The Institute for Safe Medication Practices Canada (ISMP Canada) is an independent national not-for-profit agency established for the collection and analysis of medication error reports and the development of recommendations for the enhancement of patient safety.

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

Volume 9, Number 10

ISMP Canada Safety Bulletin

December 30, 2009

Analysis of International Findings from Incidents Involving Fentanyl Transdermal Patches

Over the past several years, there have been numerous reports in the medical literature and from medication safety centres around the world concerning adverse events involving fentanyl transdermal systems (also referred to as "fentanyl patches"). Many of these incidents have resulted in harm, and some have caused death. Alerts and warnings have been issued by patient safety and medication safety centres and regulatory agencies in various countries.[1-12] In 2008, the International Medication Safety Network (IMSN)* undertook an analysis of aggregated findings from reports about such incidents submitted to programs in Canada, Ireland, the United Kingdom, and the United States. This bulletin highlights the findings from this analysis and includes recommendations for coordinated, systems-based solutions.

Background

Fentanyl is a highly potent opioid. Transdermal patches of this drug are applied topically to provide continuous delivery over a period of 72 hours. The patches are indicated for management of "persistent, moderate to severe chronic pain that cannot be managed by other means such as opioid combination products or immediate-release opioids and only in patients:

- who require continuous around-the-clock opioid analgesia for an extended period of time and
- who are already receiving opioid therapy at a total daily dose of at least 60 mg/day Morphine Equivalents."[13]

Despite its potential benefits, inappropriate or incorrect use of transdermal patches for administration of fentanyl can lead to significant patient harm. Adverse events, including death, have been caused by inappropriate prescribing of this drug, as well as by dispensing and administration incidents.[1-10,12]

Analysis Findings

As its contribution to the IMSN initiative, ISMP Canada reviewed findings from a total of 3291 fentanyl patch-related incidents that occurred in 4 jurisdictions, 271 of which had resulted in harm, including 8 deaths. A sequential analysis was used, in which a quantitative analysis of 3271 incidents was possible followed by a qualitative analysis of narrative findings available in 1076 cases.

The quantitative analysis provided a "snapshot" of the findings and suggested potential areas of focus for improvement. In particular, incidents involving wrong dose, wrong strength or quantity, and omission of doses accounted for 70% of the incidents resulting in harm.

The qualitative analysis identified 3 primary themes:

- Dose was higher than required or patch was replaced too soon.
- Patient should not have received the medication.
- Dose was lower than required or patch was replaced too late or omitted.

Common Contributing Factors

More than 20 factors that might have contributed to the incidents were identified through the qualitative analysis. These factors were categorized into 6 areas of focus:

- healthcare practitioners' lack of knowledge or awareness of indications for and potency and pharmacokinetics of transdermal fentanyl patches
- lack of or incomplete understanding among patients and families that this noninvasive route of fentanyl administration is highly potent
- complexity of dosing for transdermal administration of fentanyl (e.g., every 3 day dosing or need for multiple patches for a single dose)
- lack of clear communication among multiple caregivers regarding date, time, and location of application of a patch and/or date and time when next patch is due to be applied
- problems with product design (e.g., colourless, translucent patches; poor adhesion)
- lack of identification or recognition of use of transdermal fentanyl during transitions of care

Recommendations

Recommendations from the analysis crystallized in 2 key areas:

* The International Medication Safety Network (IMSN) was formed in 2006 at a meeting in Salamanca, Spain, and now includes representatives from more than 20 countries. Additional information about the IMSN is available at: http://www.intmedsafe.net/index.php.

- Efforts must be made to better inform healthcare practitioners about the pharmacokinetics and the safe and effective use of transdermal fentanyl.
- Effective strategies are needed to ensure that patients and their families are well informed about the use of transdermal fentanyl. Emphasis should be on the complexity of the dosing regimen, the monitoring of side effects, and the proper disposal of used patches.

At its 2009 meeting in Copenhagen, members of the IMSN reached consensus on 3 specific areas of action to support the recommendations:

- Develop an aid, such as a manual checklist or an electronic decision support tool (e.g., in practitioner order entry systems) to assist practitioners with "just in time" review of critical information when prescribing, dispensing, and administering transdermal fentanyl. Such an aid could include prompts to confirm opioid tolerance, to verify appropriate indications for use, and to inform patients or caregivers of vital information, such as the signs and symptoms of toxicity.
- Manufacturers of transdermal fentanyl should provide clear and easy-to-understand warnings in their patient education materials, including pictograms to facilitate communication. In turn, healthcare practitioners must give these materials to patients receiving fentanyl patches.
- Manufacturers of transdermal fentanyl must produce patches that, through use of colour and printed drug name and strength, remain noticeable and identifiable after application.

Conclusion

Despite multiple safety alerts, preventable harm from transdermal fentanyl continues to occur. IMSN members will work with manufacturers to advance the recommendations from this international analysis. Practitioners are urged to review the use of transdermal fentanyl in their practice settings and to incorporate safeguards into each stage of the medication use process for this potent opioid.

Acknowledgements

Reporting is the first step in enhancing medication safety. The International Medication Safety Network (IMSN) expresses sincere appreciation to the many healthcare professionals for their initiative, efforts, and demonstrated support for a culture of safety, exemplified by their willingness to share information about medication incidents and related findings.

References

1. Fentanyl transdermal system (marketed as Duragesic) information [FDA alert]. Silver Spring (MD): Food and Drug Administration; 2005 Jul 15 [updated 2007 Dec 21; cited 2009 Dec 17]. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm114961.htm
2. Transdermal fentanyl: a misunderstood dosage form. ISMP Can Saf Bull. 2006 Aug 14 [cited 2009 Dec 18];6(5):1-3. Available from: http://www.ismp-canada.org/download/ISMPCSB2006-05Fentanyl.pdf
3. Fentanyl patch linked to another death in Canada. ISMP Can Saf Bull. 2007 Nov 13 [cited2009 Dec 18];7(5):1-2. Available from: http://www.ismp-canada.org/download/safetyBulletins/ISMPCSB2007-05Fentanyl.pdf
4. Fentanyl transdermal patch and fatal adverse reactions. Can Adverse React Newsl 2008 July [cited 2009 Dec 18];18(3):1-2. Available from: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v18n3-eng.php#Reactions
5. Health Canada endorsed important safety information: Duragesic fentanyl transdermal system. Toronto (ON): Janssen-Ortho Inc; 2005 Sep 13 [cited 2009 Dec 18]. 2 pp. Available from: http://www.janssen-ortho.com/joi/pdf_files/Duragesic_DDL_E.pdf
6. Ongoing, preventable fatal events with fentanyl transdermal patches are alarming! ISMP Med Saf Alert. 2007 Jun 28 [cited 2009 Dec 18];12(13):1-3. Available from: http://www.ismp.org/newsletters/acutecare/articles/20070628.asp
7. New fentanyl warnings: more needed to protect patients. ISMP Med Saf Alert. 2005 Aug 11[cited 2009 Dec 18];10(6):1-3. Available from: http://www.ismp.org/Newsletters/acutecare/articles/20050811.asp
8. Little patches … big problems: new safety warnings about fentanyl patches - part 1. ISMP Med Saf Alert Community Ambul Care Ed. 2005 Aug [cited 2009 Dec 18];4(8):1-3. Available from: http://www.ismp.org/newsletters/ambulatory/issues/community200508.pdf
9. Little patches…big problems: protecting children from unintentional harm - part 2. ISMP Med Saf Alert Community Ambul Care Ed. 2005 Sep [cited 2009 Dec 18];4(9):1-3. Available from: http://www.ismp.org/newsletters/ambulatory/issues/community200509.pdf
10. Little patches: big problems - part 3: widespread education necessary! ISMP Med Saf Alert Community Ambul Care Ed. 2005 Oct [cited 2009 Dec 18];4(10):1-3. Available from: http://www.ismp.org/newsletters/ambulatory/issues/community200510.pdf
11. Alert: analgesic skin patches. Darlinghurst (Australia): New South Wales Therapeutic Advisory Group, Safer Medicines Group; 2006 Jul [cited 2009 Dec 18]. Available from: http://www.ciap.health.nsw.gov.au/nswtag/publications/otherdocs/Fentanylalert0706.pdf
12. Fentanyl patches: serious and fatal overdose from dosing errors, accidental exposure, and inappropriate use. Drug Saf Update 2008 Sep [cited 2009 Dec 18];2(2):2-3. Available from: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON025632&RevisionSelectionMethod=Latest
13. Product monograph: [N]Duragesic* 12, [N]Duragesic* 25, [N]Duragesic* 50, [N]Duragesic* 75, [N]Duragesic* 100 fentanyl transdermal system. Toronto (ON): Janssen-Ortho Inc.; 1991 Dec 20 [revised 2009 Apr 30; cited 2009 Dec 17]. 40 pp. Available from: http://www.janssen-ortho.com/JOI/pdf_files/Duragesic_E.pdf

Incidents Reported with Spiriva Capsules and Inhalation Device

As of December 2009, ISMP Canada has received 24 reports of Spiriva (tiotropium bromide monohydrate) being taken orally instead of by inhalation. In addition, there have been 2 reports of hydromorphone controlled release capsules being inserted into the inhalation device for Spiriva (the HandiHaler[1]) and administered by inhalation.

Spiriva is indicated for "long term, once daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema".[2] The drug is provided as a powder-filled capsule (Figure 1) that is intended for inhalation through the HandiHaler, a specifically designed inhalation device.

Incidents have been reported to ISMP Canada by both acute care and long-term care facilities and by consumers receiving care as outpatients. One consumer commented, "I am wondering why capsules such as those used for Spiriva are designed such that they look like an oral capsule….I am amazed that medications designed for inhalation are not distinctively different from those to be taken by mouth."

The reports have documented incorrect orders (e.g., "spiriva 1 capsule NG daily") and incorrect transcription of appropriate orders. However, most of the reports have described inadvertent oral administration of the drug after the capsule was placed in a medication cup within the patient's reach.

Spiriva has low *oral* bioavailability.[2] As such, the concern about these incidents is related not to the effects of the drug taken orally, but rather to the potential for poor therapeutic outcomes with repeated omission of inhaled doses. Concerns about this problem have been raised by others, including the Food and Drug Administration in the United States.[3,4,5]

The 2 reports describing inadvertent administration by inhalation of Hydromorph Contin (hydromorphone controlled release) 3 mg capsules, instead of Spiriva, noted the similar colour and shape of the capsules (compare Figure 2 with Figure 1).

Figure 1. Spiriva (tiotropium bromide monohydrate) is distributed as a powder-filled capsule for inhalation through a specifically designed inhalation device.

Figure 2. Hydromorph Contin (hydromorphone controlled release) 3 mg capsule for oral administration.

This information has been provided to raise awareness and to emphasize the need to ensure adequate differentiation between oral and inhalation products, and the need to ensure distinctive processes for labelling, handling, and administering these products. For example, Spiriva capsules should *NOT* be placed into medication cups, but rather, only provided to the patient together with the HandiHaler. Additional recommendations have been made by ISMP (US)[5] and include:

- Incorporate clear instructions for both patient and staff, when ordering and dispensing Spiriva that the medication is to be inhaled.
- Provide prominent auxiliary messages on Medication Administration Records (MARs)—e.g., "FOR INHALATION ONLY. FOR USE ONLY WITH INHALER."

More detailed information on recommendations is available from the August 2009 Pennsylvania State Board of Pharmacy Newsletter: http://www.dos.state.pa.us/bpoa/lib/bpoa/20/phabd/03_august_09_pharmacy.pdf

ISMP Canada has notified both the manufacturer, Boehringer Ingelheim Canada Ltd., and Health Canada about these reports.

Please refer to page 4 for references.

References

1. How to take Spiriva. Boehringer Ingelheim Pharmaceuticals, Inc.; 2007 [cited 2009 Dec 22]. Available from: http://www.spiriva.com/consumer/taking-spiriva/how-to-take-spiriva.jsp
2. Product monograph: [Pr]Spiriva®. Burlington (ON): Boehringer Ingelheim Canada Ltd.; [revised 2009 Dec 2; cited 2009 Dec 22]. Available from: http://www.boehringer-ingelheim.ca/en/Home/Human_Health/Our_Products/Product_Monographs/Spiriva-pm.pdf
3. Public health advisory: important information on the correct use of Spiriva and Foradil capsules [internet]. Silver Spring (MD): Food and Drug Administration; 2008 Feb 29 [cited 2009 Dec 22]. Available from: http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm051132.html
4. Worth repeating: unit dose capsules for inhalers mistaken as oral capsules. ISMP Med Saf Alert. 2004 Nov 18;9(23):2.
5. Capsules for inhalation mistaken as oral capsules. Pa State Board Pharm Newsl. 2009 Aug [cited 2009 Dec 22]. pp 1-2. Available from: http://www.dos.state.pa.us/bpoa/lib/bpoa/20/phabd/03_august_09_pharmacy.pdf

ISMP Canada is a national voluntary medication incident and 'near miss' reporting program founded for the purpose of sharing the learning experiences from medication errors. Implementation of preventative strategies and system safeguards to decrease the risk for error-induced injury and thereby promote medication safety in healthcare is our collaborative goal.

Medication Incidents (including near misses) can be reported to ISMP Canada:
(i) through the website: http://www.ismp-canada.org/err_report.htm or (ii) by phone: 416-733-3131 or toll free: 1-866-544-7672.
ISMP Canada can also be contacted by e-mail: cmirps@ismp-canada.org. ISMP Canada guarantees confidentiality and security of information received, and respects the wishes of the reporter as to the level of detail to be included in publications.

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