Measurement of Response to Isoprenaline in Asthmatic Children*

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Spirometry has made possible the objective assessment of drugs used in the treatment of asthma. Many studies have been carried out to measure the bronchodilator effect of sympathomimetic amines in adults, but few studies on children have been reported.

Lukas (1951) studied 6 asthmatic children between the ages of 11 and 16 years during their symptom-free period, and showed that pulmonary function could be improved by the administration of adrenaline hydrochloride subcutaneously or adrenaline by nebulizer. In a study of 30 symptom-free asthmatic children (6–16 years), Kraepelien (1958) measured the lung volume changes before and after bronchodilators, and found that there was a significant lowering of the residual volume (RV), and functional residual capacity (FRC) after these drugs. Pain and Read (1963) measured the vital capacity (VC) and forced expiratory volume in 1 second (FEV_{1.0}), before and after 1% isoprenaline inhalations in 4 symptomatic asthmatic children (10–13 years). By repeating these measurements daily, they found that the greatest response to therapy was obtained early in an episode of asthma.

The response to bronchodilators may be underestimated, unless the correct timing for the post-bronchodilator tests is chosen. A study was therefore undertaken to measure the response to a bronchodilator in relation to time.

Materials and Methods

Isoprenaline hydrochloride (U.S.P.) was chosen, as it is one of the most active sympathomimetic amines in relaxing the smooth muscle of the bronchial tree when given by inhalation, and acts almost exclusively on the β -receptors of the post-ganglionic adrenergic nerve endings (Goodman and Gilman, 1965). Two aspects were studied: first, the response to an inhalation was measured at timed intervals to discover when the maximum effect occurred; and second, repeated inhalations

were given to test whether the response could be augmented.

The study consisted of 16 patients with asthma, 11 boys and 5 girls, between the ages of 8 and 14 years, who showed on preliminary testing that their forced expiratory volume in 1 second (FEV_{1.0}) was 65% or less of their vital capacity (VC). Their heights ranged from 107 cm. to 155 cm., and 10 patients were between 145 and 155 cm. None of the patients had received bronchodilators for at least 4 hours before the study.

Three initial measurements of the VC and FEV_{1.0} were recorded on a Warren E. Collins 9-litre spirometer.* Our own experience with 139 normal children (data to be published) and reports by Helliessen *et al.* (1958) and Cherniack (1962) indicate that this spirometer has a virtually instantaneous response time and sensitivity to within 25 ml. The highest recording was accepted and corrected to 37 °C., at saturated water vapour pressure. Only 13 of the 16 patients had expiratory peak flow rate (EPFR) measurements recorded on the Wright's Peak Flow Meter† (Wright and McKerrow, 1959).

Each patient was then given 2.5 mg. isoprenaline hydrochloride by inhalation, administered over 3 to 5 minutes, as a 0.5% solution, with a Bennett's nebulizer‡ using compressed air at 7 l./min.

The pulse rate was recorded by a pulse meters§ before, during, and immediately after the inhalation.

After the completion of the inhalation, three measurements of the FEV_{1.0} and EPFR were recorded at 5, 15, and 30 minutes, and the highest recording at each time interval was accepted and corrected as before, and is expressed as the increase, in litres, over the initial recording.

Two further 2.5 mg. inhalations were given; the first 5 minutes after completion of the 30-minute interval recording. Measurements were made again at 5, 15, and 30 minutes after this second inhalation. The whole cycle was repeated with a third inhalation.

Results

Fig. 1 shows the response of each individual

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Received November 11, 1968.

*Supported by grant from the Medical Research Council of Canada, MA 2616.

FIG. 1.—Response of 16 patients to the first isoprenaline inhalation. Results expressed as increase in $FEV_{1.0}$ from the initial baseline measurement against time (minutes).

FIG. 2.—Response of 16 patients to three isoprenaline inhalations, expressed as increase in $FEV_{1.0}$ (l.) against time (minutes).

patient after the first inhalation which is expressed as the increase in litres over the initial base-line level. 13 patients had the maximum response at 5 minutes; of the 3 remaining, 1 had the same response at 5, 15, and 30 minutes, giving a plateau effect; another had maximum response at 15 minutes; and the third not until 30 minutes.

The averaged responses are shown in Table I. The maximum response is between 5 and 15 minutes, for the difference between these measurements is not statistically significant ($0.05 < p < 0.1$). In addition, the drug is effective for at least 30 minutes, for if the average initial $FEV_{1.0}$ is compared with the actual average $FEV_{1.0}$ at 30 minutes, the difference is significant ($p < 0.01$).

Fig. 2 shows the response after three doses, again expressed as the increase of the $FEV_{1.0}$ rather

than the actual measurements. Though there is a great variation from patient to patient, there is a continuing improvement, and a far greater response was obtained 5 minutes after dose 3 in comparison with that 5 minutes after dose 1 ($p < 0.01$). This greater response was maintained for at least 30 minutes after dose 3, giving a plateau effect which can be seen by looking at the percentage improvements after dose 3 (Table I).

Comparing the initial values of the $FEV_{1.0}$ against the actual $FEV_{1.0}$ measurement 5 minutes after dose 1 (see Fig. 4), a good correlation is obtained ($r = 0.827$), but a patient with a low initial $FEV_{1.0}$ has a proportionately greater response than one with a higher initial $FEV_{1.0}$.

If one compares the initial $FEV_{1.0}$ with the

TABLE I

Response of 16 Patients to Isoprenaline Inhalations: Initial $FEV_{1.0}$ (Mean $\pm$ SE) = 0.942 ± 0.116 l.

Measurement	Time after Dose 1 (min.)			Time after Dose 2 (min.)			Time after Dose 3 (min.)		
	5	15	30	5	15	30	5	15	30
Increase in $FEV_{1.0}$ (l.)	0.587	0.526	0.494	0.716	0.691	0.639	0.759	0.732	0.731
Mean $\pm$ SE	± 0.070	± 0.084	± 0.090	± 0.080	± 0.095	± 0.092	± 0.094	± 0.084	± 0.103
% Improvement	62	56	52	76	73	68	80	78	78

TABLE II

Response of 13 Patients to Isoprenaline Inhalations: Initial EPFR (Mean $\pm$ SE) = 156 $\pm$ 19 l./min.

Measurement	Time after Dose 1 (min.)			Time after Dose 2 (min.)			Time after Dose 3 (min.)		
	5	15	30	5	15	30	5	15	30
Increase in EPFR (l./min.) Mean $\pm$ SE	53 $\pm$ 11	49 $\pm$ 11	38 $\pm$ 13	72 $\pm$ 11	65 $\pm$ 14	65 $\pm$ 14	92 $\pm$ 14	84 $\pm$ 11	73 $\pm$ 15
% Improvement	34	31	28	46	42	42	59	54	47

absolute increase in $FEV_{1.0}$, however, there is no correlation ($r = 0.125$).

In those 13 patients in whom the EPFR was also recorded, similar, but smaller, changes to those found with the $FEV_{1.0}$ measurements were seen. The individual measurements are shown in Fig. 3, and the averages are recorded in Table II. The EPFR and $FEV_{1.0}$ are measuring different portions of the flow volume curve, however (Sobol and Emirgil, 1967), and need not necessarily have a good correlation. While the EPFR may not be such a sensitive index, it provides, at the bedside, a valid measurement of the degree of obstructive airway disease, if no other spirometric test is available.

The change in pulse rate from the resting level after inhalations showed a marked individual variation, and was between 10 and 60 beats per minute. There was no correlation between the

rise in pulse rate and the degree of bronchodilatation obtained ($r = 0.248$).

Discussion

How do our results compare with previous studies carried out on adult patients? Chamberlain, Muir, and Kennedy (1962) found that the maximum response was at 5 and 10 minutes in a group of 21 asthmatic patients, when post-bronchodilator $FEV_{1.0}$ measurements were made at 5, 10, and 30 minutes.

El-Shaboury (1964), studying a group of 60 asthmatic and bronchitic patients, found the

FIG. 3.—Response of 13 patients to three isoprenaline inhalations, as measured by the increase in EPFR.

FIG. 4.—Comparison of the initial $FEV_{1.0}$ with the response at 5 minutes. The calculated regression line with 2 SD is drawn ($r = 0.827$).

maximum effect of isoprenaline to be at 15 minutes, when recordings were made at 5 and 15 minutes. Further measurements, made at 15-minute intervals thereafter for the next 3 hours, showed that the asthmatic patients had a significant response (at the 5% level) for as long as 90 minutes, while the bronchitics failed to respond after 60 minutes.

Using the indirect maximum breathing capacity (MBC)* as their parameter, Kennedy and Thursby-Pelham (1964) found a maximum response 5 to 10 minutes after isoprenaline inhalations in a group of 135 adult patients with diagnoses of asthma, bronchitis and emphysema, or both. Looking at the whole group, there was no significant response by 90 minutes.

In Crompton's group of 30 'wheezy' patients (1968), the response to a 2% isoprenaline inhalation, measured by the $FEV_{0.75}$ at 5-minute intervals, showed maximum improvement by 20 minutes. Mushin (1967), however, found that the peak response in his group of 18 asthmatic patients was not until 30 minutes.

That many of these studies were carried out on heterogeneous groups of patients may account for the varying results: a diagnosis of asthma in children may be made with much greater certainty than in adults. Other factors will also influence the results—the dose of isoprenaline administered, the manner in which the inhalation is given, the type of measurement used to assess response, the interval after administration of the drug at which the post-bronchodilator studies were carried out, and the patient's individual response to the drug.

The pulse rate change does not reflect the bronchodilator effect. Inoue (1967), measuring the effects of subcutaneous adrenaline on blood glucose, pulmonary function, and heart rate on 6 asthmatic children, found that the effect on the heart rate was much less consistent than its bronchodilator effect. No similar study, comparing heart rate change and bronchodilator effect, has been carried out after isoprenaline inhalations.

There is some discrepancy in previous studies of the relation between the severity of the initial bronchospasm and response to inhalation therapy. Hume and Gandevia (1957) and Hume and Jones (1961) felt that their patients with severe bronchospasm, as indicated by a small $FEV_{1.0}$, were less responsive to bronchodilators than those with milder disease; Mushin (1967) could find no significant correlation between the initial level of the $FEV_{1.0}$ and absolute improvement; nor could Feinmann and Newell (1963) from their results.

These authors also pointed out that percentage improvement, as opposed to absolute improvement, is negatively correlated with the initial $FEV_{1.0}$, since patients with a high value initially can only improve by 20 to 30% at the most, whereas a patient with an initial low value may improve by 50–60%. Our data in Fig. 4 show this relation clearly.

In terms of initial value against absolute increase, however, no correlation was obtained ($r = 0.125$). The fact that our data can be interpreted both ways explains the discrepancy between the conclusions in previous papers.

It must be realized that the use of the $FEV_{1.0}$ alone has its limitations, for the severity of bronchospasm is measured by the ratio of the $FEV_{1.0}$ to the VC, rather than the actual initial $FEV_{1.0}$ measurement itself. On giving bronchodilators, the $FEV_{1.0}$ and VC increase disproportionately, so that the ratio of the $FEV_{1.0}/VC$ before and after bronchodilators cannot be used for comparative purposes. Second, spirometric measurements are best correlated with height, and are not meaningful as isolated recordings. An $FEV_{1.0}$ measurement at 0.5 l., for example, improving by 0.5 l. after bronchodilators is of much greater significance in a patient who is 120 cm., than in one who is 160 cm.

Why do repeated doses give a greater response? It is probably, as Capel first suggested in 1959, that the effect of the first dose allows further penetration of subsequent inhalations down the bronchial tree.

Summary

In 16 asthmatic children, the bronchodilator effect, as measured by the increase in forced expiratory volume in 1 second from the initial value, was studied 5, 15, and 30 minutes after three successive isoprenaline inhalations.

The response 5 minutes after the first inhalation showed a mean increase in the $FEV_{1.0}$ of 0.587 l. ($SE \pm 0.070$), but with subsequent inhalations there was progressive improvement, the greatest increase occurring 5 minutes after the third dose (mean increase $FEV_{1.0}$ 0.759 l. $SE \pm 0.094$).

In asthmatic children, repeated inhalations produce greater bronchodilatation than single inhalations.

We are grateful to our technicians, Miss A. Liwanag and Mr. N. Tigas, for all their help, to the Department of Visual Education, to Miss S. Hayton for secretarial help, to Dr. Helen Reid for her advice in the preparation of this paper, and to all the physicians at the Hospital for Sick Children, especially Dr. C. Collins-Williams, for allowing us to study their patients.

*Indirect MBC = $FEV_{0.75} \times 40$.

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