Lincomycin in the Treatment of Penicillin-resistant Staphylococcal Infections in Children

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Lincomycin, a new antibiotic chemically distinct from those currently available, was first introduced into the United Kingdom in 1963. Its spectrum of activity is confined mainly to staphylococci (including penicillinase-producing strains), haemolytic streptococci, pneumococci, and *C. diptheriae* (Lewis, Clapp, and Grady, 1962), and the minimum inhibitory concentration for most strains of these organisms is less than 2 µg./ml. This concentration is easily obtainable *in vivo* with oral dosage; higher levels can be achieved with intramuscular or intravenous administration. Significant concentrations of antibiotic are attained in most tissues including bone and, though lincomycin hardly penetrates the normal blood brain barrier, there is some evidence that in the presence of meningeal infection, therapeutic levels can be achieved in CSF (Kaplan, Chew, and Weinstein, 1965). More detailed accounts of the discovery and biological properties of lincomycin have been published elsewhere (Mason, Dietz, and Deboer, 1962; Lewis *et al.*, 1962; Vavra, Sokolski, and Lawson, 1963).

Clinically, lincomycin has been shown to be effective in a number of bacterial infections including staphylococcal osteitis, septicaemia, respiratory infections, and infective dermatoses (Holloway, Kahlbaugh, and Scott, 1963; Geddes, Sleet, and Murdoch, 1964; MacLeod, Ross, Ozere, Digout, and Van Rooyen, 1964; Kanee, 1965). While some of these reports have included cases of penicillin-resistant infections, experience in conditions specifically due to penicillinase-producing strains of *Staphylococcus pyogenes* is limited, as are reports of the use of lincomycin in young children.

The following is an account of our experience with lincomycin in the treatment of 20 patients between the ages of 3 months and 12 years, suffering from infections due to penicillin-resistant staphylococci.

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Materials and Method

For a period of 26 months, infants and children admitted under our care in the Royal Hospital for Sick Children, Glasgow, were treated with lincomycin provided that they conformed to the following criteria.

1. The presence of an infection due to a penicillinase-producing *Staphylococcus pyogenes* sensitive to lincomycin *in vitro*.

2. The presence of toxicity, cellulitis, or septicaemia, such that operative treatment, unsupported by antibiotic therapy, was unlikely to produce a rapid response.

Twenty patients varying in age from 3 months to 12 years conformed to these criteria. Details of age, sex, diagnoses, and duration of infection before treatment are given in Table 1 (first five columns).

Specimens were obtained and submitted for culture in each instance. After plating on blood agar, subcultures were made. Significant colonies were confirmed by confirmatory studies on Oxoid D.S.T. agar base. *Staph. pyogenes* was identified by cultural characteristics, morphology, staining reaction, and the ability to coagulate plasma. Phage typing was not performed. Sensitivity of the organism to a variety of antibiotics was determined by the disc diffusion method using 9 mm. Multidisks, with the addition of a separate 7 mm. diameter 2 µg. disc of lincomycin. The bacteria were deemed sensitive when the diameter of inhibition on culture for 24 hours at 37° C. measured 1-5 mm. or more. Serum levels of lincomycin were not estimated during treatment, there being good evidence to indicate (Vavra *et al.*, 1963) that the dosage employed was sufficient to produce levels above the minimum inhibitory concentration for most strains of *Staph. pyogenes in vitro*. The *in vitro* disc plate sensitivities are shown in Table II.

All patients were observed for possible side-effects, and in each serum protein estimations and liver function tests including serum bilirubin, alkaline phosphatase, thymol turbidity, SGOT, and SGPT, were performed before, during, and after treatment and were repeated at weekly intervals when treatment exceeded 14 days.

* In one patient the organism was identified and its sensitivities were determined during the initial episode of femoral osteitis which antedated the introduction of lincomycin. Consequently the sensitivity to lincomycin was not assessed *in vitro*, though this antibiotic was used later to treat a relapse of the infection.
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20 Cases of Staphylococcal Sepsis Treated with Lincomycin

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex</th>
<th>Age (yr.)</th>
<th>Lesion</th>
<th>Duration of Infection Before Treatment</th>
<th>Duration of Treatment (days)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>3/12</td>
<td>Wound sepsis</td>
<td>4 dy.</td>
<td>7</td>
<td>Success</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>4</td>
<td>Wound sepsis</td>
<td>6 dy.</td>
<td>17</td>
<td>Success</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>4</td>
<td>Wound sepsis</td>
<td>4 dy.</td>
<td>28</td>
<td>Success</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>7</td>
<td>Wound sepsis</td>
<td>2 wk.</td>
<td>21</td>
<td>Success</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>8</td>
<td>Burns</td>
<td>1 mth.</td>
<td>25</td>
<td>Success</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>12</td>
<td>Burns</td>
<td>7 dy.</td>
<td>10</td>
<td>Success</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>2</td>
<td>Burns</td>
<td>2 wk.</td>
<td>42</td>
<td>Success</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>2</td>
<td>Burns</td>
<td>4 wk.</td>
<td>17</td>
<td>Success</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>11</td>
<td>Maxillary osteitis</td>
<td>2 yr.</td>
<td>33</td>
<td>Success</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>4</td>
<td>Cleft palate</td>
<td>2 wk.</td>
<td>5</td>
<td>Success</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>2</td>
<td>Skin sepsis</td>
<td>1 wk.</td>
<td>12</td>
<td>Success</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>2</td>
<td>Pre-auricular sinus</td>
<td>3 dy.</td>
<td>10</td>
<td>Success</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>1</td>
<td>Skin sepsis</td>
<td>6 wk.</td>
<td>19</td>
<td>Success</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>2</td>
<td>Pre-superficial sinus</td>
<td>2 mth.</td>
<td>21</td>
<td>Success</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>11</td>
<td>Cervical abscess</td>
<td>11 dy.</td>
<td>7</td>
<td>Success</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>2</td>
<td>Cervical abscess</td>
<td>10 dy.</td>
<td>14</td>
<td>Success</td>
</tr>
<tr>
<td>17</td>
<td>F</td>
<td>7/12</td>
<td>Cervical abscess</td>
<td>10 dy.</td>
<td>14</td>
<td>Success</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>7/12</td>
<td>Cervical abscess</td>
<td>10 dy.</td>
<td>14</td>
<td>Success</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>4</td>
<td>Otitis ext.</td>
<td>3 dy.</td>
<td>12</td>
<td>Success</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>2</td>
<td>Laceration</td>
<td>12 dy.</td>
<td>7</td>
<td>Success</td>
</tr>
</tbody>
</table>

Each patient received lincomycin by mouth, either as capsules or in the form of syrup, in a dose of 30 mg./kg. day. The total dose was divided into three equal parts and given at intervals of 8 hours, the initial dose being given in each case only after specimens had been taken for culture. Treatment was continued either until the infection appeared on physical examination to have been eradicated or, in patients with unhealed wounds, until swabs, which were cultured at weekly intervals, provided objective evidence of eradication of the infection.

Results

A summary of the results achieved is given in Table I (last two columns) from which it can be seen that a satisfactory outcome was achieved in all patients after a course of lincomycin varying in duration from 5 days to 42 days. The cases fall into four groups.

(1) Infection of surgical wounds. Four patients with initially clean surgical wounds developed infections which were treated with lincomycin. Two of these had been treated with tetracycline or ampicillin during the immediate post-operative period for other infections (respiratory or urinary tract), but despite this medication their wounds became infected. After treatment with lincomycin each of these infections was eradicated and the wounds healed well. The time taken for cultures to cease growing further staphylococci varied from 7 to 28 days.

(2) Burns. The colonization of cutaneous burns by 'hospital' staphylococci is a serious hazard in patients treated in an open general surgical ward, and to clear the organism often proves a difficult and protracted task (Grant and Findlay, 1957). Four patients with full thickness burns so infected were treated with lincomycin, and the staphylococcus was eradicated from the burned areas in 10, 17, 25, and 42 days, respectively.

(3) Osteitis. Recurrent infantile maxillary osteitis can be notoriously difficult to eradicate (Cavanagh, 1960). Case 10 was first referred in 1961, at the age of 9 months. The lesion gradually became quiescent, but a discharging malar abscess reformed in 1964. This recurred in 1965 and culture of the purulent nasal discharge yielded a staphylococcus sensitive to tetracycline, though this antibiotic had been prescribed for the previous four months without evident benefit. The abscess was drained and lincomycin was given for 10 days. Healing took place promptly and the nasal discharge ceased for the first time. Two months later there had been no recurrence of discharge.

Although acute osteitis of a long bone seldom heals without some radiological evidence of damage, x-ray changes of femoral osteitis were not demonstrated in our patient (Case 9) until the infection relapsed two years after the primary illness. She was first admitted at the age of 9 with signs of septic arthritis of the right knee. The synovial fluid was clear, and treatment with methicillin was instituted for three days pending the results of culture of the synovial fluid and of the blood. A staphylococcus sensitive to tetracycline was recovered from both specimens, and treatment with this antibiotic was then substituted for methicillin. The clinical response was good, and no radiological evidence of bone damage could be demonstrated during the
next 6 months. Two years later, however, signs of infection recurred, and radiographs then showed a small sequestrum related to the back of a slightly eroded femoral metaphysis. Lincomycin was administered and the symptoms ceased rapidly. Treatment was continued until the ESR fell from an initial level of 20 mm./hr. to 7 mm./hr., for a total of 33 days. There has been no recurrence during the subsequent two years.

(4) Cleft palate closure and infections of soft tissues and sinuses. Recovery was prompt and satisfactory in all 10 patients. The duration of treatment with lincomycin varied from 5 to 21 days.

Side-effects and toxicity. Previous reports have described isolated gastro-intestinal disturbances, pruritus, and mild aches in the limbs during treatment with lincomycin. Loose stools, which have occurred mostly when the drug has been taken by mouth, have occasionally necessitated cessation of therapy (Geddes et al., 1964; MacLeod et al., 1964; Holloway et al., 1963; Harnecker, Contreras, Gilabert, and Ubilla, 1963).

In our series, lincomycin was free from evidence of serious toxicity in infants and children. No gastro-intestinal or other reactions were detected during the study, and specifically there was no diarrhoea, even after lincomycin had been administered for seven weeks.

In 18 patients liver function tests and serum protein estimations were normal; minor and transient abnormalities were observed in 2 patients. One was a boy aged 11 in whom the serum transaminase levels became raised to 31 units in the middle of a 10-day course of treatment. The other was a 7-month infant girl who developed a serum bilirubin of 1·33 mg./100 ml. and a blood urea of 54 mg./100 ml. in the middle of a 14-day course of treatment: her twin sister with an identical infection also treated with lincomycin showed no abnormality in the corresponding tests.

Development of resistance to lincomycin. The studies of various workers suggest that very few strains of staphylococcus are naturally resistant to lincomycin and that resistance develops less readily in vivo to lincomycin than it does to erythromycin (Lewis et al., 1962; Clapper, Meade, and Stewart, 1964; Geddes et al., 1964). Out of a total of 510 cultures of staphylococci routinely tested for sensitivity to lincomycin in vitro but isolated from patients who were not receiving lincomycin, only 2 were resistant. No resistant strains were cultured from the 20 patients who received the antibiotic.

Summary

Twenty patients, comprising infants and children varying in age from 3 months to 12 years, were treated with lincomycin. All were suffering from infection with penicillinase-producing Staphylococcus pyogenes. In all patients improvement was rapid and the infection was eradicated. There were no side-effects or evidence of serious toxicity. No resistant strains emerged.

We wish to thank Mr. W. M. Dennison and Mr. S. L. Mann for allowing us to include their patients in this
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