Drug Therapy in the Neonate and Small Infant

Edited by
Tsu F. Yeh, M.D.

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The authors and publisher of this book have made every effort to ensure that the recommended drug dosage schedules presented are accurate and in accord with sound medical practice. However, since new research and experience may lead to changes in drug therapy, the reader is advised to verify drug dosage schedules in the manufacturer's product information insert prior to administration of the drug. This is particularly important with infants' and children's dosages, as well as for new or infrequently used drugs. In addition, many of the drug regimens included here have not yet received FDA approval for application in children. It remains the responsibility of the individual physician to determine the suitability for use of a particular drug in these situations.

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Preface

The art of medicine changes rapidly and few areas reflect more frequent changes than therapy. Recent advances in neonatal therapy have kept pace with our increasing knowledge of the etiology and pathology of many neonatal diseases. Newer drugs, many of them quite specific in action, are employed clinically or experimentally. These rapid changes have created the need for a practical and concise summary of our current knowledge and understanding of the drugs commonly used in neonates and small infants. This book has been written to provide just such a summary for residents and pediatric practitioners.

Because adequate diagnosis is a prerequisite of effective therapy, this book is divided into chapters based on diagnostic entities but does not treat diagnosis in great detail. Each chapter begins with a brief discussion of pathogenesis, clinical and laboratory diagnosis, and general management followed by a more detailed discussion of drug therapy. The book concludes with a chapter on the drugs commonly used during medical, surgical, and radiologic procedures.

It is the authors' intention to give the physician responsible for the care of neonates and small infants more information on drug therapy than has been available in general pediatric textbooks. We hope this book and future editions reflecting the changes and advances in neonatal therapy will provide a firm base for the pediatric practitioner.

I am deeply grateful to the contributing authors who have made this volume possible and to Dr. Rosita S. Pildes, Chairman of the Division of Neonatology at Cook County Children's Hospital, for her encouragement. I thank Helen Coppage and Lula Johnson for the preparation of the manuscript and G. K. Hall Medical Publishers for their kind assistance in making this publication possible. Finally, I thank all the medical and nursing staff of the Cook County Children's Hospital Neonatal Intensive Care Unit whose questions and interest in caring for sick newborns are a continuous stimulus to me.

T. F. Yeh, M.D.

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Foreword

During the past decade substantial progress has been made in laboratory and clinical research studies related to drug therapy in neonates, infants, and children. Some of these advances have come through better understanding of the pathophysiology of the specific conditions treated. An appreciation that neonates may not dispose of drugs in the same manner as older infants and children has led to major improvements in the study of drugs and their metabolites in minimal size samples. The provision of results to the clinician in a prompt fashion has made it possible to use drugs in a rational fashion. It is thus fitting that a monograph be written devoted to drug therapy in neonates and small infants.

Dr. Yeh and his colleagues have combined current knowledge of pharmacokinetics with pathophysiology of the disease process with a practical approach to the sick infant. The authors have vast clinical experience in neonatal intensive care and are well aware of the numerous problems faced by physicians involved in the care of these infants. I am privileged to have been able to play a small part in the development of this monograph.

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Introduction

1

Factors Modulating Drug Therapy and Pharmacokinetics

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The goal of drug therapy is to produce an appropriate and desired pharmacologic effect in each patient. This requires the administration of an appropriate dosage that accounts for individual variations in genetic makeup, disease processes, and patient history—all of which may influence the disposition and biological effects of the drug. The effects of most therapeutic agents are related to the drug concentration at the site of action, the length of time the concentration is maintained, and the rate at which active levels are achieved. Thus the major factors that modulate individual variability in drug response are drug disposition in the body and sensitivity of the body to the drug. In general, although individual differences to drug response do exist at the molecular level, these are often of lesser magnitude than those resulting from individual variation in drug disposition. In this respect, therefore, age-related changes in drug disposition are of major concern in drug therapy.

Dosage

Until 15 to 20 years ago drug dosing in infants was empirically based on several rules using weight, height, age, or body surface area to calculate the neonatal dose as a fraction of the adult dose. These parameters are important correlates of many physiologic functions in development that change in accordance with body weight (e.g., lean body mass), body length (e.g., long axis of the heart), or body surface area (e.g., oxygen uptake and basal metabolic rate). Although none of these rules are ideal in neonatal dose determination, body surface area

appears to be the most applicable as this parameter has been shown to best correlate with a number of physiologic parameters that have importance for drug kinetics. It should be noted that significant differences in calculated dosage may arise depending on the method selected. For example, the full-term neonate ratio of body surface area to body weight is more than twice the adult value; in the premature infant it can exceed 4 times the adult value. Thus a neonatal medication dosage calculated on the basis of this ratio would be twice as large as that calculated on the basis of body weight. The use of body surface area in dose determination is not optimal either, however, as the relative weight of various tissues and organs changes significantly during development.

Differences in pharmacodynamic aspects of drugs in the neonate also may complicate the use of drugs in pediatrics, as demonstrated by the diminished responsiveness of the cardiovascular system to digitalis, which is associated with a decreased number of receptor sites in the neonate (Boerth 1975).

Pharmacokinetics

It is generally accepted that the newborn cannot be treated therapeutically as a small adult. It should also be appreciated that the qualitative differences between infants and adults in anatomic composition and physiologic functions that contribute to the altered disposition of drugs in the neonate are not always uniform in development. Furthermore, the great variability in kinetic properties (absorption, protein binding, metabolism, distribution, and excretion) according to birth weight and gestational age and the possible existence of abnormalities and pathologic syndromes further complicate the therapeutic approach in the pediatric patient.

The science of pharmacokinetics involves the application of mathematical and biochemical techniques to describe the disposition of chemicals. The physiologic factors that determine the concentration and duration of a chemical at the local site of action are absorption, distribution, and elimination. In general the rate for each of these factors is well described by first-order exponential kinetics in which the absolute rate of the process is proportional to the concentration. The higher the chemical concentration, the higher the absolute rate of the process, and as the concentration becomes smaller, the absolute rate of the process decreases proportionally. On a proportional scale (i.e., the absolute amount of the drug that is absorbed, distributed, or eliminated per unit time divided by the total amount of drug available

for this process) the rate of the process under first-order kinetics is a fixed value.

This principle is illustrated by the equation $\frac{dx}{x} = -Kdt$, where $\frac{dx}{dt}$ is the change in x per unit time (t) and x is the absolute concentration at time (t). A negative sign is used to indicate loss of x. Thus for a first-order process the half-life of the reaction is dependent on a fixed-rate constant (K) and independent of concentration (x). Processes that generally follow first-order kinetics include passive diffusion or filtration across membranes and metabolism. These processes underlie the physiologic parameters of absorption, distribution, and renal clearance. In first-order kinetics the rate of decrease is such that the time required for a specified percent loss is a constant and independent of the starting concentration. However, not all substances follow first-order (fixed-rate constant) kinetics. The elimination-rate constant, for example, can become smaller as dose or serum concentrations become larger, resulting in dose-dependent elimination kinetics. Ethanol, aspirin, and phenytoin are three common examples of chemicals that exhibit a dose-dependent elimination in the therapeutic range. As the dosage is increased for these compounds, the elimination half-life is increased and the plateau steady-state concentration is disproportionally increased (Wagner 1975). This deviation from first-order kinetics is characteristic of a saturation process in which the rate of the reaction becomes limited owing to a finite biochemical/physiological capacity and approaches a fixed value (zero-order kinetics). Explanations for zero-order kinetics include possible inhibitory effects of metabolites, saturation of a rate-limiting enzyme involved in membrane transport, or metabolism of a compound.

Compartment Models

In a comprehensive treatment of chemical disposition, the structural complexity of the body and the multiplicity of ways in which it deals with foreign compounds can result in exceedingly complicated pharmacokinetic analyses. Fortunately many of the quantitative formulas that are derived can be simplified through the use of compartment models. In these models the body is conceived as a series of compartments that have characteristic input and output rates for each particular chemical. A *compartment* is defined as a kinetically distinguishable "pool" in terms of the chemical concentration-time profile.

A realistic approach for describing the disposition of chemicals is the two-compartment open model shown in Fig. 1.1. This system designates an initial, rapid distribution for the chemical throughout a