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Clinical Pharmacokinetics in Neonates

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Summary

Recent concern over toxic effects of drugs in newborns, infants and children have stressed the need for better knowledge of drug kinetics during development. The present review focuses on the available data on clinical pharmacokinetics in the neonate. Despite the lack of systematic approaches on drug disposition during the first month of life, the body of data currently available indicates profound differences in drug disposition between neonates and older infants, children and adults.

In terms of physiological and anatomical factors the neonate has to be considered as a 'unique drug recipient'. For all the specific variables which govern the drug kinetic pattern (absorption, blood esterase activity, plasma protein binding, metabolic degradation and renal excretion), there are clear differences between neonates and older infants and children. Such differences are not always unidirectional. In the case of absorption, they depend on the maturational stage, but more on the physico-chemical properties of the individual compound. Esterase activity and renal excretion are also related to the physico-chemical properties of the drug, but are more clearly linked with the developmental stage.

Plasma protein binding is generally reduced, and depends on several factors, not all of which are as yet clearly identified and understood. Biotransformation activities are usually very low, but may be increased several-fold by exposure to inducing agents. Hydroxylating activity and conjugation with glucuronic acid appear to be the two metabolic pathways which are most defective at birth, while sulphate and glycine conjugation, and dealkylation activities are close to the adult pattern.

The material reviewed is fragmentary and does not always permit a comparison of the data obtained in newborns with those reported for adults. Differences in the methodology used and in the kinetic criteria further complicate the matter. It is, however, clearly emerging that drug disposition may vary greatly in the newborn in relation to its developmental age. The reported differences may be relevant for clinical practice and stress the need for more detailed information on drug kinetics in the neonate. Such information may be achieved by carefully planned clinical trials, but more meaningfully, and more profitably for the individual patient, by a very carefully, well integrated monitoring of the neonate at risk. By such an approach, where drug plasma levels are related to drug effects and to the pathophysiological condition, the significance of various factors on drug disposition during development will be better clarified, thus allowing a more rational and safer therapy in the newborn.
In the last 10 years, with the development of pharmacokinetic concepts and with the acceptance of clinical pharmacology, many of the factors determining the therapeutic and toxic effects of drugs in man have been better understood. The identification of the toxic and therapeutic threshold and the understanding of alteration of kinetic variables (such as absorption, plasma protein binding, metabolism and excretion) due to various pathophysiological conditions have not only been shown to be valuable but also in many instances essential for rational selection and use of drugs (Kunin, 1967; Breckenridge, 1971; Anton, 1973; Prescott, 1973, 1974, 1975; Morselli and Tognoni, 1974; Goldstein et al., 1974; Wilkinson, 1975).

Among the various factors capable of significantly altering the kinetic profile of an individual drug and hence its effect, age is a very important one (Done, 1964; Sereni and Principi, 1968; Mirkin, 1970; Yaffe and Rane, 1971; Yaffe and Juchau, 1974; Weber and Cohen, 1975; Kretchmer, 1975; Stern, 1975; Orzalesi, 1975; Morselli, 1975). However, despite these very widely accepted concepts, the kinetic data available on human subjects or patients other than adults, are very few (Wilson, 1975). Furthermore, in most instances they are derived from occasional studies. Thus, no systematic approach has been followed to better understand what really occurs in every day practice, when drugs are administered, intentionally or not, to a newborn infant.

Our lack of knowledge in paediatric clinical pharmacology has several origins. Among them we may remember: the emotional impact of a false ethical issue, which for many years has prevented drugs from being evaluated in a more controlled manner in newborns, infants and children; the lack of micromethods suitable for drug assay in small plasma samples; and the refusal to accept routine monitoring of plasma levels as an approach capable of generating scientific and valuable data (Tognoni et al., 1975; Morselli, 1976).

The fact that the newborn infant cannot be considered as a small adult is today generally accepted; however, the qualitative differences between infants and children in various physiological functions are not so often remembered. More importantly, the neonate is an organism who is adapting very rapidly to the new environment throughout a continuous and rapid sequence of anatomical and physiological changes. The immaturity of various organs involved in drug disposition may alter profoundly, not only the pharmacokinetics but also the toxicity of several drugs. Furthermore, the great variability in kinetic properties such as absorption, protein binding, metabolism, distribution and excretion, according to birth weight and gestational age, and the possible existence of abnormalities and pathological syndromes further complicates the therapeutic approach and makes mandatory the need for more information for optimum dosage in the individual patient.

The data available up to now, even if not yet provided by systematic study, suggest that the newborn handles drugs in a substantially different way from the adult. This review focuses on drug kinetics in the neonate and emphasises the known or possible clinical consequences of this altered kinetic pattern.

In addition to the specifically treated topics (absorption, protein binding, metabolism and excretion), it may be worthwhile to remember that:

1) The arterial blood pressure increases constantly in the first month of life, and that such an increase is paralleled by concomitant changes in vascular resistances and regional blood flows.

2) The brain, as the liver, is much larger during the first month of life in relation to body weight, but it contains less myelin than adults.

3) Considering the inability to retain bicarbonates at tubular levels, the urinary pH, even if lower than in older children and adults, is rather elevated in comparison with the blood pH (which is particularly low).

4) Furthermore, the various body compartments are relatively and absolutely different from the adult pattern.