

# Comparative Nephrotoxic Effects of Gentamycin and Tobramycin

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## ABSTRACT

**Objective** To compare the nephrotoxic effects of two aminoglycosides namely, gentamycin and tobramycin on rabbits.

**Study design** Comparative study.

**Place & Duration of study** Allama Iqbal Medical College Lahore, from January 2010 to December 2010.

**Methodology** The serum levels of creatinine and electrolytes (sodium and potassium) were measured in different groups of rabbits (control group-A, gentamycin group B and tobramycin-group C). Rabbits in group B and C received laboratory diet and 32 mg/kg/day of gentamycin and tobramycin were given through intramuscular (IM) route twice daily for 7 days. Blood samples were collected on day 1, 10, 16, and 22 of drug administration. Each rabbit of all groups was sacrificed on 22<sup>nd</sup> day of experiment. Kidneys were removed and histological examination of the 4 components of the renal tissue (glomeruli, tubules, blood vessels and interstitial tissue) was carried out.

**Results** Level of serum creatinine was significantly increased in both experimental groups (B and C) as compared to the control group A. On the other hand, level of serum sodium was insignificantly increased in groups B and C, whereas level of serum potassium was significantly decreased in groups of rabbits receiving gentamycin and tobramycin as compared to control group.

**Conclusions** There was no significant difference in nephrotoxicity between gentamycin and tobramycin.

**Key words** Nephrotoxicity, Gentamycin, Tobramycin.

## INTRODUCTION:

Aminoglycosides are bactericidal for gram negative bacteria and act by interfering with protein synthesis at ribosomal level in susceptible organisms. Serious toxicity is a major limitation to usefulness of aminoglycosides. The most important targeting organs are kidneys, internal ear and neuromuscular junction. It can lead to acute renal, vestibular, and auditory toxicities.<sup>1,2</sup> Gentamycin is frequently used in patients with serious infection, particularly gram negative

bacilli. These bacilli are one of the major health problems in all age groups. A number of physiological changes in drug disposition occur that can affect their pharmacokinetics.<sup>3</sup>

Recently it is reported that gentamycin acts mainly in proximal tubular cells, where its uptake is through organic anion transport system and induces a high incidence of nephrotoxicity, which is characterized by tubular necrosis leading to acute renal failure in 10 to 50% of patients.<sup>4</sup> Tobramycin is produced by streptomyces tenebrarius.<sup>5</sup> In contrast to gentamycin, tobramycin shows poor activity in combination with penicillin against enterococci.<sup>6</sup> It is ineffective against mycobacteria. It is usually used in the treatment of bone, wound, skin, soft tissue and CNS infections.<sup>7</sup>

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A study suggested that tobramycin causes nephrotoxicity less frequently than does gentamycin.<sup>8</sup> The frequent use of aminoglycosides in bacterial infections led us to compare tobramycin and gentamycin because some studies in adults and animals suggested a safety advantage for tobramycin.

#### METHODOLOGY:

A comparative study was conducted on rabbits with the purpose of finding out nephrotoxic effects of gentamycin and tobramycin on renal function and to document the histological changes produced in renal cortex. A total of 24 male rabbits weighing 1.5 to 1.7 kg, age ranging 8-10 months, were taken from Postgraduate Medical Institute (PGMI), Lahore. Their diet was fresh green *chara* (animal food). All rabbits had a free access to water throughout the study period. Each group of rabbits was kept in metabolic cages for 22 days. Study was conducted on the following groups each group having eight animals.

In group A (control group) the rabbits were given standard laboratory diet. Same volume (equal to drugs) of isotonic saline was injected IM twice daily for one week. The group B (gentamycin) and group C (tobramycin) rabbits received laboratory diet and 32 mg/kg/day of respective drug IM twice daily for 7 days. Blood sample was collected on day 1, 10, 16 and 22<sup>nd</sup> day of drug administration. Blood sample in all groups was collected on day 1, 10, 16 and 22 of drug administration. Five cc of blood was drawn from the pinna of shaved ear. Estimation of serum creatinine was done by standard kit. Level of serum sodium and potassium were estimated by flame photometer.

Each rabbit of all groups was sacrificed on 22<sup>nd</sup> day of experiment. Kidneys were removed, sliced and fixed in 10% formalin for 24 hour. Slides were examined by light microscopy. Histological study mainly consisted of the 4 components of the renal tissue (glomeruli, tubules, blood vessels and interstitial tissue).

The data was entered into a perform and standard error of mean was calculated for each variable and compared using statistical test. A p value of less than 0.05 was labeled as statistically significant.

#### RESULTS:

On gentamycin alone the serum creatinine on the first day of injection was 1.57 mg/dl. On the 10<sup>th</sup>, and 16<sup>th</sup> day, it was significantly increased and showed highly significant difference ( $p < 0.001$ ).

Maximum increase was observed on 16<sup>th</sup> day of administration. On 22<sup>nd</sup> day serum creatinine was decreased (table I). The level of serum sodium was slightly increased in both experimental groups as compared to the control group (table II). On the other hand, level of serum potassium was markedly decreased in both experiment groups and it was more significantly decreased at 10<sup>th</sup> and 16<sup>th</sup> day ( $p < 0.001$ ) than at 22<sup>nd</sup> day ( $p < 0.01$ ) of administration (table III). Histological examination after 22<sup>nd</sup> day of gentamycin use showed atrophy of the tubules lining and tubular casts. Thickened glomerular basement membrane were also seen (fig I).

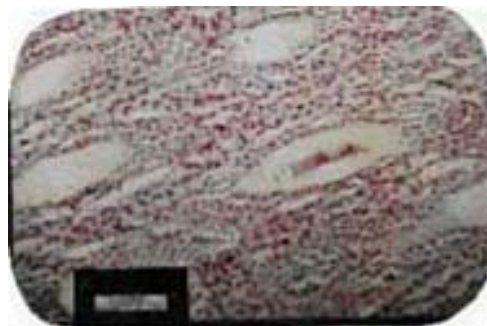


Fig I: Histological examination after 22<sup>nd</sup> day of gentamycins. Atrophy of tubules lining and tubular cast are apparent.

On tobramycin alone the serum creatinine on the first day of injection was 1.53 mg/dl. On the 10<sup>th</sup>, 16<sup>th</sup> and 22<sup>nd</sup> day it was significantly increased and shows highly significant difference ( $p < 0.001$ ) (table I). Level of serum sodium was slightly increased in both experiment groups as compared to the control group (table II). On the other hand, level of serum potassium was markedly decreased in both experiment groups but the significant decrease ( $p < 0.001$ ) was only observed at 10<sup>th</sup> and 16<sup>th</sup> day of administration (table III). Histological examination after 22<sup>nd</sup> day of tobramycin use showed thyroidization of tubules, cloudy swelling and tubular cast (fig II).

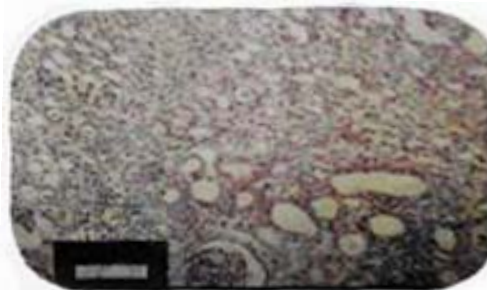


Fig II: Histological examination after 22<sup>nd</sup> day tobramycins Cortex of kidney showing thyroidization of tubules, cloudy swelling and tubular cast.

**Table I: Comparison of Effect of Gentamycin with Tobramycin on Serum Creatinine in Rabbits**

	Group A (control)	Group B (gentamycin)	Group C (tobramycin)
Time of administration	Mean±SEM. (mg/dl)	Mean±SEM (mg/dl)	Mean±SEM (mg/dl)
At 1 day	1.52±0.01	1.57±0.03	1.53±0.54
After 10 days	1.50±0.02	2.25±0.03**	2.20±0.05**
After 16 days	1.53±0.02	4.46±0.03**	4.68±0.03**
After 22 days	1.55±0.02	3.86±0.05**	3.75±0.05**
**P<0.001 = Highly significant difference			

**Table II: Comparison of Effect of Gentamycin with Tobramycin on Serum Sodium in Rabbits**

	Group A (control)	Group B (gentamycin)	Group C (tobramycin)
Time of administration	Mean±SEM. (mg/dl)	Mean±SEM (mg/dl)	Mean±SEM (mg/dl)
At 1 day	139.5±0.63	140.87±1.01	144.25±1.23
After 10 days	139.62±0.6	139.62±0.6	141.75±2.18
After 16 days	142.75±1.00	142.28±1.28	144.12±1.3
After 22 days	143.5±1.14	139.57±0.76	143.25±1.26

**Table III: Comparison of Effects of Gentamycin with Tobramycin on Serum Potassium**

	Group A (control)	Group B (gentamycin)	Group C (tobramycin)
Time of administration	Mean±SEM. (mg/dl)	Mean±SEM (mg/dl)	Mean±SEM (mg/dl)
At 1 day	3.90±0.06	3.42±0.13	3.77±0.01
After 10 days	3.91±0.05	2.68±0.11**	2.65±0.01**
After 16 days	3.8±0.03	2.96±0.03**	2.59±0.09**
After 22 days	3.82±0.05	3.38±0.07*	3.39±0.17*
**P<0.001 = highly significant difference			

**DISCUSSION:**

The acute renal failure (ARF), that still presents a high mortality rate (50%), can be defined as an abrupt decline of the glomerular filtration, resultant of ischemic or toxicity event. The drug nephrotoxicity is one of the most frequent causes (27%) of ARF and it is suggested that the interval of administration of the drug can be a factor.<sup>9</sup> In this study, administration of tobramycin showed an increase in serum creatinine on all days. It was observed that maximum increase was on 16<sup>th</sup> day of administration and at 22<sup>nd</sup> it decreased but not nears the normal value. Increased level of serum creatinine was also reported in a number of studies.<sup>10, 11</sup> It was reported that proximal tubular cells express a calcium sensing receptors that mediates calcium mobilization and phosphatidylinositol biphosphate-specific

phospholipase C dependent extracellular signal regulated kinase activation in response to aminoglycosides and thus could play a role in aminoglycoside induced nephrotoxicity.<sup>12</sup> A contradictory report shows that no patient demonstrated changes in serum creatinine suggestive of clinically apparent nephrotoxicity.<sup>13</sup>

The nephrotoxicity is confirmed by histological examination of the cortex of kidney. With tobramycin alone, the section of cortex showed peritubular fibrosis, thyroidization of tubules with atrophy of tubular epithelium. In this experimental study we used two doses of tobramycin/day. It is reported by a group of workers that the single dose of tobramycin regimen may be the preferred dosing method in patients to reduce the incidence and extent of renal

damage.<sup>14</sup> Recently a study observed that the reduced elimination rate in single dose of tobramycin may either be caused by circadian pharmacokinetic behavior of tobramycin or indicates early renal damage caused by high tobramycin that is not detected by biochemical measurements.<sup>15</sup>

Present study observed an increased level of creatinine after 10<sup>th</sup>, 16<sup>th</sup> and 22<sup>nd</sup> days of administration of gentamycin. Our study is in accord to another study which showed administration of gentamycin alone at a dose of 100 mg/kg/day for 8 days resulted in an increased level of serum creatinine with obvious nephrotoxicity.<sup>16</sup> Present study also observed a non significant level of serum sodium after 10<sup>th</sup> and 16<sup>th</sup> day of gentamycin administration. Experimental models of a study reported that gentamycin-induced nephrotoxicity shows histopathological, ultra-structural and functional alteration with blood urea nitrogen, electrolytes (sodium and potassium) and serum creatinine increase leading to acute renal insufficiency.<sup>17</sup> Administration of gentamycin showed significant decrease in serum potassium throughout the experiment in our study. The results are in contrast to the present study that observed disturbances of electrolytes except, the fall of serum potassium.<sup>18</sup> A study stated that the risk of hyperkalemia is small, particularly if baseline and follow-up GFR is higher than 40 ml/min.<sup>19</sup> Another study suggested that accumulation of potassium by the cells of the rats' renal cortex slices, is consequent upon excitation of the beta-adrenoreceptors.<sup>20</sup>

The study is in accord with other studies concluding that there was no significant difference in nephrotoxicity between gentamycin and tobramycin.<sup>21,22</sup> Our study is in contrast to the study of group of workers who observed that tobramycin was less nephrotoxic than gentamycin.<sup>23,24</sup>

#### CONCLUSIONS:

Both gentamycin and tobramycin have the potential for systemic toxicity and should be used according to guidelines and with increased vigilance and prudent monitoring in patients at increased risk for nephrotoxicity. As gentamycin is more economical it can be used instead of tobramycin, because there is no statistically significant difference in their nephrotoxicity.

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