ANTIMICROBIAL THERAPY FOR NEWBORNS:

PRACTICAL APPLICATION OF PHARMACOLOGY TO CLINICAL USAGE

GEORGE H. McCRACKEN, JR., M.D.

JOHN D. NELSON, M.D.

ANTIMICROBIAL THERAPY FOR NEWBORNS:

PRACTICAL APPLICATION OF PHARMACOLOGY TO CLINICAL USAGE

GEORGE H. McCRACKEN, JR., M.D.

JOHN D. NELSON, M.D.

Department of Pediatrics
University of Texas Health Science Center at Dallas
Southwestern Medical School
Dallas, Texas

GRUNE & STRATTON
A Subsidiary of Harcourt Brace Jovanovich, Publishers
New York San Francisco London

Library of Congress Cataloging in Publication Data

McCracken, George H.
Antimicrobial therapy for newborns.

(Monographs in neonatology)
Includes bibliographical references and index.
1. Infection in children—Chemotherapy.
2. Infants (Newborn)—Diseases—Chemotherapy.
3. Antibiotics. I. Nelson, John D., joint author. II. Title.
RJ275.M3 618.9'201 77-6251
ISBN 0-8089-1014-0

Grune & Stratton, Inc.
111 Fifth Avenue
New York, New York 10003

Distributed in the United Kingdom by
Academic Press, Inc. (London) Ltd.
24/28 Oval Road, London NW 1

Library of Congress Catalog Number 77-6251
International Standard Book Number 0-8089-1014-0
Printed in the United States of America

Foreword

A physician who is writing orders for 2½ mg/kg of gentamicin, and 25 mg/kg of ampicillin to be administered every 12 hours to a newborn who is suspected of having sepsis neonatorum, rarely concerns himself with the reasons why these specific antibiotics and dosages are used to treat this syndrome. He orders the drugs because he has learned that they are effective and that neither agent, if appropriately administered for a suitable period of time, is associated with any short- or long-term toxicity.

During a contemplative moment, however, the doctor might wonder, Why gentamicin rather than a cephalosporin? Why not penicillin G instead of ampicillin? Why not increase the dosage of ampicillin to a range more nearly equivalent to that used for a one-year-old?

Until recently, there were no rational answers to these questions. Despite the fact that antimicrobial agents represented the most commonly used drugs for infants (excluding perhaps vitamin K), there was no systematic information about their pharmacokinetics or toxicity, nor was efficacy in specific circumstances clearly known. Now it is difficult to believe that streptomycin was once administered to infants for over a decade, in various dosages that were apparently derived from formulas applied to adult data. Initially, kanamycin usage in neonates was similarly uncontrolled, and resulted in considerable deafness in the recipients—a problem that disappeared once proper dosages were specified. Chloramphenicol and sulfonamide administration to babies often resulted in death or permanent damage, before the effects produced by these drugs in the immature human were recognized.

Considering what has been known for decades about the relative immaturity of organ function in the newborn, these "therapeutic misadventures" could have been avoided or perhaps, at least, drugs might have been used more cautiously in limited situations, rather than in the widespread manner in which they were employed.

These unfortunate occurrences brought about predictable reactions. The FDA (Food and Drug Administration) quite correctly insisted that antimicrobial and other drugs not specifically tested in infants be labeled with the now famous "orphan" clauses, restricting their usage to older children and/or adults. Secondly, physicians became understandably cautious about

prescribing relatively new agents for a baby even though the patient might (theoretically at least) profit from them. Finally, and most importantly, a few investigators, such as George McCracken and John Nelson and their group at the University of Texas Health Sciences Center at Dallas, began systematic investigations of the pharmacokinetics, relative efficacy, and short- and long-term toxicity of newer and widely-used older antimicrobial agents in infants of varying levels of maturity.

The hypothetical physician in the first paragraph probably does not know (or even care) how much he and his patients owe to these investigators and their careful observations. Despite the unspectacular nature of this type of sometimes tedious work, much of modern pediatric infectious disease therapeutics rests on the framework of knowledge that these studies built.

Because of Dr. McCracken's and Dr. Nelson's deep involvement with the specific area of investigation, I know of no individuals more qualified to write this particular book. By summarizing the considerable data which has accumulated in the last several years, they provide the physicians who are treating infants, with the practical as well as theoretical basis for decision making.

From a personal standpoint, my long-term association with these two colleagues and sometime collaborators has been a source of great pride and satisfaction for me. I am pleased that they have seen fit to share their considerable knowledge and experience more widely.

Heinz F. Eichenwald, M.D.
William Buchanan Professor and Chairman
Department of Pediatrics
The University of Texas Health Science Center at Dallas

Preface

Newborn infants are very special creatures in many ways. They present two special challenges to the physician—recognizing the existence of an infectious problem and trying to give effective and safe dosages of antimicrobials. Recognition of infection and localizing it to an organ system are often difficult because the manifestations are frequently nonspecific. Selection of antibiotics is complicated because of newborns' physiologic immaturity. There is always the danger of unsuspected toxicity that may not be recognized for many years, e.g., chloramphenicol toxicity. Appropriate dosage schedules are difficult to establish because of a baby's rapidly changing physiologic status during the first days and weeks of life.

Some years ago newborns were characterized as therapeutic orphans because so little was known of the pharmacology and safety of antibiotics for this age group. The package insert for most drugs carried the caveat that the drug was not recommended for newborns and young infants because of insufficient data—the famous "orphan clause." Due to the efforts of several investigators over the past 10 years, we now have solid pharmacokinetic and safety data for the drugs that are most commonly needed to treat newborns' infections. As a matter of fact, it is somewhat ironic that we have better information about newborns than about older children for many drugs.

Unfortunately, pharmacology sounds dull to most physicians. We hope that the readers will overcome the temptation to skip Chapter 2, because without the background information of these simplified concepts of pharmacology, it will be difficult to understand the rationale behind our dosage recommendations. We have tried to make this mini-course in pharmacology painless.

To avoid endless repetition we have not, for the most part, included dosages in the section on antimicrobial therapy. Chapter 2 can be referred to for dosage regimens. We hope that the Quick Reference Guide and the markings on the edge of the pages simplify the process of hunting for dosages.

Our secretaries, Roberta Rosales and Becky Hoffman, bore up under the burden of typing three manuscript drafts with better grace and good humor than we could have mustered. We gratefully acknowledge their major contribution.

It is almost easier to say what this book is *not* than to characterize what it *is*. It is not intended to be a textbook on newborns' infectious diseases. The reader will have to look elsewhere for detailed information on the pathologic anatomy, epidemiology, clinical manifestations, and other aspects of the diseases. But it is impossible to write about therapy without mentioning certain clinical features that are important to the recognition of the need for that therapy. We hope that this compilation of the available information on antimicrobial agents for newborns will be a useful reference source, and that our thoughts on selection of drugs and dosages will help provide safe and effective therapy for newborns' infectious diseases.

GEORGE H. MCCRACKEN, JR., M.D.

JOHN D. NELSON, M.D.

Contents

Foreword *by Heinz F. Eichenwald, M.D.* vii

Preface ix

1. Pharmacologic Concepts in the Newborn 1
2. Clinical Pharmacology and Dosage 5
3. Cultures 69
4. Clinical Application of Laboratory Tests 73
5. Septicemia 81
6. Central Nervous System Infections 87
7. Cardiovascular Infections 93
8. Lower Respiratory Tract Infections 97
9. Eye, Ear, and Throat Infections 107
10. Cutaneous and Glandular Infections 115
11. Bone and Joint Infections 125
12. Gastrointestinal and Liver Infections 129
13. Genitourinary Infections 137
14. Miscellaneous Systemic Infections 141
15. Prophylactic Antibiotics 153

Appendix A: Initial Drug Therapy According to Clinical Diagnosis 165

Appendix B: Usual Drugs of Choice According to Etiologic Agents 171

Index 173

1
Pharmacologic Concepts in the Newborn

PHYSIOLOGIC FACTORS AFFECTING PHARMACOLOGY

The rapidly changing physiologic processes that are characteristic of the neonatal period may profoundly affect the pharmacokinetic properties of antimicrobial agents. Infant maturity as reflected by gestational and chronological ages must be considered in relation to dosage and timing of dose intervals. Dosage recommendations for 1-day-old infants do not necessarily apply to infants who are 10 days or 30 days old. Data derived from studies of normal adults cannot be applied to infants without risking administration either of ineffective or of toxic drug dosages.

Absorption, distribution, metabolism, and excretion of drugs are constantly changing during the neonatal period. Many physiologic and metabolic processes, acting either singly or in concert, influence the pharmacokinetics of antibiotics in neonates. These include, among others, drug biotransformation, extracellular fluid volume, protein binding, and renal immaturity.

A number of enzyme systems are deficient or absent during early neonatal life. As a result, the metabolism of antibiotics may be profoundly altered. For example, immaturity of hepatic glucuronyl transferase in neonates results in diminished conjugation of chloramphenicol to the inactive acid glucuronide. This, coupled with diminished glomerular and tubular

function, produces elevated serum concentrations of both free and conjugated chloramphenicol. Accumulation of the free, antimicrobially active drug in serum is associated with cardiovascular collapse and death (gray syndrome) in some infants treated with excessive dosages of this drug.

Drugs may directly inhibit enzyme action resulting in accumulation of metabolic products that are toxic to the infant. A good example of this phenomenon is hyperbilirubinemia associated with administration of novobiocin to neonates. This macrolid drug is a potent inhibitor of hepatic glucuronyl transferase which catalyzes bilirubin conjugation. Another adverse effect observed between drug administration and enzyme deficiency is hemolysis produced by sulfonamides or nitrofurantoin in infants with erythrocyte glucose-6-phosphate-dehydrogenase deficiency.

The extracellular fluid volume of the newborn is approximately 35 percent of body weight, which is considerably larger than that of children and adults. Although there is a rapid loss of excess fluid during the first days of life, the extracellular fluid volume does not attain adult proportions until late infancy. The volume of distribution is different for each class of antibiotics, and peak serum concentrations of a drug generally correlate inversely with the distribution volume. For example, after being given identical dosages, peak serum concentrations of kanamycin in preterm infants are larger than those in fullterm infants, which is due in part to a smaller volume of kanamycin distribution in the premature baby. An additional consideration is that drugs distributed in the expanded extracellular volume of preterm infants usually have delayed excretion. This may explain the observation of shorter serum gentamicin half-life values in older infants compared with neonates, even when the rates of creatinine clearance are similar.

The clinical significance of antibiotic protein binding is unknown. As a general rule, a protein-bound drug has little or no antibacterial activity. Because protein–drug complexes tend to be retained in the intravascular space, distribution into tissues may be limited. Excretion of a protein-bound drug is primarily by renal tubular mechanisms. Generically similar drugs with lower protein binding may have enhanced antimicrobial activity and greater tissue distribution. With one possible exception, there are no clinical data to confirm this assumption. In the early 1940s penicillin K, a preparation that is highly protein-bound, was found to be less effective in treatment of syphilis than were other penicillins with less protein binding.[1] By contrast, methicillin and dicloxacillin appear to have comparable clinical efficacy in the treatment of staphylococcal disease despite greater protein binding of the latter drug (98 percent versus 37 percent). However, a well-designed prospective study comparing these two drugs in staphylococcal disease has not been performed.

The affinity of a drug for serum protein may have important clinical consequences. For example, sulfisoxazole is known to compete with bilirubin

for binding sites on albumen. This greater affinity of the sulfonamides for albumen releases bound bilirubin into the circulation, which may then deposit into extravascular sites such as the geniculate ganglia to produce kernicterus in some neonates. Novobiocin may also displace substances from protein binding sites, but the clinical significance of this displacement in neonates is unknown.

The penicillins and aminoglycosidic drugs are excreted primarily by glomerular filtration in newborn and young infants. Diminished glomerular filtration rates during the neonatal period result in sustained serum concentrations of drug and prolonged half-life values. Because renal function is constantly changing in the first month of life, pharmacokinetic data must be obtained at various times during this period in order to determine the proper dosage and frequency of administration for each antibiotic. The two pharmacologic functions used to evaluate diminished glomerular and renal tubular function in neonates are the serum half-life and clearance of drug from plasma. These two pharmacokinetic properties are used to calculate dose intervals of a drug. Improper dosage schedules have resulted in administration of excessive antibiotic dosages, which lead to accumulation of drug in serum to potentially toxic concentrations. Permanent ototoxicity in some neonates caused by streptomycin and kanamycin is explained in part on this basis.

PHARMACOLOGIC EVALUATION OF ANTIMICROBIAL AGENTS IN NEONATES

Basic pharmacokinetic data must be obtained from studies of sick neonates because of the ethical injunctions against testing drugs in healthy babies. The antimicrobial agent to be tested must first have completed Phase I studies in adults. Phase I studies, as defined by the FDA, usually involve administration of drugs to healthy adult volunteers in order to obtain data regarding absorption, metabolism, excretion, and acute safety. These data serve as guidelines for initial dosage and safety precautions in neonates.

The first step in evaluating an antibiotic for use in neonates is determination of *in vitro* susceptibilities against commonly encountered bacterial pathogens of this age group. Organisms that are resistant to the currently available drugs of the same class should be susceptible to this new antimicrobial agent. For example, a new aminoglycosidic drug should be effective *in vitro* against kanamycin and gentamicin-resistant coliforms and ideally, against *Pseudomonas* strains also.

The next step in evaluation of an antibiotic is to obtain pharmacokinetic data by substitution of a single dose of the new drug for the prescribed drug of the same class. The decision to treat an infant with antimicrobial agents is

made by the physician caring for the infant and not by the investigators. Substitution of only one dose does not expose the infant to the jeopardy of a prolonged period of either possible ineffective therapy or toxic concentrations that might occur if an untested new drug were administered repeatedly. Multiple serum samples are obtained by heelstick technique and assayed by a micromethod that is capable of measuring antimicrobial activity in 0.02 ml specimens. Urine is also collected in 4-hour fractions for the 12-hour or 24-hour test period in order to determine rate and amount of antibiotic excretion.

From the serum concentration-time curve constructed from these data, the regression line for the disappearance rate is calculated by least mean squares analysis and used to estimate the serum half-life, volume of distribution, and plasma clearance of the drug. These basic pharmacokinetic data are analyzed with regard to gestational and chronological ages, and used to formulate dosage schedules and intervals of drug administration for newborn infants. The dosage regimen is then tested in a larger number of neonates, and concentrations of the antibiotic in serum are monitored after repeated administration. Thus, amplification of clinical pharmacologic data is obtained at the same time that efficacy and safety are being evaluated. Studies of safety must involve the following minimum number of tests obtained at the start and completion of therapy: complete blood count, urinalysis, serum creatinine, serum glutamic oxalic transaminase, and serum bilirubin (direct and indirect fractions). Safety studies of antimicrobial agents in neonates are not complete when drug therapy is stopped. Long-term prospective studies of infants who are treated with new antimicrobial agents must be undertaken to rule out possible adverse effects such as ototoxicity, renal dysfunction, or impairment of physical or mental development.

We have found that this method of dosage formulation and antibiotic evaluation assures safe and effective usage of a new drug in newborns.

REFERENCES

1. Committee on Medical Research, The United States Health Service and the Food and Drug Administration. JAMA 131:271–275, 1946

2
Clinical Pharmacology and Dosage

BETA-LACTAM ANTIBIOTICS

Introduction

The penicillins have been used for many years in the treatment of neonatal bacterial infections. In general, these drugs are safe and effective for therapy of streptococcal, pneumococcal, and susceptible staphylococcal diseases. The broader spectrum of antimicrobial activity possessed by ampicillin and carbenicillin has led to greater usage of these drugs against such pathogens as *Listeria monocytogenes*, enterococci, *Proteus mirabilis*, some *E. coli* strains and, in the case of carbenicillin, against *Pseudomonas aeruginosa*.

Adverse reactions to the penicillins are rare in the newborn. A significant clinical problem is erythema and induration which may occur at the site of repeated intramuscular injections. We have documented diminished absorption of penicillin and ampicillin injected into such indurated areas. Immune-mediated reactions such as urticaria, serum sickness, or anaphylaxis rarely occur during the early months of life. Further, administration of a penicillin to an infant of a known hypersensitive mother has not been a clinical problem, presumably because of the privileged immunologic sanctuary that the placenta provides for the fetus. It is theoretically possible that an adverse reaction could develop in an infant who is breast feeding from a hypersensitive mother, because of the gastrointestinal absorption of sensitized lymphocytes present in colostrum and milk.

Although the cephalosporins have been used extensively in children and adults, there are few pharmacologic data and little clinical experience with these drugs in newborns and young infants. They represent limited purpose antibiotics for neonates because of the greater efficacy and safety record of penicillins in this age group. Furthermore, the cephalosporins should not be used for systemic therapy of neonatal bacterial infections unless meningitis has been definitely excluded. The commercially available cephalosporins do not penetrate into cerebrospinal fluid in sufficient concentrations to inhibit the bacterial pathogens of neonatal meningitis.

The antibacterial activity of the cephalosporins is similar to that of ampicillin, the important difference being that the former drugs are effective against penicillinase-producing *S. aureus* and *Klebsiella* species. Available information indicates that cephalothin is well-tolerated by neonates and few, if any, adverse reactions occur in this age group.

Penicillin G

Penicillin has been used for treatment of neonatal bacterial disease for three decades. Although it is universally accepted as a standard for therapy in newborns, there have been few studies of its clinical pharmacology during the neonatal period.

The penicillins act by interfering with biosynthesis of bacterial cell wall mucopeptides. For the past 20 years many *S. aureus* and coliform strains have shown increased resistance to penicillin G by virtue of R-factor mediated penicillinase production. In most hospitals, over 50 percent of *S. aureus* strains are resistant (MIC > 1.0 μg/ml) to penicillin G. By contrast, the MIC values for pneumococci and beta hemolytic streptococci have not changed substantially during the past two decades. Most pneumococci and group A streptococci are inhibited by 0.005 μg/ml penicillin G. Strains of *S. pneumoniae* with somewhat greater resistance have been encountered but they are still exceedingly rare. The MIC values for group B streptococci are approximately 10 times greater than those for group A organisms, 90 percent of group B strains being inhibited by 0.06 μg/ml.

Mean peak serum concentrations of 22–25 μg/ml (range, 8–41 μg/ml) are observed a half hour to one hour after a 25,000 unit/kg (15.5 mg/kg) dose of penicillin G is given intramuscularly (see Fig. 2-1).[1] Serum concentrations 12 hours after the dose is administered are dependent on the plasma clearance rates, and vary from 4 μg/ml in infants who are less than 2000 grams at birth and 0–7 days old, to 0.4 μg/ml in infants weighing 2000 grams or more at birth and older than 7 days.

When dosages of 50,000 units/kg (31 mg/kg) are administered to newborn infants, mean peak serum concentrations of approximately 40 μg/ml

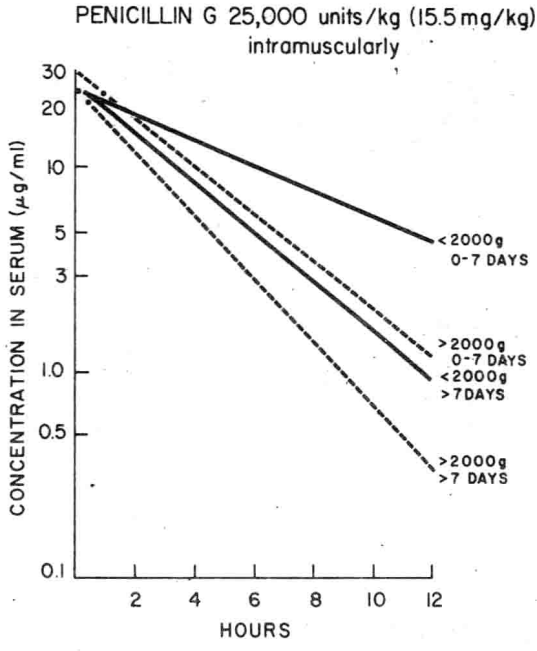

Fig. 2.1. Serum concentration-time curves for penicillin G in newborn infants (dosage, 25,000 units/kg). Data on right of figure refer to birthweight (< 2000 g or > 2000 g) and postnatal age (0-7 days or > 7 days). The point at which the serum concentration-time curve intersects the ordinate represents the theoretical peak serum concentration at 0 time. The actual observed peak value is shown as a separate point on each curve.

are observed.[1] Grossman and Ticknor[2] administered 1 million units of penicillin G intramuscularly to 19 infants (average dose 330,000 units/kg). An average serum level of 140 μg/ml was observed 2 and 4 hours after injection, and concentrations of approximately 7 μg/ml were present 24 hours later.

The half-life of penicillin in serum is inversely correlated with birthweight and postnatal age (see Table 2-1). During the first week of life, average half-life values of 4.9 hours and 2.6 hours are seen in infants less than 2000 grams and 2000 grams or more at birth, respectively. These values are shortened to 2.6 hours in the low birthweight babies, and 2.1 hours in the larger infants who are 7 days of age and older.[1]

The calculated volumes of penicillin distribution in the newborn are slightly larger in the low birthweight infants than in larger babies, but the differences are small enough so that there is no substantial effect on peak concentrations of penicillin in serum.

Table 2-1
Pharmacokinetic Properties of Penicillin G in Newborns

Birthweight/Age Groups	Peak Serum Concentration (μg/ml)	Serum Half-life (hrs)	Volume of Distribution (ml/kg)	Plasma Clearance (ml-min-1.73 M^2)
*I. Crystalline Penicillin G**				
⩽ 2000 grams				
⩽ 7 days	24	4.9	668	30.4
8 to 14 days	23.6	2.6	650	47.7
> 2000 grams				
⩽ 7 days	22.3	2.6	511	51.6
8–14 days	21.0	2.1	603	75.2
II. Procaine Penicillin G†				
⩽ 7 days‡	8.9	6.1	1702	50.2
8–14 days	6.2	5.4	2755	92.6

*Dosage: 25,000 units/kg (15.5 mg/kg)
† Dosage: 50,000 units/kg (31 mg/kg)
‡Average weight = 3100 grams

The clearance of penicillin from plasma is directly correlated with birthweight and postnatal age. As the clearance rates increase, the half-life values of penicillin in serum decrease.

The concentrations of penicillin in urine vary considerably. The highest concentrations are noted during the first 4 hours after a 25,000 units/kg dose of penicillin G, and range from 31–2000 μg/ml.[1] Approximately 30 percent of the administered dose is excreted in the urine over a 12-hour period. Excretion of penicillin in newborns is correlated directly with clearance of creatinine.[1, 3]

Penicillin G does not penetrate well into cerebrospinal fluid. Peak concentrations of approximately 1–2 μg/ml are observed a half hour to one hour after 50,000 units/kg doses of penicillin G are given intramuscularly.[4] These concentrations are maintained for approximately 4 hours during the first days of treatment for meningitis, but by day 5 of illness, the concentrations of penicillin in cerebrospinal fluid 4 hours after the dose is administered are approximately 0.1 μg/ml. By the 10th day of illness, it is often impossible to detect penicillin in cerebrospinal fluid 2 hours after the dose is given.

Table 2-2
Dosage Recommendations for Penicillin G

Individual Dosage:	25,000 units/kg (15.5 mg/kg); 50,000–75,000 units/kg (31–47 mg/kg) for meningitis
Intervals	Every 12 hours for infants 0–7 days; Every 8 hours for infants > 7 days (every 6 hours for meningitis)
Route	IV (preferred) as 15–30 min infusion; IM
Total Daily Dosage	50,000 units/kg for infants 0–7 days; 75,000 units/kg for infants > 7 days;100,000–150,000 units/kg for infants 0–7 days with meningitis;150,000–250,000 units/kg for infants > 7 days with meningitis
Comments/Cautions	Larger dosages recommended for treatment of group B streptococcal meningitis than for pneumococcal meningitis; excessive dosage (> 250,000 units/kg/day) should be avoided because of possible CNS toxicity
Trade Names	Potassium or sodium penicillin G for injection (Squibb)
Supplied As	Potassium penicillin G for injection, 1 million unit vials for reconstitution; sodium penicillin G for injection, 5 million unit vial for reconstitution

The dosage recommendations for penicillin G are shown in Table 2-2. For bacterial diseases other than meningitis, 25,000 units/kg (15.5 mg/kg) are administered every 12 hours for infants 0–7 days old, and every 8 hours for infants older than 7 days. For patients with suspected or confirmed meningitis, the individual dosage is 50,000–75,000 units/kg (31–47 mg/kg)