THE EFFECT OF VERAPAMIL ON TOBRAMYCIN NEPHROTOXICITY

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

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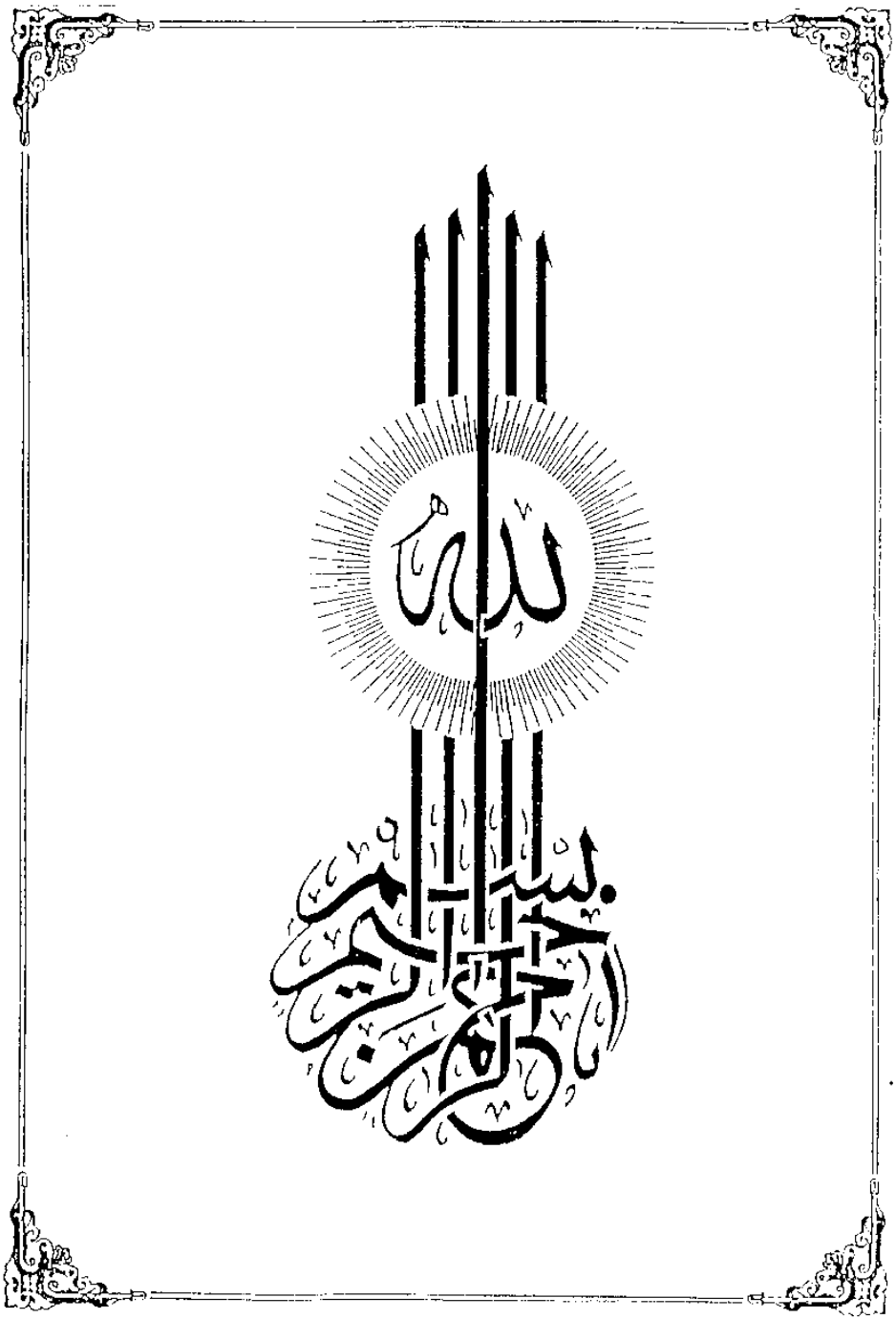

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Introduction and Aim of the Work

INTRODUCTION:

Aminoglycosides represent a major group of bactericidal drugs which kept its place in the medical field since 1945. This group includes gentamicin, tobramycin, amikacin, netilmicin, kanamycin and neomycin and others *(Jawetz, 1992)*. However, the clinical use of aminoglycosides is limited chiefly by their nephrotoxicity *(Lerur et al., 1984)*. In some series, up to 7% of cases of acute renal failure in hospitalized patients were due to aminoglycosides and in more recent studies the overall incidence of aminoglycoside induced nephrotoxicity was 5-10% of recipients *(Appel, 1990)*.

Results of animal studies have demonstrated that calcium dependent events are involved in aminoglycoside nephrotoxicity. Calcium has been shown to inhibit the uptake and binding of aminoglycosides to the renal brush border luminal membrane in vitro and supplementary dietary calcium attenuates experimental nephrotoxicity *(Benett et al., 1984; Humes et al., 1986)*.

AIM OF THE WORK:

The experimental study aimed to evaluate the nephrotoxic potential of tobramycin then to find out the effect of concomitant use of the calcium channel blocker verapamil on tobramycin induced nephrotoxicity.

The theoretical part of the work is a review of pharmacokinetics, pharmacodynamics, therapeutic uses and adverse effects of both tobramycin and verapamil.

Review of Literature

REVIEW OF LITERATURE

I. Tobramycin

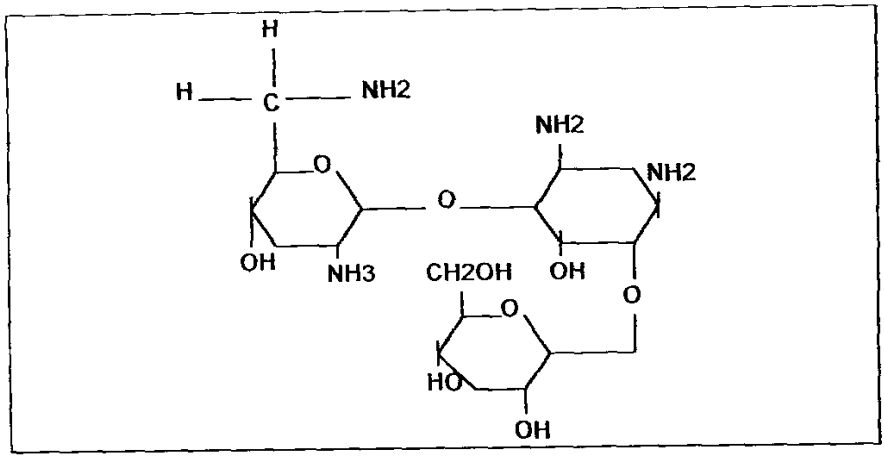
Historical Review:

The first public announcement of the discovery of streptomycin was made by *Schatz, Bugie, and Waksman in 1944. In 1949, Waksman* and Lechevalier isolated a soil organism, streptomyces fradiae, which produced a group of antibacterial substances that were named neomycin. On the other hand, kanamycin, an antibiotic elaborated by streptomyces kanamyaticus was produced and isolated by *Umezwa and co-workers in 1957. Later on, in 1963,* gentamicin was first studied and described by Weinstein and his colleagues.

Tobramycin is one of several components of an aminoglycoside complex (nebramycin) that is produced by streptomyces tenebrurius and it was introduced into clinical practice in the 1970s *(Sande andMandell, 1991).*

Chemistry:

Tobramycin consists of two aminosugars linked to a centrally located 2-deoxystreptamine moiety; one of these is a 3-aminohexose *(Sande and Mandell, 1991)*.



Chemical Properties:

Tobramycin is a white or almost white hygroscopic powder. It is soluble in water and is very slightly soluble in ether. A 10% solution in water has a pH of 9.0 to 11. It should be stored at a temperature not exceeding 25°C in air tight containers *(Reynolds, et al., 1993)*.

Pharmacokinetics:

* **Absorption:**

Being a highly polar cation, tobramycin is absorbed poorly or not at all from the intact gastrointestinal tract but absorption is increased if ulcerations are present. Less than 1% of a dose is absorbed following either oral or rectal administration *(Edson and Terrell, 1991)*.

On the other hand, tobramycin is rapidly absorbed from intramuscular sites of injection and a peak serum level is attained within 30 minutes. In critically ill patients, especially those in shock, absorption of the drug may be reduced from intramuscular sites because of poor perfusion *(Neu, 1987)*.

Instillation of tobramycin into body cavities with serosal surfaces may result in rapid absorption and unexpected toxicity *(Dee and Kozin, 1987)*.

* **Distribution:**

Tissues:

Because of its polar nature, tobramycin is largely excluded from most cells. So, its concentrations in tissues and secretions are low. High concentrations are found only in renal cortex and also in the endolymph and perilymph of the inner ear. The high levels

may contribute to the nephrotoxicity and ototoxicity caused by tobramycin *(Fikes et al., 1994)*.

Protein Binding:

Binding of tobramycin to serum proteins is low and it has been estimated to vary from zero% *(Gorden et al., 1989)* to 25% *(Naber et al., 1989)*. Serum protein binding of tobramycin and other aminoglycoside antibiotics increases progressively with decreasing concentrations of the divalent cations, calcium and magnesium.

In cerebrospinal fluid (C.S.F.), levels less than 10% are achieved. This value may approach 20% in meningitis. Higher concentrations in neonates are explained by immature blood brain barrier *(Strausbaugh et al., 1987)*. In animals with induced bacterial meningitis, corticosteroid pretreatment reduces tobramycin concentration in the C.S.F. but this has no deleterious effect on the course of treated experimental meningitis *(Scheld and Brodeur, 1990)*. However, in animals rapid infusion of manitol into the internal carotid artery causes osmotic disruption of the blood brain barrier and this enhances penetration of tobramycin into the C.S.F. and the brain tissue *(Perkins and Strausbaugh, 1989)*.

Tobramycin levels are low in peritoneal fluid but they usually reach 50% or more of simultaneous serum levels in patients with ascites and bacterial peritonitis *(Gerding et al., 1990)*.

The drug penetrates well into the synovial fluid even in the absence of bacterial infection where concentrations consistently exceed 50% of the serum level *(Dee and Kozin, 1987)*.

Tobramycin passes into bronchial secretions but concentrations are only 25-50% of simultaneous serum levels. In patients with pneumonia, mean concentrations of tobramycin in bronchial secretions are almost twice those found in normal subjects *(Alexander et al., 1992)*.

Also, in patients with cystic fibrosis, tobramycin penetrates the sputum where after a period, it accumulates *(Mendelman et al., 1985)*. Tobramycin reaches satisfactory concentrations in non-inflamed human interstitial fluid *(Carbon et al., 1992)*.

Distribution Kinetics:

The normal volume of distribution (Vd) of tobramycin is 0.25 L/Kg, so it is 25% of lean body weight and approximated the volume of extracellular fluid *(Kisor et al., 1992)*. Variations in Vd have been demonstrated in special patient populations. In the elderly, the Vd was calculated to be 0.35-0.37 L/Kg *(Lackner and*