Off-Label Uses of Drugs in Children

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ABBREVIATIONS. PDR, Physicians’ Desk Reference; FDA, US Food and Drug Administration; NDA, new drug application; IND, investigational new drug.

As we approach the new millennium, very little has changed regarding the labeling of prescription drugs for use in infants and children. Along with pregnant women, infants and children remain therapeutic orphans. This condition is understandable because there are very few therapeutic indications that are unique to this patient population and the absolute quantities of drugs required by these patients remains relatively small. On an actuarial basis, humans spend only approximately 16 years as children, whereas they spend another 60 to 80 years as adults. As a result, there is very little incentive for pharmaceutics companies to develop drugs and drug dosing guidelines for infants and children. Careful review has revealed that >70% of all the Physicians’ Desk Reference (PDR) entries have either no existing dosing information for pediatric patients or explicit statements that the safety and efficacy in children have not been determined. In the best of circumstances, there are age-specific admonitions because of lack of dosing information for infants and children.

The resulting conundrum can be illustrated best by a case presentation.

CASE 1

A 6-month-old infant, born 29 weeks premature, presents to a physician’s office in respiratory distress. His medical history is significant for developing bronchopulmonary dysplasia as well as for prematurity. Vital signs are temperature: 37.7°C; pulse: 180; respiration: 72; blood pressure: 84/56; physical examination: intercostal retractions, increased anteroposterior diameter, bilateral diffuse expiratory wheezing, nasal flaring; treatment: albuterol 2.5 mg in 2 mL normal saline by nebulization.

While receiving the aerosol, the patient’s pulse rate climbs to 215 beats per minutes and he becomes cyanotic despite the O2 used to nebulize the drug. The physician is called by the nurse and witnesses the patient turn black with eyes rolled back. He then suffers a respiratory arrest. Resuscitation is unsuccessful.

When confronted with a similar clinical emergency, most clinicians would have treated the child in the same manner. However, when the labeling for albuterol is examined, there is no information concerning the safe and effective dosing of albuterol in this age group. According to the label, “Safety and effectiveness have not been established in children below 12 years of age (for inhalation solution); in children below 6 years of age (with tablets); in children below 4 years of age (for aerosol); and in children below 2 years of age (for syrup).”

DRUG REGULATION

What does this mean? Is it against the law to administer albuterol to young infants? Is the treating physician in this case negligent for using the drug outside of its labeling parameters?

At the basis of this problem is the US Food and Drug Administration (FDA) and the drug regulations that exist in the United States today. For most of us, the FDA is shrouded in mystery. It is not clear what it is that the FDA is actually able to approve and what authority the FDA has over the licensing and marketing of prescription drugs in our county. The history of drug regulation in our country probably dates back to the Federal Food and Drug Act of 1906. This was preceded by the deaths of a large number of soldiers exposed to adulterated formulations of quinine as well as of a significant number of children exposed to tainted food products.

As we move forward in time, virtually all the additional regulatory mandates have their origins in serious adverse events in pediatric therapeutics. The 1938 Amendment to Federal Food and Drug Act was preceded by the deaths of almost 100 children who received the new wonder drug elixir of sulfanilamide. Investigation revealed that the deaths were attributable to the ingestion of the diethylene glycol excipient rather than to the drug itself. Unfortunately, in this instance, the drug label, although clearly identifying the formulation as an elixir, did not specify that the alcohol was used in its compounding. As a result, a law was passed that demanded truthful labeling and documented safety of drugs. This led to the development of the new drug application (NDA) process, which required that toxicity studies be conducted and reviewed before a drug could be promoted and distributed. The FDA was empowered with enforcement. Nevertheless, drugs could still go from the laboratory to testing in humans without FDA approval.

The result of this amendment was to create a relaxed atmosphere in drug regulation. Research flourished, resulting in a tidal wave of new so-called wonder drugs. The public, feeling reassured that the federal government would vouch for the safety of marketed products, began to shun home remedies in favor of patent medicines. Innovators were not yet...
required to demonstrate efficacy. Moreover, the concept of risk/benefit ratio was seldom raised. Thus, in this era, most of our cancer chemotherapeutic agents would have been denied marketing privileges because their toxicity would have been construed as a negative attribute.

Then came thalidomide. The Harris–Kefauver Amendment to the Food, Drug and Cosmetic Act in 1962 was introduced after the demonstration of teratogenic effects of thalidomide in humans. As a result, there are mandated preclinical animal trials before the testing of drugs in humans. This Act initiated the current investigational new drug (IND) process, which established three phases of clinical testing (Fig 1) after the preclinical testing an IND application is submitted. If approved, in phase I the drugs are evaluated for safety and pharmacokinetics. In phase II patients, the drugs are evaluated for initial effectiveness and dose ranging. Then in phase III, comparative clinical trials are conducted. Every effort is made to document safety in terms of risk/benefit ratio relative to the disease entity being treated. Unfortunately, the end result has been increased time for drug development. The average time from IND to NDA approval increased to 8 to 9 years, and an increased tension developed between the FDA and drug developers. As this Act truly took effect, practitioners began to criticize the FDA for delay in market availability of new effective drugs. This led to the birth of consumer activists who individually and in groups applied substantial political and financial pressure on the government to have certain drugs approved and available for select patient populations.

In response to political pressure, the FDA developed a new solution called the treatment IND. This resulted primarily from demands of patients with AIDS who felt that they were being deprived of life-saving medications because of the long drug development and testing process. The treatment IND allows patients with life-threatening diseases to receive drugs before general marketing when there are no satisfactory alternatives. Although this may appear to be a major advance in patient advocacy, there are negative sequelae for clinicians. A treatment IND must be requested by a physician and, once granted, the responsibility for ensuring the safety and effectiveness of the therapy shifts from the drug manufacturer to the physician. This creates an enormous conflict for practitioners who, on the one hand, certainly want to provide their patients with life-saving remedies, but who have little experience with investigational drugs. It requires them to take responsibility for the safety and monitoring of a new and often unevaluated chemical entity.

**DRUG LABELING AND THE LAW**

NDAs are filed for specific indications. The evidence provided in support of the NDA must support the use of the drug or the specific indication in the application. When approving a drug, the FDA regulates the claims that can be made for the drug by the company that will sell it. These include the package insert or label. These package inserts are published in a compendium called the PDR and are provided with each commercial package of the drug. The FDA is also responsible for regulating advertising. The concepts, images, and words are subject to FDA scrutiny before being presented to the public.

There are several things the FDA cannot do. First, the FDA is forbidden by law from regulating how a drug is used. They are expressly forbidden to “inter-

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**Fig. 1. The phases of drug development in the United States.**
fere with the practice of medicine.” Therefore, once a drug is approved, it may be prescribed by a duly licensed physician for any indication he or she deems appropriate. No physician is bound by law to follow the instructions on the drug label. It is even legal for a poorly informed physician to use a drug inappropriately, although it may constitute malpractice. In contrast, a physician prescribing a drug in such a manner that the prescribing conforms to the community’s standard of care is unlikely to be found negligent.

CASE 2

L.W. is a 2-month-old with bronchiolitis admitted to the pediatric intensive care unit in respiratory failure. The infant is intubated and placed on a mechanical ventilator. A right radial arterial line is placed for arterial blood gas monitoring, and a peripheral intravenous catheter is placed in a vein on the dorsum of the right hand.

The infant remains intubated receiving bronchodilator therapy and peripheral parenteral nutrition for 3 days. Intravenous diazepam was used for sedation. Extubation is successful on day 4, with transfer to the general pediatric ward on day 5. The infant is discharged from the hospital on day 7 on no therapy.

The case chronology is as follows: 1983, admission to pediatric intensive care unit; 1985, contact with family because of swelling in right hand; 1985, seen by pediatric surgeon and a vascular surgeon, lymph edema diagnosed; 1986, notification of intent to sue for negligence; 1987, deposition, case dropped.

The legal proceeding in this case was initiated based on a phrase in the label for diazepam, which stated, “. . . do not use in small veins such as those in the dorsum of the hand or wrist.” When it was empathetically pointed out to the plaintiff’s attorney that this was a global practice in pediatric critical care in the early to mid-1980s, the suit was dropped.

OFF-LABEL USE OF DRUGS

The prescribing of drugs for off-label use is entirely proper. The decision regarding how to use a drug must be made based on what is good medicine and what is best for the patient, regardless of conforming to labeling. In a liability suit, drug labeling may have evidentiary weight for or against the physician, but drug labeling per se is not intended to set a standard for good medical practice. In fact, a physician conceivably could be held liable for departure from accepted standards of care if a patient was denied what is potentially the best treatment solely because it is not included in the official label.

When undertaking off-label prescribing, decisions should be made based on rational scientific theory, expert medical opinion, or controlled clinical trials. The physician is obligated to be aware of the content of the package insert and give it due consideration (e.g., precautions, contraindications, and warnings); however, this information need only serve as a guide rather than a mandate. The following case serves as an useful example.

CASE 3

A 2-month-old is brought to a physician’s office because of frequent vomiting. The infant has lost 500 g in the past 2 weeks. The mother reports that the infant feeds well but vomits approximately 30 minutes after each feed and has occasional choking episodes. This has continued despite thickening of feeds.

Vital signs are temperature: 36.5°C; pulse: 156; respiration: 42; blood pressure: 70/45; physical examination: small, thin, wasted infant sucking vigorously on a pacifier; diagnosis: gastroesophageal reflux; treatment: unknown.

Whenever a question such as this is raised, a number of answers are provided by experienced clinicians. Most can identify four or five agents, such as those listed below, from their experience in practice. They will even be able to provide reasonable and, often, effective doses for these agents. The agents noted are metoclopramide (Reglan): 0.15 mg/kg q6 hours; or ranitidine: 4 mg/kg/d divided q8 hours; or Bethanechol 0.2 mg/kg q6 hours before a meal; or cisapride: 0.6 mg/kg q8 hours; or Maalox liquid: 2–4 mL before each feed.

Nevertheless, when the actual labels for these drugs are scrutinized, the following prescribing information may be obtained from the package insert: metoclopramide, no dosing information; ranitidine, safety and effectiveness in children have not been established; Bethanechol, no dosing information; cisapride, safety and efficacy in children have not been established; Maalox, no dosing information.

SOURCES OF INFORMATION ON DRUG USE

There is a wide variety of sources available to guide drug utilization (Table 1). Perhaps the most complete source of drug information pertaining to all patients is the AMA Drug Evaluations Annual. This book is updated annually and provides monographs on each of the drugs of interest, including references to pediatric use. The US Pharmacopeia is attempting to improve its pediatric coverage; however, it does not yet provide the same level of information that is available through the AMA Drug Evaluations Annual. By far the most important source of information is the peer-review medical literature. With the availability of home computers and access to vast libraries of information both at home and at the office, it is becoming more and more important that physicians take advantage of the opportunity to review the medical literature as it pertains to all their patients. This is true even when they do not actively subscribe to a particular publication. The information is available, and the prudent clinician is being held responsible for what is available.

Other useful sources of information include the Clinical Pharmacology/Clinical Pharmacy Services available in many hospitals, as well as the FDA itself. Various groups within the agency welcome inquiries from physicians regarding specific agents and through the Freedom of Information Act, they often can provide unpublished material reported to them with respect to side effects and toxicity.

Other important sources of information-specific therapeutic agents are the pharmaceutical companies themselves. Each of the companies has a drug information service to provide extensive information about their products. All the companies have telephone lines that are answered by information specialists, usually pharmacists or physicians, who can provide in-depth material about a specific product. In addition, most of the companies have field representatives who also are a wealth of information. These individuals, who visit hospitals and physician’s offices, often are well equipped to discuss the effectiveness and safety of their products as well as how their products compare with others in the therapeutic class. Additionally, when inquiries are beyond the bounds of their knowledge, they have

*Recent labeling changes have extended dosing information to 1 year of age for certain indications.*
healthy to, age, to assess the true risk. It also is patient-specific considerations including, but not
Nevertheless, these must be cast in the context of any the drug and the population for which it is labeled.
clinician must be aware of the known side effects of challenging of these considerations. Obviously, the
particular drug in the particular patient should be approached, the physiologic rationale for this and pharmacodynamics of the drug to be prescribed.
and use it as a guide to their therapeutic interven-
tions that require careful consideration before any
efficacy will be determined. These are critical ques-
tions that require careful consideration before any off-label drug administration.
In considering whether the therapy considered is reasonable, the clinician must establish that it is based on sound physiologic principles and true pathologic need. In most cases, the contemplated pediatric indications will parallel those in adult patients. Therefore, a precedent in peer-reviewed scientific literature already may be established. It is incumbent on practitioners to find this precedent and use it as a guide to their therapeutic intervention. If the therapy contemplated is reasonable but also novel, it is incumbent on the prescriber to have a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug to be prescribed.
Along with this, the physiologic rationale for this particular drug in the particular patient should be well documented.
Evaluating the potential safety of any contemplated off-label prescribing is probably the most challenging of these considerations. Obviously, the clinician must be aware of the known side effects of the drug and the population for which it is labeled. Nevertheless, these must be cast in the context of any patient-specific considerations including, but not limited to, age, to assess the true risk. It also is important that there exists effective means for assessing toxicity. For example, if the only known toxicity of a drug is headache, it is unlikely that this could be easily assessed in a 2- or 3-month-old infant. On the other hand, assessing for irritability after drug therapy may be a more appropriate measure in the target population.
In assessing inherent safety, the concepts of acceptable risk and acceptable uncertainty must be considered. With any drug exposure, there are risks of untoward effects. Most of these are known; however, there are indeed those that are unknown or may be limited to an individual patient or small group of patients. In deciding to undertake off-label prescribing, the clinician must assess what level of risk is acceptable and appropriate for given patient, recognizing that all the risk cannot be defined in advance. The level of this uncertainty may vary from drug to drug. Both the level of risk and the level of uncertainty should be discussed with the parents as well as with the child before undertaking such a therapeutic intervention.
Whether the risks are known or unknown, a prescribing physician must decide on the parameters to be monitored and the frequency of monitoring before drug dosing begins. It is only in this manner that patient safety can be ensured. Previous experience carries very little weight: Should an untoward effect occur, the fact that the particular therapeutic intervention selected has been used many times before does not absolve the physician of any responsibility. Unless he or she can prove that the intervention was prudent, an untoward effect occurring with the drug that is not labeled for the clinical situation for which it is being applied can be construed as malpractice.
Drug dosing remains one of the most urgent considerations in off-label prescribing. To provide effective dosing, one must accept that there are basically two strategies for providing drug therapy. The first is a target-concentration strategy in which drugs are dosed to achieve a certain range of concentrations in the blood with the understanding that these concentrations reflect the concentrations at the drug’s site of action. Monitoring of therapy is performed by relating either the therapeutic effect or some side effect to the drug concentration in the blood. Although this is a very powerful therapeutic strategy, it applies only to a small number of the drugs and drug classes available. More commonly, we must adopt what is called a target-effect strategy. In this case, drugs are dosed until the desired effect is achieved or toxicity supervenes. A reasonable starting point for pediatric dosing is to take the adult dose divided by 60 and multiplied by the child’s body weight to the 0.7 power. This will provide at least a weight-adjusted dose that can serve as a reasonable starting point. It must be recognized, however, that depending on the age of the child and the particular class of drug used,

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<th>TABLE 1. Sources of Information on Drug Use</th>
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<th>TABLE 2. Problems Related to Off-label Use for Pediatricians</th>
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<td>Lack of age-related dosing guidelines</td>
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there may be either pharmacokinetics or pharmaco-
dynamic imperatives that mandate the use of higher
or lower doses of drug. As such, it is important that
once a dose is administered, it is titrated to the de-
sired endpoint. Ideally, these titrations should be
based on the available pharmacokinetic information
and the patient population in which the drug is to be
used. Alternatively, the pharmacokinetic data from
adult populations can be considered in making these
decisions. Of course, to apply these principles, the
clinician must have some rudimentary understand-
ing of the ontogeny of these pharmacokinetic pro-
cesses in infants and children.

Ultimately, the drug must be administered and the
effect assessed. Although all therapy is administered
to achieve an effect, the means to evaluate the effec-
tiveness of the drugs prescribed is often forgotten. It
is vital that the parameters on which therapeutic
success is described are determined before drug-
dosing. For example, in using a new drug to treat
seizures in children, it is important to know what
degree of seizure reduction is going to be considered
a beneficial effect before initiating off-labeled use.
The outcome variables used must be age-appropriate
and germane to the particular drug being used. This
type of therapy requires careful collaboration among
clinicians, patients, and their families. Especially
when the drug is being used in an outpatient setting,
it is vital that the family be able to provide reason-
ably objective input concerning drug efficacy as well
as side effects. Often this will require the use of what
is considered N of 1 randomized trial. In this para-
digm, the patient is exposed randomly to drug and
placebo, while parents, blinded to the nature of the
intervention, and clinicians are asked to assess the
impact of the therapy. This may be the only way to
determine whether the drug is beneficial for a human
patient.

CONCLUSION

In summary, off-label use of drugs in children is
perfectly appropriate and, in fact, may be necessary.

Because most of the drugs currently marketed for
administration by prescription do not have pediatric
dosing information as part of the label, clinicians are
faced with the dilemma of either using drugs with-
out much information to support them or depriving
their patients of potentially effective and sometimes
life-saving therapy. In this context, reasonable ther-
apy based on medical literature, previous experience,
or expert opinion maybe appropriate and fully sup-
portable. The package label, although an important
source of information about drugs and their utiliza-
tion, is not meant to determine medical practice and
is no substitute for sound medical judgment.

REFERENCES

2. American Academy of Pediatrics, Committee on Drugs. Unapproved
uses of approved drugs: the physician, the package insert and the Food
3. Specific requirements on contract and format of labeling for human
prescription drugs: revision of “pediatric use” subsection in the labeling;
Final Rule, Tuesday, December 13, 1994. Part II. Department of
Health and Human Services Food and DrugAdministration. Federal
Register. 21 CFR Part 201:
4. American Academy of Pediatrics, Committee on Drugs. Guidelines for
the ethical conduct of studies to evaluate drugs in pediatric populations.
5. Grodin MA, Alpert JJ. Children as participants in medical research.
7. Jansen AR. Research involving children: recommendations of the Na-
tional Commission for Protection of Human Subjects in Biomedical and
9. Svensson CK. Ethical considerations in the conduct of clinical pharma-
10. Protection of human subjects—proposed regulations on research in-
11. Additional protections for children involved as subjects in research.
Federal Register. March 8, 1993;48:114–117
12. Redman RB. How children can be respected as “ends” yet still be used
13. Dworkin G. Legality of consent to nontherapeutic medical research on
Off-Label Uses of Drugs in Children
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Pediatrics 1999;104;598

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