

Overview of Similarities and Differences Between Children and Adults: Implications for Risk Assessment

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The need for and value of risk assessment for drugs and chemicals has been obvious to both the public and private sectors. But the acquisition of a useful risk assessment data base for children, in particular, has been a significant challenge. Adverse effects which appear uniformly across all age groups with clear dose-response relationships represent an exception rather than a rule. Children are a unique population to assess for risk to drug and chemical exposure.

Table 1 lists important factors responsible for known outcome differences between children and adults in toxic effects of drugs and chemicals. An understanding of these factors will provide the basis for understanding the impact of the similarities as well as the differences between children and adults for risk assessment.

Certainly from the standpoint of pediatrics, there is a tremendous potential for adverse effects during growth and development transcending the period between birth and adulthood. A newborn has fewer cells and there is often a difference in the state of maturation of these cells relative to adults. There is a maturation of many cell types as they continue to divide and multiply as the individual progresses toward adulthood. This presents a rather unique opportunity for influence, including modification or disruption of maturation. There is substantial potential for toxicity in children, because of this intrinsic feature of growth and development, which is vulnerable to extrinsic influences.

As an example, the lung is very much in a period of growth and maturation during infancy. The full complement of mature cells is not realized in the lung until several years after birth. Therefore, there is considerable vulnerability, particularly in the premature infant, whose lung is significantly less mature than the infant born at term. The lung of a child might be able to tolerate the acute effects resulting from a toxic exposure but subsequently develops chronic changes as a result of influences of the toxin on lung maturation. Perhaps some forms of adult lung disease such as emphysema have their true origin in childhood.

Table 1. Factors responsible for differences in risk assessment between children and adults

• Growth and development
• Time between exposure and manifestation
• Diet and physical environment
• Parameters of toxicity assessment
• Biochemical and physiological responses
• Drug and chemical disposition

Time between the exposure and manifestation of toxicity can be a major determinant of toxic outcome. If we think about an average lifetime being 65, 75, or maybe even 85 years in the future, that is a long period of time over which a toxic exposure has an opportunity to "mature" to elicit the full potential of the injury. Also, one exposure at one time of life may have no adverse outcome, but multiple opportunities for exposure to the material over many years could result in cumulative toxicity. If a cascade of toxic events has to occur before the toxicity is manifest, the opportunity for realizing these events could be far greater if they begin at 1 year of age versus at 65 years of age.

Toxicity can represent an accumulation of multiple agents and/or events which interact to result in an adverse outcome. The opportunity for such toxic interactions to occur over a lifetime could be greater in children than adults, given the additional elements of their unique diet and physical environment. Later discussions in these proceedings about radiation and vinyl chloride toxicity illustrate the issues of exposure time and opportunity for effect (see papers by Merkle and Miller and by Swenberg et al.).

The diet, obviously, can be a source of exposure to toxins. There are major differences in diet between infants, children, and adults which would affect the incidence of exposure to a foodborne toxin. The amount of dietary intake will also differ with age, resulting in differences in quantity of exposure (amount per unit weight).

The physical environment can be very different for infants, children, and adults. For example, in the home environment a 1-year-old spends a great deal of time at a "lower level of elevation" than the adults in that home. This will result in a different level of exposure between the child and adults in the home to an airborne toxin if it is not uniformly distributed in the air. Day care facilities and schools introduce young infants and children to a unique "workplace" environment where exposure of large numbers of children to a potential toxin could occur should it gain access to these environments. The duration of play time in a selected location cannot be overlooked in assessments of environmental safety. Later discussion on insecticides details some of the principles that have been described, particularly the issue of physical environment (see, e.g., the papers by Fenske and by Ross).

The functional ability of children, infants in particular, is different from that of adults, which necessitates a different approach to toxicity assessment.

Communication skills, motor skills, and intellectual skills of newborns are such that the known toxicities of many of the drugs used to treat these infants cannot be monitored adequately using techniques appropriate for adults. For example, dizziness, ataxia, slurring of speech, and hearing impairment cannot be detected with the same techniques employed for adult patients. Certainly, it is very hard to determine whether an infant has lost 10 to 20 IQ points as a result of an exposure early in life to a certain environment where there is no baseline for comparison. Obviously, we can use the average IQ, but that is not very helpful when you are attempting to assess risk for an individual patient. So, there are challenges relative to measurements of toxicity in children.

Another danger in our adult orientation to toxicity and its assessment is the assumption that the toxicity of a particular agent in the child is going to be exactly the same as it is in the adult, and so we ought to use the same parameters of toxicity. In fact, toxicities in children can be different either in quantity, or more importantly, in the nature (quality) of the adverse effect. Lack of an awareness of the potential for qualitative differences in toxicity between children and adults has led to delays in recognition of toxic events. More is presented on this aspect of toxicity in the presentations on heavy metals (see the papers by Mortensen and by Davis and Grant).

Alterations of fertility and reproductive capacity represent ramifications of toxicity that should be mentioned. If the toxicity of an agent is to influence fertility or reproduction and this capability is not apparent until later in life, loss of capacity may be erroneously assigned to an intrinsic error in a reproductive ability rather than a previous environmental or other type of toxic exposure.

In the growth and maturation process there is an evolution of membranes including receptors in infants and children as they approach adulthood. These changes reflect a potential for a different environment for chemical and drug interactions with receptors. What is the affinity of the binding? What are the dissociation characteristics of binding between a drug or chemical and a receptor? What opportunity is there for disruption of growth and maturation of the receptor population? This is potentially a very important area and one about which very little is known. Some possible examples of differences in drug-receptor interactions between children and adults include phenobarbital and Ritalin. One of the effects seen with phenobarbital considered to be a side effect is central nervous system stimulation. Phenobarbital, a sedative-type agent in adults, produces hyperactivity in children, which can lead to discontinuation of a needed therapy. Ritalin, which is used as an antihyperactive agent in children who are hyperkinetic, produces an opposite effect in adults. The explanation for these paradoxical responses in children and adults may reside in differences in receptor-drug interactions.

Drug disposition refers to drug or chemical movement through the body including absorption, distribution, biotransformation, and excretion. Drug or chemical absorption can effectively occur through the skin or muscle, by inhalation, or through the gastrointestinal (GI) tract. Differences in rate and extent of

absorption in children compared to adults relate to differences in membrane composition, surface area, or perfusion. The composition of some membranes changes with maturation. The environment of the GI tract differs between children and adults with respect to transit time, pH, and enzymatic activity. The diet is different in children, and that certainly can also influence the physical/chemical environment of substances and, thereby, influence their absorption rate and extent. In regards to inhalation absorption, differences in tidal volume, respiratory rate, and pulmonary surface area exist in children compared with adults. All of these can have significant influences on the quantity and rate of absorption of certain drugs and, probably, of many toxic agents as well. More will be presented by others with respect to lead and the GI tract (see the papers by Snodgrass, Davis and Grant, and Plunkett et al.).

After absorption, the agent enters the so-called primary compartment, the plasma or serum compartment, from which the drug or chemical can move to a variety of other loci. The site of action of an anticonvulsant, e.g., would be the brain. Inactive sites, which some would consider not very important, are in equilibrium with the site of action and, thereby, compete for drug or chemical agent. Inactive sites can also be storage sites for later action of the agent or drug when mobilized from these sites.

Body composition constantly changes throughout life. These changes can influence drug or chemical body storage capability. Many drugs and chemicals are lipid in character and, therefore, have capacity to be stored in body fat. Mobilization of body fat or rapid changes in body fat composition can effect changes in drug or chemical movement in the individual.

There has been considerable study of plasma protein binding and drugs, particularly in regards to differences between infants, children, and adults both in the quantity of the drug bound and in the affinity characteristics of that binding. There are data showing differences between infants and older children and adults with respect to protein-binding capability for certain drugs and chemicals. Once a drug is removed from protein, equilibrium changes occur, including access to sites of action or metabolism or excretion. Binding of drugs and chemicals with proteins outside the plasma is an important phenomenon and includes receptor-type binding. There is evidence of significant differences between infants, children, and adults in these tissue-drug binding phenomena that can influence pharmacologic activity.

A great deal is known about drug and chemical biotransformation, particularly maturational influences. The quantity of drug or chemical subject to biotransformation, and number and nature of metabolites have been linked to effects of maturation. A great deal is known about such quantitative and qualitative changes in biotransformation influencing toxicity. Several of the presentations to follow will detail examples of drug and chemical metabolism influenced by genetics and age (see, e.g., the papers by Spielberg, Kauffman, and Clarren).

Excretion, obviously, is the mechanism by which the body burden of a foreign substance is reduced. Capacity for excretion, as it relates to the kidney, undergoes

a considerable amount of maturation. Renal clearance of foreign compounds is typically reduced at birth and matures to adult capability in the first few years of life. The liver, as an organ of excretion of foreign compounds, is also undergoing maturational change.

In summary, intrinsic differences between children and adults linked to molecular, biochemical, physiological, or functional phenomena exist to justify the need for different approaches and criteria for risk assessment. Additional knowledge is needed to fully characterize and define the magnitude and nature of the differences in risks to drugs and chemicals between children and adults.