefamol (△) were still showing an improvement in PEFR. For the other drugs this occurred at times intermediate between those for isoprenaline and salmefamol.*

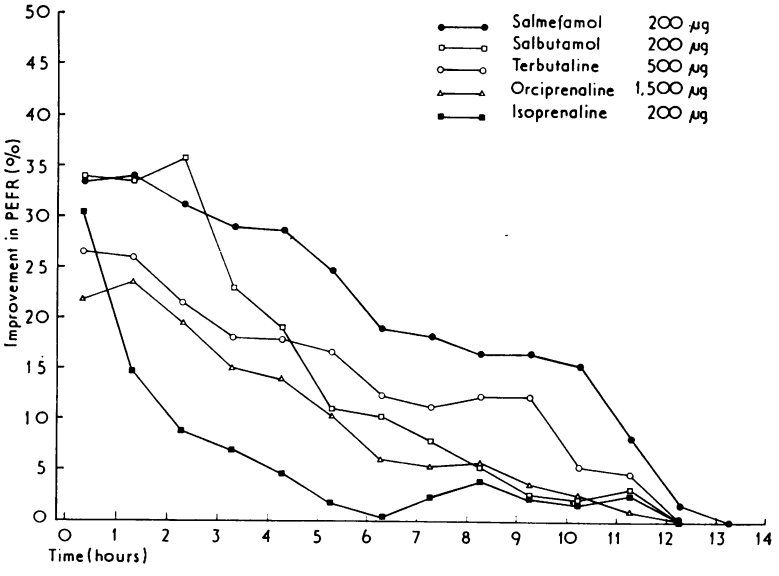

FIG. 2. *Mean improvement in peak expiratory flow rate as a percentage of baseline recordings after subtraction of the 'placebo' effect.*

strated for both parameters a significant difference between treatments ($P<0.001$). The means of these parameters are shown in Tables II and III.

TABLE II

MEAN DURATION OF BRONCHODILATATION FROM EACH AEROSOL

Treatment	Mean Duration (hr)	Results of Duncan's test (Harter, 1960)
Placebo	5·1	}
Isoprenaline	5·6	}
Orciprenaline	6·1	}
Salbutamol	6·5	}
Terbutaline	7·0	}
Salmefamol	8·4	

The brackets indicate those treatments which are not significantly different from one another but which are different from the treatments outside the brackets ($P < 0.05$).

TABLE III

MEAN PEAK IMPROVEMENT IN PEFR FROM EACH AEROSOL

Treatment	Mean Peak Improvement (l/min)	Results of Duncan's test (Harter, 1960)
Placebo	42	}
Isoprenaline	77	}
Orciprenaline	87	}
Terbutaline	93	}
Salbutamol	99	}
Salmefamol	109	

The brackets indicate those treatments which are not significantly different from one another but which are different from the treatments outside the brackets ($P < 0.05$).

Application of Duncan's test allows comparisons between all the treatments and revealed significant differences ($P<0.05$) between the group of drugs within and the drugs outside the brackets in the tables. Orciprenaline, salbutamol, and terbutaline differed from the others in duration of effect but not from one another, as did placebo, isoprenaline, orciprenaline, and salbutamol. Salmefamol had a significantly longer effect than any of the others (Table II). The peak bronchodilator effect of salmefamol, salbutamol and terbutaline differed from that of the others but not between one another; the same holds true for orciprenaline, terbutaline, and salbutamol and also for isoprenaline, orciprenaline, and terbutaline. The increase in PEFR after placebo aerosol was significantly less than after any of the drugs tested (Table III).

The patients' subjective assessment each day was scored one for 'very much worse' to five for 'very much better' than the previous day (Table IV).

TABLE IV

MEAN SCORES FOR SUBJECTIVE COMPARISONS OF TWO DRUGS GIVEN ON CONSECUTIVE DAYS

Drug comparisons[1]	Score[2]	Preferred Drug of the Pair
Same two drugs	3·02	
Orciprenaline/terbutaline	2·84	Orciprenaline
Terbutaline/isoprenaline	2·59	Terbutaline
Isoprenaline/salbutamol	3·54	Salbutamol
Orciprenaline/salmefamol	3·27	Salmefamol
Salbutamol/salmefamol	3·35	Salmefamol

[1]For any pair of drugs in this column the order of administration of the aerosols was approximately equal.
[2]A score of 3 indicates no preferred drug; a score of less than 3 indicates preference for the day when the first mentioned drug was taken; greater than 3 indicates preference for the second specified drug.

Therefore, the same drug given on consecutive days should give a score of three ('the same')—the actual mean score from such comparisons was 3·023. The scores for other drug comparisons are in agreement with those from the objective measurements, except for one comparison—orciprenaline with terbutaline. The days when the former was used were favoured to those when the latter was used, which is at variance with the data in the figures and tables. However, none of these subjective differences was statistically significant.

DISCUSSION

The majority of the patients in this study were able to comprehend and perform the instructions and the results of the controlled comparisons between the drugs are in general agreement with published data obtained by tests done under supervision in the laboratory.

Thus, Choo-Kang, Simpson, and Grant (1969), in a double-blind trial of inhaling isoprenaline 1000 μg, orciprenaline 1500 μg, salbutamol 200 μg, and a placebo, found that salbutamol had a much longer action on FEV_1 and VC than isoprenaline and a slightly more intense and prolonged action than orciprenaline. We also obtained similar responses from these drugs. Freedman (1972) compared the effect of 250 μg terbutaline and 100 μg of salbutamol inhaled by pressurized aerosols in a group of asthmatics and showed that with each drug there were rapid bronchodilatation responses, the amplitude of which was the same for 90 minutes, but the effect was maintained at a higher level after terbutaline than after salbutamol. We, on the other hand, have used twice the doses of terbutaline and salbutamol and shown that the mean PEF is higher with salbutamol but the action lasts longer with terbutaline. However, there is no statistically significant difference in

either of these measurements with these two drugs (Tables II and III). Formgren (1970), using similar dosages to us, showed a longer bronchodilatation with terbutaline than with orciprenaline although the maximum responses were similar. Kennedy and Dash (1972), using 200 μg of both salbutamol and salmefamol, showed salmefamol to be marginally better than salbutamol. Shenfield and Paterson (1973) suggest that 100μg of salmefamol is equivalent to 100 μg of isoprenaline in its bronchodilator effect.

Freedman and Hill (1971) recommend that, to compare the duration of action of different bronchodilator drugs, the maximum effect of each drug should be the same. However, the object of our study was to assess the effect of the drugs in a realistic way, that is to say, in the patient's normal surroundings and in the dosage he is likely to use from the commercially available aerosols (except salmefamol which is not yet available). Therefore, a metered dose of the drug found to be equipotent with isoprenaline by Shenfield and Paterson (1973) was used and compared with the other compounds in their commercial presentations.

The mean peak effect of salmefamol in this study was significantly greater than that of isoprenaline but was not greater than that of salbutamol or terbutaline. However, the duration of action of salmefamol was significantly greater than that of all these other drugs.

Most investigators have either reported the results after the placebo as a comparison with that of active bronchodilator drugs or have apparently not measured the 'placebo' effect. It seems appropriate to subtract the 'placebo' effect from each of the test drugs, particularly when one is studying the newer longer acting drugs, as it is necessary to start each test drug early in the morning when the 'placebo' effect is likely to be most marked.

There are a number of advantages of using the method reported here to compare bronchodilators. First, it does not require a technician and is less time-consuming for the patient. Second, it allows a large number of drugs to be compared, at least in theory. Third, the drug effect is assessed in the patients' normal environment. Finally, a large number of patients can be studied simultaneously, which would not be possible in the laboratory. This reduces the variations between patients due to changes in the weather. In spite of the fact that a number of patients are being studied at the same time, discussion between patients on the progress of the trial is avoided.

The method can readily assess the duration of bronchodilatation produced by aerosol or oral sympathomimetics, whereas the method described by Shenfield and Paterson (1973) is eminently suitable for comparisons of the potency of such drugs by aerosol. This latter method will be of benefit to the pharmaceutical industry by allowing a rapid and accurate decision to be made as to the amount of drug dispersed in each metered dose for clinical trials.

There are some disadvantages inherent in our method. First, the data available are limited by the capabilities of the patients. For example, no information can be collected on the cardiovascular effects of the drugs. Second, slight discrepancies must be accepted concerning times at which the measurements are made, and the patient must be relied upon to carry out the procedures, to take the readings, and to record them precisely.

If this method is used, care is required in selection and instruction of the patients. For this purpose, it is helpful if the patients are instructed in small groups. Not only does this save the physician's time but it also ensures that patients receive similar instructions. It is also essential to have simple instructions on the record sheets. Adequate space must be provided for recording the data, particularly the times of measurements and when other drugs are taken, so that these can be correctly interpreted in the analysis. Of course, the number of patients that can be studied at any one time depends on the number of PEF meters available for any trial; the larger the number of patients studied simultaneously, the greater would be the cost of the meters, but the quicker the trial would be concluded. As we explained the protocol to patients in batches of five to six, this would seem to be an economical number of patients which could be studied at any one time.

CONCLUSIONS

The method of this study, involving self-recording by the subjects as outpatients, would appear to give results which are comparable to those obtained by the more simple of laboratory tests and it would seem that salmefamol has a longer bronchodilator effect than the other drugs tested.

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