Experiences with Tetraethyl Ammonium Chloride in Bronchial Asthma*

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Since the introduction of tetraethyl ammonium as a ganglionic blocking agent, it has been used in the experimental induction of postural hypotension,¹ as a diagnostic aid in pheochromocytoma,² and, tentatively, in bronchial asthma and left ventricular failure.³⁴ Not only is the arterial blood pressure lowered, but the venous,⁵ the pulmonary arterial,⁶ and the pulmonary “capillary bed”⁷ pressures are decreased as well. The cardiac output remains constant in human,⁸ or falls in animal,⁹ experiments. Tetraethyl ammonium compounds probably evoke epinephrine and norepinephrine hypersecretion.²¹⁰ These effects of the drug, as well as its autonomic blockade, should influence various cardiopulmonary derangements. The asthmatic state is definitely affected, as shown in the following study.

Methods and Materials

Twenty patients with bronchial asthma were studied. They were given at various times tetraethyl ammonium chloride (Etamon†), 7 mg./kg. intravenously, epinephrine, 0.2 to 0.6 mg. intramuscularly, or aminophylline, 0.24 to 0.48 mg. intravenously. The vital capacity was determined in triplicate before administering the drug and at 30 to 60 second intervals immediately thereafter for five minutes, then less frequently up to the observed duration of effect. Previous experience indicated that serial vital capacity measurements were much more easily made and, in conjunction with the respiratory rate, as accurately reflective of the pulmonary function as the maximum breathing capacity.¹¹

In many instances the patient was in status asthmaticus and unresponsive to the usual measures. Hence, some readings were obtained with two or more different drugs in succession. During these periods of remission a mild attack was induced with histamine in three cases, and Etamon and epinephrine then used as in spontaneous asthmatic attacks. Intravenous isotonic saline solution control readings were obtained in 11 cases.

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Results

The results are summarized in Table I. Significant rises (25 per cent or more) in vital capacity followed intravenous Etamon administration in 16 instances. In 19 other attempts, however, the vital capacity was unchanged (i.e., 13 cases) or fell 25 per cent or more (6 cases). Those patients responding favorably to Etamon showed drops in respiratory rate, pulse rate, and often marked diminution in dyspnea, cyanosis, apprehension, and signs of bronchospasm—within 60 to 120 seconds. Mild asthmatic attacks generally subsided rapidly, as is seen following epinephrine.

One severe case of status asthmaticus in a 58 year old woman in coma and in extremis, and refractory to epinephrine, aminophylline and oxygen, responded dramatically to 0.2 gm. of intravenous Etamon. The attack subsided and there was no recurrence up to 24 months. Of five patients refractory to epinephrine, two received Etamon with relief, whereas it had no effect upon the three other cases. Two persons refractory to aminophylline

<table>
<thead>
<tr>
<th>Vital Capacity</th>
<th>Etamon (7 mg./kg. I.V.)</th>
<th>Epinephrine (0.2-0.6 mg. I.M.)</th>
<th>Aminophylline (0.24-0.48 gm. I.V.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rise</td>
<td>Same</td>
<td>Fall</td>
</tr>
<tr>
<td>Alone</td>
<td>12</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>After Epinephrine</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>After Aminophylline</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>After Histamine</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>16</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

TABLE I

Effects of Tetraethyl Ammonium, Epinephrine, and Aminophylline Upon the Vital Capacity of 20 Patients with Bronchial Asthma. A Rise was Defined as 25 Per cent or Greater Increase, a Fall as 25 Per cent or Greater Decrease, in Vital Capacity. Saline Injections (not shown, same criteria) Produced no Change in 10 Cases and a Fall in One Instance.
bronchial asthma failed to respond to Etamon. In histamine-induced asthma, Etamon was successful in two and unsuccessful in one instance.

Patients responding unfavorably to Etamon had continued symptoms and signs. The fall in vital capacity in six instances was accompanied by increased apprehension and dyspnea. No precordial pain was noted. The hypotensive effect of Etamon occurred equally in the favorable and unfavorable groups of cases.

Epinephrine, in contrast to Etamon, showed no unfavorable effects. In spontaneous, and, in one instance, in a histamine-induced attack, it caused a rise in the vital capacity of at least 25 to 50 per cent, or else no change (refractory asthma). In most instances the attack was consequently terminated within 60 to 120 seconds. Intravenous aminophylline had similar good results (Table I). Intravenous isotonic saline solution had no significant effect. The vital capacity never fell more than 25 per cent following epinephrine, aminophylline, or isotonic saline solution injections.

The following case reports elucidate the results obtained.

Case 1: J.M., a 14 year old colored male, had repeated moderate attacks of bronchial asthma. The vital capacity usually fell from about 3.0 liters between attacks, to 1.0-1.4 liters during the bouts of asthma. Figure 1 indicates that Etamon raised the vital capacity not more than 30 per cent in severe asthmatic bouts (IIc, III), and that epinephrine (III) and aminophylline (IV) were no more successful. In less severe asthma, however, both spontaneous and histamine-induced, the Etamon vital capacity ceilings rose both relatively and absolutely (IIa, IIb, V). In this case, Etamon consistently proved to be the best therapeutic measure. Control saline injections were ineffective (I).

Case 2: E.M., a 20 year old colored female, constantly affected by mild asthma (vital capacity 1.8 to 2.8 liters), occasionally very severe (vital capacity 0.2 to 0.4 liters). Figure 2 indicates the equivalent success of Etamon, aminophylline and

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**FIGURE 1:** Effect of various drugs, alone and in combination, upon the vital capacity in patient J.M.
epinephrine in the mild attacks and their failure in the severe bouts of asthma. One moderate attack was unaffected by Etamon, then relieved by aminophylline (Iib). In another, an unusual diphasic effect of Etamon, a fall, then a rise in the vital capacity, was noted (Iia). Saline had no effect (Ia).

Case 3: M.B., a 49 year old colored male, with mild asthma. Severe attacks were induced by histamine (0.01 mg. intravenously), and then the therapeutic drugs injected. In this case (Figure 3), epinephrine (III, V, VI) and aminophylline were consistently superior to Etamon in raising the vital capacity and relieving the bronchospasm. Saline (I) caused no change.

![Figure 2: Effect of various drugs, alone and in combination, upon the vital capacity in patient E.M.](image)

![Figure 3: Effect of various drugs, alone and in combination, upon the vital capacity in patient M.B.](image)
Case 4: W.F., a 44 year old white female with severe atopic bronchial asthma. Figure 4 indicates the failure of all drugs during severe status asthmaticus and the unfavorable effects of Etamon both in spontaneous (II) and histamine-induced (V) asthma. In milder asthmatic attacks aminophylline or epinephrine raised the vital capacity to approximately the same ceiling values. Following Etamon, epinephrine had strikingly beneficial effects (II, V). In this patient, as in other cases, too, the asthma was frequently refractory to epinephrine or aminophylline alone. However, after Etamon was administered, relief would be afforded.

To determine whether Etamon acted in part through release of epinephrine from the adrenal medulla, intramuscular epinephrine (0.003 mg./kg.) and intravenous Etamon (1 mg./kg.) were compared in their effects upon the four-hour afternoon eosinophil count and the urine uric acid/creatinine ratio in nine patients, and upon the serum potassium (and sodium) levels in seven and eight patients respectively. (The subjects utilized were convalescent cases on the medical wards and free from allergic or endocrine disorders.)

Table II summarizes the eosinophil and the uric acid/creatinine ratio effects, and Figure 5 the serum potassium (and sodium) alterations of epinephrine and Etamon. Only four of the nine subjects, J.McN., B.D., C.P., and G.M., showed a significant fall in eosinophils four hours following both Etamon and epinephrine. A marked rise in the uric acid/creatinine ratios was seen only in case C.P. The potassium effects were grossly similar in that both Etamon and epinephrine caused rapid slight lowering of serum potassium in eight subjects each. Immediate falls in serum potassium following epinephrine in man have been reported previously. The corresponding serum sodium alterations were inconclusively variable.

Discussion

It is clear that intravenous Etamon, in contrast to saline solution, has marked effects on bronchospasm. The latter, especially if not severe, is often dramatically relieved, even in cases refractory to epinephrine or aminophylline. However, there are cases and occasions in which Etamon has no effect, or the bronchospasm is actually augmented. Theoretically,
If the bronchial obstruction were primarily due to vagotonic bronchospasm, and if Etamon were to block primarily the vagal ganglia, the effect would be favorable, and if these conditions were not present—unfavorable. In this connection, another ganglionic blocking, and anticholinergic agent—Banthine,* was found in preliminary trials to raise the vital capacity favorably in some patients with bronchial asthma.14

*G. D. Searle & Company brand of methantheline bromide.

### TABLE II

Effect of Epinephrine (intramuscular, 0.003 mg./kg.) and Tetraethyl-ammonium (intravenous, 7 mg./kg.) Upon the Eosinophil Count and the Urinary Uric Acid/Creatinine Ratio (percentage change) in Normal Subjects

Four Hours After Injection of the Drugs.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>EOSINOPHILS</th>
<th>URIC ACID/CREATININE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epinephrine</td>
<td>Tea</td>
</tr>
<tr>
<td>A.F.</td>
<td>-53</td>
<td>-5</td>
</tr>
<tr>
<td>J.M.</td>
<td>-18</td>
<td>-13</td>
</tr>
<tr>
<td>B.D.</td>
<td>-22</td>
<td>-55</td>
</tr>
<tr>
<td>C.P.</td>
<td>-70</td>
<td>-22</td>
</tr>
<tr>
<td>G.M.</td>
<td>-48</td>
<td>-32</td>
</tr>
<tr>
<td>C.B.</td>
<td>-60</td>
<td>-7</td>
</tr>
<tr>
<td>N.T.</td>
<td>-70</td>
<td>+11</td>
</tr>
<tr>
<td>H.F.</td>
<td>-67</td>
<td>+10</td>
</tr>
<tr>
<td>F.H.</td>
<td>-47</td>
<td>-7</td>
</tr>
</tbody>
</table>

**FIGURE 5:** Effect of Intramuscular epinephrine (0.003 mg./kg.) and of intravenous Etamon (7 mg./kg.) upon the serum sodium and potassium of human subjects. Note immediate falls (of 5 to 10 per cent or more) in five of seven cases following epinephrine and in five of eight cases following Etamon in serum potassium.
It is possible that the effects of Etamon in patients with asthma, as occasionally seen in patients with emphysema and left ventricular failure with pulmonary congestion,\cite{3,4} may be, in part, due to its hemodynamic actions. The fall in pulmonary vascular resistance may be beneficial. Epinephrine and its analogs are, however, classically remedial, although they raise both the pulmonary and the systemic arterial pressures.

On the other hand, the systemic hypotension due to Etamon has caused serious, even fatal, coronary insufficiency in individuals with heart disease. While our patients had no heart disease and developed no anginal pain following Etamon, there was severe aggravation of asthma in a few cases. Like others,\cite{15} we unfortunately had one fatality within 30 minutes following 0.3 gm. of intravenous Etamon, and are acquainted with another which occurred in a severe asthmatic attack treated with 0.5 gm. of intramuscular Etamon two hours previously. The fall in arterial pressure in these two cases was excessive, and epinephrine was of no aid.**

Despite some parallelisms in the effects of Etamon and epinephrine upon the eosinophil count, urinary uric acid/creatinine ratio, and serum potassium, our data do not definitely prove the concept\cite{10} that Etamon produces epinephrine release. In some instances, epinephrine following Etamon relieved previously refractory status asthmaticus; in other cases it failed to do so. Whether sensitization to, or increased secretion of, endogenous epinephrine and/or nor-epinephrine occurs following Etamon remains, therefore, sub judice.

**Summary

1) In 20 cases of bronchial asthma the effects of parenteral Etamon were compared with those of epinephrine and aminophylline during mild, severe, and histamine-induced attacks.

2) Parenteral tetraethyl ammonium chloride usually altered the asthmatic state: relief was more frequent than aggravation. Occasional fatalities contraindicate the use of TEA in bronchial asthma as well as in coronary heart disease.

3) The effects of TEA in asthma may be linked to ganglionic blockade, decreased pulmonary vascular resistance and pressure, and epinephrine sensitization. Some favorable effects of Banthine may support the first mode of action. Indirect signs of the intermediation of endogenous hyper-epinephrinemia in TEA action are discussed.

**Resumen

1) En 20 casos de asma bronquial los efectos del Etamón parenteral fueron comparados con los de la epinefrina y la aminofilina durante ataques moderados, o severos, o bien en los ataques provocados por la histamina.

2) En general el tetraetilamonio cambió el estado asmático: El alivio fue más frecuente que la agravación. Las defunciones ocasionales contraindican el uso del TEA en asma bronquial así como en la afeción coronaria.

3) Los efectos del TEA pueden estar en relación con un bloqueo gan-
glonar, con una resistencia vasculor pulmonar disminuida, y sensibilización a la epinefrina. Pueden apoyar el primer modo de actuar algunos efectos favorables de la Banthina. Se discuten los signos indirectos de la intervención de la hiper-epinefrinemia en la acción del TEA.

RESUME

1) L'auteur a comparé dans 20 cas les effets de l'action parentérale de "l'Etamon" (chlorure tétra-éthyl-ammonium) avec l'action obtenue par laadrénaline et l'aminophylline au cours de crises d'asthme moyennes, sévères, ou provoquées par l'histamine.


3) L'action du tétra-éthyl-ammonium dans l'asthme peut être lié au blocage des ganglions nerveux, à une diminution de la résistance et de la pression du système vasculaire pulmonaire et à une sensibilisation des surrénales. Les effets favorables de la "Banthine" peuvent apporter une confirmation au premier de ces mécanismes. L'auteur discute les manifestations indirectes d'un relais surrénalien au cours de l'action du tétra-éthyl-ammonium.

REFERENCES


7 Work in progress (John Sealy Memorial Laboratory).


14 Greer, A.: Unpublished data.