DEVELOPMENTAL ASPECTS OF DRUG TOXICITY

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The inability of the neonate to metabolize drugs has been known for over 25 years (1). Together with poor renal function this is seen as a major source of risk of drug toxicity in early stages of development. In fact, several examples of drug toxicity (chloramphenicol, sulfonamides, digoxin etc.) in the neonate are associated with their excessive accumulation in body compartments.

However, the toxicity of several exogenous compounds (drugs, environmental pollutants) is thought to be due to their transformation into toxic intermediates in the body. Most foreign compounds undergo biotransformation such as oxidation, reduction, hydrolysis and conjugation. The first three mechanisms constitute phase I reactions during which intermediate metabolites are formed that are further converted to more polar compounds by phase II reactions. Both phase I and phase II reactions undergo developmental changes, but it may be hypothesized, and it has been shown in some cases, that an imbalance may occur between these two processes during maturation leading to an increased availability of potentially toxic, highly reactive intermediates (arene or alkene oxides) which may react with intracellular organelles and with DNA thus causing an elevated risk of mutagenesis. The P₄₅₀ related monooxygenase, epoxide hydrolase and glutathione-S-transferase are the systems which have been best characterized during the development of various animal species (2-4) and data are also available for human fetuses (5,6).

Recent evidence has also shown that drug metabolizing enzymes are also present in the nuclear membrane. This system has potential importance since toxic or unstable metabolites formed in the nuclei may interact more easily with the genome than when formed in the microsomal fraction. Nuclear membrane enzymes have been found before birth in different species including man. They undergo developmental changes similar, but not identical, to those observed in the microsomal fraction. There are interspecies variations. The nuclear activity of styrene monooxygenase and epoxide hydrolase at the 15th day of gestation in the rat is as important as the microsomal one. In human fetuses at 15-17 weeks of gestation the microsomal metabolism is already predominant (6). This indicates the necessity for studies at earlier stages of pregnancy to better assess the role of nuclear drug metabolism in human developmental toxicology. In addition to the developmental aspects of the balance between toxifying and detoxifying enzymes the availability of endogenous substrates influences drug toxicity and teratogenicity. For example, gestational fluctuations in reduced glutathione have been found to be related to the teratogenicity of phenytoin (7). In addition to its biological interest this observation may provide a rationale for studies on the prevention of fetal toxicity.

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SELENIUM REQUIREMENT IN CHILDREN

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Selenium - first known as a naturally occurring toxicant - belongs to the essential trace elements. Biological effects occur at selenium concentrations mainly in the range of 0.05-5.0 µg/g of diet or tissue. Besides some seleno-enzymes and specific selenoproteins in bacterial and animal tissues glutathione peroxidase is the only seleno-enzyme proven to occur in humans. Its activity is dependent on the selenium state. This enzyme protects membranes against oxidative damage. The requirement for optimum health and growth is far from being known and its role in human deficiency diseases is complicated. During childhood selenium state shows a marked age relationship. At birth the selenium content of the liver is higher than in adults suggesting the accretion of selenium stores in gestation (1,2,8). Hair selenium shows a similar phenomenon, in neonates the selenium content is 200% of the mother's selenium (790 ng/g versus 400 ng/g) (9). In contrast the plasma selenium concentration is low reflecting probably a reduced selenium placental transport during the last days of pregnancy. The erythrocyte or whole blood value may still be normal or low. During the first months of life the selenium content of serum, whole blood decreases. This decrease is steeper in premature than in mature babies, more pronounced in formula-fed infants than in breast-fed infants and most profound in parenterally-fed infants. Thus reflecting the low selenium-intake. Whereas the selenium intake during the first trimester is between 10 and 22 µg with mothers milk in so-called selenium adequate areas it is 20 to 67% lower in formula-fed infants.

During the second half year of life the selenium intake and consequently the selenium state is rising. This increase is produced in western countries mainly by the addition of cereals to the milk and to a lower degree by animal proteins with a higher selenium content f.e. egg yolk. In West Germany at the end of the first year the selenium intake amounts to 34 µg of which 44% derive from cereals. The