CORRELATION BETWEEN CAPILLARY AND ARTERIAL SERUM GENTAMICIN CONCENTRATIONS IN NEONATES

by

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University of Utah in partial fulfillment of the requirements
for the degree of

Doctor of Pharmacy

College of Pharmacy

University of Utah

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UNIVERSITY OF UTAH COLLEGE OF PHARMACY

FINAL READING APPROVAL

TO THE DOCTOR OF PHARMACY COMMITTEE OF THE UNIVERSITY OF UTAH COLLEGE OF PHARMACY:

I have read the clinical research project report of Robert A. Mead in its final form and have found that 1) its format, citations, and bibliographic style are consistent and acceptable; 2) its illustrative materials including figures, tables, and charts are in place; and 3) the final manuscript is satisfactory to the Supervisory Committee and is ready for submission to the Doctor of Pharmacy Committee.

6/1/83
Date

Chairman, Supervisory Committee

Approved for the Department of Pharmacy Practice

Chairman

Approved for the Doctor of Pharmacy Committee

Chairman, Doctor of Pharmacy Committee

6/8/83 GIFT

UNIVERSITY OF UTAH COLLEGE OF PHARMACY

SUPERVISORY COMMITTEE APPROVAL

of a clinical research project report submitted by

Robert Arthur Mead

We, the undersigned, have read this clinical research project report and have found it to be of satisfactory quality for a Doctor of Pharmacy Degree.

5/25/83
Date

Chairman, Supervisory Committee

5/27/83
Date

Member, Supervisory Committee

6/1/83
Date

Member, Supervisory Committee

ACKNOWLEDGEMENTS

I would like to thank the members of my Supervisory Committee, Dr. John A. Bosso, Dr. Gary M. Chan, and Dr. Arthur G. Lipman, for the time and guidance they have given in evaluating this research paper.

To the physicians, nurses, and clerical staff of the University of Utah Hospital Newborn Intensive Care Unit, I would like to extend my appreciation for their assistance during the data collection portion of this research project.

To Sue, a very special thank you for her seemingly endless supply of support, patience, and understanding during the past two years.

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INTRODUCTION

Critically ill neonates in newborn intensive care units require frequent monitoring of body functions. This monitoring includes sampling of blood for laboratory analysis. Blood samples are commonly obtained through an umbilical artery catheter. However, if an umbilical artery catheter is not in place, blood samples are frequently obtained by heel stick due to difficulties inherent in venous sampling in this age group. These difficulties include the inability to find a suitable site for venipuncture, the fragility of the veins at this age, and the trauma associated with repeated sampling. Sirinavin et al, recommended that the method of heel stick sampling be used for the assay of antibiotics, such as gentamicin and kanamycin, when the only access is the same line through which the drug has been administered.[1] This recommendation is based on the finding that obtaining blood specimens for antibiotic assay through the same intravenous line used for antibiotic administration may result in falsely elevated drug concentrations due to drug adhesion to the plastic tubing,[1] or incomplete flushing of the line after drug administration. Finally, vigorous flushing of the tubing with several milliliters of fluid before sampling may cause rupture and/or collapse of the blood vessel in young children.[1]

The heel stick sampling method assumes that capillary blood drug concentrations are the same as venous or arterial blood drug concentrations on which most drug concentration-effect/side effect relationships

are based. This correlation has been proven for some laboratory parameters in the neonate. Segall et al, found a highly significant correlation ($r = 0.76$, $p < 0.001$) between venous and heel stick capillary serum ferritin concentrations in 58 healthy term infants.[2] Karna and Poland studied arterial and digital capillary blood PO_2, PCO_2, and pH in 33 critically ill newborn infants. A statistically significant correlation between the two sampling methods was found for all three parameters measured (PO_2: $r = 0.92$, $p < 0.05$; PCO_2: $r = 0.84$, $p < 0.05$; pH: $r = 0.94$, $p < 0.05$).[3]

Other monitoring parameters do not share this good correlation between capillary and venous or arterial blood. Rivera and Rudolph found a statistically significant difference ($p < 0.05$) between venous and heel stick capillary hematocrit and hemoglobin in 44 low birth weight and term infants, even at eight to ten postnatal weeks of age.[4] Sluggish peripheral circulation or immature autonomic control of the peripheral microcirculation during the neonatal period are proposed mechanisms for this difference.[4]

Whether free flowing capillary blood antibiotic concentrations correlate well with those obtained when the foot is manipulated during collection of the blood sample remains unanswered. Presumably, vigorous manipulation such as application of pressure and/or flexion to stimulate blood flow might dilute the blood with interstitial fluids. This could result in falsely lowered antibiotic concentrations. Such falsely lowered concentrations may lead to inappropriate dosage increases possibly resulting in toxicity.

OBJECTIVE

The objective of this study was to determine the relationship between gentamicin serum concentrations determined from arterial and heel stick capillary blood with and without manipulation of the foot.

MATERIALS AND METHODS

Subjects

Ten subjects who were patients in the University of Utah Hospital Newborn Intensive Care Unit were admitted to the study after informed consent was obtained from the parents. This study was previously approved by the University of Utah Institutional Review Board. All patients had stable renal and hepatic function, an umbilical artery catheter in place, and were receiving gentamicin for suspected or proven bacterial infection. Patient characteristics are listed in Table 1. There were five females and five males, with an average age of 5.7 days (range 2 to 24 days), and an average estimated gestational age of 31 weeks (range 26 to 38 weeks).

Antibiotic Concentrations

Arterial and capillary blood samples were obtained one hour after completion of a gentamicin infusion. Since the umbilical artery catheter was used for both drug administration and arterial sampling, it was flushed with 2 ml of normal saline solution after the gentamicin infusion ended, and 3 ml of blood was withdrawn prior to sampling. Blood samples (0.6 ml from each site) were obtained no sooner than after the third dose of gentamicin given.

Heel Stick Determinations

Heel stick sampling was performed by either phlebotomists or Newborn Intensive Care Unit nurses trained in this method of sampling. The method of obtaining the heel stick was observed by the same investigator (RAM) each time in order to assure consistent and proper sampling, and to place the patient in one of the following groups: 1) capillary/free flowing heel stick, and 2) capillary/manipulated heel stick.

Antibiotic Assay

The blood samples were centrifuged and the serum frozen at -20°C immediately after being obtained. All samples were analyzed within 24 hours at the University of Utah Hospital Clinical Toxicology Laboratory using the TDX fluorescence immunoassay.[5] The sensitivity of the assay for serum was 0.16 mcg/ml. The coefficient of variation for both between-run and within-run was less than 3 percent.

Fluorescence polarization provides a direct measure of bound and free tracer in a competitive binding immunoassay.[6] When the tracer is bound to the antibody, the complex is highly polarized upon emission after linearly polarized light is used to excite the tracer. Conversely, when the tracer is free, the emitted light is depolarized. Thus, the greater the concentration of the analyte, the larger the fraction of tracer that is unbound, and the resultant emitted light is less polarized.[6] The sensitivity of the fluorescence polarization immunoassay allows high dilutions of sample to be made, thereby minimizing interferences from protein matrix effects, lipemic samples, and those specimens with abnormally high hemolysis.[6]

Data Analysis

The null hypothesis for this study was that there is no difference between capillary and arterial serum gentamicin concentrations. The Student's t-test was used for statistical analysis for the difference between mean arterial and heel stick capillary serum gentamicin concentrations ($\alpha = 0.05$). If a statistically significant difference was found, the degree of correlation between arterial and capillary concentrations was determined using the least square analysis of the concomitantly obtained concentrations from the two sites. The resultant correlation coefficient (r) would represent the degree of correlation, and the significance limits for this value would then be determined ($\alpha = 0.05$).[7] These analyses were then performed separately for the two study groups to test the effect of heel manipulation.

RESULTS

The results of the arterial and capillary peak gentamicin serum concentrations are listed in Table 2. The average difference between these concentrations was 0.81 mcg/ml (range -0.4 to 3.2 mcg/ml). No statistically significant difference between mean arterial and mean capillary serum gentamicin concentrations was found (6.31 ± 1.61 mcg/ml vs 5.6 ± 1.10 mcg/ml, respectively; $p > 0.05$). There was also no significant difference between the umbilical artery catheter and heel stick serum gentamicin concentrations in the capillary/free flowing or the capillary/manipulated heel stick groups ($p > 0.05$).

DISCUSSION AND CONCLUSIONS

Peak gentamicin serum concentrations obtained from umbilical artery catheter and heel stick blood samples appear to be similar.

Manipulation of the heel while obtaining capillary blood appears to have no effect on the resultant peak gentamicin concentration, as there was no significant difference ($p > 0.05$) between umbilical artery catheter and heel stick concentrations in either the capillary/free flowing or capillary/manipulated heel stick groups.

Although no statistically significant difference ($p > 0.05$) was found between mean umbilical artery catheter and mean heel stick peak gentamicin serum concentrations for the entire patient group, the difference in these concentrations in patients weighing less than 1,000 Gm (Patient 1: 2.7 mcg/ml; Patient 6: 3.2 mcg/ml) may be clinically significant, as inappropriate dosage adjustments leading to toxicity or suboptimal therapy could have been made. The reason for this difference in these two patients is unknown. Possibly, the distribution of gentamicin is impaired in critically ill neonates weighing less than 1,000 Gm. Further studies are needed to elucidate the actual mechanism.

We conclude that in the eight patients weighing more than 1,000 Gm there was agreement between umbilical artery catheter and heel stick peak gentamicin serum concentrations. There was also no significant difference ($p > 0.05$) in umbilical artery catheter and heel stick peak gentamicin serum concentrations in the capillary/free flowing and manipulated heel stick study groups, indicating that manipulation of the heel to stimulate blood flow does not result in lower gentamicin concentrations. We therefore recommend that heel stick sampling for gentamicin concentration determination is an appropriate alternative to arterial sampling in critically ill neonates weighing more than 1,000 Gm.

TABLES

TABLE 1. Patient Characteristics

Patient Number	Age (Days)	Estimated Gestational Age (Weeks)	Weight (Gm)	Sex	Reason for Gentamicin Therapy
1	24	27	980	M	Gram Negative Sepsis
2	2	29	1320	M	Rule Out Sepsis
3	6	28	1020	M	Rule Out Sepsis and Pneumonia
4	2	28	2200	F	Rule Out Sepsis and Pneumonia
5	2	36	2040	M	Group B Streptococcus Sepsis
6	3	26	980	F	Rule Out Sepsis
7	2	38	3000	F	Group B Streptococcus Sepsis
8	10	38	2200	M	Pneumonia
9	3	30	1380	F	Rule Out Sepsis
10	3	30	1260	F	Rule Out Sepsis

TABLE 2. Capillary and Arterial Peak Gentamicin Serum Concentrations/Type of Heel Stick

Patient Number	Peak Gentamicin Serum Concentrations (mcg/ml) Arterial	Capillary	Type of Heel Stick
1	6.8	4.1	Free Flowing
2	5.1	5.1	Manipulated
3	6.8	6.3	Manipulated
4	6.9	6.9	Free Flowing
5	4.9	4.8	Manipulated
6	10.3	7.1	Manipulated
7	5.3	4.9	Free Flowing
8	5.1	4.4	Free Flowing
9	6.4	6.8	Manipulated
10	5.5	5.6	Free Flowing

APPENDIX

DETERMINATION OF CORRELATION BETWEEN ARTERIAL AND CAPILLARY SERUM GENTAMICIN CONCENTRATIONS

Date_____

Consent Form

Your child is suspected of having an infection for which he or she is receiving an antibiotic named gentamicin. Part of the routine care carried out with this treatment is to obtain a small blood sample to measure the amount of antibiotic present. This allows the physicians to determine if the antibiotic dosage is correct. In your child, the blood sample will be collected through a small plastic tube which has been temporarily placed in an artery. If a child did not have this tube in place, the blood would be obtained by piercing the skin of the heel of the foot (heel stick) which causes a small amount of blood to flow.

Some controversy exists as to whether the concentration of antibiotic in a blood sample obtained from a heel stick is the same as that obtained through an artery. It is the purpose of this study, in which your child is invited to participate, to determine if the antibiotic levels obtained with the two different methods are the same. As the more common method of obtaining blood samples in newborn infants is through a heel stick, this is an important question to answer.

If your child is enrolled in this study (10 patients will be studied) a blood sample will be obtained through the artery tube (as ordered by the physician) and at the same time, an extra sample (0.6 ml or about 1/10 teaspoonful) will be obtained by heel stick. The only risks involved are the small chance of infection and mild discomfort at the heel stick site. Although there are no direct benefits to your child, other babies will benefit from the new knowledge generated. There will be no cost to you to perform this extra test.

If you have any questions during the study, you may contact Dr. John Bosso (581-7545) or Dr. Cary Chan (581-7052). In the event you sustain physical injury resulting from the research project in which you are participating, the University of Utah will provide you, without charge, emergency and temporary medical treatment not otherwise covered by insurance. Furthermore, if your injuries are caused by negligent acts or omissions of University employees acting in the course and scope of their employment, the University may be liable, subject to limitations prescribed by law, for additional medical costs and other damages you sustain. If you believe that you have suffered a physical injury as a result of participating in this research program, please contact the Office of Research Administration, phone number 581-6903.

Participation in this study is voluntary. I acknowledge that I have had a fair opportunity to ask questions about the above procedures. I understand that I am free to withdraw my consent and to

discontinue participation in the project at any time without prejudice. I agree that data from these experiments may be used for medical and scientific purpose, including publications, with the understanding that my identity will not be revealed unless I expressly consent thereto.

Patient Name:_____ Parent's Signature_____

Witness:_____

Responsible Investigator's Signature:_____

LITERATURE CITED

1. Sirinavin S et al: Pitfalls in collecting blood specimens for antibiotic assay. Antimicrob Agents Chemother 1979; 15(3):481-483.

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7. Koosis DJ: Statistics, 2nd edition. John Wiley and Sons, New York, 1977.

CURRICULUM VITAE

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PERSONAL DATA

Home Address:	821 Medical Plaza Salt Lake City, UT 84112 (801) 582-2241
Office Address:	Department of Pharmacy Practice University of Utah College of Pharmacy Salt Lake City, UT 84112 (801) 581-5941
Birth:	October 22, 1955 Stamford, CT
Social Security Number:	047-50-0177
Marital Status:	Married - Susan W. Hamlin, R.Ph.
Professional Licensure:	Pharmacist Licensure: Connecticut #5163 (by exam) Florida #16399 (by exam) Utah #3505 (by reciprocity)

EDUCATIONAL BACKGROUND

Doctor of Pharmacy The University of Utah College of Pharmacy Salt Lake City, UT	1983
Bachelor of Science in Pharmacy University of Connecticut School of Pharmacy Storrs, CT	1977

TRAINING

Residency in Clinical Pharmacy University of Utah Hospital Salt Lake City, UT	1981-1983

TRAINING (continued)

Chief Resident 1982-1983

Duties: Teaching (clerkship, didactic), clinical rotations, night call, cardiac arrest team participation, journal club, clinical seminars, committee meetings, management clerkship, Poison Control Center night shifts

Gerontology Program 1982-1983
Rocky Mountain Gerontology Center
University of Utah
Salt Lake City, UT
Graduate Gerontology Certificate 1983

EDUCATIONAL EXPERIENCE

Clinical Rotations

Adult Internal Medicine	12 weeks
Ambulatory Care	6 weeks
Cardiology	6 weeks
Drug Information	9 weeks
Family Practice	6 weeks
General Pediatrics	12 weeks
General Surgery	6 weeks
Geriatrics	6 weeks
Hospital Pharmacy Management	3 weeks
Infectious Disease	6 weeks
Perinatology (Ob-Gyn)	6 weeks
Poison Control Center	48 hours
Psychiatry	6 weeks
Rheumatology	3 weeks

PROFESSIONAL EXPERIENCE

Director of Pharmacy, Masonic Home & Hospital, Wallingford, CT. August 1978 - June 1981. Responsible for the total drug usage in this JCAH-accredited, 440-bed geriatric institution.

Staff Pharmacist, Masonic Home & Hospital, Wallingford, CT. January 1978 - July 1978

Staff Pharmacist, Lake Drug Co., Waterbury, CT. June 1977 - December 1977

Pharmacy Intern, Lake Drug Co., Waterbury, CT. December 1976 - June 1977

TEACHING EXPERIENCE

Didactic lectures to baccalaureate pharmacy students and first year Pharm.D. candidates.

Preceptor for baccalaureate pharmacy students and first year Pharm.D. candidates on clinical rotations.

Lectures

"Glaucoma" Presented to fourth year undergraduate pharmacy students in Diseases and Drug Therapy, May 1983.

"Seizure Disorders" Presented to first year Pharm.D. candidates in Advanced Pharmacotherapeuties, March 1983.

"Seizure Disorders" Presented to fourth year undergraduate pharmacy students in Diseases and Drug Therapy, January 1983.

"Pharmacokinetics of Tricyclic Antidepressants" Presented to first year Pharm.D. candidates in Advanced Clinical Pharmacokinetics, August 1982.

Teaching Assistant

Common Medicines course for undergraduate liberal arts students, for the 1982-1983 academic year. Duties: Preparation of lecture materials, information source for students, proctoring and grading of examinations.

Special Project

Preparation of an oncology learning manual for use in Advanced Pharmacotherapeutics course for first year Pharm.D. candidates, Summer 1981

RESEARCH

Correlation Between Capillary and Arterial Serum Gentamicin Concentrations in Neonates. John A. Bosso, Pharm.D., Gary M. Chan, M.D., John M. Matsen, M.D., Robert A. Mead, B.S. Completed May 1983

INVITED PRESENTATIONS

"Gerovital (GH-3) Reviewed" Presented to physicians and staff, Geriatric Evaluation and Treatment Unit, Veterans Administration Medical Center, Salt Lake City, UT, June 1982.

INVITED PRESENTATIONS (continued)

"Urinary Incontinence in the Elderly" Inservice presented to nursing staff, Hill Haven Convalescent Center, Salt Lake City UT, June 1982.

"Antibiotic Prophylaxis in GI Surgery" Presented to surgeons and medical students, University of Utah Hospital, Salt Lake City, UT, March 1982.

"Pharmacology of Antidepressant Agents" Presented to graduate student nurses, University of Utah College of Nursing, Salt Lake City, UT, February 1982.

"Pharmacology of Antianxiety and Antipsychotic Agents" Presented to graduate student nurses, University of Utah College of Nursing, Salt Lake City, UT, November 1981.

"Geriatric Pharmacology" Lecture series presented biannually to newly hired and other interested nurses, Masonic Home & Hospital, Wallingford, CT, 1979-1981.

PUBLICATIONS

Mead RA: Sucralfate: the latest in the treatment of duodenal ulcer disease. Drugs in Patient Care, University of Utah Hospital, Department of Pharmacy Services. 5(1):3, 1982.

Mead RA: Nifedipine: the first oral calcium channel blocker admitted to the formulary. Drugs in Patient Care, University of Utah Hospital, Department of Pharmacy Services. 5(1):2, 1982.

Mead RA: Barbiturates: adjunct use in psychiatric interviews. Drugdex Rocky Mountain Drug Consultation Center, 1982.

COMMUNITY SERVICES

"Medication in the Elderly" Presented at the Senior Citizen Health Fair, Salt Lake City, UT, March 1982.

"Poison Prevention in the Home" Presented to the Methodist Women's Group, Christ United Methodist Church, Salt Lake City, UT, January 1982.

Health Screening Center. Functioned as consultant, drug information source, and hypertension screener in free clinic operated for the elderly, Salt Lake City, UT, August-September 1981.

UNIVERSITY SERVICE

Member, Doctor of Pharmacy Committee, University of Utah, College of Pharmacy, July 1982 - June 1983.

PROFESSIONAL ORGANIZATIONS

American Society of Hospital Pharmacists	1977-present
Connecticut Society of Hospital Pharmacists	1977-1981
Membership Committee Member, 1981	
Utah Society of Hospital Pharmacists	1982-present