Some Adrenergic Drugs and Atropine Methonitrate Given by Inhalation for Asthma: A Comparative Study

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Since Barger and Dale (1910) described the chemical structure and sympathomimetic action of adrenaline-like amines, adrenaline and adrenergic drugs have been extensively used for the treatment of asthma. Adrenaline itself is active only when it is given parenterally or by inhalation, whereas the more recently introduced isoprenaline is more stable and can be given by inhalation or as a sublingual tablet, though it is not suitable for parenteral use. Over the past two decades the number of inhalants that have been available for the treatment of asthma has increased enormously. They consist basically of adrenaline or isoprenaline; many proprietary brands also contain other ingredients—for example, atropine sulphate, atropine methonitrate, benzocaine, papaverine, posterior pituitary extract, stramonium, as well as other trace ingredients.

In recent years inhalation therapy has become more practical as a result of technical advances in the administration of dry fine particulate aerosols, which are stored under pressure in small cartridges and delivered in metered doses. The purpose of this investigation was to compare the efficacy of a number of such commercially available preparations.

Inhalants Investigated.—Proprietary preparations containing isoprenaline sulphate or adrenaline bitartrate alone, and a mixture containing both isoprenaline sulphate and atropine methonitrate, were investigated. For the purpose of the investigation, inhalers were also prepared which contained atropine methonitrate alone and isoprenaline alone. These five preparations were administered from a pocket apparatus consisting of a cartridge containing an inert propellant with the active drugs in a non-aqueous suspension. A valve mechanism delivered a standard dose through a detachable mouthpiece. A further proprietary mixture of adrenaline hydrochloride and benzocaine, which had been used extensively in the past in this department, was administered as a wet aerosol by means of a Collison inhaler. Details concerning the doses of the drugs and the devices used for their administration are given in Table I.

The investigation was planned to assess (1) the magnitude of the initial bronchodilator effect of the inhalations, and (2) the duration of bronchodilator action of each of the different inhalations.

TABLE I.—*Inhalants Investigated*

Code Letter	Active Ingredient	Dose per Puff	Trade Name	Delivery
A	Adrenaline hydrochloride 1/1000. Benzocaine 1%	0·2–0·3 mg. adren. hcl. during 2-min. inhalation	Apneugene	Via Collison inhaler as wet aerosol
B	Isoprenaline sulphate	0·1 mg.	Specially prepared (Benger)	From cartridges delivering metered doses of dry particulate aerosol propelled by a gaseous mixture
C	„	0·075 mg.	Iso-medihaler (Riker)	
D	Isoprenaline sulphate + Atropine methonitrate	0·1 mg. + 0·04 „	Prenomiser plus (Benger)	
E	Adrenaline bitartrate	0·15 „	Epi-medihaler (Riker)	
F	Atropine methonitrate	0·04 „	Specially prepared (Benger)	

Clinical Material.—Different groups of patients, as indicated below, were investigated in assessing the magnitude of response and the duration of effect.

Method of Assessment.—A simple objective physiological test, the indirect M.B.C.[1] (Kennedy, 1953), was used to assess ventilatory capacity before and at intervals after drug administration.

Results: Magnitude of Initial Response

The magnitude of the initial bronchodilator effect of five (A–E Table II) different preparations was assessed on 135 patients. These patients were all adults who had been attending the department for months or even years on account of asthma, bronchitis, or emphysema.

The wet aerosol preparation A was administered for two minutes. Two puffs were given from cartridges C and E, and one puff was administered from cartridges B and D.

All patients were treated with each of the five different inhalants in a random order at roughly weekly intervals. The ventilatory capacity (indirect M.B.C.) was estimated before and five minutes after each inhalation. The average percentage improvement in the indirect M.B.C. of the group of 135 patients after each of the five inhalations is listed in Table II.

TABLE II.—*Mean Change in Indirect M.B.C.* (135 *Patients*) *Five Minutes after Inhalation*

Inhalant	Average Percentage Change in Indirect M.B.C. 5 Minutes after Inhalation	Maximum Estimated Dose of Active Drugs Inhaled
A	+17·17%	0·3 mg. adrenaline hydrochloride and 3 mg. benzocaine
B	+17·11%	0·1 mg. isoprenaline sulphate
C	+18·93%	0·15 „ „ „
D	+16·87%	0·1 „ „ „ + 0·04 „ atropine methonitrate
E	+15·32%	0·3 „ adrenaline bitartrate
F	(Atropine methonitrate not included in magnitude of initial effect study)	

Statistical analysis has shown that there is no significant difference between the five different values. Thus as regards the immediate effect there was nothing to choose between the five different inhalations.

Duration of Effect

The duration of effect of atropine methonitrate alone and of inhalations containing adrenergic drugs was investigated in asthmatics who from previous studies were known to respond to adrenaline fairly consistently. Twelve asthmatic individuals were given one of the six inhalations at intervals of two or three days. After each individual inhalation serial readings

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[1] Indirect M.B.C.$\equiv$F.E.V.$_{0.75}$ × 40.

of the indirect M.B.C. were carried out at half-hourly intervals over three and a half hours. At the end of this time a further two-minute inhalation of adrenaline hydrochloride with benzocaine was given, and a final indirect M.B.C. was recorded five minutes later.

The results of these investigations have been analysed in two ways (1) to show the overall response of the group of 12 patients to the different inhalants, and (2) to show the response of each individual to the six inhalations.

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

An overall picture of the response of the 12 patients to the different drugs under trial was obtained by plotting the average indirect M.B.C. values as a percentage change of the pretreatment values (Fig. 1). The following general observations can be made from the curves obtained.

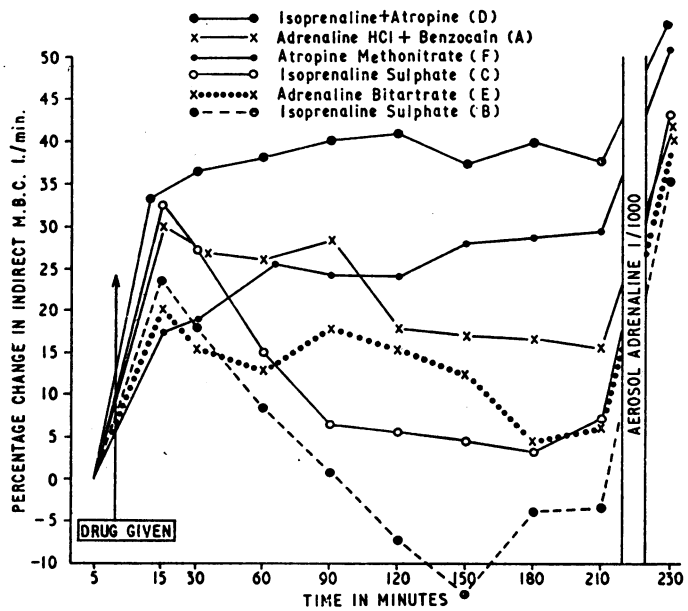

FIG. 1.—Response of 12 asthmatic subjects to six different drugs under trial.

(*a*) The two different brands of *isoprenaline* showed remarkably similar response curves, with a peak effect at 15 minutes; at 90 minutes the curves were almost back to their pretreatment level. The slight difference in the magnitude in the two isoprenaline curves was probably related to the dose of isoprenaline administered.

(*b*) The *adrenaline bitartrate* curve and the *adrenaline hydrochloride plus benzocaine* curve mimicked each other closely. Each had a peak effect at 15 minutes, and the effect was fairly well sustained up to the 90-minute mark. The better response after adrenaline hydrochloride compared with adrenaline bitartrate may be related to the higher dose of adrenaline hydrochloride administered and/or to the addition of 1% benzocaine included with it.

(*c*) Although the response at 15 minutes after the inhalation of *atropine methonitrate* alone was less than the response achieved at this time from any of the other inhalants, the atropine methonitrate curve continued to climb throughout the period of observation and was at its highest 210 minutes after the inhalation.

(*d*) The *combined inhalation of isoprenaline and atropine methonitrate* showed substantial advantages over the other drugs. At 15 minutes the response was as good as the best isoprenaline response; it continued to improve for 120 minutes, after which the response was maintained for the duration of observation (210 minutes).

(*e*) The inhalation of aerosol adrenaline hydrochloride with benzocaine 210 minutes after all the test inhalants 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 this aerosol adrenaline. On reviewing the individual curves it was clear that the values recorded at 230 minutes (15 minutes after the second inhalation) were higher than any recorded during the previous three and a half hours after the first inhalation.

Response of Individuals to the Six Different Inhalations

The response of each individual to the six different inhalations was assessed from the serial readings of the indirect M.B.C. plotted on a time basis as shown in Fig. 2.

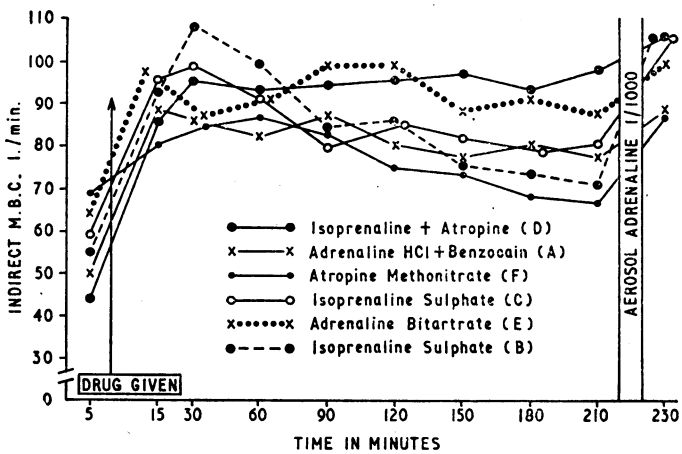

FIG. 2.—Showing the change in the absolute values in the indirect M.B.C., before and at intervals after the inhalation of various inhalants, of a man aged 57 who had had labile asthma for 10 years. It will be seen that there is a considerable variation in the pretreatment values, which range from 50 to 70 l./min. The improvement at 15 minutes is roughly the same for all the five inhalants tested, and the duration of the response is roughly the same after each test inhalant. In this patient the adrenaline bitartrate curve would appear to be the best response-curve, whereas in most individuals the isoprenaline-atropine curve comes out best, as shown in Figs. 1 and 3.

The individual graphs of the 12 patients showed that there was usually some difference in the pretreatment values, but even allowing for this difference there was obviously some individual variation in the response to the different inhalants. From the visual appraisal of the individual graphs it was found that the majority showed a good immediate response to inhalations of isoprenaline alone (inhalers B and C), but the greater part of the positive improvement in the indirect M.B.C. was lost in all except two cases after 90 minutes. Frequently the adrenaline hydrochloride with benzocaine and the adrenaline bitartrate curves were similar in shape (inhalers A and E): a sustained effect up to 120 minutes after both the adrenaline hydrochloride with benzocaine and the adrenaline bitartrate inhalations was observed in 6 of the 12 patients. After the inhalation of atropine there was evidence of a sustained effect in 10 patients at 120 minutes, which was still present at 210 minutes. After the use of isoprenaline-atropine (inhaler D) there was evidence of a sustained effect up to 120 minutes in 11 patients, and this sustained effect was still evident at 210 minutes in 7 of the 12 patients.

Further Duration of Effect Studies

In view of the findings of Altounyan (1964) that asthmatics in the acute phase respond poorly to atropine, a second group of 12 asthmatic individuals who suffered from a more stable form of asthma than the previous group were tested in a similar manner with five of the six test inhalants (the adrenaline bitartrate, inhalant E, was not used). As in the first group, the second group were selected on the basis of their consistent response to aerosol adrenaline; the majority would have been labelled by some authorities as suffering from "chronic bronchitis." The percentage change of the indirect M.B.C. of this

second group, assessed at intervals after treatment with the various inhalants, is shown in Fig. 3.

In this further study the isoprenaline-atropine mixture gave the best results, and the responses to isoprenaline alone and to adrenaline hydrochloride were also very similar to those previously obtained.

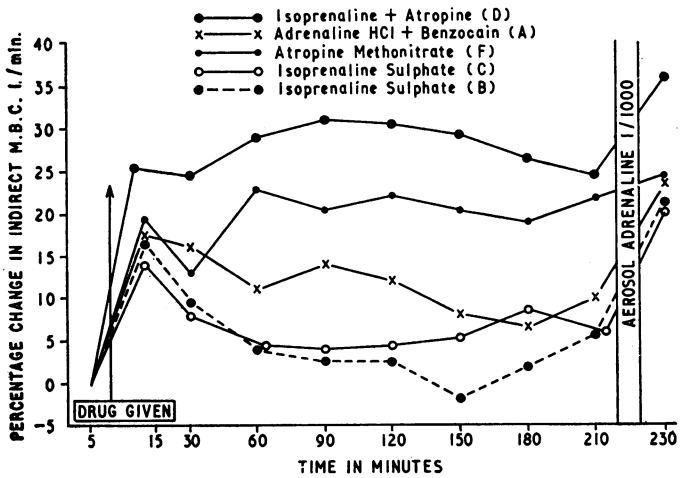

FIG. 3.—Response of a second group of 12 subjects having a more stable form of asthma than the group in Fig. 1.

The atropine methonitrate curve is similar to both Figs. 1 and 3, except that in Fig. 3 there is evidence of an immediate effect following atropine methonitrate at 15 minutes which was as good as the normal response to isoprenaline or adrenaline hydrochloride. The other difference between the two groups of patients tested—namely, Figs. 1 and 3—is that the percentage change is greater in the group with the more labile form of asthma (Fig. 1).

Discussion

In an attempt to map out the natural history of the many varieties of the asthma-bronchitis-emphysema syndrome, some 500 patients suffering from various forms of defective breathing* have been investigated week by week over the past few years. As part of this investigation it has been a routine practice to measure the indirect M.B.C. before and five minutes after a two-minute inhalation of an aqueous aerosol of adrenaline hydrochloride 1/1,000 plus benzocaine. From these observations an objective measure is obtained of the adrenaline response of individuals at regular intervals throughout the year, and certain generalizations about the effect of adrenaline in individuals with defective breathing can be made.

The adrenaline response is very variable; in some individuals the response to aerosol adrenaline is consistently large and, in fact, occasionally aerosol adrenaline alone will temporarily abolish a significant breathing defect. In a great number of individuals there is usually a small but significant response, and often this response is of roughly the same magnitude throughout the year even though the breathing defect is variable. The adrenaline response during acute respiratory episodes, however, is frequently unpredictable, and in such situations, when the breathing defect is at its worst, there is often little or no response to adrenaline. The magnitude of the adrenaline response often changes when an individual is given other therapy such as corticosteroids (Kennedy, 1961). This change in the response when on other therapy is in itself interesting in that it may provide additional evidence concerning the mechanism of the breathing defect. There is a small group of individuals who are consistently made worse by an adrenaline inhalation.

The distinctive time-response curves of various adrenergic agents which are given by mouth have already been described (Kennedy and Jackson, 1963), and it is interesting that in this present investigation the various adrenergic inhalants also have quite distinctive time-response curves. Although the magnitude of the immediate effect (five minutes after the inhalations) of the four dry aerosols and the one wet aerosol described in this communication is of roughly the same order, the addition of atropine afforded a greater increase in the average M.B.C. after a latent period of 30 to 60 minutes. Thus the relative merits of different inhalants should be judged on their time-response curves and the absence of side-effects. As regards duration of effect, the studies on the two groups of individuals show that isoprenaline has the shortest action, adrenaline bitartrate and adrenaline hydrochloride are intermediate, and atropine methonitrate has the most sustained effect. In addition, the time-response curves show that the combined administration of isoprenaline and atropine methonitrate give an enhanced response which is sustained better than the other inhalants.

Altounyan (1964) showed that whereas atropine methonitrate afforded the best protection against carbachol challenge, it was significantly less effective than adrenergic compounds against histamine and antigen challenge. It also showed that atropine has little or no effect in acute asthma. The findings of Chamberlain, Muir, and Kennedy (1962) that atropine methonitrate is a bronchodilator in its own right are fully confirmed in this communication.

Post-mortem examination of cases of status asthmaticus have shown partial or complete occlusion of the bronchi with thick sputum plugs (Williams and Leopold, 1959). Labile asthmatic individuals, who normally have a good adrenaline response, often show a negligible response during an acute exacerbation, and it is at such times that patients tend to use their inhaler excessively. The indiscriminate use of atropine, which may dry up bronchial secretions during status asthmaticus, is therefore definitely contraindicated. In the event of inhalation therapy becoming progressively less effective all patients should be instructed to seek medical advice at once so that their basic treatment may be reviewed and the possibility of the harmful effects of indiscriminate inhalation therapy avoided.

Over the past eight months more than 50 asthmatics have been issued with pocket inhalers containing a mixture of isoprenaline and atropine methonitrate with strict instructions to limit the use of this inhaler to two puffs three times a day. They were also issued with a second inhaler containing either adrenaline bitartrate or isoprenaline, with instructions that they may use this inhaler whenever further relief was necessary. This dual inhaler regime has proved to be quite practicable and is recommended.

Summary

A comparative study of the effect of some adrenergic drugs and atropine methonitrate given to asthmatic subjects by inhalation is reported. The adrenergic inhalants investigated included two brands of isoprenaline and one proprietary brand of adrenaline bitartrate. Two mixed proprietary preparations were also investigated, one containing isoprenaline with atropine methonitrate and one containing adrenaline hydrochloride with benzocaine.

To assess the immediate effect of the different inhalants the indirect maximum breathing capacity was estimated on 135 asthmatic and bronchitic patients before and five minutes after the inhalation of the test inhalants. From these

* For the purpose of this communication the terms "defective breathing" or a "breathing defect" are applied to individuals whose maximum ventilatory capacity is diminished.

observations it was found that the immediate effect of the adrenergic drugs was similar.

To obtain a measure of the duration of effect of the different inhalants, serial assessments were continued for three and a half hours after each inhalant therapy on two groups of asthmatic subjects containing 12 subjects in each group. From these serial studies it was found that the inhalants gave distinct time-response curves.

The duration of isoprenaline was shortest; its action had been completely lost by 90 minutes. Adrenaline bitartrate and adrenaline hydrochloride combined with benzocaine were similar: a peak effect occurred at 15 minutes and was maintained up to 90 minutes, after which response gradually waned. Atropine methonitrate was found to have some immediate effect; the response reached a maximum at 90 minutes and was usually maintained throughout the three and a half hours of observation. The inhalation of isoprenaline in combination with atropine methonitrate showed substantial advantages over the other drugs tested. At 15 minutes the response was as good as the best isoprenaline response; it continued to improve for 120 minutes, after which it was maintained at this level during the three and a half hours of observation.

It is recommended that the frequency of administration of atropine methonitrate with or without adrenergic inhalants should be strictly controlled, especially in acute asthma.

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., Mrs. K. Tattersfield, who prepared the graphs, and also Mrs. E. Turner and Mrs. E. C. Wright for the analyses.

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Use of Krypton-85 in the Study of Hypoxia in Porto-pulmonary Bilharziasis (Schistosomiasis)

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Porto-pulmonary bilharziasis often presents as hepatosplenomegaly and cor pulmonale (Zaky, 1952; Zaky *et al.*, 1959). The haemodynamic changes in this disease have already been discussed (Foda, 1959; Zaky *et al.*, 1962). We found that in about 10% of these cases hypoxia of less than 94% was present. This hypoxia could not be corrected by 100% O_2 inhalation.

When the alveolar CO_2 tension was matched simultaneously against the arterial CO_2 tension either at rest or on moderate exercise, a significant gradient was found between the alveolar P_{CO_2} and the arterial P_{CO_2}, the latter being raised from 2 to 7 mm. Hg. Studies of pulmonary function in these cases revealed almost normal findings (Ashba, 1959), particularly the minute alveolar ventilation and the helium-mixing time. These findings can only mean a veno-arterial admixture either inside the lung from pre-capillary pulmonary-artery/pulmonary-vein shunting or from the portal-vein blood to the pulmonary vein. In order to elucidate the above findings it was decided to carry out further investigations using the gas krypton-85.

Materials and Methods

Krypton-85 is a very interesting gas in that it is cleared by the alveoli to the extent of 95–99% in one circulation. We followed the method described by Fritts *et al.* (1960) to investigate the problem of a pre-capillary pulmonary-artery/pulmonary-vein shunting. By this method a gas solute is injected with a known quantity of a blue dye into the superior vena cava and both are recovered from the brachial artery within the period of one circulation. The concentration of dye is obtained from spectrophotometer readings, while the radioactivity is read on the scaler. The percentage of shunt is calculated from the formula:

$$\frac{^{85}\text{Kr counts in integrated radial} \times \text{conc. of dye injected mg./l.}}{^{85}\text{Kr counts injected} \times \text{conc. of dye in integrated radial mg./l.}} \times 100$$

The pulmonary-artery concentrations after injection into the superior vena cava were calculated from the radiological size of the heart after the method of Hanson (1961), and the ratio of the right to the left cavities was considered to be 55–45%. This gave the cardiac volume in which the dilution of superior-vena-cava injection could have taken place.

To investigate the problem of portal-vein/pulmonary-vein shunting, the same amount of krypton-85 was injected into the splenic pulp in bolus form; the bilharzial spleen lends itself admirably for the purpose as it is easily accessible and firm. We had no trouble while using this route in our cases apart from a moderate degree of pain after the injection. Samples were collected simultaneously from the pulmonary artery and the radial artery at approximately 10-second intervals for the first minute after the injection and at every 30 seconds for the next three to five minutes. The samples were then sealed in mica cuvettes and counted through an appropriate G.M. tube for five minutes.

Results

The first experiment, when the krypton-85 solute and the blue dye were injected into the superior vena cava, showed the

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