Is Pediatric Labeling Really Necessary?

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ABBREVIATIONS. FDA, US Food and Drug Administration; FDCA, Food, Drug and Cosmetic Act; GFR, glomerular filtration rate; BSA, body surface area.

Labeling refers to the label on the drug container and all printed materials, including the package insert, that accompanies the product. Labeling of a drug indicates that there is substantial evidence from adequate and well controlled clinical trials for the safe and effective use of that drug. Labeling provides important information on clinical pharmacology, indications and usage, contraindications, precautions, adverse effects, dosage, and administration. Unfortunately for children, most drug labeling contains the precautionary disclaimer, because safety and efficacy in children have not been established.

The availability of safe and effective drugs has been directly responsible for the improvement in health over the past 50 years. Children essentially have been excluded from the benefit of the many therapeutic advances that have marked pharmacologic drug development. The failure to include children in clinical trials during drug development leads to delay in implementing potentially effective treatment. Most US food and Drug Administration-approved drugs lack approval for use in all children or are restricted to certain pediatric age groups, primarily older children. Only a few of the new drugs released in this country each year are approved for use in children. This lack of information on the safe and effective use of drugs in the most vulnerable patients, infants and neonates, is of greatest concern. Only five of the 80 most frequently used drugs released in this country each year are approved for use in children. Another problem is that most drugs are not available in suitable pediatric dosage forms. They are not available in appropriate dosage sizes, lack liquid formulation, and taste peculiar to the child, making compliance difficult. Pharmacies extemporaneously prepare many drugs in liquid dosage forms for use in children. These dosage forms are not sufficiently tested to determine stability, efficacy, or expiration dating.

For solid dosage forms, parents often must divide adult tablets in halves or quarters to get an appropriate dose for their child. This results in imprecise dosing that can lead to poor therapeutic response. Practitioners are left to use empiric therapy in treating their pediatric patients because of the inadequate information available for prescribing of drugs. They often must choose between not treating children with potentially beneficial medications because they are not approved for use in children, or to treat them with these medications based on adult studies and limited or anecdotal experience in children. In either case, children may not be prescribed optimal therapy.

FOOD, DRUG AND COSMETIC ACT

Concern for the risk to public health and safety with unsanitary food and adulterated drugs, a common problem during that time, lead to passage of Federal Food and Drug Act in 1906 (Table 1), which prohibited interstate commerce in misbranded or adulterated food, drink, and drugs. A major stimulus for passing the act was quinine being used by the American Army in Mexico that was found adulterated. The Act was completely rewritten as the Food, Drug and Cosmetic Act (FDCA) in 1938, after the death of 107 children from sulfanilamide elixir that used diethylene glycol as a solvent. No toxicity testing had been done on the product before marketing. Also, new drugs had to be labeled with adequate directions for use. A problem with the latter requirement was that many newer drugs being developed and coming onto the market were not safe for use except under medical supervision. These drugs did not meet the adequate directions for use requirement. A 1951 amendment to the FDCA solved the problem by establishing two classes of drugs: over-the-counter drugs that could maintain adequate directions for use on the label, and prescription drugs that could only be used under medical supervision.

Another pediatric tragedy, this time fetal malformation from maternal ingestion of thalidomide, led to an amendment in 1962 that drugs not only had to be safe, but also effective in the population for which they were to be marketed. The safety and efficacy in one population could not be transferred to another. Thus, safety and efficacy in adults cannot be applied to children. These two significant changes to the FDCA were the result of therapeutic tragedies in children. Remarkably, the problem recognized with the use of medications in children and the amendments to the FDCA has not encouraged increased study of drugs in children. On the contrary, it has
discouraged the evaluation of drugs in children because of perceived concerns over ethical issues, fears of harming children, and perceived increased liability in testing drugs in children. Children also represent a small market share for most drugs, which discourages sponsors from pursuing drug labeling for children.

The recognition that only a minority of drugs were labeled safe and effective for use in children led to the 1979 US Food and Drug Administration (FDA) regulations that specific pediatric indications, if any, are described in the indications and usage section of the labeling, with appropriate pediatric dosage provided in the dosage and administration section. The Act also requires that recommendations for pediatric use be based on substantial evidence derived from adequate and well controlled studies in the pediatric population, unless the requirement was waived. The pediatric use subsection was intended to encourage drug labeling in pediatric patients. As with the 1962 amendment, it had the opposite effect. The requirement further discouraged pediatric labeling for most drugs because it required extensive data in the intended population. Surveys continued to show that the vast majority of newly approved drugs do not carry pediatric labeling. The FDA, concerned that without adequate information practitioners may be reluctant to prescribe certain drugs for their pediatric patients or may prescribe them inappropriately, pressed for implementation of the 1994 Final Rule for pediatric labeling. The Rule clarifies the FDA position on various procedures that can be used to get pediatric labeling of drugs. The Final Rule also placed greater responsibility on the sponsor to justify why pediatric labeling should not occur for the drug. In certain cases, drugs may be labeled for pediatric use based on adequate and well controlled studies in adults, with pharmacokinetic and safety data in children. The Final Rule also recognizes the hazards that inactive ingredients can pose to the pediatric population. Compliance with the Final Rule by the pharmaceuticals industry is not clear at this time.

### CONTINUED PEDIATRIC THERAPEUTIC DISASTERS

The FDCA has not prevented the continued occurrence of therapeutic disasters from drug use in children. Acute toxicity to chloramphenicol caused by immature glucuronidation in the neonate was described in the 1950s. The use of large doses of chloramphenicol in the neonate, coupled with a decrease metabolic clearance, led to accumulation of chloramphenicol. The high level of chloramphenicol is associated with lethargy, abdominal distention, hypotension, hypoxemia, and decreased perfusion causing a gray appearance, or gray baby syndrome.

### ESTRAPOLATING DATA FROM ADULTS TO CHILDREN

Extrapolating dosing information from adults implies that children are simply small adults. We clearly recognize that the effects of many drugs on infants and children may vary considerably from the effects seen in adults. The most distinguishing feature differentiating children from adults are the significant physical and maturation changes that occur. Ontogeny of drug absorption, metabolism, and excretion restricts substantially the ability to extrapolate data from adults to children.

The gastric pH at birth is neutral and falls during the first 48 hours. There appears to be a biphasic pattern to gastric and secretion in neonates. High acid concentrations are seen in the first 10 days, followed by a decrease in acid secretion through day 30. Levels of gastric acid secretion reach adult values at 5 to 12 years of age. These changes in gastric pH can affect drug absorption. Higher concentrations of acid-labile drugs such as penicillin and lower concentrations of weak acids such as phenobarbital have been reported in premature infants. Gastric emptying and intestinal transit time are reported to be delayed in newborns. Both are best characterized by irregular and unpredictable peristaltic activity and are affected by gestational age, postnatal age, and composition of feeding. Gastric emptying appears to reach adult values by 6 to 8 months of life.

Hepatic metabolism of most drugs is reduced in
the neonatal period. Phase I metabolism appears reduced at birth and matures rapidly during the neonatal period. There are differences in the maturation of enzymes involved in phase II metabolism.

Glucuronidation pathway is not well developed in infants, not reaching adult values until 3 years of age. By contrast, sulfate and glycine conjugation appear well developed. The inadequacy of one metabolic pathway may lead to metabolism by alternative pathways. Methylation, which is insignificant in the adult, appears functional in the neonate, as evidenced by the methylation of theophylline to caffeine. Also, theophylline oxidation to dimethyluric acid is less prominent in infants compared with adults.

Certain drug metabolic processes are known to be polymorphic. N-acetyltransferase (acetylation) and certain cytochrome P-450 drug-oxidation polymorphisms are known. Little is known about the time course for the phenotypic expression of polymorphic drug metabolism. There is a predominance of slow acetylators in infants that may result in higher sensitivity to the pharmacologic and toxic effects of drugs that undergo this type of metabolism. Cytochrome P-450 polymorphism has not been well studied in infancy.

At birth, the kidneys only receive 5% to 6% of cardiac output, compared with 15% to 25% in the adult. Glomerular filtration rate (GFR) for term infants ranges from 2 to 4 mL/minute, increasing to 8 to 20 mL/minute during the first 2 to 3 days of life and reaches adult levels at 5 to 12 months of age. GFR is at a rate comparable with chronic renal insufficiency over the first few weeks of life. Maturation of GFR has clinical implications in the dosing of drugs eliminated primarily by the kidneys.

Tubular secretion of weak organic anions is initially low. Tubular secretion increases twofold over the first week of life and 10-fold over the first year of life. The ability of the kidney to secrete weak acids actively such as penicillins, sulfonamides, and cephalosporins is markedly reduced in the neonate.

Formulas that have been used to extrapolate adult doses to children are available. The first is simple adjustment based on weight (Table 2). The weight method is arbitrary and does not account for any specific differences in drug disposition between children and adults. Adjusting doses solely based on weight will often underdose infants and children and may overdose neonates. The second method is a modification of the former, scaling weight to surface area. The second method results in a dose about twice that of the weight method. The surface area method may give a better estimate of the appropriate dose for an infant or a child. Many physiologic parameters including cardiac output, renal blood flow, extra cellular fluid, and GFR correlate better with body surface area (BSA) than with weight. Pharmacokinetic parameters adjusted for body surface area among children and adults show little difference, but differences are seen when adjusted for weight.

To illustrate the limitations of these two methods from extrapolating dosing from adults, three representative drugs were chosen. Gentamicin was chosen as a paradigm for a drug eliminated by urinary excretion. Table 2A provides both weight- and surface area-adjusted doses and recommended dosing guidelines for various pediatric age groups taken from the literature. The use of adult dosing recommendations in the neonate would result in a lower dose and a more frequent dosing interval. In the child, the dosing interval would be the same, but the dose would be underestimated. Theophylline was chosen as a paradigm for drugs metabolized by the liver, which holds true except in the neonate, in whom renal excretion predominates. Dosing guidelines are given in Table 2B. It can be seen that adult extrapolated doses overestimate the total daily dose in neonates and underestimate the total daily dose in children. Finally, in Table 2C, dosing guidelines for digoxin, a paradigm for drugs eliminated by both hepatic metabolism and renal excretion, is given.

Again, adult extrapolated doses overestimate the dose in neonates and underestimate the dose in children. Adult-extrapolated dosing in children may lead to either toxic effects from excessive doses or ineffective therapy from underdosing.

### Extrapolating from Medical Literature

The absence of FDA-approved labeling for most of the drugs for children has left the selection and dosing of these drugs to the discretion of the physician and has been referred to as off-label use or unapproved use of an approved drug. The lack of pediatric labeling does not limit a practitioner from prescribing an approved drug for unapproved uses. Without pediatric labeling, the rational selection and dosing of most drugs have to be made by the clinician based on clinical studies published in the med-

### Table 2. Pediatric Dose Adjustment

- **Weight**
  - \[ \text{Dose}_P = \frac{\text{Dose}_A}{\left(\frac{\text{WT}_P}{\text{WT}_A}\right)} \]
- **Body surface area**
  - \[ \text{Dose}_P = \frac{\text{Dose}_A}{\left(\frac{\text{BS}_P}{\text{BS}_A}\right)^{0.7}} \]

P indicates pediatric; A, adult.

### Table 2A. Extrapolating Pediatric Dosing from Adults—Gentamycin Paradigm for Renal Eliminated Drugs

<table>
<thead>
<tr>
<th>Extrapolated dosing</th>
<th>Weight-adjusted</th>
<th>1 mg/kg every 8 h</th>
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<tbody>
<tr>
<td>BSA-adjusted</td>
<td>2 mg/kg every 8 h</td>
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<tr>
<td>Recommended dosing</td>
<td></td>
<td></td>
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<tr>
<td>Premature neonate</td>
<td>2.5 mg/kg every 12-24 h</td>
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<tr>
<td>Term neonate</td>
<td>2.5 mg/kg every 8-12 h</td>
<td></td>
</tr>
<tr>
<td>Infant/child</td>
<td>2.5 mg/kg every 8 h</td>
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TABLE 2B. Extrapolating Pediatric Dosing From Adults—
Theophylline, Paradigm for Hepatic Metabolism

<table>
<thead>
<tr>
<th>Extrapolated dosing</th>
<th>Recommended dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-adjusted 10 mg/kg/d</td>
<td>10 mg/kg/d</td>
</tr>
<tr>
<td>BSA-adjusted 20 mg/kg/d</td>
<td>20 mg/kg/d</td>
</tr>
<tr>
<td>Preterm neonate 3 mg/kg/d</td>
<td>3 mg/kg/d</td>
</tr>
<tr>
<td>Infants 10 mg/kg/d</td>
<td>10 mg/kg/d</td>
</tr>
<tr>
<td>6–12 mo 12–18 mg/kg/d</td>
<td>12–18 mg/kg/d</td>
</tr>
<tr>
<td>1–9 y 20–24 mg/kg/d</td>
<td>20–24 mg/kg/d</td>
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<tr>
<td>9–12 y 16 mg/kg/d</td>
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<tr>
<td>12–16 y 13 mg/kg/d</td>
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TABLE 2C. Extrapolating Pediatric Dosing From Adults—
Digoxin, Paradigm for Renal Elimination and Hepatic Metabolism

<table>
<thead>
<tr>
<th>Extrapolated dosing</th>
<th>Recommended dosing</th>
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<tr>
<td>Weight-adjusted 2.5–5 mcg/kg/d</td>
<td>2.5–5 mcg/kg/d</td>
</tr>
<tr>
<td>BSA-adjusted 5–10 mcg/kg/d</td>
<td>5–10 mcg/kg/d</td>
</tr>
<tr>
<td>Preterm neonate 5–7.5 mcg/kg/d</td>
<td>5–7.5 mcg/kg/d</td>
</tr>
<tr>
<td>Term neonate 6–10 mcg/kg/d</td>
<td>6–10 mcg/kg/d</td>
</tr>
<tr>
<td>Infant 10–15 mcg/kg/d</td>
<td>10–15 mcg/kg/d</td>
</tr>
<tr>
<td>Child 7.5–10 mcg/kg/d</td>
<td>7.5–10 mcg/kg/d</td>
</tr>
<tr>
<td>Adolescent 2.5–5 mcg/kg/d</td>
<td>2.5–5 mcg/kg/d</td>
</tr>
</tbody>
</table>

ical literature and on extrapolation of adult labeling information. The medical literature becomes the foundation by which therapeutic decisions are based. However, practitioners often are poorly trained in the critical evaluation of the medical literature. The reporting of clinical research in the medical literature is fraught with many deficiencies, which have been the topic of numerous reports. Common criticisms include poor study design, incomplete documentation, questionable data collection methods, inappropriate statistical analyses, and indefensible conclusions. Small numbers of subjects and limited evaluation of various age groups limit further the application of results in the medical literature to children. Journal editors and reviewers usually do not have access to all the data when reviewing the results of a clinical trial. The FDA, on the other hand, has access to all data before the labeling of a drug. Therefore, decisions on drug therapy based on the medical literature may lead to ineffective therapy or toxic results.

There are legislative efforts underway to allow the greater dissemination of off-label uses of drugs to practitioners. Currently, off-label information can be provided to practitioners only by request. Proposed legislation would allow dissemination of off-label information directly to practitioners. The principal sources for this information are the medical literature and the data on file with industry that has not undergone peer or FDA review. This potential limited information may not adequately support safe and effective use. The risk to children may even be greater when this information is disseminated to nonpediatric specialists and nonphysicians who are gaining greater prescribing authority.

CONCLUSIONS

The answer to the question, “Is pediatric labeling really necessary?” is most assuredly YES! Pediatric labeling is the only way to ensure the safe and efficacious use of drugs in infants, children, and adolescents. The child is not a small adult. The failure of the pharmaceutics industry to sponsor the necessary studies, the FDA to enforce its regulations, and the legislature to mandate that all drugs with potential use in children be evaluated appropriately has allowed the child to remain a therapeutic orphan some 30 years after the term was coined by Dr Harry Shirkey.27

We are now past the deadline of December 13, 1996, and the April 30, 1997, extension for sponsors to submit supplemental data for the “pediatric use labeling.” It is unclear as to the compliance by sponsors with the Final Rule or whether the Final Rule has had an impact on increasing the number of drugs for pediatric labeling. Pediatric practitioners have some reason for optimism for increased clinical trials in children and the eventual increase in the number of drugs approved for use in children.28 What is not clear is how many drugs are in development that have potential application in children that are not being studied? The FDA’s Center for Drug Evaluation and Research has formed a pediatric committee. The committee is composed of an individual from each of the drug review divisions whose purpose is to focus attention on use of drugs in the pediatric population throughout the drug development process. Additionally, the Network of Pediatric Pharmacology Research Units was established by the National Institute of Child Health and Human Development to serve as a resource for the study of drug action and disposition in children. There are currently seven units actively working with the pharmaceutics industry to develop the necessary data to establish the safe and efficacious use of drugs in children. The evaluation of drugs in all populations for which there is potential use must remain a high priority in the drug development process.

ACKNOWLEDGMENT

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