

An account of the treatment of five chronic asthmatic patients

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Summary

An account is given of the progress of five patients with intrinsic asthma who have received terbutaline continuously to control airways obstruction over a period of up to 2 years. One aim of this investigation was to find out whether there is any evidence of the development of tachyphylaxis to this drug. No such evidence was found. Two of the patients benefited from the administration of an α -blocking drug (indoramin).

THIS is an account of the changes in ventilatory mechanics observed in five patients who are the victims of chronic variable airways obstruction. Over the last 2 years they have all been seen and examined by one or other of us every month. Treatment of their ailment has included the daily administration by inhalation of terbutaline (Bricanyl—Astra) in all five as well as steroids, antibiotics and intal as indicated. One point of particular interest when the study was started was to find out whether continuous administration of one sympathomimetic drug over this period would result in any loss of response to this drug or to isoprenaline in a comparable dose by the same route. To this end each patient was given a Wright peak flow meter and instructed in the method of using it. The patients were asked to keep daily records of their peak expiratory flow rates in the morning soon after rising and in the evening before going to bed both before and about 10 min after taking the terbutaline. The basic dose of this drug was two puffs from a metered-dose inhaler delivering 250 μ g of terbutaline in each puff. The propellant was a mixture of three freons (11, 12 and 114), the inhalation of which without terbutaline had no detectable effect on airway mechanics. This dosage could be exceeded by the patient if she felt her condition required it, but she was asked to record the number of times she took the drug each day and to indicate in a word or two the severity of her dyspnoea and whether wheezing was more or less obvious than on the previous day. She was also asked to record any acute respiratory infections which were sufficiently severe to occasion a visit to her doctor. Any alterations in dosage of steroids or antibiotics were also recorded. These records were

entered on a special form and collected at the end of each month when the patient came to the clinic. On this occasion, the patient was asked to avoid taking her bronchodilator in the morning but not to alter any other aspect of her daily treatment. After clinical examination, blood pressures and pulse rate were recorded and then plethysmographic measurements of total airways resistance (R_{aw}) and volume of thoracic gas V_{tg} were made, followed by a recording of forced vital capacity (FVC) from which was read the forced expiratory volume in 1 sec (FEV_1). She then inhaled one puff of isoprenaline (100 μ g) followed 5 min later by a second puff and 10 min after this blood pressures and pulse rate were measured as before together with a second set of plethysmographic and spirometric data. In the light of these findings supplemented by the account given by the patient of her progress over the previous month, changes in daily treatment were prescribed when necessary and this concluded the visit. The patient's own doctor was informed of any such changes. He was also told that any of these patients would be admitted to hospital at once if he wished it at any time between the monthly visits.

At the end of 2 years the amount of data collected both numerical and verbal on each patient was large and presented certain difficulties in presentation and interpretation. A computer program was employed to deal with the numerical data, and the output from this was collated by hand with the relevant clinical and therapeutic material. From this, diagrams were prepared showing the changing trends of clinical and lung functional status of each patient over the 2-year period.

The findings on each patient on admission to the trial are shown in Table 1, together with drug treatment at the start of the period of observation.

The most useful data that we have to illustrate that terbutaline retains its activity are the daily measurements of peak flow rate. The monthly averages of control and response for the five patients are shown in Fig. 1, which is based on the measurements made each morning. The measurements made in the evening varied in the same way but were rather higher than those shown. It will be seen that there is

TABLE 1. Showing the salient symptoms, diagnosis and drug treatment of the five patients (all female) described in the text on admission to the trial

Patient	Age (years)	Symptoms	Diagnosis	Drug therapy	Remarks
N.K.	56	Variable dyspnoea on exertion Headaches	Intrinsic asthma Hypertension	Alupent Chlorothiazide	Took medicines irregularly.
S.M.	50	Breathless on exertion Attacks of wheezy dyspnoea Cough and sputum Headaches and tachycardia	Intrinsic asthma Chronic bronchitis	Intal Salbutamol Isoprenaline Prednisone Valium Antibiotics	Heavy smoker, chronic anxiety, irregular taker of all medicines, no cutaneous allergies, kept four dogs, X-ray normal.
C.H.	42	Wheezing and dyspnoea Cough and sputum in episodes	Intrinsic asthma Recurrent bronchitis	As for S.M. + Franol and deftropine, etc.	Intelligent, temperamental, took many medicines irregularly, heavy smoker.
N.H.	62	Asthma Headaches. ? migraine	Allergic asthma with chronic airways obstruction	Ephedrine Aminophylline	Admitted to hospital in severe status asthmaticus, unwilling to have isoprenaline at first because of mortality, sensitive to pollens, yeasts and danders.
M.D.	42	Asthma Cough and sputum Headache and nausea or vomiting every 2-6 weeks	Intrinsic asthma Migraine	Steroids Salbutamol Aminophylline Ephedrine	Asthmatic all her life, wide range of skin sensitivities, non-smoker.

no evidence of loss of response. What such a diagram cannot show is the great value of the daily readings which give a very good picture of the variability of the effects of the disease. We found that an examination of the daily reports brought to us by each patient gave us a very firm basis on which to judge the advisability of varying the treatment. We do not wish to underrate the importance of the monthly visits; the individual measurements made on these occasions are valuable as an epidemiological picture of the progress of the disease over a long period. Clearly an individual measurement made at intervals of 1 month cannot convey the actual day-to-day effects of treatment. On certain days some patients will not respond to their bronchodilator. This is due to factors other than the pharmacological action of the drug. The reason why this could be said with confidence is that on succeeding days the response can be seen to recover. Hume and Gandevia (1957) point out that the increase in FEV₁ after inhaling isoprenaline should be, and often is, related to the initial state of tone of the bronchial muscle; the same should also be true of the change in PEF_R so that when, for example, peak flow is extremely low or near normal very little response may be seen, whereas at intervening levels the response is increased. It is a little surprising to note in the present data that the responses did not always follow this rule. This must be because the physical state of the system (i.e. the bronchi) had been changed by pathological processes such as sputum retention or super-added infection.

A persistent fall over the course of weeks in peak flow rate is an indication for the addition of steroids

to the therapeutic regime. It is commonly followed by an increase in peak flow rate. We usually give a basic dose of 10 mg daily of prednisolone by mouth but if obstruction is very severe initial dosage of up to 60 mg a day may be necessary, but in these conditions the patient would normally be admitted to hospital as in the case of patient N.H. Sometimes prednisolone may be partly replaced by inhaled steroid (beclomethasone, 4 × 2 puffs/day or more).

Three of the patients took terbutaline by mouth as well as by inhalation in doses ranging from 5 to 10 mg/day. The general policy with all these patients was not to interfere with established treatment to which they were accustomed, but there is some evidence to support the contention that beta-adrenoceptor stimulants may best be given by inhalation only, because total dosage may be kept very low in this way.

Intal is indicated for patients who have a clearly defined allergic background to their affliction. The patient M.D. had such evidence in her history of asthma as a child and is an allergic subject; she was taking two capsules of intal throughout the whole period. One patient (C.H.) was given intal for 19 months on two occasions but this was not found to be beneficial. It was in cases like these that the daily measurements of peak flow rate proved their worth.

During this follow-up we were able to assess the effects of adding an α -adrenoceptor blocking drug (indoramin) as an adjuvant to the other drugs. This drug has important bronchodilator activity, but has also been found to be extremely useful in controlling migraine, from which two of our patients suffered.

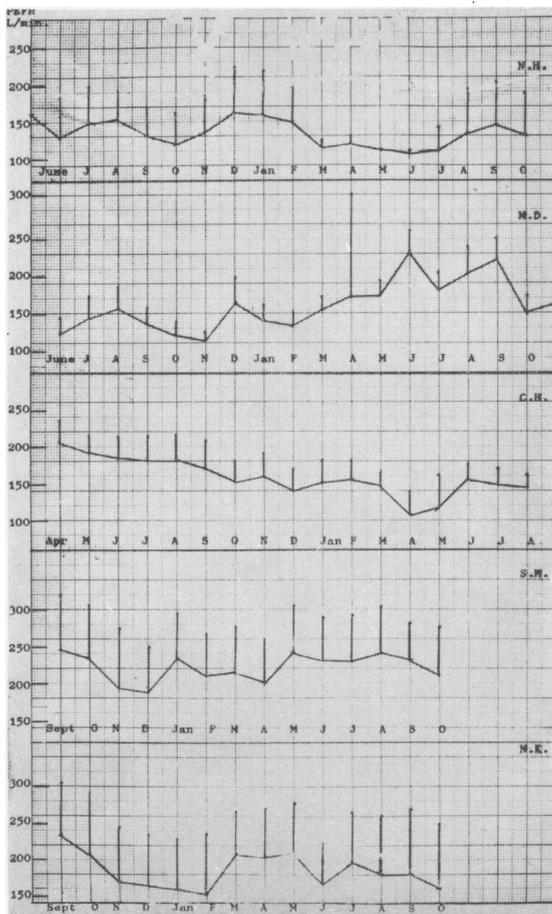


FIG. 1. Diagram illustrating the monthly means of daily readings of peak flow over a period of up to 18 months in five patients with intrinsic asthma. The vertical bars show the effect of inhaling 250 µg of terbutaline; these are read in the evening. Similar results were obtained in the morning but the general level was systematically lower. The initials of each month are marked on the abscissa.

Also, thanks to its antihistaminic properties, it serves as a mild sedative and this may also contribute to its usefulness. Patient M.D. takes 30 mg of this drug daily. If she fails to do so she develops severe headache. N.H. was also given indoramin on account of headaches and nausea. It is interesting to note that during this time her response to terbutaline was improved, and that the general level of ventilatory capacity also improved; when the drug was withdrawn her peak flow rate fell again. We found the same effect in the case of M.D.

Antibiotics have been given to C.H. and M.D. for obvious acute episodes of infection characterized by purulent sputum and a decline in ventilatory

capacity. In both these instances treatment was withdrawn at the end of 10 days when the acute infection had subsided.

It will be seen from the foregoing account that there is no single form of treatment for patients of this sort (adult asthmatics often with bronchitis), nor can the treatment restore lung function to normal. They are always difficult therapeutic problems and demand careful individual consideration, which is greatly helped by frequent objective measurements of ventilatory capacity. The daily measurements of PEFR are very useful indications of ventilatory function; in general they correlate well with estimates of FEV₁ and usually indicate the effects of bronchodilator drugs. For these reasons and because the Wright peak flow meter is not expensive, PEFR is a very useful measurement to make in general practice. In the present instance the mean morning and evening readings for PEFR for each month show the important fact that PEFR improves during the day—sometimes conspicuously. This finding in the bronchitic is often related to the clearance of sputum by coughing but in some asthmatics also who may have very little sputum, PEFR may be very low in the early hours of the day and this has been correlated with low values for circulating blood catecholamine levels. In such instances long-acting β₂-adrenoceptor stimulants may be especially beneficial.

However, it is important to know that there is no evidence to support the belief that the pharmacological effects of β-adrenoceptor drugs are lost by the development of tachyphylaxis. This is certainly true in the case of terbutaline and has been shown to be true also of isoprenaline (Svedmyr, 1974). There is some evidence that the response to ephedrine may diminish during chronic administration (Herxheimer, 1946) and also the response to a slow-release formulation of isoetharine (Numotac—Riker) given by mouth has been shown to decrease as administration continues over the course of a year (Macdonald *et al.*, 1971).

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