Effect of Probenecid and Ranitidine on Urinary Excretion of Lomefloxacin in Rats

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ABSTRACT—To examine the renal tubular transport pathways of lomefloxacin, a new quinolone antibiotic, the agent was injected intravenously with or without pretreatment with probenecid, an organic anion, or ranitidine, an organic cation, in rats. Urinary excretion of lomefloxacin significantly decreased in the probenecid-treated animals. However, no significant decrease was observed in this parameter by pretreatment with ranitidine. These results suggest that lomefloxacin is mainly secreted in urine by the organic anion transport system, while the pathway mediated by the organic cation transport system is negligible.

Keywords: Lomefloxacin, Renal secretion, Drug interaction

Lomefloxacin, a new quinolone antibiotic, is frequently used in the therapy of bacterial infections. About 80% of the agent is excreted in the urine by glomerular filtration and renal tubular secretion (1, 2). Lomefloxacin has two pK_a values (6.0 for the carboxy group and 9.0 for the amino group) and may exist as a zwitterion (E. Okezaki et al., unpublished data). Cephalexin, another zwitterionic agent, is secreted in urine by both organic anion and cation transport systems (3). Therefore, it is speculated that urinary secretion of lomefloxacin is also mediated by both transport systems. To prevent any possible drug interaction-related adverse effect of lomefloxacin, it is important that the renal transport pathways of the agent be studied.

Male Wistar rats (SRC, Shizuoka), weighing 200–310 g and fasted overnight, were anesthetized by oral administration of ethanol. One milliliter of 24% ethanol/100 g body weight (b.w.) was given orally 2 or 3 times every 30 min through a gastric tube. A polyethylene cannula was inserted into the right femoral vein and thereafter, constant intravenous infusion of a hypotonic solution consisting of 1.2% ethanol, 1.7% glucose and 0.3% NaCl was started at a rate of 0.5 ml/100 g b.w./10 min. A small incision was made in the midsection of the lower abdominal wall, the urinary bladder was exposed, and then a polyethylene tube (PE 190; Clay Adams, Parsippany, NJ, USA) was inserted into the bladder through the incised wall to make a bladder fistule.

Lomefloxacin (Shionogi & Co., Ltd., Osaka) was dis-

solved in distilled water, which was brought to pH 5.5 using 0.1 N NaOH. Solution of probenecid, an organic anion, was prepared by dissolving probenecid powder (Sigma Chemical Co., St. Louis, MO, USA) in distilled water to which 10 N NaOH was added dropwise until all the powder was dissolved. The solution was brought to pH 7.4 using 1 M KH_2PO_4 . Ranitidine, an organic cation, (Sigma) was dissolved in distilled water.

Experimental protocols were usually started at 3–4 hr after the operation when urine flow became constant at a rate of more than 0.35 ml/100 g b.w./10 min. Drugs were gradually injected into the femoral vein (10 min for lomefloxacin and probenecid and 5 min for ranitidine). As the preliminary study, several doses of drugs (lomefloxacin: 10, 15 and 30 mg/kg, probenecid: 40 and 100 mg/kg, ranitidine: 10, 25 and 50 mg/kg) were injected intravenously to determine the doses at which they did not decrease the rate of urine flow below 0.35 ml/100 g b.w./10 min. Lomefloxacin at 10 mg/kg, probenecid at 40 mg/kg and ranitidine at 10 mg/kg did not influence the urine flow, while higher doses of the agents decreased it. Therefore, 10 mg/kg of lomefloxacin, 40 mg/kg of probenecid and 10 mg/kg of ranitidine were used in the following experiments: 1) Ten mg/kg of lomefloxacin alone was injected (group I, $n=8$). 2) After injection of probenecid (40 mg/kg), 10 mg/kg of lomefloxacin was given (group II, $n=8$). 3) After injection of ranitidine (10 mg/kg), 10 mg/kg of lomefloxacin was given (group III, $n=8$). Urine was collected into small measuring syringes every 10 min for 4 hr after the end of the lomefloxacin

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Fig. 1. Urinary excretion of lomefloxacin after injection of the agent (10 mg/kg) in the control (I, $n=8$) and in the probenecid (II, $n=8$)- and ranitidine (III, $n=8$)-pretreated groups. Mean $\pm$ S.D. * $P < 0.05$, ** $P < 0.01$, compared with group I.

injection. The urinary concentration of lomefloxacin was measured by HPLC (4).

The results are expressed as the means $\pm$ S.D. Data were analyzed by analysis of variance and the unpaired Student's *t*-test. This experiment was performed in accordance with the 1993 Jichi Medical School Guide for Laboratory Animals.

Urinary excretion of lomefloxacin significantly decreased during the first but not the next 2 hr by pretreatment with probenecid (Fig. 1). However, no significant difference was observed at any collection period between the control and ranitidine-treated groups.

In this study, the urinary amount of lomefloxacin was significantly decreased during the first 2 hr by pretreatment with probenecid. Probenecid is an organic anion and disturbs renal secretion of other organic anions (5). Therefore, the present data are compatible with the hypothesis that lomefloxacin is secreted into the tubular lumen by the renal organic anion transport system. A marked drop of blood pressure might decrease urine flow which, in turn, causes a reduction in urinary excretion of an agent. This, however, would be unlikely because the rate of urine flow was maintained at over 0.35 ml/100 g b.w./10 min during the entire period in this study. No decrease in the urinary excretion of lomefloxacin was observed in the animals treated with ranitidine. Ranitidine inhibits renal secretion of other organic cations (5). Based on the present as well as previous data, it is sus-

pected that the amount of lomefloxacin secreted by the organic cation transport system is small. However, as a larger dose of ranitidine could not be used in this study, it remains possible that lomefloxacin is also secreted by the cation transport system. Further studies using other cationic agents are needed to evaluate this issue.

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