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Oral isotretinoin: prescribers beware

Neil H. Shear, MD

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Oral isotretinoin (Accutane™) has become widely used in the treatment of acne since its arrival on the Canadian market in 1983. This is because it is uniquely effective in the treatment of disabling, intractable cystic acne. It was clear from the outset that this treatment came with a price. Oral isotretinoin is highly teratogenic and must never be given during pregnancy.[1] However, by approximately 1 month after cessation of therapy, when the drug is no longer in the circulation, the risk of fetal malformation is the same as at baseline.[2]

The use of oral isotretinoin in women of childbearing age became a concern because of the potential for these patients to become pregnant during therapy. Since 50% of pregnancies are unplanned, a great deal of effort was invested in trying to prevent pregnancy during isotretinoin therapy. The most effective approach, currently in use in the United States and Canada, is a multipronged communication strategy called the Pregnancy Prevention Program, which was developed by the manufacturer of Accutane™ and the US Food and Drug Administration.[3]

In this issue (page 1719) Drs. Gordana Atanackovic and Gideon Koren of the Motherisk Program in Toronto describe the cases of 4 women who became pregnant while taking oral isotretinoin therapy.[4] Because the goal of the Pregnancy Prevention Program is a zero pregnancy rate during oral isotretinoin therapy, these cases represent a failure in the responsible use of the drug. It is not known how many failures occur in Canada, but even 4 cases are enough to draw our attention. The report by Atanackovic and Koren highlights the inherent risk in giving oral isotretinoin to young women who may not fully comprehend the risk of teratogenesis or strategies for pregnancy prevention.

Mitchell and colleagues[3] conducted a survey to assess the effectiveness of the Pregnancy Prevention Program. They found that most pregnancies during oral isotretinoin therapy occurred in women who were taking oral contraceptives concurrently with the isotretinoin. Surprisingly, these women were well counselled, remembered being informed about pregnancy prevention and yet became pregnant because of normal contraception failure. The Pregnancy Prevention Program has enrolled approximately 400 000 patients since 1989 and is now enrolling patients at a rate of 50 000 per year (Dr. Allen Mitchell, Director, Slone Epidemiology Unit, Boston University, Boston, MA: personal communication, 1999). This is estimated to represent almost half the women of childbearing age using oral isotretinoin in the United States. More than half of the

women who participated in Mitchell and colleagues' survey were not sexually active; of these, 37% used contraception. Of the 42% of women who were sexually active, 99% used contraception. There were 3.4 pregnancies per 1000 20-week courses of oral isotretinoin. Although this is not an overly high rate of contraceptive failure, it is still unacceptable. Of the pregnancies, 72% were terminated by elective abortion and 8% resulted in live births.[3]

The clinical use of oral isotretinoin is now extending beyond the treatment of severe acne to the treatment of milder but recalcitrant disease.[5] This drug has usually been reserved for nodular (cystic) acne. Not only is it the most effective treatment for this most severe form of acne, but it is usually curative. However, oral isotretinoin is also indicated for acne that does not respond to traditional antibiotic therapy. This indication is less clearly defined. Many women whose acne does not improve with the use of antibiotics such as tetracycline will find an improvement with hormonal therapy using oral contraceptives. In my view, the likelihood of cure with oral isotretinoin in such cases is low, and it is preferable to use therapies that are more appropriate for chronic therapy. Since long-term therapy may be needed, this must be approached very cautiously and should be placed in experienced hands.

A new marketing effort under way for isotretinoin includes consumer and direct-to-physician advertising. But while the efficacy of oral isotretinoin is stressed, the responsibility of prescribing and using the drug is not. The product monograph will be available to physicians on the manufacturer's Web site (www.rochecanada.com) but is not as yet, and the components of the Pregnancy Prevention Program are available only on request; no plans are evident for Web site posting. Despite this criticism, it is clear that the current Pregnancy Prevention Program in Canada covers the major issues.

Where do we go from here?

Oral isotretinoin is an effective and cost-effective treatment for a disabling disease.[6,7] Despite a proliferation of treatment guidelines,[8] the best physicians can do is to follow the manufacturer's advice. That advice is sound and puts the responsibility of appropriate use squarely on the shoulders of the prescribing physician.

The Patient Information and Consent to Treatment Form (available from the manufacturer) includes 9 points to be initialled by the patient. Seven of these relate to pregnancy and the responsibility of the patient. The patient must be proven to be not pregnant at the beginning of therapy, and she must use "effective birth control" for at least 1 month before starting therapy and at least one month after stopping therapy. Effective birth control is defined as either total abstinence from sexual intercourse or 2 reliable kinds of birth control at the same time. The birth control pill can and does fail. Two methods of contraception are mandatory.

On the back of the form, the manufacturer provides advice to physicians. This is an important statement regarding the patient's ability to comply with appropriate contraceptive measures. Unfortunately, it is very difficult to read. To supplement this, there is a checklist in the form of a set of questions. If the answer to any of the questions is no, oral isotretinoin must not be prescribed. One question relates to the physician's assessment of the reliability of the patient.

If prescribers use the program material they will have guidelines to help determine which patients should receive isotretinoin and what should be done about pregnancy prevention. Some patients may need extra counselling; this should be sought where appropriate.

I can't imagine practising dermatology and looking after patients with diseases as devastating as cystic acne without oral isotretinoin. If physicians do not fulfil their responsibilities, patients will lose a good treatment. On the other hand, needless suffering from unnecessary fetal exposure is not acceptable. Physicians who cannot follow the program or are not experienced prescribers of oral isotretinoin should refer the patient to the most experienced practitioner available — to protect themselves and to serve their patients. Prescribers beware.

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Competing interests: Dr. Shear is a consultant for 2 companies that make topical anti-acne medications and has received funding to give continuing medical education talks on acne therapy.

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