Cisapride, before and after: still waiting for ADE-reporting reform

For 2 decades Health Canada has been studying and tinkering with its prescription drug surveillance system. It's switched to cost recovery, slashed staff and talked about creating an independent agency, and now it's asking the US to merge the 2 countries' adverse drug event reporting systems in order to give Canada access to more information. But no deal is imminent.

Quick action was expected in the wake of recommendations from the inquest into the death of 15-year-old Vanessa Young of Oakville, Ont., who died of a cardiac arrhythmia in March 2000 while taking cisapride (Prepulsid) to treat digestive problems. The antireflux drug was contraindicated for bulimic patients like Young. At the time of her death, manufacturer Janssen-Ortho had issued 4 *Dear Health Professional* letters concerning cisapride, while Health Canada had discussed it in 3 issues of the *Canadian Adverse Drug Reaction Newsletter* (*CADRN*).

Fourteen recommendations from the April 2001 inquest report into Young's death were aimed at improving Health Canada's drug-monitoring system. These included mandatory reporting of all "serious" adverse drug events (ADEs) within 48 hours and promotion of an international database of adverse drug reports.

The negotiations to share data with the US are a step toward the latter. Dr. Robert Peterson, director general of Health Canada's Therapeutic Products Directorate (TPD), says Canada doesn't generate enough data to detect problems at an early stage. Canada accounts for 2% of the world market for pharmaceuticals, the US 40%. Peterson says the extra data would allow Canada to make more informed decisions.

Since the inquest, Health Canada has improved communications, including using specially marked envelopes to mail *Dear Health Professional* letters (see note). However, there has been no move toward mandatory reporting, despite evidence that voluntary reporting doesn't work (*JAMA* 2000;284[23]:3036-9).

Voluntary reporting

Canadian health professionals report about 7000 ADEs annually. In 1999, more than 258 000 were reported in the US, so if Canadian reporting matched US levels, there would have been roughly 25 000 reports here.

And reported events are but the tip of the iceberg. Peterson agrees with the FDA's estimate that 10 incidents go unreported for every ADE that is reported. Peterson adds that deciding whether to file a report involves a "tremendous degree of interpretation." For example, Dr. Peter Norton of the University of Calgary reviewed 160 charts at 4 Calgary hospitals and uncovered 39 ADEs (see *CMA Interface* 2001;2[9]:3). One had been reported. Peterson said Health Canada "will explore incentives [for reporting]."

McMaster University clinical pharmacologist Stuart MacLeod says voluntary reporting is "absolutely" a problem, but mandatory reporting would be difficult to enforce. (Eleven countries, including France, have mandatory reporting.) "Health care professionals could say they didn't recognize it as an adverse event, and how can you argue with that?" says MacLeod. And the volume of ADE reports might be unmanageable.

However, mandatory reporting is gaining some political support. In September, NDP MP Judy Wasylycia-Leis told the Commons that even though mandatory reporting wouldn't prevent all deaths due to adverse drug reactions, "if we take steps to require a systematic way of sharing information on adverse reactions, if we require our physicians and our hospitals to report any problems associated with drugs and their interactions with other drugs or with foods, then we will have made a big difference."

However, MacLeod says that instead of mandatory reporting, Canada needs targeted investigations of certain drug classes so that it can conduct prospective epidemiologic studies, and it needs to monitor all new drugs.

That's what the UK does. Under its university-coordinated system, physicians fill out cards documenting reactions to new drugs and the information is compiled and disseminated quickly to modify use of the drug at an early stage, when health care practitioners are vigilant. "It's better than what we have," says MacLeod, a member of the Scientific Advisory Board of the federal minister of health. In Canada, the reality is that the reporting system is uneven, with ADE-reporting decisions left to the provider's discretion.

Collaborative relationship

Documents related to cisapride and its eventual withdrawal from the Canadian market in August 2000 indicate that Health Canada and Janssen-Ortho collaborated on messages being developed for the media, and negotiated about drug warnings. According to one document, they shared information about the number of "Prepulsid associated deaths" because of a report being prepared for the CBC's *Marketplace*. The day after the program aired, Janssen-Ortho faxed Health Canada its "standby media statement on prepulsid" to be "used as needed."

In this issue, *CMAJ* has endorsed the creation of a new regulatory agency that would work at arm's length from Health Canada officials (*CMAJ* 2001; 165[10]:1293). MacLeod says the main advantage is that this type of new agency would not be "accountable to someone who was elected." However, this also means that no political advantage comes from establishing such an agency — MacLeod says the idea has been discussed for years.

Peterson says the agency idea will be discussed at meetings between Health Canada, the colleges, drug companies and public-interest groups. Australia uses an external committee to assess ADE reports and make recommendations, but Peterson says it's too early to say whether Canada's agency would make decisions or issue recommendations.

Whatever the final result, most agree something must be done. "The TPD is reactive, not proactive," says MacLeod, "It reacts to the [ADE] reports." — *Barbara Sibbald*, CMAJ

NOTE: Electronic subscriptions to *CADRN* and other advisories are available at **www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/index.html**. To report ADEs, Health Canada has a new toll free number (866 234-2345) and a dedicated fax line (866 678-6789).