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Valdecoxib (Bextra™): severe cutaneous reactions

Valdecoxib (Bextra™), a selective inhibitor of cyclo-oxygenase 2 (COX-2), is indicated for the treatment of acute and chronic signs and symptoms of adult rheumatoid arthritis and osteoarthritis as well as for the relief of pain associated with primary dysmenorrhea.¹

Severe cutaneous adverse reactions (ARs) associated with valdecoxib, including erythema multiforme (EM), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported internationally.² This resulted in the issuance of a Dear Health Care Professional Letter in Canada to coincide with the Canadian launch of valdecoxib (Bextra™).³ The Canadian product monograph¹ contains the following important safety information:

• a warning about the risk of serious cutaneous reactions;
• a recommendation to discontinue valdecoxib therapy at the first appearance of a rash or other sign of hypersensitivity;
• a contraindication for use in patients who have had allergic-type reactions to sulfonamides;
• a contraindication for use in patients who have experienced asthma, urticaria or an allergic-type reaction after taking ASA or other NSAIDs.

Health Canada received 9 Canadian reports of suspected cutaneous ARs associated with valdecoxib from the date of marketing, Dec. 11, 2002, to Aug. 1, 2003. Five cases were labelled serious; however, none of the patients had EM, SJS or TEN. There were no reported deaths. Two of the 5 serious reports indicated a history of allergy to sulfonamides. Given the seriousness of SJS and TEN, physicians should not prescribe valdecoxib to patients with any previous allergic reactions to sulfonamides¹ and should exert caution when prescribing it to patients prone to multiple drug allergies.⁴

In a published case report, a patient with a previous allergy to an antimicrobial sulfonamide was diagnosed with TEN after treatment with valdecoxib.⁵ Controversy exists regarding the potential for cross-reactivity between sulfonamide antimicrobials and other sulfonamide-containing compounds.⁶ A recent study reported that cross-reactivity between antimicrobial sulfonamides and celecoxib appears to be low.⁷ Another study suggests that a predisposition to allergic reactions, rather than a cross-reactivity with sulfonamide-based drugs, is possible.⁴ Health Canada has received reports of serious cutaneous reactions associated with celecoxib and rofecoxib in patients with and without a history of sulfa allergy. Valdecoxib and celecoxib have similar structures: both contain a benzenesulfonamide moiety.⁵ The structure of rofecoxib contains a methylsulfonyl moiety.⁸ The progression from rash to desquamation can occur within a
few days, or hours, and may result in fatal complications, such as infection and renal or respiratory failure.\textsuperscript{4,5} It has previously been shown that early discontinuation of drugs with half-lives of less than 24 hours may decrease the rate of death from TEN and SJS.\textsuperscript{1} Because valdecoxib has a half-life of about 8 hours,\textsuperscript{1} withdrawal of this drug when flu-like symptoms develop may decrease the risk of TEN and SJS in certain patients. Therefore, health care professionals should encourage patients taking valdecoxib to seek medical attention if any cutaneous or flu-like symptoms occur.\textsuperscript{1}

\textbf{Violetta Skalski, PhD, Health Canada}

\textbf{References}
\begin{itemize}
\item 1. \textit{Bextra\textsuperscript{TM} (valdecoxib) [product monograph]. Kirkland (QC): Pfizer Canada Inc.; 2002.}
\item 5. \textit{Glasser DL, Burroughs SH. Valdecoxib-induced toxic epidermal necrolysis in a patient allergic to sulfonamide drugs. Pharmacother 2003;23(4):551-3.}
\end{itemize}

\textbf{Natural health products and adverse reactions}

The Natural Health Products Regulations are in force as of January 2004\textsuperscript{4} and will be implemented in stages over 6 years. As with other product lines, reporting of ARs to natural health products is now mandatory for industry. Also, because of their role in reporting ARs, health care professionals and consumers need to be aware of the AR reporting system for natural health products.

We chose 3 popular herbal medicines (echinacea, ginkgo biloba and St. John's wort) to illustrate some current safety concerns associated with the use of natural health products. We searched Health Canada's database of spontaneous ARs for the period Jan 1, 1998, to June 30, 2003.

\textbf{Echinacea}

Echinacea species belong to the same family as ragweed and daisies (Asteraceae). Allergic reactions, including anaphylaxis, following the use of echinacea have been reported.\textsuperscript{2} The Health Canada database had 23 reports of suspected ARs associated with echinacea; 4 cases were allergic reactions, 3 of which involved single-ingredient products. Symptoms ranged from rash to swelling of the tongue and lips, to anaphylactic reaction.

\textbf{Ginkgo biloba}

There were 21 reports of suspected ARs associated with ginkgo. Most involved platelet, bleeding and clotting disorders, which is in line with its ability to inhibit platelet activating factor. One report was of a fatal gastrointestinal hemorrhage in which the suspect products included ticlopidine and ginkgo, both taken over 2 years, along with multiple concomitant medications. There was also a report of stroke in a patient taking multiple drugs, including clopidogrel and ASA, as well as an herbal product containing ginkgo. Caution should be exercised when ginkgo is used concomitantly with antiagulants and drugs that affect platelet aggregation (e.g., warfarin, ASA, NSAIDs,\textsuperscript{3-5} ticlopidine and clopidogrel). Patients also need to heed medical instructions regarding pre- and postoperative use of herbal products; for example, it has been recommended that patients stop taking ginkgo at least 36 hours before surgery.\textsuperscript{4}

\textbf{St. John's wort}

Because St. John's wort (\textit{Hypericum perforatum}) is a potent inducer of cytochrome P450 (CYP3A4), its concomitant use with CYP3A4 substrates may result in subtherapeutic levels of these drugs and may necessitate increased dosage requirements.\textsuperscript{6,7} St. John's wort may trigger serotonin syndrome, a result of potentiated disorders and psychiatric disorders. Of the psychiatric reactions, 2 cases involved suspected serotonin syndrome as a result of an interaction with venlafaxine. There were 2 cases in which St. John's wort was suspected of inducing mania (1 involved concomitant lithium and the other concomitant buupon treatment).

Many natural health products contain 2 or more herbal ingredients, all of which, including nonmedicinal ingredients, would need to be considered in an AR report. Currently, for most natural health products without a Drug Identification Number, or DIN, the concentrations of herbs or active ingredients may not be provided, and specific product dosage information may not be available, which makes it difficult to determine the exact dosage the patient received. Furthermore, different species within the same genus of an herb exist, and different plant parts (root or aerial parts) containing varying concentrations of phytochemicals may be used.\textsuperscript{8} Not all products state the species of plant or plant part on their labels, which adds to the
challenges of reporting and assessing ARs associated with herbal medicines.

Health Canada’s new regulations will facilitate reporting ARs associated with natural health products. For example, every registered product will have a unique Natural Product Number, or NPN, which will enable Health Canada to determine more easily the number and identity of ingredients contained in the product. Despite the new regulations, it will take up to 6 years before the above provisions are widely adopted by industry.

Jenna Griffiths, MSc; Scott Jordan, PhD; Karen Pilon, RN, Health Canada

References

Case Presentations

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Ciprofloxacin: suspected association with deafness and reduced hearing

Health Canada has received 4 serious case reports of deafness or decreased hearing suspected to be associated with ciprofloxacin. They involved men aged 35, 47, 65 and 67 years old. Three were receiving 1000 mg/d orally and one was receiving 800 mg intravenously. In all cases, the reactions began within 1 week after initiation of therapy. Three patients recovered, and the fourth experienced partial permanent deafness.

Finasteride: suspected association with depression

A white man in his mid-40s with no prior history of psychiatric problems was treated with finasteride for male-pattern hair loss. Clinical depression developed about 3 months after the onset of therapy. The depression was described as moderately severe but was unresponsive to treatment with various antidepressants. Treatment was maintained for 4 years. Following cessation of the finasteride therapy, the depression resolved in about 2 weeks, and the patient made a complete recovery. A published report has described 19 cases (14 males, 5 females) in whom moderate to severely severe depression developed during treatment with finasteride (1 mg/d orally) for androgenetic alopecia.1

Reference

Communicating Drug Safety Information Workshop II: summary report available

In March 2003, Health Canada hosted the second of two invitational workshops entitled Communicating Drug Safety Information. This workshop was a follow-up to the first one, held Nov. 29–30, 2001.

The March workshop, whose theme was “A Shared Responsibility,” brought together health care practitioners, patient and consumer advocacy groups, health professional associations and industry representatives. Participants examined the current practices for collecting and communicating drug safety information and discussed strategies to enhance their efficiency and effectiveness. The 2 summary reports highlighting the discussions are available at www.hc-sc.gc.ca/english/protection/drugs.html.
Human growth hormone (somatropin) and use in children with Prader–Willi syndrome

The US Food and Drug Administration issued a Dear Health Care Professional Letter in association with Pfizer Inc. on May 30, 2003, regarding the long-term use of the human growth hormone Genotropin® (somatropin) in children with Prader–Willi syndrome. Pfizer is aware of 7 deaths worldwide associated with one or more of the following risk factors: severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection. The US product monograph has recently been amended to contraindicate the use of growth hormone in children with PWS who have severe obesity or severe respiratory impairment, and warnings have been added recommending that physicians evaluate these patients for upper airway restriction before prescribing growth hormone therapy.

In Canada, 7 somatropin products have a notice of compliance (Biotropin and Genotropin [not marketed in Canada], Humatrope®, Nutropin®, Protropin®, Saizen® and Serostim®). None of them is indicated for use in PWS. Although somatropins are not indicated for PWS in Canada, should a physician decide that their use is in a patient’s best interest, the physician should assess the patient for severe obesity, history of respiratory impairment or sleep apnea, or unidentified respiratory infection before prescribing this therapy.1

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Summary of health professional and consumer advisories posted from Sept. 1 to Nov. 14, 2003 (advisories are available at www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/index_advisories_e.html)

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Canadian Adverse Reaction Newsletter

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Suggestions?
Your comments are important to us. Let us know what you think by reaching us at cadrmp@hc-sc.gc.ca

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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.