The Effects of Bromhexine on Oxytetracycline Penetrance into Sputum*


SUMMARY

The addition of bromhexine to oxytetracycline significantly increases the sputum concentration of oxytetracycline. Oxytetracycline is cleared from plasma more effectively in the presence of bromhexine. These results suggest that the combination of bromhexine with oxytetracycline may prove of value in the treatment of certain pulmonary infections.


Bromhexine (N-cyclohexyl-N-methyl-(2-amino-3,5-dibrombenzyl)-ammonium chloride) was introduced into clinical practice as a mucolytic agent for use in the treatment of chronic bronchitis. Evidence for the efficacy of this agent is inadequate, although bromhexine in daily doses of 48 mg clearly alters the flow properties of bronchial mucus. Bürgi et al. have reported that oxytetracycline levels are increased in the sputum of bronchitics when bromhexine 4 mg is given with the antibiotic, but Ingold and Shaylor have been unable to confirm this finding.

This study was undertaken to determine whether a combination of bromhexine (8 mg) with oxytetracycline (250 mg) affected the plasma kinetics or sputum penetrance of oxytetracycline.

METHODS

Ten patients with chronic bronchitis or non-tuberculous lung abscess were given oxytetracycline (250 mg) or a mixture of oxytetracycline (250 mg) and bromhexine (8 mg), every 6 hours for 7 days. Patients were divided randomly in a double-blind study. Three patients were given both preparations separated by a 5-day interruption in treatment.

Sputum was collected during the 7 days of each study and stored in sealed sterile plastic containers at −20°C until analysis. The sputum was digested enzymically by a method based on that described by Campbell. Between 3 g and 8 g of sputum were incubated for 2-4 hours at 40°C with 6.0 mg bacterial pronase (Sigma Chemical Co., USA) in 0.5 ml/g sputum of 0.5M tris-HCl buffer (pH 9.5), containing 0.005M CaCl₂. Oxytetracycline concentrations were determined in aliquots of liquefied sputum by the method of Hayes and Du Buy.

Plasma oxytetracycline levels were measured in 8 healthy male volunteers. Single capsules containing oxytetracycline 250 mg or oxytetracycline 250 mg with bromhexine 8 mg were given 7 days apart in a double-blind study. No food was taken until 4 hours after drug ingestion. Antacids and calcium-containing foods were strictly avoided by volunteers during this study because of their possible interference with oxytetracycline absorption. Blood samples were collected in heparinized tubes before ingestion of the antibiotic and 2, 4 and 6 hours thereafter. Plasma oxytetracycline concentrations were determined as above.

All oxytetracycline assays were carried out in duplicate and arithmetical means used for calculations. Sputum oxytetracycline levels were statistically analysed by Student's t-test for 2 samples with N₁ + N₂ − 2 degrees of freedom. Plasma data were analysed by Student's t-test for correlated samples with N − 1 degrees of freedom.

RESULTS

Sputum Concentrations of Oxytetracycline

Results are set out in Tables I and II. A statistically significant increase in sputum oxytetracycline levels was observed in patients who took bromhexine 8 mg with the antibiotic (P<0.01) and in patients who took both drugs (P<0.05).

Plasma Oxytetracycline Concentrations

Results are set out in Table III. A significant decrease in plasma oxytetracycline levels was noted 4 and 6 hours after the ingestion of the oxytetracycline-bromhexine mixture (P<0.02).

DISCUSSION

The data presented here indicate that oxytetracycline levels may be significantly increased in sputum by ingesting bromhexine 8 mg with the antibiotic. This finding confirms that of Bürgi et al. and not that of Ingold and Shaylor, who had difficulty in detecting oxytetracycline in any sputa examined.

Campbell has stated that the minimum inhibitory concentration of tetracycline for sensitive respiratory
TABLE I. MEAN DAILY OXYTETRACYCLINE CONCENTRATION IN PATIENTS TAKING OXYTETRACYCLINE 250 mg PLUS BROMHEXINE 8 mg OR OXYTETRACYCLINE 250 mg EVERY 6 HOURS FOR 7 DAYS

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean daily oxytetracycline concentration (µg/g sputum)</th>
<th>Patient</th>
<th>Mean daily oxytetracycline concentration (µg/g sputum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
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<td>Diagnosis</td>
<td>Sex</td>
</tr>
<tr>
<td>M</td>
<td>64</td>
<td>Bronchitis</td>
<td>M</td>
</tr>
<tr>
<td>M</td>
<td>43</td>
<td>Bronchitis</td>
<td>M</td>
</tr>
<tr>
<td>M</td>
<td>47</td>
<td>Lung abscess</td>
<td>M</td>
</tr>
<tr>
<td>M</td>
<td>47</td>
<td>Bronchitis</td>
<td>F</td>
</tr>
<tr>
<td>F</td>
<td>37</td>
<td>Bronchitis</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1,48</td>
<td></td>
<td>Mean</td>
</tr>
</tbody>
</table>

Statistical analysis was based on daily oxytetracycline estimations. Mean and standard deviation figures were 1,48 and 1,15 for patients given bromhexine and 0,40 and 0,47 for those given oxytetracycline alone.

TABLE II. MEAN DAILY OXYTETRACYCLINE CONCENTRATION IN PATIENTS TAKING OXYTETRACYCLINE 250 mg PLUS BROMHEXINE 8 mg AND OXYTETRACYCLINE EVERY 6 HOURS FOR 7 DAYS

| Patient | Mean daily oxytetracycline concentration (µg/g sputum) | | Probability |
|---------|------------------------------------------------------|--------------|
| Sex     | Age | Diagnosis | Oxytetracycline-bromhexine | Oxytetracycline | Probability |
| F       | 37  | Bronchitis | 3,59 | 0,80 | P<0,01 |
| M       | 47  | Lung abscess | 1,45 | 0,37 | P<0,05 |
| M       | 47  | Bronchitis | 0,72 | 0,44 | P<0,05 |

TABLE III. MEAN PLASMA OXYTETRACYCLINE CONCENTRATIONS (µg/ml) IN MALE VOLUNTEERS HAVING TAKEN OXYTETRACYCLINE 250 mg AND OXYTETRACYCLINE 250 mg PLUS BROMHEXINE 8 mg

<table>
<thead>
<tr>
<th>Volunteers</th>
<th>Plasma concentrations (µg/ml plasma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
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</tr>
<tr>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
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<tr>
<td>7</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
</tr>
</tbody>
</table>

flora lies between 0,125 and 0,50 µg/ml. In the experiments described here, mean oxytetracycline levels of 0,40 µg and 1,48 µg/g sputum were found following ingestion of the antibiotic and antibiotic-bromhexine mixture, respectively (1-2 g sputum equals 1 ml sputum approximately). The increased penetration of oxytetracycline in the presence of bromhexine may be due to increased lysosomal activity with resultant hydrolysis of mucopolysaccharide fibrils in sputum or possibly some change in capillary permeability. The increased plasma clearance of
Oxytetracycline noted in subjects given bromhexine could feasibly be due to rapid excretion or distribution of plasma oxytetracycline to tissues. This question awaits further investigation.

The practical implications of the findings set out in this article are uncertain at present. Adequate, controlled clinical trials are needed to determine whether increased penetration of oxytetracycline into sputum is of therapeutic advantage.

We wish to thank Dr M. H. Dürre of Boehringer Ingelheim (Pty) Ltd for supplying capsules containing oxytetracycline 250 mg, or oxytetracycline 250 mg and bromhexine 8 mg (Bisolvomycin); and the Medical Superintendents of King Edward VIII and Wentworth Hospitals, for access to patients. The assistance of Miss J. Hall and Mrs B. Bima, is also acknowledged.

REFERENCES


Granuloma in Systemic Lupus Erythematosus*

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SUMMARY

A case of systemic lupus erythematosus (SLE), with pleural granuloma is presented. This manifestation of SLE is rare and has important implications in differential diagnosis and in understanding the pathogenesis of the disease.


Granuloma is a rare manifestation of systemic lupus erythematosus (SLE). This lesion provides a link with other connective tissue disorders and may be important in understanding the pathogenesis of the disease. All previous reports of granuloma in SLE have been based on necropsy material. This is the first time that diagnosis has been made during life.

CASE REPORT

A 22-year-old man entered the hospital on 28 March 1971, because of swelling of the legs and face. A month earlier he had had a sore throat, followed within a week by swelling of the legs and face, shortness of breath, vomiting, chills, weakness and drowsiness.

The main findings were drowsiness, generalized oedema, ascites, an enlarged liver, and bilateral pleural effusions. The blood pressure was 140/90 mmHg and the optic fundi were normal. The urine contained much protein and a telescopic sediment.

The haematocrit was 26%, the white cell count 8 100 with a normal differential, the sedimentation rate was 64 mm/hour and the Coombs test was negative. Serum creatinine was 21.6 mg, total proteins 6.1 g (albumin 1.4 g, gamma globulin 1.77 g) and complement (beta,C) was 43 mg/100 ml (normal 145±22). Cold agglutinins and cryoglobulins were absent and the latex agglutination test was negative. Tests for antinuclear antibodies (ANA) were strongly positive and the lupus erythematosus test showed extracellular homogeneous round masses of purple-staining nuclear material on two occasions. An infusion pyelogram showed renal shadows of normal size with no obstruction. The pleural fluid was clear and yellow with a protein content of 4.1 g/100 ml, and a lactic dehydrogenase level of 500 units. PPD tests, and microscopy and culture of sputum, pleural fluid and pleural biopsy for acid-fast organisms were negative on several occasions.

* Date received: 18 January 1972.