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Isotretinoin: Improving Patient Education and Reducing Risk

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Isotretinoin, marketed as Accutane® by Roche Pharmaceuticals, has become a mainstay in the management of severe recalcitrant acne. It is increasingly being prescribed for milder acne cases as well. An estimated 500,000 new patients are treated each year.[1] While the efficacy of isotretinoin has been clearly demonstrated, the benefits of therapy must be weighed against the potential for significant adverse events. In the last year, changes in the product labeling and new informed consent documents have been created in an effort to better educate patients about the risks associated with isotretinoin use. This issue of *Pediatric Pharmacotherapy* will review the data available on isotretinoin adverse events and discuss recent actions by the manufacturer and the Food and Drug Administration (FDA) to reduce risk.

Therapeutic Use

Isotretinoin, 13-*cis*-retinoic acid, acts by inhibiting sebaceous gland function and keratinization. While the exact mechanism remains unknown, isotretinoin appears to cause improvement in patients with nodular acne by reducing sebum secretion. Isotretinoin is currently approved by the FDA for the management of patients with severe recalcitrant nodular acne. The recommended starting dose of isotretinoin is 0.5 to 1 mg/kg/day given in two divided doses. The dose may be increased to a maximum of 2 mg/kg/day. Treatment is typically continued for a period of 15 to 20 weeks. Patients who fail to respond may be given a second treatment course 8 weeks after completion of the first course.[2]

Teratogenic effect

The ability of isotretinoin to cause severe birth defects was first documented in humans in 1983,[3] the year of its introduction in Canada and a year after its approval for marketing in the United States.[2,4] The teratogenic effect of excessive doses of vitamin A derivatives (retinoic acids) had already been established and similar results were anticipated with isotretinoin. The drug has carried a category X pregnancy designation since its release. The embryopathies associated with isotretinoin use during the first trimester include central nervous system, craniofacial, cardiac, and thymic malformations.[5] It has been suggested that these defects result from an alteration of neural crest cell morphology and motility during critical stages of development.[6]

Initial attempts to educate women about the teratogenic effect of isotretinoin focused on a voluntary, manufacturer-supported Pregnancy Prevention Program.[7,8] The program, initiated in July 1988, consisted of printed educational materials for the patient, instructions for the prescriber about the scheduling of preliminary pregnancy tests, and information about enrollment in a patient-tracking survey. As part of the program, female patients were asked to sign a consent form acknowledging that they had received counseling.

While this program had considerable success, it was unable to achieve the goal of a zero pregnancy rate.[9-11] In a survey of women participating in the program from 1989 to 1993, nearly all knew the damage isotretinoin could produce in a developing fetus.[9] Of the 42% who were sexually active, 99% reported using contraception. Despite this level of compliance, there were 3.4 pregnancies per 1000 documented treatment courses. Of the pregnancies reported, nearly three-quarters were terminated. Thirty-two live births occurred, with data available on

30. Of those, 7 infants had malformations believed to be caused by isotretinoin.

In a more recent survey of women enrolled in the voluntary program in California over a two year period, 23 patients reported a pregnancy.[11] Of those women, 14 consented to be interviewed. These cases resulted in one infant born with major malformations, four infants born without defects, four miscarriages, and five terminations. Neither report was able to identify patient characteristics which might predict an increased risk for becoming pregnant.

The total number of pregnancies which have occurred during isotretinoin use remains unknown.[10-12] In a report to the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee during their September 2000 meeting, Roche provided information on a total of 1,995 pregnancies which had occurred during isotretinoin treatment.[10,12] This number, while already unacceptably high, is likely an underestimate because of the voluntary nature of the program. It is estimated that only 40% of women taking isotretinoin enroll in the program.[11] The frequency of isotretinoin-exposed pregnancies might also be expected to rise as the drug is prescribed for increasingly larger numbers of women with milder disease.

Based on the growing concern over isotretinoin's teratogenic risk, Roche, working with the FDA, voluntarily completed an extensive revision of their Accutane® product labeling in May 2000.[12] The product insert now contains a strengthened series of boxed warnings in bold type (known as "black box" labeling). The warnings stipulate that all female patients **must**:

- have severe acne resistant to other therapies
- be capable of understanding instructions
- be reliable in complying with all testing
- receive written and verbal warnings on the risk of teratogenicity
- receive written and verbal information on the need for two forms of contraception
- have a negative serum or urine pregnancy test at the time of initial evaluation and a second test on the second day of the next menstrual period or 11 days after the patient's last sexual intercourse, whichever is later (free urine test kits are provided by Roche)
- receive information on the Accutane® Survey and watch a videotape provided by Roche

The insert also highlights the need for monthly pregnancy tests and recommends that prescriptions be written without refills to encourage compliance with testing. The product insert also contains a revised patient consent form requiring women to document that they understand the potential risks of therapy. A copy of the product insert with the new consent form is available on the company's website.[2] With the May 2000 revision, the label was also changed to **require** all prescribers to present the Accutane® Survey enrollment form at the time of initiating therapy in a female patient.

It is recommended that prescribers use the Pregnancy Prevention Program kit provided by Roche to assist with counseling. The kit, revised in July 2000, contains a qualification checklist for the prescriber, a patient self-evaluation, the consent forms (with copies for both the prescriber and patient), the Accutane® Survey enrollment form, documentation for referral for pregnancy testing, and patient educational materials, including a toll-free phone number of a confidential contraceptive counseling service and a toll-free phone number for additional product information, available in 13 different languages. Kits may be obtained without cost by calling Roche at 1-800-937-6243.

Accutane® should only be dispensed in its original blister package. The box contains most of the warnings from the insert, as well as a drawing of an affected infant. The FDA has also developed a patient medication guide (MedGuide) for isotretinoin that provides information in a question and answer format at a sixth grade reading level.[13] The MedGuide was released in January 2001 and is expected to become a requirement for dispensing the drug within the next year. In addition to these resources, a supplement on counseling women taking teratogenic drugs was recently published in *The Journal of Reproductive Medicine* which may also aid clinicians in the discussion of these risks with patients.[14,15]

Female patients should know that the precautions against pregnancy must be continued for at least a month after treatment has ended. Patients also cannot donate blood during treatment or for one month after the completion of therapy. Blood from donors taking isotretinoin may pose a risk to pregnant recipients.[2]

<u>Association with depression and suicide</u>

While much work has been done in the area of preventing isotretinoin-exposed pregnancies, there has also been considerable attention recently to the association between psychiatric symptoms and this drug. In October 2000, Rep. Bart Stupak of Michigan began a public media campaign following the suicide of his 17 year old

son. Stupak believes the suicide to be related to his son's use of isotretinoin over the 7 months prior to his death.[16]

The potential for a link between isotretinoin and depression or suicide has been suggested for many years. Reports of psychiatric adverse events began shortly after the introduction of the drug. Between 1982 and 2000, the FDA accumulated 431 reports of depression, suicidal ideation, suicide attempts, or suicide in patients taking isotretinoin. Thirty-seven of the reports were suicides. Of those patients, the overwhelming majority (84%) were male, with an average age of 17 years. A prior history of psychiatric illness was present in 8 of the cases.[17]

Roche first amended the product insert for Accutane® to list depression as an adverse effect in 1985. In February 1998, the FDA approved a further change in labeling to include a bold-face (black box) warning about psychiatric disorders, including suicide.[12,18] This last modification was made a full year after a similar change was made in France, calling into question the rapidity with which this important information was provided to prescribers in the United States.[18]

The role of isotretinoin in causing psychiatric illness remains unproven. A recent review of databases from Canada and the United Kingdom, including over 7,000 patients, failed to identify any evidence supporting a link between depression or suicide and isotretinoin.[19] Last September, the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee reviewed all of the available data and concluded that causality had not been established.

Despite the lack of conclusive evidence, there is clearly a need to educate patients about this potential risk. A separate consent form has been developed by Roche which focuses on psychiatric adverse events. This new consent form was released in January 2001, with an initial mass mailing to prescribers at the same time it was added to the product insert. On the form, patients are required to disclose any symptoms of depression or psychosis in themselves or family members prior to initiating therapy. The form also stipulates that patients promptly inform their prescriber of any psychiatric symptoms during treatment.[2,12] The potential for psychiatric adverse events has also been included in the FDA MedGuide.[13]

Additional adverse effects

In addition to the two adverse events highlighted, isotretinoin has been linked to a number of other toxicities. Transient hypertriglyceridemia develops in approximately 25% of patients during treatment. Hepatotoxicity, while less common, has also been reported. Serum triglyceride levels and liver function studies should be evaluated prior to beginning treatment and at weekly intervals until the response to isotretinoin has been established (usually within 4 weeks).

Other adverse effects associated with isotretinoin use include photosensitivity, visual impairments, inflammatory bowel disease with severe diarrhea, skeletal changes, hearing impairments, pancreatitis, neutropenia, agranulocytosis, and hypersensitivity reactions. Rare reports have also linked isotretinoin with the development of pseudotumor cerebri. In several of these reports, the patients have also been taking tetracycline. Concomitant treatment with tetracycline is not recommended. Patients should be made aware of symptoms associated with this condition, including severe headache, nausea, vomiting, and visual disturbances.[2]

Future regulatory changes

The changes taking place in isotretinoin prescribing are not likely to be completed for several years. At their September 2000 meeting, the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee recommended several additional steps, including a mandatory registry for all patients, similar to the one for thalidomide. The program would allow the manufacturer to provide reminders and educational materials to prescribers and patients on a more regular basis, as well as track all pregnancies occurring during treatment.

The details of how the registry will be administered and the impact on prescribers, pharmacists, and patients have not yet been determined. The American Academy of Dermatology and the American Medical Association have voiced opposition to this measure, citing the increased economic and administrative burden the registry might create.[20]

Summary

Isotretinoin remains a highly beneficial therapy for the management of severe recalcitrant acne. Its adverse effect profile, however, is substantial. Increasing concern over the known teratogenic effect and the potential association with depression and suicide has prompted renewed efforts to educate patients and reduce the number of affected individuals. Health care professionals need to be aware of new regulations regarding patient education and monitoring, as well as the

tools available to assist with the educational process.

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Pharmacology Literature Review

Caffeine metabolism in premature infants

While the development of metabolic pathways for caffeine has been studied by many investigators, controversy remains over which patient variables are most likely to predict changes in metabolism. In one of the largest studies published to date, these authors report the results of monitoring metabolite production in 80 premature infants. Patients were stratified by birthweight, weight at enrollment, postnatal age, postconceptional age, and gestational age. Multivariate linear regression revealed a significant relationship only between demethylation and postnatal age, suggesting that this variable is the most predictive of maturation of the metabolic process. Al-Alaiyan S, Al-Rawithi S, Raines D, et al. Caffeine metabolism in premature infants. **J Clin Pharmacol 2001;41:620-7.**

Nitrofurantoin in breastmilk

Nitrofurantoin remains one of the most commonly prescribed antibiotics for treating urinary tract infections. While the American Academy of Pediatrics considers nitrofurantoin to be "usually compatible with breastfeeding," it is known to cross into breastmilk. In this evaluation of 4 women, serial milk and serum samples were analyzed following a single 100 mg oral dose to evaluate transfer into breastmilk. The observed milk to plasma ratio was 6.21±2.71, with a maximum concentration of 1.3 mg/L in the milk. The authors recommend that nitrofurantoin not be used in mothers with infants less than 1 month and that older infants be monitored for anemia resulting from unrecognized glucose-6-phosphate deficiency. Gerk PM, Kuhn RJ, Desai NS, et al. Active transport of nitrofurantoin into human milk. **Pharmacotherapy 2001;21:669-75.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/22/01:

1.Bismuth subgallate epinephrine (BSE) paste, a compounded topical hemostatic agent, was added to the Formulary for the control of bleeding after adenotonsillectomy.

2. Tolterodine LA (Detrol LA®) was added to the Formulary for the control of overactive bladder. Oxybutynin XL (Ditropan XL®) was rejected.

3. A request for the addition of a leuprolide acetate implant (Viadur®) was rejected because the product lacks significant advantages over the 4 month depot injection.

4. Valganciclovir (Valcyte®) was added for the management of CMV retinitis.

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