Research Update • Le point sur la recherche

Heart-valve disease linked to common diet drug

A common weight-loss medication that combines fenfluramine and phentermine (fen-phen) may have led to serious heart-valve damage in 24 patients seen at the Mayo Clinic in Rochester, Minn. The case series is to be published in the *New England Journal of Medicine*, but the journal waived its usual embargo and the study was released by the Mayo Clinic before publication.

Seven physicians associated with the clinic saw 24 women with no previous history of cardiac disease who presented with symptoms of heart-valve disease or a murmur. Five of the patients have required operations and eight have newly documented pulmonary hypertension; none has died.

On examination, the heart valves of these patients had an unusual morphology and were causing regurgitation of blood. The valves appeared to be a glistening white colour and to have plaque-like encasement of the leaflets and chordal structures with a "stuck-on" appearance. The physicians first suspected ergotamine poisoning or carcinoid, both of which can cause these findings. However, the patients had no history or evidence of either, but all had been taking fen-phen for an average of just over a year.

The physicians think the drug may lead to valve disease because of its effect on circulating serotonin levels. Patients with carcinoid have high levels of circulating serotonin, and ergotamine has a chemical structure similar to that of serotonin. It is thought that these high levels of circulating serotonin or serotonin-like compounds can cause valve damage and that a similar mechanism may be at work with fen-phen.

The authors, who stressed that they have highlighted an association and that a causal connection has not been proved, are urging physicians who prescribe fen-phen to discuss these serious possible side effects with patients.

On July 11 Health Canada's Therapeutic Products Directorate warned physicians that the use of fenfluramine and phentermine in combination has not been approved in Canada, although "it is known that some physicians may prescribe the 2 drugs in combination to treat obesity." It warned that the drugs should not be prescribed in combination until more information is available. One (possibly 2) cases of adverse cardiac events related to the use of fen-phen have been reported in Canada. Physicians should report any adverse reactions associated with the use of anti-obesity or other drugs to the Canadian Adverse Drug Reaction Monitoring Program, 613 957-0335. — *C.J. Brown*

Epidurals and the c-section question

A Calgary anesthetist is launching a study in an attempt to determine what kind of pain relief during childbirth is best for mothers and babies. Dr. Terrance Breen, director of obstetric anesthesia at the Foothills General Hospital in Calgary, has designed a multicentre study to examine the effects of epidural and intravenous narcotic pain relief on mothers, babies and the progression of labour. The study will involve 1600 patients at centres in Calgary, Toronto, Halifax and Saskatoon.

Some recent studies have shown a link between epidural analgesia and cesarean section, but Breen feels this work suffers from "serious methodological problems." His prospective, randomized study, funded by the Alberta Heritage Foundation for Medical Research, will follow deliveries in nulliparous women who have spontaneous, active labour; it should answer the question about a connection between epidurals and cesarean-section births.

"If epidurals are a problem, we need to know they are and we need to deal with it," Breen says. "Clearly they provide the best form of pain relief, but if they cause a problem we need to form a strategy and solve it. If not, we need to lay this issue off to the side and go on to find the real problem."

The study cannot be blinded — it would be clear to everyone involved in a delivery that a patient has chosen intravenous narcotics or an epidural. Because epidural analgesia is a superior form of pain relief, it is also impossible to deny it to patients in the intravenous-narcotics arm of the trial. And that could present a problem: if too many participants in the study cross over from intravenous narcotics by requesting an epidural, the study's results could become fouled. To avoid this, Breen and his team will monitor the number of participants crossing over. If their numbers grow too large, more participants will be recruited for the intravenous-narcotics arm.

The study will measure the effects of analgesia on progression of labour, pain relief, a newborn's first day of life, breast-feeding, fever and back pain after delivery.

"Whatever the results, they will provide the best information to women and their caregivers [and] allow everyone to make a better informed choice of different treatments." — *Richard Cairney*