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ORAL SYMPATHOMIMETIC AMINES IN TREATMENT OF ASTHMA

BY

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Since the work of Barger and Dale (1910) adrenaline has been one of the most effective remedies in certain forms of acute asthma. It has usually been given by subcutaneous injection or by inhalation as a wet or dry aerosol. Its obvious value has led to much research by pharmaceutical firms into the development of sympathomimetic analogues that could be given by mouth in tablet form. Obviously the most desirable analogue would be one with the following properties: (1) it would be active—that is, relieve asthma—when taken by mouth; (2) it would be without undesirable side-effects, especially pressor side-effects such as tachycardia, palpitations, and hypertension; and (3) its action would be more sustained than the transient action of adrenaline by injection or inhalation.

Four sympathomimetic amines with adrenaline-like properties have been investigated—namely, ephedrine sulphate, isoprenaline sulphate, methoxyphenamine hydrochloride ("orthoxine"), and orciprenaline ("alupent"). Crude ephedrine has been known to Chinese medicine for some five thousand years, and since the work of Chen and Schmidt in 1924 ephedrine sulphate has been widely used for the treatment of asthma, but has often caused undesirable side-effects, such as palpitations, sleeplessness, and dysuria. Of the newer sympathomimetic drugs, isoprenaline sulphate has been used extensively during the past ten years in the form of sublingual tablets and was reported to have a quicker but shorter action than ephedrine (Konzett, 1940). More recently still, methoxyphenamine has been given by mouth in the treatment of asthma. Curry *et al.* (1948) reported that they found methoxyphenamine to be at least as effective as ephedrine, and in roughly 30% of the cases more effective than ephedrine in the treatment of "mild spontaneous asthma." These authors also found that a number of patients who were "jittery" on ephedrine were free from this complaint when treated with methoxyphenamine. Ten years later Pearson (1958) reported that the bronchodilator effect of methoxyphenamine and ephedrine was approximately the same but the great majority of patients had a preference for methoxyphenamine, and that there was no advantage in giving methoxyphenamine in doses larger than 100 mg. t.d.s. (Pearson, 1957).

The most recent oral antispasmodic with sympathomimetic properties to come on the market is orciprenaline. Preliminary continental clinical trials on patients with chronic bronchitis and asthma (Günthner, 1961; Zidek, 1961) reported that orciprenaline had a spasmolytic effect when given by mouth or inhalation. These preliminary reports of the efficacy of orciprenaline by mouth, by

inhalation, and by subcutaneous injection have been confirmed (Kennedy, 1963).

The purpose of the comparative trial which is reported here was to study the effects of these different preparations in asthmatic individuals who were known to have usually a consistently good response to aerosol adrenaline. It has been reported (Kennedy, 1961) that individual asthmatics react very differently to aerosol adrenaline, and for this reason only individuals who were known to respond to adrenaline were chosen for the comparative trial, as it is rather pointless to assess the effect of sympathomimetic drugs in individuals who do not benefit from them.

Material and Methods

Twelve asthmatics (five women and seven men) were chosen for this trial; their ages ranged from 16 to 64 years. Most of them had had perennial asthma for many years. Eight of the 12 were receiving supportive therapy in the form of oral corticosteroids or intramuscular corticotrophin at the time of the trial. Earlier studies in these patients had shown that usually they had a consistently good response to aerosol adrenaline. The magnitude of the response varied from individual to individual—adrenaline inhalations usually effected an improvement of 20% or more in the indirect maximum breathing capacity (M.B.C.)

The effect of the individual drugs was assessed by the indirect M.B.C. test (Kennedy, 1953)* before the start of the trial and at half-hourly intervals after the administration of each drug for a period of four hours. At the end of that period an inhalation of adrenaline was given and a further assessment of the indirect M.B.C. was made.

Sympathomimetic Amines Investigated.—The dose of the drugs under trial was as follows: (1) ephedrine 30 mg. by mouth, (2) isoprenaline 10 mg. sublingually, (3) methoxyphenamine 100 mg. by mouth, (4) orciprenaline 10 mg. by mouth, (5) orciprenaline 20 mg. by mouth, (6) a placebo tablet consisting of lactose by mouth. Tests with the various drugs were carried out on different days and were started at 9 a.m. and carried on until 1 p.m. Apart from the respiratory physiological indices, serial recordings of the pulse were taken and the incidence of untoward side-effects was noted.

Results

The results have been analysed in two ways. (1) An analysis of the behaviour to the different test substances was made by preparing separate charts for each individual patient on which were plotted the serial indirect M.B.C.

*Indirect M.B.C. \equiv F.E.V._{0.75} \times 40.

readings recorded during each trial run. (2) A group analysis has been made by listing the mean indirect M.B.C. of the 12 patients before and at intervals after the administration of each drug. The absolute values are shown in Fig. 4 and the percentage changes from the pretreatment values in Fig. 5.

Changes in Individual Patients

From the scrutiny of the separate charts showing the behaviour of each patient to the different drugs it was found that there was great variation in the response of individuals. Three charts are shown to illustrate this individual variation (Figs. 1, 2, and 3).

An independent observer was asked to assess the individual charts. From this visual analysis, five

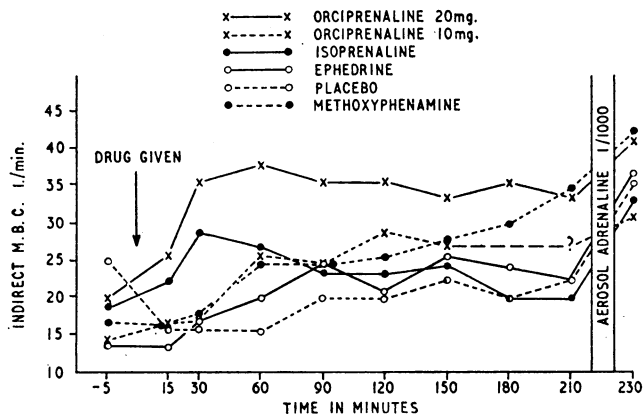


FIG. 1.—In this patient, a woman aged 60 with perennial asthma since the menopause, the pretreatment values were reasonably comparable. On comparing the various curves, her ventilatory capacity was obviously best after orciprenaline 20 mg., which produced a maximum effect at 60 minutes and was sustained up to 210 minutes after giving the drug. Isoprenaline, orciprenaline 10 mg., and methoxyphenamine all produced a similar positive change but after different intervals of time. There was also an improvement after ephedrine, which in this individual had its maximum effect after 150 minutes. After placebo the indirect M.B.C. was at no time higher than the pretreatment reading.

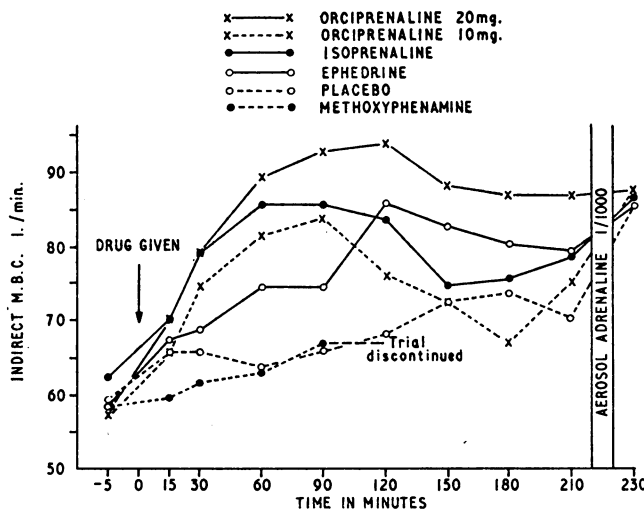


FIG. 2.—The patient, a woman aged 46, had had asthma since childhood. All the pretreatment values were roughly comparable. Orciprenaline 20 mg. gave the best curve, and isoprenaline and ephedrine gave the next best curves; the isoprenaline curve was better in the first half of the trial and the ephedrine was better in the second half. Taking into account the slight difference in the pretreatment values, the changes after orciprenaline 10 mg. were similar to those after isoprenaline. In this particular patient the trial of methoxyphenamine had to be discontinued because of the occurrence of tetany, which was relieved by breathing from a closed bag. This patient showed a slow gradual spontaneous improvement during the period of observation after the lactose placebo.

individuals were judged to have responded best to orciprenaline 20 mg., four to orciprenaline 10 mg., one to ephedrine, one to methoxyphenamine, and one to isoprenaline. Of the nine who responded best to orciprenaline, five responded better to the 20 mg. dose.

Changes in Mean Indirect M.B.C. of 12 Asthmatic Subjects

Fig. 4 gives the mean value of the indirect M.B.C. of the 12 patients before and at intervals after the administration of the placebo, isoprenaline, ephedrine, methoxyphenamine, orciprenaline 10 mg., and orciprenaline 20 mg.

A better overall picture of the behaviour of the 12 individuals to the different drugs under trial is obtained by plotting the indirect M.B.C. values as a percentage change over the initial pretreatment figure. This percentage change in the indirect M.B.C. after treatment with the different drugs is shown in Fig. 5, and from scrutiny of the different curves one can make the following general observations:

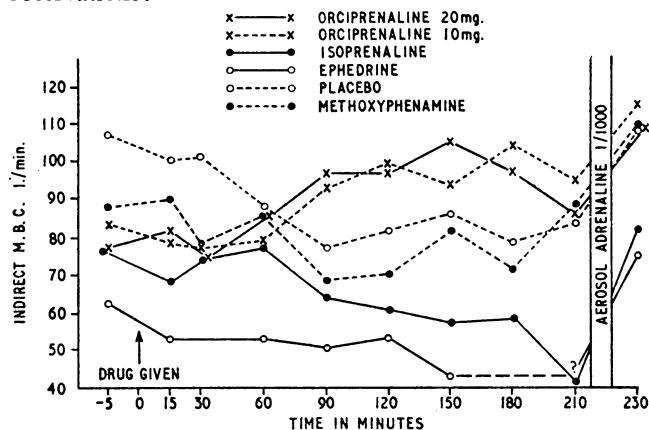


FIG. 3.—In this patient, a boy aged 16 who had had asthma since infancy, there was a progressive deterioration in the indirect M.B.C. values after administration of the placebo tablets, ephedrine, isoprenaline, and methoxyphenamine. Only after orciprenaline 10 mg. and orciprenaline 20 mg. was a significant and sustained improvement of the indirect M.B.C. observed. It was also interesting that the orciprenaline 10 mg. and the orciprenaline 20 mg. curves were almost identical, whereas many of the other patients showed an obviously better response to orciprenaline 20 mg. than to orciprenaline 10 mg.

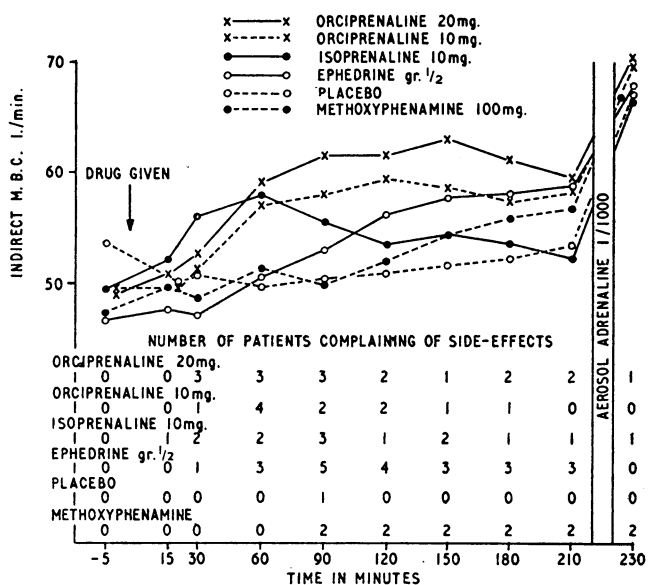


FIG. 4.—Mean value of indirect M.B.C. in 12 patients

1. After administration of the placebo (lactose) the indirect M.B.C. of the group was 5% worse for the greater part of the four hours of observation.

2. After administration of all the active compounds there was a definite improvement in the indirect M.B.C.

3. The isoprenaline curve showed a substantial quick improvement. There was a 13% rise at 30 minutes, and the maximum isoprenaline effect occurred at 60 minutes (16.5%). After 60 minutes the isoprenaline effect was diminishing and had been almost entirely lost after 210 minutes.

4. The orciprenaline 20 mg. curve showed an improvement of 6% at 30 minutes and steadily climbed to 20% at 60 minutes, reaching a peak of 27% at 150 minutes; at 210 minutes the orciprenaline 20 mg. curve was still showing a change of 20%.

5. The orciprenaline 10 mg. curve was very similar to the orciprenaline 20 mg. curve though less impressive. It showed a rise of 3% at 30 minutes, a rise of 14% at 60 minutes, and reached its peak at 120 minutes, when there was 19% increase. At 210 minutes there was still a positive change of 17%.

6. The ephedrine 30 mg. curve showed virtually no change at 15 minutes and 30 minutes, but there was a remarkably uniform rise between 30 minutes and 150 minutes. At 60 minutes there was a gain of 8%, at 90 minutes a gain of 14%, at 120 minutes a gain of 20%, and at 150 minutes a gain of 24%. A very small further gain occurred between 150 and 210 minutes, when the positive gain was 26%.

7. The methoxyphenamine 100 mg. curve showed very little positive change at 15 and 30 minutes. At 60 minutes there was a gain of 8%; at 120 minutes a gain of 10%; at 150 minutes a gain of 15%; and at 210 minutes a gain of 20%. In fact, the curve showed a slow gradual improvement between 90 and 210 minutes.

8. In general the inhalation of aerosol adrenaline 210 minutes after giving the oral antispasmodic or placebo tablet resulted in a further substantial increase in the indirect M.B.C. The lower the reading at 210 minutes the greater the percentage change following aerosol adrenaline. However, it is clear that the combined effect of oral antispasmodics and aerosol adrenaline is greater than that of aerosol adrenaline alone.

Side-effects

The side-effects noted by patients included mild palpitations, dizziness, headaches, and trembling sensations. Palpitations and headaches occurred more often after ephedrine, while palpitations and dizziness occurred more often after orciprenaline. It was notable that the incidence of side-effects was higher in women than in men. The side-effects in one or two individuals were probably serious enough to preclude further use of the drug in question. The actual incidence of side-effects with each drug is recorded at the bottom of Fig. 4. One patient complained

of transient palpitations 90 minutes after taking the placebo lactose tablet.

Discussion

It is useful to know the different time-response curves of the various adrenaline-like analogues for the more effective planning of treatment with these drugs. However, in practice in the past a sustained effect has rarely been achieved, either because of the occurrence of unwanted side-effects when such a regime is tried or because the individual became unresponsive to the drug. The failure to achieve a sustained effect in many patients may simply be a result of giving ineffective doses wrongly spaced. Further trials are now in progress to see if a sustained effect can be obtained.

Adrenaline analogues are often useful in the treatment of certain types of asthma which tend to occur at a particular time of the day or night. It is then usually only necessary to prescribe the drug once a day at the appropriate time interval before the attack usually occurs, and in such cases it is helpful to know the time-response curves of the different adrenaline analogues.

Discussion of the relative frequency and severity of reactions to the drugs is hardly profitable in such a small series in view of the individual susceptibility to the different drugs. However, it was apparent that ephedrine gave rise to the highest incidence of side-effects.

From the results the newer drug, orciprenaline, on the whole seemed to compare favourably with the older well-tried ephedrine. The results after orciprenaline 20 mg. were usually substantially better than the results after 10 mg. Thus there is obviously an advantage in giving the higher dose when this is tolerated. In general, orciprenaline 20 mg. was more effective than any of the other drugs tried. However, it was the only drug investigated at two dose levels. It is possible that the other adrenaline analogues might have produced better results if they had been given in higher doses. Methoxyphenamine and ephedrine have a similar time-response curve, but ephedrine 30 mg. is more effective than methoxyphenamine 100 mg. Usually a simple inhalation of aerosol adrenaline is just as effective as, or more effective than, sublingual isoprenaline, which often produces side-effects not associated with aerosol adrenaline, and we feel that sublingual isoprenaline is of very limited value. It is interesting that some asthmatics show a good response to certain adrenaline-like analogues and little or no response to others. Since all these patients were known to respond to aerosol adrenaline, the varying response to the oral compounds may simply have been a reflection of how well, or how badly, the different compounds were absorbed from the intestinal tract or the buccal mucosa.

The fact that patients respond differently to the various oral adrenaline-like analogues suggests the need to try a number of them to discover the most suitable in each case.

Summary

The short-term effect of certain adrenaline-like analogues which are prescribed by mouth for the treatment of asthma is reported. The drugs under trial included ephedrine 30 mg., orciprenaline 10 mg., orciprenaline 20 mg., isoprenaline 10 mg., methoxyphenamine 100 mg., and also a placebo tablet (lactose).

Twelve asthmatic individuals who from previous observations had been known to respond consistently well to aerosol adrenaline were treated. The indirect M.B.C. of each individual was assessed before and at regular

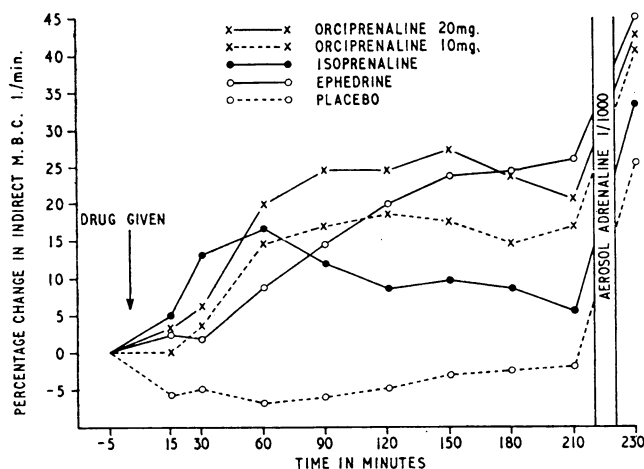


Fig. 5.—Percentage change in indirect M.B.C.

intervals for four hours after the administration of each analogue.

The results show that the placebo did not improve the asthmatic condition, whereas all the active compounds effected some improvement. From the analysis of the group results, quite distinct time-response curves for the different analogues were obtained. Isoprenaline had the quickest but most transient action. Ephedrine and methoxyphenamine had the most prolonged action, but were the slowest to take effect. Orciprenaline occupied an intermediary position. In general, orciprenaline 20 mg. gave the best results as regards duration and magnitude during the four hours of observation.

The maximum response occurred 60 minutes after isoprenaline, 120 minutes after orciprenaline, and 210 minutes after both ephedrine and methoxyphenamine.

We are indebted to the staff of the Department of Respiratory Physiology for carrying out the investigations described in this report, especially Mr. James Booth, S.R.N., Mr. Peter Wilkes, S.R.N., Mr. Norman Curnock, S.R.N., Mrs. Sheila Clarke, S.R.N., and also Mrs. K. Tattersfield, who prepared the graphs.

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BRONCHODILATORS AND CORTICOSTEROIDS IN CHRONIC BRONCHITIS AND EMPHYSEMA

BY

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Many patients suffering from chronic bronchitis and emphysema are disabled by respiratory insufficiency even during remission from exacerbations of acute infection. Impaired breathing capacity due to increased airway resistance is an important factor in the causation of this disability. Expiration may be prolonged, wheezy, and accompanied by rhonchi. In this respect the pattern of breathing resembles that seen in bronchial asthma. The value of bronchodilators and corticosteroids in the treatment of asthma is now well established. The points of resemblance seem close enough to justify a trial of these drugs in bronchitis and emphysema, notwithstanding certain differences which are believed to exist in the mechanisms of airway narrowing. While expiratory airway narrowing in bronchitis and emphysema is doubtless irreversible, inasmuch as it is due to destruction of pulmonary elastic tissue and consequent rise in transpulmonary pressure, bronchodilators and corticosteroids might conceivably widen the bronchial lumen in so far as narrowing is due to oedema or hyperaemia of the mucosa or to secretion of mucus.

Bronchodilators, such as isoprenaline sulphate, are widely used in the treatment of chronic bronchitis by patients who complain of shortness of breath.

As to the value of steroids in chronic bronchitis and emphysema, some statements of a general nature have been made; in the main they are non-committal in their recommendations, suggesting that steroids are perhaps worth trying (Nicholson, 1955; Birch, 1960). Bickerman *et al.* (1955) claimed good results in emphysema and other non-asthmatic pulmonary conditions, but the criteria of diagnosis and of improvement were not defined, nor was the cause of the emphysema stated, and doubts must arise whether this was chronic bronchitis as it is seen in England. Davies and Williams (1955) treated six cases with "good results" in two. Moyes and Kershaw (1957) found that prednisolone given with tetracycline was no more effective than oral aminophylline with tetracycline. As the aminophylline dosage was small by present standards, it may be inferred that prednisolone played no active part. Lorrinan (1959), investigating six chronic bronchitics, obtained improvement in one case, a worsening in another,

and no material change in the remainder on prednisolone. Cullen and Reidt (1960) made ventilatory, blood-gas, and diffusion studies on 14 patients who obtained no benefit from steroids. Clifton and Stuart-Harris (1962) gave steroids to 28 patients, in two-thirds of whom a 20% increase in ventilatory capacity was obtained, and in a quarter a 60% increase, but these authors express doubt regarding the ultimate benefit.

This paper describes a trial of isoprenaline sulphate aerosol and of oral prednisolone in the treatment of patients suffering from chronic bronchitis and emphysema showing impairment of breathing capacity during remission from acute infection.

Material

The patients, all of whom suffered from chronic bronchitis and emphysema with ventilatory impairment, were drawn from those referred to the out-patient department at Dulwich Hospital, and from patients previously admitted with acute infective episodes. The latter were not submitted to trial until acute infection had subsided. All patients were in remission at the time of testing. The diagnosis of chronic bronchitis was based on a history of at least two years' continuous or intermittent productive cough in the absence of other disease to account for it. The diagnosis of emphysema was based on a history of progressive exertional dyspnoea in the absence of other non-bronchitic pulmonary disease, or significant cardiovascular disease, and on confirmatory physical signs and radiological appearances. Excluded from the trial were patients suffering from bronchial asthma and those over 70 years of age. The term "bronchial asthma" is here taken to mean a condition in which episodic dyspnoea, with wheezing or other evidence of expiratory airway narrowing, occurs unrelated to exertion, bronchitis, left ventricular stress, or inhalation of chemical irritants such as smog. Patients were also excluded whose status was uncertain as regards bronchitis or asthma, or who suffered from both conditions.

Of the 26 patients, 24 were men. The mean age was 58 years (range 45 to 68), and the ages of over half of them lay within the range of 61 to 66. It is believed that this