Phenazopyridine-Sulfonamide Combination Antibacterial Therapy in Mice

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Phenazopyridine, at its maximum tolerated dose, did not affect the effectiveness of sulfonamides against uropathogenic bacterial species in mice.

Phenazopyridine, because of its putative analgesic effect on the mucosa of the urinary tract, is frequently used as an adjunct to sulfonamides in the treatment of bacterial infections in that area. Because no previous experimental data on combination antibacterial therapy with these compounds was known, and because Neter and Loomis (5) reported that phenazopyridine enhanced the activity of sulfonamides against B. coli in vitro, the possible influence of phenazopyridine on the in vivo antibacterial efficacy of three sulfonamides, sulfacytine, sulfisoxazole, and sulfamethoxazole, was evaluated in acute mouse protection tests.

A range of dose levels of sulfonamides, mixed with 100 mg of phenazopyridine per kg or given alone, was administered in single, oral doses to parallel groups of CF-1 mice, concurrently receiving lethal, intraperitoneal, mucinized challenges (3) with the uropathogenic bacterial species Escherichia coli and Proteus vulgaris. Generally, >90% of controls, untreated or treated with phenazopyridine only, died within 48 to 72 hr. Final survival percentages, obtained after 4 to 7 days of observation among groups of 10 mice in duplicate tests, were used to estimate median protective doses (PD₅₀) of sulfonamide by the log-probit procedure of Miller and Tainter (4). An experimentally determined approximate-maximum-tolerated, single oral dose of phenazopyridine, 100 mg/kg, was used to assure an adequate level of the compound in the mouse tissues. This dose was about one-sixth the median acute oral lethal dose of 602 ± 102 mg/kg, which agrees well with the rat intraperitoneal data of Walton and Lawson (6). Sulfisoxazole and sulfamethoxazole were donated by Hoffman-La Roche, Inc., and phenazopyridine was a gift of the Nepera Chemical Co. Sulfacytine is a new soluble sulfonamide (1, 2) currently undergoing clinical investigation.

The test results are summarized in Table 1. The PD₅₀ of the three sulfonamides alone, against three strains of bacteria, were about 80 to 140% of those obtained in combination with phenazopyridine. The geometric means of the

<table>
<thead>
<tr>
<th>Challenge organism</th>
<th>Sulfonamide</th>
<th>Single oral dose (PD₅₀) of sulfonamide (mg/kg)</th>
<th>Mixed with 100 mg of phenazopyridine/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alone</td>
<td>Mixed</td>
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<tr>
<td>Escherichia coli MGH-1</td>
<td>Sulfacytine</td>
<td>4.6 (3.5–5.7)</td>
<td>5.9 (5.1–6.7)</td>
</tr>
<tr>
<td></td>
<td>Sulfisoxazole</td>
<td>17.0 (12–22)</td>
<td>12.8 (8.8–16.8)</td>
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<tr>
<td></td>
<td>Sulfamethoxazole</td>
<td>8.0 (5.7–10.3)</td>
<td>5.7 (2.7–8.7)</td>
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<tr>
<td></td>
<td>Sulfacytine</td>
<td>4.4 (3.5–5.3)</td>
<td>4.1 (3.2–5.0)</td>
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<td></td>
<td>Sulfisoxazole</td>
<td>15.5 (10.9–20.1)</td>
<td>14.0 (11.0–17.0)</td>
</tr>
<tr>
<td></td>
<td>Sulfamethoxazole</td>
<td>3.4 (2.5–4.3)</td>
<td>4.0 (2.9–5.1)</td>
</tr>
<tr>
<td></td>
<td>Sulfacytine</td>
<td>2.0 (1.2–2.8)</td>
<td>2.1 (1.5–2.7)</td>
</tr>
<tr>
<td></td>
<td>Sulfisoxazole</td>
<td>13.0 (8.9–17.1)</td>
<td>13.0 (7.3–18.7)</td>
</tr>
<tr>
<td></td>
<td>Sulfamethoxazole</td>
<td>2.5 (1.8–3.2)</td>
<td>2.2 (0.9–3.4)</td>
</tr>
</tbody>
</table>

* Median protective dose, 95% confidence limits in parentheses. The geometric mean for all tests was 5.96 for sulfonamide alone and 5.66 for sulfonamide mixed with phenazopyridine.
results in both groups are almost identical. These results clearly indicate that phenazopyridine did not alter the effectiveness of the sulfonamides in these tests.

LITERATURE CITED