Nephrotoxicity of Teicoplanin in Rats

Yuji Yoshiyama*, Tomoko Yazaki and Motoko Kanke
Division of Clinical Pharmacy, Kyoritsu College of Pharmacy,
Minato-ku, Tokyo 105-8512, Japan

Denis Beauchamp
Research Center for Infectious Diseases, Laval University,
Ste-Foy, Quebec, Canada G1V 4G2

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Teicoplanin, a glycopeptide antibiotic, is marketed in a number of European countries and has recently been put on the market in Japan. The spectrum of antibacterial activity of teicoplanin is equivalent or superior to that of vancomycin. The aim of the present study is to examine the nephrotoxicity of teicoplanin compared with vancomycin in rats. Wistar male rats, housed in a light-controlled room at room temperature for 1 week, were used. They were injected with either 15 or 50 mg/kg/day of teicoplanin or 50 or 200 mg/kg/day of vancomycin at 13:00 daily for 14 days. The rats were randomly assigned to groups of five rats each and were housed individually in metabolic cages to collect urine. Urine samples were collected 24 hours prior to the drug treatment and every 24 hours thereafter for 14 days. N-Acetyl-β-D-glucosaminidase (NAG) activity was determined in the supernatant and expressed in international units per total urine collected for 24 hours. The group which was given vancomycin 200 mg/kg/day had significantly elevated urinary NAG levels compared with the other groups (p<0.05). No significant differences were observed in the NAG levels in urine among the remaining three groups. These results suggest that the nephrotoxicity of teicoplanin may be only one-fourth that of vancomycin in rats. It appears that by extrapolating the dose amount required for the treatment in humans to rats, the high dose of teicoplanin was set at 50 mg/kg/day and that of vancomycin, 200 mg/kg/day. The recommended dose for teicoplanin will probably be 200 mg/day compared to 2 g/day of vancomycin. If the teicoplanin dose is only one-tenth that of the vancomycin dose, then teicoplanin should be better tolerated than vancomycin in terms of nephrotoxicity.
coccus species with MRSA and vancomycin-resistant enterococci (VRE) causing particular problems\(^3,4\). Vancomycin resistance has been observed among some Staphylococcus aureus strains, and alternative antibiotics are being developed\(^5\). Early preparations of vancomycin were associated with some adverse events, probably caused by the many impurities present. Highly purified forms are now available but some adverse events will occur\(^6\). Nephrotoxicity is seen when vancomycin is used together with aminoglycosides\(^7-10\). Teicoplanin, a glycopeptide antibiotic, has been marketed in a number of European countries and was recently put on the market in Japan\(^11\). Teicoplanin has a similar structure to vancomycin and the spectrum of antibacterial activity of teicoplanin is equivalent or superior to that of vancomycin\(^2,12,13\). And teicoplanin have different safety profiles which can affect choice\(^14,15\). The aim of the present study is to examine the nephrotoxicity of teicoplanin compared with vancomycin only and under concomitant administration with gentamicin in rats.

**Materials and Methods**

Adult male Wistar rats weighing between 130–150 g were used. The animals were housed in a light-controlled room (light on from 08:00 to 20:00) at a room temperature of 24±1°C and humidity of 60±10% for 1 week. They were acclimated for one week, and they had free access to food and water throughout the experiment.

The rats were randomly assigned to the groups of five rats each and were housed individually in metabolic cages to collect urine. The first groups of rats were injected with teicoplanin either 15 or 50 mg/kg/day (intraperitoneally) or vancomycin 50 or 200 mg/kg/day (intraperitoneally) for 14 days. Other groups of rats were injected with teicoplanin at doses of either 15 or 50 mg/kg/day intraperitoneally and with gentamicin at dose of 80 mg/kg subcutaneously or they were injected with vancomycin at doses of either 50 or 200 mg/kg/day intraperitoneally and with gentamicin at dose of 80 mg/kg subcutaneously for 3 days. Animals were injected once daily at 13:00.

Urine samples were collected 24 hours prior to the drug treatment and every 24 hours thereafter. Urine volumes were measured and the urine samples were centrifuged at 3000 rpm for 10 minutes. The N-acetyl-β-D-glucosaminidase (NAG) activity of the supernatant was determined and expressed as international units per total urine volume collected over 24 hours\(^16\). Blood samples were collected from the inferior vena cava and then centrifuged, and the serum was frozen (−80°C) for the determination of BUN and serum creatinine levels. Kidneys were removed for histopathological observation. Histopathological samples were prepared by standard periodic HE staining and were evaluated under a microscope. Sections came from three different regions of the renal cortex for each rat, and five rats per group were used. Histopathological sections of kidney were evaluated independently by a pathologist who was unaware of the regimens used. Statistical analysis of the differences between groups was first performed by analysis of variance. If \( p \) values were <0.05, group comparisons were done by the Fisher protected least-significant-difference post hoc test.

**Results**

Animals of all groups gained weight regularly throughout the experiment. Figure 1 shows 24 hours urine NAG levels for each group for the 14 days of the experiment. The group given vancomycin
200 mg/kg/day exhibited a significant increase in the urinary NAG levels compared with other groups (p<0.05). No significant differences were observed in the NAG levels in urine among the remaining three groups. Thus the increase in urinary NAG levels was significantly lower when teicoplanin was given at 50 mg/kg as compared with when vancomycin was given at 200 mg/kg (p<0.05). Blood urea nitrogen and serum creatinine levels showed no significant difference among the drug-treated animals (Figs. 2 and 3). Histopathological examination of renal tissue revealed the degeneration of proximal tubular cells in the group administered vancomycin at 200 mg/kg/day. The remaining three groups showed no significant change in kidney morphology (Fig. 4).

In gentamicin-coadministration group, the urinary NAG levels in rats given vancomycin 200 mg/kg with gentamicin 80 mg/kg were significantly higher than in rats given the other three groups (Fig. 5).

Discussion

Teicoplanin is a glycopeptide antibiotic used in the treatment of a variety of aerobic and anaerobic Gram-positive infections. The antibacterial activity of teicoplanin, like vancomycin, is achieved by binding to the terminal acyl-D-alanyl-D-alanine residue of cell wall peptidoglycan, with subsequent inhibition of cell wall biosynthesis. Teicoplanin appears to be generally well tolerated unlike vancomycin. For example, teicoplanin dose not produce the red-neck syndrome associated with vancomycin administration. An assessment of the type and frequency of adverse effects experienced with teicoplanin in a multicenter open trial has been reported and the most common teicoplanin-related event was an allergic-type skin reaction (2.4%) while renal toxicity was rare (0.1%).

We examined the nephrotoxicity of teicoplanin compared with vancomycin single administration and/or concomitant administration with gentamicin in rats. The present study shows that the nephro-
Fig. 2. BUN levels in animals treated with vancomycin or teicoplanin for 14 days. Vancomycin 200 or 50 mg/kg/day and teicoplanin 50 or 15 mg/kg/day were administered. Each point represents the mean and standard deviation for five rats.

![BUN levels graph](image)

Fig. 3. Serum creatinine levels in animals treated with vancomycin or teicoplanin for 14 days. Vancomycin 200 or 50 mg/kg/day and teicoplanin 50 or 15 mg/kg/day were administered. Each point represents the mean and standard deviation for five rats.

![Serum creatinine graph](image)

toxicity of teicoplanin may be less than one-fourth that of vancomycin as shown by lower urinary NAG levels as well as fewer histopathological signs of nephrotoxicity in the group treated with teicoplanin at 50 mg/kg as compared with vancomycin at 200 mg/kg in rats. It appears that by extrapolating the dose amount required for the treatment in humans to rats, the high dose of teicoplanin was set at 50 mg/kg/day and that of vancomycin, 200 mg/kg/day. Nephrotoxicity was significantly less likely to occur during treatment with teicoplanin than vancomycin when an aminoglycoside was being given concur-
Fig. 4. Light micrographs of proximal tubular cells in the renal cortex of rats treated with vancomycin or teicoplanin for 14 days.

Vancomycin 200 (A) or 50 (B) mg/kg/day and teicoplanin 50 (C) or 15 (D) mg/kg/day were administered.

Magnification, ×100.

Currently, teicoplanin has a similar structure to vancomycin but was less nephrotoxic when combined with aminoglycosides. It has been reported that the incidence of nephrotoxicity with teicoplanin plus an aminoglycoside is lower than that of vancomycin plus an aminoglycoside. There was a greater incidence of abnormal renal function with vancomycin than with teicoplanin (12.4% vs. 5.6%). A meta-analysis of eight studies suggested that the incidence of nephrotoxicity in patients given vancomycin plus an aminoglycoside was 13% greater than in those patients given vancomycin alone and 4.3% greater than in those patients given an aminoglycoside alone. The recommended dose for teicoplanin will probably be 200 mg/day compared to 2 g/day of vancomycin. If the teicoplanin dose is only one-tenth that of the vancomycin dose, it can be expected that teicoplanin will be better tolerated than vancomycin in terms of nephrotoxicity.

When treating infections in which teicoplanin and vancomycin have similar efficacy, teicoplanin offers an advantage because nephrotoxicity appears less common with teicoplanin than vancomycin although arguments remain as to the proportion due to the glycopeptide or a concomitant aminoglycoside.

Teicoplanin has an advantage over vancomycin in its ease of administration and choice of routes.
Fig. 5. Urinary NAG activities in animals treated with vancomycin or teicoplanin concomitant administration of gentamicin for 3 days.

The rats are treated for 3 days with an injection of vancomycin at either 200 or 50 mg/kg/day (intraperitoneally) with gentamicin 80 mg/kg (subcutaneously) or teicoplanin at 50 or 15 mg/kg/day (intraperitoneally) with gentamicin 80 mg/kg (subcutaneously). Each point represents the mean and standard deviation for five rats. *, Significantly different from all other groups (p<0.05).

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References