THE ADVERSE RENAL EFFECTS OF AMINOGLYCOSIDES: A PILOT CLINICAL STUDY TO ISOLATE RISK FACTORS

by

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INTRODUCTION

Gentamicin has become the most widely used and extensively studied aminoglycoside in the United States. Commercially available gentamicin is produced by Micromonospora purpurea and is supplied as a mixture of the sulfate salts of Gentamicin C_1, Gentamicin C_{1a}, and Gentamicin C_2. Gram negative bacteria are implicated as pathogens in a majority of infections in hospitalized patients. Dr. Dennis Maki has estimated this figure to be seventy percent of pathogenic infections. The increase in incidence of gentamicin resistant strains of gram negative bacteria is well documented in the literature.[2,17,34,38,43] Due to this situation, the search for new aminoglycosides with gram negative activity and low toxicity is an ongoing process.

Sisomicin is an investigational aminoglycoside produced by Micromonospora inyoensis. Sisomicin closely resembles Gentamicin C_{1a}. Figure I illustrates the structural formula of sisomicin and Figure II illustrates the structural formula of the gentamicin complex. Studies of nephrotoxicity in the dog indicate that sisomicin is as nephrotoxic as Gentamicin.[1] Animal pharmacology indicates that sisomicin is equivalent to neomycin in neuromuscular blocking activity.[1] Sisomicin may produce greater vestibular toxicity than gentamicin.[1]

The microbial spectrum of sisomicin appears to be very similar to that of gentamicin when evaluated on both an In vitro and In vivo basis. However, In vitro evidence suggests that sisomicin is more active than gentamicin against strains of Pseudomonas aeruginosa, indole positive proteus and enterobacteriaceae.[1] Table I compares the bacteriostatic

and bactericidal concentrations of gentamicin and sisomicin on various test organisms. Bacterial strains resistant to gentamicin are usually resistant to sisomicin, although cross resistance is not always complete.[1,22]

There is no question that aminoglycosides cause nephrotoxicity in some patients who receive them. Falco, Hewitt, and a review article in "Drug Therapy" report the incidence of this untoward effect to be in the vicinity of five to ten percent of patients treated.[11,13,16] Two distinct types of aminoglycoside induced nephrotoxicity appear to exist.[16] The first is a gradual, transient decrease in renal function which is reversible in almost all cases when the aminoglycoside is discontinued. The second type of nephrotoxicity is an acute renal failure syndrome which is often associated with a ten to twelve day oliguric phase. This acute syndrome is not always reversible. In the reversible case, it may take three or four months to return to fifty percent of pretreatment renal function with no improvement beyond this level.[9,14]

The most common reporting format for aminoglycoside-induced nephrotoxicity in humans is a case study approach.[4,5,7,12,18,23,27,40] Frequently, the clinical course of one to fifteen specific patients who developed nephrotoxicity is presented. The tendency of these articles is to provide specific patient data separately rather than statistically analyzing multiple factors or trends. It is possible to review all of these articles simultaneously in order to develop a profile of implicated risk factors which appear frequently in these case reports. Falco and Hewitt have published articles which collate the specific patient data of numerous case studies.[11,16] However, these articles are not optimal

due to limitations encountered when data from numerous independent studies with varying data bases and methodologies is utilized. Table II contains a compilation by this author of implicated nephrotoxicity risk factors.

Within the past few years, clinicians have learned that gentamicin may accumulate in the body.[9,14] The mechanism for this accumulation is unknown, although it appears to be related to trough serum levels of drug greater than two to four micrograms per milliliter.[9,14] The mechanism of this accumulation of drug in the body is not yet resolved. In addition, when nausea, vomiting and state of hydration or dehydration are mentioned, no explanation with regard to duration of degree is offered. For this reason, the importance of fluid balance is not well documented in the literature. It has been shown in the literature that there is no clear relationship between total daily dose, duration of therapy, and nephrotoxicity.[11,16,42]

In 1971, Wilfert completed a review of the records of one hundred consecutive patients treated with gentamicin.[42] He concluded that patients receiving aminoglycosides required more extensive monitoring of renal parameters and identified the need for a large scale study to determine which patients have the greatest risk of developing nephrotoxicity. A comprehensive literature search has failed to produce a study which responds adequately to this need.

OBJECTIVES

The purpose of this pilot study was to conduct a comprehensive evaluation of the clinical course in a small patient population who received gentamicin or sisomicin during their hospitalization at University of Wisconsin Hospitals. The primary objective was to determine if nephrotoxicity risk factors could be isolated for further study. The plan was to examine twenty patients in order to provide the background and directional work for a future study of one hundred patients. Figure III contains the original project proposal which was submitted for advisory approval.

Secondary objectives were very important considerations in the design and direction of the study. One secondary objective was to determine if there was a correlation between various trends or patterns and specific events which occurred during the course of treatment. In addition, fluid balance and accumulation of drug in the body were specific parameters closely examined for significance. The final goal was to incorporate preliminary findings in newsletter format for dissemination to the pharmacy staff at University of Wisconsin Hospitals. Hopefully, this would assist the pharmacist to provide optimal monitoring of patients during aminoglycoside therapy.

METHODOLOGY

Twenty patients were examined as a subgroup of a phase three clinical trial comparing sisomicin and gentamicin. After these patients had fulfilled phase three admission criteria and had given their informed consent, they were randomized by Dr. Maki's group to determine which drug they received. Evidence of probable infection was required and patients treated prophylactically with gentamicin were excluded from both studies.

After patients were admitted to the phase three clinical trial, they were considered for admission to the nephrotoxicity study. The primary additional admission criteria included; the opportunity to collect the necessary parameters with the required frequency and a minimum of five days of gentamicin or sisomicin therapy.

Data was collected from the day preceding initiation of therapy to the day after therapy was discontinued. If a patient developed nephrotoxicity, data was collected periodically after therapy was discontinued to determine if the condition was reversible. If the toxicity was reversible, the time necessary for recovery and extent of return to pretreatment levels of renal function were recorded. Parameters were recorded in daily intervals to allow for evaluation of trends and patterns.

The individual patient data base was initiated with a review of the past medical history, with special attention given to previous renal function. The current medical history and problems were then reviewed and a current medication profile established. Medications and conditions which could affect parameters measured were noted.

(For example; steroids increasing blood-urea nitrogen). In addition, a profile of the fluid balance at the onset of aminoglycoside therapy was developed. Figure IV illustrates the actual data collection sheets.

Parameters with required frequencies included; a minimum of four serum creatinine and blood-urea nigrogen (B.U.N.) measurements paired on four different dates to allow calculation of four blood-urea nitrogen/serum creatinine ratios and a minimum of two sets of measured parameters to allow determinations of actual creatinine clearance. Actual creatinine clearances were calculated by use of the formula in Figure V.

Peak serum levels of drug were obtained from blood samples drawn one hour after administration of an intramuscular (IM) dose or immediately after the completion of infusion of an intravenous (IV) dose. Trough serum levels were obtained from blood samples drawn seven and one-half hours after the previous dose. Drug serum level assays were performed by Dr. Craig at the Veterans' Hospital. The dose interval for each patient was eight hours. The final parameters which were followed included; daily body weight, lowest blood pressure and highest temperature in a twenty-four hour period, urinary pH and daily fluid intake and output totals.

RESULTS

Twenty patients, twelve females and eight males, were studied. Nine patients received gentamicin, three females and six males, and eleven patients received sisomicin, nine females and two males. The mean age of the twenty patients was 50.55 years and the median age was 52.5 years. The mean age of the patients who received gentamicin was 51.22 years and the median age was 54 years. The mean age and median age of the patients who received sisomicin was 50 years. Table III illustrates these age distributions of the sample.

Six of the twenty patients (thirty percent) developed suspected aminoglycoside induced nephrotoxicity. Of these six patients, two developed the acute renal failure syndrome (one on sisomicin, one on gentamicin) and the remaining four patients developed gradual, transient decreases in renal function (one on sisomicin, three on gentamicin). The mean age of these six patients who developed suspected nephrotoxicity was 56.5 years and the median age was 59.5 years. Table IV illustrates the distribution of age, type of nephrotoxicity and drug received for these six patients.

The first case of acute renal failure was reversible and in one month after the drug was discontinued, the renal function returned to thirty-five percent of pretreatment levels. The second patient who developed acute renal failure expired due to multiple factors. Two of the four patients who developed gradual, transient decreases in renal function experienced reversal of the syndrome when the drug was discontinued. One month later, renal function in these patients returned to thirty-nine and fifty-five percent of pretreatment levels, respectively.

Table V illustrates the trend of creatinine clearance values in the three patients who experienced reversible episodes of toxicity. The remaining two patients who developed gradual, transient decreases in renal function expired due to multiple factors.

Patients were divided into the following groups; Group I, no toxicity (thirteen patients, sixty-five percent), Group II, probable aminoglycoside induced nephrotoxicity (six patients, thirty percent), and Group III, possible aminoglycoside induced nephrotoxicity (one patient, five percent).. Group II was divided into two subgroups; II-A, acute renal failure (two patients, ten percent), and II-B, gradual, transient decreases in renal function (four patients, twenty percent). Patients were alphabetically sorted into the appropriate group after careful evaluation of their clinical course and consultation with Dr. Dennis Maki. A cumulative master data sheet was developed in order to determine comparisons within a given group of patients and between patient groups. Figure VI illustrates the cumulative master data sheet which was utilized.

The results are presented in Table VI with the percentage of response to any one parameter within a group of patients. Comparisons were made between Group I (no toxicity) and Group II (probable toxicity). Since Group III (possible toxicity) contained only one patient, no comparisons were made with this group. The most interesting comparisons from the results are listed in Table VII as a subsection of Table VI. Statistical significance of the results is lacking due to the small sample size of the pilot study.

DISCUSSION

The parameters which distinguish Group I (no toxicity) patients from Group II (probable toxicity) patients indicate that older patients with dehydration either before or during treatment with gentamicin or sisomicin may be high risk patients. It is well known that renal function decreases with increasing age. Most clinicians appear to be aware of this fact. Currently, many patients who receive gentamicin are not monitored by daily fluid intake and output totals. In addition, body weights of patients are obtained with varying frequency from one nursing unit to another. In order to collect necessary data, these parameters were often prescribed for the patient through intervention by a member of the study team.

Insensible water losses are defined as loss of water from the body by way of the lungs, from the skin apart from sweat gland secretion and from sweat gland secretion which evaporates so quickly that dectable perspiration does not occur. Also, patients with fever have a greater water loss through the skin than the loss at their normal temperatures. No statements may be made concerning the effects of fever on water losses in these patients because this loss is impossible to measure.

With the present data, no comments may be made with regard to the patient's past medical history, history of present illness, previous renal function or urine analysis. No trends or differences between Group I and Group II patients are noted. The absence of hypotensive episodes was recorded in an attempt to rule out shock and decreased renal perfusion as the cause of nephrotoxicity.

Only three of twenty patients did not receive any of the implicated drugs listed in Table II. Therefore, no inference may be made concerning these drugs. The dose of drug on a milligram per kilogram basis was found to be meaningless due to varying regimens for degrees of renal function and frequent adjustment of a given patient's dose. It is not possible at this time to determine if accumulation of drug in the body is related to toxicity. Drug serum levels for several patients are not yet available from Dr. Craig's laboratory.

CONCLUSIONS

Despite the lack of statistical significance in the pilot study, there are interesting trends of certain parameters which warrant further investigation. There is a clinical need for a large study to resolve the question of importance of fluid balance during aminoglycoside therapy. Specifically, age, state of hydration at onset of therapy, nausea and vomiting, daily fluid intake and output totals, and daily weights should be followed to determine their statistical significance. Plans for this endeavor are now being formulated.

If significant factors which clinicians are unaware of could be identified, perhaps the incidence of nephrotoxicity could be decreased through improved patient monitoring.

TABLE I

COMPARISON OF BACTERIOSTATIC AND BACTERICIDAL CONCENTRATIONS OF GENTAMICIN AND SISOMICIN

	MIC (mcg/ml)		MBC (mcg/ml)	
Organism	Gentamicin	Sisomicin	Gentamicin	Sisomicin
Enterococcus sp. DA 800	2.5	2.5	3.5	3.5
Escherichia coli DA 3	1.5	2.0	3.0	3.0
Klebsiella pneumoniae ATCC 10031	3.5	2.5	4.5	3.5
Proteus vulgaris DA 2	5.0	3.0	7.0	7.0
Pseudomonas aeruginosa 14145	3.0	3.0	7.0	7.0
Pseudomonas aeruginosa DA 11	2.5	1.5	5.0	2.5
Streptococcus faecalis ATCC 10541	4.5	3.5	5.0	3.5
Streptococcus pyogenes C	3.0	3.0	7.0	5.0
Streptococcus pyogenes DA 15	2.5	2.5	5.0	3.5

MIC = Minimum Inhibitory Concentration (Bacteriostatic)

MBC = Minimum Bactericidal Concentration

TABLE II

COMPILATION OF FREQUENTLY IMPLICATED RISK FACTORS IN PATIENTS WHO DEVELOPED SUSPECTED AMINOGLYCOSIDE INDUCED NEPHROTOXICITY

RISK FACTOR	REFERENCE
Abnormal renal function parameters; or changes in; blood-urea nitrogen (BUN)	
serum creatinine	7, 10, 11, 16, 19, 22, 25, 27, 42
creatinine clearance	
Accumulation of drug in body	9, 11, 14, 19, 40
Age	7, 16, 19, 23
Dehydration or state of hydration	5, 13, 23
Drug therapy (concurrent)	
cephalothin (cephalosporins)	5, 7, 13, 14, 15, 16, 23
carbenicillin	20, 21
furosemide, ethacrynic acid	13, 27
methicillin	20, 21
Hypotension or shock	5, 7, 10, 11, 16, 19, 23, 27, 42
Nausea or vomiting	7, 13, 19, 27
Pre-existing renal disease	7, 11, 16, 19, 23, 27, 42
Urine analysis; proteinuria and/or casts	5, 7, 10, 11, 19, 25, 27, 42

TABLE III

AGE DISTRIBUTION OF PATIENTS

	Total Study (20 Patients)	On Gentamicin (9 Patients)	On Sisomicin (11 Patients)
Mean Age	50.55 Years	51.22 Years	50 Years
Median Age	52.5 Years	54 Years	50 Years

TABLE IV

DISTRIBUTION OF AGE, TYPE OF NEPHROTOXICITY AND DRUG RECEIVED IN SIX PATIENTS WHO DEVELOPED SUSPECTED AMINOGLYCOSIDE INDUCED NEPHROTOXICITY

Mean Age (6 Patients) 56.5 Years

Median Age (6 Patients) 59.5 Years

	Acute Renal Failure (2 Patients)	Gradual Renal Changes (4 Patients)
Gentamicin	One Patient	Three Patients
Sisomicin	One Patient	One Patient

TABLE V

TREND OF CREATININE CLEARANCE VALUES
IN CASES OF REVERSIBLE NEPHROTOXICITY

Patient A (Acute Renal Failure)		Patient B (Gradual Changes)		Patient C (Gradual Changes)	
Date	Creatinine Clearance	Date	Creatinine Clearance	Date	Creatinine Clearance
22Jan76	98.3 ml/min	22Nov75	75.8 ml/min	26Jan76	40 ml/min
26Jan76	22.8 ml/min	29Nov75	64.7 ml/min	31Jan76	26 ml/min
7Feb76	10 ml/min	4Dec75	37.2 ml/min	5Feb76	28 ml/min
26Feb76	34 ml/min	9Dec75	28.2 ml/min	7Feb76	18 ml/min
		12Dec75	16.3 ml/min	9Feb76	9 ml/min
		29Dec75	29.3 ml/min	25Feb76	22 ml/min

TABLE VI

COMPARISON OF EACH PARAMETER
BY PATIENT GROUP: PERCENTAGES

Parameter	GROUP I No Toxicity (13 Patients)	GROUP II Probable Toxicity (6 Patients)
Age, Sex	Mean 47.4 Years 6 Female, 7Male	Mean 56.5 Years 4 Female, 2 Male
Hypotensive Episode	69 % NO	66% NO
Nausea or Vomiting	69 % NO	33% NO
Dehydration at onset	23 %	50 %
Fluid Intakes and Outputs	100 % I>0	17 % I>0
Weight Changes	trend 7.7 % loss	trend 83 % loss
Temperature Changes	No Consensus	No Consensus
Accumulation of Drug	Data Unavailable	Data Unavailable
Urine Analysis	77 % NO CASTS	100 % NO CASTS
Concurrent Drugs	62% on one implicated drug	100 % on one implicated drug
Dose mg/kg	UNABLE TO DETERMINE	UNABLE TO DETERMINE
History of Present illness	No Common Factors	No Common Factors
Past Medical History	No Common Factors	No Common Factors

TABLE VII

INTERESTING COMPARISONS
(Subsection of Table VI)

	GROUP I (No Toxicity)	GROUP II (Probable Toxicity)
Mean Age	47.4 Years	56.5 Years
Nausea or Vomiting	31 % Yes	66.7 % Yes
Dehydration at onset	23 % Yes	50% Yes
Fluid Intakes Greater Than Outputs	100 %	17 %
Trend of Weight Loss	7.7 %	83 %

FIGURE I

SISOMICIN STRUCTURAL FORMULA

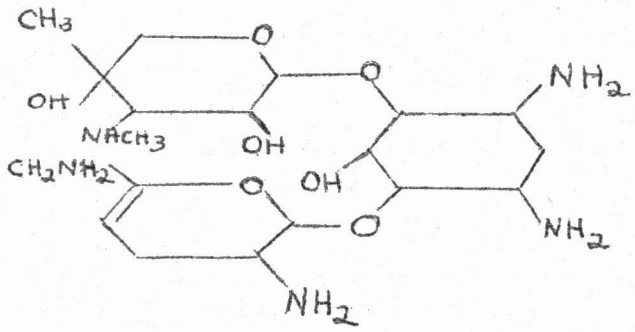
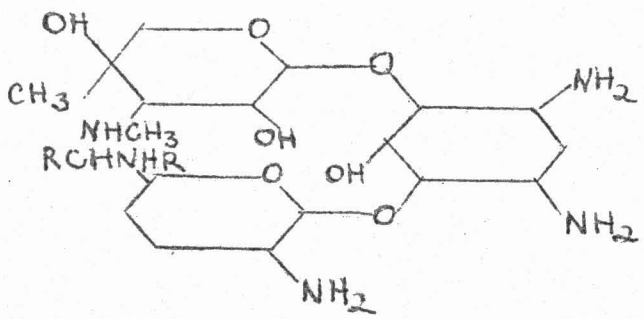


FIGURE II

GENTAMICIN COMPLEX STRUCTURAL FORMULA



Gentamicin C_1 ; R = CH_3 , R' = CH_3

Gentamicin C_{1a} ; R = H , R' = H

Gentamicin C_2 ; R = CH_3 , R' = H

FIGURE III

AMINOGLYCOSIDE NEPHROTOXICITY

PROJECT PROPOSAL

I. Purpose:

A) To explore the relative nephrotoxicity of gentamicin and sisomicin,

B) Examine factors which may contribute to aminoglycoside nephrotoxicity, with special attention given to the patient's state of hydration,

C) Determine optimal methods to monitor aminoglycoside therapy in order to reduce nephrotoxicity.

II. Methodology:

A) Complete a literature search, including animal pharmacology, to determine current knowledge of aminoglycoside nephrotoxicity and the individual agents gentamicin and sisomicin.

B) Define criteria for patient study admission criteria and parameters to be monitored for data collection. (See Attachment A)

C) Conduct a concurrent review of a statistically significant number of patients receiving gentamicin or sisomicin, as a subgroup of Dr. Maki's sisomicin clinical investigation, at University of Wisconsin Hospitals.

D) Statistically analyze the results to determine the clinical significance of the study objectives.

E) Disseminate the results to medical and pharmacy staff if clinical significance is discovered.

III. Drugs to be examined:

A) Gentamicin

B) Sisomicin (investigational drug)

IV. Principal Investigators: Michael Flagstad, R.Ph. and Dennis Maki, M.D.

V. Advisors: Dennis Maki, M.D., David Angaran, M.Sc., R.Ph., and David Perlman, PhD.

ATTACHMENT A

Patient Study Admission Criteria

1. Fulfillment of admission criteria for Dr. Maki's Sisomicin clinical investigation

2. Informed consent of patient to above

3. Ability to collect data on parameters indicated on nephrotoxicity data sheet

FIGURE IV

NEPHROTOXICITY DATA SHEET

NAME _____ DRUG _____

AGE _____ DOSE _____

HEIGHT _____ ROUTE _____

WEIGHT _____ HOW LONG ON? _____

FRAME _____ LOADING DOSE? _____

UNIT _____ HISTORY NO. _____

PMH (Check for History of Renal Function) _____

_____

_____

CURRENT MEDICAL HISTORY/PROBLEMS _____

_____

_____

CURRENT MEDICATION PROFILE _____

_____

_____

CURRENT FLUID STATUS (I & O at Onset of Therapy) _____

_____

_____

CURRENT PHYSICAL SIGNS (e.g. N,V,D, Increased Losses, Decreased Intake, Rales)

_____

_____

_____

PARAMETERS TO BE MONITORED _____

_____

_____

TEST	DATE							
Serum Creatinine								
BUN								
BUN/Creatinine								
Na								
Urine pH								
8Hr.Cr.Cl. (Base)								
8Hr.Cr.Cl. $\overline{p}$ Drug								
Drug peak								
Drug trough								
Drug urine								
Intake								
Output								
Temperature								
Daily Weights								
BP								

FIGURE V

FORMULA FOR CALCULATION OF ACTUAL
CREATININE CLEARANCE FROM MEASURED PARAMETERS

$$\text{Creatinine Clearance (ml/min)} = \frac{[U] \cdot V}{[P]}$$

[U] = Concentration of creatinine in collected urine (mg %)

$$V = \frac{\text{Volume of Urine in collection period}}{\text{Time in collection period (minutes)}}$$

P = Serum Creatinine (mg %)

FIGURE VI

CUMULATIVE MASTER DATA SHEET

Parameter	GROUP I (13 Patients) I-1, I-2, I-3 .... I-13	GROUP II (2 Patients) II-A-1, II-A-2	GROUP II (4 Patients) II-B-1 .. II-B-4
Age, sex			
Hypotensive episode			
Nausea or Vomiting			
Dehydration at onset			
Intake & output			
Weight changes			
Temperature changes			
Accumulation of drug			
Changes in serum creatinine			
Changes in creatinine clearance			
Urine analysis			
Concurrent drugs			
Dose (mg/kg)			

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