doubtedly a limit to their understanding.

So goes the art and practice of medicine. Sometimes when I reach for my prescription pad, I treat it like a loaded weapon, to be used with extreme caution if at all.

David Rapoport
Family physician
Toronto, Ont.

Reference

1. Vioxx: lessons for Health Canada and the FDA [editorial]. *CMAJ* 2005;172(1):5.

DOI:10.1503/cmaj.1050016

Canada has one of the safest drug systems in the world and we at Health Canada are always looking for ways to improve it. For example, the Minister of Health recently committed to mandatory reporting of adverse drug reactions and has indicated his support for more transparency regarding clinical trials.

The *CMAJ* editorial on the Vioxx case and its implications for drug safety[1] notes some of the difficulties inherent in postmarketing surveillance, such as extrapolating conclusions from clinical trials to real-world clinical practice and detecting signals and relating them to a specific drug. The editorial also points to areas for improvement: better mechanisms for physician reporting, active surveillance targeting serious adverse events and improved use of other databases. Health Canada agrees and looks forward to active discussion of these issues with *CMAJ* readers, who are on the front line of postmarketing surveillance.

However, other comments in the editorial are inaccurate. Reference to a "built-in bias toward approving drugs" and a low bar for approval of drugs for sale in Canada are incorrect and misleading. The review process in Canada is thorough; involves extensive assessment of the safety, efficacy and quality of all medications; and is in line with international standards.

It is important to continue to raise the profile of adverse event reporting within the health care community and to work together to improve the system. The cooperation of *CMAJ* in the publication and distribution of the Canadian Adverse Reaction Newsletter is greatly appreciated, but much more must be done. One example of Health Canada's commitment in this area is its pilot project on active surveillance (undertaken with the Canadian Paediatric Society), which brings together a network of 2300 pediatricians to collect and analyze information on adverse reactions (see www.cps.ca/english/CPSP/Studies/drugreactions.htm). In addition, we are opening 2 new centres in our system of regional adverse reaction centres to enhance our ability to promote the reporting of adverse reactions nationally.

My colleagues and I look forward to working with *CMAJ* as well as the key players in the drug safety process to improve on the good and safe foundation that already exists.

Diane C. Gorman
Assistant Deputy Minister
Health Canada
Ottawa, Ont.

Reference

1. Vioxx: lessons for Health Canada and the FDA [editorial]. *CMAJ* 2005;172(1):5.

DOI:10.1503/cmaj.1050026

It was with disappointment that I read the *CMAJ* editorial on the withdrawal of rofecoxib (Vioxx).[1] In particular, I am disappointed with the narrow perspective on the safety of our industry's medicines and the supposed conflict caused by a relationship between industry and Health Canada.

The member companies of Rx&D (Canada's Research-Based Pharmaceutical Companies) are committed to patients, to their health and well-being, and to the assurance that new medicines are as safe and efficacious as humanly and scientifically possible. No company wants to launch a medicine on the market to have it withdrawn at some future date. The impact for the company, in terms of both reputation and financial perspective, can be devastating. That is why any negative effect experienced by patients in the development phase of a medicine must be reported. Once a medication is made available to patients, any serious and unexpected adverse effects reported to the manufacturer must, in turn, be reported to Health Canada within 15 days.

When should a medicine be allowed to go to market? Once all possible combinations with other drugs or commonly used products have been studied? For many patients, this is not an option. Who would have thought a few years ago that grapefruit juice could have a dramatic impact on the health of patients taking certain types of medicines? Yet pharmacists now alert their patients to potential interactions between grapefruit juice and medications.[2] Patients who take medicines must understand that any pharmaceutical chemical introduced into the body is not natural; hence, they should, with the consultation and supervision of their physician, weigh concerns against benefits and make an informed decision.

Reference to potential conflict caused by an emphasis on Health Canada's "partnerships with industry" is simply not true.

When taken appropriately, medicines can provide positive health outcomes and value to patients, their families, our health care system and society as a whole.

Russell Williams
President
Canada's Research-Based Pharmaceutical Companies (Rx&D)
Ottawa, Ont.

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2. Maskalyk J. Grapefruit juice: potential drug interactions. *CMAJ* 2002;167(3):279-80.

DOI:10.1503/cmaj.1050027

Importance of open access for clinicians and researchers in developing countries

The *CMAJ* editorial on the topic of open access[1] is of special relevance for developing countries. I am a South

Asian physician pursuing graduate studies in a Canadian institution, and the online availability of the latest medical literature through my university's subscription has opened up a new world for me, helping me to improve the quality of my research and my understanding of the issues. I am already dreading the loss of this privilege when I return home.

Medical schools and research centres in developing countries often cannot pay for the high cost of online journal access, and subscriptions to print versions are limited. In many cases, researchers have access only to abstracts (through PubMed [www.ncbi.nlm.nih.gov/entrez/query.fcgi] and, more recently, Google Scholar [www.scholar.google.com]). It is difficult for residents on limited stipends to buy even single articles, which cost anywhere from US$10 upward. Furthermore, Internet access is limited, and safe online banking and credit card use are not available. As a result, residents and scientists use outdated sources for their research, which is reflected in the final quality and scientific rigour of their work.

The initiatives promoting open access that have been undertaken by *CMAJ*, BioMed Central (www.biomedcentral.com/), SciDev.Net (www.scidev.net/) and the Public Library of Science journals, among others, are laudable. However, the practice of making authors pay for online publication of their articles, as described in the *CMAJ* editorial,[1] might dissuade researchers in developing countries from sharing their research results in international journals. Special discounts will need to be worked out, and journals will need to continue exploring innovative ways to support progress in open access and offset their costs.

CMAJ's experience has shown the advantages of an open-access policy.[1] I hope that the journal continues its leadership in promoting equal opportunities and access in the global medical community.

Anant Bhan
Fogarty International Fellow
University of Toronto Joint Centre for Bioethics
Toronto, Ont.

Reference

1. Open access in medical publishing: trends and countertrends [editorial]. *CMAJ* 2005;172(2):149.

DOI:10.1503/cmaj.1050038

DKA and thrombosis

Josephine Ho and associates[1] report an unfortunate case of a 6-year-old girl with diabetic ketoacidosis (DKA) and thromboembolic stroke. Although the authors do a credible job of describing the diverse causes of pediatric stroke and the controversies surrounding treatment of children, there was little emphasis on the danger of extreme hyperosmolar states and risks of thrombosis. More information about the initial presentation of the patient, with specific reference to the concentration of serum sodium and serum osmolarity, would have been helpful in determining her risks of thrombosis.

Diabetes is associated with a prothrombotic state through a number of mechanisms.[2] The mostly adult entity of hyperosmolar nonketotic coma has had various degrees of association with thrombosis,[2,3] as has extreme hypernatremia in breast-feeding neonates.[4] Recent evidence has also demonstrated that among children with DKA, there is a higher incidence of deep venous thrombosis with femoral central venous lines.[5,6] Serum glucose and sodium concentrations and hence effective plasma osmolarity were significantly higher in those patients with blood clots.[5]

Although there is no direct evidence for its efficacy, our practice has been to use prophylactic anticoagulation in patients with DKA who are in a significant hyperosmolar state, as well as to eliminate the use of femoral catheters in patients with these risk factors. There is significant controversy surrounding the dose of anticoagulant therapy, specifically whether the efficacy of dosages for prophylaxis of deep venous thrombosis outweighs the risks associated with full systemic anticoagulation.[7] As with most clinical issues, particularly in pediatric critical illness, this controversy lends itself well to a clinical trial in patients with extreme hyperosmolar states, including those with DKA.

Jeff Burzynski
Assistant Professor of Pediatrics
Division of Critical Care
University of Iowa
Iowa City, Iowa

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[Three of the authors respond:]

Jeff Burzynski raises an interesting point about the danger of the hyperosmolar state and risk of thrombosis. In the patient that we described (a 6-year-old girl with DKA and stroke),[1] the initial serum sodium level was 132 mmol/L and initial blood glucose, 43.4 mmol/L. The corrected sodium level was 144 mmol/L with a calculated serum osmolarity of 331 mOsm/L. We agree that patients with DKA have hyperosmolarity because of hyperglycemia and hypernatremic dehydration, and we[1] and others[2,3] have suggested that the hyperosmolarity contributes to the prothrombotic tendency of children with DKA.

Worly and associates[2] described 3 patients aged 14–18 months with DKA and calculated serum osmolarity of 291–356 mOsm/L who experienced deep venous thrombosis associated