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CMIRPS Canadian Medication Incident Reporting and Prevention System
SCDPIM Système canadien de déclaration et de prévention des incidents médicamenteux

ISMP Canada Safety Bulletin

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Acetaminophen: Preventing Harm through Safe Use

- *Review the patient's medical and medication-use history to assess whether the patient has risk factors warranting a reduction in the acetaminophen dosage.*
- *Use the Health Canada guide "Let's Talk About Acetaminophen" to educate patients on how to use acetaminophen safely.*
- *Ensure that doses for pediatric patients are calculated using an accurate weight and that an appropriate measuring device is used to administer all liquid doses.*

Despite its reputation for safety, acetaminophen has been identified as the leading cause of liver failure in Canada; approximately 4500 Canadians are hospitalized for acetaminophen overdose annually, and about 6% of these patients experience liver injury.[1] Injury to the liver, which has occurred with both intentional and unintentional acetaminophen overdoses, may be irreversible.

Acetaminophen is a commonly used analgesic that is widely available in either single- or multiple-ingredient products. As of early 2017, almost 500 acetaminophen-containing products were marketed in Canada, with over 350 of them available as nonprescription, over-the-counter (OTC) products.[2] Health Canada recently estimated that 4 billion dosage units of acetaminophen are sold in the country annually.[1]

This bulletin highlights, for both healthcare professionals and manufacturers, key safety efforts, important resources, and strategic recommendations based on recent Health Canada initiatives supporting the safe use of acetaminophen in Canada.

Canadian Initiatives to Support Safe Use of Acetaminophen

Health Canada has conducted safety reviews (described in more detail below), issued public advisories, and instituted changes to the labelling requirements for OTC products containing acetaminophen. Practitioners and the public can find links to these and other related resources on a Government of Canada webpage dedicated to acetaminophen safety.[3]

ISMP Canada's efforts to support the safe use of acetaminophen have included publishing an acetaminophen newsletter as part of its consumer medication safety program at SafeMedicationUse.ca,[4] launching Spotlight on Acetaminophen,[5] a webpage dedicated to acetaminophen safety, and publicizing acetaminophen safety strategies on social media.

Health Canada's Acetaminophen Safety Review and Recent Regulatory Changes

In 2009, there was an initial safety review of non-prescription acetaminophen products which led to updated labelling standards that included increased warnings about the potentially serious and possibly fatal risk of liver injury in the event of

acetaminophen overdose with these products.[1] In 2014, Health Canada completed a greater in-depth safety review of acetaminophen,[6] which showed that although most acetaminophen overdoses are intentional, nearly 20% are unintentional (see Box 1). Furthermore, the proportion of cases of acetaminophen-related injury due to unintentional overdose rose from 27% in 2006 to 45% in 2011. The safety review noted that severe liver injuries were more common in unintentional overdoses and involved either single-entity acetaminophen products or combination prescription medications containing both acetaminophen and an opioid.[6]

Box 1. Possible causes of unintentional acetaminophen overdose

- Belief that over-the-counter medications cannot cause serious harm
- Lack of awareness of the importance of adhering to the maximum daily dose of acetaminophen
- Pediatric dose errors related to:
  - miscalculation of doses
  - incorrect measurement of doses
- Confusion caused by umbrella names (i.e., use of the same brand name for products containing different ingredients)
- Taking more than one product containing acetaminophen at the same time

Although most liver injuries involving acetaminophen are caused by doses higher than 4 grams per day (the recommended daily maximum in Canada), the safety review noted that hepatotoxicity has been reported in patients receiving lower daily doses. Many of these patients had pre-existing liver disease, used alcohol excessively, were malnourished, and/or used acetaminophen for a longer duration than is recommended. In the United States, Johnson & Johnson, the manufacturer of Tylenol brand acetaminophen, voluntarily reduced the labelled daily maximum dose for adults from 4 g to 3 g,[7] but the company has not implemented this labelling change in Canada.

Table 1 (page 3) outlines selected risk-minimization options considered in the acetaminophen safety review, some of which have been implemented in other jurisdictions, such as the United States (US), the United Kingdom (UK), Australia (AU) and New Zealand (NZ).

To further address the problem of liver damage caused by acetaminophen, in September 2016 Health Canada released an updated labelling standard for OTC acetaminophen products, as well as an information update for the general public.[8] Improvements to the labelling standard are summarized in Box 2.

Box 2. Safety improvements to the Canadian labelling standard for OTC acetaminophen instituted in 2016[8]

- Clearer instructions on packages emphasizing that
  - the lowest effective dose should be used
  - the recommended maximum daily dose should not be exceeded
  - the recommended duration of treatment should not be exceeded
  - precautions must be followed if taken with alcohol
- Enhancement of layout to display that the product contains acetaminophen, by specifying the exact wording, font, and colour to be used, for both single- and multiple-ingredient products.
- Inclusion of a Drug Facts table, to provide instructions, warnings, and other safety information in a consistent, user-friendly format (mandatory by 2021).
- A recommendation that a calibrated dosing device should be provided in all liquid formulation packages and that directions for use should state "Use only the measuring device provided" (recommended, not mandatory).

Links to resource materials, including a fact sheet, "Let's Talk About Acetaminophen", and an "Acetaminophen Know Your Dose" poster, were implemented on Health Canada's acetaminophen information webpage in 2016.[3] In addition, Health

Table 1. Selected risk-minimization strategies

Risk-Minimization Strategy	Considered in the Acetaminophen Safety Review[6]	Implemented in Other Jurisdictions
Add warnings to packages and inserts	**Yes** – to strengthen and improve product labelling	**Yes** (US,[6] UK[6])
Use blister packs	**No**	**Yes** (UK[9])
Limit package size	**Yes**	**Yes** (UK,[10] AU,[11] NZ[6])
Limit the amount of acetaminophen contained in prescription products	**Yes** – limit amount of acetaminophen contained in opioid combination products	**Yes** (US[12])
Include an accurately calibrated dose-delivery device with all pediatric liquid acetaminophen-containing products	**Yes** – recommended in 2016 guidance[13]	**Yes** (US,[14] UK[6])
Reduce the maximum recommended daily dose	**Yes** – but not implemented as a result of stakeholder feedback	**No** – not implemented by the FDA, but voluntarily by Johnson & Johnson in the US[7]
Limit all products to maximum 325 mg acetaminophen per unit dose	**Yes** – already in place for prescription products, but lacked sufficient support to be implemented for nonprescription products	**Yes** (US for prescription products)[6]
Develop and implement an education strategy	**Yes**	**Yes** (US,[6] UK[6])

Canada issued a notice to industry[15] limiting the amount of acetaminophen in prescription combination products to 325 mg per dosage unit.

Analgesic Alternatives to Acetaminophen

Both the public and healthcare professionals are increasingly aware of the potential for harm related to acetaminophen therapy. As such, it might seem to make sense to treat pain with other analgesic options, including nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids; however, these medications carry their own risks and may not be appropriate for use by certain patients. NSAIDs may increase the risk of gastrointestinal, renal, and cardiovascular adverse events. The adverse effects of opioids include sedation and constipation, and use of these drugs is associated with the risk of addiction and overdose.[16]

Nonpharmacological strategies, including psychological and sociological interventions and exercise therapy, can be effective for treating chronic pain in some patients.[17] Therefore, the risks and benefits of available therapies must be carefully weighed by the clinician and the patient and/or family, before deciding on a treatment plan.

Recommendations

Healthcare Providers

- Review the patient's medical and medication-use history before prescribing or recommending acetaminophen, to identify use of any other acetaminophen-containing products and to assess whether the patient has risk factors warranting a dosage reduction.

- Inform patients about using acetaminophen safely; use the Health Canada guide Let's Talk About Acetaminophen to reinforce this information.[18]
- For pediatric patients, assist parents in the following aspects of therapy:
  - calculating the dose of acetaminophen required
  - ensuring the child's weight has been determined accurately, in both pounds and kilograms, given that the Canadian labelling standard permits dosing to be expressed in either of these units (emphasize to parents that they should read the label directions carefully to ascertain the unit of measure for weight, as this unit may vary from one product to another)
  - understanding the amount (dose) to be administered, whether in tablet or liquid form
  - knowing about an appropriate measuring device for liquids and how to use it
- Provide patients with information about nonpharmacological options to treat pain.

Manufacturers

- Implement the measures recommended by Health Canada for acetaminophen packages:
  - provide a Drug Facts table, as outlined in the 2016 Health Canada Labelling Standard[8,13]
  - provide an appropriate, accurately calibrated dosing device for all liquid preparations
- Reduce the labelled maximum daily dose recommendation for acetaminophen, as has been done voluntarily by some manufacturers in other jurisdictions, despite the fact that this labelling change has not been mandated in Canada or elsewhere.
- Although not required by Health Canada, eliminate the use of umbrella names. This measure, as well as the requirement to indicate "contains acetaminophen" on the primary display panel, can inform consumers and reduce confusion among different products.
- When designing package labels, incorporate the recommendations from the Good Label and Package Practices Guides for Prescription Drugs and Non Prescription Drugs and Natural Health Products, as well as the International Medication Safety Network's statement "Making Medicines Naming, Labeling and Packaging Safer".[19]

Conclusion

In spite of efforts to enhance the safety of acetaminophen use, incidents of serious liver injury from acetaminophen continue to be reported in Canada and globally. ISMP Canada supports ongoing monitoring of the incidence of hepatotoxicity from acetaminophen and the continued implementation of safety measures to mitigate the risk of harm from this commonly used medication.

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Updated Paper to Electronic MedRec Implementation Toolkit Now Available!

The Institute for Safe Medication Practices Canada, in collaboration with the Canadian Patient Safety Institute and the University of Victoria and with the support of Canada Health Infoway, is pleased to release the second edition of the Paper to Electronic MedRec Implementation Toolkit.

Highlights of this edition:

- evidence for eMedRec to improve patient safety
- eMedRec vignettes to support Health Canada's opioid strategy
- testimonials from early adopters
- improved guidance for evaluating eMedRec
- updated screenshots of exemplary eMedRec solutions
- a comprehensive checklist to support the selection of an eMedRec solution with ideal features

The updated toolkit and checklists can be found at https://www.ismp-canada.org/medrec/#tab3

This segment of the bulletin describes a recent SafeMedicationUse.ca publication from ISMP Canada's Consumer Program.

March 2017 Newsletter:

Suddenly Stopping a Medication Can Be Harmful

SafeMedicationUse.ca received an incident report describing a patient who was told to stop using her antidepressant but was not given instructions on how to do so safely (i.e., no taper schedule was provided). After abruptly discontinuing her medication, the patient experienced withdrawal symptoms, including tremors and extreme sweating. In the newsletter, consumers are reminded that certain medications must be stopped slowly under the supervision of a healthcare provider, to minimize the risk of withdrawal symptoms and potential harm.

Tips for Practitioners:

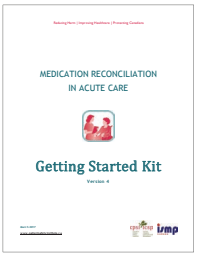
- For medications that should not be stopped abruptly (i.e., those that require tapering), apply an auxiliary label alerting the patient to consult a healthcare provider before discontinuing the medication.
- Inform your patients if a medication they are taking needs to be tapered before discontinuation.
- When tapering the dose of a medication, make sure the patient is aware of warning signs that the dose is being reduced too quickly and understands when to seek medical attention.

For more information, read the full newsletter:
https://www.safemedicationuse.ca/newsletter/newsletter_StoppingMedication.html

Consumers Can Help Prevent Harmful Medication Incidents

SafeMedicationUse.ca

Check Out the Updated Medication Reconciliation Kits!



ISMP Canada is delighted to release 2 newly revised medication reconciliation (MedRec) Getting Started Kits. These new kits highlight the most current evidence, knowledge, and practices in both acute care and long-term care settings.

- Medication Reconciliation in ACUTE CARE Getting Started Kit
  https://www.ismp-canada.org/download/MedRec/MedRec-AcuteCare-GSK-EN.pdf
- Medication Reconciliation in LONG-TERM CARE Getting Started Kit
  https://www.ismp-canada.org/download/MedRec/MedRec-LTC-GSK-EN.pdf

More than 100 Endorsements for *5 Questions to Ask*!

You can request a customized 5 Questions to Ask about Your Medications poster for your organization by emailing medrec@ismp-canada.org

To date, more than 100 organizations have endorsed 5 Questions to Ask about Your Medications, including international, national, and provincial associations and programs.

For more information, please visit https://www.ismp-canada.org/medrec/5questions.htm

CMIRPS SCDPIM

Canadian Medication Incident Reporting and Prevention System

Système canadien de déclaration et de prévention des incidents médicamenteux

The Canadian Medication Incident Reporting and Prevention System (CMIRPS) is a collaborative pan-Canadian program of Health Canada, the Canadian Institute for Health Information (CIHI), the Institute for Safe Medication Practices Canada (ISMP Canada) and the Canadian Patient Safety Institute (CPSI). The goal of CMIRPS is to reduce and prevent harmful medication incidents in Canada.

HIROC

The Healthcare Insurance Reciprocal of Canada (HIROC) provides support for the bulletin and is a member owned expert provider of professional and general liability coverage and risk management support.

ISMP CANADA

The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit organization committed to the advancement of medication safety in all healthcare settings. ISMP Canada's mandate includes analyzing medication incidents, making recommendations for the prevention of harmful medication incidents, and facilitating quality improvement initiatives.

Report Medication Incidents

(Including near misses)

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