Accutane™ Roche®: risk of teratogenic effects

Accutane (isotretinoin) is a very effective drug for the therapy of cystic acne, conglobate acne and severe acne that have not responded to an adequate course with a systemic antimicrobial. Physicians, pharmacists and female patients must be made aware of the risks associated with this potent agent, particularly its teratogenic potential, in order to be able to use the drug appropriately and safely.

Accutane has been available as a prescription drug in Canada since April 1983 and in the United States since September 1982. When the drug was introduced in Canada Hoffmann–La Roche's information program for health professionals contained clear contraindications and warnings regarding its use during pregnancy because of the risk of teratogenic effects. In addition, an information pamphlet for patients was prepared containing instructions for proper use and warning women of the potential dangers to the fetus should they take Accutane while pregnant or become pregnant within 1 month of discontinuing therapy. To promote distribution of this information to patients the pamphlet was attached to each bottle of Accutane (containing 30 capsules), with instructions to the pharmacist to dispense the information when filling a prescription.

Canadian health professionals were advised by Hoffmann–La Roche in July 1983 of the initial reports of teratogenicity in humans,[1] and the contraindications and warnings were repeated. Additional reports appeared in the literature,[2,3] and, most recently, 17 cases of birth defects and 20 cases of spontaneous abortion in the United States were reviewed.[4] A syndrome involving major central nervous system abnormalities and cardiovascular and ear defects has been identified.[5]

Hoffmann–La Roche has been informed of pregnancies in 13 women in Canada who were taking Accutane, of whom 1 had a spontaneous abortion and 8 an induced abortion. In one of the cases of induced abortion the 20-week-old fetus showed the syndrome of malformations. The birth of one unaffected infant whose mother had used Accutane during the first trimester has been reported. Three patients are continuing their pregnancies.

In several of the cases reported to Hoffmann–La Roche effective contraceptive measures may not have been used or may have been used incorrectly either before or during treatment. I therefore underline the need for physicians to inform their female patients of the risk, to determine that the women are not pregnant and to ensure that effective contraceptive measures are used correctly before and during treatment and for 1 month after treatment is stopped.

CMAJ readers are asked to inform Hoffmann–La Roche as soon as possible of cases in which pregnancy occurs during therapy with Accutane. Each such case and its outcome must be monitored in order to continue epidemiologic evaluation of the degree of risk associated with the use of Accutane.

DONALD P. ZAROWNY, M SC, MD
Vice-president and medical director
Hoffmann–La Roche Limited
401 The West Mall, Ste. 700
Etobicoke, Ont.
M9C 5J4
(416) 620-2800

References

1. ROSA FW: Teratogenicity of isotretinoin [C]. *Lancet* 1983; 2: 513
2. BRAUN JT, FRANCIOSI RA, MASTRI AR et al: Isotretinoin dysmorphic syndrome [C]. *Lancet* 1984; 1: 506–507
3. STERN RS, ROSA F, BAUM C: Isotretinoin and pregnancy. *J Am Acad Dermatol* 1984; 10: 851–854
4. MARWICK C: More cautionary labeling appears on isotretinoin. *JAMA* 1984; 251: 3208–3209
5. BENKE PJ: The isotretinoin teratogen syndrome. Ibid: 3267–3269

[Readers are also asked to inform Dr. Edward Napke, chief, product-related disease division, health protection branch, Department of National Health and Welfare, Ottawa, Ont. K1A 0L2 of cases in which pregnancy occurs during therapy with Accutane.—Ed.]

Can vitamins prevent neural tube defects?

Dr. J. Mark Elwood's article "Can vitamins prevent neural tube defects?" (*Can Med Assoc J* 1983; 129: 1088–1092) reviews critically the studies by the group associated with me that suggest that periconceptional vitamin supplementation reduces the risk of recurrence of neural tube defects. While I agree with much of what he wrote and accept that our findings await confirmation, the complexity of the problem and editorial condensation of some of our papers seem to have caused some misunderstandings. The following comments are made not in any defensive sense but as a contribution to the continuing debate.

On the main issue of nonrandomization Dr. Elwood first comments that "the group that did not take supplements had a less favourable distribution of social class and included a considerably larger number of women from Northern Ireland".

Our most recent paper showed that the difference in social class distribution between the women who took supplements and those who did not was not great and was unlikely to account for more than a very small part of the difference in recurrence rates of neural tube defects.[1] Women from Northern Ireland who did not take supplements were overrepresented in our first cohort[2] but not in the second.[1] The data from Northern Ireland *alone* showed a significant difference in the recurrence rates.[3]

The recurrence rates, by study centre and social class, are presented in Tables I and II respectively. There were only 3 recurrences of neural tube defects in children of the women who took supplements, in contrast to 24 in children of those who did not. Even in social class III, which had all three recurrences, the excess of recurrences in children of the women who did not take supplements was highly significant ($p = 0.009$).

We did not offer any dietary advice to the women who took supplements and have no evidence that the supplement worked by causing the women to change their eating habits. We also measured the levels of folate, vitamin C and riboflavin in a sample of the women who took supplements before they became pregnant and of the women who did not take supplements and were pregnant; we found no significant differences between the two groups.

Dr. Elwood states that "one of the difficulties in accepting the dramatic effect on recurrence risk is a natural incredulity that such a small degree of supplementation would produce such a dramatic effect". As he is applying strict scientific criteria to our research, "natural incredulity" is possibly out of place. The "small degree of supplementation" provided the recommended daily allowances of all major vitamins, and the folate (requirements for which are still debated) was in monoglutamate form and therefore more readily available than some dietary sources of folate. We have demonstrated impressive rises in folate and vitamin C levels using this supplement.[4]

The statement that "the most usual assumption is that folic acid is the active agent" is true, but the assumption may be wrong. It arises from the fact that the level of folic acid in pregnant women has received a lot of attention; the levels of other vitamins have not.

In saying "it has been suggested that the active ingredient of the multivitamin and mineral supplement could be . . . vitamin B_{12}" Dr. Elwood has misinterpreted an observation on serum B_{12} levels.[5] There is

Table I—Recurrence rates of neural tube defects for 973 women who took or did not take vitamin supplements, by study centre

	Women who took supplements			Women who did not take supplements		
Study centre	Total no.	No. with subsequent affected child	Recurrence rate (per 1000)	Total no.	No. with subsequent affected child	Recurrence rate (per 1000)
Leeds, n = 117	76	0	0	41	2	49
Guy's/London, n = 316	140	2	14	176	9	51
Belfast, n = 392	152	1	7	240	12	50
Manchester, n = 115	66	0	0	49	1	20
Chester and Liverpool, n = 33	20	0	0	13	0	0
Total	454	3	7	519	24	46

Table II—Recurrence rates of neural tube defects for 973 women who took or did not take vitamin supplements, by social class

	Women who took supplements			Women who did not take supplements		
Social class	Total no.	No. with subsequent affected child	Recurrence rate (per 1000)	Total no.	No. with subsequent affected child	Recurrence rate (per 1000)
I, n = 81	53	0	0	28	0	0
II, n = 164	90	0	0	74	4	54
III						
Nonmanual, n = 111	60	1	17	51	5	98
Manual, n = 406	176	2	11	230	10	43
IV, n = 125	47	0	0	78	3	38
V, n = 28	13	0	0	15	0	0
Other, n = 58	15	0	0	43	2	47
Total	454	3	7	519	24	46

no vitamin B_{12} in the supplement we used.

The same theme — namely, that if the supplement is effective, the effect must be due to *one* component — is reiterated in the review. No such assumption can be made. If the mode of action of the supplement (if it has any) is correction of dietary deficiency, an isolated vitamin deficiency is improbable. By the same token, if it were to be shown that each component of the supplement alone was without effect, it could not be concluded that the total supplement was without effect.

Dr. Elwood is incorrect in stating that in the British Medical Research Council (MRC) trial one group of women will receive "folate and other vitamins plus minerals (as used in the trial of Smithells and colleagues)". The MRC will use a single tablet daily, and the dose of folic acid will be 4 mg; we used one tablet three times a day, and the dose of folic acid was 0.36 (3 × 0.12) mg daily.

Dr. Elwood reports that in one study the recurrence rates of neural tube defects in four maternity hospitals in Dublin were 0.6% (1/157), 4.6% (6/130), 6.2% (4/65) and 10.3% (19/185). It is interesting to note that at the time to which these data relate it was the practice in the hospital with the highest rate to stop folate supplementation at the time of delivery, while in the hospital with the lowest rate all mothers were sent home with sufficient folic acid and iron tablets to last 6 weeks.[6] This would have a significant effect on the blood folate level for 3 to 4 months after the tablets were discontinued.[4]

Finally, and perhaps most important, Dr. Elwood's review perpetuates the misunderstanding about the difference between the women who took supplements and those who did not. He implies, as have others, that the women selected themselves into one group or the other. The criteria for receiving supplements were that women (a) had had at least one affected infant, (b) were considering a further pregnancy and (c) were not pregnant. All the women satisfying these criteria were offered supplements. To the best of my knowledge only 2 of over 700 women refused. The women who did not receive supplements did not "opt out": they did not meet the third criterion for supplementation.

R.W. SMITHELLS, MB, BS, FRCP (LOND), FRCP (EDIN), DCH
Professor of pediatrics
Department of pediatrics and child health
University of Leeds
Leeds, England

References

1. SMITHELLS RW, NEVIN NC, SELLER MJ et al: Further experience of vitamin supplementation for prevention of neural tube defect recurrences. *Lancet* 1983; 1: 1027–1031
2. SMITHELLS RW, SHEPPARD S, SCHORAH CJ et al: Apparent prevention of neural tube defects by periconceptional vitamin supplementation. *Arch Dis Child* 1981; 56: 911–918
3. NEVIN NC: Prevention of neural tube defects in an area of high incidence. In DOBBIN GJ (ed): *Prevention of Spina Bifida and Other Neural Tube Defects*, Acad Pr, London, 1983: 127–144
4. SCHORAH CJ, WILD J, HARTLEY R et al: The effect of periconceptional supplementation on blood vitamin concentrations in women at recurrence risk for neural tube defect. *Br J Nutr* 1983; 49: 203–211
5. SCHORAH CJ, SMITHELLS RW, SCOTT J: Vitamin B_{12} and anencephaly [C]. *Lancet* 1980; 1: 880
6. SMITHELLS RW: Prevention of neural tube defects by vitamin supplements. In DOBBIN GJ (ed): *Prevention of Spina Bifida and Other Neural Tube Defects*, Acad Pr, London, 1983: 75–76, 81–82

Torture and human rights in Chile

Over the past 10 years there has been considerable international concern regarding torture in Chile. It has been a particular concern to the Canadian physicians who have examined many of the victims of this torture who have sought refuge in Canada. Health care workers have been especially upset by the unethical participation, either voluntary or forced, of some physicians in torture. These problems have been noted in *CMAJ*,[1-4] in an Amnesty International report[5] and in many other publications. In the past year the Colegio Médico de Chile (Chilean Medical Association) has taken an active public role in condemning the practice of torture in Chile.

On Oct. 28, 1983 at the 35th Assembly of the World Medical Association (WMA) a resolution presented by the Colegio Médico de Chile and the Confederación Médica de la República Argentina (Medical Association of Argentina) was accepted. The resolution called upon the WMA, in light of its Declaration of Tokyo and the United Nation's Principles of Medical Ethics (1982), to protest the "disappearance", torture and forced exile of physicians; to emphatically condemn the reported participation of physicians in torture; and to support WMA member associations that were enforcing the foregoing principles. The WMA has issued a statement embodying support for these points.

On Nov. 23, 1983 the general council of the Colegio Médico de Chile issued a statement calling upon the Chilean government to end torture and unlawful detention and stating their duty as physicians to stress the physical and psychologic sequelae of torture and to condemn the practice. They resolved to undertake a number of steps to work towards the abolition of torture in Chile, including establishing a special medical commission to document cases in which medical examination revealed that physical injury had been inflicted during detention. They are now investigating the case of a Chilean physician alleged to be involved in torture.

This courageous action by our colleagues in the Colegio Médico de Chile, asserting positive medical ethical standards in spite of the difficult political situation in Chile, deserves our greatest respect and support.

DONALD E. PAYNE, MD
Coordinator, medical network
Canadian section (English-speaking)
Amnesty International
Toronto, Ont.

References

1. CATHCART LM, BERGER P, KNAZAN B: Medical examination of torture victims applying for refugee status. *Can Med Assoc J* 1979; 121: 179–180, 183–184
2. BERGER PB: Medicine and torture: the struggle for human rights [E]. *Can Med Assoc J* 1981; 124: 839–840
3. KENNEDY E: Evidence of torture in Chile [C]. *Can Med Assoc J* 1983; 129: 928
4. SAGARIS L, LANFRANCO P: Chile: medicine under military rule. Ibid: 616–617,