EFFECT OF GENTAMICIN ON THE PROXIMAL CONVOLUTED TUBULES OF MICE

DESAI.S.D, SREEPADMA SUNKESWARI
DEPARTMENT OF ANATOMY, SHRI B.M.PATIL MEDICAL COLLEGE

ABSTRACT

One among the most commonly used aminoglycoside, gentamicin, is shown to cause renal damage. The proximal tubules, through which most water is reabsorbed , experience the greatest concentration and hence suffer most of the drug induced injuries. Serious toxicity is said to be major limitation to the usefulness of aminoglycosides ,the most notable being ototoxicity and nephrotoxicity. The present study depicts the effect of this drug when given at a dose of 100mg/Kg body weight/day in divided doses for different duration of time period in mice. And the study showed that light microscopic changes were minimal after seven days and were much extensive after 10 days following administration of gentamicin.

KEY WORDS:

Gentamicin , nephrotoxicity, proximal convoluted tubule, basement membrane, necrosis.

INTRODUCTION:

Gentamicin, a commonly used aminoglycoside is documented to cause injuries to the kidney[1]. Amongst the toxic effects, ototoxicity and nephrotoxicity are the serious side effects[2].

The kidney is the primary route of excretion for most of the antibiotics with nephrotoxic potential ; during excretion, renal tubule cells are usually are exposed to drug concentrations many times higher than that on the other cells in the body[3]. Tubular reabsorption per se of aminoglycosides does not occur,but internalization of molecule into lysosomal structures in the proximal tubule cell does occur. Gentamicin, a broad-spectrum aminoglycoside antibiotic widely used in treatment of serious infections of aerobic gram-negative bacilli. The drug is shown to be nephrotoxic in both animals and man. The renal damage, centered on proximal tubule is dose related[4].

The present study was undertaken to evaluate effect of gentamicin at 100mg/Kg body weight in divided doses for different duration on kidney with special emphasis on light microscopic changes in proximal convoluted tubules. The following parameters are studied on injection of gentamicin at the dose of 100mg/Kg-body weight per day in divided doses.

a) Changes in weight of the animal.
b) Gross changes in the kidney.
c) Light microscopic changes in glomeruli and proximal convoluted tubules.

MATERIALS AND METHODS:

All reagents used were analytical grade .Gentamicin sulphate was obtained from TADHA pharmaceutical limited , Madras. Swiss Albino mice aged one year and weighing about 40 gms kept under standard condition were used in the study.

Animals were divided into three groups:

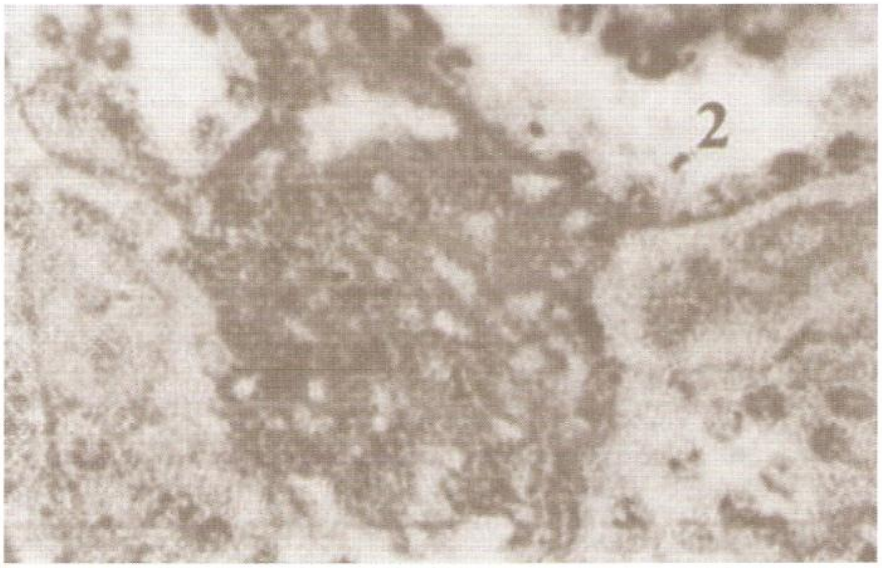
Group A : 10 Animals received gentamicin 100 mg/Kg body weight/day in divided doses intraperitoneally for seven days.

Group B : 10 Animals received gentamicin 100 mg/Kg body weight/day in divided doses intraperitoneally for Ten days.

Group C : 20 Animals received equivalent normal saline for Seven and ten days intraperitoneally.

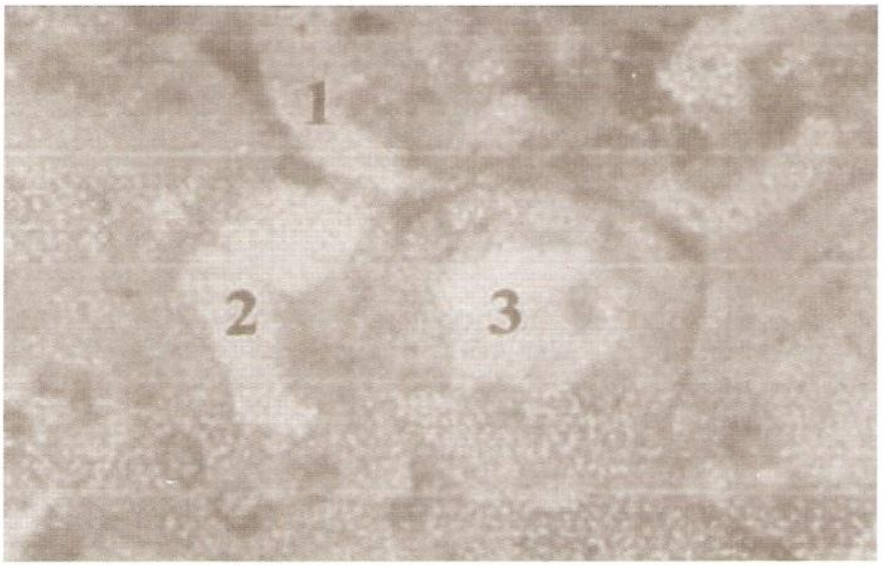
0.1 ml (4 mg) injection given intraperitoneally in the morning at 9:00 AM for 7 days to group A and for 10 days to group B . At the end of 7 days, group A animals were

G 10 PAS



100 X

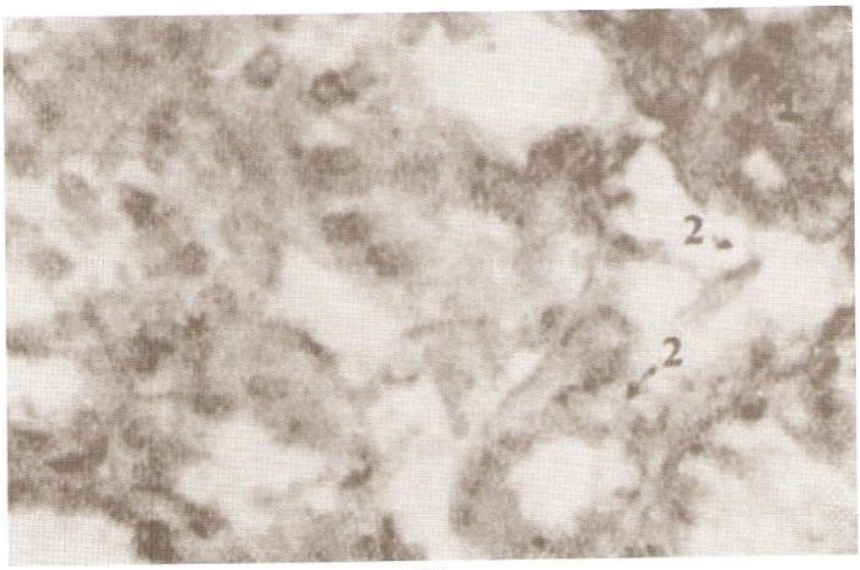
CONTROL PAS



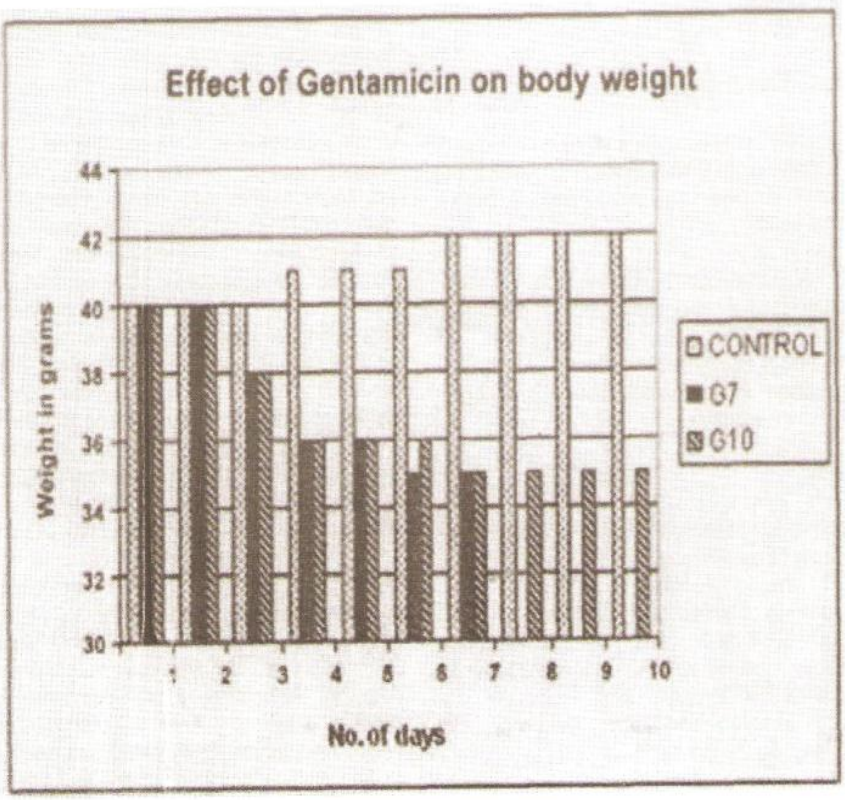
100 X

1. GLOMERULUS 2. PCT 3. DCT

G 10 PAS


1
2
2

100 X


Effect of Gentamicin on body weight
Weight in grams
44
42
40
38
36
34
32
30
1
2
3
4
5
6
7
8
9
10
No. of days
CONTROL
G7
G10

sacrified and by the end of 10 days, group B animals were sacrificed by cervical dislocation and kidneys were dissected out, fixed in 10% formalin and labeled accordingly.

Standard histological technique was followed and sections were stained by haemotoxylin & eosin and special PAS stains.

RESULTS:

1. Body Weight
- Control animals gained body weight (+2g)
- Group A showed decrease in body weight (≈5 g)
- Group B also showed decrease in body weight of ≈4 g .

2. Gross Changes in Kidney
- Group A showed swollen kidney and larger than control.
- Group B showed swollen and thicker kidneys than control.
- Group C the kidneys were normal.

3. Histological Changes in Kidney

Light microscopic lesions were quantitated using a scale from 0 to +3 where '0' indicated normally appearing proximal tubular epithelial cells.

- +1 Focal slight epithelial swelling.
- +2 Moderate and generalized proximal tubular swelling.
- +3 Focal proximal tubular necrosis involving most proximal tubular segments of all the nephrons.

GROUP A

- Bowman's space obliterated, thickening of basement membrane.
- PCT shows lumen occlusion with thickening of basement membrane.
- Proximal tubule showed generalized edema, matting and rupture of basement membrane in some tubules.
- Nuclei showed shrinkage, mild necrotic changes & stained dark.

GROUP B

- PCT showed characteristic focal necrosis (+3).
- Loss and desquamation of epithelial cells.
- Basement membrane and brush border ruptured.
- Necrotic nuclei desquamated into the lumen.
- Glomeruli appeared to be normal though Bowman's space appear to be normal.

CONTROL GROUP C

Show normal characteristic features.

DISCUSSION

The aminoglycoside antibiotics are still important causes of nephrotoxic acute renal failure .Since aminoglycosides undergo no metabolism in the body, the kidney is responsible almost exclusively for excretion. Studies in animals and man have shown that these agents lead to a syndrome of slowly developing acute renal failure. Aminoglycosides are highly charged basic molecules that attach to negatively charged phospholipids in the apical membranes of proximal tubular cells[5].The complexes are moved into the cells by endocytosis. Disruption of normal lysosomal functions by accumulated aminoglycoside is believed ultimately to lead to cellular necrosis. High renal cortex tissue concentrations of aminoglycosides usually accompany nephrotoxicity. Additional factors that may be involved in the toxicity of these drugs include disruption of normal tubular cell mitochondrial function with impaired oxidative phosphorylation. Gentamicin known to cause tubular necrosis in experimental animals .the toxic effects were centered on PCT cells which showed myeloid bodies together with focal cellular necrosis[6]. In the present study, proximal tubular destruction was observed on 7th day and was nearly total proximal tubular destruction on 10th day of

administration. Proximal tubular cells are highly dependent on oxygen and ATP to support transport functions. The aminoglycosides ave been shown to decrease glomerular hydraulic conductivity and to decrease renal blood flow[7].

Several workers have reported severe damage or disruption of tubular basement membrane in both experimental and clinical settings[8]. We observed destruction and thickening of the tubular basement membrane. In the present work the basement membrane destruction and thickening were pronounced in the proximal tubules of group 'B' (treated with gentamicin for 10 days).

Light microscopic alterations in kidney were minimal after 7 days administration of gentamicin. After 10 days administration of gentamicin , there was much extensive damage in superficial cortex. The morphologic changes--vacuolar degeneration in the epithelial cells of the proximal tubule, the inflammatory infiltrates in the interstitial tissue and the increased number of lysosomes with myelinic structures as well as mitochondrial oedema, the increased number of peroxysomes in the epithelial cells of the proximal tubules indicate the toxic influence of gentamicin on the proximal tubule.

There were patchy tubular necrosis and desquamation. Many epithelial cells were vacuolated and appeared to be undergoing disintegration. After ten days of drug administration, in the cells of proximal convoluted tubules of kidney there were observed the dilution of cytoplasm of various intensity, increases in amount and size of lysosomes, widening of endoplasmic reticulum tubules and swelling of mitochondria.

CONCLUSION:

Despite the nephrotoxicity , the aminoglycosides remain the main stay in the clinical management of gram negative infections, as the toxicity is dose related[9] . In our study there is destruction of proximal tubular cells when gentamicin is given for 7 days and there is nearly complete destruction of the proximal tubular cells when given for 10 days which substantiates its relation with the duration of the drug exposed to the proximal tubular cells which gets accumulated and the starts to damage the kidney.

REFFERENCES

1. Jacobson , Striker, Klahr The principles and practice of Nephrology, in Mechanisms of nephrotoxic injury, Edn-2, Mosby year book,Inc,St.Louis,Missouri,USA,1995, pp-784-87

2. Parvaneh Espandiari Et al, The Utility of a Rodent Model in Detecting Pediatric Drug-Induced Nephrotoxicity, Toxicol Sci. 2007 ,99 (2),Pp- 637–48.

3. Shanley PF, Burke TJ, Differential susceptibility to gentamicin toxicity within the proximal convoluted tubule. Renal failure,1990,12(2):83-7

4. Izzettin F.V., Ayça B, Uras F, Uysal V, Çevikbaş U, Yardimci T, Stohs S.J, Nephrotoxicity of gentamicin and co-trimoxazole combination in rats,General Pharmacology: The Vascular System,1994,Vol 25, (6), Pp-1185-89

5. Martine lelievre Et al., Effect of Fetal Exposure to Gentamicin on Kidneys of Young Guinea Pigs, Antimicrobial Agents And Chemotherapy,1987, vol. 31(1) Pp-88-92

6. Rymgayłło-Katska M, Studies of the effect of gentamicin on the kidneys of healthy young rats and Studies of renal parenchyma of experimental animals in the light and electron microscopy after gentamicin load, Pediatr Pol.1989;64(7):Pp- 456-66.

7. Bulger RE Et al, ,Endothelial characteristics of glomerular capillaries in normal, mercuric chloride induced, and gentamicin induced acute renal failure in the rat, J clinical Invest, 1983;72;Pp-128

8. Michael J. Kuhar, Linda Mak, Paul S. Lietman, Autoradiographic Localization of [3H]Gentamicin in the Proximal Renal Tubules of Mice. Antimicrobial Agents And Chemotherapy,1979, Vol.15,(1),Pp-131-33

9. Haughey et al, Two-compartment gentamicin pharmacokinetics in premature neonates: A comparison to adults with decreased glomerular filtration rates, the Journal of Paediatrics, 1980,96(2), Pp-325-30.

CORRESPONDING ADDRESS:

DR.S.D.DESAI
PROF. & HOD
Department Of Anatomy
Shri B.m.patil Medical College
Bijapur-586103
Karnataka
Mobile No: 09448210445
Office No: 08352-262770-ext:2211
EMAIL ID: dr.desaisd@gmail.com