Principles of Drug Biodisposition in the Neonate
A Critical Evaluation of the Pharmacokinetic-
Pharmacodynamic Interface (Part I)1

James B. Besunder, Michael D. Reed and Jeffrey L. Blumer

Division of Pediatric Pharmacology and Critical Care, Rainbow Babies and Children's Hospital, Departments of Pediatrics and Pharmacology, Case Western Reserve University School of Medicine, Cleveland

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1 A complete reference list will appear in Part II of this article in the following issue of the Journal.
Rational pharmacotherapy is dependent upon an understanding of the clinical pharmacokinetic and pharmacodynamic properties of the drugs employed. Although the available data on drug biodisposition and action in the neonate have increased considerably in the last few years, pharmacokinetic-pharmacodynamic interactions for many drugs remain poorly understood.

The ontogeny of drug absorption, distribution, metabolism, and elimination are addressed in this review. Drug absorption from any site depends upon both the physicochemical properties of the drug and a variety of patient factors. Absorption of orally administered drugs may be affected by changes in gastric acidity and emptying time as well as by bile salt pool size, bacterial colonisation, and extraintestinal disease states such as congestive heart failure. Factors affecting drug absorption following intramuscular, percutaneous, and rectal administration are also discussed.

Drug distribution in the neonate is influenced by a variety of important and predictable age-dependent factors. The developmental aspects of protein binding and body water compartments are described. Additionally, hepatic drug metabolism assumes an important role in understanding the pharmacokinetic and pharmacodynamic properties of many compounds. Certain biotransformation pathways, including hydroxylation by the P450 mono-oxygenase system and glucuronidation, demonstrate only limited activity at birth, while other pathways, such as sulphate or glycine conjugation, appear very efficient at birth.

Elimination of drugs excreted unchanged in the urine is dramatically reduced in the newborn, compared with older infants and children, due to immaturity of both glomerular filtration and tubular secretory processes. The glomerular filtration rate remains markedly reduced prior to 34 weeks gestational age, increasing as a function of post-conceptual age until adult values are achieved by approximately 2.5 to 5 months of age. Tubular secretory capacity is also limited at birth, approaching adult values by approximately 7 months of age.

Published reports describing the pharmacokinetics and pharmacodynamics of commonly used drugs in the neonatal period, as well as differences in drug biodisposition among premature infants, full term neonates, and older infants and children, are reviewed. Our recommendations for neonatal drug therapy are based upon a critical interpretation of these data, an understanding of fetal development and maturational processes, and an understanding of how disease states may affect drug biodisposition in the neonate.

Rational drug therapy in the newborn is often confounded by a combination of unpredictable and poorly understood pharmacokinetic and pharmacodynamic interactions. As a result, neonatologists and other practitioners of paediatric medicine have been extremely conservative in their use of drug therapy; a strategy which has proved both beneficial and potentially harmful. The beneficial aspects of this approach have been the fulfilment of the physician's oath to 'do no harm'. Indeed, catastrophes associated with drug therapy have been rare since the advent of neonatal medicine as a bona fide subspecialty. In contrast, the conservative attitude commonly espoused may also inhibit the adoption and adaptation of new and perhaps lifesaving advances in pharmacotherapy.