"Therapeutic Orphans" and the Package Insert

In the practice of pediatrics, drugs which are not approved by the Food and Drug Administration (FDA) as safe and effective in children are prescribed daily. This is due in part to the fact that many drugs released since 1962 carry an "orphaning clause" in the package insert such as, "not to be used in children, since clinical studies have been insufficient to establish recommendations for its use." What is the status of the package insert? Is it a legal directive to the physician, or is it intended as a guide for the physician in prescribing a drug?

The package insert, by legal definition of the Federal Food, Drug and Cosmetic Law, is the official information piece for a drug. The information it contains is derived from data supplied by investigators and submitted by the pharmaceutical firm to the FDA. The insert is written and printed by the drug manufacturer, but its contents must be approved by the FDA. The Food, Drug and Cosmetic Law, as amended in 1962, requires full disclosure of all known facts pertaining to the use of the drug. Therefore, a great deal of information is included in the insert, including the chemical structure of the drug, a summary of its pharmacological and toxicological action, its clinical indications and contraindications, precautions, reported adverse reactions, dosage recommendations, and available dosage forms.

Many drugs have package inserts approved by the FDA before the Drug Amendments of 1962 when manufacturers were required to show the safety but not the effectiveness of their products. On the basis of evaluations of the efficacy of these older drugs by panels of experts selected by the National Academy of Sciences—National Research Council, the FDA is now requiring revision of these package inserts to eliminate unsupported claims and thus to make them more useful to the practitioner.

Is the pediatrician breaking the law when he prescribes drugs for his patients which carry the "orphaning clause?" No, he is not. The physician may exercise his professional judgment in the use of any drug. However, if he deviates from the instructions in the package insert and adverse reactions occur, he must be prepared to defend his position in court if there is a malpractice suit.

Many drugs are used by clinicians in the treatment of conditions not listed in the package insert. The FDA cannot require a pharmaceutical firm to include a new use for the drug product in the insert even if it has been clinically tested and found useful for a given problem. Economic considerations are among a number of factors that may influence such a policy on the part of the company. If a new use for a drug is not yet included in the package insert, the manufacturer cannot advertise his product for that particular use. The package insert is legally binding on the manufacturer in limiting the conditions under which he can promote the use of the drug.

Another fact not generally recognized is that a physician's failure to use a drug approved as effective treatment for a specific disease might be construed as malpractice. In regard to this, it is important that the physician be informed about the availability of the drug and base his decision to use it or not to use it on rational grounds. It would be unlikely that information taken from the package insert could be used successfully as evidence against the physician in a liability suit.

The dilemma facing the physician is illustrated by imipramine (Tofranil) when used in the treatment of enuresis. In 1965 a controlled study was published showing that this drug was useful in "training enuretic children to be dry." Its mechanism of action was not defined, but it appeared to be...
effective when given to children between the age of 5 and 12 years in a dosage up to 50 mg at bedtime. Following publication of this paper, imipramine became widely used for the treatment of enuresis. A straw poll of 15 pediatricians in the Cleveland area showed that 12 had prescribed imipramine for this condition. When one examines the package insert supplied with imipramine, two points are clear: (1) the treatment of enuresis is not listed under conditions for the use of this drug; and (2) there is a clear statement that the drug is not recommended for use in patients under 12 years of age. If a severe reaction occurred and litigation followed, how would a court react if a physician admitted to the use of this drug for the treatment of enuresis in view of the prohibitions in the package insert? Would the published clinical study, plus the physician's judgment in prescribing the drug, suffice? Possibly, if other physicians made themselves available to give expert medical testimony and if other physicians in the community used the drug for this purpose.

The purpose of the FDA control of the package insert is not to legislate the practice of medicine. As in the past, the physician is the individual prescribing the drug. The fact that he followed the recommendations in the package insert does not absolve him from responsibility for harm resulting to his patient, nor does failure to follow the recommendations in the package insert necessarily render him legally culpable.

The statements made in the package insert and approved by the FDA are not in themselves legally binding on the physician in his practice of medicine. Furthermore, no physician should rely on the package insert as his sole source of drug information. Drug dosages, as given in the insert, are guides for instituting therapy. The dose may have to be increased or decreased, depending on the patient's response. And, each time a drug is used, the question of benefit versus risk to the patient must be considered.

Dr. Walter Modell, editor of Clinical Pharmacology and Therapeutics, has taken the view that the insert should be viewed as a useful guide to the physician; its recommendations should be judged on an equal footing with other publications and research reports.²

The Committee on Drugs concurs with Dr. Modell. The package insert contains useful information, but the physician's decision on therapy should be based on cumulative knowledge derived from many sources. When sound scientific data exist which have shown that a drug is reasonably safe and effective in the treatment of a specific disease in adults, it should not necessarily be withheld from a sick child with the same disease just because its use has not been studied in children. But, if used under these circumstances the physician should be cautious and the use of the drug should be reported to the manufacturer, FDA, or in the medical literature to add to the knowledge concerning such use. The foregoing situation must be distinguished from use of the drug when the package insert states that the drug is contraindicated in infants or children on the basis of studies showing it to be unsafe or ineffective in these age groups.

The Committee feels that the pediatrician is likely to ignore the “orphan clause” in the insert if, in his judgment, his patient requires a particular medication for optimal treatment. Whether or not this places him in unusual legal jeopardy is a question not yet resolved by the courts. It is the opinion of the Committee that this practice should not be a problem if the physician is well informed on the pharmacology and toxicology of the drugs he uses and closely follows his patient's response to treatment.

Changing the directives in the package insert, except to disclose pertinent new data, will not solve the problem of “therapeutic orphans.” Echoing Dr. Harry Shirey's³ stand, the Committee believes that the ultimate solution requires the development of programs in pediatric clinical pharmacology to ensure that all drugs used in infants and children are adequately tested for safety and efficacy.
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