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# INFLUENCE OF OCHRATOXIN A-INDUCED NEPHROTOXICITY ON THE PHARMACOKINETICS OF GENTAMICIN IN RATS

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***ABSTRACT:*** *To evaluate the influence of ochratoxin A on the pharmarcokinetics of gentamicin, gentamicin concentrations in the serum, renal cortex and medulla together with parameters of the renal function and histological changes were compared between ochratoxin A-treated rats (0.1 mg of ochratoxin A/kg of body weight, ip, daily for 14 days) and normal rats. Gentamicin was given with a single intramuscular injection (10 mg/kg of body weight). Ochratoxin A resulted in an increase of the half-life, the area under the concentration-time curve, the apparent volume of distribution and a decrease of the total body clearance of gentamicin, and accumulated significantly ($p<0.01$) more gentamicin in the kidneys. The increase of the elimination half-life ($\beta$-phase, $p<0.01$) and the volume of distribution of gentamicin might be associated with the marked uptake or binding of the drug in the kidneys by ochratoxin A. Serum creatinine and blood urea nitrogen were within normal limits in both normal and ochratoxin A-treated rats. Histologically, mild degenerations of the proximal tubular cells were demonstrated in rats treated with ochratoxin A. Conclusively, by accumulating the total amount of gentamicin within the kidneys, ochratoxin A increased the nephrotoxic potentials and the drug residues. Futhermore, ochratoxin A modified the pharmacokinetics of gentamicin under subclinical states in the absence of any major pathophysiological alterations.*
***Key words:*** *Ochratoxin A, nephrotoxicity, pharmacokinetics, gentamicin*

# INTRODUCTION

Gentamicin nephrotoxicity is generally associated with the accumulation of the drug within the renal cortex (Fabre *et al.*, 1976; Kaloyanides and Pastoriza-Munoz, 1980). The narrow margin of safety between therapeutic and toxic concentrations of gentamicin presents the importance of risk factors associated with a greater incidence of nephrotoxicity (Conzelman, 1980; Riviere, 1984).

Ochratoxin A has been of particular interest because of the widespread occurrence in foodstuffs and the nephrotoxicity of food animals such as swine and poultry, resulting in a threat to animal industry and public health (Elling *et al.*, 1975; Krogh, 1978; Hult *et al.*, 1980). The effects of ochratoxin A may be reversible simply by removing toxin sources, but the hidden renal damage can produce future challenges to renal function due to other nephrotoxic agents with the similar target site in the renal tissues (Glahn *et al.*, 1989), probably leading to nephrotoxicity and renal insufficiency with the alteration of the pharmacokinetics (Riviere, 1984). There is few data concerning the relationship between ochratoxin A and gentamicin with a similar target tissue and nephrotoxicity. Therefore, the purpose of the present study was to evaluate the influence of ochratoxicin A on the serum concentrations and the intrarenal distribution of gentamicin.

# MATERIALS AND METHODS

## Animals, Treatment and Sample Collection

Eighty male healthy Sprague-Dawley rats of 28 days old (Laboratory Animal Center, Medical School, Seoul National University) were utilized in all experiments with a standard pelleted laboratory rodent diet (Samyang Feed Co., Korea) and water *ad libitum*. Forty rats (included 10 rats for standard curves) in tested group (78.4±2.1 g) were each given intraperitoneally 0.1 mg of crystalline ochratoxin A/kg of body weight (0.1 mg/ml; Sigma Chemical Co., USA) dissolved in 0.1 M sodium bicarbonate (Shinyo Pure Chemicals Co., Japan) daily for 14 days. Control animals (76.2±2.3 g) were administered an equivalant volume of 0.1 M sodium bicarbonate under the same experimental condition. The low dosing and the intraperitoneal injection of ochratoxin A were chosen to avoid any major pathophysiological disturbances except the nephrotoxicity (Munro *et al.*, 1973) and acute catarrhal enteritis produced possibly by the peroral route (Suzuki *et al.*, 1977). And then, rats were each given a single intramuscular injection of 10 mg of gentamicin sulfate/kg of body weight (10 mg/ml; Sigma Chemical Co., USA) with the withdrawal of food for 18 preinjection hours and the free access of water. Rats were anesthetized by a single intraperitoneal injection of sodium pentobarbital (60 mg/kg; Pitman-Moor, Inc., USA) before sacrifice. Serial blood samples were obtained from *inferior vena cava* at postinjection hours of 0.5, 1, 2, 4 and 8. The serum was separated by centrifugation at 3,000 rpm for 10 minutes and kept frozen at −20℃ until analyzed. The renal tissues removed at the same time of blood sampling were stored at −20℃ for antibiotic assay and prepared for microscopic examination with hematoxylin and eosin staining (Culling

*et al.*, 1985), respectively.

### Analysis

The concentrations of gentamicin in the serum were determined by a standard cylinder plate microbiological assay (Aszalos, 1986; Lorian, 1986) and done in triplicate on antibiotic medium No. 5 (Difco Laboratories, Detroit Michigan, USA) by using *Bacillus subtilis* ATCC 6633 as the test microorganism with the Nunc Bio-Assay Dishes (Nunc, Denmark). The renal cortex and medulla were separated by a careful dissection and gentamicin levels were measured by the same assay in the serum on the basis of the method of Brown *et al.*, (1988) and Fox (1989) with sodium hydroxide. Standard curves for the antibiotic assays were prepared in normal and ochratoxin A-treated rats, respectively, because of the inhibitory action of ochratoxin A in the growth of *Bacillus subtilis* and *Bacillus stearothermophilus* (Bunge *et al.*, 1978). The diameter of zone sizes of inhibition was measured with a calculator and calculated the exponential regression.

Serum creatinine and blood urea nitrogen were determined with Abbott Bichromatic Analyzer (ABA-200; Abboott Laboratories, USA). The thymus, spleen, liver and kidneys were removed and weighed with the measurement of body weight throughout the experimental period.

### Pharmacokinetics

The area under the gentamicin concentration-time curve (AUC) was determined by the trapezoidal rule (Rowland and Tozer, 1989). The total body clearance (Cl), the half-life of elimination ($t_{½}$) and the volume of distribution (Vd) were calculated as follows: dose/AUC, 0.693/the elimination rate cnstant (k) and Cl/k or dose/AUC · k, respectively (Baggot, 1980; Sams, 1984).

### Statistics

Data are presented as the means±standard erros (SE). The statistical significance of differences between groups was determined by using the Student *t* test (Hayes, 1989).

## RESULTS

### Pharmacokinetics and Gentamicin in the Serum

Gentamicin levels in the serum are shown in Fig. 1. Mean peak serum concentrations were 9.05±1.66 μg/ml in normal rats and 10.43±1.95 μg/ml in ochratoxin A-treated rats at 1 hour after gentamicin injection, respectively. The mean concentrations at each time point were always higher in ochratoxin-treated animals with significant differences ($p<0.01$) at the initial (0.5 hour) and the terminal time point (8.0 hours).

Table 1 shows the pharmacokinetic data for normal and ochratoxin A-treated animals after gentamicin administration. Ochratoxin A-treated rats showed higher values in AUC and Vd with $t_{½}$ ($p<0.01$), but lower values in Cl than normal values.

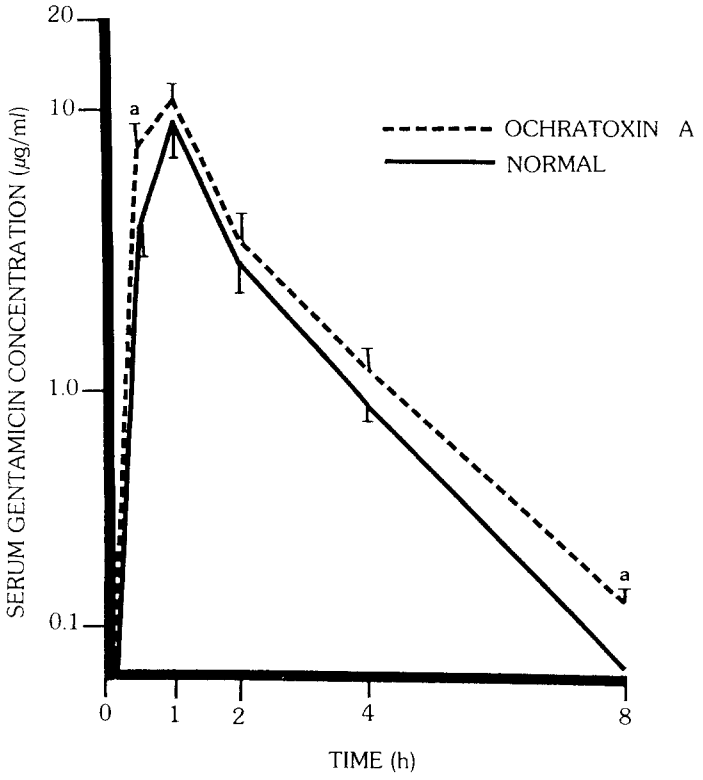


**Fig. 1.** Serum gentamicin concentrations of norml and ochratoxn A-treated rats ($n=6$/point time, respectively) from 0.5 to 8 hours after a single intramuscular injection of 10 mg/kg.
a.$p<0.01$ compared with the value for normal animals.

**Table 1.** Area under the serum curve, the elimination half-life, the volume of distribution and the total clearance of gentamicin in normal and ochratoxin A-treated rats

| Kinetic values | Normal ($n=30$) | Treated ($n=30$) |
|---|---|---|
| k ($hr^{-1}$) | 1.02± 0.10[a] | 0.48± 0.02[b] |
| $t_{½}$ ($hr^{-1}$) | 0.67± 0.07 | 1.41± 0.07[b] |
| AUC (ug · h/ml) | 15.79± 2.67 | 20.69± 3.11 |
| Vd (ml/kg) | 639.39±130.27 | 1027.43±171.07 |
| Cl (ml/kg · min) | 10.80± 2.30 | 8.21± 1.54 |

k=The elimination rate constant from the terminal slope of a semilogarithmic plot of serum drug concentration versus time.
$t_{½}$=The biological half-life obtained from 0.693/k.
AUC=Area under the gentamicin concentration-time curve for 8 hours.
Vd=Apparent volume of drug distribution obtained by neglecting the (distributive) phase of drug disposition.
Cl=Total body clearance.
[a] The values in parentheses are the means±standard errors.
[b] $p<0.01$ compared with the value for normal rats.

## Pharmacokinetics of Gentamicin in the Kidneys

Fig. 2 shows gentamicin levels in the renal cortex and medulla of normal and ochratoxin A-treated animals at 0.5 to 8 hour(s) after drug administration. The concentrations of gentamicin in the renal cortex and medulla were higher in ochratoxin A-treated animals with significant differences ($p<0.01$). Gentamicin levels of ochratoxin A-treated rats were nearly 14 times higher in the renal cortex and 7 times higher in the renal medulla than those of normal animals.

AUC values within the renal cortex and medulla were 17.58±13.33 and 8.74±0.92 ug · h/100 mg of normal rats, and 942.91±197.51 and 56.30±6.59 ug · h/100 mg in ochratoxin A-treated rats with significant differences ($p<0.01$), respectively.

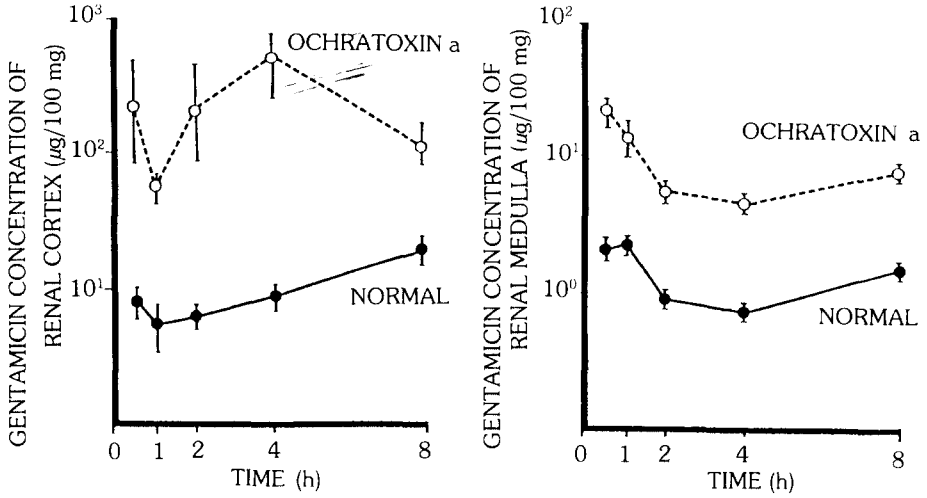


**Fig. 2.** Gentamicin concentrations of the renal cortex and medulla in normal and ochratoxin A-treated rats ($n=6$/point time, respectively) at 0.5 to 8 hours after a single intramuscular administration of 10 mg of drug/kg of body weight.

**Table 2.** Ratios of the drug levels in the renal cortex and medulla between normal and ochratoxin A-treated rats (n=6/point time, respectvely) at 0.5 to 8 hours after a single intramuscular administration of 10 mg of gentamicin/kg of body weight

| Time (h) | Renal cortex/renal medull | |
|---|---|---|
| | Normal | Treated |
| 0.5 | 4.72±0.04[a] | 6.57±0.47[b] |
| 1.0 | 2.90±0.93 | 4.68±0.25 |
| 2.0 | 6.18±0.72 | 20.80±3.10[b] |
| 4.0 | 11.17±0.25 | 33.77±4.82[c] |
| 8.0 | 8.78±1.85 | 12.43±0.88 |

[a] The values in parentheses are the means±standard errors.
[b] $p<0.05$ compared with the value for normal rats.
[c] $p<0.01$ compared with the value for normal animals.

The ratio levels of gentamicin in the renal cortex and medulla between normal and ochratoxin A-treated rats are shown in Table 2 with greater concentrations in ochratoxin A-treated animals.

### Clinical Biochemistry, Physical Aspects and Histopathology

Serum creatinine and blood urea nitrogen as a parameter of the renal function were within normal limits in both normal and ochratoxin A-treated rats. There was no changes significantly of body weight gains over the experimental period between the groups, but a downward trend in ochratoxin A-treated rats. Relative weight gains of wet organs such as kidney, liver, spleen, thymus and testicle showed no significant changes between normal and ochratoxin A-treated animals. Some ochratoxin A-treated animals showed non-specific moderate to extensive loss of brush borders and obvious detachment from basement membrane of individual tubular cells per the renal proximal tubule.

## DISCUSSION

### Pharmacokinetics of Gentamicin in the Serum

Aminoglycosides, particularly gentamicin, are rapidly eliminated from the serum of rats, but persist in the renal tissue. Large amounts of gentamicin are quickly excreted by the kidney predominantly in the first 6 hours (Luft and Kleit, 1974). In this study, the peak serum leveles of gentamicin were attained at postinjection 1 hour in both normal and ochratoxin A-treated rats, as being identical to many other studies (Bergeron *et al.*, 1982; Auclair *et al.*, 1988). The high mean serum levels of gentamicin throughout the full time course in ochratoxin A-treated rats could be considered due to the increase of drug absorption (Halkin *et al.*, 1981), the prolongation of elimination half-life and the decrease of total clearance (Riviere, 1984).

Synthetically, pharmacokinetics of serum gentamicin concentrations in ochratoxin A-treated animals could be affected by the reduction of total clearance and the prolongation of elimination half-life with an increase of Vd, indicating a greater drug accumulation within the renal tissues (Baggot, 1980).

### Pharmacokinetics of Gentamicin in the Kidneys

The distribution of gentamicin is primarily accumulated in the kidneys (Luft and Kleit, 1974; Silverblatt and Kuehn, 1979; Kaloyanides and Pastoriza-Munoz, 1980; Aronoff *et al.*, 1983). The kidneys of ochratoxin A-treated rats accumulated significantly ($p<0.01$) more gentamicin. Luft and Kleit (1974) reported that 85% of gentamicin residued in the cortex compared with the renal medulla. This study showed 88.5% and 94.3% of drug residues in the renal cortex of normal and ochratoxin A-treated rats, respectively, indicating more cortical specificity of the drug and enhanced effects by ochratoxin A.

Ochratoxin A-treated animals showed more rapid maximum gentamicin concentrations in both the renal cortex and medulla than normal animals did. It might be impossible to predict accurately the levels of gentamicin uptake in accordance with the concentrations-time course in the renal tissues because of

a saturable and nonlinear uptake characteristics of aminoglycosides (Brier *et al.*, 1985; Giuliano *et al.*, 1986). Nevertheless, significant differences in the gentamicin concentration of the renal cortex and medulla between normal and ochratoxin A-treated rats ($p<0.01$) were observed throughout all time points, indicating more uptake and binding of the drug into the kidneys (Baggot, 1980).

**Nephrotoxicity**

Many studies revealed that both gentamicin (Luft and Kleit, 1974; Silverblatt and Kuehn, 1979; Kaloyanides and Pastoriza-Munoz, 1980; Aronoff *et al.*, 1983) and ochratoxin A (Suzuki *et al.*, 1977) had the same target portion of the renal cortex for the nephrotoxicity with their accumulations and a similar mechanism of absorption (Collier *et al.*, 1979; Silverblatt and Kuehn, 1979; Tulken, 1986; Pitout, 1969). Gentamicin leads to lysosomal toxicity of the proximal tubular cells with the accumulations of the drug and phospholipids (Morin *et al.*, 1980; Hostetler and Hall, 1982; Tulkens, 1986). And then lysosomal enzymes released into cytoplasm damage to mitochondria with the inhibition of respiration (Simmons *et al.*, 1980; Whelton and Solez, 1982), inducing the renal insufficiency (Kaloyanides and Pastoriza-Munoz, 1980; Knauss *et al.*, 1983; Meyer, 1986). Therefore, the dysfunction of mitochondria by gentamicin may be secondary toxicity due to primary lysosomal toxicity. Ochratoxin A affects primarily mitochondria instead to lysosomes in the proximal convoluted tubules of the renal cortex, indicating the inhibition of respiration (Meisner and Chan, 1974; Meisner, 1976; Dwivedi *et al.*, 1984). The nephrotoxicity of ochratoxin A is similar to the terminal nephrotoxicity of aminoglycosides on the mitochondria. Therefore, it may be generally considered that ochratoxin A induces the augmentation of aminoglycoside nephrotoxicity based on a rapid uptake of the drug into the renal tissues, earlier peak levels, and remarkably high intrarenal concentrations with the reaction of aminoglycosides on the distribution of subcellular compartments (Vera-Roman *et al.*, 1975) and multiple subcellular membranes (Knauss *et al.*, 1983).

This study presented that the subclinical states of the initial toxicity of gentamicin on the lysosomes or/and the main toxicity of ochrotoxin A similar to the terminal toxicity of aminoglycosides on the mitochondria could produce the clinical states of nephrotoxicity by gentamicin or/and ochratoxin A. The interaction between ochratoxin A and gentamicin might cause the mutual synergistic nephrotoxicity with abnormally rapid rates of tissue accumulation and adverse effects on the same target tissues. Ochratoxin A could be an important risk factor for nephrotoxicity during gentamicin treatments with subclinical renal changes.

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