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Comparative effect of NR-AG-I and NR-AG-II (polyherbal formulations) against Gentamicin - induced nephrotoxicity in rats

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Abstract:

Objective: To study the comparative effect of NR-AG-I and NR-AG-II (polyherbal formulations) against gentamicin- induced nephrotoxicity in rats. Materials and methods: Nephroprotective activity was evaluated in gentamicin induced nephrotoxicity (80mg / kg / day s.c) in male albino rats. NR-AG-I and NR-AG-II were tested at a dose of 150mg/kg/day p.o. All the treatments were given for 12days. Urea clearance and microscopical examinations of kidney performed after the treatment. Results: Gentamicin treatment caused nephrotoxicity as evidenced by significant decrease in urea clearance and was prevented by both formulations. Study of renal microscopy showed necrosis, epithelial loss with granular degeneration and fatty changes in gentamicin treated rats and was reversed by both formulations, but NR-AG-I proven to be better formulation in our experimental study. Conclusion: Our data suggest that treatment with NR-AG-1 and NR-AG-II may be useful in reducing gentamicin nephrotoxicity in rats.

Key Words: NR-AG-I, NR-AG-II, Nephrotoxicity, Gentamicin, Urea clearance

1. Introduction

Besides liver, kidney is the most important organ for the elimination of endogenous metabolites and foreign chemicals from the body and hence like liver, the renal system also faces high risk of toxicity.

Nephrotoxicity is the major side effect of aminoglycosides accounting for nearly 10 - 15% of drug toxicity [1]. Acute renal toxicity may be induced experimentally by using drugs like aminoglycosides, mercuric chlorides, cisplatin, cyclosporins and urinary nitrates, etc. Aminoglycosides are one of the major class of drugs that induce nephrotoxicity and are also one of the five principal causes of hospital acquired acute renal failure. Aminoglcosides including gentamicin are very important agents for the treatment of gram-negative bacterial infection. The specificity of gentamicin renal toxicity is apparently related to its preferential accumulation in the renal convoluted tubules and its effect on biological membranes [2-4].

Ayurveda, an indigenous system of medicine, offers wide scope for the treatment of nephrotoxicity. NR-AG-I (M/s Natural Remedies Pvt. Ltd., Bangalore) is a polyherbal formulation containing extracts of

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Crataeva nurvala, Dolichus biflorus, Tribulus terrestris and *shilajit*. NR-AG-II (M/s Natural Remedies Pvt. Ltd., Bangalore) is also polyherbal formulation containing extracts of *Crataeva nurvala, Boerhaavia diffusa, Saccharum officinarum and Butea frondosa*. The present investigation was planned to study the comparative effect of NR-AG-I and NR-AG-II against gentamicin-induced nephrotoxicity in rats.

2. Materials and Methods

2.1 Animals

Male albino rats of Wistar strain weighing between 110-160 g were used. The animals were fed with commercially available standard pelleted feed (M/s Lipton India Ltd., Mumbai) and water *ad libitum*. Gentamicin was subcutaneously injected to rats at a dose of 80 mg/kg/day for 12 days to induce the acute renal failure [1].

2.2 Nephroprotective activity

The rats were divided into four groups of six animals each. Group I control - was administered saline s.c., Group II gentamicin control - was administered gentamicin sulphate (80 mg/kg/day s.c) Group III and IV received NR-AG-I and NR-AG-II (150 mg/kg/day p.o) respectively and after one hour, gentamicin (80mg/kg/day s.c) was administered to these groups. All the treatments were given for 12 days.

On the 12th day, after the treatment, rats were housed in metabolic cages for 24 hours for urine collection. Urea clearance was determined using urea kit (M/s Nice Chemicals Pvt. Ltd., Cochin). Sections of kidney stained with haematoxylin and eosin were used for histopathological studies. The histological damage to kidney was scored by using following criteria: (0) normal; (1) normal appearance with minimal necrosis; (2) fatty changes; (3) minimal necorsis and fatty changes; (4) severe necrosis and fatty changes.

2.3 Statistical analysis

The results are expressed as mean ± SEM. Statistical analysis was carried out with Student's *t* - test. A probability value less than 0.05 was considered significant.

3. Results and Discussion

Results of this study confirmed that gentamicin at a dose of 80mg/kg/day produces significant nephrotoxicity as evidenced by decrease in urea clearance (Table-1) and tubular epithelial damage with intense granular degeneration, more fatty changes and severe necrosis. Pretreatment with NR-AG-I has shown normal appearance with minimal necrosis and epithelial regeneration, whereas with NR-AG-II has shown minimal necrosis, fatty changes and less epithelial regeneration of renal tubules. (Table 2)

Table 1
Effect of NR-AG-I and NR-AG-II in gentamicin induced nephrotoxicity.

Group	Urea clearance (ml/min)
Control	0.5349 ± 0.01
Gentamicin	0.2925 ± 0.09***
NR-AG-I + Gentamicin	0.5118 ± 0.04*
NR-AG-II + Gentamicin	0.5285 ± 0.07**

Values are in mean ± SEM; n = 6; ***P < 0.001 *Vs* Control, *P <0.05 & **P < 0.005 *vs* Gentamicin.

Table 2
Grading of histopathological examination of rat kidney treated with gentamicin, NR-AG-I and NR-AG-II.

Group	Average grade
Control	0.167 ± 0.17
Gentamicin	3.833 ± 0.17***
NR-AG-I + Gentamicin	1.0 ± 0.26***
NR-AG-II + Gentamicin	2.667 ± 0.21**

Values are in mean ± SEM; n = 6; ***P < 0.001 *vs* Control, **P < 0.005 and *vs* ***P <0.001 Gentamicin.

Both the treatments provided marked functional and histological protection against acute renal damage in rats treated with gentamicin, but NR-AG-I proved to be better formulation in our studies. Aminoglycoside antibiotics are still widely used in the treatment of severe life threatening infections due to gram negative bacteria. Although the acute

renal failure induced by aminoglycosides is reversible, the medical burden and cost of treatment for nephrotoxicity are very high.

Although nephrotoxic effects of gentamicin have been well demonstrated, the patho-physiological mechanism for reduction in the glomerular filteration rate (GFR) remains to be clarified. Gentamicin produces proximal tubular injury, such as myeloid body formation and tubular necrosis. Gentamicin induced reduction in the GFR is associated with decrease in renal blood flow and glomerular filteration co-efficients [5].

A role of lipid peroxidation in gentamicin induced acute renal failure has been described by evaluating the effect of diphenyl-phenylenediamine and vitamin-E[6]. Both the formulations tested significantly reduced the renal tubular damage caused by gentamicin,which may be due to *Crataeva nurvala* (lupeol), a free radical scavenger present in both formulations [7] .

In conclusion, the present study provides evidence that coadministration of both the formulations (NR-AG-I and NR-AG-II) along with gentamicin prevents both funtional and histological renal changes induced by gentamicin in rats.

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