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Canadian Adverse Reaction Newsletter

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www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index_e.html

In this Issue

Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Monitoring Office free of charge

Phone: 866 234-2345
Fax: 866 678-6789

Form available at:

www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/index_e.html

Adverse reactions in children: Why report?

Like other patients using health products, children are also at risk of adverse reactions (ARs). In 2005, 7.3% of the domestic AR reports received by Health Canada described ARs associated with health products* in patients 18 years and younger (excluded were reports in which age was not indicated). ARs reported in adults do not always predict ARs in children.[1] Several factors help explain why a child's risk of an AR differs from that of an adult when taking the same health product. Some ARs are specific to the paediatric population because of the growth and development that children undergo (e.g., enamel dysplasia with tetracyclines, gray syndrome with chloramphenicol), whereas other ARs occur in adults as well but are more common in children (e.g., dystonia with metoclopramide).[2–6]

Many health products used in paediatrics have not been developed and assessed specifically for this population and are prescribed to children outside the authorized indications listed in the product monographs (commonly referred to as off-label use).[2,4,5] Furthermore, clinical trials, which usually enrol adults, may not be a reliable measure in revealing the risk of ARs in the paediatric population. Scientific evaluations of ARs in children are further complicated by the fact that there are fewer paediatric than adult patients in the general population.[7] In addition, there are age-specific subgroups in the paediatric population that often require separate investigations;[7] during childhood physiologic changes take place that may have an impact on the pharmacokinetic processes and pharmacodynamic effects of a compound.[2] All of the above can result in a relative scarcity of prospectively generated safety information for health products prescribed to children.[5,7]

Therefore, voluntary reporting[4] through the Canadian Adverse Drug Reaction Monitoring Program and other programs such as the Canadian Paediatric Surveillance Program (www.cps.ca/english/CPSP/Studies/drugreactions.htm) and the Genotype-specific Approaches to Therapy in Childhood Program (www.genomecanada.ca) remain important as postmarketing surveillance tools to help identify ARs in

*Includes pharmaceuticals, biologics (e.g., fractionated blood products as well as therapeutic and diagnostic vaccines), natural health products and radiopharmaceuticals.

Key points

- Voluntary reporting is important to identify potential adverse reactions (ARs) in children
- Report all safety issues, including abuse and unsafe use of health products
- A plausible timeline from use of a health product to onset of an AR and a suspicion that they are related are sufficient to report an AR
- Include clinical information in the report to facilitate the causality assessment

children. They can contribute to the identification of which types of health products are more likely to cause ARs in children.[6] Spontaneous reporting systems may also uncover other types of health-product–related safety issues, such as drug abuse, unsafe drug use and the outcome of accidental drug exposure (Table 1, examples 6, 9 and 13).

The safe use of health products in children is a responsibility shared by various stakeholders, such as health care professionals, research communities, manufacturers, regulatory agencies, and parents and caregivers. Parents and caregivers need to be informed of the benefits as well as potential safety issues related to health products and be encouraged to report any observations to their health care providers to enable better monitoring for possible ARs. The prevention of ARs is highly dependent on communication from health care professionals to Health Canada.[8] A plausible timeline from the use of a health product to the occurrence of an AR and a suspicion that the AR is related to its use are sufficient to report an AR. To help evaluate the causality of the association, it is useful to include clinical information in the report, such as the indication for therapy, the dose and therapy dates, concomitant medications, concurrent medical conditions, laboratory results, and the treatment and outcome of the AR.

Health Canada communicates safety information surrounding the use of health products in children in this newsletter; some examples are shown in Table 1. Paediatric safety issues are also conveyed through Health Canada's communications to health professionals and the public as well as those issued by manufacturers.[9–11] The ongoing sharing of safety information through voluntary reporting of ARs is key to enhancing the benefit–risk profile of health products used in children.

Table 1: Examples of paediatric safety issues reported in the *Canadian Adverse Reaction Newsletter* (CARN) from 1991 to 2006*

Example	Title of article or case presentation	CARN issue
1	Iodoquinol: suspected association with hypertensive encephalopathy and seizures	July 2006;16(3)
2	Extended-release methylphenidate (Concerta) withdrawal: suspected association with priapism	July 2006;16(3)
3	Isotretinoin (Accutane): myocardial infarction, cerebrovascular and thromboembolic disorders	April 2006;16(2)
4	Overnight orthokeratology and *Acanthamoeba* keratitis	April 2006;16(2)
5	Intrathecal baclofen (Lioresal): suspected adverse incidents associated with implantable drug pump system	October 2005;15 (4)
6	Transdermal fentanyl (Duragesic): abuse in adolescents	July 2005;15(3)
7	Ibuprofen: Stevens–Johnson syndrome	July 2005;15(3)
8	Ceftriaxone (Rocephin) and immune hemolytic anemia in children	January 2005;15(1)
9	Transdermal fentanyl (Duragesic): respiratory arrest in adolescents	October 2004;14(4)
10	Sterol and sterolin-containing products: hematologic adverse reactions	April 2004;14(2)
11	Fluticasone and adrenal suppression	October 2003;13(4)
12	Ibuprofen pediatric oral liquid: gastrointestinal bleeding	January 2002;12(1)
13	Brimonidone (Alphagan) ophthalmic drops: accidental ingestion	October 2001;11(4)
14	Pemoline (Cylert): market withdrawal	January 2000;10(1)
15	Isotretinoin and depression	January 1999;9(1)
16	Cefaclor-associated serum sickness-like reaction	October 1996;6(4)

*The CARN index is available at www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/ar-ei_index_e.html.

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1. Titchen T, Cranswick N, Beggs S. Adverse drug reactions to nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and paracetamol in a paediatric hospital. *Br J Clin Pharmacol* 2005;59(6):718-23.
2. De Zwart LL, Haenen HE, Versantvoort CH, et al. Role of biokinetics in risk assessment of drugs and chemicals in children. *Regul Toxicol Pharmacol* 2004; 39(3):282-309.
3. Strolin Benedetti M, Baltes EL. Drug metabolism and disposition in children. *Fundam Clin Pharmacol* 2003;17(3):281-99.
4. Kimland E, Rane A, Ufer M, et al. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. *Pharmacoepidemiol Drug Saf* 2005;14(7):493-9.
5. Vernacchio L, Mitchell AA. Epidemiology of adverse drug effects. In: Yaffe SJ, Aranda JV, editors. *Neonatal and pediatric pharmacology — therapeutic principles in practice*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 813.
6. Choonara I, Gill A, Nunn A. Drug toxicity and surveillance in children. *Br J Clin Pharmacol* 1996;42 (4):407-10.
7. Rose K. Better medicines for children — Where are we now, and where do we want to be? *Br J Clin Pharmacol* 2005;59(6):657-9.
8. Peterson RG, Turner C. The physician's role and responsibility in reporting adverse drug events in children. *Paediatr Child Health* 2003;8:213-4.
9. *Important safety information on Strattera (atomoxetine hydrochloride) and the potential for behavioral and emotional changes, including risk of self-harm*. Ottawa; 2005 Sept 28. Available: www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/index_e.html (accessed 2006 Apr 13).
10. *Important safety information on Adderall XR*. Ottawa; 2005 Aug 31. Available: www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/index_e.html (accessed 2006 Apr 18).
11. *Health Canada endorsed important safety information on Xigris [drotrecogin alfa (activated)]*. Ottawa; 2005 May 6. Available: www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/index_e.html (accessed 2006 Apr 18).

Why do surveillance for adverse drug reactions?

- Pre-market clinical drug trials often do not include children
- Many drug products are not labelled for use in specific paediatric age groups
- Data on a drug safety profile is critical in improving care in the paediatric population
- Adverse drug reactions are a major cause of childhood morbidity and mortality, yet alarmingly less than 5% are ever reported to regulators

Canadian Paediatric Surveillance Program
ADR Tip of the Month 03/2004

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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.

Extended-release methylphenidate (Concerta) withdrawal: suspected association with priapism

A 16-year-old boy taking extended-release methylphenidate (Concerta), with no history of sexual dysfunction, experienced priapism (a painful, persistent and abnormal erection unaccompanied by sexual desire or excitation) that would last up to 24 hours whenever he forgot to take his medication. He had been taking 54 mg of the drug daily for about 1 year for attention deficit hyperactivity disorder (ADHD) and was not taking any other medications. The priapism would resolve after he took his medication. Treatment with extended-release methylphenidate was continued because the product worked well in controlling his ADHD. The patient did not appear to have any sexual dysfunction when he remembered to take his medication. Priapism is not labelled in the Canadian product monograph.[1]

A case of priapism associated with withdrawal from sustained-release methylphenidate has been reported in the literature.[2]

References

1. *Concerta (extended- release methylphenidate)* [product monograph]. Toronto : Janssen-Ortho Inc.; 2006.
2. Schwartz RH, Rushton HG. Stuttering priapism associated with withdrawal from sustained-release methylphenidate. *J Pediatr* 2004;144(5):675-6.

Iodoquinol: suspected association with hypertensive encephalopathy and seizures

A 10-year-old boy with a 2.5-year history of occasional loose stools with vague intermittent abdominal and back pain received a diagnosis of a *Dientamoeba fragilis* trophozoites infection. The child had no history of seizures, hypertension, current use of prescription drugs or exposure to toxins. Allergy to dust mites and hay fever were reported. An oral suspension of iodoquinol (500 mg/5 mL, 5 mL 3 times daily for 20 days) was prescribed. The suspension was compounded according to a Professional Compounding Centers of America (PCCA) formula using diiodohydroxyquin powder provided by the PCCA (www.pccarx.ca). According to the reporter, no information regarding potential adverse reactions (ARs) had been given with the prescription. The child had been taking 2 Quest chewable vitamins daily and 500 mg of vitamin C daily when the iodoquinol was started.

By day 14 of the iodoquinol therapy, the patient experienced worsening, painful abdominal cramps and muscle pain. A physician advised to continue treatment. Symptoms progressed, and pinaverium (50 mg 3 times daily) was prescribed. On day 19 of the iodoquinol therapy, new symptoms of pins-and-needles sensation in his feet, ataxic gait, foot drop, stiff legs, general weakness and headache developed. The patient was seen by another physician, and treatment with iodoquinol was advised to continue. That evening, the child experienced a seizure and was taken to hospital, where more tonic-clonic seizures occurred. His blood pressure on admission was 165/120 mm Hg. The iodoquinol therapy was stopped, and treatment with midazolam, phenytoin, clobazam, amlodipine, atenolol, cefotaxime, metronidazole, morphine and acetaminophen was started. The patient was admitted to the intensive care unit. A head CT scan and MRI were in keeping with findings seen in hypertensive encephalopathy. Results of other investigations, including CT of the abdomen and pelvis, blood work, microbiologic tests and chest radiograph, were normal.

After 12 days in hospital, the child was discharged with a normal blood pressure; the amlodipine and clobazam therapies, continued after discharge, were stopped within 2 months. The child followed physiotherapy for over a month. A subsequent MRI of the head indicated complete resolution of previous abnormalities. Five months later, results of a neurologic examination remained normal except for persistence of residual effects such as tingling and sensitivities in the child's legs. Other causes for the hypertension were eliminated.

A paediatric case of encephalopathy and seizures following iodoquinol use was published in 1993.[1]

Reference

1. Fisher AK, Walter FG, Szabo S. Iodoquinol associated seizures and radiopacity. *J Toxicol Clin Toxicol* 1993;31(1):113-20.

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Symposium on drug, food and natural health product interactions

Health Canada's Therapeutic Products Directorate (TPD) hosted a symposium in February 2006 to raise awareness about drug, food and natural health product (NHP) interactions. The symposium assembled internationally distinguished speakers and was attended by 260 participants from academia, industry and health care associations as well as consumer and patient advocacy groups.

The sessions addressed scientific and regulatory issues: adverse reactions due to drug–food–NHP interactions; mechanisms of action and means to evaluate the data; international surveillance strategies; and discussions on improvements to assist the consumer in avoiding these interactions.

The effort to increase awareness about drug–food–NHP interactions is a shared responsibility between government, industry, health care professionals and consumers. More dissemination of user-friendly information is required to assist the consumer in making informed choices about safe health product use. Health Canada will continue to work collaboratively to implement risk management strategies to minimize the potential risk of adverse interactions between drugs, foods and NHPs. For more information on the symposium, go to: www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/announce-annonce/index_e.html

Summary of health professional and consumer advisories posted from Feb. 17 to May 12, 2006
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

Date	Product	Subject
May 12	Minitran 0.6 mg	Recall by the manufacturer of one specific lot
May 3	Nasutra	Potential health risks
May 3	Sandoz Prednisolone 1%	Ophthalmic suspension: potential health risk
Apr 28	Miracle Bion	Warning not to use Miracle Bion product
Apr 28	Complexed Potassium	Possible Salmonella in LifeTime Complexed Potassium tablets
Apr 28	Eucalyptus oil BP bottles	Advisory of a problem with the child resistant cap
Apr 28	Mineral oil	Advisory not to use certain oral laxative mineral oil products
Apr 24	Salus-Haus vitamins	Advisory not to use certain liquid vitamin products
Apr 21	Anabolic steroids	Advisory not to use certain unauthorized products
Apr 10	Colleague pump	Important safety information — Baxter Corporation
Apr 10	Yohimbine	Advisory not to use unapproved products containing yohimbine or yohimbe bark including Strauss Energy SIX capsules
Apr 5	Weight loss products	Advisory not to use Super Fat Burning and LiDa Daidaihua Slimming capsules
Mar 30	Evra	Update on status of Evra
Mar 28	Avian flu products	Advisory against counterfeit and unapproved products
Mar 14	Medical telemetry systems	Interference with medical telemetry systems
Mar 10	Newer antidepressants	Rare serious lung disorder in newborns
Mar 1	Hydrea	Cutaneous vasculitic toxicities — Bristol-Myers Squibb Canada
Mar	Segufix	Recall: Segufix-Standard and Segufix-Simplex — Segufix Systems Ltd.
Feb 22	Esophageal dilators	Information on reprocessing of Mercury-filled esophageal dilators
Feb 22	Weight loss products	Two weight loss products contain controlled substances
Feb	Trasylol	Important safety information — Bayer Inc.
Jan 9	Infusion pumps	Potential delivery of unrequested patient-controlled analgesia doses — Baxter Corporation
Dec 28	Respiratory ventilator circuits	Recall of certain adult respiratory ventilator circuits — Source Medical Corporation

To receive the Newsletter and health product Advisories free by email, join Health Canada's ***MedEffect*** mailing list. ***Go to*** **www.hc-sc.gc.ca/dhp-mps/medeff/subscribe-abonnement/index_e.html**

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

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