EFFECTS OF BODY WEIGHT AND COMPOSITION ON GENTAMICIN VOLUME OF DISTRIBUTION

By

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B.Sc.(Pharm), The University of Alberta, 1981

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE in

THE FACULTY OF GRADUATE STUDIES (Faculty of Pharmaceutical Sciences) Division of Clinical Pharmacy

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

August 1988

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Date **October 10, 1988**
ABSTRACT

Gentamicin is an aminoglycoside antibiotic that possesses bactericidal activity against many gram-positive and gram-negative organisms. Clinically, it is used most often to treat life-threatening infections due to Pseudomonas, Proteus, and the Klebsiella-Enterobacter group.

A relationship between gentamicin serum concentrations and clinical response has been demonstrated. Toxicities, notably ototoxicity and nephrotoxicity, are also associated with serum concentrations. Gentamicin is given intermittently either intramuscularly or intravenously resulting in peak and trough concentrations. The therapeutic range is defined as peak concentrations between 4-15mg/L (depending in part on the site of infection and the susceptibility of the infecting organism), and trough concentrations less than 2mg/L (to minimize toxicity).

Gentamicin distributes into a space similar to the extracellular fluid volume (ECFV). Pathophysiologic changes which alter the extracellular fluid compartment also alter gentamicin volume of distribution (Vd). One intrinsic factor known to alter gentamicin Vd is obesity. Leanness is also thought to alter gentamicin Vd but its effect has not been quantitated.

The objectives of this study were to: 1) accurately describe a Vd in "normal" patients, that is, those with no factors known to alter gentamicin volume of distribution; 2) determine if there is a continuous
linear relationship between gentamicin volume of distribution (L/kg) and percent body fat; 3) determine if that relationship is associated with changes in ECFV; and 4) develop a formula for predicting Vd in a similar patient population.

Twenty patients with no extrinsic factors known to alter gentamicin Vd participated in the study. Five blood samples were drawn around one steady state dose of gentamicin. A one-compartment model was used to calculate Vd. Tritiated water and anthropometric measurements were conducted simultaneously to provide estimates of body composition. Together these values were used to examine the relationship between gentamicin Vd and body composition.

We have described a Vd for gentamicin that is larger but no less variable than is currently used to determine initial dosage regimens. This volume may be larger either due to the selection of patients or method of serum gentamicin analysis. This larger volume should be used to calculate empiric dosage regimens for similarly selected patients to decrease the risk of treatment failure.

We were not able to describe a linear relationship between percent body fat and gentamicin volume of distribution. We have postulated several reasons as to why this relationship could not be detected; 1) the sample size may not have been large enough, 2) the relationship is not important in patients who are not at extremes of weight, or 3) the variations caused by changes in body composition were not as significant as other factors that may cause fluid alterations in hospitalized patients.
There was a strong correlation between gentamicin Vd and total body water noted. Having eliminated all patients in whom the relationship between total body water and ECFV could not be assumed to be normal and constant, we have indirectly demonstrated a strong relationship between ECFV and gentamicin Vd. This relationship still leaves variability in gentamicin’s distribution characteristics to be explained.

The predictive formula is based on measurements of height, weight, and a larger Vd \([L/kg(\text{ideal body weight})]\) than has previously been used. The predictive formula recommended for clinical use in adults is \(Vd=0.30L/kg\) (Dosing Weight). Dosing weight equals ideal body weight (IBW) when actual body weight (ABW) is \(< IBW\), or \(0.4(ABW-IBW)+IBW\), when ABW is \(> IBW\). The consequences of estimating a larger Vd are that patients empirically would receive larger doses than are currently being administered, thus more patients should obtain therapeutic serum concentrations within the first 24 hours of therapy. This information will be useful in our attempts to optimize gentamicin therapy.
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SYMBOLS AND ABBREVIATIONS

ABW      Actual body weight
AUC      Area under the plasma concentration versus time curve
BUN      Blood urea nitrogen
C        Centigrade
CCR      Critical care recovery
CCU      Coronary care unit
cm       Centimetres
cpm      Counts per minute
CrCl     Creatinine clearance
dl       Decilitre
dpm      Disintegrations per minute
ECFV     Extracellular fluid volume
EMERG    Emergency
EMIT     Enzyme immunoassay
h        Hours
IBW      Ideal body weight
ICU      Intensive care unit
IM       Intramuscular
in.      Inches
IV       Intravenous
kg       Kilograms
L        Litres
LBM      Lean body mass
LFT      Liver Function Tests
Max      Maximum
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This thesis is dedicated to my parents, for giving me the courage to believe in my capabilities, and to my husband Mark, whose unfailing support and encouragement have carried me through to the completion of this thesis.
ACKNOWLEDGEMENTS

The author would like to thank Dr. Robin Ensom for suggesting the problem and for the time he has devoted to this program. Sincere thanks is also extended to Dr. Francis Rosenberg and Dr. Allan Belzberg for their enthusiasm, assistance, and for the time their very willing and capable staff donated to this project.

The author is grateful for the guidance and constructive criticism provided by Dr. Robert Rangno, Dr. Peter Jewesson and Dr. John Sinclair. The author is deeply indebted to Dr. James Axelson for the advice, encouragement and friendship provided throughout the course of this study.

The support and direction received from Dr. Gail Bellward has been greatly appreciated. The author would also like to thank fellow graduate students for their inspiration and humour.

The author is grateful for the fellowship received from Merck Frosst Canada and to the Vancouver Foundation for their financial support.
1. INTRODUCTION

1.1 CLINICAL APPLICATION

Gentamicin is a basic, water-soluble, aminoglycoside antibiotic complex. It was isolated from *Micromonospora* species in 1963 by Weinstein and co-workers (1), and is bactericidal for many gram-positive and gram-negative bacteria (1-5). Gentamicin is most often used to treat life-threatening infections due to gram-negative organisms, such as *Pseudomonas*, *Proteus*, and the *Klebsiella-Enterobacter* group (6,7).

Toxicities, notably ototoxicity and nephrotoxicity have been associated with its use since the first clinical trials (8,9). Since that time several studies have examined the relationship between serum concentrations, efficacy, and toxicity in an effort to maximize efficacy and minimize toxicity.

1.2 CONCENTRATION VERSUS RESPONSE

In determining the optimal dosing regimen for any drug, its efficacy must be balanced against its toxicities. Traditionally antibiotic doses have been determined based on ability to obtain peak concentrations that are above the minimum inhibitory concentration (MIC) of the infective organism. The dosing interval is determined by the half-life of the drug, or the length of time that the serum concentration is below the MIC of the causative organism.

Initially gentamicin was given intermittently, either at six (8), eight (5,9), or twelve (5) hour intervals.
Bodey et al. (10) proposed using continuous infusions for dosing aminoglycosides in neutropenic patients. In animals intermittent dosing was demonstrated to be as effective and less toxic than continuous infusions (11-13). Studies in humans are not comparable and have provided conflicting results (10,13). Intermittent dosing is the regimen most often recommended in humans.

In vitro, Gerber et al. (14) demonstrated by comparing continuous infusions to intermittent dosing, that survival of *Pseudomonas aeruginosa* was related to area under the concentration versus time curve (AUC). MacArthur et al. (15) and Jackson and Riff (16) have demonstrated that kill of *Ps. aeruginosa*, in vitro, occurred in at least two phases; an initial concentration dependant phase and a concentration independent phase. Specifically MacArthur and co-workers (15) found that a 1/10 log increase in serum concentration resulted in a 1 log increase in bacterial kill rate. This appears to indicate, in vitro, there is a relationship between concentration and survival of bacteria. It has not been determined whether total AUC or peak concentration is most important.

In vivo, several authors have related peak concentrations to efficacy (16-19). From these experiments therapeutic peak serum concentrations have been established as being between 4-15mg/L, depending on the site of infection and the infecting organism (16,17,19).

It is also essential that therapeutic concentrations be obtained early in therapy (16-19). Jackson and Riff in 1971 (16) demonstrated that an increasing proportion of their patients survived
as progressively higher concentrations of gentamicin were obtained. In 1974, Noone and Pattison (17) reported that in patients who had gram-negative septicemia, 10/15 survived, and all obtained peak serum concentrations of 5mg/L within the first 3 days of therapy. Of the 5/15 patients who died, only one reached a peak serum concentration of 5mg/L. Zaske and co-workers (18) found that if conventional dosage regimens were used for gentamicin the survival rate was 33%. Whereas, if individualized dosage regimens were established within 24 hours, patient survival increased to 64%. Moore et al. in 1984 (19), analyzed case reports from 4 prospective trials of gentamicin, tobramycin, and netilmicin. Eighty-nine patients had proven gram-negative bacteremia. They found a significantly larger proportion of patients (9/43) with subtherapeutic peak plasma levels drawn within 24-48 hours of starting antibiotic therapy died, compared to those who obtained therapeutic peak concentrations (1/41) within that same time period.

It has been established, in vivo, that peak concentrations are related to efficacy and that they should be obtained early in therapy. Whether there is an optimal peak concentration, or value for AUC, relative to the MIC, the minimum bactericidal concentration (MBC), or site of infection, that can be related to efficacy has not been established.

1.3 CONCENTRATION VERSUS TOXICITIES

Many authors have investigated the toxicities associated with gentamicin in an attempt to identify the cause(s). To date, a predictive relationship between serum concentrations and toxicities
has not been identified. However, several investigators have been able to demonstrate an association between serum concentrations and toxicities.

1.3.1 NEPHROTOXICITY

Gentamicin induced nephrotoxicity predominantly occurs within the proximal tubular cells (20,21), and most often manifests as a gradual rise in serum creatinine (SCr), or blood urea nitrogen (BUN), which is usually reversible upon discontinuation of therapy (9,22,23).

The incidence and risk factors for the development of nephrotoxicity in humans have been studied by several authors (24-28). The incidence reported varies depending on the population studied, and the definition of nephrotoxicity used. It is most often reported as occurring in approximately 10-20% of patients receiving gentamicin (24-26).

Risk factors have been assessed by several authors (23-26,29). Dahlgren et al., 1975 (24) were one of the first investigators to prospectively monitor nephrotoxicity associated with gentamicin therapy. They found nephrotoxicity was associated with trough serum concentrations >2mg/L.

Schentag and co-workers in 1982 (25), also examined gentamicin nephrotoxicity prospectively. Initially, patients were dosed based on nomograms, but subsequently they individualized dosage regimens to maintain peak concentrations between 4-10mg/L and troughs between 0.5-2.0mg/L. Nephrotoxicity was defined as an increase in SCr by
0.5mg/dl before or within 5 days of discontinuing therapy. They found no predictive relationship between total dosage, sex, initial blood levels, initial renal function, or duration of treatment and nephrotoxicity. There was a statistically significant difference between initial trough concentrations of patients who became nephrotoxic and those who were nontoxic. Final trough concentrations averaged 4.9±3.0mg/L in nephrotoxic patients compared to 2.1±1.7mg/L in nontoxic patients.

Moore et al. (26) also established risk factors for the development of nephrotoxicity. In their studies they maintained peak concentrations between 5-10mg/L but did not control trough concentrations. The factors found to be associated with nephrotoxicity were: high initial CrCl, peak aminoglycoside levels, age, sex, liver disease, and shock. In these studies all patients received the same dosage regimen and duration of therapy was short (6.3±3.1 days). In later studies it became apparent that duration of therapy was also important (23,29).

1.3.2 OTOTOXICITY

The ototoxicity noted as a result of aminoglycoside administration encompasses both cochlear and vestibular damage. Most authors report loss of function is due to a degeneration of the sensory hair cells (30,31). Hinojosa and Lerner, 1987 (32) recently demonstrated a decrease in the number of ganglion cells in two patients with gentamicin induced ototoxicity, but no alteration of the number of sensory hair cells.
Clinically significant vestibulotoxicity is reported more frequently than auditory impairment. In most instances vestibulotoxicity is reversible. In other cases balance can be maintained through reliance on visual and proprioceptive inputs. There are few reports of vestibulotoxicity that is permanent and incapacitating (33). Conversely, auditory impairment associated with gentamicin toxicity is usually permanent. It is most often associated high frequency hearing impairment (23), thus, is not often clinically apparent (9,23).

As with studies of nephrotoxicity, comparability of studies of gentamicin ototoxicity is complicated by the heterogeneity of patient populations, dosing methods, and assessment indices. Data from clinical reports to the Food and Drug Administration between 1962 and 1969 indicated the incidence of ototoxicity was approximately 2% (34). Two-thirds of those patients experienced vestibular toxicity, whereas, only one-third noted auditory impairment. In approximately half of the patients with auditory impairment vestibular toxicity was also noted (34). More recent studies of select populations have found the incidence of ototoxicity to be higher (20-50%) (23,35,36).

In 1971, Jackson and Arcieri (34) in their review of clinical trials reported that risk factors associated with the development of ototoxicity included: impaired renal function, daily dose mg/kg, and previous use of ototoxic drugs. Moore et al. in 1984 (35) prospectively examined 135 patients receiving one of the following aminoglycosides; tobramycin, gentamicin, or amikacin. Patients receiving gentamicin were individually dosed to maintain peak concentrations between 5-10mg/L. This trial revealed that duration
of therapy, total aminoglycoside dose, peak temperature, and bacteremia were associated with aminoglycoside ototoxicity.

In summary, although the incidence and factors which best predict toxicity depend on the population studied, as well as the definition of toxicity, it appears that either minimizing the dose (decreasing the AUC) or maintaining low trough concentrations will assist in preventing gentamicin associated nephrotoxicity and ototoxicity.

Therefore, in order to maintain efficacy but decrease toxicity we must not only use substantial doses to achieve therapeutic values for peak or AUC, but also sufficient intervals to minimize toxicity.

1.4 PHARMACOKINETICS

1.4.1 ABSORPTION

Gentamicin is not well absorbed after oral administration (8). Similar serum levels are achieved by either intramuscular or intravenous injection (37,38).

Intramuscular absorption is known to be altered by blood flow (39). Therefore, diseases which alter blood flow to the muscle may delay the absorption of an intramuscularly administered drug. For this reason gentamicin is most often given by the intravenous route.

1.4.2 EXCRETION

Gentamicin is not metabolized. Elimination occurs predominantly through glomerular filtration (6,40), thus, renal failure decreases the elimination of gentamicin. A negative, linear
relationship between creatinine clearance and gentamicin serum half-life has been demonstrated (41-43).

1.4.3 PHARMACOKINETIC MODELLING

Gentamicin elimination, after an IV bolus injection, is best described by a three compartment model (44-46). After an IV bolus, a distribution phase (\( \pi \)), with a half-life equal to 0.556h (45), is seen. In the second phase (\( \alpha \)) gentamicin is removed from the serum via glomerular filtration and through distribution to the tissues. The half-life of elimination from this compartment is approximately two hours in patients with normal renal function. The third phase (\( \beta \)) depicts redistribution of the drug from tissue binding sites and subsequent elimination (46,47). Elimination from this compartment has a half-life of 80-110h in patients with normal renal function (46,47).

1.4.4 DISTRIBUTION

Gentamicin is a polar compound that has been reported to be 0 to 30 percent bound to plasma proteins (48-50). Because gentamicin is a polar compound and therefore will not penetrate cells easily, and because it is relatively unbound in blood, one would expect it to preferentially distribute into the extracellular fluid compartment. The association between gentamicin volume of distribution (Vd) and extracellular fluid volume (ECFV) has been made by several investigators (6,38,42,47). The apparent Vd used to base empiric dosage regimens on for normal healthy adults is 0.25-0.26L/kg (51,52).
1.4.5 FACTORS AFFECTING DISTRIBUTION

If gentamicin Vd is similar to the extracellular fluid compartment, one would expect the Vd to vary as the volume of the extracellular fluid compartment changes. Pathophysiological changes such as congestive heart failure (53), peritonitis (53-56), ascites (55,57), edema (58), and dehydration (53,59) alter the volume of the extracellular fluid compartment as well as the Vd of gentamicin.

Several other groups of patients including: critically ill patients with sepsis (60), surgical intensive care patients (61), patients post-operative (62), cancer patients (63), and patients with renal failure (6,64), all have been found to have an increased apparent Vd of gentamicin. Most of the investigators attribute the larger apparent Vd to expansion of the extracellular fluid volume, although none specifically measured the extracellular compartment.

1.4.6 DOSING METHODS

There has been a relationship established between serum concentrations and both response (16-19), and toxicities (24-26,34-36) of gentamicin. An optimal dosage regimen has not yet been established. Currently, gentamicin is given intermittently. Therapeutic peaks are described as between 4-15mg/L, while trough concentrations should be kept to less than 2mg/L.

Current approaches to dosing aminoglycosides involve estimating patient pharmacokinetic parameters to initiate therapy. In centres where the facilities and expertise are available, subsequent dosage adjustments are based on serum concentrations of the drug, which are
used to establish individual pharmacokinetic parameters. When individualized methods are not utilized, assumptions regarding the Vd have demonstrated to be a primary source of error (65). In order to improve our accuracy in obtaining therapeutic peak concentrations a less variable Vd in "normal" patients (those with no extrinsic factors known to alter gentamicin Vd) needs to be established. Once a Vd has been established in "normal" patients, one will be able to more precisely determine the effect of individual disease states on gentamicin Vd.

An intrinsic factor known to alter Vd is obesity (51,66-68). If the effects of leanness or obesity on the Vd of gentamicin were known, the accuracy of our estimation of Vd would be increased, as estimations of body composition are readily available in the clinical setting. This knowledge would also provide a more accurate description of the "normal" patient population and serve as a better comparison for future studies.

Optimal efficacy from gentamicin is related to obtaining therapeutic peak concentrations as soon as possible. This can be realized if one is able to estimate a patient's Vd of gentamicin accurately.
1.5 OBJECTIVES:

1. To accurately describe the gentamicin Vd in "normal" patients.

2. To determine if there is a continuous relationship between gentamicin Vd and percent body fat, through lean, normal and obese groups.

3. To determine if the association between volume of distribution of gentamicin and body composition can be attributed to changes in extracellular fluid volume.

4. To develop a clinically useful formula for estimating Vd using clinically available measurements (height and weight) which will accurately predict Vd for all body weights, in similarly selected patients.

1.5.1 VOLUME OF DISTRIBUTION IN "NORMAL" PATIENTS

Currently, 0.25-0.26L/kg is the assumed Vd of gentamicin used to predict dosage requirements in adult patients of average weight (51,52).

HEALTHY VOLUNTEERS: Regamey et al. (38) studied Vd when gentamicin was given either IV or IM in 4 healthy volunteers. They found that Vd after IV injection was 30.8±3.4%(SD) of total body weight and after IM injection was 27.9±3.9%(SD) of body weight. These values were not significantly different. Wilson et al. in 1973 (44) examined Vd in 7 young adults with normal renal and hepatic function, using tritiated gentamicin, and found it to be 28%±1.2 (SEM) of the body weight.
PATIENTS: Gentamicin volume of distribution was initially found to be similar to inulin (6). In 1972, Cutler et al. (42) described gentamicin Vd as being 24% of body weight. More recently, large variations in gentamicin Vd have been reported in patients. Barza and co-workers in 1975 (69) found that the apparent Vd varied six fold from 12-70% of body weight in 21 patients studied. In that same year Siber et al. (70) reported that Vd varied from 14.6 to 46.9% of body weight. Zaske, Cipolle, and Strate in 1980 (53) looked at 242 surgery patients. They reported Vd’s ranging from 0.06-0.63L/kg of actual body weight. This is a tenfold variation. Zaske and co-workers (71) examined kinetics in 1640 patients with gram-negative infections and found, in patients with normal renal function, the Vd varied from 0.04 to 0.74L/kg. The average Vd was 0.19±0.08L/kg. These studies, while reporting large variations in gentamicin Vd, did not exclude patients with conditions or factors now known to alter the Vd of gentamicin.

Clinical experience of the investigators indicates that large variations in gentamicin Vd are not seen in individuals presenting with an absence of factors known to alter the Vd of gentamicin. As yet, the Vd of gentamicin in these "normal" patients has not been firmly established. It is necessary to define the Vd in "normal" patients so that the effects of disease states (ie. sepsis) can be examined and compared to a less variable standard.

1.5.2 RELATIONSHIP BETWEEN GENTAMICIN VD AND PERCENT BODY FAT

EFFECT OF OBESITY: As early as 1964 it was noted by Erlanson and Lundgren (72) that obesity alters the Vd of aminoglycoside
antibiotics. Since that time several investigators (51,66-68) have examined the relationship between obesity and gentamicin Vd. These investigators have demonstrated that the Vd for obese patients is smaller per kg of actual body weight (ABW) as compared to normal weight individuals.

Hull and Sarubbi (51) looked at 40 patients, 10 of whom were defined as obese. In their study obese was described as 5.0kg above ideal body weight (IBW), (defined by Geigy's scientific tables (73)). They were able to decrease the error associated with their predictions of peak plasma concentrations by using IBW, instead of ABW to calculate Vd for obese subjects.

Schwartz and co-workers (66) examined gentamicin pharmacokinetics in 6 obese (ie. more than 30% above lean body weight as defined by Geigy's scientific tables (73)) and 6 normal volunteers. Their obese volunteers were on average 76% overweight. They reported a Vd for obese individuals as 0.185L/kg (ABW), while Vd for their normal weight volunteers was 0.244L/kg (ABW).

Korsager in 1980 (67) confirmed the findings of Schwartz et al. (66). This trial looked at 17 markedly obese patients (average of 82.7% overweight as defined by Geigy's scientific tables (73)), and 10 normal weight patients (average of 4.5% overweight). The apparent Vd in their normal patients was 0.232±0.05L/kg (ABW), while in the obese patients the apparent Vd was 0.177±0.028L/kg (ABW).

In 1981 Sketris et al. (68) studied the effects of obesity on gentamicin pharmacokinetics. Their patients included 30 normal weight patients (within 20% of IBW), and 30 obese patients (ie. more
than 30% above IBW) with an average of 51% above IBW. IBW was based on tables produced by Katch et al. (74). The apparent mean Vd of gentamicin in their obese group was 0.15L/kg (ABW) compared to 0.19L/kg (ABW) in their control group.

These studies demonstrate a decreased Vd L/kg (ABW) for obese individuals compared to normal weight patients. Schwartz et al. (66), Korsager (67), and Sketris et al. (68) proposed that gentamicin, being a polar compound distributes into extracellular fluid in both lean body mass and adipose tissue. Adipose tissue contains 12-13% extracellular fluid (75).

**EFFECT OF LEANNESS:** The relationship between weight and gentamicin Vd is less well defined in lean patients.

**Pediatrics:** Bravo et al. in 1982 (76) described the Vd in 10 malnourished infants as 0.46±0.02L/kg, while in their eutrophic infants (n=7) the Vd was 0.39±0.02L/kg. This was in close agreement with the mean Vd reported by Buchanan et al. (77) for 6 children with kwashiorkor. Buchanan et al. (77) found upon admittance to hospital the average Vd of gentamicin was 0.45L/kg.

**Adults:** Counts et al. (78) assuming a Vd of 0.26L/kg, reported they overpredicted peak serum levels, in 10/13 patients receiving gentamicin who were 10 to 35kg below their estimated IBW (Geigy's scientific tables (73)).

Tointon and co-workers in 1987 (79) retrospectively examined the charts of patients receiving gentamicin. Fifty-one patients were classified as lean (below IBW as determined from Devine's formulas
while 20 patients formed the control group. There were 9 patients in the lean group and 6 patients in the control group who received gentamicin. Amikacin or tobramycin had been given to the other patients. In the lean population the Vd was found to be 0.30±0.07L/kg (IBW), the range was 0.15-0.53L/kg. The control group had an average Vd of 0.25±0.04L/kg (IBW), the range was 0.17-0.34L/kg.

These studies in lean patients indicate that the apparent Vd of gentamicin is expanded compared to normal weight individuals.

The patient population being treated with gentamicin is usually comprised of patients with serious infections and/or severe diseases. Therefore, it is not uncommon to find them malnourished. Several previous studies have indicated that lean patients, constitute a significant portion of hospitalized patients (81-84). Willard et al. (84) reported on 200 hospital-admitted patients, 30.5% of the population studied were malnourished. In a recent study (85) comprising of 112 patients receiving gentamicin in community hospitals, the percentage of patients whose ABW was less than IBW was 30.3%, confirming that lean patients constitute a significant portion of the patients receiving this drug.

Studies to date indicate in the obese population the Vd in L/kg (ABW) is decreased compared to normal weight individuals. Conversely in lean patients the Vd in L/kg (ABW) is increased. In this study patients classified as lean, normal weight, and obese, were examined to determine if a relationship between volume of distribution and
body composition exists, in the absence of other factors known to alter Vd.

1.5.3 CORRELATION BETWEEN GENTAMICIN VD AND CHANGES IN ECFV

Gyselynck et al. in 1971 (6) found the Vd of gentamicin to be comparable to the space that inulin distributes into. Inulin is used to measure the extracellular fluid volume. These investigators concluded that the Vd was similar to the ECFV. Several authors have since determined the Vd in varying patient populations and found it to be 24-31% of total body weight, and concluded that this is similar to the ECFV (38,42,44).

The studies which have examined the effects of body composition and disease states on gentamicin Vd have assumed that deviations from normal were due to changes in the ECFV.

To date there is only one study (6) that has examined the relationship between gentamicin Vd and ECFV directly, by simultaneously measuring both compartments. In order to demonstrate that alterations in gentamicin Vd are associated with ECFV fluctuations, measurements of both gentamicin Vd and total body water (TBW) were performed on each subject. ECFV was assumed to be a constant fraction of total body water.

1.5.4 FORMULA FOR ESTIMATING GENTAMICIN Vd

Several methods of predicting dosage requirements are available. Studies have shown that calculating dosages based on individually determined pharmacokinetic parameters, such as volume of distribution, clearance, and half-life will best predict serum levels
(40,65,86-89). However, this method requires that doses be given, blood samples drawn, and serum gentamicin levels determined. Individualizing a patient's dosing requirements takes time and requires a knowledge of kinetics. In many centres the facilities and expertise are not available to perform this method.

When individualized patient parameters are not utilized, as is the case when therapy is initiated, assumptions regarding the Vd have demonstrated to be a primary source of error when making dosage predictions (53,69.89). When evaluated, it was found that predictive methods currently employed tend to underdose patients with severe infections 50% of the time (65). As well, approximately 20% of the patients dosed with these methods had serum concentrations of gentamicin that are associated with an increased risk of both ototoxicity and nephrotoxicity. With few exceptions these nomograms assume a constant value for Vd, and do not account for volume changes resulting from differences in body composition. In those nomograms which do make volume adjustments based on body composition, obesity is accounted for but not leanness.

If lean patients have a larger Vd [L/kg(ABW)] than normal weight patients, for any dose given, the serum level obtained will be lower. This leaves lean patients exposed to a greater risk of treatment failure because therapeutic concentrations are less likely to be obtained early in therapy.
SUMMARY: It is the intent of the study to:

1. accurately describe a volume of distribution for gentamicin in "normal" patients;

2. determine if the relationship between gentamicin volume of distribution and body composition is significant;

3. determine if this relationship is associated with extracellular fluid alterations; and

4. develop a predictive formula for estimating gentamicin dosage requirements.

With this information clinicians should be able to use this drug more effectively, maximizing its efficacy and minimizing its toxicities.
2.0 METHODS

Patients, with no extraneous factors known to alter gentamicin Vd, were selected from those receiving gentamicin at St. Paul's Hospital. Once informed consent was obtained, five blood samples were drawn, around one steady-state dose of gentamicin. Steady-state was assumed to have been obtained if, 5 half-lives of the drug had elapsed since therapy was initiated and the patient was stable in the previous 24 hours. A one-compartment model was used to calculate Vd. Tritiated water measurements conducted simultaneously provided estimates of total body water, and lean body mass. Anthropometric measurements provided a second estimate of body composition. Together, these values were used to examine the relationship between gentamicin Vd and body composition.

2.1 SITE

The study was conducted at St. Paul's Hospital, Vancouver, B.C.. St. Paul's Hospital is a 550 bed, acute care teaching hospital. As part of its services St. Paul's offers a drug measurement service (90). This service provides interpretations and recommendations for aminoglycoside therapy.

2.2 SELECTION CRITERIA

A list of all patients receiving gentamicin was generated daily by the pharmacy department. From this list patients were screened to determine eligibility. The selection criteria was as follows:
a. Absence of conditions known to alter the pharmacokinetic parameters (ie. congestive heart failure, amputation, liver failure, pregnancy or postpartum, patients less than 72 hours post-operative, and sepsis), as determined from the health records and from discussion with the attending physician.

b. Patients had normal values for the following laboratory indices:
   1. Creatinine Clearance (CrCl) (60 - 120ml/min/72Kg), estimated from Scr using the equation developed by Cockcroft and Gault (91);
   2. BUN (8-22mg/dl);

c. Normal Fluid Balance, identified by a combination of the following:
   1. Normal specific gravity (urine) 1.003 to 1.030;
   2. Normal fluid balance = 0 - 1500ml/24h; and
   3. Absence of signs and symptoms of dehydration, overhydration, edema, ascites, and vomiting or diarrhea.

d. Able to complete a series of physical measurements, including; height, weight, and skinfold measurements.

e. Absence of concurrent medication known to interfere with the analysis of gentamicin (ie. heparin, ticarcillin, carbenicillin or piperacillin).

2.3 GENTAMICIN DOSAGE AND ADMINISTRATION
MATERIALS: Gentamicin sulphate was supplied by Schering Canada Inc. Travenol Canada Ltd. manufactured the 100ml minibags of normal saline.

EQUIPMENT: Balance (Mettler PC 440); balance (Sartorius -model 1601AMP8-1); pharmaceutical weights (Henry Troemner Inc.); volumetric pump (IVAC 580 Starflow); infusion tubing (IVAC S9870).

METHODS: Gentamicin dosage requirements were determined by the attending physician in conjunction with the clinical pharmacokinetic consultation service (90). The dose of gentamicin sulphate was measured using a syringe. The syringe was weighed immediately before and after use to determine the weight of gentamicin, and thus the dose of gentamicin administered. The gentamicin was then added to a 100ml minibag of normal saline.

The infusion of the solution was supervised by the investigator, and controlled by an IVAC infusion pump. The infusion was given over a 60 minute period, and the exact time of the infusion was noted by the investigator. After the infusion was complete the minibag and tubing were immediately flushed with three, 15ml solutions of normal saline. The tubing contained approximately 14ml of solution. A sample of the solution remaining in the tubing was collected and frozen at -20°C until analyzed for its gentamicin content.

2.4 BLOOD SAMPLING
EQUIPMENT: Vacutainers® (Becton Dickinson SST 10ml clotted non-heparinized).

METHODS: Blood samples were drawn by a phlebotomist and timed by the investigator. Samples were drawn from the arm contralateral to the site of injection. A total of five samples were drawn per patient according to the following schedule:

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>TIME* (min)</th>
<th>VOLUME (ml)</th>
<th>TESTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₀</td>
<td>-30</td>
<td>10</td>
<td>gentamicin, 3-H₂O</td>
</tr>
<tr>
<td>C₁</td>
<td>120</td>
<td>10</td>
<td>gentamicin, 3-H₂O</td>
</tr>
<tr>
<td>C₂</td>
<td>210</td>
<td>10</td>
<td>gentamicin, 3-H₂O</td>
</tr>
<tr>
<td>C₃</td>
<td>300</td>
<td>10</td>
<td>gentamicin, 3-H₂O</td>
</tr>
<tr>
<td>C₄</td>
<td>360</td>
<td>10</td>
<td>gentamicin, 3-H₂O</td>
</tr>
</tbody>
</table>

* Relative to the start of the 60 minute infusion.

2.5 GENTAMICIN SERUM LEVEL DETERMINATIONS

MATERIALS: Reagents (EMIT, Syva Co., Palo Alto, CA).

EQUIPMENT: Centrifuge (Western Scientific-Silencer H-103NA series); spectrophotometer (COBAS B-10, Roche Analytical Instruments Inc. Nutley, NJ) fitted with a DENS (Data evaluation of non-linear standard curves) option.
METHODS: Samples were allowed to clot, then spun at 3000 rpm for 15 minutes. The serum was stored at -20°C until the assay was performed. Reagent preparation involved some modification of the manufacturer's instructions (92).

2.6 GENTAMICIN PHARMACOKINETIC PARAMETER CALCULATIONS

EQUIPMENT: SPSS:X2 (Statistical package for the social sciences) (92).

METHODS:

a) ELIMINATION RATE CONSTANT: Linear regression analysis of the log concentration versus time data, obtained during the elimination phase (samples C₁-C₄), was used to determine the patient's elimination rate constant (Kₑ). Patients were only considered for statistical evaluation if the correlation coefficient for the post-dose serum gentamicin levels (C₁-C₄) was greater than 0.95.

b) VOLUME OF DISTRIBUTION: A single compartment model was used to determine the volume of distribution.

EQUATION: Once steady-state had been achieved, the Vd was calculated using information obtained from the serum gentamicin
levels and the following equation (94):

\[ V_d (L) = \frac{K_o (1-e^{-K_d T})}{K_d[C_p - C_o (e^{-K_d t})]} \]

Where: 
- \( K_o \) = infusion rate (mg/h) 
- \( C_o \) = pre-dose concentration (mg/L) 
- \( C_p \) = peak serum concentration (mg/L) - determined by back extrapolation of the elimination curve, to the time of the end of the infusion. 
- \( K_d \) = elimination rate constant (h\(^{-1}\)) 
- \( T \) = infusion time (h) 
- \( t \) = time interval between \( C_o \) and the end of the infusion (h)

2.7 ACTUAL BODY WEIGHT MEASUREMENTS

EQUIPMENT: Single beam balance

METHODS: Measurements of body weight were taken within four hours of the start of the infusion. Patients wore only a hospital gown for this measurement.

2.8 IDEAL BODY WEIGHT CALCULATIONS

EQUIPMENT: Metric measuring tape; flat edge.

METHODS: Height was determined using a metric measuring tape and a flat edge. Patients stood erect, barefoot, heels together against a wall. Measurements were made to the nearest 1.0cm.
EQUATIONS: Calculations for IBW are based on formulas that incorporate sex and height (80). The formulas used to calculate IBW (kg) are:

Males \[= 50 + 2.3(\text{height (in.)} - 60)\]

Females \[= 45 + 2.3(\text{height (in.)} - 60)\]

2.9 BODY COMPOSITION - ANTHROPOMETRIC MEASUREMENTS

EQUIPMENT: Skinfold calipers (Harpenden\textsuperscript{R}, British Indicators Inc).

METHODS: The skinfold measurements were performed by the investigator, using skinfold calipers. The following anatomical sites were used; triceps, biceps and subscapular. Measurements were made in triplicate and the median values to the nearest 0.1mm were recorded.

EQUATIONS: Employing age-specific formulas, established by Durnin and Womersley (95), skinfold measurements were used to determine total body fat.

2.10 BODY COMPOSITION - TRITIATED WATER MEASUREMENTS

MATERIALS: Tritiated water (DuPont); Trichloroacetic acid (Fisher Scientific); PCS-phase contrast system (Amersham); and xylene (Fisher Scientific).
EQUIPMENT: Vortex mixer (Scientific Industries Inc.- model K-550-G); centrifuge (International Equipment Co.- model HN-S); automatic pipette (Clay Adams-Selectapette, 1ml volume); glass counting vials (Fisher Scientific); balance (Sartorius-Model 1601 AMP8-1); liquid scintillation counter (Beckman Instruments Inc.- Beckman LS9800).

METHODS: Percent adiposity was determined from total body water which was calculated from an isotope dilution equation. Tritiated water (300uCi) was administered orally to the patient. Serum drawn for gentamicin determinations was also used for tritium counting.

Sample preparation: Proteins were precipitated from the serum using a method employing 10% trichloroacetic acid, as described by Langham in 1956 (96). The tritium was counted on a Beckman counter. Each sample was counted in triplicate, 10 minutes each time. The average of the last two counts for each sample was used in calculations. Counting efficiency averaged 35%. Standards were prepared in the same manner as the samples and counted at the same time. Urine samples were prepared in the same manner as the serum samples.

EQUATIONS: Total Body Water was calculated from the isotope
dilution equation described below:
\[
TBW = \frac{C_1}{C_F}
\]
Where: TBW = Total body water (ml)

\[C_1\] = Activity of administered test substance (dpm)
\[C_F\] = Activity of the test substance (dpm/ml) after equilibrium has occurred.

Percent Adiposity was then calculated from TBW based on the following equations (97):
\[
\text{Lean Body Mass (LBM)} = \frac{TBW \times 100}{732}
\]
\[
\text{Percent Adiposity} = \frac{(ABW - LBM)}{LBM} \times 100
\]

2.11 DATA COLLECTION

For each patient all measurements were performed within a 12 hour period. All information was recorded on standardized data collection forms (see Appendix 1).

2.12 STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences, version X2 (93).

Pearson correlation coefficients for Vd [L/kg(IBW)] versus percent body fat (determined by skinfold caliper, and total body water measurements) were calculated.
Analysis of Vd (L) versus TBW was completed using linear regression analysis.

A stepwise multiple regression analysis was used to determine the relative contribution of the following predictive factors: weight, height, age, sex, SCr and percent adiposity, to the measured volume of distribution (L). Statistical significance for all tests was set at p<0.05.
3.0 RESULTS

3.1 DESCRIPTION OF SCREENED/EXCLUDED PATIENTS

Over a 26 week period, between March 1987 and January 1988, 666 patients receiving gentamicin were screened to determine eligibility. Of the 45 patients who were eligible to participate in the study, 22 refused; 23 patients were entered and of these, 20 patients were eligible for data analysis. Of the 3 remaining patients, 2 did not complete the tritiated water measurements, and 1 did not meet the criteria for normal CrCl.

Weights were obtained for 489/666 patients. They are classified according to body composition in Table 1.

Table 1 - PATIENTS CLASSIFIED ACCORDING TO BODY COMPOSITION

<table>
<thead>
<tr>
<th></th>
<th>LEAN (%)</th>
<th>NORMAL (%)</th>
<th>OBESE (%)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCREENED</td>
<td>53 (11.0%)</td>
<td>304 (62%)</td>
<td>132 (27%)</td>
<td>489</td>
</tr>
<tr>
<td>RECRUITED</td>
<td>2 (3.8%)</td>
<td>12 (3.4%)</td>
<td>9 (6.8%)</td>
<td>23</td>
</tr>
</tbody>
</table>

A categorical description of excluded patients is presented in Table 2.
<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>Total (%)</th>
<th>Lean</th>
<th>Normal</th>
<th>Obese</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors known to alter ECFV:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &lt;60ml/min/72kg</td>
<td>145 (22.4)</td>
<td>11 (21.6)</td>
<td>65 (22.3)</td>
<td>35 (28.5)</td>
<td>34 (19.2)</td>
</tr>
<tr>
<td>&lt; 72h POST-OPERATIVE</td>
<td>122 (18.9)</td>
<td>2 (0.3)</td>
<td>51 (17.5)</td>
<td>24 (19.5)</td>
<td>45 (25.4)</td>
</tr>
<tr>
<td>FLUID STATUS ABNORMAL</td>
<td>52 (8.1)</td>
<td>7 (13.7)</td>
<td>26 (8.9)</td>
<td>12 (9.7)</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>ABNORMAL LFT</td>
<td>24 (3.7)</td>
<td>5 (9.8)</td>
<td>8 (2.7)</td>
<td>7 (5.7)</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>AMPUTEE</td>
<td>10 (1.6)</td>
<td>0</td>
<td>4 (1.4)</td>
<td>0</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>SEPTIC</td>
<td>6 (0.9)</td>
<td>1 (2.0)</td>
<td>3 (1.0)</td>
<td>1 (0.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>ALBUMIN LOW</td>
<td>2 (0.3)</td>
<td>0</td>
<td>2 (0.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Factors not known to alter ECFV, but prevented patient participation:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLOOD AND BODY FLUID PRECAUTIONS</td>
<td>27 (4.2)</td>
<td>7 (13.7)</td>
<td>13 (4.5)</td>
<td>2 (1.6)</td>
<td>5 (2.8)</td>
</tr>
<tr>
<td>NEUTROPENIC/ANEMIC/THROMBOCYTOPENIC REFUSED</td>
<td>26 (4.0)</td>
<td>4 (7.8)</td>
<td>16 (5.5)</td>
<td>3 (2.4)</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>WEIGHT NORMAL</td>
<td>22 (3.4)</td>
<td>4 (7.8)</td>
<td>10 (3.4)</td>
<td>8 (6.5)</td>
<td>0</td>
</tr>
<tr>
<td>NOT ORIENTATED</td>
<td>18 (2.8)</td>
<td>1 (2.0)</td>
<td>8 (2.7)</td>
<td>2 (1.6)</td>
<td>7 (4.0)</td>
</tr>
<tr>
<td>UNABLE TO STAND</td>
<td>6 (0.9)</td>
<td>1 (2.0)</td>
<td>4 (1.4)</td>
<td>1 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>DID NOT SPEAK ENGLISH</td>
<td>4 (0.6)</td>
<td>0</td>
<td>2 (0.7)</td>
<td>1 (0.8)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td><strong>Technical reasons for exclusion:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU/CCU/CCR/EMERG</td>
<td>78 (12.1)</td>
<td>3 (5.9)</td>
<td>22 (7.5)</td>
<td>7 (5.7)</td>
<td>46 (25.4)</td>
</tr>
<tr>
<td>DISCHARGED/DISCONTINUED</td>
<td>33 (5.1)</td>
<td>3 (5.9)</td>
<td>17 (5.8)</td>
<td>5 (4.1)</td>
<td>8 (4.5)</td>
</tr>
<tr>
<td>TIMING OF DOSES</td>
<td>12 (1.9)</td>
<td>0</td>
<td>6 (2.1)</td>
<td>5 (4.1)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>COULD NOT CONTACT MD</td>
<td>8 (1.2)</td>
<td>0</td>
<td>4 (1.4)</td>
<td>3 (2.4)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>DRUG NOT GIVEN IV</td>
<td>8 (1.2)</td>
<td>1 (2.0)</td>
<td>2 (0.7)</td>
<td>1 (0.8)</td>
<td>4 (2.3)</td>
</tr>
<tr>
<td>CENTRAL LINE</td>
<td>7 (1.1)</td>
<td>1 (2.0)</td>
<td>4 (1.4)</td>
<td>0</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>UNKNOWN</td>
<td>11 (1.7)</td>
<td>0</td>
<td>3 (1.0)</td>
<td>6 (4.9)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>643</td>
<td>51</td>
<td>292</td>
<td>123</td>
<td>177</td>
</tr>
</tbody>
</table>
A demographic description of the patients eligible for data analysis is provided in Table 3.

Table 3 - PATIENTS ELIGIBLE FOR DATA ANALYSIS

<table>
<thead>
<tr>
<th>BODY COMPOSITION</th>
<th>AGE (years)</th>
<th>SEX (M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean</td>
<td>x = 52</td>
<td>2/0</td>
</tr>
<tr>
<td></td>
<td>SD = 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(46 &amp; 57)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>x = 43</td>
<td>5/5</td>
</tr>
<tr>
<td></td>
<td>SD = 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(22-75)</td>
<td></td>
</tr>
<tr>
<td>Obese</td>
<td>x = 55</td>
<td>4/4</td>
</tr>
<tr>
<td></td>
<td>SD = 18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(23-82)</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>x = 49</td>
<td>11/9</td>
</tr>
<tr>
<td></td>
<td>SD = 18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(22-82)</td>
<td></td>
</tr>
</tbody>
</table>

3.2 GENTAMICIN PHARMACOKINETIC PARAMETERS

The data used to estimate gentamicin volume of distribution and Ke (h⁻¹) for each patient are displayed in Table 4. A representation of the serum concentration versus time curve is displayed in Figure 1.

3.3 BODY COMPOSITION ESTIMATES

Anthropometric measurements used to estimate percent body fat according to Durnin and Womersley's formulas (95) are reported in Table 5. The mean value for percent body fat was 22.7±0.3% (8.9%-43.0%).

31
### TABLE 4 - GENTAMICIN PHARMACOKINETIC PARAMETERS

<table>
<thead>
<tr>
<th>Initials</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Dose (mg)</th>
<th>Infusion Time (h)</th>
<th>Gentamicin Serum Level Determinations (C=mg/L; T0=h predose; T1-T4=h postdose)</th>
<th>R</th>
<th>Ke (h⁻¹)</th>
<th>t1/2 (h)</th>
<th>Vd (L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PW</td>
<td>M</td>
<td>57</td>
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Figure 1 - Plot of Mean Log Concentration versus Time

Log Gentamicin Concentration (mg/L)

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Tritiated water measurements utilized in the estimation of LBM and percent body fat are shown in Table 6. The mean value for percent body fat using this method was 29.1±24.2% (-5.6%-78.9%).

3.4 VOLUME OF DISTRIBUTION IN "NORMAL" PATIENTS

The gentamicin volumes of distribution for each patient in [L/kg(ABW), L/kg(IBW), L/kg(LBM)] are reported in Table 7.

The mean Vd [L/kg(ABW)] was 0.30±0.08L/kg.

The mean Vd [L/kg(IBW)] was 0.31±0.06L/kg.

The mean Vd [L/kg(LBM)] was 0.36±0.07L/kg.

3.5 RELATIONSHIP BETWEEN GENTAMICIN Vd AND PERCENT BODY FAT

The relationship between Vd (L) and ABW, IBW, and LBM are depicted in Figures 2, 3 and 4 respectively. Correlation coefficients calculated for these three measurements of weight, indicate that LBM correlated best with Vd (r=0.739, p<0.001), followed by IBW (r=.617, p<0.01) and ABW (r=.404, p<0.05). In the clinical setting measurements of LBM are not practical, therefore estimates of body composition were compared to Vd [L/kg(IBW)] to determine if the predictive ability of IBW could be improved upon.

The calculated values for percent body fat (as determined by skinfold caliper (95) and tritiated water measurements (97)) are presented in Table 8. A statistically significant correlation between gentamicin Vd [L/kg(IBW)] and percent body fat (estimated
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<td>186785</td>
<td>42.29</td>
<td>57.8</td>
<td>37.7</td>
</tr>
<tr>
<td>MY</td>
<td>81.5</td>
<td>48</td>
<td>8708</td>
<td>192580</td>
<td>33.35</td>
<td>45.6</td>
<td>78.9</td>
</tr>
<tr>
<td>AA</td>
<td>82.0</td>
<td>51</td>
<td>6513</td>
<td>214440</td>
<td>49.77</td>
<td>68.0</td>
<td>20.6</td>
</tr>
</tbody>
</table>

| MEAN     | 67.2     |            |             |            | 39.15  | 53.4   | 29.1             |
| SD       | 12.9     |            |             |            | 9.63   | 13.1   | 24.2             |
| MIN      | 40.3     |            |             |            | 25.50  | 34.8   | -5.6             |
| MAX      | 86.9     |            |             |            | 60.36  | 82.4   | 78.9             |
TABLE 7 - VOLUME OF DISTRIBUTION DESCRIBED AS A FUNCTION OF WEIGHT

<table>
<thead>
<tr>
<th>BODY COMPOSITION</th>
<th>INITIALS</th>
<th>Ratio ABW/IBW</th>
<th>Vd [L]</th>
<th>Vd [L/kg(IBW)]</th>
<th>Vd [L/kg(ABW)]</th>
<th>Vd [L/kg(LBM)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAN</td>
<td>FW</td>
<td>0.59</td>
<td>15.1</td>
<td>0.23</td>
<td>0.39</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>TM</td>
<td>0.78</td>
<td>16.7</td>
<td>0.29</td>
<td>0.37</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>MEAN</td>
<td>0.69</td>
<td>15.9</td>
<td>0.26</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.09</td>
<td>0.84</td>
<td>0.03</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>NORMAL</td>
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<td>0.24</td>
<td>0.26</td>
<td>0.28</td>
</tr>
<tr>
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<td>0.29</td>
<td>0.36</td>
</tr>
<tr>
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<td>JD</td>
<td>0.93</td>
<td>31.6</td>
<td>0.31</td>
<td>0.34</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>DV</td>
<td>0.93</td>
<td>23.8</td>
<td>0.39</td>
<td>0.42</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>AW</td>
<td>0.97</td>
<td>25.9</td>
<td>0.36</td>
<td>0.38</td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td>KE</td>
<td>0.97</td>
<td>27.9</td>
<td>0.48</td>
<td>0.49</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>MS</td>
<td>0.97</td>
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<td>0.26</td>
<td>0.27</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>RE</td>
<td>1.10</td>
<td>16.5</td>
<td>0.28</td>
<td>0.25</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>RG</td>
<td>1.04</td>
<td>16.4</td>
<td>0.32</td>
<td>0.31</td>
<td>0.44</td>
</tr>
<tr>
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<td>DP</td>
<td>1.00</td>
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<td>0.22</td>
<td>0.29</td>
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<tr>
<td></td>
<td>MEAN</td>
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<td>0.32</td>
<td>0.40</td>
</tr>
<tr>
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<td>SD</td>
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<td>0.07</td>
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<td>0.08</td>
</tr>
<tr>
<td>OBESE</td>
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<td>0.28</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>AM</td>
<td>1.30</td>
<td>29.3</td>
<td>0.40</td>
<td>0.30</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>SS</td>
<td>1.41</td>
<td>16.7</td>
<td>0.33</td>
<td>0.23</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>LR</td>
<td>1.33</td>
<td>16.9</td>
<td>0.27</td>
<td>0.20</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>PJ</td>
<td>1.44</td>
<td>15.0</td>
<td>0.35</td>
<td>0.25</td>
<td>0.41</td>
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<tr>
<td></td>
<td>EL</td>
<td>1.14</td>
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<td>0.27</td>
<td>0.24</td>
<td>0.33</td>
</tr>
<tr>
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<td>MY</td>
<td>1.57</td>
<td>15.1</td>
<td>0.31</td>
<td>0.19</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>1.22</td>
<td>35.7</td>
<td>0.32</td>
<td>0.27</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>MEAN</td>
<td>1.34</td>
<td>21.8</td>
<td>0.33</td>
<td>0.25</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.13</td>
<td>7.2</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>MEAN</td>
<td></td>
<td>21.0</td>
<td>0.31</td>
<td>0.30</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td></td>
<td>6.4</td>
<td>0.06</td>
<td>0.08</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>MIN</td>
<td></td>
<td>15.1</td>
<td>0.22</td>
<td>0.19</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>MAX</td>
<td></td>
<td>29.3</td>
<td>0.48</td>
<td>0.49</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Figure 2 - Plot of Vd (L) versus ABW (kg)

Volume of Distribution (L)

\[ y = 0.145x + 9.79 \]

\[ r = 0.404 \]

\[ p < 0.05 \]
Figure 3 - Plot of Vd (L) versus IBW (kg)

Volume of Distribution (L)

\[ y = 0.27x + 2.48 \]

\[ r = 0.617 \]

\[ p < 0.01 \]
Figure 4 - Plot of Vd (L) versus LBM (kg)

Volume of Distribution (L)

\[ y = 0.26x + 5.59 \]

- \[ r = 0.739 \]
- \[ p < 0.001 \]

Lean Body Mass (kg)
### TABLE 8 - GENTAMICIN VOLUME OF DISTRIBUTION VERSUS PERCENT BODY FAT

<table>
<thead>
<tr>
<th>INITIALS</th>
<th>Vd(I) ([L/kg(IBW)])</th>
<th>DURNIN/WOMERSLEY (skinfold caliper)</th>
<th>PACE/RATHBUN (tritiated water)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FW</td>
<td>0.23</td>
<td>8.9</td>
<td>-5.6</td>
</tr>
<tr>
<td>TM</td>
<td>0.29</td>
<td>N/A</td>
<td>3.5</td>
</tr>
<tr>
<td>LT</td>
<td>0.23</td>
<td>17.0</td>
<td>6.5</td>
</tr>
<tr>
<td>DL</td>
<td>0.30</td>
<td>23.5</td>
<td>22.7</td>
</tr>
<tr>
<td>JD</td>
<td>0.31</td>
<td>17.0</td>
<td>-1.1</td>
</tr>
<tr>
<td>DV</td>
<td>0.39</td>
<td>18.1</td>
<td>4.0</td>
</tr>
<tr>
<td>AW</td>
<td>0.36</td>
<td>19.7</td>
<td>16.1</td>
</tr>
<tr>
<td>KE</td>
<td>0.48</td>
<td>21.4</td>
<td>17.4</td>
</tr>
<tr>
<td>MS</td>
<td>0.26</td>
<td>16.9</td>
<td>46.0</td>
</tr>
<tr>
<td>RE</td>
<td>0.28</td>
<td>30.9</td>
<td>63.0</td>
</tr>
<tr>
<td>RG</td>
<td>0.32</td>
<td>14.4</td>
<td>44.9</td>
</tr>
<tr>
<td>DP</td>
<td>0.22</td>
<td>27.8</td>
<td>29.6</td>
</tr>
<tr>
<td>FJ</td>
<td>0.35</td>
<td>24.2</td>
<td>14.4</td>
</tr>
<tr>
<td>AM</td>
<td>0.40</td>
<td>21.4</td>
<td>13.8</td>
</tr>
<tr>
<td>SS</td>
<td>0.33</td>
<td>40.4</td>
<td>62.6</td>
</tr>
<tr>
<td>LR</td>
<td>0.27</td>
<td>36.3</td>
<td>39.1</td>
</tr>
<tr>
<td>PJ</td>
<td>0.35</td>
<td>33.9</td>
<td>67.9</td>
</tr>
<tr>
<td>EL</td>
<td>0.27</td>
<td>25.1</td>
<td>37.7</td>
</tr>
<tr>
<td>MY</td>
<td>0.31</td>
<td>43.0</td>
<td>78.9</td>
</tr>
<tr>
<td>AA</td>
<td>0.32</td>
<td>15.0</td>
<td>20.6</td>
</tr>
</tbody>
</table>

**CORRELATION COEFFICIENTS**

- \(R = .0030\)  
- \(R = -.0703\)  
- \(p > .05\)  
- \(p > .05\)
from either anthropometric or tritiated water measurements) could not be demonstrated (Figures 5 & 6).

When the groups (lean, normal and obese) were compared with respect to Vd measured in L/kg (ABW, IBW, or LBM) using a Mann Whitney U test, the only significant difference found was between the lean and obese group when volumes were reported as L/kg(ABW), (p<.05, two tailed).

3.6 CORRELATION BETWEEN GENTAMICIN Vd AND ECFV

Linear regression analysis of gentamicin Vd (L) versus TBW produces a correlation coefficient of r=.739 (p<0.001). See Figure 7.

3.7 A PREDICTIVE EQUATION FOR GENTAMICIN Vd

A stepwise multiple regression analysis of gentamicin Vd (L) versus height, weight, age, sex, SCr, found height to be the only significant predictive variable (r²=0.36, F=10.29(df 1,18)).

A stepwise multiple regression analysis of gentamicin Vd (L) versus IBW, age, sex, SCr, found IBW to be the only predictive variable (r²=0.36, F=11.35, (df 1,18)).
Figure 5 - Plot of Vd [L/kg(IBW)] versus PBF (%)

PBF determined from Tritiated Water Measurements

\[ y = -0.00018x + 0.32 \]

\( r = 0.07 \)

\( p > 0.05 \)
Figure 6 - Plot of Vd [L/kg(IBW)] versus PBF (%)
PBF determined from Skinfold Caliper Measurements

Volume of Distribution [L/kg(IBW)]

$y = 0.00002x + 0.32$

$r = 0.003$

$p > 0.05$
Figure 7 - Plot of Vd (L) versus TBW (L)

Volume of Distribution (L)

y = 0.36x + 5.69
r = 0.739
p < 0.001
4.0 DISCUSSION

4.1 METHODS

The major difficulty encountered in the study was patient recruitment. In particular the number of recruited lean patients was significantly lower than the number of eligible normal weight or obese patients. A larger percentage of the lean patients were excluded because of fluid volume alterations, blood and body fluid precautions, abnormal liver function tests and neutropenia, anemia, or thrombocytopenia compared to the normal weight or obese groups. This may indicate that the larger volumes that are noted clinically in lean patients are due to factors other than weight.

The difficulties encountered in recruiting patients, and thus the small sample size limit the conclusions that can be drawn from this study. It was necessary to have the strict selection criteria which eliminated approximately 70% of the eligible patients, in order to meet our objectives. Therefore, ways in which recruitment could have been increased are: 1) have a larger population to sample patients from or 2) increase the recruitment of eligible patients, perhaps by having their physician discuss the study with them.

4.2 GENTAMICIN VOLUME OF DISTRIBUTION IN "NORMAL" PATIENTS

This study was designed to demonstrate that a less variable, more precise, volume of distribution for gentamicin could be described, through the elimination of factors known to alter
gentamicin Vd, in hospitalized patients. This would allow one to better estimate initial dosage requirements in the uncomplicated patient population, as well as serve as a baseline for evaluation of the effect of factors which alter gentamicin Vd.

Our results indicate that the volume of distribution of gentamicin in this population was $0.30 \pm 0.08 \text{L/kg(ABW)}$.

It is known that gentamicin Vd is best described by a three compartment model (44-46). In this study we have used a one compartment model to describe gentamicin Vd. Assuming a one compartment model may lead to an over-estimation of Vd (98). However, it is the model which is most practical in a clinical setting and, therefore, most frequently used to estimate volumes in various patient populations.

Gentamicin Vd in this study was calculated based on serum gentamicin concentrations which were assayed by EMIT. An excellent correlation between this methodology and other assays has been described (99-101), although differences have been noted (102). Therefore, the results of this study may not be strictly comparable with studies that have used other methods of analysis.

INTERPRETATION: This mean value is similar to that reported for normal healthy volunteers (38,44), but differs from those obtained by Zaske et al. (1980,1982) where 242 (53) and 1640 (71) patients respectively had serum gentamicin levels monitored. In these large
patient populations, the mean Vd described was 0.195L/kg (ABW) and 0.19±0.08L/kg (ABW).

Rotschafer et al. (102) has demonstrated that RIA (method of gentamicin analysis used by Zaske et al. (53,71)) consistently measured serum concentrations higher than EMIT. They found the calculated Vd of gentamicin was 25% lower when serum levels were measured using RIA compared to EMIT. This may explain the observed difference between Zaske et al’s (53,71) reported mean Vd and the mean Vd reported in this study.

Trials which have examined the correlation of the newer assays (EMIT, RIA, and fluorescent immunoassay) all have demonstrated excellent correlations with the disc diffusion technique (99). When the studies that described a relationship between gentamicin serum concentrations and response (16-19) were conducted, gentamicin serum concentrations were assayed by either by disc diffusion or radioenzymatic assay. As concentration-response information is not available from patients who have had serum levels assayed by EMIT, or RIA, we cannot determine which of these assays will provide the most accurate or clinically applicable measurement of serum gentamicin levels.

Selecting patients who had no factors known to alter gentamicin Vd did not decrease the reported variability in gentamicin Vd, hence, the source of variability in gentamicin’s Vd remains to be described and explained.
In this study we have reported a Vd for gentamicin in a highly selected group of patients, that is larger than is currently used to determine initial dosage requirements. This larger Vd may be due either to, the method of gentamicin analysis, or the selection of patients, or a combination of the effects of both of these factors.

It would be therapeutically advantageous to base initial dosing regimens on this larger Vd. The support for this statement arises from two facts. First, there are more known factors that increase gentamicin Vd in hospitalized patients as compared to the number of factors known to decrease gentamicin Vd. Without being able to accurately estimate the changes in gentamicin Vd due to disease states, we will be able to achieve serum concentrations within the therapeutic range for the majority of patients by utilizing the larger Vd in our calculations of dosage requirements. Second, underdosing the patient, which may occur as a result of assuming a smaller Vd, may expose the patient to a greater risk of treatment failure. In the minority of patients who would receive excessive doses using this larger volume, the use of serum level monitoring would minimize their risk of developing toxicities associated with aminoglycoside therapy.

RECOMMENDATIONS: The mean Vd for gentamicin described here, in this highly selected group of patients, is larger than is currently used to base empiric dosing recommendations. Therefore, in this patient population we should use this larger Vd and consequently larger doses in order to achieve therapeutic concentrations earlier in therapy.
To describe the variability in volumes due to all causes one would need to conduct a controlled prospective trial, calculating gentamicin Vd's in a large number of patients, using minimal selection criteria. Patients with similar conditions could be categorized and similarities and differences between and within groups noted.

4.3 RELATIONSHIP BETWEEN GENTAMICIN VOLUME OF DISTRIBUTION AND PERCENT BODY FAT

This study was designed to determine if the relationship between gentamicin Vd and percent body fat is continuous, throughout the lean, normal weight, and obese population.

It was demonstrated that estimates of LBM provide the best estimates of gentamicin Vd (L). However since these estimates are not practical in the clinical setting estimates of IBW provide the next best estimate of gentamicin Vd (L). Measurements of percent body fat were not able to increase the accuracy of prediction of that relationship.

Recruitment of an adequate sample size in this study was hindered by the selection processes. The strict selection criteria determined that the majority of patients receiving gentamicin were excluded. Of the patients screened, only 7% were eligible and half of those refused to participate.
The other difficulty encountered in attempting to determine the relationship between gentamicin Vd and percent body fat, was the inherent error associated with the measurement of obesity. Estimates of obesity by methods currently available all incur some degree of error.

Previous studies utilized Geigy's scientific tables (73) for a description of IBW. These values were based on weights at which mortality was lowest in adults who had bought life insurance. Therefore, they are not necessarily representative of the entire population, nor reflect a physiologic ideal body weight.

Our methodology in assessing percent body fat also had errors associated with it. When skinfold calipers or TBW measurements are used to estimate percent body fat an underlying assumption is that fat is a constant density. This has been disproven in recent cadaver studies (103). In addition skinfold caliper measurements suffer from several other difficulties. They are useful in assessing one individual over a period of time. However, when comparing individuals, several factors can decrease their usefulness. It has been demonstrated that individuals differ with respect to: the compressibility of fat (103), skin thickness (103), internal to external adiposity ratios (103), adipose tissue composition and distribution (103), all which are assumed to be constant when using skinfold calipers to estimate percent body fat.

INTERPRETATION: Investigators that have examined, and found a relationship between obesity and gentamicin Vd have defined obese as
being at least 30% over lean body weight. Schwartz and co-workers in 1978 (66) reported a volume of 0.185±0.027L/kg(ABW);n=6. Their obese patients were 30% over IBW as defined by Geigy’s scientific tables (73). In 1980 Korsager (67) found the volume in obese patients (50% over IBW as defined by Geigy’s scientific tables (73)) to be 0.177±0.028L/kg(ABW);n=17. The most recent study (1981) was conducted by Sketris et al. (68). Their obese patients demonstrated a Vd=0.15±0.04L/kg(ABW);n=30. In their study obese was 30% above IBW as defined by Katch (74). They were all able to show a statistically significant difference between their normal weight and obese patients.

Lean patients have also been shown to have an increased volume of distribution [L/kg(ABW)] compared to normal weight patients. Siber et al. (70) first suggested that lean adults have larger calculated extracellular fluid volumes. He also noted decreased peak concentrations in these individuals compared to the normal weight individuals they studied. Counts et al. in 1982 (78) also found, when they based dosage requirements for lean patients (ABW-IBW=-35 to -10Kg) on a Vd=0.26L/kg, that they overpredicted peaks in 10/13 patients. The most recent findings (1987) reported by Tointoin were the results of a retrospective study. In their lean patients (ABW < IBW, as defined by Devine (80)), they reported a Vd=0.30±0.07L/kg(IBW) which was statistically different from the volume noted in their normal weight population.

While it was noted that IBW was the best predictor of gentamicin Vd, which indicates that body composition does influence
gentamicin Vd, we were not able to demonstrate that estimations of body composition improved the correlation between gentamicin Vd and IBW.

There are several reasons that may be postulated as to why this relationship could not be detected in this study. First, the number of patients examined may not have been large enough to detect the relationship between percent body fat and gentamicin Vd.

Second, we may not have been able to detect a relationship due to the low variability of percent body fat in our patient population. In this study obese was defined as any weight 10% above their IBW, and lean as any weight 10% below their IBW. The studies which have previously examined this relationship have used populations at greater extremes of weight. Martin et al. (103) have found that the fat content of adipose tissue varies depending on the quantity of adipose tissue. This may indicate that the relationship between ECFV and percent adiposity and thus, gentamicin Vd is not linear but rather curvilinear. If this were so, the relationship between gentamicin Vd and percent body fat may be only of importance in those patients at extremes of body weight, rather than those who are close to normality.

Another reason we may not have been able to detect a relationship between percent body fat and gentamicin Vd may lie in the characteristics of this particular patient population. The variation caused by changes in body composition were not as important, or as large, as other factors that cause fluid alterations.
in hospitalized patients. We attempted to exclude patients who would have abnormal fluid distributions, however changes in volume of up to 10% may occur and not be clinically detectable (104).

Measurements of body compartments using radioactive tracers conducted since the 1950’s have demonstrated a relationship between percent body fat and extracellular fluid volume (105,106). The information obtained from studies which have examined the relationship between Vd and body weight, also indicate that the relationship between gentamicin Vd and percent body fat exists and is continuous (66-68,76-79).

The results of this study suggest, that either the relationship between gentamicin Vd and percent body fat is not linear, or our methodology of assessing leanness and obesity could not detect linearity. This study also indicates that even if one can detect a linear relationship in healthy adult volunteers, there are many variables that alter gentamicin Vd in hospitalized patients. Thus, it appears that leanness and obesity, except at extremes of weight are not important determinants of gentamicin Vd in hospitalized patients.

RECOMMENDATIONS: When dosing patients empirically we should continue to use the correction factor suggested by Schwartz et al.(66). Although it may not be clinically important to include this factor until a patient is 30-40% above their IBW, for convenience and standardization it would be useful to use this correction factor for all patients whose ABW is greater than IBW.
For extremely lean patients a Vd for gentamicin has not been described. There are indications that it is indeed larger, although it has not been quantified. Until this information is available one should empirically dose gentamicin on the basis of IBW, since IBW has been demonstrated to correlate better with gentamicin Vd compared to ABW. Serum levels should be monitored promptly to ensure the therapeutic range has been obtained.

The Vd in the lean patient remains to be described in patients with an absence of factors known to alter Vd. Presently, it appears to be of greater clinical importance to pursue the characterization of the variability of gentamicin Vd in hospitalized patients, for extrinsic variables, rather than weight.

4.4 CORRELATION BETWEEN ECFV AND GENTAMICIN VOLUME OF DISTRIBUTION

It was the intention of this study to demonstrate a relationship between TBW and gentamicin Vd, in patients where the relationship between ECFV and TBW was normal and stable. This could then be used to reinforce conclusions previously made that gentamicin distributes into the ECFV (6,38,42,47).

We were able to demonstrate a correlation between gentamicin volume of distribution and total body water ($r=0.739; p<0.001$).

In this study TBW was measured. ECFV was assumed to be a constant proportion of TBW, and within normal limits. Patients with
clinically detectable variations in the ratio between ECFV and TBW were excluded. Since we did not measure both ECFV and TBW we cannot conclude that the ratio was normal and constant.

Gyselynck et al. (6) performed simultaneous measurements of ECFV (using inulin) and gentamicin Vd. They found there was no statistically significant difference between mean inulin and gentamicin volumes (n=10, T=0.745, p>0.3). A correlation coefficient, calculated from their data was 0.146, which may indicate that in their patients ECFV was not predictive of gentamicin Vd.

Siber et al. (70) calculated ECFV for their adult patients based on equations established by Skrabal and co-workers (107). Siber et al. (70) found the ECFV was inversely related to peak concentrations obtained after giving 17 patients a gentamicin dose of 1mg/kg (r=-.74, p<0.05).

Our results are similar to those reported in the above studies.

INTERPRETATION: If gentamicin is distributed only into the ECFV, the theoretical correlation between gentamicin Vd and ECFV would be r=1. Only Gyselynck et al. (6) have directly examined that relationship, and in order to confirm their results, it is necessary to repeat the experiment. Siber’s values (70) for ECFV may be subject to inaccuracies because they are calculated values. Our methodology assumes that the relationship between total body water and ECFV is normal, which we did not confirm in the patients studied.
Since the time that Gyselynck's article (6) was published, there are reports in the literature which indicate that gentamicin may not only distribute freely within the ECFV, but may concentrate in tissues as the result of either an active transport mechanism (108), or pinocytosis (109). Gentamicin has been shown to concentrate in renal tissue (110,111) and in perilymph (112).

Therefore, it appears that although gentamicin may distribute primarily into the ECFV, a better understanding of its transport mechanisms would assist us in identifying and quantifying changes observed in disease states.

RECOMMENDATIONS: Few guidelines exist to assist in the empiric dosing of acutely ill patients, therefore it is necessary to note when fluid volumes have deviated from normal. In these patients, a best estimate of the deviated volume must be made on the basis of clinically available information. This is especially important in patients who have expanded fluid volumes, as underdosing of these patients may result in treatment failure. The lack of our ability to accurately estimate gentamicin Vd reinforces the need to monitor serum levels, to ensure they are maintained within the therapeutic range.

The relationship between gentamicin Vd and ECFV remains to be quantified in patients with an absence of factors known to alter ECFV. In order to establish the relationship between gentamicin Vd and ECFV one would need to measure the ECFV directly, this would avoid errors in assumptions made either through calculations of ECFV,
or measurements of total body water. This information would provide a baseline to which the effect of diseased states could be identified, compared, and quantitated.

4.5 DEVELOPING A CLINICALLY APPLICABLE PREDICTIVE FORMULA

It was the intention of this study to develop a formula for calculating gentamicin Vd, using clinically available information, which would improve our ability to estimate gentamicin Vd. This would enable clinicians to prescribe doses which are more likely to provide therapeutic concentrations within the first 24 hours of therapy.

Multiple regression using a stepwise approach of gentamicin Vd with IBW, SCr, age, and sex provided the following predictive equation, \( Vd(L) = 0.27(IBW) + 2.5L \).

The predictive formula we have established is based on information obtained from a highly selected population which is not necessarily representative of the population who are usually prescribed gentamicin.

INTERPRETATION: We have described a formula which will calculate a larger volume of distribution than is currently used to estimate empiric dosing regimens for gentamicin. Current recommendations estimate Vd as follows: \( Vd = 0.25L/kg(ABW) \) (52). We have also described an intercept in our predictive formula, which has not previously been reported.
Through the elimination of factors known to alter ECFV we have described a predictive formula for patients that is similar to that reported for healthy adult volunteers. This may be due to the elimination of these factors, or to differences in assay methodology.

It is thought that the intercept noted in this formula indicates the relationship between gentamicin Vd and weight is not linear through all ranges of weights. This is reinforced by the knowledge that in infants, ECFV consists of a larger proportion of their body weight (113,114). For example, in a 3 month old fetus, ECFV accounts for 65% of body weight (113). At term gestation, the percentage has decreased to 35-44% (113). At 12 months of age the ECFV comprises 26-30% of body weight (113). After the first year ECFV decreases slowly until adult values are attained at puberty (113). Thus the relationship between ECFV and body weight may not be linear, as has previously been described, but rather curvilinear.

If this formula were used to estimate dosing requirements, in the "normal" patient, larger volumes would be calculated. Therefore larger doses would be administered. The resulting dosing regimens for gentamicin would allow more patients to obtain therapeutic serum levels within the first 24 hours.

RECOMMENDATIONS: For this predictive formula to be clinically useful it would be important to simplify it. To calculate dosing requirements in adult patients with no known factors which may alter Vd, Vd should be estimated as = 0.30L/kg(dosing weight). When ABW is
>IBW, the dosing weight should be calculated as follows: \( DW = 0.40(ABW - IBW) + IBW \) (66). Presently, in cases where \( ABW \leq IBW \), \( ABW \) is used as the dosing weight. This study has found that \( IBW \) is a better predictor of gentamicin \( V_d \) than \( ABW \). This is in agreement with results reported by other authors (51,78). Therefore it seems appropriate at this time to empirically dose lean patients based on \( IBW \) until their \( V_d \) can be described in a larger patient population. This would result in larger doses being administered, thus decreasing the risk of underdosing this important sector of the hospitalized population.

This predictive formula needs to be tested prospectively, in order to demonstrate that it does provide better estimations of gentamicin \( V_d \), in similarly selected patients. This formula will still not adequately estimate gentamicin \( V_d \) for the majority of hospitalized patients, therefore our efforts to describe and quantitate variations in volumes in gentamicin \( V_d \) should continue.
5.0 CONCLUSIONS

5.1 VOLUME OF DISTRIBUTION IN "NORMAL" PATIENTS

We have described a Vd for gentamicin, in a highly selected group of patients, that is larger than is currently used to base empiric dosage regimens on. Since response to this antibiotic is related to serum concentrations of the drug, it would be therapeutically advantageous to use this larger Vd to determine initial dosing recommendations.

5.2 RELATIONSHIP BETWEEN GENTAMICIN Vd AND PERCENT BODY FAT

This study could not detect a linear relationship between gentamicin Vd and percent body fat. It is thought that this relationship may be curvilinear, and as such it may be an important variable in hospitalized patients who are at extremes of weight. Studies should be conducted to determine the Vd in extremely lean patients, as the volume changes in this population have not been quantified.

5.3 CORRELATION BETWEEN ECFV AND GENTAMICIN Vd

A strong relationship between TBW and gentamicin Vd was noted. We excluded patients in whom ECFV could not be assumed to be a constant and normal fraction of TBW. Thus, indirectly we have demonstrated a strong relationship between gentamicin Vd and ECFV.
Although the relationship is strong, it does not account for all of the variability of gentamicin Vd. Therefore, a better understanding of gentamicin's distribution characteristics would allow us to better predict the Vd in "normal" and diseased patients.

5.4 DEVELOPMENT OF A CLINICALLY APPLICABLE PREDICTIVE FORMULA

The data gathered on these patients suggest that the Vd for uncomplicated patients should be calculated as follows:

\[ Vd = 0.30L/kg(Dosing \ Weight) \]

Where dosing weight equals:

IBW, when \( ABW < IBW \),
or \( 0.4(ABW-IBW)+IBW \), when \( ABW > IBW \).

This predictive formula must be tested prospectively before one can conclude that it provides better estimations of gentamicin Vd in similarly selected patients.

There are several areas which still need to be explored. First, the relative association between gentamicin efficacy, toxicity and serum concentrations or AUC needs to be further clarified. Second, gentamicin's distribution characteristics have yet to be accurately described and quantitated. Third, the relative change of Vd in extremely lean patients should be quantitated. Fourth, we should continue our attempts to describe the variability of gentamicin's Vd in "normal" patients. This may become apparent once the characteristics of gentamicin Vd are further delineated. We also should quantify gentamicin's Vd in patients whose survival may depend
depend on obtaining therapeutic concentrations within the first 24 hours of therapy.
6.0 REFERENCES


7.0 APPENDICES

7.1 APPENDIX 1 - DATA COLLECTION FORMS

7.1.1 - DATA COLLECTION FORM - SCREENING PATIENTS

<table>
<thead>
<tr>
<th>NAME</th>
<th>WARD</th>
<th>HT</th>
<th>MT</th>
<th>IBW</th>
<th>AGE</th>
</tr>
</thead>
</table>

DIAGNOSIS: ___________________________  PHYSICIAN: ___________________________

<table>
<thead>
<tr>
<th>SCP</th>
<th>CRCL</th>
<th>BUN</th>
<th>S ALB</th>
<th>HCO</th>
<th>FLUID</th>
<th>URINE</th>
<th>S.C.</th>
<th>DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
7.1.2 DATA COLLECTION FORM - ENROLLED PATIENTS

DATA COLLECTION FORM

Pt. Name ___________________________ ID _______ Sex _______ Ht. _______ Wt. _______

SCREENING CRITERIA:

AGE: ____________________________

DIAGNOSIS:

SURGERY: YES NO

If yes when ____________________________

FLUID BALANCE:

Intake/Output ratio

Urine Specific Gravity

Any indications of fluid imbalance ie edema, dehydration, overhydration, ascites vomiting, diarrhea.

TEMPERATURE: ie less than 37.5°C for the past 24 hours. Yes No

LAB VALUES:

Serum Albumin

Hemoglobin

CONCOMITANT MEDICATION:


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DATA COLLECTION FORM - PAGE 2

WEIGHT OF DRUG AND SYRINGE

WEIGHT OF SYRINGE

WEIGHT OF DRUG ADMINISTERED

MG OF DRUG ADMINISTERED (44.35mg/ml)

---

SKINFOLD CALIPER MEASUREMENTS:

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triceps</td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td></td>
</tr>
<tr>
<td>Subscapular</td>
<td></td>
</tr>
<tr>
<td>Suprailiac</td>
<td></td>
</tr>
<tr>
<td>Thigh</td>
<td></td>
</tr>
<tr>
<td>Calf</td>
<td></td>
</tr>
</tbody>
</table>

GIRTH MEASUREMENTS

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triceps</td>
<td></td>
</tr>
<tr>
<td>Chest</td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
</tr>
<tr>
<td>Thigh</td>
<td></td>
</tr>
<tr>
<td>Calf</td>
<td></td>
</tr>
</tbody>
</table>

DRUG ADMINISTRATION:

Start: ________
Stop: ________
Administration Time: ________

RADIOACTIVE NUCLIDE ADMINISTRATION:

Time: ________
Nuclides Administered: ____________________________

BLOOD SAMPLING

<table>
<thead>
<tr>
<th>Time</th>
<th>HR PD</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Dose (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Dose (2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Dose (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Dose (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Dose (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

URINE COLLECTIONS:

<table>
<thead>
<tr>
<th>Time</th>
<th>HR PD</th>
<th>ML Counted</th>
<th>SA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Dose (1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Dose (2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Dose (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Dose (4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post Dose (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Volume Collected</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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7.2 APPENDIX 2 - STANDARDIZATIONS

A. GENTAMICIN SERUM LEVEL DETERMINATIONS

1. Calibration of Mettler PC 440 balance

A Mettler PC 440 balance was used at St. Paul's Hospital to weigh syringes and thus determine the dose of gentamicin administered. This balance was calibrated using a set of pharmaceutical weights (Henry Troemner Inc.) and two other balances (Sartorus model AMP8-1). The recordings for the various weights are recorded below:

<table>
<thead>
<tr>
<th>Pharmaceutical Weight Set</th>
<th>Sartorius Balance</th>
<th>Sartorius Balance</th>
<th>Mettler PC Balance</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.050</td>
<td>0.0501</td>
<td>0.0501</td>
<td>0.050</td>
</tr>
<tr>
<td>0.100</td>
<td>0.0997</td>
<td>0.0996</td>
<td>0.103</td>
</tr>
<tr>
<td>0.200</td>
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<td>0.2006</td>
<td>0.200</td>
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<tr>
<td>0.500</td>
<td>0.4986</td>
<td>0.4989</td>
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</tr>
<tr>
<td>1.000</td>
<td>1.0031</td>
<td>1.0031</td>
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<tr>
<td>2.000</td>
<td>2.0021</td>
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</tr>
<tr>
<td>5.000</td>
<td>5.0038</td>
<td>5.0039</td>
<td>5.003</td>
</tr>
<tr>
<td>10.000</td>
<td>10.0106</td>
<td>10.0109</td>
<td>10.010</td>
</tr>
<tr>
<td>20.000</td>
<td>19.9970</td>
<td>19.9970</td>
<td>19.997</td>
</tr>
<tr>
<td>50.000</td>
<td>50.0156</td>
<td>50.0160</td>
<td>50.020</td>
</tr>
</tbody>
</table>

2. Gentamicin Serum Assay

Serum samples were frozen at -20°C until assayed. A standard curve was constructed daily, based on six serum samples (0, 1, 2, 4, 8, and 16 mg/L) and one control (6mg/L). Day to day coefficients of variation for the hospital assay are 6.0% at 2.1mg/L and 3.6% at 6.32mg/L.
B. TRITIATED WATER MEASUREMENTS

1. Measurement of dose of tritiated water

The dose of tritiated water was measured in a 1 cc tuberculin syringe. Prentice et al. (115) determined gravimetrically the variation in the volume of water delivered by a tuberculin syringe and found the maximum error was 2%.

2. Calibration of automatic pipette (Clay Adams, Selectapette; 1ml volume)

The pipette was tested at three increments (0.5, 0.9 and 1.0ml). At each increment it was filled with distilled H₂O ten times and the volume delivered weighed on a Sartorius balance (model AMp8-1). The results of those weighings are presented below:

<table>
<thead>
<tr>
<th>Pipette Setting</th>
<th>0.5ml</th>
<th>0.9ml</th>
<th>1.0ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weights</td>
<td>0.4927</td>
<td>0.9092</td>
<td>0.9990</td>
</tr>
<tr>
<td></td>
<td>0.5006</td>
<td>0.9119</td>
<td>1.0038</td>
</tr>
<tr>
<td></td>
<td>0.4935</td>
<td>0.9124</td>
<td>1.0055</td>
</tr>
<tr>
<td></td>
<td>0.4910</td>
<td>0.9193</td>
<td>1.0210</td>
</tr>
<tr>
<td></td>
<td>0.4923</td>
<td>0.9100</td>
<td>0.9902</td>
</tr>
<tr>
<td></td>
<td>0.4906</td>
<td>0.9146</td>
<td>1.0142</td>
</tr>
<tr>
<td></td>
<td>0.4988</td>
<td>0.9078</td>
<td>1.0083</td>
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<td></td>
<td>0.4933</td>
<td>0.9118</td>
<td>0.9976</td>
</tr>
<tr>
<td></td>
<td>0.4880</td>
<td>0.9057</td>
<td>1.0068</td>
</tr>
<tr>
<td></td>
<td>0.4877</td>
<td>0.9048</td>
<td>0.9590</td>
</tr>
<tr>
<td>Mean</td>
<td>0.4928</td>
<td>0.9107</td>
<td>1.0054</td>
</tr>
<tr>
<td>Std Dev</td>
<td>±0.004</td>
<td>±0.004</td>
<td>±0.017</td>
</tr>
</tbody>
</table>

3. Liquid Scintillation Counting

A Beckman LS 9800 liquid scintillation counter was used to determine the activity of the patients serum. Five serum samples were counted in triplicate for each patient. Channel were set at 0
and 400 nanometers. Quench correction is computed automatically using a $^{137}$Cs source and an unquenched $^3$H sample. The quench limits were 24 to 347. All samples fell within this range. Counting efficiency ranged between 34 and 38%, the mean value was 35%. 
GENTAMICIN - VOLUME OF DISTRIBUTION

INVESTIGATORS?
Ms. M. Boyce  M.Sc. (Clinical Pharmacy) candidate, University of B.C.
Dr. R. Ensom, Faculty of Pharmaceutical Sciences, University of B.C.
Dr. R. Rosenberg, Head of Clinical Chemistry, St. Paul's Hospital
Dr. A. Belzberg, Director of Nuclear Medicine, St. Paul's Hospital

PURPOSE OF STUDY?
To determine the relationship between the amount of antibiotic in your bloodstream and the amount of body fat you have.

BENEFITS OF THE STUDY?
The study will improve our future ability to predict the exact dose of this antibiotic that patients will need to produce the most beneficial effect.

WHAT PROCEDURES WILL YOU HAVE TO UNDERGO?

(1) Normally when these drugs are used in patients at St. Paul's Hospital the amount that appears in the bloodstream is always measured to insure safe and effective amounts are present. This procedure involves taking at least two blood samples (or venepunctures). In order to improve the accuracy of our study two more venepunctures may need to be taken in exactly the same manner.

(2) We will also determine your height and weight and, using skinfold calipers, your body fat measurement while in hospital.

(3) Another method of measuring body fat will also be employed. This involves drinking a glass of tritiated water (radioactive) and having the concentration in the blood measured at some time afterwards. The tritiated water technique has been used for several years in different hospitals for various studies. The radioactivity of the water used is 100 times weaker than an X-ray. There are no known harmful effects associated with this technique. One of the blood samples taken to measure the amount of drug in the bloodstream will also be used to measure the tritiated water concentration.

HOW MUCH TIME IS REQUIRED?
Skinfold measurements are completely painless and will take about fifteen minutes of your hospital time.
DESCRIPTION OF POPULATION

11 How many subjects will be used? 30 patients total divided into 3 weight groups:

<table>
<thead>
<tr>
<th>Weight Group</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (± 20% of ideal body weight)</td>
<td>(1) 10</td>
</tr>
<tr>
<td>Obese (≥ 20% over ideal body weight)</td>
<td>(2) 10</td>
</tr>
<tr>
<td>Lean (&lt; 20% under ideal body weight)</td>
<td>(3) 10</td>
</tr>
</tbody>
</table>

12 Who is being recruited and what are the criteria for their selection?

The study population will consist of inpatients at St. Paul's Hospital who are receiving gentamicin intravenously and,

(a) have reached a steady state blood level of the drug in the body,
(b) are posologically and physiologically stable with respect to factors known to influence aminoglycoside pharmacokinetics
and (c) have pharmacokinetic data available from the Drug Measurement Service at St. Paul's Hospital.

13 What subjects will be excluded from participation?

Exclusions will be an important part of our selection process and will include those patients:

(a) unable to stand for height, weight and skinfold thickness measures,
(b) with factors known to affect the Vd of aminoglycoside antibiotics including
   (i) pathological increases in body fluid such as edema, ascites, burns, etc.
   (ii) compromised renal function with creatinine clearance less than 70 mL/min.
   (iii) certain drugs
(c) with conditions or treatments known to affect the accuracy of serum concentration determinations.

14 How are the subjects being recruited? (If initial contact is by letter or if a recruitment notice is to be posted, attach a copy) NOTE that UBC policy prohibits initial contact by telephone

Patients will be identified as receiving gentamicin from the records of the Drug Measurement Service at St. Paul's Hospital. The patient will then be approached by one of the co-investigators in person to describe the study and solicit participation.

15 If normals are involved, and if their selection and/or recruitment differs from the above, provide details.

Not applicable.
DESCRIPTION OF METHODOLOGY & PROCEDURES

A summary of methodology and procedures. Include details of any specific manipulations, type, quantity and route of administration of drugs or radiation, operations, tests, use of medical devices that are prototype or altered from those in clinical use; interviews or questionnaires.

Patients receiving gentamicin for moderate to severe infections are monitored by the Drug Measurement Service at St. Paul's Hospital to assure therapeutic, non-toxic blood levels. A standard protocol is followed. Patient specific pharmacokinetic information is calculated which will be available for our study.

Patients will be selected by excluding all those with known factors affecting Vd.

Assessment of percent body fat will be undertaken by anthropometric methods. Skin fold thickness will be determined using skin fold thickness calipers (Harpenden). Six anatomical sites will be measured (three measurements per site) and values obtained will be converted to a percentage body fat determination utilizing the appropriate equations. Height and weight will be determined by conventional scales and measuring tape. Both measurements will be undertaken by the experimenter: with the patient standing to reduce potential variation in results.

A data collection form will be implemented to record all pertinent information regarding patients height, weight, percentage body fat and pharmacokinetic variables.

Where the project will be conducted (room or area)
St. Paul's Hospital ward areas.

Who will actually conduct the study?
Ms. N. Boyce

If the procedures described above are limited to any of the following, please check the appropriate box(es) and skip to item 17 of this form. If this is the case, only the original protocol and one copy need be submitted:

☐ withdrawal of blood
☐ examination of medical records and/or recorded data
☐ use of specimens acquired non-invasively or of materials normally discarded
☐ the project is a modification of that approved under clinical protocol #...
18. What is known about the risks and benefits of the proposed research? Do you have additional opinions on this issue?

"As all procedures described (excluding skin fold thickness determinations) are typical of the medical management patients will receive when treated for moderate to severe gram-negative infections, no additional risk to the patient will be apparent. Only patients who are ordered gentamicin by their physician will be admitted to the study. The benefit of this research is explained in section #8.

20. What discomfort or incapacity are the subjects likely to endure as a result of the experimental procedures?

Patients who are to receive gentamicin typically undergo venepunctures to ascertain serum levels of the drug before and after administration. The experimental procedures described will not result in any additional discomfort or incapacity. The determination of percent body fat using skinfold calipers is not associated with any discomfort or incapacity.

21. Provide details of any known side effects which may result from the experimental treatment.

The administration of gentamicin intravenously is associated with potential side effects. However, for the purposes of this study, all patients involved will be receiving this drug for indications independent of the study protocol.

22. What procedures in this project involve an experimental approach in that there may be treatment options dictated by the protocol rather than by treatment-of-choice decisions?

All patients admitted to the study will undergo identical procedures with respect to venepunctures and skinfold thickness determinations. No variation in treatment options dictated by protocol will occur.

23. What provisions are made to break the code of a double-blind study? Who has the code?

The study will not be double-blind.

34. If monetary compensation is to be offered the subjects, provide details of amounts, and payment schedules.

No monetary compensation will be offered to the subjects.

36. How much time will a subject have to dedicate to the project beyond that needed for treatment?

Sometime after reaching a stable clinical condition, skin fold thickness, height and weight measurements will be taken for each subject, requiring 15 min.

36. How much time will a normal volunteer (if any) have to dedicate to the project?

None.
Who will have access to the data?

Only the investigators mentioned in §1 and §2.

How will confidentiality of the data be maintained?

No names or identifying numbers of subjects will be listed in publications resulting from this study. Identification of subjects will be limited only to professional personnel directly involved in the study.

What are the plans for future use of the data (beyond that described in this protocol)?

No present plans exist for the future use of the data.

Will any data which identifies individuals be available to persons or agencies outside the University?

No data will specifically identify individuals except to hospital admission number. The information will not be available to persons or agencies outside the University.

Informed Consent

Will the group of subjects have any problems giving informed consent on their own behalf? Consider physical or mental condition, age, language, or other barriers.

All subjects will be capable of giving informed consent on their own behalf.

If the subjects are not competent to give fully informed consent, who will consent on their behalf?

Not applicable.

33 USC Policy requires written consent in all cases. Please check each item in the following list before submission of this form to ensure that the written consent form attached contains all necessary items.

- Title of project
- Identification of investigators
- Brief but complete description in Lay Language of the purpose of the experiment and of all experimental procedures
- Statement of all known side effects and an estimate of the probability of their occurrence
- Assurance that identity of the subject will be kept confidential and description of how this will be accomplished
- Statement of the total amount of time that will be required of a subject beyond that needed for treatment
- Details of monetary compensation, if any, to be offered to subjects
- An offer to answer any inquiries concerning the procedures to ensure that they are fully understood by the subject
- An unambiguous statement that the subject may decline to enter or withdraw from the experiment at any time without any consequences to continuing medical care
- Signature of subject consenting to participate in the research project, investigation or study, and acknowledging receipt of a copy of the consent form including all attachments
- Signature of a witness
### ATTACHMENTS

- [ ] letter of initial contact (item 14)
- [ ] advertisement for volunteer subjects (item 15)
- [ ] subject consent form (item 23)
- [ ] normal subject consent form (if different from above)
- [ ] questionnaires, tests, interviews, etc
- [ ] other, specify:

NOTE THAT ATTACHMENTS SHOULD BE RESTRICTED TO THE ABOVE. ADDITIONAL MATERIAL PROVIDED (INCLUDING DRUG COMPANY PROTOCOLS) WILL BE ADDED TO THE FILE BUT WILL NOT BE DISTRIBUTED TO THE REVIEW COMMITTEE.

### ADDITIONAL INFORMATION

35 Use this space to provide information which you feel will be helpful to the review committee or to continue any item for which sufficient space was not available.
MEMORANDUM

To: Clinical Screening Committee for Research and Other Studies Involving Human Subjects

From: Dr. Robin Ensom, Principal Investigator
       Faculty of Pharmaceutical Sciences

Title: Gentamicin Volume of Distribution (Vd) Study - Relation Between Actual Vd and Percent Body Fat

Number: C84-212

Date: May 13, 1985

Dr. A. Belzberg, Director of Nuclear Medicine at St. Paul's Hospital, will be joining our study as a Co-Investigator.

In addition, the following changes in this study are submitted for ethical review by the Clinical Screening Committee:

DESCRIPTION OF METHODOLOGY & PROCEDURES

16. Summary of methodology and procedures. (Inclusion)

Total body water will be determined by the tritiated water dilution method. From this value body fat can be derived. The subject will have a baseline blood sample, followed by the oral administration of 300 μC of tritiated water and another blood sample approximately 2 hours later. Measurement of tritium activity in serum will be with a scintillation counter.

19. What is known about the risks and benefits of the proposed research? (Inclusion)

The subjects will receive 300 μC of tritiated water (3H-water) orally for the calculation of total body water content. It is considered to be the tracer of choice for
calculation of body water and was first described by Pace in 1947. The average biologic half-life of the tracer is 11.5 days. The estimated radiation exposure is 0.004 rads. A standard chest x-ray delivers 0.4 rads. There are no known harmful effects associated with this technique. This method is expected to provide an objective means of corroborating estimates of body fat determined by anthropometric measurements.

20. What discomfort or incapacity are the subjects likely to endure as a result of the experimental procedures? (Inclusion)

The tritiated water dilution method is not expected to result in any discomfort to the subjects. Blood samples for measuring tritium activity are expected to be taken at the same time that blood is drawn for gentamicin concentration measurements.

INFORMED CONSENT

A revised subject consent form is attached.
TO: Clinical Screening Committee for Research and Other Studies Involving Human Subjects
FROM: Dr. Robin Ensom, Principal Investigator
Faculty of Pharmaceutical Sciences

TITLE: Gentamicin Volume of Distribution (Vd) Study - Relation Between Actual Vd and Percent Body Fat

NUMBER: C84-212

DATE: July 21/86

The following changes in this study are submitted for ethical review by the Clinical Screening Committee:

DESCRIPTION OF METHODOLOGY AND PROCEDURES

17. Summary of methodology and procedures. (Inclusion)

Total body water and extracellular fluid volume will be measured simultaneously. The total body water will be determined by the tritiated water dilution method. Extracellular fluid volume will be determined using a method described by Moore in 1956. Total body water measurements will be used to calculate percent adiposity. Extracellular fluid volume is a measure of Vd for gentamicin.

The blood sample currently used for the gentamicin trough level will also be used to determine the background radiation for the tritiated water and bromine measurements. The tritiated water and bromine will be given orally in doses of 300uCi and 25uCi respectively. The serum blood samples drawn after the dose of gentamicin will also be used to do plasma tritium and bromine counts. Simultaneous urine samples will be used to determine the amount of tritium and bromine excreted in the urine. A 24 hour urine collection will be carried out from the time the tritium and bromine is administered. At the end of this 24 hour period a final blood sample will be drawn to determine the tritium and bromine counts.

Measurement of the tritium and bromine activity in serum will be with a scintillation counter.
20. What is known about the risks and benefits of the proposed research? (Inclusion)

The subjects will receive 300uCi of tritiated water (3H-water) orally for the calculation of total body water content. It is considered to be the tracer of choice for the calculation of body water and was first described by Pace in 1947. The average biologic half life of the tracer is 11.5 days. The estimated radiation exposure is 0.004 rads. 82-Bromine (25uc1) will be administered orally for the determination of extracellular fluid volume. The biologic half-life of this tracer is 36 hours. The estimated radiation exposure from this tracer is 0.030 rads. Therefore the total radiation exposure is 0.034 rads. A standard chest x-ray delivers 0.4 rads. There are no known harmful effects associated with this technique. These methods will provide us with objective measurements of percent adiposity and volume of distribution of gentamicin.

21. What discomfort or incapacity are the subjects likely to endure as a result of the experimental procedures? (Inclusion)

The measurement of total body water and extracellular fluid volume should not result in any discomfort to the subjects. One extra blood sample will be drawn 24 hours after the tracers are administered.

Informed Consent

A revised informed consent form is attached.