EXPERIMENTAL STUDIES ON BLOOD, CEREBROSPINAL FLUID AND PERILYMPH KANAMYCIN LEVELS IN RELATION TO BRAINSTEM AUDITORY EVOKED POTENTIALS

A THESIS SUBMITTED FOR PARTIAL FULFILLMENT
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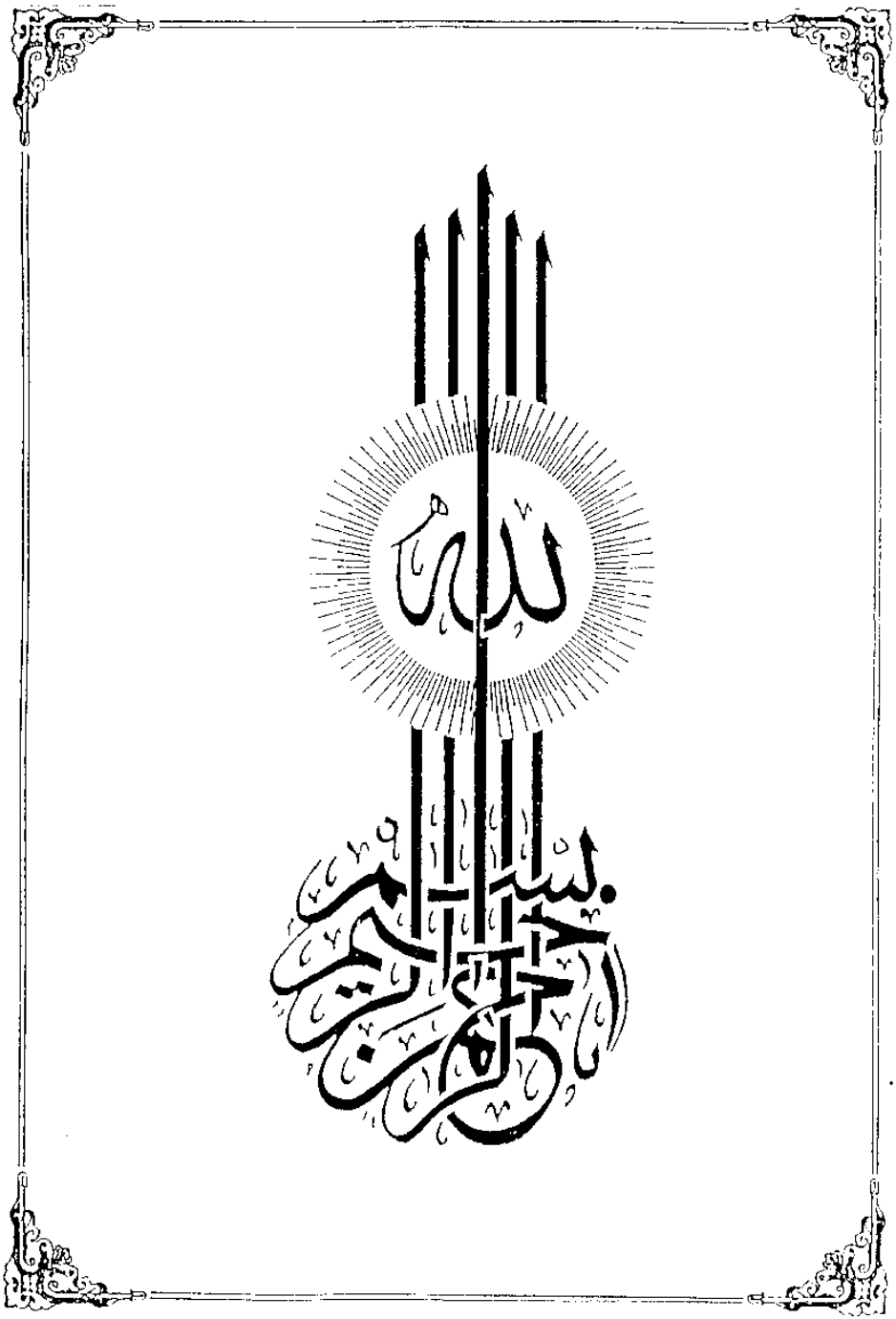
TO THOSE PEOPLE
WHOSE DEVOTION, UNDERSTANDING AND ECOURAGEMENT
MADE THIS WORK POSSIBLE



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FORWARD

This study evaluates the effectiveness of Brainstem Auditory Evoked Potentials [BAEP] in monitoring aminoglycoside therapy. The purpose of this work was to examine the potenial of BAEP as a predictor of aminoglycoside ototoxicity. This study also had the following objectives :

1- To document BAEP changes as a result of ototoxicity.
2- To determine the relationship between BAEP changes and dosage and duration of the drug.
3- To determine the relationship between BAEP changes and serum, cerebrospinal fluid and perilymph drug levels.
4- To study the reversibility of ototoxic BAEP chnges.
5- To study delayed ototoxic changes.

A pilot study was first carried out to establish methodology, solve unexpected technical problems and test the validity of the hypothesis. Results suggested minor changes in the original experimental plan. A major problem was in defining experimental ototoxicity. It was decided to use sensory hair cell loss as objective evidence of ototoxicity. Accordingly, this part was added to the study.

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CHAPTER 1

INTRODUCTION
and
REVIEW
OF THE LITERATURE

1.1. INTRODUCTION

The action of any substance on an organ can be beneficial or detrimental, depending on many factors. In the inner ear [cochlea and vestibular labyrinth], certain drugs or chemicals which are sometimes harmful are called ototoxic. Ototoxicity is "the tendency of certain therapeutic agents and other chemical substances to cause functional impairment and cellular degeneration of the tissues of the inner ear, and especially of the end organs and neurons of cochlear and vestibular divisions of the VIIIth cranial nerve" [Hawkins 1976].

The aminoglycosides are valuable antibiotics, but can be ototoxic. They are very effective against different microbial infections, especially those caused by *Pseudomonas aeruginosa* and enterobacteriaceae which often show resistance to other commonly used antibiotics [Young and Hewitt 1973, and Karney et al. 1973]. Many severe infections, especially in hospitalized patients with altered host defences, are caused by gram-negative bacilli which require aminoglycosides [DuPont and Spink 1969, and McGown et al. 1974]. Bacteria isolated from patients with disseminated tumours, leukaemias, haematosarcomas and other debilitating diseases show good response to aminoglycosides, either alone or in combination with other antibiotics [Klastersky et al. 1974, and Bodey and Rodriguez 1973]. Patients in neonatal care, infectious disease, dialysis and burn units frequently are given aminoglycosides. Streptomycin

also is commonly used in treating tuberculous infections.

Aminoglycoside toxicity has been identified since the beginning of the 1940s when streptomycin was first introduced to treat tuberculosis. In an attempt to lessen the toxicity of streptomycin and increase the efficacy of this new group of antibiotics, other aminoglycosides were discovered in the following order: neomycin [1949], kanamycin [1957], gentamicin [1963], tobramycin [1967], amikacin [1972] sisomycin and netilmicin [late 1970s] [Quick 1980]. All of these drugs are potentially ototoxic.They may affect the cochlea, the vestibular end-organ or both systems, and many of them are nephrotoxic [Table 1.1] [Hawkins et al. 1976].

Physicians are always faced with a critical question: How should one monitor the potential for aminoglycoside ototoxicity? To answer this question, a brief review of the pharmacokinetics and mechanism of toxicity of aminoglycosides will be discussed first.

1.2. PHARMACOKINETICS OF AMINOGLYCOSIDES

Aminoglycosides are poorly absorbed from the gastrointestinal tract; therefore they are administered parenterally, either by the intravenous or intramuscular route. They are distributed into the extracellular fluids. Aminoglycosides do not undergo significant degradation in the body and are excreted as such almost exclusively via the kidneys.

In animals following one single injection, the serum level of the aminoglycoside rises rapidly reaching a peak in 30-60 minutes, and then

Table 1.1

Aminoglycoside Toxicity

OTOTOXICITY	NEPHROTOXICITY
Cochleotoxicity	
Neomycin	Neomycin
Kanamycin	Gentamicin
Amikacin	Kanamycin
Sisomycin	Tobramycin
Vestibulotoxicity	
Streptomycin	
Vestibulo-cochleotoxicity	
Dihyrostreptomycin	
Gentamicin	
Tobramycin	
Netilmicin	

After Hawkins 1976
Drugs are arranged in a descending order of severity of toxicity.

decreases in a sequential manner to a negligible amount over the next six hours. The serum half life [$t_{1/2}$] is usually about three hours [Federspil et al. 1976, and Quick et al. 1976]. The concentration of the drug in the inner ear fluids following a single injection increases slowly to a peak level in three to six hours. It remains in the perilymph for a considerably longer period of time, then falls to a negligible amount in 24-36 hours. The average $t_{1/2}$ in perilymph for different aminoglycosides is about 11 hours [Federspil et al. 1976, and Lerner and Matz 1980]. This slow elimination from the inner ear fluids has been clearly demonstrated in both man [Gottesberge and Stupp 1969] and animals [Stupp et al. 1967; Watanabe et al. 1971, and Tran Ba Huy et al. 1983].

On the other hand, repeated daily injections of aminoglycosides have shown higher concentrations in the perilymph [Stupp et al. 1967; Watanabe et al.1971, and Quick 1976]. Repeated injections may exceed adequate excretion by the kidneys; consequently, the serum level will rise and the end result will be higher concentration in the perilymph [Brummett et al. 1978a and Quick 1980]. However, Stupp and associates [1967 and 1973] showed that the accumulation of aminoglycosides in the inner ear following daily administration was not necessarily accompanied by simultaneous accumulation in the blood or other tissues.

The relationship between aminglycoside serum level and perilymph level in response to dosage has always been a controversial issue. Federspil et al. [1976] demonstrated aminoglycoside level in the perilymph

at a given time after injection to rise linearly with the dose over a twentyfold range. However, Stupp et al. [1967 and 1973] and Watanabe et al. [1971] demonstrated a direct relationship between dose of aminoglycoside and drug concentration in the blood [Linear Curve Relationship], but inner ear fluids showed a "Saturation Curve Relationship". They mentioned that a slight elevations of dosage led to a markedly greater increase of concentration in the inner ear, e.g., doubling the dose gave a tenfold increase in the perilymph until it reached a certain level, after which increasing the dose did not lead to further increases in the perilymph.

Concerning the dynamics of aminoglycosides in the cerebrospinal fluid [CSF], Vrabec et al. [1965] and Stupp et al. [1967] showed that aminoglycosides can appear in the CSF. On the other hand, Tuazon [1981] demonstrated that aminoglycosides were not distributed in the CSF.

1.3. MECHANISM OF AMINOGLYCOSIDE OTOTOXICITY

Aminoglycosides injure the hair cells of the inner ear by interfering with the synthesis of proteins and nucleic acids [Watanabe et al. 1971, and Gonzalez et al. 1972], and/or with lipids of the cell membranes [Schacht 1974 and 1976]. The precise mechanism by which aminoglycosides exert this toxic effect is not certain. Many theories have been proposed:

1. Blood-Labyrinth Barrier:

Hawkins [1973] suggested the presence of a haemato-labyrinthine barrier which may prevent the transport of undesirable blood-borne substances into the inner ear fluids. This barrier depends upon the integrity of the spiral ligament and stria vascularis which can be damaged by aminoglycosides. This theory is supported by the observation that some drugs are ototoxic only when applied locally in the ear, because they can not penetrate the blood-labyrinthine barrier, e.g., polymyxin and chloramphenicol [Stupp et al. 1973].

2. Aminoglycoside Retention In The Inner Ear Fluids:

The peculiar behavior of aminoglycosides in the inner ear and kidney, i.e., the tendency to accumulate with slow elimination, makes many authors attribute their ototoxicity to drug accumulation in perilymph [Vrabec et al. 1965 and Stupp et al. 1967]. Moreover, they suggested a correlation between the individual ototoxic potential of each aminoglycoside and its $t_{1/2}$ in the perilymph. The higher the concentration in the perilymph, the more toxic the aminoglycoside. However, the mechanism of aminoglycoside ototoxicity cannot be explained entirely by this phenomenon because of the following observations:

i. The same kind of behavior has been observed in the liver which is not believed to be influenced by aminoglycosides [Toyoda and Tachibana 1978].

ii. Cephazolin, an antibiotic known not to be ototoxic was found to accumulate in the inner ear fluids with slow excretion, even up to 24 hours [Tachibana et al. 1980].

iii. Aminglycoside ototoxicity may occur suddenly after several injections [Quick 1980].

iv. Brummett et al. [1978b] found netilmicin to be much less ototoxic than gentamicin although netilmicin has a longer $t_{1/2}$ in perilymph.

Therefore, accumulation of aminoglycosides may be fundamental, but the vulnerability of the tissues to these antibiotics could also contribute to ototoxicity.

3. Hair Cell Affinity To Aminoglycosides:

Ilberg et al. [1971] suggested that dihydrostreptomycin ototoxicity was in part due to the specific affinity of the drug for hair cell cytoplasm. Schacht [1979], using the affinity chromatography, was able to isolate aminoglycoside receptor sites from kidney and inner ear tissues. This receptor was found to be phosphatidyl inositol phosphate and diphosphate which control membrane-bound calcium responsible for membrane stability [Kai and Hawthorne 1969]. If aminoglycoside unites with the receptor, calcium is displaced, affecting the plasma membrane integrity. This may lead to entrance of the drug into the cell where it exerts further toxic effects.