Pharmacokinetic inequalities between adult and neonate drug dosages create toxicologic challenges in neonatal pharmacetics. This was brought to the authors' attention when several neonates in a neighboring hospital died in a mysterious manner. Investigators from the Centers for Disease Control (CDC) concluded that these deaths were most likely attributed to the parenteral administration of a vitamin E preparation, E-ferol. Similar toxic effects of drugs in the neonate which have been cited include the gray baby syndrome (chloramphenicol), the gasping syndrome (benzyl alcohol), and the floppy infant syndrome (diazepam administration during labor). All of these problems are iatrogenic, and, thus, it is incumbent on the physician and the laboratory toxicologist to be able to identify and control these problems. As recently pointed out, the reasons for the unique toxic susceptibility of the neonates is related to their maturity, particularly those infants who are born significantly before their expected parturition date. Size or even gestational age is not an adequate criterion to predict the inability of the neonate to handle certain drugs. The maturity of neonates may have to be based on the maturity of certain biochemical pathways.

The metabolism of drugs and their excretion are interrelated; often specific drugs cannot be excreted unless they are metabolized. Thus, differences in the ability of the neonate, as compared to the adult, to metabolize drugs can account for most of the toxic experiences listed. Introduction of toxic agents, such as plasticizers and even oxygen can occur as a result of the life support systems which are used to maintain the neonate. However, the bulk of the toxic experiences are the result of agents such as parenteral feeding solutions or pharmaceuticals given to overcome certain morbidity problems. For example, there are a number of excipient items in normal adult formulations which are used to aid in the preparation and delivery of drugs. These include emulsifying agents, such as polysorbate, stabilizers like methyl parabens, and agents to maintain sterility, such as benzyl alcohol.

In addition, preparations can contain contaminants which are toxic. Contaminants pose a special problem for the toxicologist. Detection and quantification of a contaminant of unknown identity,
source, toxicity or, for that matter, existence is a sizable task. One contaminant which has recently come to light is aluminum. This can be present in a number of parenteral infant feeding preparations. Aluminum has been found at levels greater than 500 μg per liter in calcium and phosphorous containing salts, vitamin preparations, and concentrated albumin solutions. This element has been known to be toxic in adult humans, particularly those with end-stage renal disease on chronic dialysis. Accumulation occurs through contamination of the water source and the inability of the patient to eliminate aluminum by renal excretion.

In infants, the major source of aluminum intake is through parenteral nutrition. It has been shown that renal elimination of aluminum in infants is incomplete, as assessed by lower urine aluminum excretion versus load, elevated serum aluminum concentration, and bone deposition of aluminum (determined from autopsy samples). The unexpected presence of aluminum in large amounts points out that we do not know of all the potentially toxic agents which can be present in such preparations. Most drug preparations have not been completely characterized as to their content of potential trace elements and other excipient items which could be toxic.

The possibility of E-ferol toxicity was not considered because this agent contained components that had been widely used in pharmaceutical formulations. E-ferol was a therapeutic agent designed to provide premature infants with supplemental levels of vitamin E for the prevention of retinopathy of prematurity. In addition to dl-alpha-tocopheryl acetate, the preparation contained nine percent polysorbate 80 and one percent polysorbate 20. The patients who received this preparation were typically low birth weight (less than 1,500 g), premature infants in neonatal intensive care units. Although the tocopheryl could be the toxic agent, the most likely possibility is polysorbate. This agent has been used in food and drug preparations since the 1950s. Extensive studies have been performed to determine its toxicologic effects. The oral LD-50 (30 ml per kg in the adult rat) indicates it is particularly nontoxic. Even intravenous administrations are relatively innocuous with LD-50s in rats of approximately 0.7 ml per kg. Thus, by a common criteria of toxicology, this agent is judged very safe for injection. The usual pathway for elimination of this molecule is by urinary excretion after hydrolysis of the fatty acid chain from the polyoxyethylated moiety. Excretion of polysorbate in mature humans and rats is very fast; approximately 90 percent appears in the urine in 24 hours. The neonate excretes only the polyoxyethylated metabolite. Therefore, metabolism of the polysorbate is essential for excretion to occur.

In the fetal rat liver, enzyme activities are only five percent of those present in adult liver. In addition, neonatal urinary excretion rates can be significantly less than those of adults. Preliminary observations on some of the body fluids from infants who died from E-ferol toxicity indicate that high levels of polysorbate were present. Thus, although the adult can handle large amounts of this agent, the neonate cannot. The reasons for this appear to be in the inability of the neonate to metabolize the compound. The lack of maturity of a specific enzyme system needed for handling this xenobiotic agent may have been the cause of the toxicity and unfortunate mortality which occurred.

The polysorbate experience demonstrated our failure to identify potential toxicity, even with an agent which has been known for 30 years. In this particular circumstance, the neonatal biochemical pathways of metabolism were pre-
sumered analogous to adults in both the rats and human, and metabolism in the neonate was presumed to be at the same rapid rate. Before a drug can be administered in the neonate, some methods of measurement should be developed which allow for monitoring the drug’s metabolism. One possibility is the use of non-metabolizable analogs to establish what the possible effect would be if the drug is not metabolized. That is, would there be an accumulation of the drug or would it simply be excreted by the normal excretory pathways of the neonate? The neonatologist has become more successful in maintaining the survival of smaller and smaller infants with the potential for having less mature metabolic systems. How can one establish some degree of safety when the systems of metabolism and excretion are immature? That is, if an agent is safe in a 1,000 g infant, will it be safe in an 800 g infant or a 300 g infant?

The E-ferol incident also points out there is a need to test all of the ingredients in formulations in appropriate models. The particular problem with this polysorbate preparation was that the concentration used in this formulation was 10 times higher than that used in previous formulations. Thus, a basic principle of toxicology may have been violated, i.e., ignoring the effect of concentration of a potentially toxic agent. The case of aluminum points out that the toxicologist and the laboratory should review all ingredients of drug preparations. Certainly this can be difficult in those circumstances where there are natural substances, but it is unacceptable to forgo testing for the potential toxicity of all possible synthetic agents in preparations. Finally, the case of the E-ferol shows there is a need to retest current drugs and agents.

The field of neonatal toxicology is a new one. It is still not known if all the morbidity and deaths caused by iatrogenic agents in the neonate have been identified. Good criteria is not available to establish whether or not infant morbidity or death is due to toxicity or natural causes. In the case of the E-ferol poisoned infants, the lesion which was observed was new to the pathologist. A good model is not available to study neonatal toxicity. From our own experience, rat pups are an invalid model. These animals are much too mature compared to the 1,500 g human neonate. There is great difficulty in using mammals delivered before their expected parturition date. These pre-term animals cannot be maintained long enough to be used in many types of toxicological studies. In addition, the cost and difficulty in doing these types of experiments preclude their routine use. Thus, most experiments are done on animals which are much more mature than their human counterparts into which these drugs are given.

No systematic examination of toxicity in the neonate has been done. Drugs cannot be tested in the healthy neonate, and therefore, our experience is anecdotal and comes only from experiences such as the E-ferol, benzyl alcohol, and chloramphenicol cases. There may well be a more sophisticated approach, i.e., a biochemical index based on the measurement of metabolic markers such as carbonic anhydrase, fetal hemoglobin, and alphafetoprotein. In summary, the toxicologist faces difficulties which require novel approaches as well as serendipity to resolve the problems of this particular patient population.

References


