COMPARISON OF INTRAMUSCULAR ABSORPTION
ABOVE AND
BELOW THE LEVEL OF A SPINAL CORD INJURY

by

VALERIE JEAN SPURRELL

B.S.N., The University of British Columbia, 1980

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

in

THE FACULTY OF GRADUATE STUDIES
School of Nursing

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

March 1992

© Valerie Jean Spurrell, 1992
In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

(Signature)

Department of Nursing
The University of British Columbia
Vancouver, Canada

Date Jan 20/92
Abstract

This study was designed to determine the difference in drug absorption between intramuscular injections given above and below the lesion in persons with a spinal cord injury.

The theoretical framework identified three categories of factors known to influence serum drug absorption following intramuscular injections: drug action, diffusion area, and blood flow, with a focus on muscle innervation as one factor in the blood flow category.

Hypotheses tested in this study were that serum trough and serum peak levels are greater and absorption time is shorter when I.M. injections of gentamicin are given above the level of a spinal cord injury than when given below.

The study used an experimental, repeated measures design with counterbalancing and subjects acted as their own controls by receiving injections both above and below the level of injury. A total of five serum samples were drawn before and after a series of injections in each site to determine any differences in serum drug absorption.

When it was not possible to obtain the sample size intended, case analysis was used to study the three subjects who enrolled in the study. Factors which may have influenced the difficulty in obtaining a larger sample are identified and discussed.

The results of the study indicated that of the three cases, only in the first case were the serum trough and peak levels higher following deltoid injections than following gluteal injections. The contrary results for the second and third case may have been related to differences in the number of injections
and differences in the dosing intervals.

The time between serum samples was too great to accurately differentiate the absorption times, but pharmacokinetic values associated with the elimination phase suggested that absorption was delayed following injections below the level of injury. In all three cases the elimination rate constant was smaller, the half-life longer, and the volume of distribution larger following injections below the level of injury. In addition, the logarithmic plotting of serum levels following injections in paralyzed muscle was non-linear, adding further support to the supposition that absorption was delayed.

With a sample size of three, conclusions are tentative. The findings suggest that peak and trough serum levels may be greater following injections above the level of injury as compared to below if the dosing interval is every 12 hours and steady state is achieved prior to serum samples being drawn. Given possible delayed absorption from paralyzed muscle, shortened dosing intervals may result in drug accumulation.

The results of this study have implications for practice related to I.M. site selection, dosing levels, and serum levels. Education for health professionals must address innervation as a possible influence on I.M. drug absorption. This study provides insight into areas for further refinement of the theoretical framework as well as areas for further research.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>11</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>v1</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>vii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>viii</td>
</tr>
<tr>
<td><strong>CHAPTER ONE: INTRODUCTION</strong></td>
<td>1</td>
</tr>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Background to the Problem</td>
<td>1</td>
</tr>
<tr>
<td>Problem Statement</td>
<td>3</td>
</tr>
<tr>
<td>Purpose</td>
<td>3</td>
</tr>
<tr>
<td>Theoretical Framework</td>
<td>3</td>
</tr>
<tr>
<td>Drug Action</td>
<td>5</td>
</tr>
<tr>
<td>Diffusion Area</td>
<td>5</td>
</tr>
<tr>
<td>Blood Flow</td>
<td>5</td>
</tr>
<tr>
<td>Hypotheses</td>
<td>7</td>
</tr>
<tr>
<td>Definition of Terms</td>
<td>7</td>
</tr>
<tr>
<td>Significance</td>
<td>9</td>
</tr>
<tr>
<td>Overview of Thesis Content</td>
<td>10</td>
</tr>
<tr>
<td><strong>CHAPTER TWO: REVIEW OF THE LITERATURE</strong></td>
<td>11</td>
</tr>
<tr>
<td>Introduction</td>
<td>11</td>
</tr>
<tr>
<td>Serum Drug Absorption</td>
<td>11</td>
</tr>
<tr>
<td>Drug Action</td>
<td>14</td>
</tr>
<tr>
<td>Drug Properties</td>
<td>14</td>
</tr>
<tr>
<td>Interacting Drugs</td>
<td>14</td>
</tr>
<tr>
<td>Area for Diffusion</td>
<td>15</td>
</tr>
<tr>
<td>Needle Size</td>
<td>15</td>
</tr>
<tr>
<td>Massage</td>
<td>16</td>
</tr>
<tr>
<td>Withdrawal Technique</td>
<td>16</td>
</tr>
<tr>
<td>Blood Flow</td>
<td>16</td>
</tr>
<tr>
<td>Renal and Cardiovascular Function</td>
<td>17</td>
</tr>
<tr>
<td>Muscle Group</td>
<td>17</td>
</tr>
<tr>
<td>Muscle Innervation</td>
<td>18</td>
</tr>
<tr>
<td>Spinal Cord Injury and Drug Absorption</td>
<td>19</td>
</tr>
<tr>
<td>Summary</td>
<td>22</td>
</tr>
<tr>
<td><strong>CHAPTER THREE: METHODS</strong></td>
<td>24</td>
</tr>
<tr>
<td>Introduction</td>
<td>24</td>
</tr>
<tr>
<td>Research Design</td>
<td>24</td>
</tr>
<tr>
<td>Sample Selection and Sample Criteria</td>
<td>26</td>
</tr>
<tr>
<td>Assumptions</td>
<td>27</td>
</tr>
<tr>
<td>Limitations</td>
<td>27</td>
</tr>
<tr>
<td>Data Collection Instruments</td>
<td>27</td>
</tr>
<tr>
<td>Abbott TDX</td>
<td>27</td>
</tr>
<tr>
<td>Data Collection Tool</td>
<td>29</td>
</tr>
<tr>
<td>Data Collection Procedure</td>
<td>29</td>
</tr>
<tr>
<td>Protection of Human Rights</td>
<td>31</td>
</tr>
<tr>
<td>Data Analysis</td>
<td>32</td>
</tr>
<tr>
<td>Summary</td>
<td>33</td>
</tr>
</tbody>
</table>
### CHAPTER FOUR: PRESENTATION AND DISCUSSION

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>34</td>
</tr>
<tr>
<td>Characteristics and Discussion of Results</td>
<td>34</td>
</tr>
<tr>
<td>Sample</td>
<td>34</td>
</tr>
<tr>
<td>Influencing Factors</td>
<td>35</td>
</tr>
<tr>
<td>New Laboratory Protocol</td>
<td>35</td>
</tr>
<tr>
<td>Concurrent Research Study</td>
<td>36</td>
</tr>
<tr>
<td>New Antibiotics</td>
<td>37</td>
</tr>
<tr>
<td>Findings and Discussion of Case Studies</td>
<td>38</td>
</tr>
<tr>
<td>Case 1</td>
<td>38</td>
</tr>
<tr>
<td>Case 2</td>
<td>45</td>
</tr>
<tr>
<td>Case 3</td>
<td>53</td>
</tr>
<tr>
<td>Case 1-3</td>
<td>59</td>
</tr>
<tr>
<td>Summary</td>
<td>62</td>
</tr>
</tbody>
</table>

### CHAPTER FIVE: SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>64</td>
</tr>
<tr>
<td>Summary</td>
<td>64</td>
</tr>
<tr>
<td>Conclusions</td>
<td>68</td>
</tr>
<tr>
<td>Implications</td>
<td>70</td>
</tr>
<tr>
<td>Recommendations for Further Research</td>
<td>73</td>
</tr>
</tbody>
</table>

### REFERENCES

- REFERENCES                                                      76

### APPENDICES

- A. Consent Form                                               79
- B. I.M. Injection Procedure                                   81
- C. Data Collection Form                                       85
- D. Venipuncture Procedure                                    90
- E. Calculations for Pharmacokinetic Parameters                92
- F. Concurrent Research Study                                  94
List of Tables

Table 1. Subject 1 - Comparative Serum Levels........... 39
Table 2. Subject 1 - Pharmacokinetic Values............. 43
Table 3. Subject 2 - Comparative Serum Levels........... 47
Table 4. Subject 3 - Comparative Serum Levels........... 54
Table 5. Subject 3 - Pharmacokinetic Values............. 57
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Intramuscular Absorption Framework</td>
<td>4</td>
</tr>
<tr>
<td>2.</td>
<td>Serum Drug Absorption Following Intramuscular Injection</td>
<td>12</td>
</tr>
<tr>
<td>3.</td>
<td>Study Design</td>
<td>25</td>
</tr>
<tr>
<td>4.</td>
<td>Subject 1 - Serum Concentration Time Curve</td>
<td>40</td>
</tr>
<tr>
<td>5.</td>
<td>Subject 1 - Logarithm of Serum Levels Versus Time</td>
<td>44</td>
</tr>
<tr>
<td>6.</td>
<td>Subject 2 - Serum Concentration Time Curve</td>
<td>48</td>
</tr>
<tr>
<td>7.</td>
<td>Subject 2 - Logarithm of Serum Levels Versus Time</td>
<td>51</td>
</tr>
<tr>
<td>8.</td>
<td>Subject 3 - Serum Concentration Time Curve</td>
<td>55</td>
</tr>
<tr>
<td>9.</td>
<td>Subject 3 - Logarithm of Serum Levels Versus Time</td>
<td>58</td>
</tr>
</tbody>
</table>
This thesis is dedicated to my husband for giving me the courage to believe in my capabilities, and whose unfailing support and encouragement have carried me through to the completion of this thesis.
ACKNOWLEDGEMENTS

I would like to thank the members of my thesis committee, Dr. Ann Hilton (chairperson) and Marilyn Devis for sharing their expertise and providing guidance and support.

The pharmacological expertise provided by Marilyn Boyce, M.Sc. Pharm. and Terri Betts, B.Sc. Pharm. was invaluable, as was the assistance that Dr. W. B. Boldt provided in analyzing the data.

I would like to thank the research assistants, Lorna Dick R.N., Colleen Powers R.N., and Anna Krzyzanawoski R.N. who diligently collected the data for this study.

My appreciation is extended to the nursing staff and physicians on the spinal cord injury service at the rehabilitation centre where the study was conducted. Sincere thanks are also extended to Dr. Gribble for her efforts in identifying potential subjects.

I am grateful to the British Columbia Rehabilitation Society for their financial assistance.

Finally, I would like to thank the patients who participated in this study.
CHAPTER ONE

Introduction

Background to the Problem

It is estimated that there are 150,000 spinal cord injured persons in North America, and that each year approximately 10,000 more are injured (Martin, Holt & Hicks, 1981). Annually in British Columbia, approximately 130 persons suffer a spinal cord injury (Canadian Paraplegic Association, 1989). There is a multitude of physical and psychosocial consequences of spinal cord injury. Physical impairments include loss of motor function, loss of sensation, alterations in sexual relationships, and loss of bowel and bladder control.

Loss of bladder control places the individual at high risk for the complication of bladder infection because of the need for repeated catheterizations (Trieschmann, 1982). According to Martin, Holt, and Hicks (1981), the greatest incidence of morbidity and mortality in the spinal cord population occurs because of infections of the urinary tract. Serious infections due to gram-negative organisms are often treated with intramuscular (I.M.) or intravenous (I.V.) gentamicin (Goodman & Gilman, 1981). For clients in the community or in non-acute rehabilitation settings such as the centre participating in this study, intramuscular therapy is preferable to intravenous therapy as it does not require admission to an acute care facility.

In general, physicians at the participating centre prefer to order a medication be given I.M. rather than I.V., but practice is mixed when it comes to ordering gentamicin in the spinal cord injured population. The majority of physicians order gentamicin
I.M. but a few physicians suspect that gentamicin given by the I.M. route is not as effective in the spinal cord injured population as compared to the general population. Although these physicians have not been able to validate their suspicions, it has influenced their practice. They tend to order gentamicin be given I.V. rather than I.M. when it is indicated as the drug of choice for persons with a spinal cord injury. (Medical staff interview, 1989). Although physicians choose the route of drug administration, it is the nurse who selects the site.

When I.M. administration of medication is prescribed for patients with a spinal cord injury, the nurse selects from a range of possible sites. Administration below the level of the injury where there is loss of sensation generally provides a pain-free injection, whereas administration above the level of injury is likely to cause slight discomfort. Administration below the level of injury is the most frequent choice according to a survey of approximately 30 registered nurses, working with patients with spinal cord injuries (Spurrell, 1989). Although administration below the level of the injury is more comfortable for the patient, there is perhaps a more important factor to consider in site selection. With paralysis there is some tone in the smooth muscles of the blood vessels, but this cannot compensate for the flaccidity of the skeletal muscles, resulting in reduced blood flow in paralyzed tissue (Guttman, 1974; Seifert, 1972). Administration of I.M. medication to these sites would therefore likely influence drug absorption (Segal, 1988). How influential this factor is in site selection has not been studied in the spinal cord injured population.
Problem Statement

Although we have information to suggest that injections below the level of spinal cord injury are not absorbed as well as those same sites on able-bodied persons (Segal, 1988), no research was found which compared absorption levels above and below injury sites. The question arises, would gentamicin absorption in spinal cord injured patients be improved if nurses gave intramuscular injections in "normal" rather than paralyzed muscle?

Since nurses are the prime caregivers and persons responsible for I.M. site selection, information which helps to clarify the best sites in persons with a spinal cord injury would assist the nurse to make decisions that would produce the best drug effect. The current nursing literature offers no direction regarding I.M. injections in the spinal cord injured population (Dittmar, 1989; Sorensen & Luckmann, 1979; Martin, Holt, & Hicks, 1981).

Purpose

The purpose of this study was to determine the difference in drug absorption between intramuscular injections given above and below the lesion in persons with a spinal cord injury, when the lesion is within the range of C-6 to L-2. Injuries within this range affect the gluteal muscle but not the deltoid muscle (Warwick, 1973).

Theoretical Framework

The theoretical framework for this study focused on serum drug absorption following intramuscular injections. It was a combined physiological and pharmacological framework which identified factors influencing serum drug absorption. Figure 1
divides the factors into three broad categories - diffusion area, drug action and blood flow. Identified within each of these broad categories are a number of specific factors which influence serum drug absorption following intramuscular injections.

**FIGURE 1**
Intramuscular absorption framework reflecting factors influencing serum drug absorption with intramuscular injections.
Drug Action

The framework identified drug action as one of the three categories of factors influencing serum drug absorption. Drug action, and in turn serum drug absorption, is influenced by two factors - individual drug properties and interacting drugs. Kock-Weser (1974) identified three individual drug properties known to influence serum drug absorption - drug lipophilicity (ability to diffuse directly through the capillary wall), drug volume and drug concentration. Interacting drugs can affect serum drug absorption by either enhancing or inhibiting drug activity (Tindula, 1983).

Diffusion Area

According to the framework, surface area for diffusion affects serum drug absorption. Three factors identified as influencing absorption by affecting diffusion area were needle size, massage and withdrawal technique.

Surface area, and thus absorption, can be increased by increasing the depth of the injection with a longer needle and through massage of the area following injection (Zellman, 1961; Kock-Weser, 1974). The withdrawal technique can influence whether all the medication remains in the muscle or some has leaked into the subcutaneous tissue. In the latter case, absorption is slower (Zellman, 1961).

Blood Flow

Of the three categories of factors identified as influencing serum drug absorption, blood flow is known to have the primary influence. Early studies suggested diffusion had the greatest influence, but a study by Bederka (1971) identified blood flow as
the key factor influencing the rate of serum drug absorption of substances administered intramuscularly.

The framework identified four factors which influence serum drug absorption through their effect on blood flow. These four factors were renal function, cardiovascular function, muscle group and muscle innervation. First, it was noted, with renal dysfunction there is a reduced ability to clear the drug from the system. This may make it appear as though absorption is enhanced by elevating the peak and trough serum levels (Emms & Norwak, 1983). Second, decreased cardiac output reduces blood flow. Conversely, increased cardiac output, such as occurs with exercise, increases blood flow (Emms & Norwak, 1983; Seifert, 1972). Third, Evans (1975) found that blood flow varied in different muscle groups. The blood flow in the deltoid muscle was found to be faster than that of the vastus lateralis, which in turn was found to be faster than blood flow in the gluteal muscle. Fourth, if muscle innervation is reduced, as occurs with paralysis, the tone and muscle mass decrease and blood flow becomes reduced (Guttman, 1974).

In summary, the framework identified three categories of factors influencing serum drug absorption with intramuscular injections - drug action, area for diffusion and blood flow. Within each category there were specific factors identified as influencing absorption. This study focused on the influence that muscle innervation (paralysis) has on serum drug absorption. It tested the theory that decreased muscle innervation decreases blood flow, and thus decreases serum drug absorption.
Hypotheses

The following hypotheses were tested in this study.

1. The serum trough level of gentamicin, following I.M. injections, in persons with a spinal cord injury is greater when the injections are given above the level of injury than when they are given below.

2. The peak serum level of gentamicin, following I.M. injections, in persons with a spinal cord injury is greater when the injections are given above the level of injury than when they are given below.

3. The absorption time of I.M. gentamicin, in persons with a spinal cord injury, is shorter when injections are given above the level of injury than when they are given below.

Definition of Terms

The theoretical and operational definitions of the terms addressed in the hypotheses are described below. The terms addressed include those pertaining to serum drug absorption and those pertaining to spinal cord injury.

Serum Drug Absorption

Serum drug absorption refers to the amount of drug reaching the systemic circulation (Winter, 1989).

Operational Definition: Serum drug absorption was defined in terms of the trough level, the peak level, and the absorption time.

Trough Level

The trough level was defined as the lowest level of drug in
the systemic circulation (ug/ml) determined by taking a measurement just prior to drug injection (Shlafer & Marieb, 1989).

**Peak Level**

The peak level was defined as the highest level of drug in the systemic circulation (ug/ml) determined by taking the highest of the four measurements following drug injection.

**Absorption Time**

The absorption time was defined as the time required for all of the drug injected into the muscle to be absorbed into the blood stream. It was determined by measuring the time from drug injection until the peak serum level was achieved.

**Spinal Cord Injury (lesion)**

Spinal cord injury referred to trauma to the spinal cord resulting in either temporary or permanent loss of motor and/or sensory function below the level of injury (Trieschmann, 1882).

Operational Definition: For the purposes of this study spinal cord injury referred to a complete injury within the range of C-6 to L-2 in which there was a complete loss of motor function below the level of injury. The injury was classified as a complete injury regardless of sensory function.

**Above the Level of Injury**

Above the level of injury referred to that area of the body innervated by segmental levels above the spinal cord lesion (Guttmann, 1974).

For the purposes of this study, above the level of injury referred to a specific muscle unaffected by the spinal lesion - the deltoid muscle; the muscular cap of the shoulder.
Innervation for the deltoid muscle occurs at C-5 in the spinal cord (Williams, 1973).

**Below the Level of Injury**

Below the level of injury referred to those areas at or below the segmental level of the lesion; areas affected by motor paralysis (Guttmann, 1984).

For the purposes of this study, below the level of injury referred to a specific muscle affected by motor paralysis - the gluteal (dorsal gluteal) muscle in the upper outer quadrant of the buttocks. Innervation for the gluteal muscle occurs at L-4 in the spinal cord (Williams, 1973).

**Significance**

This study was significant in terms of increasing the body of knowledge in nursing as well as other disciplines such as pharmacology, medicine, and physiology. The theoretical framework for this study indicated that reduced muscle innervation (paralysis) reduces blood flow which decreases serum drug absorption. This study tested that relationship, and thus tested the theory.

On a more concrete level the results of this study allow nurses and other health care professionals to make more informed decisions when working with spinal cord injured patients who require I.M. injections. Physicians have more information on which to base their decisions regarding route of administration of gentamicin, or other medication which may be given I.M. or I.V., with spinal cord patients. Nurses have further data on which to base site choice when giving I.M. injections to persons with a spinal cord injury.
Regardless of whether the hypotheses were rejected or accepted, this study contributed to the knowledge base in nursing and other health professions. Quality of patient care is enhanced when the best choices in terms of route and/or site of gentamicin treatment for persons with a spinal cord injury are clarified.

Overview of Thesis Content

This thesis is comprised of five chapters. In Chapter One, the background to the problem, problem statement, purpose, conceptual framework, hypotheses, definitions and significance of the study were given. In Chapter Two, a review of selected literature presents the factors that affect serum drug absorption with intramuscular injections, followed by a critical review of studies which have focused on the specific influence of muscle innervation (paralysis) on serum absorption of intramuscular injections. In Chapter Three the research methods, including a description of the research design, sample selection, assumptions, limitations, data collection instruments and procedures, and ethical considerations and proposed statistical procedures to be used in data analysis are presented. Chapter Four begins with a description of the sample and a discussion of factors which may have influenced sample size. This is followed by a presentation of the results and discussion of these results. The summary, conclusions, implications and recommendations for future research are presented in Chapter Five.
CHAPTER TWO

Review of the Literature

Introduction

The literature relevant to this study can be viewed within the context of the theoretical framework presented in Figure 1. The review begins with an in-depth examination of serum drug absorption and the three categories of factors influencing absorption - drug action, surface area for diffusion, and blood flow. This is followed by a critical review of studies which have focused on the specific influence of muscle innervation (paralysis) on serum absorption of intramuscular injections.

Serum Drug Absorption

Looking first at serum drug absorption, literature in the field of pharmacology was consistent in its description of this concept. The terms peak drug level, trough drug level and absorption time, or rate of absorption were generally used to describe intramuscular absorption.

As seen in Figure 2, the trough level is the lowest level of drug in the systemic circulation (Winter, 1989). The peak level is the highest level of drug in the systemic circulation following intramuscular injection. The absorption time refers to the time from injection until the drug reaches the peak serum level (Winter, 1989).

The three pharmacokinetic parameters - peak level, trough level and absorption time, offer a basic picture of drug absorption. If indicated, additional parameters may be calculated for the absorption or elimination phase of a drug, to provide a more complete picture of a drug's disposition.
Figure 2. Serum drug absorption following intramuscular injection. Adapted from Basic Clinical Pharmacokinetics by M. Winter, 1989)

The concepts of absorption phase and elimination phase are depicted in Figure 2. The upward slope of the plotted serum levels correlates with the absorption phase of the drug while the downward slope correlates with the elimination phase of the drug.

With drugs such as gentamicin, absorption is thought to be complete by the time the peak is achieved. With this type of drug disposition, the elimination phase can be characterized by first-order elimination kinetics - "a process in which the amount or concentration of drug in the body diminishes logarithmically over time" (Winter, 1989, p. 383). Parameters used to measure this type of elimination include elimination rate constant, half-life, and volume of distribution.
The intent of this study was to focus on the trough level, peak level, and time of absorption, but as necessary additional calculations were made to give a more complete picture of a drug's disposition following intramuscular injections.

The desired/usual parameters for serum drug levels can be found in the literature. Using intramuscular injections of gentamicin in healthy subjects as an example, the peak therapeutic plasma concentration is in the range of 4-8 mg/L (Winter, 1989). Therapeutic trough levels are less than 2 mg/L. Sustained trough levels higher than this have been associated with toxicity (Winter, 1989). Winter notes that absorption time is less predictable with I.M. injections than intravenous. However, in most patients gentamicin plasma concentrations peak approximately one hour after an I.M. injection. Standards of practice in Vancouver seem to support this assumption. A survey of the major hospitals in Vancouver indicated the laboratories have set a standard of one hour post I.M. injection for the collection of all peak serum gentamicin levels. The pharmacology literature was not only consistent in the definition of absorption, but also in the levels and absorption times identified for specific drugs such as gentamicin.

The theoretical framework for this study identified three categories of factors which influence serum drug absorption. The categories of factors which were identified as having a potential influence on the serum trough level, peak level, and/or absorption time were drug action, area for diffusion, and blood flow. What follows is a detailed description of each of these categories beginning with drug action.
Drug Action

The framework identified drug action as one category of factors influencing serum drug absorption. This category can be divided into influences on absorption related to drug properties, and influences related to interacting drugs.

Drug Properties

Drug properties which may affect absorption include lipophilicity, volume and concentration. Kock-Weser (1974) identified high lipophilicity as being associated with rapid absorption. His findings indicated that drugs that are poorly water soluble may precipitate at the injection site and become unable to diffuse into capillaries. Gentamicin is very water soluble and is therefore absorbed well following intramuscular injections (Winter, 1989).

Drug volume and concentration have been identified as influencing the rate of absorption, but this relationship appears to vary with different drugs as Jebson (1971) demonstrated. His study revealed that atropine is absorbed from muscle more rapidly when it is administered in a smaller volume of more concentrated solution, whereas this did not hold true for lidocaine. Although noted as an influence, generalizations about the effect of drug volume and concentration on absorption cannot be made. Research regarding the influence of volume and concentration of gentamicin on serum drug absorption was not found.

Interacting Drugs

In addition to drug properties, the literature indicated that interacting drugs may enhance or inactivate absorption. Once again using gentamicin as the example, it is noted that patient
serum samples which contain the drugs sagamicin, sisomycin and netilimicin will yield falsely elevated values for gentamicin. High concentrations of penicillins or cephalosporins have been shown to inactivate gentamicin in vitro (Tindula, 1983).

It is clear from the literature that both drug properties and interacting drugs may influence drug action and thus serum drug absorption. In addition to being affected by drug action, absorption is affected by the surface area for diffusion.

**Area for Diffusion**

The theoretical framework (Figure 1) identified surface area for diffusion as one of three categories of factors which influence absorption. A frequently quoted article by Zellman (1961) reports research findings and case studies which provide insight into the influence that three specific factors - needle size, massage, and withdrawal technique - have on diffusion area and thus absorption.

**Needle Size**

Needle size was identified as an important factor influencing absorption. Zellman noted that if the length of the needle is not sufficient to reach the "belly of the muscle" there is danger of injection into subcutaneous tissue which results in slower absorption and greater tissue reaction. His findings suggest that a needle must be no shorter than 1 1/2, and generally needs to be no longer than 2 1/2 inches. In addition to needle length, bore size is important. According to Zellman, a large bore size increases the likelihood of subcutaneous leakage, and slower absorption.
Massage

A second factor which was identified as influencing surface area for diffusion was massage. According to Zellman (1961) and Kock-Weser (1974) deep, firm massage of the muscle tissue favors spread of the medication through a wider area of tissue, increasing the area of absorption and decreasing the intensity of discomfort.

Withdrawal Technique

Withdrawal technique was the third factor which was identified as influencing absorption by affecting the surface area for diffusion. Zellman reported that radiographs of injections reveal that quick withdrawal, without leaving the needle in place for a few moments, and failure to apply immediate pressure result in subcutaneous leakage and thus slower absorption. Zellman suggested that 0.2 cc of air in the syringe barrel held upright provides the means for clearing the needle of medication before withdrawal, thus reducing subcutaneous leakage.

In summary, the literature identified needle size, massage, and withdrawal technique as three factors influencing absorption through their effect on surface area for diffusion. The next section addresses those factors known to alter absorption through their effect on blood flow.

Blood Flow

The third, and most critical of the factors influencing absorption, has been identified as blood flow. Testing the rate of absorption of a variety of compounds with different diffusion coefficients, Bederka (1971) demonstrated that blood flow is the most critical factor affecting absorption from muscle. Blood
flow was altered through the absorbing site by adding drugs known for their vasoconstrictor and dilator effects. The significance of this study is noted repeatedly in the literature.

The framework for this study identified four factors influencing blood flow - renal and cardiovascular function, muscle group and muscle innervation.

**Renal and Cardiovascular Function**

Blood flow is influenced by renal and cardiovascular function. The literature in the field of physiology supports the theory that renal and cardiac dysfunction are both associated with reduced blood flow (Emes & Nowak, 1983). In the case of renal dysfunction, drug excretion is hampered. Gyselynck and colleagues (1971) studied the renal clearance of gentamicin in 18 patients with different degrees of renal function. They found that in cases of severe renal failure the half life of gentamicin was unusually prolonged. The half-life of a drug is the amount of time required for the plasma drug concentration to decrease by one-half (Winter, 1989). In a review article (1968) Ballard cited a number of studies which found that in the case of cardiac failure the half-life was prolonged, and serum levels were lower due to reduced blood flow.

**Muscle Group**

Blood flow is influenced not only by renal and cardiovascular function, but also by muscle groups. Evans (1971) demonstrated that blood flow varies with different muscle groups by measuring the resting muscle blood flow in normal subjects. She performed simultaneous measurements in the usual intramuscular injection sites in 20 subjects. Her findings indicated that the deltoid
muscle had the greatest blood flow, followed by the vastus lateralis, and the gluteal muscle. She found the differences to be consistent and suggested they were of sufficient magnitude to affect the rate of absorption and peak serum levels following intramuscular administration of drugs. She noted, however, that further study is needed to determine for which drugs the difference has clinical significance.

**Muscle Innervation**

The final factor identified as influencing blood flow, and thus serum drug absorption was muscle innervation. A spinal lesion blocks nerve pathways interfering with muscle innervation. Reduced innervation leads to muscle atrophy and flaccidity, which in turn results in reduced blood flow in the paralyzed tissue (Guttman, 1974).

Seifert and colleagues (1972) studied the blood flow in muscles of paraplegic patients using a double isotope measurement technique. They compared blood flow in the normal bicep muscle with the paralyzed anterior tibial muscle. They concluded that blood flow was significantly reduced in paralyzed muscle, however, no consideration was given to possible differences in blood flow in normal biceps versus normal anterior tibial muscles.

The literature supported the theory that renal and cardiovascular function, and muscle groups influence blood flow and absorption. Seifert's study was the only study found which looked at the relationship between muscle innervation and blood flow. Although the results suggested a relationship they did not account for "normal" differences in blood flow in the biceps.
versus the anterior tibial muscles. It is also unknown, from this study, whether the effect of muscle paralysis on blood flow was significant enough to affect serum drug absorption following intramuscular injection.

**Spinal Cord Injury and Drug Absorption**

There is limited literature on the effects of spinal cord injury on drug absorption. Only three studies were found that examined I.M. administration of gentamicin in spinal cord injured patients. Segal, 1986, compared absorption of intramuscularly administered gentamicin in 17 spinal cord injured subjects to that administered to 8 able-bodied control subjects. The study controlled for interacting drugs, cardiac function, renal function, and injection technique. Single injections were given in the vastus lateralis of all subjects. Blood samples were obtained and the serial time-course of serum gentamicin absorption was followed. Pharmacokinetic parameters were estimated from semi-logarithmic plots of serum drug concentration versus time.

Segal found that the mean peak serum level (μg/ml) achieved was higher in the controls (5.84 ± 1.14) than in the spinal cord injured population (4.27 ± 0.68). He found that the mean absorption time was 0.69 hours ± 0.18 in the controls versus 1.1 ± 0.4 in the spinal cord injured population. In addition to finding an increased absorption time and decreased serum peak level in the spinal cord injured group, Segal found that elimination appeared to be delayed (decreased elimination rate constant, increased half-life and increased volume of distribution). He suggested that the apparent delay in
elimination probably reflected the influence of a slowed absorptive phase on the terminal elimination kinetics. Although his findings appear significant, the study only examined serum levels following one dose of gentamicin, and may not be reflective of the serum levels after repeated doses. No indication was given as to why equal numbers of subjects were not included in the control group. The presumption that apparent delays in elimination are related to delayed absorption is plausible but requires further study with more explicit control for factors which could influence elimination. In examining the changes in gross body composition with spinal cord injured patients, Greenway and associates (1970) found that pathophysiological changes such as alterations in motor tone and muscle mass contributed to an increase in total extracellular fluid volume. It would be difficult to identify what portion of the delay in elimination was attributable to slowed absorption, and what was attributable to an increase in volume of distribution as a result of an increase in extracellular fluid volume.

A more complex follow-up study was done by Segal in 1988. In this study paraplegics, tetraplegics and able-bodied subjects receiving I.M. and I.V. gentamicin were compared. The subjects were divided into: I.M. only, I.V. only, and a cross-over group. In this study Segal looked at both the rate and completeness of gentamicin absorption. He found that the amount of drug reaching the systemic circulation was undiminished in able-bodied and spinal cord injured subjects regardless of whether the drug was administered intramuscularly or intravenously. While Segal found
that the completeness of absorption was not affected by spinal cord injury, he duplicated his earlier findings which suggested that rate of absorption is altered in spinal cord injury. He found, once again, that I.M. gentamicin was absorbed more slowly and the peak level reached was lower in spinal cord injured patients than in the "normal" population. In this study, as in the previous one, he linked a delayed elimination half-life to a prolonged absorption phase following injections in paralyzed muscle. Further support was given to this proposition by the semi-logarithmic plotting of the absorption profiles. Segal found that the profile for the spinal cord injured group was not linear, suggesting that for this group absorption may not be a simple first order process.

The final study found was done in India by Sankaranarayanan and associates in 1989. In this study the I.M. absorption of gentamicin from the deltoid muscle was compared using six bed-ridden paraplegics and six able-bodied subjects. The study controlled for a number of factors known to influence absorption such as: cardiac function, renal function and hepatic function, but no mention was made as to whether there was any control for interacting drugs.

The study found that the peak serum level was lower and the time to reach the peak was delayed following injections in the paraplegics as compared to the controls. The authors recognized that the results could possibly be attributed to the increased volume of distribution seen as a result of pathophysiological changes associated with spinal cord injury. The authors also suggested that in paraplegics who are bedridden, as is the case
in India, there may be a generalized decrease in muscle blood flow contributing to impaired absorption from non-paralyzed limbs. To test this the authors would need to repeat the study with a control group made up of persons with intact neuraxis who are bedridden - not an easy group to find.

Summary

In summary, serum drug absorption was discussed in the literature using pharmacokinetic parameters such as serum trough level, peak level, and absorption time/rate. In addition information about drug absorption/elimination was described in the literature using parameters such as elimination rate constant, half-life and volume of distribution.

The literature supported the theory that drug action, surface area for diffusion and blood flow influence serum drug absorption following intramuscular injections. In addition the literature supported the specific factors identified within each of these three broad categories of influence.

There were relatively few studies exploring the absorption of I.M. gentamicin in the spinal cord injured population. Two studies found suggest that gentamicin is not absorbed as well in the spinal cord injured population as in the "normal" population when injections/infusions are given below the level of injury. One study found that absorption was impaired in non-paralyzed deltoid muscle of bedridden spinal cord injured patients as compared to deltoid injections in an able-bodied control group. This study needs to be replicated in active paraplegics before any generalizations can be made. No studies were found that compared absorption above and below the lesion in spinal cord
injured patients. This leads one to question if absorption would be improved if injections were given above the level of injury, in non-paralyzed muscle where the blood flow is greater. This study was designed to test this hypothesis.
CHAPTER THREE

Methods

Introduction

This chapter provides a description of the methods used to compare intramuscular injections above and below the level of injury. Content includes a discussion on the research design, sample selection and criteria, assumptions and limitations, data collection instruments, data collection procedures, procedures for protection of human rights and data analysis.

Design

This study used an experimental, repeated measures design with counterbalancing (Figure 3). The subjects acted as their own controls by receiving injections both above and below the level of spinal cord injury. The initial site of medication injection was randomly assigned. Before and after the fourth medication injection in each site, serum samples were drawn to determine comparable trough levels, peak levels, and absorption times. Choosing to draw blood samples before and after the fourth dose was based on the fact that steady state is achieved by the third dose (Winters, 1989). Figure 3 illustrates the sequence of events.

Five serum gentamicin samples were taken at each site. In Figure 3, subject 1, X represents injections in the deltoid muscle. Just prior to the fourth injection, a serum sample was taken (01). According to Winter (1989) serum trough levels should be obtained within the half hour prior to the next dose.
Figure 3. Study design illustrating sequence of injections and serum samples.

Subject order   Treatment Sequence
1.  R X1-3 01 X4 02-5 Y1-3 01 Y4 02-5
2.  R Y1-3 01 Y4 02-5 X1-3 01 X4 02-5

Symbol Guide
R = random assignment
X = above lesion injections (deltoid)
Y = below lesion injections (gluteal)
0 = measurement of serum gentamicin

Further samples were taken at 1, 2, 3, and 4 hours post injection (02 - 05). These times were determined in consultation with clinical pharmacologists. Because the hospital research committee specified that no more than four samples could be collected post medication injection, the times were spaced in order to provide a picture of both the absorption and elimination phases of the drug.

Once the five samples were collected the site was changed and the entire process repeated. This means that, for subject 1 in Figure 3, just prior to the fourth injection in the gluteal muscle (Y4) a serum sample (01) was drawn, followed by samples at 1, 2, 3, and 4 hours post-injection (02-5). Once the 10 samples were collected, the site of any remaining injections was of no
Sample Selection

The target population of this study was persons with spinal cord injuries between the levels of C-6 and L-2 with complete loss of motor function below the level of injury. A convenience sample of 10 patients from one rehabilitation centre was to be selected based on the following criteria:

1. All subjects had a gram negative bladder infection which their physician had determined was best treated with I.M. gentamicin.
2. All subjects had a physician's order for I.M. gentamicin for a minimum of four days in equally divided doses over equal time intervals. The dosage and time interval between injections were individually calculated. Between patients there were varying dosages and time intervals, but individual treatment regimes were to remain constant.
3. All subjects had no clinical or laboratory evidence of hematologic, cardiac, renal or hepatic disease.
4. During the two weeks prior to being in the study none of the subjects received any drugs known to alter muscle blood flow, influence gentamicin disposition, or interfere with assay methods.
5. All subjects were diagnosed as having a complete spinal cord injury (no motor function below the level of injury), in the range of C-6 to L-2.
6. All subjects had signed written informed consents (Appendix A).

While it was the intention of this researcher to have a sample size of 10, after a year and a half of data collection,
the actual sample size was only three. Possible explanations for the lack of subjects are detailed in chapter four.

**Assumptions**

It was assumed that I.M. injections are preferred over I.V. therapy.

It was assumed that there was no cross-over of gentamicin four doses after the site change, based on known renal clearance times for gentamicin. (Winter, 1989).

**Limitations**

The major limitation of this study was that of the sample size, which was dependent upon the frequency of patients being diagnosed with a gram negative bladder infection best treated by I.M. gentamicin, during the length of time feasible for the study. The actual sample size had to be reduced to three from the proposed 10.

The I.M. injections were given by a number of nurses. Although they were all following a set procedure (Appendix B) there may have been minor variations in technique.

Limits placed on the number of serum samples which could be collected, restricted the types of pharmacokinetic parameters which could be calculated.

**Data Collection Instruments**

The two instruments that were used to collect the data in this study included an Abbott TDX and a data collection sheet.

**Abbott TDX**

In this study the serum gentamicin levels were measured by means of fluorescence polarization amino assay. The specific instrument used was the Abbott TDX. Watson and colleagues
(1976), reported that serum gentamicin results by florescence polarization correlate with both bioassay \((r = 0.93)\) and radioimmunoassay \((r = 0.97)\) methods of analysis. Results which correlate this highly with two well established methods of analysis suggest the Abbott TDX is a valid tool to use in measuring serum gentamicin.

The accuracy and reproducibility of this instrument have been the subject of a number of studies in recent years. Comparisons of bioassay, enzyme multiplied immunoassay and fluorescence polarization immunoassay identified the latter as the most accurate (Araj et al., 1985). Cheng, Lam & French (1987) did a comparative evaluation of the Abbott TDX, the Abbott ABA200 and Syva LAB5000 for assay of serum gentamicin. They found all three produced a high degree of accuracy and reproducibility with spiked samples when the concentrations of gentamicin were within the range of 3-8 mg/l. However, with concentrations below 2 mg/l or above 8 mg/l, only the TDX system gave acceptable coefficients of variation and accurate recoveries. With 10 repeated samples, and control gentamicin values of 1, 4, and 8 ug/ml, the TDX determined the levels to be 0.99 \(\pm\) 0.08; 4.04 \(\pm\) 0.15; and 7.91\(\pm\) 0.11 respectively. As the results indicate, the Abbott TDX is a reliable tool for measuring serum gentamicin.

According to the users' manual, the Abbott TDX is sensitive to a level of 0.3 ug/ml. This means that 0.3 ug/ml is the lowest measurable level of serum gentamicin that can be distinguished from zero with 95% confidence. The laboratory used for this study makes no distinction between gentamicin levels ranging from zero to 0.3 ug/ml. Any levels within this range are reported as
< 0.3 ug/ml.

The Abbott TDX has been well tested and is currently in use in over four hundred institutions in Canada. The accuracy of the Abbott TDX is measured in terms of accuracy by recovery. By adding clinically relevant concentrations of gentamicin to gentamicin-free pooled human serum and doing replicate assays one determines the average recovery. The user's manual for the Abbott TDX identifies the average recovery as 99% ± 3.5%. Cheng et al (1987) found similar results, confirming the validity of the tool.

The serum testing for this study was done by a major teaching hospital where the instrument is part of a blind quality control program and precision testing is done on a daily basis.

Data Collection Sheet

The data collectors recorded relevant information pertaining to the patient's current health status, recent lab values, and specific information related to gentamicin injections and serum sample collection. Recording was done on the data collection sheet which is shown in Appendix C.

Data Collection Procedure

Prior to beginning the study, the investigator met with all of the rehabilitation centre physicians caring for patients with spinal cord injuries to explain the study and ensure their support.

All Registered Nurses who could have been involved in giving the injections were given inservice preparation by the investigator to ensure standardization of the injection technique (Appendix B). The critical injections were those administered
just prior to the observations. To decrease the risk of technique variance, the critical injections were given by one of three nurses who acted as research assistants to the study. These three nurses were given more extensive preparation.

In addition to giving the critical injections, the assistants were responsible for drawing the serum samples. The assistants were Registered Nurses experienced in venipuncture. The investigator reviewed the venipuncture procedure with these nurses (Appendix D) to ensure standardization of technique.

When gentamicin I.M. was ordered for a patient, the pharmacy department informed the investigator. If the patient met the criteria, the nurse clinician asked his permission to be approached by the investigator. If the patient agreed to participate, an informed consent was signed (Appendix A). The patient's physician, and other staff who were affected by the study were notified.

The individual patient doses were labelled according to date, time, dose and site. Nurses were made aware of the importance of following the exact directions. These same parameters were noted on the medication sheet, and in the Kardex. The samples were analyzed at a hospital laboratory and the results returned to the investigator.
Protection of Human Rights

The proposal was approved by the University of British Columbia Clinical Screening Committee for Research and Other Studies Involving Human Subjects and by the Research Review Committee at the participating rehabilitation centre.

Potential subjects were given an information letter (Appendix A). If they agreed to be in the study a signed consent was completed. For the one subject who was unable to sign his own name, due to impaired motor function, a witnessed 'X' satisfied the criteria for a signed consent. Parental consent was obtained for the one subject under the age of 19. Subjects were assured in writing that they could withdraw from the study at any time and that such action would in no way jeopardize their care.

If any of the serum levels appeared above the therapeutic or "safe" level, the subject's physician would have been notified immediately. Subject names did not appear on any of the written documentation resulting from the study. Subjects were informed in writing that all results were confidential with the above exception.

Burns and Grove (1987) would define this study as one of "minimal risk" as it caused temporary discomfort, but the potential benefits outweighed the risks. Temporary discomfort came from injections given above the level of injury where the subject had sensation. It must be noted that the injections would have been given regardless of study participation; it was only the site of injection that was being manipulated. The venipunctures required to test serum gentamicin levels also caused temporary discomfort. It is usual practice for physicians
to order the collection of two serum gentamicin levels during a period of treatment. This study required patients to have an additional eight samples collected (2ml/sample).

Data Analysis

If there had been 10 subjects, it was the intent of this investigator to analyze the data using descriptive statistics and to test the hypotheses using one-tailed t-tests for dependent samples. Descriptive statistics would have been used to detail each of the serum drug measures - trough level, peak level and absorption time - for each site. The mean level/time and the variance would have been calculated for each parameter and each site. To test the hypotheses a one-tailed t-test would have been used; one-tailed because the literature suggested that gluteal absorption would be slower/longer. Given 10 subjects the power of such a test would have been approximately 0.7 if a 0.05 level of significance was used.

Because the sample size of 10 was not obtained, an alternate method of analysis was required. It was the learned opinion of the consultant statistician that given a sample size of three, the results were most appropriately viewed as three individual case studies. Kennedy (1979) notes that one of the advantages of case analysis is the greater degree of detail which can be provided for the reader. To provide more detail about serum drug absorption, in each of the cases in this study, additional pharmacokinetic parameters were calculated. In addition to calculating the serum trough level, serum peak level, and absorption time, the elimination parameters of elimination rate constant, half-life, and volume of distribution were calculated.
(see Appendix E for definitions and equations). Further information about serum drug absorption was gleaned by graphing the logarithm of the serum levels for each site.

Summary

This chapter has described the methods intended for use in comparing intramuscular absorption above and below the level of injury in persons with a spinal cord injury. The study was designed as an experimental repeated measures design with counterbalancing. The sample was to consist of a convenience sample of 10 subjects who met the criteria - in actuality the sample consisted of three subjects. An overview of the assumptions and limitations of this study were presented. The instruments used to collect the data included an Abbott TDX and a data collection sheet. Three nurses, trained by the investigator, collected the data. The proposal was approved by the UBC Clinical Screening Committee for Research and Other Studies Involving Human Subjects and the Research Review Committee at the participating rehabilitation centre. It was proposed that the hypotheses be analyzed using descriptive statistics and t-tests, but given the reduced sample size the analysis method was changed to case analysis.
CHAPTER FOUR

Presentation and Discussion of Results

Introduction

This chapter is divided into two sections. The first section includes a description of the sample and a discussion of factors which may have influenced the sample size. The second section is a presentation of the case studies with subsequent discussion of the findings.

Characteristics and Discussion of Sample

Although the original plan to have a sample of 10 subjects was considered reasonable based on the information available in 1988-90, it was only possible to recruit four subjects into the study and have complete findings for three of these subjects during the data collection period which lasted from July 1990 to September 1991. Possible factors contributing to a smaller sample size included a new laboratory protocol, a concurrent research study and availability of new antibiotics. Each of these factors will be presented and efforts taken to increase the sample size will be described.

Sample

During the period of data collection for this study only seven patients with spinal cord injury were ordered gentamicin. Of the seven patients ordered gentamicin, one refused to participate in the study. Two of these patients did not meet the study criteria with regards to paralyzed and non-paralyzed muscle - One had been injured at C-4 resulting in paralyzed deltoid and gluteal muscle and the other had an incomplete injury with intact gluteal and deltoid muscles. Another patient was started on the
study, but due to a high fever he was transferred to acute care for intravenous antibiotics. The remaining three patients, who were ordered gentamicin, made up the subjects for this study.

**Possible Factors Influencing Sample Size**

Information was collected during the preparation of the research proposal to ensure that there would be sufficient potential subjects who met the criteria. For the two years prior to the data collection, there were approximately 30 patients per year at the Centre with spinal cord injury who were ordered gentamicin. During the 14 months of data collection however, only seven patients were ordered gentamicin.

After 10 months of data collection, in an effort to increase those eligible for participation, the medication choice was extended to include amikacin and tobramycin. Like gentamicin, these drugs are in the aminoglycoside family and follow first order kinetics. The expansion of inclusion criterion did not contribute to a larger sample size. Factors which probably influenced this drop in potential subjects include a new laboratory protocol for urine cultures, a concurrent research study involving the same subjects, and new antibiotics on the market.

**New laboratory protocol.** It is likely that a change in laboratory protocol resulted in fewer patients within the participating centre being ordered gentamicin. The protocol was initiated to reduce time and cost related to processing urine specimens on asymptomatic patients. After June 1990 urine specimens for culture and sensitivity would only be analyzed if "significant bacteriuria" was present. The criteria for analysis
was based on a minimum number of colony forming units per litre (CFU/L) and in some cases on the presence of specified clinical symptoms.

While the pre-requisites were eased in April 1991, the policy appeared to have a significant impact on the number of patients having urine specimens analyzed. This in turn probably reduced the number of patients being diagnosed as having a urinary tract infection, and thus the number being treated with aminoglycosides. To illustrate the difference, a comparison was made between the number of urine specimens collected in the three months prior to the policy being implemented with the same three months period after it was implemented. The average number of specimens dropped from 30/month to 8/month - a 75% reduction, while there was no decrease in the number of patients with spinal cord injuries in the Centre. Although it is beyond the realm of this study to unequivically establish the impact of the new laboratory protocol - it appears to be a possible factor which influenced the sample size of this study. A second possible influence was a concurrent research study.

Concurrent research study. At approximately the same time as this study began and the laboratory set up the new protocols, a concurrent urinary research study on spinal cord injured patients was being conducted at the same rehabilitation centre. Subjects for the concurrent study were those persons with a neurogenic bladder as a result of spinal cord injury who were about to be put on intermittent catheterization. A majority of the spinal cord population were involved in this study. Subjects were randomly assigned to one of two groups, A and B. Those in group
A received standardized antimicrobial therapy for all episodes of bacteriuria (BU), whether symptomatic or asymptomatic, (see definitions in Appendix F). Those in group B were only treated for "symptomatic" bacteriuria.

There are two ways that the concurrent study may have influenced the sample size for the present study. Firstly, utilizing standardized treatment protocols may have decreased the subjects' exposure to a range of antibiotics, thus decreasing the possibility of resistances developing. The Centre pharmacist indicated that if the subjects had infections which remained sensitive to oral antibiotics they would not require gentamicin for gram-negative infections.

Secondly, half of the subjects (those in Group B) were only treated for "symptomatic" bacteriuria. Regardless of the number of colony forming units per litre, this group was only treated for specific symptoms identified in Appendix F. Symptoms which had previously been considered grounds for treatment such as dysreflexia, reflex sweating, increased spasticity, malaise, urinary incontinence, and cloudy urine, were labelled as non-specific symptoms in this study and were not to be treated. By restricting half of the subjects to treatment only for limited symptoms, there was a decrease in the possible use of gentamicin.

**New Antibiotics.** The recent development and release of quinolone drugs on the market is the third factor which probably affected the sample size of this study. While the use of aminoglycosides decreased in the participating centre in the past year, the use of quinolones increased dramatically.

Two quinolines currently on the market are norfloxacin and
ciprofloxacin. Quinolones are effective against gram negative bacteria, but unlike the aminoglycosides they can be given orally and are therefore preferable (Winslade, 1991). The combination of factors - change in laboratory protocol, concurrent research study, and the marketing of quinolones, appeared to have had a major effect on the sample size for this study.

Findings and Discussion of Case Studies

Originally it was the intent of this investigator to analyze the data using descriptive statistics and hypotheses testing using one-tailed t-tests for dependent samples. Due to a final sample size that was smaller than originally intended, the results were more appropriately viewed as individual case studies (Boldt, 1991). To consider the subjects as cases requires one to employ a replication rather than sampling logic. When employing replication logic, it is appropriate to look at clinical rather than statistical significance (Yin, 1989). Each case was considered akin to a single experiment which had been replicated. Findings for each of the three subjects is presented and discussed both individually and jointly.

Case #1

The first case involved a 29 year old male who suffered a complete spinal cord injury at T-12 six weeks prior to participating in the study. He weighed 56.5 kg and was approximately 5'10" with a muscular build. A previously healthy person, he met the criteria for the study. Gentamicin was ordered when it was presumed he had pyelonephritis. His symptoms included fever, malaise, and lower abdominal discomfort. The physician ordered 80 mg. of gentamicin I.M. q12h. The subject
was randomly assigned to receive the first four injections in the gluteal muscle and the subsequent four in the deltoid. The first set of serum samples were obtained before and after the fourth injection, and the second set of serum samples were obtained before and after the eighth injection. The protocols for injections and data collection were followed. Table 1 identifies the serum levels obtained following injections in each site, and Figure 4 visually displays the findings.

**Table 1**

Subject 1 - Comparative Serum Levels

<table>
<thead>
<tr>
<th>Time</th>
<th>Deltoid Muscle</th>
<th>Gluteal Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 hr. pre-injection</td>
<td>0.5ug/ml</td>
<td>&lt;0.3ug/ml</td>
</tr>
<tr>
<td>1 hr. post injection</td>
<td>4.2ug/ml</td>
<td>3.8ug/ml</td>
</tr>
<tr>
<td>2 hr. post injection</td>
<td>3.2ug/ml</td>
<td>2.8ug/ml</td>
</tr>
<tr>
<td>3 hr. post injection</td>
<td>2.3ug/ml</td>
<td>2.0ug/ml</td>
</tr>
<tr>
<td>4 hr. post injection</td>
<td>1.7ug/ml</td>
<td>1.6ug/ml</td>
</tr>
</tbody>
</table>

The results can be viewed in terms of supporting/rejecting the three hypotheses of this study. The first hypothesis was that the serum trough level would be greater when the injections are given above the level of injury than when they are given below. The trough serum level 1/2 hour pre-injection, (<0.3 ug/ml.) was lower following injections in the paralyzed gluteal muscle, than the trough level of 0.5 ug/ml in the non-paralyzed
Figure 4. Subject #1 - Serum Concentration Time Curve

Serum Levels (ug/ml.)

<table>
<thead>
<tr>
<th>Time</th>
<th>Deltoid</th>
<th>Gluteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 hr. pre</td>
<td>0.5</td>
<td>&lt; 0.3</td>
</tr>
<tr>
<td>1 hr. post</td>
<td>4.2</td>
<td>2.8</td>
</tr>
<tr>
<td>2 hr. post</td>
<td>3.5</td>
<td>2.6</td>
</tr>
<tr>
<td>3 hr. post</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td>4 hr. post</td>
<td>1.7</td>
<td>1.6</td>
</tr>
</tbody>
</table>
deltoid muscle. These findings support the first hypothesis.

The peak serum level, the highest of the four post injection measurements, was 3.8 ug/ml following injections in the paralyzed muscle as compared to 4.2 ug/ml following injections in the non-paralyzed muscle. This supports the second hypothesis that the peak serum level would be greater when the injections are given above the level of injury than when they are given below.

In the literature review it was noted that the therapeutic range for gentamicin was 4-8 ug/ml. In case #1, while the injections in the deltoid muscle reached a therapeutic level, the injections in the gluteal muscle did not. According to discussions with a clinical pharmacist working with spinal cord injured patients, a peak level of 3.8 ug/ml, as was the situation following the gluteal injections, would lead her to recommend that the gentamicin dosage be increased. On the other hand she stated that if she was shown a peak level of 4.2 ug/ml, as was the case following deltoid injections, she would recommend the dosage not be changed. It is evident that the choice of injection site in this case could have affected the recommended treatment protocol.

The third hypothesis was that the absorption time/rate of I.M. gentamicin is faster when injections are given above the level of injury than when given below. In examining Figure 4 it appears that the absorption time was one hour for both sites. Unfortunately with limited serum samples it was not possible to specify the exact time that the serum levels peaked and therefore not possible to make conclusive statements regarding any possible differences in the absorption times without doing further
pharmacokinetic calculations.

Given limited data about serum levels during the absorption phase, indirect inferences regarding absorption times/rates came from the calculation of three elimination phase pharmacokinetic parameters - the elimination rate constant, the half-life, and the volume of distribution.

Determination of these parameters required the drug to have reached steady state. According to Winter (1989) steady state is achieved by the fourth injection. Since levels were drawn after the fourth and eighth injections, in this case, one could assume the drug was at steady state.

Calculation of these parameters required two serum measures. The half hour pre-injection and one hour post-injection levels are generally used, although using any measure for the trough is acceptable as long as the time between serum levels spans at least one half-life (Winter, 1989, p. 44). In case #1, with a trough level of questionable accuracy (<0.3), it was more appropriate to use the one and four hour post injection levels for the calculations. Having two serum levels drawn at steady state allowed the following elimination phase pharmacokinetic parameters to be calculated.

In this case injections in the gluteal muscle resulted in a smaller elimination rate constant, a prolonged half-life and an increase in the apparent volume of distribution as compared to values following deltoid injections. Generally these findings would suggest that elimination was delayed following gluteal injections, but in this case it is likely that the differences were attributable to a prolonged absorption phase rather than
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Deltoid Site</th>
<th>Gluteal Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination Rate Constant</td>
<td>0.30h⁻¹</td>
<td>0.29h⁻¹</td>
</tr>
<tr>
<td>Half Life</td>
<td>2.3 hours</td>
<td>2.4 hours</td>
</tr>
<tr>
<td>Volume Distribution</td>
<td>14.5 litres</td>
<td>16.3 litres</td>
</tr>
</tbody>
</table>

delayed elimination. Using the subject as his own control eliminated many factors which could have influenced elimination. Gentamicin is nearly totally eliminated by the kidneys, and given that during the time of data collection this subject had no apparent changes in renal function or fluid volume it seems unlikely that the differences were a result of delayed elimination.

Gentamicin is thought to be characterized by first-order elimination kinetics, meaning that absorption is complete at the time the peak is reached, and the drug diminishes logarithmically over time. Since the drug concentration diminishes logarithmically, a graphic plot of the logarithm of the plasma level versus time should yield a straight line. In Figure 5, while the logarithm for the deltoid site appears linear, the same cannot be said for the gluteal site. This suggests that the elimination was not of the first order. Given that the subject acted as his own control, and there was no apparent change in renal function, it is likely the non-linear logarithm reflected a prolonged absorption phase rather than a delayed elimination.
Figure 5. Subject #1 - Logarithm of Serum Levels vs Time

<table>
<thead>
<tr>
<th>Time Post-injection</th>
<th>Deltoid</th>
<th>Gluteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 hr pre</td>
<td>0.5</td>
<td>&lt;3</td>
</tr>
<tr>
<td>1 hr post</td>
<td>4.1</td>
<td>3.8</td>
</tr>
<tr>
<td>2 hr post</td>
<td>3.2</td>
<td>2.8</td>
</tr>
<tr>
<td>3 hr post</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td>4 hr post</td>
<td>1.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>

- Deltoid Site
- Gluteal Site
In terms of whether one site created more discomfort than the other site, this subject described the injections in the deltoid as painful. He stated that it felt like "a pulled muscle for a few days", and slowed down his ability to wheel his chair. No discomfort was noted with gluteal injections.

In summary, in case #1 the serum trough and peak levels were higher following deltoid injections, supporting the first two hypotheses. While a measure of the time from injection to the peak did not appear to differ in either site, this may only be a reflection of the limited serum levels that were measured. A decrease in the elimination rate constant, an increase in the half-life and an increase in volume of distribution, combined with a non-linear logarithm of serum levels versus time suggested that the absorption phase may have been delayed following gluteal injections. Although discomfort was not being measured, it is worth noting that the patient described significant discomfort following deltoid injections.

Case #2

Case #2 involved a 28 year old male who sustained an incomplete spinal injury at C4-5 four months prior to participating in the study. He presented as a fairly muscular individual weighing 81 kg. and reaching 6' in height. Although this subject did not meet study inclusion criteria in relation to level of injury, an exception was made because sensory and motor return post-injury left him with an intact deltoid muscle on the left side. With motor return limited to his left arm at the time of the study, he presented with an intact left deltoid muscle, a
partially paralyzed right deltoid muscle, and paralyzed gluteal muscles. A comparison of paralyzed versus non-paralyzed muscle absorption was done by eliminating the right deltoid muscle as an injection site. The subject met all other criteria for inclusion. The physician ordered gentamicin 80mg. I.M. B.I.D. for 7 days.

Subject #2 was randomly assigned to have the first set of injections in the gluteal muscle. Serum samples were drawn before and after the fourth injection. Following the collection of the first set of serum samples, the injection site was changed to the left deltoid. Serum samples were to be taken before and after the fourth injection in the new site (8th injection in total). Unfortunately the physician discontinued the gentamicin after the second deltoid injection and started the patient on Ciprofloxacin 500 mg. p.o. B. I. D. for 14 days. This was done in response to receiving the results of sensitivity tests and in response to noting much improvement in the client's status. Following discussions with the client and physician, the gentamicin was restarted, but only for three doses. Although the study protocol called for four doses, a pre-planned week-end pass by the client combined with the physician's desire to have him on oral antibiotics, and restricted laboratory hours, limited the injections to three. Twenty-four hours elapsed from the time of the last injection before the gentamicin was discontinued until the next deltoid injection was given. Once the drug was restarted serum samples were collected before and after the third injection in the deltoid muscle. Table 3 identifies the serum levels obtained following injections in each site, and Figure 6
Table 3

**Subject 2 - Comparative Serum Levels**

<table>
<thead>
<tr>
<th>Time</th>
<th>Deltoid Muscle</th>
<th>Gluteal Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 hr. pre-injection</td>
<td>&lt;0.3ug/ml</td>
<td>0.4ug/ml</td>
</tr>
<tr>
<td>1 hr. post injection</td>
<td>3.0ug/ml</td>
<td>3.6ug/ml</td>
</tr>
<tr>
<td>2 hr. post injection</td>
<td>2.2ug/ml</td>
<td>2.4ug/ml</td>
</tr>
<tr>
<td>3 hr. post injection</td>
<td>1.7ug/ml</td>
<td>1.9ug/ml</td>
</tr>
<tr>
<td>4 hr. post injection</td>
<td>1.3ug/ml</td>
<td>1.3ug/ml</td>
</tr>
</tbody>
</table>

visually displays the findings.

According to Yin (1989) replication case studies should either a) predict similar results (literal replication) or b) produce contrary results but for predictable reasons (theoretical replication). This case can be considered a theoretical replication because although it has many common features to case #1, it has a unique attribute - the serum levels taken following deltoid injections were drawn around the third not the fourth injection. The literature predicts that steady state is not achieved until the fourth dose, therefore one would anticipate the serum levels taken before and after the third injection would be lower than serum levels taken at steady state - before and after the fourth injection (Winter, 1989). While the intent was to do a literal replication, all of the factors were not
Figure 6. Subject #2 - Serum Concentration Time Curve

Serum Levels
(ug/ml.)

<table>
<thead>
<tr>
<th>Time</th>
<th>Deltoid</th>
<th>Gluteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 hr pre</td>
<td>&lt;.3</td>
<td>0.4</td>
</tr>
<tr>
<td>1 hr. post</td>
<td>3.0</td>
<td>3.6</td>
</tr>
<tr>
<td>2 hr. post</td>
<td>2.2</td>
<td>2.4</td>
</tr>
<tr>
<td>3 hr. post</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>4 hr. post</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>
duplicated. Kennedy notes that "it is acceptable to define unique attributes post-hoc" (1979, p. 667). The results of this case can be described according to the study hypotheses.

The results in Table 3 do not support the first hypothesis related to serum trough levels being higher when injections are given above the level of injury. The results in this case suggest that the hypothesis does not hold true when serum levels following injections in the deltoid are not at steady state and the serum levels following gluteal injections are at steady state. From the results one cannot say whether the hypothesis would have been supported had there been four injections in each site.

The second hypothesis related to peak serum levels being greater when injections are given above the level of injury was not supported in case #2. The only difference between this case and the first one where this hypothesis was supported was the fact that the serum samples were taken around the third injection in the deltoid site and around the fourth injection in the gluteal site. According to the literature on steady state, one would expect the peak level to be lower after the third injection than after the fourth injection. Once again, the question that cannot be answered in this case is whether the hypothesis would have been supported if there had been four injections in the deltoid muscle.

The peak levels can be discussed in terms of clinical significance. In this case the peak levels achieved following four injections were below the therapeutic range of 4-8ug/ml for both sites.
In comparing the results of the first case to this one, it is necessary to separate discussion of the gluteal site findings from the deltoid site findings. The procedure for injections in the gluteal muscle in case one and two were identical. The serum levels following four gluteal injections in both cases were found to be below the therapeutic range. Having two identical procedures produce the same results allows one to say that to some degree replication has taken place. This replication suggests that serum levels following gluteal injections of 80mg I.M. may not reach the therapeutic range in persons with a spinal cord injury.

The procedure for taking the peak serum levels following deltoid injections in case #1 and #2 were not identical. In case #1 the level was taken after four injections and in case #2 the level was taken after three injections. In case #1 the level was within therapeutic range and in case #2 the peak level was below the therapeutic range. Comparing these two cases suggests that therapeutic levels may be achieved in non-paralyzed muscle only after steady state is reached (four injections).

The third hypothesis for this study was that the absorption time of I.M. gentamicin is less when injections are given above the level of injury than when given below. Figure 6 plots the serum concentration time curve for this subject. While it appears that the absorption time (time to reach the peak level) was one hour for both sites, because of the limited samples, the true peak times are not known. The logarithm of serum levels versus time is depicted in Figure 7. The non-linear appearance of the plot of the levels for the gluteal site suggests that the
Figure 7. Subject #2 - Logarithm of Serum Levels vs Time

<table>
<thead>
<tr>
<th>Time Post-injection</th>
<th>Deltoid</th>
<th>Gluteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 hr. pre</td>
<td>&lt;.3</td>
<td>.4</td>
</tr>
<tr>
<td>1 hr. post</td>
<td>3.0</td>
<td>3.6</td>
</tr>
<tr>
<td>2 hr. post</td>
<td>2.2</td>
<td>2.4</td>
</tr>
<tr>
<td>3 hr. post</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>4 hr. post</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>
absorption of gentamicin from that site, unlike absorption from the deltoid, was not of the first order. In the first case, pharmacokinetic parameters were calculated to assist in predicting any differences in absorption time related to injection site. In this case the parameters could not be calculated since the levels for the deltoid site were not at steady state. The necessary pharmacokinetic calculations cannot be made if steady state is not achieved (Winter, 1989).

While the focus of this study was on serum drug absorption, the issue of discomfort was raised. In response to questions about discomfort from the injections, the subject in this case did not report any discomfort in his gluteal site, but reported an aching discomfort in his deltoid muscle. He stated "It doesn't hurt, it just feels like I had a really good work-out yesterday, and I'm feeling it today".

In summary this case differed from the first in that there were three not four deltoid injections given. The peak and trough levels were higher following the four gluteal injections, as compared to levels following the three deltoid injections. Neither site had peak levels within the therapeutic range. While the plot of serum levels versus time suggests that there were no differences in the absorption times from either site, the logarithmic plot suggests that absorption was not the same in both cases. It is worth noting that as in case #1, the subject in this case commented on discomfort associated with deltoid injections.
Case #3

The third case involved an 18 year old male whose admitting notes indicated he had "a T5 burst fracture dislocation with subsequent complete T5 paraplegia". Two months post-injury he was noted to have some sensory recovery. For the purposes of this study he was still classified as a complete injury because there was no recorded motor return. At three months post injury he was ordered gentamicin 80 mg. I.M. q8h for a gram negative bladder infection. His symptoms included a fever of 39 degrees C., sweating, and increased spasms. At the time of the study the subject weighed 64.5kg and was 5'10". The subject met the criteria for the study and agreed to participate. In addition parental consent was obtained because of his age. He was randomly assigned to receive the first four injections in the deltoid muscle, followed by four injections in the gluteal muscle. The study protocols were followed. Table 4 and Figure 8 display the serum level results.

In the same week that the serum samples were collected, this client began to recover some motor function in his lower extremities. While he was involved in the study he had no apparent motor function below the level of injury, but it is not possible to determine the degree of paralysis of the gluteal muscle at the time of the injections. The subsequent recovery of function suggested that the gluteal innervation, and blood flow were probably not reduced to the same extent as in the gluteal muscles of the first two subjects. This case differed from the others in two ways. The dosage of gentamicin given was higher than in case #1 and #2, and the gluteal muscle which was
<table>
<thead>
<tr>
<th>Time</th>
<th>Deltoid Muscle</th>
<th>Gluteal Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 hr. pre-injection</td>
<td>0.8ug/ml</td>
<td>1.6ug/ml</td>
</tr>
<tr>
<td>1 hr. post-injection</td>
<td>4.4ug/ml</td>
<td>4.8ug/ml</td>
</tr>
<tr>
<td>2 hr. post-injection</td>
<td>3.2ug/ml</td>
<td>4.4ug/ml</td>
</tr>
<tr>
<td>3 hr. post-injection</td>
<td>2.3ug/ml</td>
<td>3.5ug/ml</td>
</tr>
<tr>
<td>4 hr. post-injection</td>
<td>1.7ug/ml</td>
<td>2.6ug/ml</td>
</tr>
</tbody>
</table>

paralyzed in case #1 and #2, was possibly not totally paralyzed in this case. Rather than disregard this case because of the differences, it was examined as a theoretical replication in which there were known attributes which were unique.

The trough levels in this case were both within therapeutic range (below 2 ug/ml) but they were both notably higher than in case #1 and #2 where the dosage was lower. The hypothesis that the trough level would be greater when the injections are given above the level of injury did not hold true for this case. It was also hypothesized that the peak serum level is greater when the injections are given above the level of injury than when they are given below. In case #2 this second hypothesis was not supported. The peak serum level following
Figure 8. Subject #3 - Serum Concentration Time Curve

Serum Levels
(ug/ml.)

<table>
<thead>
<tr>
<th>Time</th>
<th>Deltoid</th>
<th>Gluteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 hr pre</td>
<td>0.8</td>
<td>1.6</td>
</tr>
<tr>
<td>1 hr post</td>
<td>4.4</td>
<td>4.8</td>
</tr>
<tr>
<td>2 hr post</td>
<td>3.2</td>
<td>4.4</td>
</tr>
<tr>
<td>3 hr post</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>4 hr post</td>
<td>1.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>
injections in the gluteal muscle was higher than the peak level following injections in the deltoid muscle.

Of the three cases, this was the only one where both the gluteal and deltoid injections resulted in peak serum levels within the therapeutic range. In case #1 therapeutic levels were found only after injections in the non-paralyzed deltoid muscle. In case #2 therapeutic levels were not achieved with either site. One possible explanation for the higher trough and peak levels following injections in the gluteal muscle as compared to the deltoid, in this case, was that the drug may not have been completely absorbed between injections. With case #1 and #2 injections were given every twelve hours. In this case injections were given every eight hours. It is possible the drug was not completely absorbed within the dosing interval. If this explanation was true there would be a compounding effect causing all of the levels in the latter injections (gluteal) to be higher than in the equivalent levels after the initial injections (deltoid).

Another possible, but less likely explanation for much higher serum levels following gluteal rather than deltoid injections is related to the return of function experienced by this client shortly after the levels were drawn. It is a less likely explanation because even in comparisons of deltoid and gluteal muscle absorption when both were non-paralyzed (intact neuraxes) Evans (1971) found that the peak levels were lower and the rate of absorption was slower in gluteal versus deltoid muscles.

The third hypothesis for this study was that the rate of absorption is faster when injections are given above the level of
injury than when given below. While Figure 8 suggests absorption time was the same in both sites (peaks at one hour), Figure 9 suggests that there were differences in the absorption from each site (linear vs nonlinear).

Since serum samples were taken around the fourth and eighth injections, one can assume steady state was achieved, and thus proceed to do the pharmacokinetic calculations. Table 5 identifies the elimination phase pharmacokinetic parameters calculated for this case.

Table 5

**Subject 3 - Pharmacokinetic Values**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Deltoid Site</th>
<th>Gluteal Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination Rate Constant</td>
<td>0.32h⁻¹</td>
<td>0.29⁻¹</td>
</tr>
<tr>
<td>Half Life</td>
<td>2.2 hours</td>
<td>3.4 hours</td>
</tr>
<tr>
<td>Volume Distribution</td>
<td>14.4 litres</td>
<td>16.8 litres</td>
</tr>
</tbody>
</table>

From the preceding table it is apparent that, in this case, there was a smaller elimination rate constant, a larger half life and a larger apparent volume of distribution following injections in the gluteal muscle than following injections in the deltoid muscle. Given that this subject had no change in renal function or fluid status during the study time, these results suggest that the absorption phase may have been delayed. The prolonged half-life is in keeping with the supposition that higher levels may have been found after the gluteal injections because of drug carry over from one dosing interval to the next.
**Figure 9.** Subject #3 - Logarithm of Serum Levels vs Time

<table>
<thead>
<tr>
<th>Time Post-injection</th>
<th>Deltoid</th>
<th>Gluteal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2 hr pre</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>1 hr post</td>
<td>4.4</td>
<td>4.8</td>
</tr>
<tr>
<td>2 hr post</td>
<td>3.2</td>
<td>4.4</td>
</tr>
<tr>
<td>3 hr post</td>
<td>2.3</td>
<td>3.5</td>
</tr>
<tr>
<td>4 hr post</td>
<td>1.7</td>
<td>2.6</td>
</tr>
</tbody>
</table>
In addition to the pharmacokinetic data collected for case #3, comments related to comfort were noted. The subject described discomfort associated with deltoid injections in terms of feeling like he had "been in a fight". He noted that he was sore for a few days.

In summary, in this case the dosing interval was shorter than in the other two cases. Although the subject appeared to have paralyzed gluteal at the time of injections, he recovered some motor function within days and this may have affected the absorption from that site. The trough and peak levels were found to be higher following gluteal injections. Possibly this was related to drug carryover due to a shorter dosing interval. While the measured peak levels suggested no difference in absorption times, the elimination phase pharmacokinetics and logarithm plot suggested otherwise. The decreased elimination rate constant, increased half-life and increased volume of distribution found following gluteal injections as compared to deltoid injections suggested that the absorption time was longer following gluteal injections. This supposition is supported by the fact that the logarithm of levels related to the deltoid injections was linear, while the logarithm of levels related to gluteal injections was nonlinear. As in the first two cases, this subject described discomfort associated with deltoid injections.

**Cases 1-3**

The findings reflect support of the hypotheses in some cases but not in others. However, explanations have been provided for these differences. The first hypothesis was that serum trough
levels are greater when the injections are given above the level of the injury than when given below. The second hypothesis was that serum peak levels are greater when injections are given above the level of injury than when given below. While the results in case #1 supported both of these hypotheses, contrary results were found for cases #2 and #3. Possible explanations for the contrary results were given.

An explanation offered for the contrary results in the second case related to achievement of steady state. It is assumed that steady state is achieved after the fourth injection, and levels drawn before that time will be lower (Winters, 1989). In the second case serum samples following deltoid injections were drawn around the third injection, not the fourth as specified by the protocol. It is unknown whether the hypotheses would have been supported if serum samples had been drawn after four injections in the deltoid muscle, as they were for the gluteal site in case two.

One explanation offered for the contrary results in case #3 was related to dosing intervals. The dosing interval in case #1 and #2 was twelve hours as compared to eight hours in case #3. It was proposed that the results in this case may have reflected a compounding of the drug due to incomplete elimination between injections. This explanation suggests that higher levels were found following gluteal injections because the gluteal injections were given subsequent to the deltoid injections and reflect compounded drug accumulation over time. While the subject in case #3 regained some motor function following the study, it is not likely that this explains the contrary results because one
would expect any differences in a comparison of normal muscles to favor the hypotheses of this study. Evans (1971) found that blood flow was slower in "normal" gluteal muscle as compared to "normal" deltoid muscle.

The third hypothesis of this study was that absorption time is longer following injections in gluteal muscle as compared to deltoid muscle. The findings from all three cases tentatively supported this hypothesis. Doing serum measures one hour apart did not allow for accurate differentiation between peak times, and thus absorption times. By calculating the pharmacokinetic values associated with the elimination phase of the drug, and by plotting the logarithm of the serum levels for each site, further predictions could be made about absorption time. In all three cases the elimination rate constant was smaller, the half-life longer, and the volume of distribution larger following gluteal injections suggesting a prolonged absorption phase.

Rather than refer to statistical significance, when using case analysis one may investigate clinical significance. The therapeutic peak level for gentamicin administered I.M. is considered to be in the range of 4 - 8 ug/ml. In case #1 a therapeutic level was achieved following injections in the deltoid muscle, but not in the gluteal muscle. In case #2 the findings in relation to the gluteal muscle were replicated but the results after only three injections in the deltoid muscle were not within therapeutic range. In case #3 serum levels were within the therapeutic range following injections in both sites.

Measuring discomfort associated with injections was not a formalized part of this study, but it is worth noting that all
three subjects indicated that deltoid injections resulted in significant discomfort. Descriptions of discomfort associated with deltoid injections ranged from "aching", to "feeling like I had been in a fight."

Summary

In this chapter a description of the sample and discussion of factors which may have influenced the sample size were presented. During the period of data collection only seven patients were ordered gentamicin and of those seven, only three were subjects in this study. Expanding the criteria to include amikacin and tobramycin did not result in any more study subjects. Three possible influences on sample size were discussed. They included: a new laboratory protocol, a concurrent research study, and new antibiotics on the market.

Because of the small sample size, the methods of data analysis originally intended for this study were no longer appropriate. After consultation with a statistician, a decision was made to consider the subjects as individual case studies. The results of the three cases were examined in relation to the hypotheses of the study. A summary of the findings was presented in the form of cross-case analysis. While some findings supported the hypotheses, others did not. Only in case #1 were the serum trough and peak levels higher following deltoid injections than following gluteal injections. Possible explanations offered for contrary results related to the number of injections, and the time between injections. The time between serum samples was too great to accurately differentiate the absorption times, but pharmacokinetic values associated with the
elimination phase suggested that absorption was delayed following injections below the level of injury. In addition to discussing the findings in relation to the three hypotheses, the researcher discussed the findings in terms of clinical significance, and made reference to client discomfort associated with deltoid injections.
CHAPTER FIVE

Summary, Conclusions, Implications and Recommendations

Introduction

This study was designed to determine the difference in drug absorption between intramuscular injections given above and below the lesion in persons with a spinal cord injury, when the lesion is within the range of C-6 to L-2. This chapter will include an overview of the study, followed by conclusions, implications for practice, education and theory, and recommendations for further research.

Summary

Staff at a major rehabilitation centre shared with this researcher their unsubstantiated belief that I.M. gentamicin did not seem to be as effective in treating urinary tract infections in individuals with spinal cord injury as it was with the general population. To identify current practice, this researcher conducted a survey of nurses working with patients with a spinal cord injury. The survey revealed that when I.M. injections were ordered nurses generally chose an injection site below the level of injury to avoid patient discomfort. This researcher questioned if perhaps there was a more important factor than comfort to consider when choosing a site for intramuscular injections for a person with a spinal cord injury. Would absorption be impaired if injections were given below the level of injury in paralyzed muscle?

The literature suggested that serum drug absorption may be impaired following intramuscular injections in persons with a spinal cord injury. What was unclear from the literature was
whether absorption was impaired in persons with a spinal cord injury regardless of the site of injection, or only when injections were given below the level of injury in paralyzed muscle. This study was therefore designed to compare the absorption of I.M. administered gentamicin above and below the lesion in spinal cord injury.

The theoretical framework for this study had its basis in physiology and pharmacology. The literature identified three categories of factors affecting serum drug absorption following intramuscular injection - drug action, area for diffusion, and blood flow. Within each of these categories, the literature suggested specific factors influencing absorption. This study controlled for all of the factors known to influence serum drug absorption in order to test the effect of muscle innervation (paralysis) on drug absorption.

A review of the literature revealed only three studies related to serum drug absorption following I.M. injections in persons with spinal cord injury. These studies suggested that I.M. absorption is impaired when injections are given below the lesion in persons with a spinal cord injury (Segal, 1986 & 1988) and may even be impaired when given above the level of injury (Sankaranarayanan, 1989). One must be cautious in drawing conclusions from the latter study which found impaired absorption above the lesion in spinal cord injury because the results may have been confounded by the comparison of active individuals to those who were bedridden. All of the identified studies compared I.M. absorption in persons with a spinal cord injury to that in able-bodied control subjects. No studies were found which
compared absorption above and below the lesion in spinal cord injury.

The first two hypotheses for this study were that the serum trough level (1st hypothesis) and peak level (2nd hypothesis) of gentamicin, following I.M. injections in persons with spinal cord injury, are greater when the injections are given above the level of injury than when they are given below. The third hypothesis was that the absorption time is shorter when injections are given above the level of injury as compared to below.

This study used an experimental, repeated measures design with counterbalancing. The subjects acted as their own control by receiving I.M. injections of gentamicin above and below the level of injury. Nurse research assistants drew serum samples before and after a series of injections in each site to determine differences in serum drug absorption.

While it was the intention of this researcher to have a sample size of 10, the actual sample size was only three after a year and a half of data collection. The change in sample size necessitated a change in the method of data analysis from one-tailed t-tests for dependent samples to case analysis. Three factors identified as possibly having influenced sample size were a new laboratory protocol which restricted the urine samples being analyzed; a concurrent research study which limited when patients could be treated and with which drugs; and new oral antibiotics on the market which began to replace gentamicin.

The sample for this study consisted of three cases. Case #1 involved a 29 year old male with a spinal injury at T12 who was ordered gentamicin 80 mg. q12h. Case #2 involved a 28 year old
male with a spinal injury at C4-5 with the same medication order. Although the patient in case #2 did not meet the criteria in terms of level of injury, he was included because post-injury return left him with an intact left deltoid muscle, and a paralyzed gluteal muscle. In case #3 the subject was an 18 year old male with a spinal injury at T-5. This subject had an order for gentamicin 80 mg. q8h. In all three cases serum samples were drawn following injections above and below the level of injury to determine differences in absorption.

The findings reflected support of the hypotheses by some cases but not for others. In all three cases findings suggested that absorption time may be slower following gluteal injections as compared to deltoid injections. The findings for each case were similar in terms of absorption time, but varied in terms of the peak and trough levels. Of the three cases, only in case #1 were the serum trough and peak levels higher following deltoid injections than following gluteal injections. The contrary results may have been related to differences in the number of injections and differences in the dosing intervals.

The lower peak and trough levels following deltoid injections, in case #2, may have been because there were only three deltoid injections as compared to four gluteal injections. It is possible that the serum levels had not reached steady state after only three injections. Of the three cases, this was the only one where the serum levels following deltoid injections were below the therapeutic range. While one would expect higher serum levels following four deltoid injections, it is not possible to predict what the results would have been had there been four
injections in each site.

The lower peak and trough levels following deltoid injections, in the third case, may have been related to a shorter dosing interval. If absorption was delayed, it is possible that with a shorter dosing interval, there was a progressive drug accumulation over time. The deltoid injections were first, followed by gluteal injections so it is possible that the results in this case reflected incomplete elimination within a single dosing interval. This was the only case in which serum levels following gluteal injections reached a therapeutic level.

Because serum samples were drawn one hour apart, differences in absorption times could not be distinguished by direct calculation. Indirect inferences about absorption were made based on calculating elimination phase pharmacokinetics. In all three cases the elimination rate constant was smaller, the half-life longer, and the volume of distribution larger following gluteal injections. Given that the subjects' renal function did not change during the course of the study, these findings may have reflected delayed absorption rather than impaired elimination. Plotting the logarithm of serum levels for each site added support to the supposition that absorption may have been delayed following gluteal injections.

Conclusions

With only three subjects, the findings from this research study are by no means conclusive, but a number of inferences or possible trends have been identified. According to Yin (1989) analytical generalizations can be used whether the case study involves one or several cases because the findings are
generalizable to theoretical propositions, not to populations or universes.

The trends identified in this study contribute toward the refinement of the theoretical framework related to serum drug absorption following intramuscular injections. Based on the findings the following tentative conclusions or trends are suggested:

1. The serum trough and peak levels following injections of 80 mg. of gentamicin I.M., in patients with spinal cord injury may be greater when injections are given above the level of injury than when they are given below, given the following conditions: serum levels are drawn around the fourth injection (after steady state is achieved) and the dosing interval is every 12 hours.

2. Peak serum levels in the therapeutic range of 4-8 ug/ml are likely following I.M. injections of gentamicin 80 mg. q12h in non-paralyzed deltoid muscle, but not likely following similar injections in paralyzed gluteal muscle.

3. Steady state appears to be achieved around the fourth I.M. injection of gentamicin. Serum levels drawn prior to this time may be lower than those drawn after steady state is achieved.

4. It is possible that injections of 80 mg. of gentamicin I.M. in paralyzed gluteal muscle over a shortened dosing interval (q8h) may result in levels which become progressively higher (even after steady state is achieved).

5. It is possible that absorption is delayed following injections in paralyzed gluteal muscle. Support for this conclusion is based on two observed trends. Firstly, the elimination rate constant tends to be lower, the half-life larger, and the
apparent volume of distribution higher following injections in paralyzed gluteal muscle as compared to non-paralyzed deltoid muscle. This trend seems to hold true regardless of dosing interval, or number of injections. Given no change in renal function, these differences suggest that the absorption phase may be delayed following injections in paralyzed muscle. Secondly, the logarithmic plotting of serum levels following injections in paralyzed muscle is non-linear, while the same plot following injections in non-paralyzed muscle is linear. This supports the proposition that absorption is delayed following injections in paralyzed muscle.

Implications for Health Care Professionals

The results of this study have implications for a number of health care professionals including nurses, physicians, and pharmacists. Implications are identified in relation to practice, education and theory development. The practice issues addressed include site selection, dosing, and drawing serum levels.

Nurses are responsible for selecting the site of intramuscular injections. In addition to the usual factors to be considered such as muscle size, skin condition, amount of drug to be administered; in patients who have a spinal cord injury, nurses must take into consideration muscle innervation. Nurses need to be aware that choosing to give injections in paralyzed muscle may result in slower absorption, and depending on the dosing interval, may result in drug accumulation. Nurses must chart the site of injections so that serum level results can be accurately interpreted.
In addition to considering innervation, nurses must take client comfort into consideration when selecting injection sites. The subjects in this study described significant discomfort associated with deltoid injections. The degree of discomfort associated with injections ranged from slight discomfort, to pain which interfered with the clients' ability to wheel his chair. Discomfort is one of many factors to be weighed by nurses in determining the best injection site.

Physicians order the amount of drug to be administered, the route of administration, the dosing interval, and any associated laboratory work such as serum levels. In ordering gentamicin I.M. a physician generally determines the dosage and dosing interval based on a patient's ideal body weight and creatinine clearance time. The results of this study suggest that the site of injections may influence the appropriate dosage and dosing interval. It is possible that the common protocol of 80 mg. I.M. q12h will result in underdosing if injections are given in paralyzed muscle. On the other hand, a dosing interval of q8h may result in drug accumulation since the absorption time appears to be delayed following injections in paralyzed muscle. If serum levels suggest that the patient requires more drug, it may be more appropriate for physicians to increase the dosage rather than decrease the dosing interval.

It is standard protocol for pre and post injection serum gentamicin levels to be drawn to determine if the dosing is appropriate. There seems to be differing opinions as to when the levels should be drawn. The results of this study suggest that it may be best to draw levels around the fourth dose for persons
with a spinal cord injury. It is possible that levels drawn before this time may not yet have reached steady state.

In addition to having implications for nurses and physicians, the results of this study may be of interest to pharmacists. Frequently, physicians seek dosing advice from pharmacists. A number of hospitals have developed empiric dosing guidelines to be used by physicians. In making recommendations about dosing guidelines for patients with spinal cord injuries, pharmacists need to take into consideration the possible effect innervation has on absorption.

The implications of this study extend beyond practice into education. There are implications for inservice and for specialized education of professionals. In health care agencies/services where persons with spinal cord injuries are treated, inservice is required. The staff need to be aware of the possible delay in absorption with I.M. injections given below the level of injury. Nurses must be informed that innervation is one more factor to consider in I.M. site selection. Physicians and pharmacists need to be aware of the possible implications the results of this study have when choosing the appropriate I.M. dosing levels and dosing intervals for patients with a spinal cord injury. In addition to the need to educate those currently working with this population, there is a need for education within specialty programs. Students who may work in this field in the future need to be aware that innervation may affect I.M. absorption.

Besides having implications for practice and education, this study has implications for theory development. The framework for
this study identified a number of factors believed to influence serum drug absorption. Controlling for these factors allowed this researcher to test the theory that innervation influences serum drug absorption. This study has lent some tentative support to that theory, and has provided insight into areas for further refinement of the framework.

Recommendations for Further Research

Further studies need to be done in the area of I.M. absorption and spinal cord injury. The proposition put forth here that absorption is delayed following injections in paralyzed muscle needs to be retested. Ideally one would have sufficient subjects to do an experimental study with statistical analysis. If subjects are limited, further case studies may be conducted. According to Kazdin (1978) the ultimate test of generality of findings among subjects is replication. As well as direct replication of the ideal case, theoretical replications are needed to determine under what conditions the proposition is not supported. In theoretical replications one would expect contrary results for predictable reasons. Attributes which need to be manipulated include the number of injections prior to levels being drawn, and the dosing interval. Replicate case studies offer one option for further research; another option is to compare absorption above and below the level of injury using a tracer substance. With this type of study the sample size would not be dependent on variables beyond the researcher's control.

Regardless of the type of study and sample size, there is a need to draw more serum samples between the time of injection and the first hour post injection in order to accurately determine
the peak serum levels. Drawing more samples during this time period would provide the researcher with the data necessary to calculate absorption phase pharmacokinetics such as the absorption rate constant and the absorption half-life. Drawing conclusions about absorption based on absorption pharmacokinetics is more credible than drawing conclusions about absorption indirectly from the elimination pharmacokinetics.

Further research needs to be done to determine the extent to which absorption may be delayed following injections in paralyzed muscle. Delayed absorption results in the drug being present in the bloodstream for longer periods of time. The results of this study suggest that while elimination appears to be complete 12 hours post injection, it may not be complete 8 hours post injection. Progressive serum samples could be drawn following an injection of gentamicin (or possibly a tracer substance) in order to determine when no measurable levels of the drug are left in the bloodstream. Knowing this would assist physicians in determining the most appropriate dosing intervals to achieve therapeutic levels without creating drug accumulation.

Steady state is achieved when the rate of drug administration is equal to the rate of elimination (Winter, 1989, p. 385). The literature suggests that steady state may be achieved as early as the third injection. The findings from this study suggest that steady state may not be achieved until around the fourth injection when gentamicin is given I.M. in paralyzed muscle. This proposition needs to be tested by giving gentamicin injections in paralyzed muscle and measuring the peak and trough serum levels around each progressive injection, starting with the
first injection and continuing until the serum levels stabilize. This will identify the point at which steady state is achieved. Once the time to reach steady state following injections in paralyzed muscle is determined, research is needed to compare this with the time required to reach steady state following injections in non-paralyzed muscle in able-bodied individuals, and following injections in non-paralyzed muscle in persons with spinal cord injury.

Nurses frequently choose to give injections in paralyzed muscle to avoid client discomfort. This study demonstrated that client discomfort was a significant factor to consider when choosing injection sites for gentamicin. If after considering all of the factors, a nurse chooses to give an injection below the level of injury to avoid discomfort, there may be more than one site to choose from. Research is needed to determine if there are any significant differences in absorption between different muscle groups - vastus lateralis, gluteal, or deltoid - when all are paralyzed as in higher level spinal cord injuries.

In summary, the results of this study suggest that under certain circumstances absorption is altered in paralyzed muscle. Further research is necessary to validate the findings, and to add to the existing body of knowledge. The theoretical framework for this study offers a basis for future testing and refinement of hypotheses related to serum drug absorption following I.M. injections.
References


APPENDIX A

Study: Absorption of Intramuscular Injections Above and Below the Level of a Spinal Cord Injury

Investigator: Valerie (Leslie) Spurrell R.N., B.S.N.


LETTER/CONSENT FORM

My name is Valerie Spurrell. I work in the nursing department at G. F. Strong Centre and am conducting a research study to satisfy requirements for my master's thesis at the University of British Columbia.

You have a bladder infection which your doctor has determined is best treated with injections of an antibiotic. Research indicates that injections into the buttocks are not absorbed as well in persons with a spinal cord injury as compared to able-bodied persons. For this reason a study is being done to determine if injections given above the level of spinal injury (in the arm) are absorbed better than those given below the level of spinal injury (in the buttocks). It is believed that the results of this study will assist nurses and doctors to make the best choices in terms of effectively treating this type of bladder infection.

Consenting to be a part of this study means that four of your injections will be given above your level of injury (in the deltoid muscle of the arm) and four will be given below your level of injury (in the gluteal muscle of the buttocks). At two different points in the course of your treatment, five blood samples will be drawn to determine how effectively the drug is being absorbed into your bloodstream. The samples will be drawn over a 4 1/2 hour period, during which time you will be asked to remain in bed with minimal activity. I also ask permission to see your medical record in order to identify information concerning your level of spinal cord injury and treatment.

Participation in this study is strictly voluntary. You have the right not to participate without jeopardy to your care. If you agree to participate you have the right to withdraw at any time and your care will in no way be affected. This study is confidential. Blood samples will be coded so your name is not revealed. If the results show you are receiving too high or too low a dose of the antibiotic, your doctor will be informed. No one else will have access to the results. You name will not be revealed in any publications which may result from this study.

If you have any questions about the study please feel free to contact me. My work number is 734-1313 local 323 and my office is on the fourth floor at G. F. Strong Centre. My supervisor is Dr. Ann Hilton. She can be reached at 228-7498.
CONSENT FORM

I __________________ have read and received a copy of the preceding information. I have had the study explained to me and fully understand what is involved. I agree to be a participant in this study.

__________
Date

__________________________
Patient's Signature

__________________________
Witness
APPENDIX B

I.M. Injection Procedure

1. Check Dr's order sheet, and check the medication sheet for the site to be used. This will also be on the medication vial.
2. Check for allergies
3. Wash hands.
4. Collect equipment: medication, 3 cc syringe, 22G 1 1/2" needle (or appropriate size if the patient's weight is not within normal range.)
5. Check medication vial with order. Make dosage calculation.
6. Use a filter needle to withdraw medication and then replace with the injection needle. If all of the medication is not used, dispose of remainder in the ampoule
7. Rid syringe and needle of air bubbles to measure dose accurately. Add 0.2 ml of air.
8. Identify patient and explain procedure.
9. Recheck the appropriate site for injection, and position patient accordingly.
10. Select the appropriate site for injection using specific anatomical landmarks.

To map the deltoid muscle, locate the lower edge of the acromion process with one hand and with the other hand identify the area of the lateral aspect of the upper arm that is in line with the axilla. The muscle is bounded by an imaginary upside-down triangle that can be envisioned between the two hands.

To map the dorsal gluteal muscle, find the posterior superior
iliac spine. Locate the greater trochanter. The diagonal line that extends from the posterior superior iliac spine toward the greater trochanter of the femur, and the horizontal line extending from the posterior superior iliac spine to the lateral hip two fingers' breadth below the iliac crest, form the boundary for the area that is safe for IM injections.

11. Cleanse the site with alcohol swab using a firm pressure in a circular motion from centre out.

12. Spread the tissue between your thumb and index finger to make the skin taut, and then insert the needle in a quick dart-like motion.

13. Supporting the barrel, pull back on the plunger and aspirate for blood. If blood is aspirated, withdraw the needle and replace the syringe, needle, and medication.

14. Inject the medication slowly to minimize discomfort and to evenly distribute the solution.

15. Wait 3 seconds before removing the needle and apply pressure to the site immediately. Massage the site for one minute with the swab.

16. Record the procedure indicating exact time, site, and dose. (Swearingen, 1984)
DELTOID INJECTION SITE

- Acromion process
- Clavicle
- Deltoid muscle
- Deep brachial artery
- Radial nerve
- Humerus
APPENDIX C

Data Collection Sheet

Research Assistant:

Today's Date:

Patient's Code:

Diagnosis:

Date of injury:

Details re: gentamicin eg. dose, date ordered, etc.

Current 'other' Medications (including date started):

Age:

Sex:

Description of infection:(type of bacteria)

Medical History:

Lab values (include any significant tests eg. renal function, cardiac function, hepatic function, aminoglycoside levels, recent urine tests)
First Set of Observations

Assistant Name____________ Date____

Code # to be used with blood work____

Prior to beginning sample collections please ensure staff are informed and therapy is cancelled for the morning so that the patient will have limited activity. You may give care to the patient between samples but please try to limit activity eg. bedrest.

1. Site of last three injections ____

2. Time and date of 1/2 hour pre-injection serum sample ________

Comments: (site used,...)

3. Time of injection ________

Comments: (site, left or right, any variation from procedure, pts comments re pain, number of injections to date....)
**First Set of Observations**

4. Time of 1, 2, 3 and 4 hour post-injection serum samples. Include comments such as arm used, etc.

1 hour post injection: (sample #2)

2 hours:

3 hours:

4 hours:

5. Time delivered to the lab ____

6. Other comments
Second Set of Observations

Assistants Name___________ Date____

Code # to be used with blood work____

Prior to beginning sample collections please ensure staff are informed and therapy is cancelled for the morning so that the patient will have limited activity. You may give care to the patient between samples but please try to limit activity eg. bedrest.

1. Site of last three injections _________

2. Time and date of 1/2 hour pre-injection serum sample _________
   Comments: (site used,...)

3. Time of injection _______
   Comments: (site, left or right, any variation from procedure, pts comments re pain, number of injections to date....)

4. Time of 1,2,3 and 4 hour post-injection serum samples.
   Include comments such as arm used, etc.
   1 hour post injection: (sample #2)

   2 hours:
3 hours:

4 hours:

5. Time delivered to the lab ____

6. Other comments
APPENDIX D

Venipuncture Procedure

1. Wash hands and collect venipuncture cart.
2. Identify patient and explain procedure.
3. Aseptically screw the double-ended needle into the plastic outer vacutainer, with the shorter needle positioned inside the outer container. Then insert a tiger-top vacuum tube into the outer container with the rubber stopper of the tube resting against the shorter needle.
4. Choose either the median basilic or cephalic vein. Observe and palpate for an appropriate site within the antecubital space.
5. Place the patient's arm in a supported position.
6. Wrap the tourniquet a few inches above the site. It should be tight enough to impede venous flow but not so tight that it occludes the arteries. You should still be able to palpate an arterial pulse distal to the tourniquet.
7. Cleanse the area with an alcohol swab using a circular motion and working outwards. Let the solution dry.
8. Stabilize and anchor the vein distal to the insertion site. With the needle's bevel up, insert it into the vein at a 30 to 45 degree angle. After puncturing the vein, stabilize the plastic outer container, and gently yet firmly advance the vacuum tube to pierce the rubber stopper with the short needle. Because of the vacuum, blood should immediately begin spurting into the vacuum tube. As soon as it does, release the tourniquet. Collect a minimum of 2cc and then remove the vacuum tube.
9. Remove the needle from the vein and apply pressure with a sterile sponge for 1-3 minutes to stop the bleeding. Once the bleeding has ceased, place a bandage over the puncture site.

10. Label the tube including date time, which sample eg. (1/2 hr pre, 1 hr post...), site of injection, drug and dose. Place specimen in the fridge until all five have been collected and then deliver to accessioning at Shaughnessy Lab (Searingen, 1984).
APPENDIX E

Equations for Calculating Pharmacokinetic Parameters

Elimination Rate Constant (Kd)

The elimination rate constant is the fraction or percentage of the total amount of drug in the body removed per unit of time (Winter, 1989, p. 40).

\[ K_d = \frac{C_p}{C_t} \cdot \frac{t}{t} \]

\(C_p\) = the highest (peak) plasma level measured (ug/ml)
\(C_t\) = the lowest post-injection level measured (ug/ml)
\(t\) = the time interval between \(C_p\) and \(C_t\)

Half-life (t1/2)

The half-life is the inverse of \(K_d\) and is defined as "the amount of time required for the total amount of drug in the body or the plasma concentration to decrease by half" (Winter, 1989, p. 43).

\[ t_{1/2} = \frac{0.693}{K_d} \text{ or } \frac{(\text{natural log of 2})}{K_d} \text{ (elimination rate constant)} \]

Volume of Distribution (Vd)

"The volume of distribution for a drug or 'apparent volume of distribution' does not necessarily refer to any identifiable compartment in the body. It is simply the size of the compartment necessary to account for the total amount of drug in the body if it were present throughout the body at the same concentration found in the plasma" (Winter, 1989, p. 21).

\[ V_d = \frac{\text{Dose (mg)}}{C_p - \frac{(C_t)(e^{-KdT})}{e^{-Kd(t)}}} \]
Cp = peak serum level (ug/ml)
Ct = post-injection trough level (ug/ml)
Kd = elimination rate constant
\( t \) = extrapolated back calculation of time from peak to time zero
\( T \) = extrapolated forward calculation of time from trough level until time zero
Concurrent Research Study - Definitions

Bacteriuria: Isolation of $\geq 10^5$ cfu/ml of midcatheter urine; or 102-105 cfu/ml from 2 consecutive specimens; or 102-105 cfu/ml from 1 specimen when frankly symptomatic.

Symptomatic bacteriuria: BU plus (i) fever $\geq 38^\circ$C and suprapubic or flank pain or tenderness; or (ii) epididymo-orchitis, periurethral abscess or prostatic abscess; or (iii) bacteremia.

Bacteriuria with fever: BU with fever $\geq 38^\circ$C and no other clinically evident source of fever.

Asymptomatic bacteriuria: BU not fulfilling criteria b) and c) above.