Theophylline Glyceril Guaiacolate (Quibron) 
In Bronchial Asthma*

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In earlier reports,1,2 attention was called to a recently formulated oral theophylline glyceryl guaiacolate compound (Quibron) which, when administered to normal subjects was found to produce rapid and sustained theophylline blood values within the known therapeutic range.3 These findings led us to observe the effects of the drug on certain measurements of pulmonary function in subjects with bronchial asthma. The results clearly indicated that this new compound was a valuable bronchodilator preparation. For these reasons, we were prompted to undertake a clinical trial with the compound in patients with asthma.

Materials** and Methods

Fifty patients with bronchial asthma, eight of whom had an irreversible component to their disease (pulmonary emphysema), were treated with theophylline glyceryl guaiacolate in the interval between April, 1961 and December, 1961. All were ambulatory and were selected from our combined practices and from the Allergy Clinic of the Boston Dispensary. There were 28 men and 22 women with ages ranging from 17 to 70 years with a median age of 42 years. As judged by history and symptoms, the duration of asthma ranged from three to 55 years with a median duration of 16 years.

Injections of allergenic extracts were being administered to the majority of the patients and many had been instructed to avoid or eliminate offending allergens and no change was made in this regimen. Unless instructed to the contrary, all were urged to avoid the use of other drugs intended for relief of symptoms. All patients had asthma of the perennial variety and were having mild to severe symptoms at the time they were included in the study. The severity of asthma at the time therapy with theophylline glyceryl guaiacolate was begun was classified as follows: mild, if there was little or no interference with daily activities or sleep and prompt relief of symptoms when a bronchodilator agent was taken; moderate, if symptoms partially disturbed daily activities and sleep with medication required several days a week; and severe, if symptoms interfered with work or sleep, requiring daily doses of bronchodilator agents by mouth or by inhalation, or both. During the period of this study, there were ten patients in the severe category who were taking one or another of the corticosteroid drugs to alleviate some of the manifestations of their respiratory symptoms.

The theophylline glyceryl guaiacolate was made available in four-ounce bottles with instructions to take three teaspoonsful before meals for the first four days and to follow this with two teaspoonsful three times a day on an “as needed” basis. (Each 5 ml. of the compound contains 50 mg. theophylline, 30 mg. glyceryl guaiacolate in a syrup vehicle of 15 per cent alcohol). When sleep was disturbed because of severe symptoms, patients were instructed to take a single dose of six teaspoonsful. Observations were made, usually at seven-day intervals, over a period of weeks to months. At each visit, inquiry was made concerning the effectiveness of the drug in relieving symptoms, the time interval between the

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administration of the medication and subjective relief, and the length of time the dose of the drug was effective. All patients were questioned about the presence of untoward reactions and those mentioned were noted.

The response ratings reflecting the patients' perceived effectiveness of theophylline glyceryl guaiacolate were scored as follows: excellent, if complete or almost complete relief of symptoms occurred within 30 minutes and lasted for four or more hours; good, if relief was between 50 to 75 per cent and lasted two or more hours; fair, if relief was between 25 and 50 per cent; and ineffective, if relief was less than 25 per cent.

RESULTS

Of the 50 patients, 14 (28 per cent) responded with an excellent rating, 20 (40 per cent) gave the drug a rating of good, 12 (24 per cent) a rating of fair, and four (8 per cent) found the drug ineffective. If one pools the excellent and good responses, also the fair and ineffective responses, at the same time pooling the mild and moderate and severe cases, one obtains the following 2 x 2 table (Table 1):

<table>
<thead>
<tr>
<th>Degree of Asthma</th>
<th>No. of Cases</th>
<th>Good or Excellent Response</th>
<th>Fair or Ineffective Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or Moderate</td>
<td>26</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>Severe</td>
<td>24</td>
<td>15</td>
<td>9</td>
</tr>
<tr>
<td>Totals</td>
<td>50</td>
<td>34</td>
<td>16</td>
</tr>
</tbody>
</table>

The above table suggests that the severe cases respond to the drug in about the same way as the mild and moderate cases. (Chi-square is less than one, hence decidedly nonsignificant). This result was contrary to clinical expectation and previous experience in assessing bronchodilator drugs where the severe cases of asthma showed less relief than the others. This leads to the conjecture that the effect of theophylline glyceryl guaiacolate has an extended range of action, but these data do not provide a confirmation of this conjecture.

Of the eight patients with asthma and emphysema, relief was excellent in four, fair in two and the compound was ineffective in two.

SIDE EFFECTS

Of the 50 patients in the study, 45 were completely free of disturbing side reactions. The remaining five (10 per cent) reported gastrointestinal complaints. Four of them had slight to moderate nausea. With the reduction of approximately one-third of the dosage of the drug, they had no further difficulty. The other patient had severe asthma and emphysema and was on maintenance steroid therapy. She found the drug ineffective and discontinued it.

DISCUSSION

For the past three decades, theophylline and especially one of its soluble salts, theophylline ethylenediamine (aminophylline), has occupied a prominent place in the treatment of asthma, even though its desirable bronchodilator properties were unavailable in full measure to the clinician. The reason for this simply was that in therapeutic oral doses the drug caused disagreeable side effects, particularly nausea and vomiting. When administered rectally in solution or in the form of a suppository, aminophylline is less effective, its absorption erratic and it occasionally produces nausea and local irritation. Although there are important limitations, when administered intravenously, aminophylline is often a dependable agent in the treatment of intractable asthma.

With the introduction about five years ago of a water-alcohol solution of theophylline (Elixophyllin), an important contribution was made in oral theophylline therapy. Numerous clinical trials with this agent found that it effectively reduced some or all the manifestations of bronchial asthma. In addition, the medication could be administered in full therapeutic amounts
to many patients without provoking gastric intolerance, especially when it was prescribed as a single dose (75 ml.) in acute asthma. However, when the medication was administered regularly or on an “as needed” basis in cases of chronic asthma, gastric distress of some significance was noted. In an endeavor to reduce to an even greater extent gastric intolerance for theophylline, theophylline glyceryl guaiacolate was recently formulated.

Despite the well known difficulties in assessing a drug in asthma, we believe that our experience with theophylline glyceryl guaiacolate is noteworthy. The results reported herein indicate that theophylline glyceryl guaiacolate is a useful agent in the management of bronchial asthma. Forty six of the 50 patients in our series gave the medication a fair to excellent response rating and only four derived no benefit. These findings are in accord with those described by other investigators.1

In only five of our 50 patients was mention made of nausea as a side effect. Other untoward effects which frequently follow the administration of oral non-water-alcohol theophylline preparations were not noted.

There is no evidence to indicate that the glyceryl guaiacolate in the compound has bronchodilator activity, yet one may speculate that its stimulating-expectorant action increased the flow and diminished the viscosity of bronchial secretions sufficiently to lessen the degree of bronchial obstruction clearly present in asthma. Our results, therefore, may have been affected by glyceryl guaiacolate. This point, however, remains to be explored.

Summary

Theophylline glyceryl guaiacolate (Quibron) was administered to 50 patients with bronchial asthma, the large majority of whom were under observation for weeks to months. The compound was taken orally as needed in daily doses of 10 ml. to 45 ml. or more. Theophylline glyceryl guaiacolate is an effective oral bronchodilator agent applicable to mild or severe cases of asthma. The only unpleasant side effect noted was nausea; this was minimal and posed no problem.

Resumen

El guaiacolato de gliceril teofilina (Quibron) fue administrado a 50 enfermos con asma bronquial, la mayoría de los cuales estaban bajo observación, por semanas o meses. El compuesto se tomó oralmente, según se necesitó, en dosis de 10 a 45 ml. o más. El guaiacolato de gliceril teofilina es un dilatador oral, bronquial, aplicable a los casos medianos o graves de asma. El único defecto desagradable, la náusea, fue mínimo y no constituyó un problema.

Résumé

Le guaiacolate glycéryl de théophylline (Quibron) a été administré à 50 malades atteints d’asthme bronchique, dont une grande majorité furent mis en observation pendant une période variant de quelques semaines à plusieurs mois. Le composé fut pris par la bouche, selon les besoins à des doses quotidiennes de 10 ml à 45 ml ou plus. Le guaiacolate glycéryl de théophylline est un agent bronchodilatateur buccal efficace, applicable aux cas bénins ou graves d’asthme. La seule complication désagréable notée consista en nausées; mais elles furent discrètes et ceci ne posa aucun problème.

Zusammenfassung


References


METASTATIC EPIDERMOID CARCINOMA TO THE HEART

An interesting case of metastatic disease to the heart has been presented illustrating the fact that extensive myocardial involvement can occur without signs or symptoms of heart failure. It further illustrates the intractability of cardiac arrhythmias due to tumor involvement of the heart. The primary tumor was an uncommon epidermoid carcinoma of the renal pelvis first manifested by a metastasis to the left calcaneous bone.


APPEARENT SITES OF ORIGIN OF CARCINOMAS OF LUNG

The apparent site of origin was investigated in a series of 463 cases of microscopically verified primary lung cancer. In 150 cases, the site could be determined with reasonable certainty by two or more of the following methods: radiologic, bronchoscopic, operative, or necropsy. In 33 cases, the site of origin could not be determined with any fair degree of probability. The percentage distribution of sites of tumor origin in the identifiable cases was as follows:

- Main bronchus (including intermediate) 11%
- Lobar bronchus 29%
- Segmental bronchus 29%
- Segmental area (i.e. peripheral tumor) 31%

The anatomic locations of 44 segmental bronchus tumors, and of 46 segmental area (peripheral) tumors are recorded. Primary lung cancer appears to originate most frequently in the segmental and subsegmental bronchi, rather than in the main or lobar bronchi, as formerly reported by some investigators.


A CASE OF TUBERCULOSIS OF THE MYOCARDIUM

A rare case of miliary tuberculosis of the myocardium in a patient with casecavernous pulmonary tuberculosis and mild diabetes is presented. At necropsy, the pancreas was calcified; this suggests a protracted pancreatitis which might be of various etiology. It is of interest that daily requirement of insulin was rather low in spite of active respiratory tuberculosis.