Diuretics Reduces Renal Toxicity of Aminoglycosides

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ABSTRACT

Gentamicin is an aminoglycoside antibiotic, well known for its gram –negative activity as well as for its toxic effects on the kidney. The renal handling of gentamicin involves both glomerular filtration and tubular reabsorption. The renal damage which is dose related is centered on proximal tubular cells which undergo a variety of structural changes with tubular enzymuria at their most severe resulting in acute renal failure. The present study depicts the effect of Gentamicin 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. This study undertaken reveals that concomitant administration of loop diuretic like frusemide with gentamicin resulted in less tubular damage than that caused by gentamicin alone.

KEY WORDS_Gentamicin, frusemide, renal damage, proximal tubular cells, glomerulus.

INTRODUCTION

In the modern era of chemotherapy of infections started in the year 1936, with the clinical use of sulphanilamide, the golden age of antibiotic therapy began with the introduction of penicilline in the year 1941.

Antibiotics –Most misused drugs in general practice. Kidneys are most vulnerable for the toxic effects of the antibiotics, especially aminoglycosides. Proximal tubules suffer most drug induced injury. Gentamicin widely used is selected in the present work. Gentamicin is a commonly used aminoglycoside antibiotic that is effective against most of gram negative microorganisms. It has high antibacterial efficacy, rapid onset of action, low rate of true resistance, synergy with β-lactam antibiotics, and low cost; however, therapeutic doses of gentamicin can cause nephrotoxicity, and it is among the most common causes of acute kidney injury.[1]

Nephrotoxicity caused by gentamicin is characterized by non oliguric acute kidney failure. It decreases renal blood flow rate and urinary concentrating ability, and eventually leads to renal insufficiency[2]. Pathologically, gentamicin induced nephrotoxicity is characterized by tubular damage, which is localized predominantly in the proximal tubules[3].

Whiting P.H, Peterson and J. G. Simpson reported that concomitant use of diuretics impart a protective effects on proximal tubules[4]. Aminoglycoside antibiotics (amikacin, gentamicin etc.) have properties that make them toxic to the ear and to the kidney. The toxic effect will be reduced by the concomitant use of Frusemide[1]. Hence in this study an attempt is made to know the protective effect of diuretics, i.e., Frusemide when used along with gentamicin.

MATERIALS AND METHODS 5

Study was conducted in the department of Anatomy. All reagents used were analytical grade. Gentamicin sulphate was obtained from TADHA pharmaceutical limited, Madras. 36 Swiss Albino mice aged one year and weighing about 40gms kept under standard condition were used in the study. 36 Swiss male albino mice arranged in six groups, six mice in each group as A, B, C, D, E, and F. the doses of drugs given is as follows.

1. **Group A**

Animals are given gentamicin sulphate at a dose of 100 mg/Kg body in divided doses weight for seven days.

2. **Group B**

Animals are given gentamicin sulphate at a dose of 100 mg/Kg body weight in divided doses for ten days.

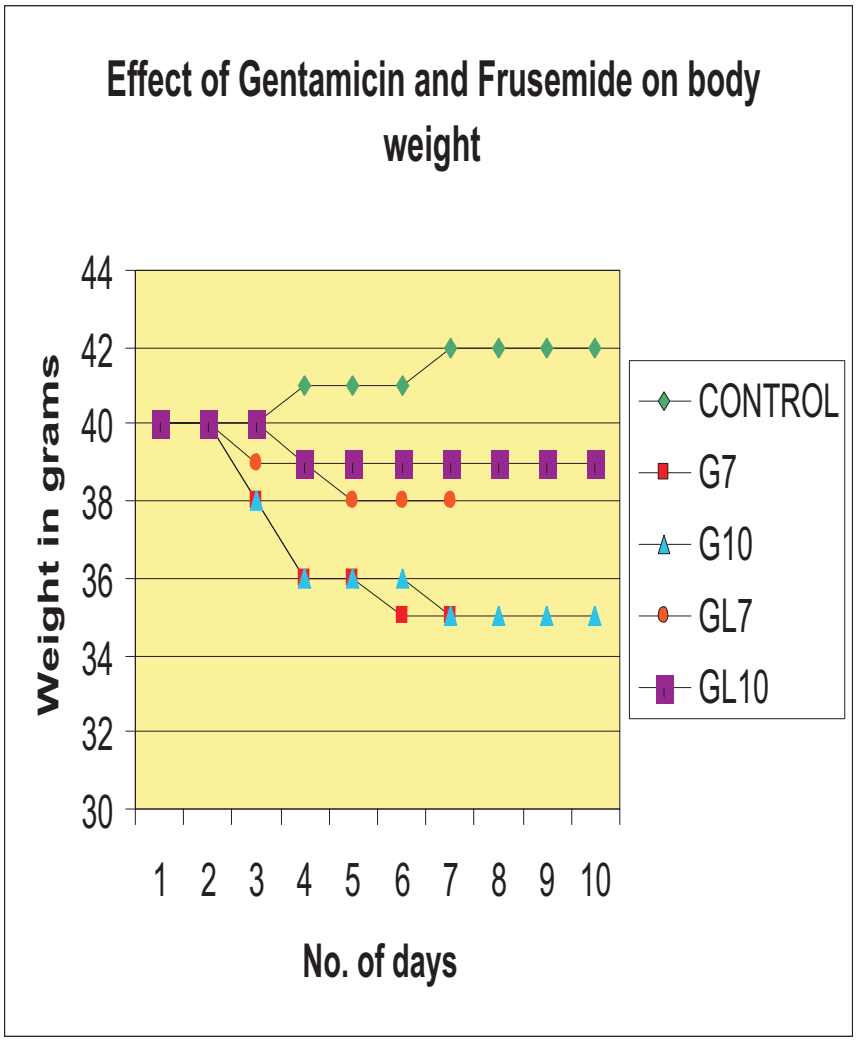
3. **Group C**

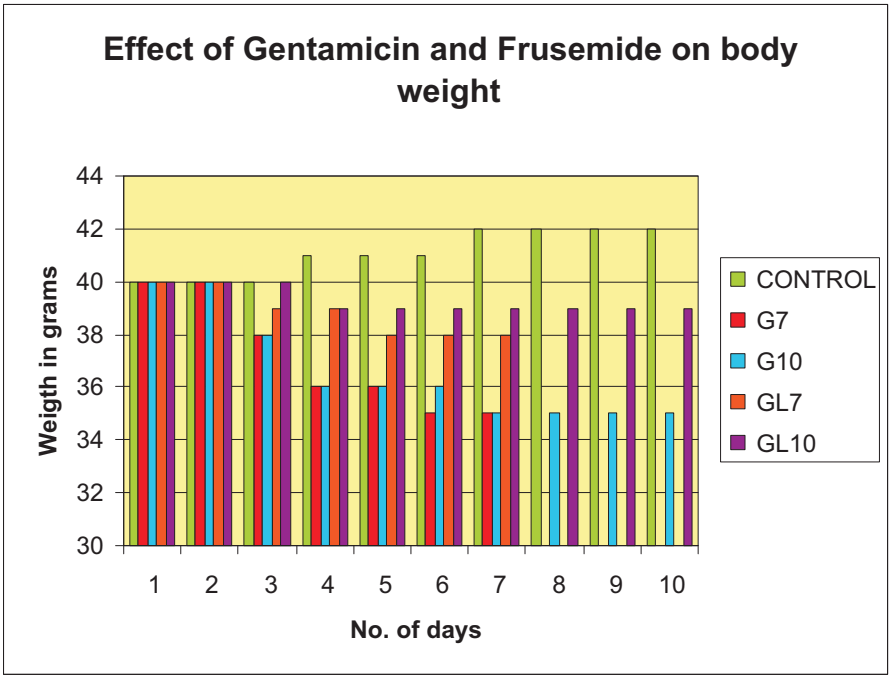
Animals are given gentamicin sulphate at a dose of 100 mg/Kg body weight in divided doses + Frusemide 5mg/Kg body weight for seven days.

4. **Group D**

Animals are given gentamicin sulphate at a dose of 100

Graph-1


Effect of Gentamicin and Frusemide 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
GL7
GL10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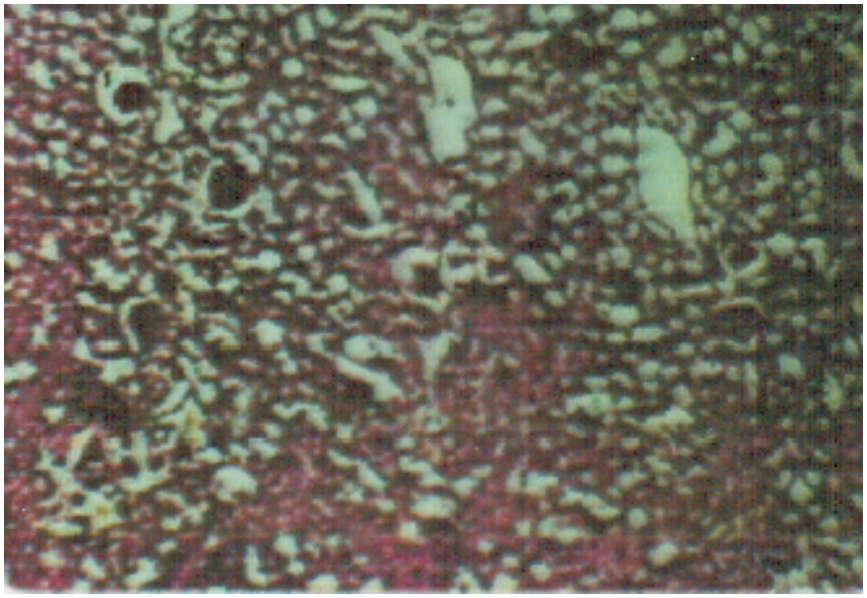

Fig -1: Group B (G-10). PCT-acute focal necrosis, Loss and desquamation of epithelium Basement membrane and brush border ruptured, Bowman's space -larger.

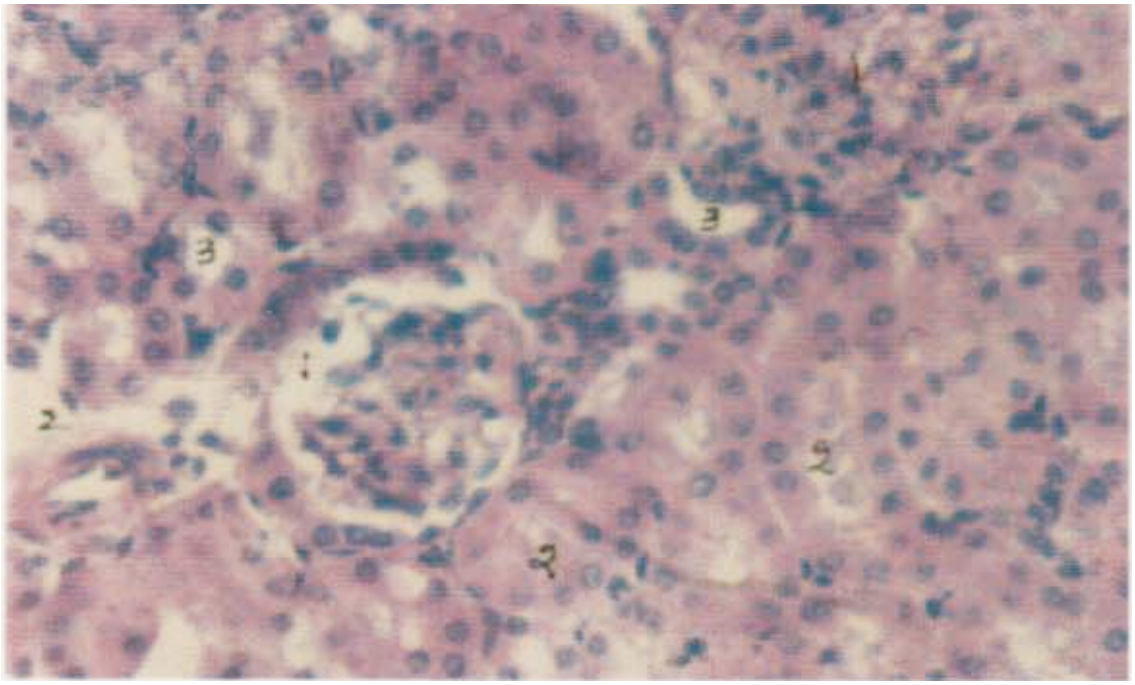

Fig -2: Group D (GL-10). 1. Glomeruli 2. PCT normal and occluded lumen 3. DCT normal

mg/Kg body weight in

Divided doses + Frusemide 5mg/Kg body weight for ten days.

5. **Group E**

Animals are given 0.9% saline 1.25 ml/Kg body weight for seven days.

6. **Group F**

Animals are given 0.9% saline 1.25 ml/Kg body weight for ten days.

Animals are sacrificed by cervical dislocation and kidneys were dissected out, fixed in 10% formalin after observing for gross changes. Sections stained with Haematoxyllin & Eosin stain and PAS stain.

OBSERVATIONS

After 10 days animals were observed for change in the body weight and mice were dissected, observed for gross features of kidney. Dissected kidneys were processed for

histological techniques and stained with Haematoxyllin & eosin and PAS techniques.

Changes in Body Weight:

Group A (G7) - Decrease in body weight about 5gms.

Group B (G10) - Decrease in body weight about 4gms.

Group C (GL7) - Decrease in body weight about 2gms.

Group D (GL10) - Decrease in body weight about 1gms.

Control groups (E & F) - Increase in body weight 2gms at the end of 10th day (graph 1&2).

Gross Changes in Kidney:

Group A - Swollen and larger

Group B - Swollen and thicker than Group A

Group C - Swollen and larger than control group

Group D - Larger

Group E & F (Control) - Normal.

Histological Observations: Light microscopic changes

Quantification of histological changes

0 - normal

+1 - Focal slight epithelial swelling

+2 - Moderate and generalized PCT swelling.

+3 - Focal & PCT necrosis involving most segments of PCT of all nephrons.

Group A (G7)

Bowman space obliterated.

Thickening of basement membrane

PCT occlusion of lumen, edema

Rupture of basement membrane (Tubulorrhexis).

Nuclei necrotic-decrease in size and darkly stained (+1)

Group B (G10 Fig- 1)

PCT- acute focal necrosis

Loss and desquamation of epithelium

Basement membrane and brush border ruptured.

Glomeruli – normal

Bowman's space –larger

Group C (Gl7)

PCT - edema and matting

Well preserved basement membrane

Brush border - well preserved

Minimal desquamation

Group D (GL10 Fig -2)

PCT – Near normal appearance

Well preserved basement membrane

Nuclei – normal

No desquamation.

DISCUSSION

Gentamicin widely used antibiotic cause's tubular necrosis. Proximal convoluted tubule is more vulnerable. Well wood et al 1976 observed that ultra structural changes were accompanied by increase in renal excretion of NAG - marker of tubular damage [6]. The gentamicin has been shown to be nephrotoxic in both animals and man [7]. The renal damage is, which is dose related, is centered on proximal tubular cells which undergo a variety of structural changes with enzymeuria [6,8]. Several authors conclude that tubular interstitial disease persisting after tubular necrosis is due to severe disruption of basement membrane. Basic mechanism underlying gentamicin induced PCT necrosis is unknown. However it has been related to inhibition of protein synthesis and sequestration of the aminoglycoside with lysosomes with altered lysosomal function [9]. Compared study of gentamicin nephrotoxicity in adults and neonates shows, Lack of nephrotoxicity in neonates is due to age related difference in drug sensitivity, i.e., in prematured infants. Drugs are not absorbed to a greater degree as in adults [10].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 have been shown to decrease glomerular hydraulic conductivity and to decrease renal blood flow [11]. Red grape seed extract significantly reduced Histological damage induced by gentamicin injection, as shown by a previous study as well [12]. 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 edema, 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. The changes were minimal with the concomitant administration of frusemide with gentamicin for seven days. The PCT are near normal after the administration of frusemide with gentamicin for ten days.

CONCLUSION

In present study light microscopic changes are minimal after seven day of administration of gentamicin. Much extensive after ten days administration of gentamicin. The changes were minimal with the concomitant administration of frusemide with gentamicin for seven days. The PCT are near normal after the administration of frusemide with gentamicin for ten days. The importance of these dose related nephrotoxic changes and protective effect of diuretic along with gentamicin in man had to be restressed.

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