Effects of Thiamphenicol and Chloramphenicol in Inhibiting *Neisseria gonorrhoeae* Isolates

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Received for publication 26 July 1978

Thiamphenicol was compared with penicillin, tetracycline, and chloramphenicol for its ability to inhibit 530 isolates of *Neisseria gonorrhoeae*, including 13 penicillinase-producing isolates. Thiamphenicol proved to be as active as chloramphenicol in inhibiting all of the isolates.

Thiamphenicol, a chloramphenicol analog in which the nitro group has been substituted with a methylsulfonyl group (2), has been suggested as a viable alternate therapy regimen to penicillin in the treatment of infections with *Neisseria gonorrhoeae* (2). This antibiotic has been successfully used in treatment of uncomplicated gonococcal infections in both men and women (4, 15), with failure rates as low as 2 to 3%. Because penicillin and tetracycline treatment failures have been correlated with increased resistance to those antibiotics (5, 6), the use of thiamphenicol as an alternate therapy regimen in the treatment of *N. gonorrhoeae* should be seriously evaluated. In the present study, we have examined the minimal inhibitory concentrations (MICs) of 530 isolates of *N. gonorrhoeae*, including 13 β-lactamase-producing isolates, to penicillin, tetracycline, chloramphenicol, and thiamphenicol.

The β-lactamase-producing isolates were obtained from Canadian, Asian, American, and African sources during the period 1976 to 1978. The other 517 nonpenicillinase-producing isolates were collected during a previous study (1a) in 1973 to 1974. All strains were maintained at −70°C in heart infusion broth (Difco Laboratories, Detroit, Mich.) plus 20% glycerol. Before determining MICs, all isolates were subcultured on GC medium base (Difco), containing 1% (vol/vol) defined supplement (8), followed by incubation for 18 h at 35°C in an atmosphere containing 5% CO₂. Penicillin-resistant isolates were tested for the production of β-lactamase by using the chromogenic cephalosporin substrate, nitrocefin (13). MICs were determined by an agar dilution technique, and antibiotic-containing plates were inoculated by an adaptation of the method of Maier et al. (10). Antibiotic media consisted of GC medium base with 2% defined supplement to which the following antibiotics were added to give the following final concentrations: penicillin G (Ayerst), 40, 20, 10, 5, 2, 1, 0.5, 0.25, 0.1, 0.05, 0.025, and 0.013 U/ml; tetracycline hydrochloride (Bristol Laboratories), 4, 2, 1, 0.5, 0.25, 0.1, 0.05, and 0.025 μg/ml; thiamphenicol (A. Siboulet, Paris), 8, 4, 2, 1, 0.5, 0.25, 0.10, 0.05, and 0.025 μg/ml; and chloramphenicol (Parke-Davis), 8, 4, 2, 1, 0.5, 0.25, 0.10, 0.05, and 0.025 μg/ml. For all susceptibility tests, World Health Organization isolates III, V, and VII (supplied by A. Reyn, Copenhagen) were used as control strains. The results were read after 18 h of incubation at 35°C in a 5% CO₂ atmosphere. The MIC was considered to be that concentration of antibiotic which completely inhibited growth; the presence of one to nine colonies was accepted as being indicative of drug susceptibility.

Table 1 shows the susceptibility of 517 non-β-lactamase-producing isolates to penicillin, tetracycline, thiamphenicol, and chloramphenicol. Penicillin and tetracycline were more active than thiamphenicol and chloramphenicol; over 60% of the isolates was inhibited by concentrations of 0.25 U of penicillin or 0.25 μg of tetracycline per ml, as compared to under 30% inhibition by chloramphenicol and thiamphenicol at this concentration level. Over 90% of the isolates was inhibited by 2 μg of thiamphenicol or chloramphenicol per ml.

In examining the β-lactamase-producing isolates (Table 2), thiamphenicol and chloramphenicol exhibited similar cumulative MICs; thiamphenicol was slightly more active than chloramphenicol. All of the penicillinase-producing isolates were inhibited by 4.0 μg of chloramphenicol or thiamphenicol per ml. Penicillin-resistant isolates were more resistant to tetracycline; only 76.9% of the β-lactamase-producing isolates was inhibited by 1.0 μg of tetracycline per ml was compared with 98.5% of the non-β-lactamase producers (Table 1).
The MICs of *N. gonorrhoeae* to thiamphenicol reported in the present study agree with data reported by Bergogne-Berezin et al. (1) on 92 isolates. These workers found that 50 and 80% of the isolates were inhibited by 0.5 and 2.0 \( \mu \text{g} \) of thiamphenicol per ml, respectively. Although 100% of the isolates from the present study was inhibited by 8 \( \mu \text{g} \)/ml, approximately 10% of the isolates examined by Bergogne-Berezin et al. (1) was resistant to this concentration and required MICs up to 128 \( \mu \text{g} \)/ml.

The *N. gonorrhoeae* MICs of thiamphenicol reported in this study, including the MICs for \( \beta \)-lactamase–positive isolates, are within reported serum levels attainable after oral, intramuscular, or intravenous injection of the antibiotic (2, 12, 14, 18). In addition, thiamphenicol shows high active concentrations in urine (2, 14); over 50% of the administered dose was excreted by the kidneys. The ability of thiamphenicol to be eliminated in an active state is one of the most important differences between chloramphenicol and thiamphenicol (2, 19). Thiamphenicol is not subject to metabolic transformations (2) which either conjugate it with other compounds or degrade it into nonactive derivatives. Chloramphenicol, on the other hand, generally undergoes a massive loss in activity after transformation into a glucuronide derivative in the liver (2, 3, 19).

Chloramphenicol, although clinically useful, has limited possibilities as a therapeutic agent due to its association with the development of aplastic anemia (11). This serious and clinically restricting side effect has so far not been observed on administration of thiamphenicol (19).

Furthermore, although thiamphenicol and chloramphenicol both produce reversible erythroid suppression, only high concentrations of chloramphenicol inhibit DNA synthesis in human lymphoblastoid cells (20). According to Yunos et al. (20), the ability of chloramphenicol to inhibit DNA synthesis might be related to its role in the development of bone marrow aplasia. The increased toxicity of chloramphenicol has also been attributed to its greater affinity for bone marrow cells as compared with thiamphenicol (9). Although thiamphenicol can depress the proliferation of immunologically active cells, the effect has been shown to be reversible after withdrawal of the drug (11).

The simultaneous development of bacterial resistance to chloramphenicol and thiamphenicol should be highly correlated. Both antibiotics can be acetylated by acetyl transferase, an enzyme commonly specified by R plasmid-bearing isolates of *Enterobacteriaceae* (3). Chloramphenicol/thiamphenicol-resistant isolates of gram-positive bacteria with R plasmids have been described (7). Although plasmid-mediated chloramphenicol or thiamphenicol resistance has not yet been described for *N. gonorrhoeae*, the recent discovery of penicillinase-producing plasmids in this organism suggests that the acquisition of other plasmid-mediated antibiotic resistance determinants is a possibility that should not be discounted. However, Ferrari and Della Bella (3) have indicated that the acetylation of thiamphenicol and chloramphenicol can be reversed in humans through the action of \( \beta \)-esterase, which hydrolyzes inactive acetylated derivatives with the resultant release of active

### Table 1. MICs of 517 *N. gonorrhoeae* isolates to penicillin, tetracycline, thiamphenicol, and chloramphenicol

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>0.013</th>
<th>0.025</th>
<th>0.05</th>
<th>0.1</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>13.5</td>
<td>32.3</td>
<td>41.2</td>
<td>47.6</td>
<td>64.4</td>
<td>69.8</td>
<td>94.8</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>2.7</td>
<td>20.7</td>
<td>56.3</td>
<td>74.1</td>
<td>97.1</td>
<td>98.5</td>
<td>98.8</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamphenicol</td>
<td>0.2</td>
<td>1.2</td>
<td>3.9</td>
<td>28.8</td>
<td>72.9</td>
<td>83.4</td>
<td>97.5</td>
<td>99.6</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>0.8</td>
<td>2.7</td>
<td>7.2</td>
<td>29.2</td>
<td>65.2</td>
<td>80.7</td>
<td>91.7</td>
<td>99.8</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

* All MICs expressed as micrograms per milliliter except penicillin (units per milliliter).

### Table 2. MICs of 13 \( \beta \)-lactamase-producing *N. gonorrhoeae* isolates

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>10</th>
<th>20</th>
<th>&gt;40</th>
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<tbody>
<tr>
<td>Penicillin</td>
<td>7.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>53.8</td>
<td>76.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamphenicol</td>
<td>76.9</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>69.2</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* All MICs expressed as micrograms per milliliter except penicillin (units per milliliter).
antibiotic. In addition, a report by Thayer et al. (17) also indicates that gonococci do not develop in vitro resistance to thiamphenicol by repeated exposure to increasing antibiotic concentrations.

We thank the Disease Statistics and Operational Planning Section, Laboratory Center for Disease Control, and Y. Mao for co-operation in computer processing the data. The technical assistance of Peter Lomax is gratefully acknowledged. We also thank B. B. Diena for his critical reading of the manuscript.

LITERATURE CITED