Studies on the Effects of Sympathicoamines in Asthma

Variability of Effect from Differing Routes of Administration*

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Introduction

This report on the use of sympathicoamines in bronchial asthma represents a portion of a continuing study of the effects of drugs on bronchial asthma,¹ using tests of ventilatory function as an objective measurement of airway obstruction.

We define asthma as a syndrome consisting of paroxysmal, recurrent and reversible partial obstruction of the lower bronchial tree resulting in the development of acute obstructive emphysema. Variability is a striking clinical feature of asthma both from patient to patient and in the same patient from day to day. The factors which produce bronchial obstruction in asthma are mucosal edema and congestion, bronchial inflammation, viscid secretion and bronchial muscle spasm. However, there is controversy regarding the relative importance of each one of these factors. From clinical observations it appears that the relative significance of these factors is not constant, but may be quite different in different patients, and may also show variation from time to time in any one patient. This accounts for the differing severity and response to treatment of asthma.

There is also no clear cut evidence as to the precise method by which epinephrine and the other sympathicoamines act to relieve human bronchial asthma. The antispasmodic action of epinephrine in relieving bronchial muscle spasm produced by vagal stimulation or drugs and the capillary constricting effects of epinephrine have been invoked.² Best and Taylor₃ and Goodman and Gillman⁴ emphasize the antispasmodic effects of epinephrine. It has been pointed out⁵ that epinephrine has a variable effect on bronchiolar musculature, depending on its tone. If the muscle is constricted, relaxation results. If it is relaxed completely, contraction of the muscle occurs. However, clinicians, such as Cooke,⁶ Fineberg⁷ and Lowell⁸ emphasize the vasoconstrictive effects of epinephrine on congested and edematous bronchial mucous membrane. This study undertakes an evaluation of the results of differing routes of administration on the effectiveness of some sympathicoamines in relieving acute asthmatic episodes.

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Method

Patients were selected for study from the Allergy Clinic and from the emergency room of the hospital. No patient had received any type of medication for at least two hours prior to the study. Control determinations of the maximum breathing capacity and one second vital capacity were made using a nine liter Benedict Roth spirometer with soda-lime tower and valves removed. The one second vital capacity was calculated by measurement from the spirographic tracing. A fifteen second interval was used for the maximum breathing capacity, and the results were expressed in liters per minute at 37 degree centigrade, wet, ambient pressure. All measurements were repeated until good agreement between duplicate determinations for each test was obtained and the largest measurement was recorded. Predicted values were calculated according to age, sex, height, and weight. In analyzing the data, when the control maximum breathing capacity was less than 50 L/min., increases of maximum breathing capacity which were at least 20 per cent of the control value were considered significant. When the control maximum breathing capacity was more than 50 L/min., significance was ascribed to an increase in maximum breathing capacity of 10 L/min. or greater.

The effect of sympathicoamine aerosols after a maximal bronchodilating effect of epinephrine subcutaneously.

On completion of control studies, the patient was given a subcutaneous injection of 0.3 mgm. of epinephrine and, after twenty minutes, the measurements were repeated. The patient was then given 0.2 mgm. of epinephrine subcutaneously, and after 20 minutes the studies were repeated.

![Graph showing response of bronchial asthma to repeated small doses of epinephrine subcutaneously](image)

**FIGURE 1:** Response of bronchial asthma to repeated small doses of epinephrine subcutaneously.

The bars at the extreme left of each diagram represent the determined maximum breathing capacity and the control point before any drugs were given. The drug recorded beneath subsequent bars was given 20 minutes prior to that determination of the maximum breathing capacity. Patient M.Y. demonstrates an almost maximal response to a single subcutaneous injection of epinephrine. S.W. demonstrates no response to a first injection of epinephrine but significant responses to the second injection and a subsequent aerosol administration. F.D. demonstrates cumulative response to 4 injections of epinephrine. Abbreviations: cpi for epinephrine; sub for subcutaneous; A for aerosol.
again repeated. The results of the measurements were then examined. If there was a significant change between the second and third maximum breathing capacity determinations, additional doses of 0.2 mgm. of epinephrine subcutaneously were given followed by repeat determinations of the maximum breathing capacity and one second vital capacity twenty minutes later until there was no significant change between two determinations. If there was no difference between the second and third maximum breathing capacity determinations, 5.0 mgm. of epinephrine or 2.5 mgm. of isoproterenol in 0.5 cc. of water was then given as an aerosol using a Vaponephrin nebulizer with compressed oxygen as the propellant. Twenty minutes later a final maximum breathing capacity and a one second vital capacity were determined. In 11 of 45 studies, the protocol was not completed in that the aerosol medication was given before a maximal effect of epinephrine subcutaneously had been demonstrated, and these studies are not included in the analysis of this portion of the data.

The effect of epinephrine subcutaneously after a maximal bronchodilating effect of sympathicoamine aerosol.

Eight studies were performed on six patients in which 0.3 mgm. epinephrine was administered subcutaneously after a maximum effect had been obtained with 0.5 per cent isoproterenol or 1 per cent epinephrine aerosol given as described above. Determinations of maximum breathing capacity and one second vital capacity were performed prior to drug administration and twenty minutes after each dose of medication.

Results

The effect of sympathicoamine aerosols after a maximum bronchodilating effect of epinephrine subcutaneously.

Forty-five studies were completed on 32 patients. Only the results of the maximum breathing capacity determinations are reported since an analysis of the one second vital did not appreciably alter the results. The control maximum breathing capacity was above 50 L/min. in 18 studies and below 50 L/min. in 27 studies indicating that, in general, the patients studied were having severe paroxysms of asthma. A significant response to sympathicoamine treatment occurred in 16 of the 18 studies where the control maximum breathing capacity was below 50 L/min. with a mean increase in M.B.C. of 22.5 L/min. There was a significant response in 22 of 27 studies in the group with control maximum breath-

| TABLE 1 — RESPONSE OF THE MAXIMUM BREATHING CAPACITY TO EPINEPHRINE SUBCUTANEously |
|-----------------------------------------------|----------------|
| Studies showing significant rise after first injection | 24 |
| Studies showing no significant rise after first injection | 8 |
| but a rise after second injection | |
| Studies showing no significant rise after subcutaneous epinephrine | 19 |
| **TOTAL** | **45** |

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ing capacity above 50 L/min. with a mean increase in maximum breathing capacity of 30.0 L/min. This difference in mean increase of maximum breathing capacity is not statistically significant.

In 38 of the 45 studies, there was a significant improvement in the maximum breathing capacity at the end of the study as compared with the control point prior to the administration of any drugs. Seven studies failed to show an increase in the maximum breathing capacity despite repeated doses of sympathicoamines by both routes of administration. No patient was worse. It is of special interest that four of these seven studies were carried out on one patient, a 10-year-old girl with severe asthma of mixed allergic and infective etiology. The control maximum breathing capacities in this patient were 11, 41, 45, and 51 L/min. with a predicted maximum breathing capacity of 70 L/min. This variation of the control maximum breathing capacity indicates that airway obstruction was reversible although not responsive to sympathicoamines.

An analysis was made of the response to repeated subcutaneous doses of epinephrine (Table 1). In 24 studies, there was a significant response to the first injection of 0.3 mgm. of epinephrine. There was an additional response to subsequent injections of epinephrine subcutaneously in 10 of these 24 studies. In eight studies, a significant rise failed to occur on the first injection, but there was a significant response after a subsequent injection of 0.2 mgm. of epinephrine. Thirteen patients failed to respond to subcutaneous epinephrine, but six of the 13 did

![FIGURE 2: Variability of responses to epinephrine subcutaneously and by aerosol in a patient on four occasions during 1957.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=data/journals/chest/21344/)

On February 21, 1957 and April 12, 1957 there is a response to both of two subcutaneous injections of epinephrine. On May 6, 1957 no response to subcutaneous epinephrine is elicited, and on September 5, 1957 there is a response to only the second injection of epinephrine. Aerosol epinephrine produces a response on three of the four occasions.
improve after sympatheticamine aerosol. Figure 1 presents typical examples of some of these responses. A cumulative effect of epinephrine subcutaneously is thus demonstrated in 18 of 45 studies.

Eight patients were studied on two or more occasions. Four patients showed a significant response to epinephrine subcutaneously on both occasions. Four patients failed to respond to epinephrine subcutaneously on one study but did respond significantly when studied on another occasion (Figure 2). This is interpreted as indicating variability in the bronchial pathology existing at the different observation points rather than variability in the pharmacologic properties of the sympathicoamines.

An analysis was made of the effects of isoproterenol aerosol as compared with the effect of aerosol epinephrine. The results are not considered to be significantly different (Table 2), and we therefore did not distinguish between isoproterenol and epinephrine aerosols in the analysis.

Thirty-four studies were performed in which it was demonstrated that maximum relief of airway obstruction had been obtained by the administration of repeated doses of epinephrine. Maximum effect of epinephrine subcutaneously was assumed to have occurred when there was no significant increase in the maximum breathing capacity between two doses.

A subsequent dose of aerosol epinephrine or isoproterenol caused a further significant rise in 10 patients, no further rise of maximum breathing capacity in 22 patients, and a significant fall in two patients.

![Figure 3: Effect of aerosolized sympathicoamines after a maximally effective dose of epinephrine subcutaneously.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21344/ on 04/19/2017)

A. J. and W. A. both show further rises after epinephrine aerosol. In W. A. the expectorant effect of the aerosol was likely an important factor in the rise of the maximum breathing capacity. Patient A. M. S. showed a significant fall in the maximum breathing capacity after aerosol isoproterenol.

<table>
<thead>
<tr>
<th></th>
<th>Better</th>
<th>Worse</th>
<th>No Change</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Isuprel Aerosol</td>
<td>4</td>
<td>1</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td>Epinephrine Aerosol</td>
<td>8</td>
<td>2</td>
<td>21</td>
<td>31</td>
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TABLE 2 — COMPARISON OF AEROSOLS OF EPINEPHRINE AND ISOPROPYLATERENOL ON THE MAXIMUM BREATHING CAPACITY AFTER REPEATED DOSES OF EPINEPHRINE SUBCUTANEOUSLY
(Table 3 and Figure 3). Thus, in one-third of the patients sympathicoamines administered topically produced an effect which could not be elicited by sympathicoamines carried to the lungs and bronchi via the blood stream. The significance of this observation is discussed below.

The effect of epinephrine subcutaneously after a maximum bronchodilating dose of sympathicoamine aerosol.

In eight studies in which subcutaneous epinephrine was administered after a maximally effective dose of sympathicoamine aerosol (Table 4), there was a significant response to the aerosol and a further significant response to epinephrine subcutaneously in three studies. There was a significant response to aerosol and a fall after subcutaneous epinephrine in two studies and no significant response to aerosol or subcutaneous epinephrine in two studies. One study showed no significant response to aerosol, but a significant rise after subcutaneous epinephrine. As noted, two patients were studied twice in this group. The responses on initial and repeat study were the same in one patient but different in the other. Thus, in three of six studies in which reversible airway obstruction was demonstrated, a bronchodilator response could be elicited by subcutaneous epinephrine which could not be elicited by aerosol sympathicoamine.

Discussion

We have demonstrated an appreciable beneficial response to sympathicoamine therapy in 83 per cent of 53 studies. In 18 of the 45 studies a beneficial response was noted after a second subcutaneous injection of epinephrine. In 10 studies there was significant response on both the first and second injections. These studies confirm our clinical experience that epinephrine in repeated small doses often has a cumulative effect.

In 15 of 53 studies no benefit was obtained by the use of the sympathicoamines in repeated dosage either subcutaneously or by aerosol. We do not believe that this indicates "epinephrine fastness," if this term means the development of tolerance to epinephrine. Variability of the pathology seems to be a more likely explanation of
the varying effectiveness of the sympathicoamines rather than a varying pharmacologic effect of these drugs. For example, if airway obstruction is primarily due to viscid adherent secretion and inflammatory infiltration, these drugs would have little effect. This concept is supported by our data showing variation in response to these drugs in 5 of 10 patients who were studied two or more times.

In 10 of 34 studies aerosolized drugs produced an effect which was additive to previously administered maximally effective doses of subcutaneous epinephrine. In three of six studies there was an additional response to subcutaneous epinephrine after a maximally effective dose of sympathicoamine aerosol. In one additional study there was no bronchodilation with the initial aerosol, but a significant response occurred with subsequently administered epinephrine subcutaneously. These findings are evidence that the effect of sympathicoamines may differ depending on the way in which they are administered. Aerosolized drug may have a more effective topical vasoconstricting effect, and the water vapor in the mist may have an effect in thinning mucus and permitting easier expectoration. Subcutaneously administered sympathicoamines may have a greater effect on vasoconstriction deep in the wall of the bronchus and on smooth muscle relaxation. Variation in response to administration of sympathicoamines by these routes in different patients and in the same patient at different times is probably due to differences in the pathology of the airway obstruction.

In two of our studies the patients were worse after aerosol therapy following benefit from subcutaneous therapy. The converse was also noted in two studies. Possible explanations of this are the well known rebound vasodilatation after epinephrine and an irritating effect of the aerosol.

SUMMARY

Thirty-nine asthmatic patients have been studied following the administration of sympathicoamines either subcutaneously or as an aerosol on 53 occasions.

The failure of a patient to respond to epinephrine with relief of airway obstruction is not believed to be due to an alteration of the pharmacologic effects of the drug but is due to other causes of airway obstruction not affected by sympathicoamine action. Aerosolized sympathicoamines may have a greater vasoconstrictive effect in the superficial portions of bronchial mucosa. Subcutaneously administered sympathicoamines may have a greater effect on vasoconstriction deep in the bronchial wall and on lysis of bronchial muscle spasm.

These studies indicate the advisability of using sympathicoamines by both the subcutaneous and aerosol routes in the treatment of the patient with severe or refractory asthma. Small repeated subcutaneous doses of epinephrine often have a cumulative effect and have far fewer side effects than the same total dose of drug given as a single injection.

ACKNOWLEDGMENT: The technical assistance of Mr. Joseph Buck is gratefully acknowledged. The complete data, on which the tables are based, is available on request from the authors.

RESUMEN

Se estudiaron treinta y nueve asmáticos después de la administración de simpaticoaminas, ya sea subcutáneamente o por aerosol en 53 ocasiones.

La falta de respuesta del enfermo a la epinefrina con alivio de la obstrucción al paso del aire, se cree que no se debe a cambio en los efectos farmacológicos de la droga sino a otras causas de obstrucción que no son afectadas por la acción simpaticomímica.

Las simpaticoaminas pueden tener una acción vasoconstrictora mayor, en las partes superficiales de la mucosa bronquial.

Las simpaticoaminas inyectadas subcutáneamente, pueden tener mayor efecto vasoconstrictor y más profundo, en la pared bronquial y sobre la lisis del espasmo del músculo bronquial.

Estos estudios indican que es aconsejable el uso de las simpaticoaminas tanto por la vía subcutánea como por aerosol en el tratamiento de las asmas severas y refractarias.

Los dosis pequeñas y repetidas de epinefrina, a menudo tienen efecto acumulativo y tienen mucho menos efectos colaterales que la misma dosis total dada en inyección única.
RESUMÉ

39 malades asthmatiques ont été étudiés après administration de sympathicoamines par voie sous-cutanée, soit 53 fois en aérosols.


Ces études montrent qu’il est indiqué d’utiliser les sympathico-amines à la fois par voie sous-cutanée et en aérosols dans le traitement d’un malade atteint d’asthme grave et réfractaire. De petites doses sous-cutanées répétées d’épinéphrine ont souvent un effet cumulatif et ont de bien moindres effets toxiques que la même dose globale du produit donnée en une seule injection.

ZUSAMMENFASUNG


Es wird die Auffassung vertreten daß, wenn ein Patient nicht auf Epinephrin mit Behebung des Atemhindernisses reagiert, dies nicht der Ausdruck einer Veränderung in der pharmakologischen Wirksamkeit des Medikamentes ist, sondern damit zusammenhängt, daß andere Ursachen für die behinderte Atmung vorliegen, die durch die sympathikomimetische Wirkung nicht betroffen werden. Vernebelte sympathikomimetische Mittel haben vielleicht einen stärkeren gefäßerweiternden Effekt in den oberflächlich gelegenen Breichen der Bronchialschleimhaut. Subkutan gegebene sympathikomimetische Mittel können eine stärkere Wirkung ausüben als die Gefäßerweiterung in der Tiefe der Bronchialwand und auf die Lösung des Spasmus der Bronchialmuskulatur.


REFERENCES