Comparative Nephrotoxicity of SCH 21420 and Amikacin in Rats


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The nephrotoxic potentials of the new aminoglycoside SCH 21420 and amikacin were compared in a rat model. Groups of rats received 100, 200, 300, or 600 mg of either drug per kg per day for 14 days. Enzymuria, urine osmolality, protein excretion, and blood urea nitrogen were monitored at periodic intervals, whereas creatinine clearance and pathological changes were determined at sacrifice. Amikacin caused more enzymuria at the two lower doses as well as greater proteinuria and blood urea nitrogen elevations at the highest dose than did SCH 21420 (P < 0.05). Pathological changes were more severe with amikacin than with SCH 21420 at the three lower doses (P < 0.05); however, at the 600 mg/kg per day dose, the pathological scores and creatinine clearances of animals receiving either drug were not significantly different (P > 0.05).

Aminoglycosides are very useful antibiotics in the treatment of patients with life-threatening bacterial infections. However, their nephrotoxic potential continues to concern clinicians (1). SCH 21420, a new derivative of gentamicin B, has in vitro bactericidal activity which compares favorably with currently available aminoglycosides (4, 12). The proposed dose for man is the same as amikacin, 15 mg/kg per day (L. Tabachnick, Schering Corp., personal communication). To compare the relative nephrotoxicities of SCH 21420 and amikacin, we studied the functional and structural effects of both drugs upon the kidney in rats.

MATERIALS AND METHODS

Adult male Sprague Dawley rats (Cox Laboratories, Indianapolis, Ind.), weighing 225 to 250 g, were housed singly in metabolic cages, fed standard Purina Rat Chow ad libitum, and allowed free access to water. Twenty-four-hour urine specimens were collected under mineral oil to prevent evaporation.

The rats were randomly assigned to 11 groups of 10 rats each. Four groups received SCH 21420 at doses of 100, 200, 300, and 600 mg/kg per day. Four groups received the same doses of amikacin. These doses are equivalent to 1, 2, 3, and 6 times the recommended dose in humans when adjusted for surface area. Two groups received saline diluent and one group received no injections.

On the day before the first injection day (day 0), day 7, and day 14, 24-h urine specimens were collected. Volume, osmolality, protein, n-acytelyglucosaminidase, and creatinine concentrations were measured. Blood was obtained from the tail for blood urea nitrogen (BUN) determination. On the day of sacrifice (day 15), creatinine was measured in serum and urine for the calculation of creatinine clearance. Kidneys from each animal were weighed and prepared for light microscopy by standard techniques (5). Histological changes were graded as follows by a pathologist unaware of the regimen: grade 0, normal; grade 1, cloudy swelling of proximal tubular epithelium without necrosis; grade 2, necrosis and/or regeneration of 25% of the cortical area; grade 3, necrosis and/or regeneration of 25% but <50% of the cortical area; grade 4, necrosis and/or regeneration of 50% but <75% of the cortical area; and grade 5, necrosis of >75% of the cortical area.

Creatinine was measured by an automated technique (AutoAnalyzer, Chauncey, N.Y.). BUN was measured by the method of March et al. (7), and n-acytelglucosaminidase was measured by the technique of Patel et al. (8). Protein was measured by the Coomassie blue dye reaction (2) and expressed as excretion per milligram of creatinine. Urine osmolality was determined by freezing-point depression. Statistical comparisons were performed by one-way analysis of variance. Where differences were shown, Duncan's multiple-range statistic was used for comparisons. Since the saline injected and noninjected groups were not significantly different, data from these groups were pooled. Ninety-five percent confidence limits were accepted as significant.

RESULTS

Changes in the variables monitored are displayed in Fig. 1. The excretion of n-acytelyglucosaminidase was the most sensitive indicator of nephrotoxicity. After 2 weeks of therapy, significant enzymuria compared to controls was observed at all four doses of amikacin and the three higher doses of SCH 21420 (P < 0.05). Urinary protein excretion was significantly increased in a dose-related fashion after 7 days of
FIG. 1. Effect of the regimens on enzymuria (A), protein excretion (B), BUN (C), and urinary osmolality (D). Control data are indicated by the dotted lines. Significant differences are indicated.

Treatment with either drug, but more so with amikacin, at doses ≥300 mg/kg per day (P < 0.05). Amikacin at 600 mg/kg per day increased protein excretion further by day 15 (P < 0.05). Amikacin at 300 mg/kg per day increased the BUN by day 15 (P < 0.05), whereas amikacin at 600 mg/kg per day increased the BUN by day 7. An additional elevation was observed by day 15 (P < 0.05). SCH 21420 caused no BUN elevations until 14 days of treatment with the 600-mg/kg per day dose. The changes observed with amikacin at that dose were greater than those with SCH 21420 on both days 7 and 15 (P < 0.05). Both drugs decreased urine osmolality at the two higher doses.

The results of creatinine clearance measurements and pathological scores are displayed in Table 1. No change in creatinine clearance was
observed until a dose of 600 mg/kg per day of either drug was administered. The pathological scores increased in a stepwise fashion as the dose of amikacin was increased. The administration of SCH 21420 at 100 mg/kg per day did not result in demonstrable pathological injury; however, above that level, stepwise increases in dose resulted in increased injury. At each dose level, except the highest, the histological changes were greater with amikacin ($P < 0.05$).

**DISCUSSION**

Differences in the nephrotoxic potential of aminoglycosides have been previously described in rats (3, 6). Generally, these differences are observed when the drugs are administered at high doses (6). However, comparison of the doses in the rat with the recommended dose in humans should be made using surface area adjustments. On that basis, the dosages used in this study were 1, 2, 3, and 6 times the human dose. The relevance of the higher doses to the clinical use of aminoglycosides in man is not entirely clear. Although gentamicin appears more nephrotoxic than either amikacin or tobramycin in rats (3, 6), double-blind prospective protocols in man suggest that these drugs are similar in their nephrotoxic potential (10, 11). Nevertheless, more subtle differences, requiring larger numbers of subjects to be demonstrable, may indeed exist.

The results of the present study indicate that SCH 21420 and amikacin differ in their nephrotoxic potential. At the lower doses, SCH 21420 caused less enzynymia, proteinuria, and histological damage than amikacin. At the highest dose, amikacin caused a greater elevation of BUN values; however, at this dose, the histological changes and creatinine clearance values were similar.

The data suggest that SCH 21420 compares favorably to amikacin with respect to its nephrotoxic potential at lower doses in the rat. SCH 21420 may exhibit a dose-response nephrotoxicity relationship which is initially less steep than amikacin. SCH 21420 does, however, cause functional and structural renal injury typical for this class of antimicrobial agents. Since SCH 21420 compares favorably to amikacin with respect to in vitro activity against many aerobic gram-negative bacilli and *Staphylococcus aureus* (4, 9, 12) and also exhibits documented synergism with penicillin against enterococci (9), it appears that SCH 21420 may be a valuable addition to the aminoglycoside armamentarium.

**ACKNOWLEDGMENTS**

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**LITERATURE CITED**


**TABLE 1. Creatinine clearance and pathology score at sacrifice**

<table>
<thead>
<tr>
<th>Aminoglycoside dosage (mg/kg)</th>
<th>Creatinine clearance (ml/min ± SD)*</th>
<th>Pathology score (mean ± SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amikacin</td>
<td>SCH 21420</td>
</tr>
<tr>
<td>100</td>
<td>1.3 ± 0.1</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td>200</td>
<td>1.4 ± 0.1</td>
<td>1.5 ± 0.1</td>
</tr>
<tr>
<td>300</td>
<td>1.2 ± 0.2</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>600</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1</td>
</tr>
</tbody>
</table>

* Saline control = 1.5 ± 0.1 ml/min. SD, standard deviation.
* Saline control = 0.
* Different from corresponding amikacin group ($P < 0.005$).
