GENTAMICIN INDUCED NEPHROTOXICITY IN RELATION TO PLASMA LIPID PROFILE IN RATS

Thesis Submitted for the Partial Fulfillment of the Master Degree in Clinical Toxicology

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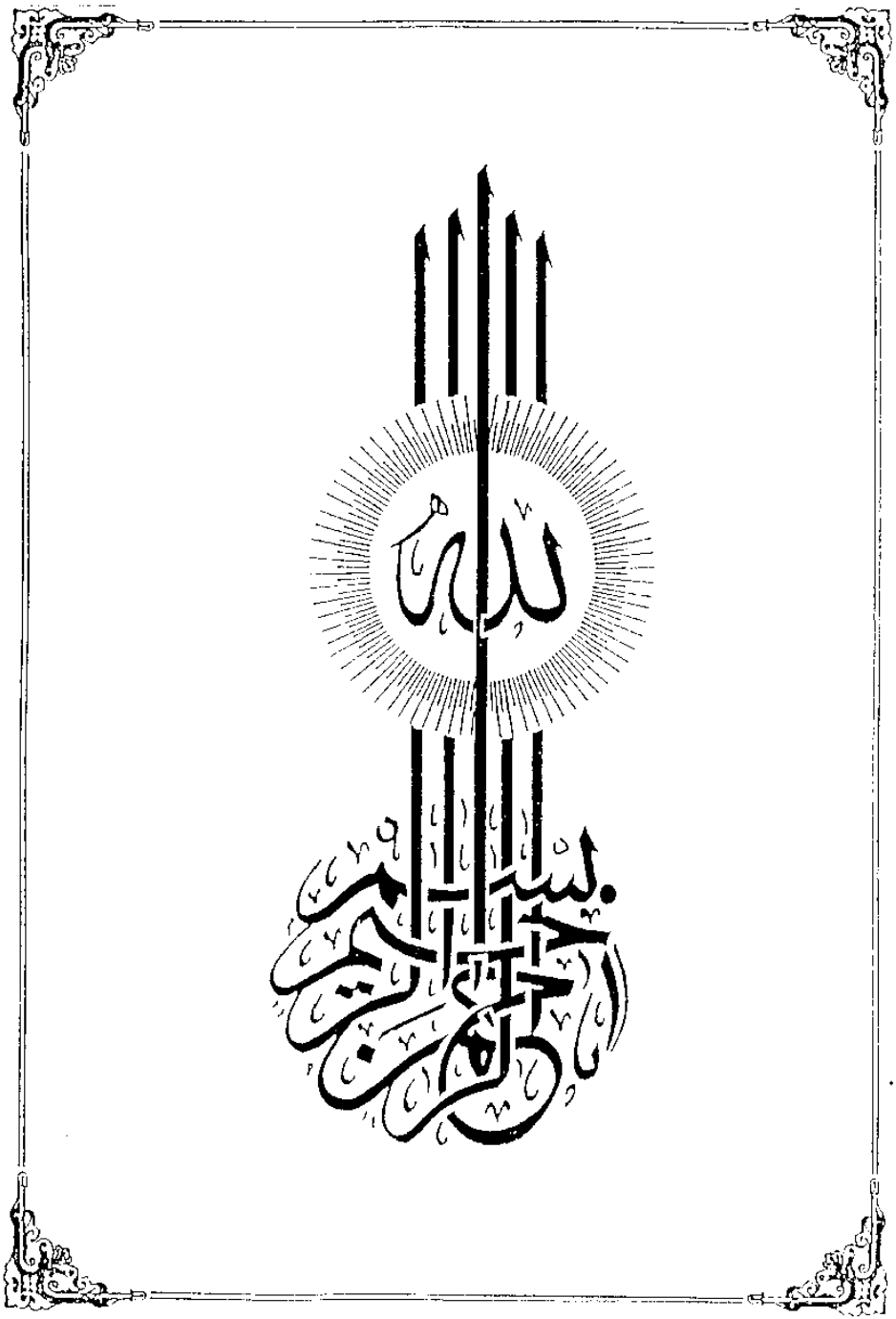

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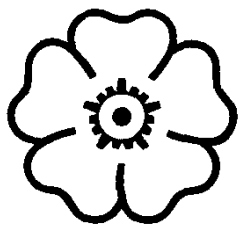
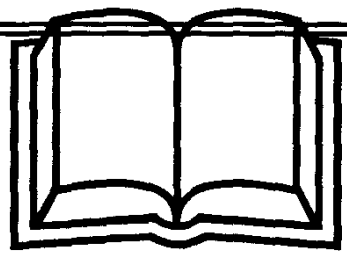


To my family

Nabil Nassif



Introduction and Aim of the Work

INTRODUCTION AND AIM OF THE WORK

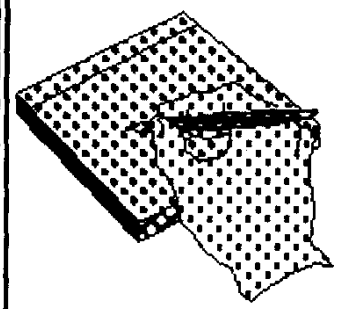
Gentamicin is a widely used antimicrobial, it belongs to the aminoglycosides group. It acts through irreversible binding to the 30S subunit of bacterial ribosomes, blocking the recognition step in protein synthesis, and causing misreading of the genetic code ***(Olin et al., 1993).***

Gentamicin nephrotoxicity is due to accumulation of the drug in renal cortex and production of morphological changes in the proximal tubular cells. This depends on duration of therapy, total dose administered and age of the patient ***(Samadian et al., 1993).***

Nephrotoxicity has been associated with plasma trough concentrations greater than 2 microgram per milliliter (µg/ml). However, evidence from clinical studies is conflicting, and nephrotoxicity may still occur despite monitoring to ensure that trough concentrations are maintained below this value ***(Katzung, 1995).***

Induction of nephrotoxicity in rats by gentamicin -as exhibited by elevation of plasma creatinine concentration-produced elevation in plasma total cholesterol and triglycerides. It also caused reduction in phospholipids level ***(Abdel-Gayoum et al., 1993).***

The objective of this study is to find out the relationship between gentamicin induced nephrotoxicity and the changes in plasma lipid profile in rats. Also to follow up these changes seven and fourteen days after withdrawal of the drug to assess the reversibility of these changes.



Review of Literature

HISTORICAL REVIEW

Aminoglycosides are a group of bactericidal drugs originally obtained from various *Streptomyces* species and sharing chemical, anti microbial, pharmacological and toxic characteristics. At present, the group includes streptomycin, neomycin, kanamycin, gentamicin, amikacin, tobramycin, sisomicin, netilmicin, and others ***(Jawetz, 1992).***

Gentamicin was discovered in the Schering Research Laboratories. It was first studied and described as a new broad spectrum antibiotic complex, produced by a species of bacteria of the genus *Micromonospora* in 1963 by Weinstein and his colleagues ***(Weinstein et al., 1964).***

Later in 1963, ***Rosselot and coworkers (1964)*** isolated, purified and characterized gentamicin as a bactericidal broad spectrum antibiotic produced by actinomycete *Micromonospora*.

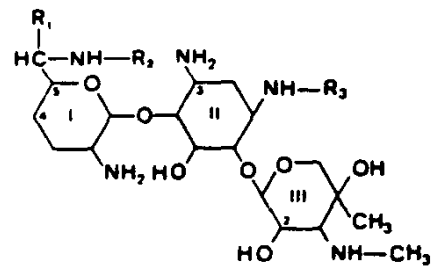
The difference in spelling "-micin" as compared with that of the other aminoglycoside antibiotic "-mycin" reflects the difference in origin, as gentamicin is produced by a species of *Micromonospora*, while other aminoglycosides are produced by different species of *Streptomyces* ***(Sande and Mandell, 1991).***

CHEMISTRY

Aminoglycosides in general consist of two or more amino sugars joined in glycosidic linkage to a hexose nucleus. In gentamicin this hexose, or aminocyclitol is 2-deoxystreptamine. Thus members of gentamicin family are aminoglycosidic aminocyclitols ***(Clark et al., 1992).***

The gentamicin family includes gentamicin C_1, C_{1A}, C_2, C_{2A}, and C_{2B}, sisomicin, and netilmicin (the 1-N-ethyl derivative of sisomicin). It contains a 3-amino sugar (garosamine) and a second amino sugar. Variations in methylation of the second amino sugar result in the different components of entamicin ***(Zenner et al., 1994).*** These modifications appear to have little effect on biological activity ***(Sande and Mandell, 1991).***

Gentamicin sulphate is a complex mixture of the sulfates of gentamicin C_1, C_{1A},and C_2,. Some commercial samples may contain significant quantities of the minor components gentamicin C_{2A} and C_{2B}. It contains when dried, not less than 590 units of gentamicin per mg ***(Bengtsson et al., 1986).*** This figure shows the chemical structures of different members of the gentamicin family ***(Katzung, 1995).***



Gentamicin, netilmicin

	Ring I			Ring II
	R_1	R_2	C4–C5 bond	R_3
Gentamicin C_1	CH_3	CH_3	Single	H
Gentamicin C_2	CH_3	H	Single	H
Gentamicin C_{1a}	H	H	Single	H
Netilmicin	H	H	Double	C_2H_5

Chemical Properties:

Gentamicin is a white to almost white powder. It is freely soluble in water, practically insoluble in alcohol, acetone, chloroform and ether. A four per cent solution in water has a pH of 3.5-5.5. The powder is sterilized by irradiation and solutions by filtration ***(Reynolds et al., 1993).***

One unit of gentamicin is contained in 0.00156 milligram [mg] of the first International Reference Preparation, which contains 641 units per mg. So, 80.000 units are approximately equivalent to 80 mg of gentamicin ***(Kucers & Bennett, 1993).***

USES AND ADMINISTRATION

Uses of Gentamicin

Gentamicin is used to treat severe systemic infections due to sensitive gram-negative and other organisms. These include biliary tract infections as acute cholecystitis or cholangitis, brucellosis, cat scratch disease and cystic fibrosis ***(Hartzen et al., 1994).*** Also it is used in the treatment and prophylaxis of endocarditis due to streptococci, enterococci or staphylococci ***(Durack, 1990).*** It is also indicated in endometritis, gastroenteritis, listeriosis, otitis externa, otitis media, pelvic inflammatory disease, peritonitis and pneumonia ***(Noone, 1989).***

It is given systemically in skin disorders, such as burns and ulcers, for pseudomonal and other gram-negative infections. It is also used in urinary tract infections as acute pyelonephritis, septicemia and prophylaxis of surgical infections ***(Clark et al., 1992).***