ORIGINAL ARTICLE

Aminoglycosides Induced Nephrotoxicity and its Protection by *Nigella Sativa*

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ABSTRACT

Backgound: The major obstacle limiting the use of aminoglycoside, antibiotics has been and continues to be the possibility of drug induced ototoxicity and nephrotoxicity.
Study dsign: Changes in biochemical parameters related to nephropathy before and after of nigella sativa were observed.
Material and methods: Ten rabbits were included in the study, comprised as group 1 and 11. Group I was only given gentamycin and its effect on kidney functions was observed. Group II was given gentamycin and extract of nigella sativa for 11 days and the biochemical changes related to kidney functions were estimated.
Results: In group 1, Level of serum proteins, albumin and cholesterol were decreased after the administration of gentamycin but significant difference was only observed in case of cholesterol before the administration of gentamycin. On the other hand the level of blood urea, serum creatinine and serum calcium was increased, but significant difference was only observed in case of serum calcium when compared with the level of calcium before the administration of gentamycin. In group 2, Level of blood-urea, serum creatinine and cholesterol were decreased after the administration of gentamycin and nigella sativa (at the 11th day of administration) but significant difference was only observed in the case of serum cholesterol. On the other hand the levels of serum protein and serum calcium were non-significantly increased, whereas the level of serum albumin remained the same.
Conclusion: It is suggested that although nigella sativa shows a significant effect on nephrotoxicity induced by gentamycin but its effect on the level of serum calcium and cholesterol may be dangerous. However further research is needed on large number of rabbits to reach on a definite conclusion.
Keywords: Aminoglycosides, Nigella sativa, Nephrotoxicity.

INTRODUCTION

Aminoglycosides are bactericidal for susceptible organisms by virtue of irreversible inhibition of protein synthesis. These enter the cell, bind to the receptors of the bacterial ribosomes and inhibit protein synthesis. Despite the introduction of several new classes of antimicrobial agents aminoglycosides are still recognized as first line therapeutics agents in the management of severe gram negative sepsis[1,2].

The major obstacle limiting the use of aminoglycoside antibiotics has been and continues to be the possibility of the drug induced ototoxicity and nephrotoxicity[3]. Patients at greatest risks for aminoglycosides induced nephrotoxicity include the elderly patients with pre-existing renal disease and those who are volume depleted[4,5].

Gentamicin is highly effective antibiotic. The nephrotoxic effect of gentamicin is directly related to treatment duration, with a decrease in endogenous creatinine clearance of 0.5% per day of gentamicin treatment[6]. On the other hand, it is reported that low-dose gentamicin, an aminoglycoside as part of therapy for S. aureus (bacteremia) is nephrotoxic and should not be used routinely, given the minimal existing data supporting its benefit[7].

Gentamicin treatment was strongly linked to declines in mRNA transcripts for several luminal membrane transporters that handle elevated level of urinary metabolites.The integrated pathway analysis that gentamicin-induced renal Fanconi-like syndromes might be better explained by the reduction of functional proximal tubule. Furthermore, this analysis suggests that renal transcription factors HNF1alpha, HNF1beta, might be the central mediators of drug-induced kidney injury and adaptive response pathways[8].

The black cumin or Nigella sativa have many acclaimed medicinal properties such as bronchodilatory, hypotensive, antibacterial, antifungal, analgesic, anti-inflammatory and immuno-potentiating and are universally accepted as a panacea[9] .

The major biological component of Nigella sativa is thymoquinone. This compound significantly decreased the number and size of calcium oxalate deposits in the renal tubules[10].

The current study has been planned to study the effect of nigella sativa on nephrotoxicity induced by gentamycin in rabbits. Changes in biochemical

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parameters related to nephropathy before and after administration of nigella sativa are also observed.

MATERIALS AND METHODS

Study was conducted on 10 rabbits weighing 1 to 1.75 kg and age ranging from 8-10 months. These were housed for 14 days at Pharmacology Department of FJMC, Lahore for acclimatization. The biological clock was maintained. The rabbits were fed on commercial diet, water and libitum.

Rabbits were divided into two groups i.e. group I and Group II. Group I was given only gentamycin and its effects in kidney functions were observed. Group II was given gentamycin and extract of nigella sativa for 11 days and the biochemical changes related to kidney functions were estimated. Gentamycin 60/mg/kg/day was injected intramuscularly in two equally divided doses for 11 days. Extract of nigella sativa 10/mg/kg/day was given along with gentamycin for 11 days.

Collection of blood sample: Eight ml of blood was drawn from the vein of shaved ear through disposable syringe. Blood samples from both groups were collected according to the following schedule:

A. Before administration of first dose of drug.
B. On the 11th day of experiment.
C. On the 21st day of experiment.

Bio chemical parameters like protein, Albumin, Calcium, urea and creatinine were estimated by standard chemical methods[11].

RESULTS

Blood samples were taken from Group I of rabbits before administration and then 11 days after the administration of gentamycin. A variation in biochemical parameters was observed. Level of serum proteins, albumin and cholesterol were decreased after the administration of gentamycin but significant difference was only observed in case of cholesterol before the administration of gentamycin. On the other hand the level of blood urea, serum creatinine and serum calcium was increased, but significant difference was only observed in case of serum calcium when compared with the level of calcium before the administration of gentamycin. (Table I).

Nigella Sativa was given for 11 days and the biochemical parameters were estimated at 0 and 11 days. Level of blood-urea, serum creatinine and cholesterol were decreased after the administration of gentamycin and nigella sativa (at the 11th day of administration) but significant difference was only observed in the case of serum cholesterol. On the other hand the levels of serum protein and serum calcium were non-significantly increased, whereas the level of serum albumin remained the same. (Table II)

Table I: Variation in biochemical parameters in group I of rabbits.

Biochemical Parameters	Before administration of Gentamycin (0 days)	After Gentamycin (11 days)
Blood Urea (mg/dl)	40.5 ± 2.5	68 **±** 9.8
Serum Creatinine (mg/dl)	0.95 **±** 0.02	1.2 ± 0.03
Serum Proteins (gm/dl)	6.7 ± 0.9	5.4 ± 0.85
Serum Albumin (gm/dl)	4.3 ± 0.21	3.0 ± 0.22
Serum Calcium	6.9 ± 0.98	9.7 ± 1.00
Serum Cholesterol	155 ± 10.5	33 ± 4.5

Table II: Variation in biochemical parameters in group II of rabbits before/ after administration of gentamycin + nigella sativa.

Biochemical Parameters	Before administration of Gentamycin (0 days)	After Gentamycin and nigella sativa (11 days)
Blood Urea (mg%)	40.5 ± 2.5	32.4 **±** 1.20
Serum Creatinine (mg%)	0.95 **±** 0.02	0.8 ± 0.02
Serum Proteins (gm%)	6.7 ± 0.9	6.3 ± 1.00
Serum Albumin (gm%)	4.3 ± 0.21	4.0 ± 0.15
Serum Calcium	6.9 ± 0.98	10.2 ± 0.91
Serum Cholesterol	155 ± 10.5	54 ± 8.50

DISCUSSION

Progression of tubular dysfunction results from accumulation of high concentration of antibiotics in renal parenchyma due to tubular filtration and secretion of drug by tubular epithelial cells[12].

It was observed that gentamycin administration causes a decreased level of serum proteins, albumin and cholesterol. The study is confirmed by a group of workers[5] who also observed a disturbed level of protein. They concluded that altered metabolism of protein and amino acid is due to altered activity of amino-transferase activity that may be one of the factors of nephrosis. In the present study a decreased level of cholesterol was calculated. Study is in contrast to a report[13] which observed that in kidney dysfunction there is an increased level of cholesterol due to a decreased activity of LCAT. Due to the deficiency of this enzyme the free cholesterol is not converted into esterified cholesterol.

Level of blood urea, serum creatinine and serum calcium were increased due to gentamycin. A number of studies confirmed these findings[1,14]. They reported that the kidneys are the primary site of aminoglycoside (gentamycin) clearance: any factor that permits renal parenchymal accumulation increases the risk of aminoglycoside nephrotoxicity that may increase the level of blood urea and serum creatinine. Another study found that the damage of kidney by the antibiotic is manifested to a greater extent in rabbits with the initial (before the administration of gentamicin) reduced ability of mitochondria to oxidize alpha-ketoglutarate[15].

A study[12] also confirmed our finding and shows an increased level of serum calcium. Study reported that increased calcium inhibits hormone stimulated cAMP level that may effect on cellular processes going on in cells.

Effect of nigella sativa on nephrotoxicity induced by gentamycin was studied. Level of blood urea, serum creatinine and cholesterol were decreased after the administration of nigella sativa (at the 11th day of administration). The study is confirmed by a report. According to a study, much of the biological activity of the nigella sativa has been shown to be due its constituent thymoquinone. The study reported that the treatment of rats with the seed extract for up to 12 weeks has been decrease in plasma concentrations of cholesterol, triglycerides and glucose. They also observed that the seeds are characterized by a very low degree of toxicity[16]. Our study is also in accord to a report, that the kidney function becomes normal due to the thymoquinone.[8] Another study[13] reported that the volatile oil of nigella sativa has an effect of hypertension and may be related with renin-angiotensin system and may effect on level of cholesterol.

On the other, the levels of serum protein and serum calcium were increased whereas the level of serum albumin was same. It is reported[17] that thymoquinone significantly suppressed drug induced proteinuria. This shows that the increased level of serum calcium may result in stone formation.

CONCLUSION

It is therefore concluded that although nigella sativa shows a significant effect on nephrotoxicity induced by gentamycin but its effect on the level of serum calcium and cholesterol may be dangerous. However further research is needed on large number of rabbits to reach on a definite conclusion.

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