The Broader Message of Accutane

Sheila R. Shulman, LLB, MPH

Who has the responsibility for conveying to patients the risks associated with prescription drugs? This question was raised in a powerful way in April 1988 by the disclosure that severe birth defects in 62 infants had been attributed to the use of the drug Accutane during pregnancy. The Epidemiology Branch within the Food and Drug Administration (FDA) subsequently estimated that between the years 1982 and 1986 the drug may have caused as many as 1,300 birth defects nationwide.[1] The agency also estimated that women who became pregnant while on the drug had spontaneous abortions at close to three times the rate in the general population.

In response to these disclosures, the FDA sought the opinion of its Dermatologic Drugs Advisory Committee on the issue of whether Accutane should be removed from the market and, if not, what measures could be instituted to eliminate inappropriate use of the drug. Following a meeting on April 26, 1988, the Committee recommended the continued marketing of Accutane with specific changes in the labeling directed to physicians and patients.[2] Factors influencing this recommendation included evidence of the substantial benefits that the drug offers to a narrowly defined group of patients, and the existence of steps that could be taken to circumscribe the risks associated with the use of the drug. The Committee's action seems appropriate. Little justification can be found for depriving patients of an effective drug for which there is no equivalent alternative until all reasonable steps have been exhausted to effectively bring home to the patient the known risks and recommended precautions. In addition, concerns were expressed by some who appeared before the Committee that even if the drug were removed from the market, patients would obtain illicit access to Accutane and would use it without medical supervision.

Accutane offers a classic example of a highly effective drug which also carries a significant risk of harm. While it is currently the only approved drug that can provide prolonged remission or, for some, permanent relief from a severe and disfiguring form of acne, it is also a potent human teratogen.[3] The birth defect syndrome most commonly associated with Accutane includes enlarged and misshapen head, cleft palate, tiny or unformed ears, facial paralysis, abnormally small jaw, and malformations of the heart and brain.[4]

The FDA approved Accutane in September 1982. The drug's serious teratogenic potential was fully recognized and acknowledged at that time. The FDA-approved labeling for Accutane specified prescribing restrictions, contraindications, and warnings. It was to be prescribed for only one indication—the treatment of severe recalcitrant cystic acne—and only for those patients who were unresponsive to other forms of therapy. The labeling, which constitutes the prescribing information prepared specifically for physicians, warned of the potential for major human fetal abnormalities should the drug be used during or just prior to pregnancy. Since 1984, specific birth defects have been cited. The message to physicians was and continues to be clear and forceful. How then does that message make its way to the women of childbearing years who not only comprise 40 percent of all Accutane consumers, but who can exercise a substantial measure of control over the conditions that may render this drug safe?

The Physician as Learned Intermediary

The distribution of prescription drugs is governed by a complex network of legislative and legal rules. The key players are the FDA, the drug manufacturer, the physician, the pharmacist, and the patient. It is the physician, however, standing between the manufacturer and the patient, who serves as legal gatekeeper, controlling both access to prescription drugs and access to information about those drugs.

The authority which physicians now exercise over this aspect of health care has evolved from statutory and common law sources. The shift to prescription drug status and mandated medical supervision which began in 1938 was grounded primarily in a concern about public safety. However, the regulatory provisions that moved physicians into a position of control also required the removal of patient labeling information, a step which fostered the distancing and eventually the exclusion of the patient from the prescribing process. The assumptions were that certain drugs could be dangerous if access were permitted without the supervision of a physician and that adequate directions for lay use were impossible to write. The 1938 regulatory changes abandoned attempts to communicate information to patients and instead linked prescription drug designation to restrictive labeling requirements.[5] Even appropriate uses for the drug were to be written in medical terms "not likely to be understood by the ordinary individual."[5]

In 1951, the Durham-Humphrey Amendment formally authorized the FDA to determine the prescription status of all drugs.[6] The Amendment, which now appears in section 503

Address reprint requests to Sheila R. Shulman, LLB, Research Associate, Center for the Study of Drug Development, Tufts University, Boston, MA 02111.

This paper was accepted for publication by the editor of the Public Health & the Law, George J. Annas, JD, MPH, Chief, Health Law Section, Boston University, Schools of Public Health and Medicine, 80 East Concord Street, Boston, MA 02118.

of the Federal Food, Drug & Cosmetic Act, requires the involvement of "a practitioner licensed by law to administer such drug" and expressly exempts prescription drugs from the statutory requirement that the drug labeling contain both adequate directions for use and adequate warnings.[7] If patients were to receive information about the drugs prescribed for them, that too, it appeared, was to come from the prescribing physician.

Court decisions have reinforced the central role played by physicians. In most instances where federal law requires a prescription, the courts have relieved pharmaceutical manufacturers of the obligation imposed on manufacturers in general to communicate directly with patients about the risks inherent in their products. At common law, the manufacturer's duty to warn is owed instead to the physician. Adequate and timely information about adverse reactions of which the manufacturer is or should be aware must be conveyed to physicians. In the courts' view, the physician then functions as a learned intermediary between the manufacturer and the patient and has an affirmative duty to be knowledgable about the drugs he or she prescribes.[8] The rationale is a familiar one. The physician is considered to be in the best position to weigh the risks and benefits of a specific drug for individual patients. The courts also are persuaded by arguments that direct communications from manufacturer to consumer may be too difficult, could unduly interfere with the doctor-patient relationship, and might frighten or confuse the patient, discouraging compliance with the prescribed therapy.[9]

Two exceptions to the learned intermediary rule have emerged. In both, the lack or perceived lack of a physician's involvement was critical. The first involves mass immunization programs. Since physicians are absent or only peripherally involved in such programs, a personal medical determination or a balancing of the risks for the individual patient is impossible. Vaccine manufacturers therefore must provide patients with a warning of the risks associated with the vaccination allowing patients themselves to weigh the benefits and risks.[10] Second, in *MacDonald* v. *Ortho Pharmaceutical Corp.*,[11] the Supreme Judicial Court of Massachusetts imposed a common law duty on manufacturers of oral contraceptives to communicate risk information directly to the user. The court found oral contraceptives unique for a number of reasons, including the substantial nature of the risks associated with the drug. Central to the decision, however, was the argument that patients take an active role in selecting this method of birth control, often deciding to take the pill before consulting a physician. This, the court determined, had the effect of relegating the prescribing physician "to a relatively passive role." The possibility was acknowledged that oral communications between the physician and the patient could be too scanty to provide an adequate warning. Therefore, the court concluded, the manufacturer's obligation encompassed a duty to warn the ultimate user.[11]

The Learned Intermediary—Who Benefits?

While the learned intermediary doctrine sets out a clear expectation of full disclosure from manufacturer to physician, there is no such expectation between physician and patient. The courts have acknowledged that the physician as the learned intermediary has complete discretion to determine what facts, if any, should be shared with the patient.[8] The Supreme Court of Illinois has characterized the extent of disclosure as "a matter of medical judgment."[12] This discretion, however, is in direct conflict with, and arguably should be displaced by, the doctrine of informed consent which incorporates elements of broad disclosure by the physician and active decision-making by the patient. In this instance, the physician has an overriding affirmative duty of disclosure which encompasses all material risks associated with proposed medical treatment including prescription drug therapy.

The interplay of these two legal doctrines, one requiring physicians to know about the drugs they prescribe and the other requiring them to share this information with their patients, should work to the patients' benefit. However, the divergence of legal theory and medical practice in the prescription drug context is striking. The criticism that the law has substantially failed to provide the competent patient with a meaningful opportunity to participate in medical decision-making on a voluntary, informed and understanding basis is perhaps most relevant to this aspect of medical care.[13]

The perfunctory nature of drug prescribing has been acknowledged by the FDA, prompted in large part by an increasing awareness of serious adverse drug reactions and a recognition that patients want more information about their drugs, a finding supported by the FDA's own studies.[14] In spite of the agency's assertion that patients have "both a right and a need to know about the drugs they use," and its conclusion that physicians generally do an inadequate job of informing their patients about prescribed drugs, little has been done to alter the situation.[15] The FDA has the authority to require a drug manufacturer to include labeling written in nontechnical language directed specifically to patients. It has done so, however, in only seven instances.* In 1979, a comprehensive patient package insert program for a wide range of prescription drugs was proposed by the FDA.[14] Prior to the effective date of the initial implementation phase in 1982, the program was revoked in favor of voluntary private sector initiatives.[15]

Response to the Accutane Crisis

The experience with Accutane forces confrontation with the ineffectiveness of the current system. The FDA-approved labeling or prescribing information prepared by Hoffmann-La Roche, the manufacturer of Accutane, is published in the Physicians' Desk Reference (PDR), a resource used by most physicians. Since 1985, the contraindications have been boxed off and stand out from the remainder of the text. They are printed in bold type and convey a strong, clear warning of the drug's teratogenic potential. A March 1984 labeling change added a recommendation that a pregnancy test be performed two weeks prior to prescribing the drug for all women of childbearing age. The physician also has been urged to counsel the patient about the potential risk to the fetus and, in the event pregnancy occurs during the course of treatment, to discuss the desirability of continuing the pregnancy. It appears therefore that, to the extent the PDR warning alerted physicians to the risks posed to the fetus, the manufacturer fulfilled its obligation to warn the physician.

It is less easy to verify whether an adequate job was done at the physician-patient level. We simply do not know how

*Oral contraceptives 21 C.F.R. 310.501(a) (1987); Estrogens 21 C.F.R. 310.515 (1987); Progestational drug products 21 C.F.R. 310.516 (1987); Depoprovera 21 C.F.R. 310.501a (1987); Diethylstilbesterol 21 C.F.R. 310.501(b) (1987); Bronchodilators containing isoproterenol 21 C.F.R. 201.305 (1987); Intrauterine devices 21 C.F.R. 21 C.F.R. 310.502 (1987).

well the risks of Accutane were communicated by physicians to young women desperate for relief from a socially stigmatizing condition. We do, however, have the statistics on birth defects cited earlier. Questions on this point also arise in the medical literature. The January 1988 issue of the *Canadian Medical Association Journal* describes a survey of patients in the Province of Saskatchewan who received four months of treatment with Accutane.[16] One-third of the women surveyed reported that they used no contraception during treatment. An earlier report in the *New England Journal of Medicine* provides results of an investigation of 154 pregnancies with fetal exposure to the drug.[4] Sixty-seven percent of the exposed pregnancies were among women who were either pregnant when therapy began or were not using contraception during treatment.

How well were the risks of Accutane shared with these women? Could a more diligent job have been done by the prescribing physicians? There is no question that recently adopted prescribing restrictions for Accutane have been designed to compel physician-patient interaction. The response of both the FDA and Hoffmann-La Roche to the Accutane crisis zeroed in on the physician and the events at the time of prescribing. The FDA recommended a doubling of the print size in the boxed contraindications section for Accutane in the PDR. The language of the warning has been further strengthened. While consideration was given to restricting prescribing authority to dermatologists, Hoffman-LaRoche opted intead to include a cautionary statement in the prescribing information suggesting that Accutane be prescribed only by physicians who have special comptence in the diagnosis and treatment of severe cystic acne, and who understand the risk of teratogenicity. The physician is required to ensure that female patients meet eight specific criteria, including a determination by the physician that the individual patient is "reliable in understanding and carrying out instructions." All criteria must be satisfied before a woman can be considered a suitable patient for treatment with Accutane. Within the two weeks prior to starting a course of therapy, the patient must have a negative serum pregnancy test. A written consent form must be signed by both the patient and the physician before the drug is prescribed. The patient is asked to acknowledge that the physician has disclosed, and that she understands, the risks of Accutane and the importance of using effective birth control. An additional reminder of the warnings now appears in the form of a red "avoid pregnancy" symbol on the back of the new blister-pack container for each capsule of the drug.

Hoffmann-La Roche has assembled a Pregnancy Prevention Program Kit for distribution to physicians who prescribe Accutane. The kit includes a large file box with forms and brochures, to be used and distributed to the patient by the physician during the consultation. A video tape accompanies the box. The 10-minute tape explains how to use the boxed materials and further cautions the physician about appropriate prescribing procedures. In addition to the consent document, the box contains a written test which the patient must complete in the physician's office prior to signing the consent form; the 10 true-false questions are intended to evaluate the patient's comprehension of the risks of Accutane. A brochure providing detailed birth control information and a general patient information brochure, which was introduced voluntarily by Hoffmann-La Roche in 1982, are also provided for distribution to the patient. The new steps in the prescribing procedure clearly raise questions as to their enforceability; however, in the event of litigation, the prescribing physician would want to produce copies of the consent and test documents as evidence of his compliance with the recommended prescribing regimen. On this point, the "Physician's Guide to Consent" which is part of the Pregnancy Prevention Kit suggests that "good medical management practices" require that physicians retain copies of these documents.

The new requirements and guidelines for Accutane are impressive and present a stark contrast to traditional prescribing routines. One aspect of the program, however, deserves more discussion. The 1988 version of the patient information brochure includes a line drawing of an infant with the characteristic deformities associated with exposure to Accutane. A larger version of this drawing is provided in the boxed materials along with the suggestion that it be used at the physician's discretion during the counseling of potential Accutane patients. No such leeway is allowed the physician with other parts of the program such as the true-false test or the signing of the consent document. Of all the boxed materials, this diagram seems to offer the most promising tool for educating patients, many of whom are teenagers, about the risks of this drug. It is a jarring attention-getter and may be exactly what is needed for these patients to appreciate and remember more than the promise the drug holds for their skin. The discretion allowed here is a remnant of the past, the old fear of frightening or upsetting the patient. Since the drawing also appears in the patient information brochure, it will be seen by the patient eventually. It seems more constructive to require the physician and patient to examine the illustration together allowing discussion of any fears or concerns it might generate.

In addition, the brochure currently carries vivid before and after photographs of Accutane patients which demonstrate how effective the drug can be. The photographs convey a strong promotional message detracting from the purpose of the brochure which presumably is to help patients stay alert to the risks of a potent drug. If photographs such as these are to be included, a balancing of risks and benefits would be better achieved by replacing the current line drawing of an affected infant with an equally vivid photograph depicting actual birth defects.

Conclusion

Possibly the most striking element of the Accutane crisis and the activity it has generated is that none of the risk information is new. Since the approval of the drug, the warning language directed to physicians in the PDR has been forceful and unambiguous, and seemed to demand an equally forceful intervention by physicians. Further, 90 percent of all Accutane prescriptions are written by dermatologists who should be intimately knowledgable about the drug.

The Florida Supreme Court recently ruled on the question of the adequacy of the Accutane warning provided to physicians.[17] In a wrongful death action brought by the mother of a child born with severe birth defects associated with the ingestion of Accutane during pregnancy, the court affirmed a lower court decision in which the manufacturer's warning as far back as 1982 was found to be "accurate, clear, and unambiguous." The court also reasoned that any inadequacy in the warning could not have been the proximate cause of the birth defects in this case since the prescribing physician admitted that he fully understood the warnings and had prior knowledge of the drug's inherent dangers.

The concept of a single learned intermediary is called into question by the Accutane experience. To restrict the disclosure of information to one party within the drug distribution system is artificial and inefficient. Manufacturers of non-pharmaceutical products have a duty to warn consumers directly about risks associated with the use of their products. The obligation should be no less for those who manufacture pharmaceuticals. The FDA could begin by reviving the patient package insert program it proposed in 1979 requiring drug manufacturers to funnel their expertise directly to consumers of prescription drugs. Clearly written materials for distribution to patients by physicians and pharmacists would supplement the information offered by the physician. The brochure prepared for Accutane is evidence that direct manufacturer to patient communications are not the impossible task so often assumed. Recent studies provide some indication that printed materials used as an adjunct to verbal counseling increase patients' knowledge about a specific drug and improve the ability to take precautionary steps when side-effect symptoms occur.[18–20] An additional point of reference will be provided by a follow-up study with female Accutane users being conducted by the Slone Epidemiology Unit at the Boston University School of Public Health which will assess the effectiveness of the new measures now linked to the prescribing of Accutane.

In their role as learned intermediaries, physicians have been stingy with information about the drugs they prescribe. Too often their involvement is as passive or detached as that of the physicians in the oral contraceptive and vaccine cases discussed earlier. This is where another critical change must take place, not just for Accutane but for all prescription drugs. All drugs carry some measure of risk. Patients need the help of their physicians to appreciate those risks. More time can certainly be devoted to this aspect of the physician-patient encounter. Specific risks must be disclosed to the patient as part of a preexisting requirement for informed consent to all medical treatment. If the physician is casual about drug therapy, we should not be surprised when patients reflect this same attitude.

REFERENCES

1. Dr. David Graham, Epidemiology and Biostatistics Division of the FDA: Memo presented to the Dermatologic Drugs Advisory Committee Hearing, April 26, 1988.
2. Marwick C: FDA ponders approaches to curbing adverse effects of drug used against cystic acne. JAMA 1988; 259:3225.
3. Stern RS: When a uniquely effective drug is teratogenic: The case of isotretinoin. N Engl J Med 1989; 320:1007–1009.
4. Lamer EJ, Chen DT, Hoar RM: Retinoic Acid Embryopathy. N Engl J Med 1985; 313:837–841.
5. 3 Fed. Reg. 3168 (December 28, 1938).
6. 65 Stat. 648 (1951).
7. 21 U.S.C. s.353(b) (1982).
8. *Terhune v. A. H. Robins Co.* 577 P.2d 975,978 (Wash. 1978).
9. *In re Certified Questions* 358 N.W.2d 873,882–883 (Mich. 1984).
10. *Reyes v. Wyeth Laboratories* 498 F.2d 1264,1276 (5th Cir.), cert. denied, 419 U.S. 1096 (1974).
11. 475 N.E.2d 65 (Mass. 1985).
12. *Kirk v. Michael Reese Hospital and Medical Center* 513 N.E.2d 387,393. (Ill. 1987).
13. Weisbard A. Informed Consent: The Law's Uneasy Compromise With Ethical Theory, 65 Nebraska Law Review 749, 751 (1986).
14. 44 Fed. Reg. 40,016 et. seq. (1979).
15. 47 Fed. Reg. 39,148 (1982).
16. Hogan DJ, Strand LM, Lane PR: Isotretinoin therapy for acne: A population-based study. Can Med Assoc J 1988; 138:47–50.
17. *Felix v. Hoffman-LaRoche,* 540 So.2d 102 (Florida Supreme Court, 1989).
18. Johnson MW, Mitch WE, Sherwood J, *et al:* The impact of a drug information sheet on the understanding and attitude of patients about drugs. JAMA 1986; 256:2722–2724.
19. Regner MJ, Hermann F, Ried LD: Effectiveness of a printed leaflet for enabling patients to use digoxin side-effect information. Drug Intell Clin Pharm 1987; 21:200–204.
20. Sand CD, Robinson JD, Orlando JB: The oral contraceptive PPI: Its effect on patient knowledge, feelings, and behavior. Drug Intell Clin Pharm 1984; 18:730–735.