Influence of Circadian-Stage-Dependent Dosing Schedule on Nephrotoxicity and Pharmacokinetics of Isepicin in Rats

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Nephrotoxicity was more marked in rats receiving isepicin at midnight than at middark. And, the once-daily administration at middark induced a lesser degree of nephrotoxicity than the twice-daily injection, which indicates that the once-daily treatment therapy may have potential value in the clinical use of aminoglycosides.

The circadian rhythm of susceptibility to the acute toxicity of aminoglycosides was first reported in mice by our group (3, 4, 7). A new aminoglycoside antibiotic, isepicin (ISP), has recently been put on the market. ISP has clinical merits such as low nephrotoxicity and a once-daily dosing schedule (2, 5). However, no information is available on the circadian rhythm of nephrotoxicity induced by ISP. The present experiment was conducted to determine the influence of a circadian-stage-dependent dosing schedule on the nephrotoxicity of ISP and to investigate the relationship between the toxicity and the chronopharmacokinetics of the drug in rats.

Male Wistar rats (5 weeks old, weighing 160 to 170 g) were used. Rats were housed in a light-controlled room (lights on from 7:00 a.m. to 7:00 p.m.) at a room temperature of 24 ± 1°C and humidity of 60% ± 10%, with food and water ad libitum. The rats were randomly assigned to seven groups of five rats each and were housed individually in metabolic cages to collect urine. Groups of 35 rats each were given ISP either by once-daily subcutaneous injection of 300 mg/kg of body weight or by twice-daily injection of 150 mg/kg for 15 consecutive days. The administration was done at midnight (1:00 p.m.) and/or at middark (1:00 a.m.). Urine samples were collected 24 h prior to the beginning of drug treatment and every 24 h after. After the urine volumes were measured, urine samples were centrifuged at 3,000 rpm for 10 min. N-Acetyl-β-D-glucosaminidase (NAG) activity was measured in the supernatant and expressed as international units per total urine collected for 24 h. Blood samples were obtained from the inferior vena cava, and kidney samples were taken for the determination of ISP concentrations in the plasma and kidney. ISP levels in plasma and kidney were determined by fluorescence polarization immunoassay (TDX; Dinabot, Ltd., Tokyo, Japan). Kidney samples were then prepared for histopathological observations by standard periodic acid-Schiff staining. Histopathological sections of kidney were evaluated independently by a pathologist who was unaware of the regimens used.

Although urine volume is known to increase significantly during the day and decrease during the night among day-active individuals, there were no significant differences in 24-h urinary volumes for the various groups. Urinary NAG activity in animals dosed only at midnight or twice daily remained low for 7 days, rose abruptly to a peak at 11 days, and fell rapidly to baseline by 14 days. In contrast, in animals dosed only at middark, urinary NAG levels remained low for 9 days and the rise after that was more gradual (P < 0.05 by Student’s t test) and without a decline through 14 days (Fig. 1). Renal tissue specimens were examined histologically. Rats given ISP at midnight or by twice-daily dosing showed tubular necrosis. Following middark dosing, the pathological abnormalities were significantly reduced (Table 1).

Levels of ISP in both kidney and plasma were significantly reduced following middark dosing compared with those of midnight dosing or twice-daily dosing (Fig. 2 and 3).

Nephrotoxicity was more marked in rats receiving ISP at midnight than at middark, and the once-daily administration at middark induced a lesser degree of nephrotoxicity than the twice-daily injections, which indicates that the once-daily treatment therapy has a potential value in the clinical use of aminoglycosides (2). A similar significant circadian change was shown for plasma and kidney ISP concentrations.
TABLE 1. Histopathologic nephrotoxicity scores in rats after administration of ISP by once-daily subcutaneous injection of 300 mg/kg at middark or at midnight and by twice-daily injection of 150 mg/kg for 15 consecutive days

<table>
<thead>
<tr>
<th>Control</th>
<th>7 Days</th>
<th>15 Days</th>
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<tr>
<td></td>
<td>NECROSIS</td>
<td>SWELLING</td>
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<td>Dark</td>
<td>-±±2±3+</td>
<td>-±±2±3+</td>
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<tr>
<td>Light</td>
<td>5</td>
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<tr>
<td>Twice</td>
<td>14</td>
<td>23</td>
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<td></td>
<td>14</td>
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- : None  ± : Mild  * : Moderate

FIG. 2. Plasma ISP levels after administration of ISP by once-daily subcutaneous injection of 300 mg/kg (left) or by twice-daily injection of 150 mg/kg (right) for 7 consecutive days. Values are expressed as the mean ± standard deviation for five rats. Statistical significance is by Student's t test.

FIG. 3. Kidney ISP levels after administration of ISP by once-daily subcutaneous injection of 300 mg/kg (left) or by twice-daily injection of 150 mg/kg (right) for 7 consecutive days. Values are expressed as the mean ± standard deviation for five rats. Statistical significance is by Student's t test.

at 30 min after drug administration. These circadian-stage-dependent changes in ISP kinetics seem to correlate well to ISP-induced renal toxicity rhythm in rats. Pharmacologic actions depend not only on the drug-receptor sensitivity, but also on kinetic factors (1). Therefore, a circadian rhythm in drug action or toxicity may be due to kinetic alterations. ISP-induced chrononephrotoxicity seems to be, at least in part, due to the chronopharmacokinetics of the drug. Thus, a circadian-stage-dependent dosing schedule has a significant influence on the nephrotoxicity of ISP in rats.

Since the pharmacokinetics of aminoglycosides are very much influenced by nephrotoxicity, because they are renally excreted, toxicity may depend on kinetics.

Since pharmacokinetics may affect efficacy, one might wonder whether the lower peak plasma levels with middark dosing might be associated with less rapid killing of bacteria and shorter postantibiotic effect, both of which might have a negative impact on efficacy. The significant circadian-stage-dependent changes in ISP kinetics were demonstrated by the lower clearance, the longer half-life, and the larger area under the curve in evening trials with humans (6).

Therefore, the dosing schedule and the choice of the most appropriate time of day for drug administration may help to achieve rational chronotherapeutics, reducing toxic effects of ISP and/or increasing therapeutic effects.

REFERENCES