Pharmacy Informer

Children's and Women's Health Centre of BC, Department of Pharmacy *Summer 2015*

Updates from C&W Pharmacy, Therapeutics and Nutrition (PT&N) Committee

Jennifer Kendrick, BScPharm, PharmD

The C&W PT&N Committee serves as the Pediatric subcommittee to the Provincial Pharmacy and Therapeutics Committee. We continue to have representation from other Health Authorities, in addition to our membership from C&W.

1. Policies & Procedures:

The following policies & procedures have been approved and are being posted on the C&W intranet:

Intranasal Midazolam is now approved for procedural sedation on inpatient units. There is an accompanying pre-printed order and updated Procedural Sedation Guidelines and Standards.

Inhaled Nitrous Oxide was approved for use in the Dentistry Clinic. Nitrous oxide is also used for procedural pain and anxiety in the Emergency Department and Orthopedic Clinic.

Fosphenytoin monographs have been updated in our BCCH Drug Dosing Handbook and Parenteral Drug Manual. Fosphenytoin dosing is now expressed as "phenytoin equivalents" (PE), which is in line with the product monograph and other dosing references. The injectable formulation is available in vials as 50 mg/mL of PE (equivalent to 75 mg/mL of fosphenytoin). Fosphenytoin is available as a second-line alternative to phenytoin for status epilepticus when IV access is not available (as it can be administered IM), or when IV access is tenuous and extravasation poses a serious risk to the patient. Fosphenytoin is similarly effective to phenytoin. Note that phenytoin drug levels following a fosphenytoin loading dose should be drawn 2 hours following an IV dose or 4 hours following an IM dose.

BCCH Empiric Antibiotic Guidelines were updated for 2015.

2. Formulary Changes:

Levofloxacin was approved for addition to formulary for the treatment of fever and neutropenia in select low-risk patients. The updated Fever and Neutropenia Guidelines will be released in the coming months.

Zoledronic acid restriction to *osteogenesis imperfecta* was removed. There is evidence to support its use in other populations of children with osteoporosis, as an alternative to pamidronate.

3. Medication Backorders:

We continue to face medication shortages and the Pharmacy Department continues to monitor supplies and usage. We appreciate the assistance in reviewing options to mitigate shortages (using oral/rectal routes, changing to alternative medications, changing to other brands and strengths, etc).

Gentamicin injectable and cefixime suspension remain on extended backorder. The anticipated return of gentamicin is in the first quarter of 2016. Cefixime tablets are available now, with anticipated return of the suspension in September 2015.

4. Pre-printed Orders

The C&W PT&N has been busy approving pre-printed orders as part of the Clinical Systems Transformation in addition to our C&W-specific pre-printed orders. The following C&W pre-printed orders have been approved since January:

Acute T Cell Mediated Kidney Rejection

Bruising or bleeding and suspected child maltreatment - initial screening panel – CPSU

Eating Disorders Unstable Patient Medical Admission

Immune Globulin (IVIG) Infusion

Intranasal Midazolam for Procedural Sedation

WH Antepartum – Admission

WH Severe Nausea & Vomiting of Pregnancy (hyperemesis) Antepartum Admission

WH Evolving Chorioamnionitis

WH Isolated Fever in Labour with Epidural

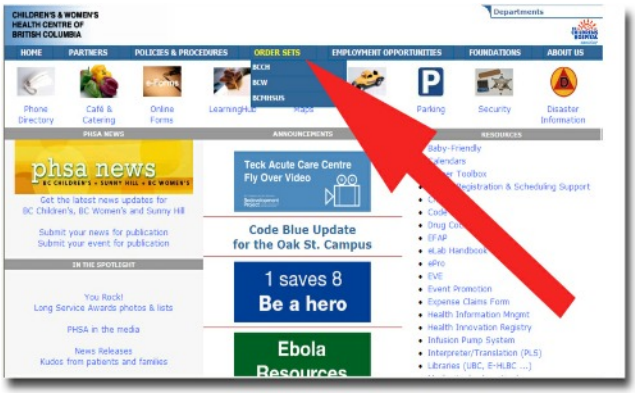
WH Mobile Labour Epidural / CSE Analgesia

WH Magnesium Sulfate ($MgSO_4$) Administration for Seizure Prevention

WH Magnesium Sulfate ($MgSO_4$) Administration for Fetal Neuroprotection

WH Magnesium Sulfate ($MgSO_4$) Administration for POSTPARTUM

Note that many of the C&W pre-printed orders are available as print-on-demand and can be found on the Intranet.



In This Issue:

Empiric Antimicrobial Guidelines 2015 Update

Karen Ng, BScPharm, PharmD, BCPS
Reviewed by Dr. Ashley Roberts, Infectious Diseases and Antimicrobial Stewardship

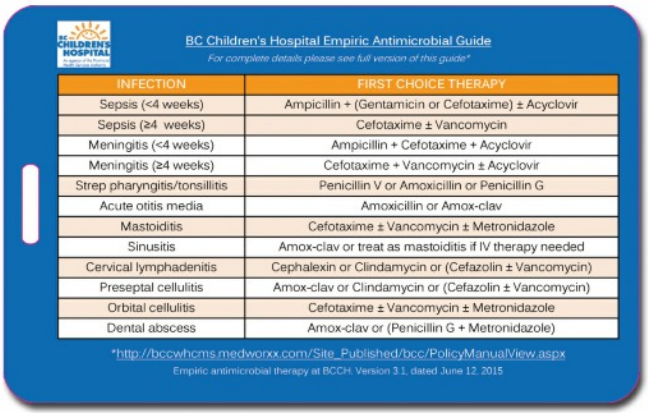
After an annual review of available evidence and guidelines, the Antimicrobial Stewardship Program has updated the BC Children's Hospital Empiric Antimicrobial Guidelines, now posted onto **Medworxx**. Therapeutic updates in this version include:

- **Sepsis and meningitis**: age cutoffs have been changed from 6 weeks to 4 weeks, in accordance to CPS[1] and IDSA[2] guidelines.
- **Sepsis <4 weeks**: the addition of acyclovir to empiric therapy has been changed to an optional "±", to curb overuse of acyclovir in infants with low suspicion of meningitis and HSV infection.
- **Meningitis <4 weeks**: the option of using gentamicin instead of cefotaxime, in combination with ampicillin and acyclovir, has been deleted. Cefotaxime is more active against *Escherichia coli* based on in vitro data as measured by MICs and MBCs, and is therefore preferred over gentamicin for the treatment of neonatal meningitis.
- **Mastoiditis, orbital cellulitis, community-acquired pneumonia, parapneumonic pneumonia and hospital-acquired pneumonia**: the addition of cloxacillin to cefotaxime for methicillin-sensitive *Staphylococcus aureus* (MSSA) has been deleted for empiric treatment, as cefotaxime provides satisfactory MSSA coverage for empiric use. For these infections, cefotaxime monotherapy is sufficient, unless if MRSA is suspected, in which case the addition of vancomycin should be considered. If MSSA is isolated, antibiotic therapy should then be tailored to optimize coverage. No evidence exists that empiric double coverage of MSSA is necessary, and double coverage is not routine in most other acute-care sites in our province. Although local susceptibility of MSSA to third-generation cephalosporins is unconfirmed because it is not tested, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) states that susceptibility is assumed in MSSA.
- **Community-acquired pneumonia>3 months, moderate and severe**: the addition of empiric oseltamivir has been given an optional "±", to align with the BCCH influenza treatment algorithm. During influenza season, empiric oseltamivir should be considered in patients hospitalized with influenza-like-illness with risk factors for complications and in those presenting with severe symptoms.
- **Pelvic inflammatory disease**: in accordance with updated guidelines from BCCDC, azithromycin has been replaced by doxycycline as first-line therapy due to its increased effectiveness for the co-treatment of *Chlamydia*.[3]
- **Cellulitis**: cloxacillin has been replaced by cefazolin for the additional streptococcal coverage.[4]
- **Necrotizing fasciitis**: this category has been divided into necrotizing fasciitis of unknown etiology requiring empiric broad coverage with piperacillin-tazobactam + vancomycin + clindamycin, and documented group A streptococcal necrotizing fasciitis requiring targeted penicillin and clindamycin.[4]
- **Cefotaxime vs. ceftriaxone**: a comment has been added that cefotaxime may be interchanged with ceftriaxone for children over 30 days-old and not on calcium-containing parenteral products (e.g. TPN). The spectrum of antibacterial coverage is very similar between cefotaxime and ceftriaxone, but ceftriaxone has a longer half-life of 5-9 hours (dosed Q12H to Q24H) and is 85-95% protein bound, versus cefotaxime which has a shorter half-life of 1-1.5 hours (usually dosed Q6H to Q8H) and is 31-50% protein bound.[5] Ceftriaxone is now slightly less costly than cefotaxime, provides more convenient dosing, is a formulary agent in BC Children's and Women's Hospital, and can be used interchangeably with cefotaxime.

  Beware that ceftriaxone can precipitate with calcium-containing parenteral products and cause end-organ damage, and thus should not be co-administered to any patient, whether mixed or administered simultaneously or via Y-site.[6,7] Ceftriaxone also competes with bilirubin for binding to serum albumin and can increase the risk of bilirubin encephalopathy by significantly decreasing the reserve albumin concentration in newborn serum and increasing free bilirubin, and is contraindicated in neonates.[8]

In addition to therapeutic updates, a hyperlink has been added to the BC Children's and Women's antibiogram, and hyperlinks have been updated for new BC Children's Hospital treatment guidelines, IDSA guidelines for skin and soft tissue infections, and to the new editions of Feigin and Cherry, Mandell, and the Red Book.

New lanyard cards with the 2015 updates are available. If you have not yet received yours, please contact Karen Ng (Karen.ng2@cw.bc.ca) or Ashley Roberts (aroberts6@cw.bc.ca) for your copy.



BC Children's Hospital Empiric Antimicrobial Guide

*For complete details please see full version of this guide**

INFECTION	FIRST CHOICE THERAPY
Sepsis (<4 weeks)	Ampicillin + (Gentamicin or Cefotaxime) ± Acyclovir
Sepsis (≥4 weeks)	Cefotaxime ± Vancomycin
Meningitis (<4 weeks)	Ampicillin + Cefotaxime + Acyclovir
Meningitis (≥4 weeks)	Cefotaxime + Vancomycin ± Acyclovir
Strep pharyngitis/tonsillitis	Penicillin V or Amoxicillin or Penicillin G
Acute otitis media	Amoxicillin or Amox-clav
Mastoiditis	Cefotaxime ± Vancomycin ± Metronidazole
Sinusitis	Amox-clav or treat as mastoiditis if IV therapy needed
Cervical lymphadenitis	Cephalexin or Clindamycin or (Cefazolin ± Vancomycin)
Preseptal cellulitis	Amox-clav or Clindamycin or (Cefazolin ± Vancomycin)
Orbital cellulitis	Cefotaxime ± Vancomycin ± Metronidazole
Dental abscess	Amox-clav or (Penicillin G + Metronidazole)

*http://bccwhcms.medworxx.com/Site_Published/bcc/PolicyManualView.aspx

Empiric antimicrobial therapy at BCCH. Version 3.1, dated June 12, 2015

References

1. Le Saux N; Canadian Paediatric Society, Infectious Diseases and Immunization Committee. Guidelines for the management of suspected and confirmed bacterial meningitis in Canadian children older than one month of age. Paediatr Child Health 2014; 19: 141-52. Full Text
2. Tunkel AR, Hartman BJ, Kaplan SL et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004; 39: 1267-84. Full Text
3. BC Centre for Disease Control [Internet]. Vancouver (BC): BCCDC Clinical Prevention Services; c2015. Pelvic inflammatory disease; 2015 March. Accessed July 3, 2015. Link to BCCDC PID Decision Support Tool
4. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014, 59: 147-59. Full Text
5. Lexicomp Online, Pediatric & Neonatal Lexi-Drugs, Hudson, Ohio: Lexi-Comp, Inc.; July 3, 2015.
6. Steadman E, Raisch DW, Bennett CL, et al. Evaluation of a potential clinical interaction between ceftriaxone and calcium. Antimicrob Agents Chemother 2010; 54: 1534-40. Full Text
7. Bradley JS, Wassel TT, Lee L, Nambiar S. Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse effects. Pediatrics 2009; 123: 609-13. Abstract
8. Gulian JM, Gonard V, Dalmasso C, Palix C. Bilirubin displacement by ceftriaxone in neonates: evaluation by determination of 'free' bilirubin and erythrocyte-bound bilirubin. J Antimicrob Chemother 1987;19: 823-9. Abstract

Health Canada Advisory: Risk of Heart Attack and Stroke with High Dose Ibuprofen

Vanessa Paquette BScPharm, PharmD; reviewed by: Rumi McGloin BScPharm, PharmD

Cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs)and non-selective NSAIDs are unequivocally associated with an increased risk of atherothrombotic events in patients with and without cardiovascular (CV) disease as demonstrated in observational studies, randomized controlled trials, systematic reviews, and meta analyses, however, uncertainty remains about the safety of specific NSAID regimens.[1-3] On April 23, 2015, Health Canada released new safety information for prescription strength ibuprofen regarding the risk of serious CV side effects when used at doses of 2400 mg or greater per day.[4]

A safety review was initiated by Health Canada following the 2013 publication of a meta-analysis conducted by the Coxib and traditional NSAID Trialists' (CNT) Collaboration that assessed vascular and gastrointestinal side effects of NSAIDs.[5] The researchers undertook the above meta-analysis to address limitations of the 2006 trial-level meta-analysis assessing the risk of atherothrombosis with COX-2 selective NSAIDs or nonselective NSAIDs which demonstrated an increase in cardiovascular events, particularly myocardial infarction (MI), with use of COX-2 selective NSAIDs and of higher dosages of diclofenac and ibuprofen, though not naproxen.[1] The 2013 CNT meta-analysis included data from 280 placebo-controlled and 474 active-controlled NSAID trials, using individual patient level data when available. Included patients were predominantly female (68%) and Caucasian (79%) with a mean age of 61 years being treated for arthritis (83%). Only 9% of patients had pre-existing atherosclerotic disease and diabetes and 20% used aspirin. The mean body mass index (BMI) was 29 kg/m^2, blood pressure was 132/79 mm Hg, total cholesterol was 5.3 mmol/L and 13% were current smokers.[5]

The primary outcome of major vascular events (non-fatal MI, non-fatal stroke, death from a vascular cause) was significantly increased in participants receiving any COX-2 selective NSAID compared to placebo. There was no significant difference in major vascular events between COX-2 selective NSAID and high dose (2400 mg per day) ibuprofen. Through an indirect comparison, high dose ibuprofen did not significantly increase major vascular events versus placebo, however, did significantly increase the subsidiary vascular outcome of major coronary events (non-fatal MI, death from coronary disease). High dose ibuprofen significantly increased the outcome of hospitalization due to heart failure but not of stroke or all-cause mortality. The study data allowed estimates of the excess absolute risk of major vascular events with varying baseline CV risk. For patients with low baseline CV risk (0.5% per annum risk of a major vascular event), high dose ibuprofen use would result in an excess of two events per 1000 persons per year. For patients with high CV risk (2% per annum risk of a major vascular event), high dose ibuprofen use would result in an excess of nine events per 1000 persons per year including three fatal events.[5] Overall, the authors concluded that ibuprofen possibly has vascular risks similar to the COX-2 selective NSAIDs.[5]

Limitations of the CNT meta-analysis to be considered and unanswered questions that still remain include the following[6]: Some trials included in the meta-analysis were missing individual patient data so trial level meta-analysis methods were necessary. Most of the data from the COX-2 selective NSAID trials were available at the patient level, whereas only half of the data from the non-selective NSAID trials (including ibuprofen) were available at the patient level. Secondly, comparisons of ibuprofen to placebo were derived indirectly from non-selective NSAIDs to COX-2 selective NSAIDs comparisons and COX-2 selective NSAIDs to placebo comparisons. Also, events were too sparse to determine to what extent the risk varies with duration of treatment and data only pertained to one dose level for ibuprofen. No associations between ibuprofen and stroke were reported in this meta-analysis, however, the number of events was relatively small.[5] Lastly, it is still definitively unclear whether the risk for CV thrombotic events is similar for all NSAIDs.[6]

At the time of Health Canada's review, they had received 26 Canadian case reports of serious heart attack and stroke related adverse events suspected of being associated with ibuprofen use. Of the 15 case reports further evaluated for causality, ibuprofen was found to be a possible cause of these adverse events in 11 of them.[4]

Health Canada concluded that there is evidence of an association between oral ibuprofen at a daily dose of 2400 mg or more and an increased risk of CV thrombotic adverse events that is comparable to the risk associated with the COX-2 selective NSAIDs.[4] This risk likely increases with dose and duration of use. The maximum recommended daily dose for prescription ibuprofen is 2400 mg, however, this dose should be avoided in patients with ischemic heart disease, cerebrovascular disease, congestive heart failure or in patients with risk factors for cardiovascular disease.[4] So far, there is no evidence that ibuprofen presents an increased cardiovascular risk at daily doses of 1200 mg or less when used for short durations.[4] Health Canada will continue to monitor any vascular risk associated with daily doses between 1800 and 2400 mg. Health Canada states that the overall benefits of ibuprofen use continue to outweigh its risks if used as recommended.[4]

Recently, on July 9, 2015, the US Food and Drug Administration (FDA) also released a safety communication and consumer report strengthening its warning that non-aspirin NSAIDs are associated with serious vascular events and are requiring updates to the drug labels of all prescription and over the counter NSAIDs including ibuprofen.[7,8] The recommendations and conclusions made by the FDA are similar to those made by Health Canada.

The bottom line is that ibuprofen is an effective treatment for pain, inflammation and fever and should continue to be offered to patients accordingly at the lowest effective dose for the shortest duration possible. The increased risk of CV thrombotic events conferred by its use should be communicated to patients especially with use at higher doses and/or known CV disease or risk factors for CV disease. Changes have been made to reflect this recommendation in the BCCH pediatric drug dosage handbook.

References (ibuprofen)

1. Kearney PM, Baigent C, Godwin J, et al. Do selective cyclooxygenase 2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk atherothrombosis? Meta-analysis of randomized trials. BMJ 2006; 332: 1302-8. Full Text
2. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population based controlled observational studies. PLoS Med 2011; 8: e1001098. Full Text
3. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011; 342: c7086. Full Text
4. Health Canada, Health Protection Branch. New safety information for prescription-strength ibuprofen: Risk of heart attack and stroke at high doses. Accessed online March 30, 2015 Link to Safety Information
5. Bhala N, Emberson J, Merhi A, et al. Coxib and Traditional NSAID Trialists' Collaboration group: Vascular and upper gastrointestinal effects on non-steroidal anti-inflammatory drugs: metal analysis of individual participant data from randomized trials. Lancet 2013; 382: 769-79. Full Text
6. FDA Briefing Document Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee. Non-steroidal anti-inflammatory drugs and cardiovascular thrombotic risk. February 10-11, 2014. Accessed July 14, 2015 Link to Briefing Document
7. FDA Drug Safety Communication. FDA strengthens warning that non aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. July 9, 2015. Accessed July 20, 2015. Link to Warning
8. FDA Consumer Health Information. FDA Strengthens Warning of Heart Attack and Stroke Risk for Non-Steroidal Anti-inflammatory Drugs. July 9, 2015. Accessed July 20, 2015. Link to Warning

Health Canada Advisory: ADHD Drugs and Suicidal Thoughts & Behaviours

Dean Elbe, PharmD, BCPP
reviewed by Dr. Russet Jones, Provincial ADHD Clinic

In March 2015, Health Canada issued an advisory[1] regarding the class of ADHD medications (including the psychostimulant drugs, such as amphetamine and methylphenidate derivatives, as well as non-stimulants such as atomoxetine and guanfacine extended-release (XR) and risk of suicidal thoughts and behaviours that will be incorporated into the official labelling for these products.

The advisory states that there have been reports of suicide-related events in patients treated with ADHD drugs. The reports involved thoughts of suicide, suicide attempts, and in a very small number of cases, completed suicide. The advisory also states: "There is little evidence to establish that these drugs cause suicidal thoughts and behaviours, but it is possible that they may contribute to the risk... It is Health Canada's view that the benefits of these drugs in the effective management of ADHD continue to outweigh their risks."

The reports cited by Health Canada stem from their internal Summary and Safety reviews on the risk of suicidal thoughts and behaviours and ADHD drugs containing amphetamines[2] and methylphenidate[3]. These reviews were based on reports received by the Vigilance Canada Adverse Reaction Reporting Database. Despite a warning being issued, there was no summary review provided for atomoxetine or guanfacine XR). Atomoxetine already carried a suicidality warning from 2005, due to its structural and pharmacological similarity to the SSRI antidepressant fluoxetine. Despite a warning being issued for the recently marketed non-stimulant ADHD treatment guanfacine extended-release, the Vigilance Canada adverse reaction reporting database does not include any reports of suicide related behaviours with this medication.

The Canadian ADHD Resource Alliance (CADDRA) issued a statement following the Health Canada warning[4], which stated in part: "…while patients and family members should be made aware of the risk of suicidal thoughts and behaviours among people with ADHD…[they]…should also be told the new warning is not a cause for panic. ADHD medication should not be changed or stopped without medical advice."

Literature shows there is a positive relationship between ADHD, impulsive behaviours and risk to self, and the effect of co-morbidities like substance use and delinquency are difficult to separate in this relationship.

In 2014 a large Swedish national health register-based study in the British Medical Journal found no evidence for a positive association between the use of ADHD drug treatments and the risk of concomitant suicidal behaviours among ADHD patients[5]. Among stimulant users, a reduced within-patient rate of suicide related adverse events was observed during treatment periods[5].

Warnings regarding the increased risk of suicidal behaviour have been incorporated into our patient medication information handouts for relevant products, which are available from the KeltyMentalHealth.ca website.

References

1. Health Canada, Health Protection Branch. ADHD drugs may increase risk of suicidal thoughts and behaviours in some people; benefits still outweigh risks. RA-52759. Ottawa, ON: March 30, 2015. Accessed online March 30, 2015 Link to Safety Information
2. Health Canada. Summary Safety Review - Amphetamines - Suicidal Thoughts and Behaviours (Suicidality). Ottawa, ON: March 30, 2015. Accessed online March 30, 2015 Link to Summary Safety Review
3. Health Canada. Summary Safety Review - Methylphenidate - Suicidal Thoughts and Behaviours (Suicidality). Ottawa, ON: March 30, 2015. Accessed online March 30, 2015 Link to Summary Safety Review
4. Canadian ADHD Resource Alliance (CADDRA). Response to March 30th, 2015: Health Canada Announcement: "ADHD drugs may increase risk of suicidal thoughts and behaviours in some people; benefits still outweigh risks". Markham, ON: April 2, 2015. Accessed online April 2, 2015 Link to Response Letter
5. Chen Q, Sjolander A, Runseon B et al. Drug treatment for attention-deficit/hyperactivity disorder and suicidal behaviour: register based study. Br Med J 2014; 348: g3769. doi: 10.1136/bmj.g3769. Full Text

Latex Containing Medication

Jennifer Kendrick (BScPharm, PharmD) and Marianne Tofan (DiplPharm)

Most products used in the hospital environment are latex-free. However, some medication vial stoppers contain natural rubber latex or have unknown latex composition. Manufacturers are not required to list the latex content of medications on the packaging. Some of the medications that are known to contain latex at this time include insulin (Humulin R® brand), alteplase, alprostadil, and magnesium sulfate (PPC brand). Vaccines known to contain latex are listed on the BC Centre for Disease Control website.

Medications should not be assumed to be latex-free unless it is explicitly stated on the packaging or the manufacturer has confirmed the absence of latex for that product.

Potential contamination of medication with latex from the vial stopper may occur with prolonged contact (e.g. during shipping or storage) or at the time of needle puncture through the stopper.[1] The risk of adverse reactions in latex-allergic patients is not clear from the literature. While there are a handful of case reports of rash and positive skin prick test and one case of anaphylaxis from medication vials known or suspected to contain latex, causality is unclear and the true frequency of reactions is unknown.[1]

In the past, hospital pharmacies and clinicians would remove the vial stopper prior to administering the medication to a latex-allergic patient in order to minimize any latex contamination from the needle puncture.[1,2] However, a study comparing this method to a single puncture of the vial stopper found no difference in latex allergen content.[3] In recent years, guidelines advocate the single puncture method.[2,4] Most hospital pharmacies, including the pharmacy at Children's and Women's Hospital (C&W), use this method.

The pharmacy at C&W recommends applying latex precautions when administering medication to a patient with latex allergy as the best way to minimize the risk of allergic reaction.

(…Continued)

If a medication vial is not listed as "latex free", assume that it contains latex and use the following precautions:

- Use a new medication vial for each dose.
- Puncture vial only once using the smallest gauge needle possible.
- If reconstituting powder with diluent, do not remove needle from stopper. Dissolve powder in vial and withdraw appropriate dose.
- Change the needle if adding the medication to an IV solution or administering directly to the patient.

All injectable medications provided by C&W Pharmacy in ready-to-administer forms (e.g. syringes, IV bags) are prepared by using latex precautions and are therefore safe to be administered to latex-allergic patients.

References

1. Heitz JW, Bader SO. An evidence-based approach to medication preparation for the surgical patient at risk for latex allergy: is it time to stop being stopper poppers? J Clin Anesth 2010; 22: 477-83. Abstract
2. Hamilton RG, Brown RH, Veltri MA et al. Administering pharmaceuticals to latex-allergic patients from vials containing natural rubber latex closures. Am J Health-Syst Pharm 2005; 62: 1822-7. Abstract
3. Canadian Society of Hospital Pharmacists. Natural rubber latex sensitive/allergic patients: guidelines for preparing medications. Ottawa (ON): Canadian Society of Hospital Pharmacists; 2001.
4. Thomsen DJ, Burke TG. Lack of latex allergen contamination of solutions withdrawn from vials with natural rubber stoppers. Am J Health-Syst Pharm 2000; 57: 44-7. Abstract

Patch Pitfalls: *Administration Errors with Transdermal Drug Delivery*

Katie Haubrich, BScPharm, PharmD
reviewed by
Charmaine Ngo, BScPharm, ACPR

Case

A 5 year-old boy presents to the emergency department with sudden onset of incoherent speech, bizarre behaviour, hyperactivity and confusion. On physical exam, the patient has slightly dilated pupils and mild tachycardia. All other vital signs are normal. Discussion with family members reveals no history of head trauma, ingestions or medication use, except for a half-patch of transdermal scopolamine (1.5 mg) applied behind the child's ear. As reported by the parents, the patch was applied 18 hours prior to presentation to prevent motion sickness on a long-distance flight.

Transdermal Drug Delivery

Drug delivery through transdermal patches provides a number of advantages over other routes of administration. Transdermal patches, for example, maintain more constant drug levels in the plasma than intermittently administered oral or parenteral dosage forms, and are convenient to use.[1] As patches provide steady drug release over a long period of time, transdermal drug delivery may reduce dose-related adverse effects, increase tolerability, and improve adherence.[2] Patches also deliver drug directly to the systemic circulation, bypassing the 'first-pass effect' and presenting a desirable option for patients unable to take medications orally. As a result of these advantages, transdermal patches have become a common route of drug delivery for medications such as narcotic analgesics, nicotine, hormones and contraceptives.

Administration of transdermal patches can be challenging, however, and medication errors involving patches have been frequently reported.[3,4] Accidental overdoses and deaths have resulted from inappropriate administration, as well as improper storage, removal and disposal of patch devices.

Transdermal drug delivery occurs via diffusion: a high drug concentration in the transdermal device creates a gradient when applied to the skin, resulting in drug absorption into the bloodstream. Transdermal patches are available in limited, set dosage strengths, which deliver doses that are often too large for children. Cutting the patch into quarters or halves to achieve tailored dosing is often seen as an appealing strategy. For some types of patches, the amount of drug delivered into the skin is directly proportional to the surface area of the patch and cutting the patch to reduce the dose may be an option.[5] For other types of patches, however, cutting the patch does not reduce the dose delivered to the patient, and can pose serious harm to patients.

Not all patches are created equal

There are two types of transdermal delivery systems currently available on the market: reservoir or 'membrane-controlled' patches and matrix or 'drug-in-adhesive-layer' patches.[6]

In reservoir or membrane-controlled patches, the drug is contained in a reservoir system, and its release into the skin is limited by a rate-controlling microporous membrane.[7] If the rate-controlling membrane is damaged in any way, the reservoir dose contents can be released immediately, posing risk of unintentional overdose. Some patches use 'micro-reservoir' systems to mitigate this risk, where the drug is contained in multiple, smaller drug reservoirs, versus one large depot.[7] If the membrane is compromised in these patches, some reservoirs may remain intact, reducing the risk of sudden "dose-dumping." A micro-reservoir system, however, does not guarantee that cutting a patch in half will result in a 50% dosage reduction. Because it is unpredictable how many microreservoirs will be damaged by cutting the device, dosing may not be consistent between each manipulated patch.

Matrix or drug-in-adhesive-layer patches, on the other hand, have drug evenly distributed in a polymer-based adhesive. In these patches, the amount of drug released is dependent on diffusion and is directly proportional to the surface area of the patch.[7] As such, cutting these patches poses less risk of unintentional overdose, and is sometimes a viable option for dose adaptation. Most commercially available patches are matrix patches (Table 1).

To cut, or not to cut?

Reservoir Patches Due to the risk of sudden "dose-dumping," reservoir, micro-reservoir or membrane-controlled patches should never be cut or altered.[10] If the required dose of a reservoir patch is not commercially available, the desired dose may be achieved by placing an impermeable material (such as Tegaderm® adhesive or Bioclusive®) on the skin underneath the patch. The surface area of the patch which is blocked should be proportionate to the desired dose reduction. It is recommended that the patch and impermeable material are then covered by placing another adhesive overtop. This technique may only be used in scenarios when exact dosing is not critical, for example with use of hormone replacement therapy patches (e.g. Estraderm®).[11] For medications with a narrow therapeutic window (e.g. fentanyl or clonidine), this technique is not recommended. While this technique is commonly used, there is very little information in the literature to support this practice.

Matrix Patches Though the amount of drug released is proportional to surface area in a matrix-system patch, most manufacturers advise against cutting the patches due to a lack of safety and efficacy data.[2,8] The available data regarding alteration of patches shows that the rate and extent of drug absorption may be less predictable in matrix patches that have been cut.[9]

(...Continued)

Cutting the patch may also result in sharp edges, which can impair adhesion to the skin.[2] The use of a cut matrix patch should take into consideration manufacturer specific recommendations, the need for exact dosing, the therapeutic index of the drug and the patient's ability to accurately alter the patch surface area. In patients using partial doses of matrix patches, careful monitoring for potential adverse effects and lack of efficacy should occur.

High risk for error and harm

Gaps in healthcare provider knowledge and awareness of transdermal patch systems, and inappropriate patient information subsequently being provided, has been identified as a major cause for transdermal patch administration errors.[1] The patch systems themselves, which vary in frequency and site of administration, shape, size, colour, and dosage units, can cause confusion with patients and healthcare professionals alike, resulting in potential for error. Additionally, the patch system may differ between interchangeable brands of the same medication. Serious harm to patients has been reported in numerous cases involving inappropriate administration of transdermal patches. In a study of medication errors with use of transdermal fentanyl and buprenorphine, 78% of errors were identified as occurring in the administration stage of the medication process.[3] Supratherapeutic doses and toxicity have resulted from patients applying multiple patches, failing to remove old patches, applying patches to incorrect body sites, applying heat to patch sites and cutting patches prior to application.[1] Failure to remove patch liners or protective foil prior to application and patch displacement due to improper application have resulted in inadequate drug absorption and poor efficacy. Appropriate education of patients and caregivers prescribed transdermal drug devices is essential in preventing such errors.

Infants and young children may be at higher risk for harm when transdermal drug delivery systems are used, due to the increased danger for patch ingestion. Ingestion of fentanyl and clonidine patches have been linked to several pediatric deaths.[12,13] Patches should be stored and disposed of safely in order to avoid inadvertent ingestion. In young children or patients with reduced mental capacity, patches should be placed on body surfaces difficult to reach (e.g. upper back), to prevent removal and ingestion.

Conclusion

Transdermal patches are prone to administration errors, and represent an important safety concern for patients, particularly as their popularity as a method of drug delivery increases. To minimize the risk of patient harm, healthcare providers should provide appropriate patient counselling.

Healthcare providers should also be aware that dose adjustment by cutting patches can result in toxicity and adverse events, and should be reserved only for certain matrix patches after considering medication and patient specific factors.

Case Discussion

Transdermal scopolamine is commercially available over-the-counter as a reservoir-system patch (Transderm-V®). If these reservoir or membrane-controlled patches are cut, the full dose contained in the device may be suddenly released when the partial patch is applied to the skin. Given scopolamine's anticholinergic effects, symptoms such as tachycardia, hyperthermia, mydriasis, hallucinations, psychoses, seizures and coma may result from overdose. In a reported case of toxicity resulting from inappropriate scopolamine patch use in a child, symptoms resolved with patch removal and supportive care.[14]

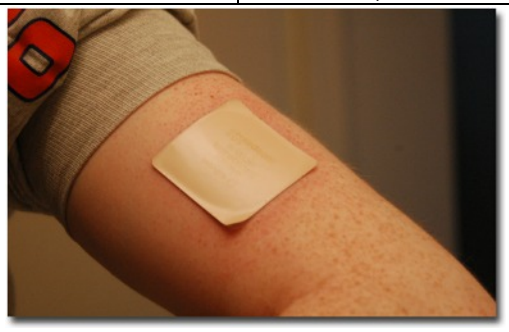
If a partial dose of transdermal scopolamine is required, an impermeable material (such as Tegaderm®) should be placed on the skin underneath the patch, covering the proportionate surface area to desired dose reduction, as discussed above.

References

1. Lampert A, Seiberth J, Haefeli WE, Seidling HM. A systematic review of medication administration errors with transdermal patches. Expert Opin Drug Saf 2014; 13: 1101-14. Abstract
2. Durand C, Alhammad A, Willett KC. Practical considerations for optimal transdermal drug delivery. Am J Health-Syst Pharm 2012; 69: 116-24. Abstract
3. Lövborg H, Holmlund M, Hägg S. Medication errors related to transdermal opioid patches: lessons from a regional incident reporting system. BMC Pharmacol Toxicol 2014; 15: 31. Full Text
4. Lövborg H, Jönsson AK, Hägg S. A fatal outcome after unintentional overdosing of rivastigmine patches. Curr Drug Saf 2012; 7:30–2. Abstract
5. Izumoto T, Aioi A, Uenoyma S et al. Relationship between the transference of a drug from a transdermal patch and the physicochemical properties. *Chem Pharm Bull (Tokyo)* 1991; 40: 456-8. Abstract
6. Lee HA, Anderson PO. Giving partial doses of transdermal patches. Am J Health-Syst Pharm 1997; 54: 1759-60. Abstract
7. Cohen MR, Smetzer JL. ISMP Medication Error Report Analysis. Risk of cutting certain medication patches. Hosp Pharm 2009; 44: 18-21. Full Text
8. Individual Product Monographs. e-CPS [Internet]. Ottawa (ON): Canadian Pharmacists Association; c2015. Accessed online July 20, 2015 from www.e-cps.ca.
9. Zuppa AF, Tejani SM, Cullen EJ Jr, Nadkarni VM. Plasma concentrations following application of whole versus cut transdermal clonidine patches to critically ill children. J Pediatr Pharmacol Ther 2004; 9: 43-8. Full Text
10. Ball AM, Smith KM. Optimizing transdermal drug therapy. Am J Health-Syst Pharm 2008; 65: 1337-46. Abstract
11. Cupp M. Characteristics of Transdermal Patches. Pharmacist's Letter/ Prescriber's Letter August 2012. Full Text
12. Horowitz R, Mazor SS, Aks SE, Leikin JB. Accidental clonidine patch ingestion in a child. Am J Ther 2005; 12: 272–4. Abstract
13. Teske J, Weller JP, Larsch K, et al. Fatal outcome in a child after ingestion of a transdermal fentanyl patch. Int J Legal Med 2007; 121: 147–51. Abstract
14. Lin YG, Chen PH, Chang FY, Wu LT, Liao KY, Wu TC. Delirium due to scopolamine patch in a 4-year-old boy. J Formos Med Assoc 2011; 110: 208-11. Abstract

Matrix System Patches	
Brand Name (Manufacturer)	**Generic**
Apo-Fentanyl Matrix®	Fentanyl
Co-Fentanyl®	Fentanyl
Bu-Trans®	Buprenorphine
Climara®	Estradiol
Climara Pro®	Estradiol and Levonorgestrel
Duragesic MAT®	Fentanyl
Estalis®	Estradiol and Norethindrone
Estradot®	Estradiol
Evra®	Ethinyl Estradiol and Norelgestromin
Exelon®	Rivastigmine
Habitrol®	Nicotine
Minitran®	Nitroglycerin
Nitro-Dur®	Nitroglycerin
Neupro®	Rotigotine
Oesclim®	Estradiol
Teva-Fentanyl®	Fentanyl
Trinipatch®	Nitroglycerin
Sdz-Estradiol Derm®	Estradiol

Reservoir System Patches	
Brand Name (Manufacturer)	**Generic**
Androderm®	Testosterone
Catapres-TTS® *(special access only)*	Clonidine
Nicoderm®	Nicotine
Transderm-Nitro®	Nitroglycerin
Transderm-V®	Scopolamine



Inside the Pharmacy Dispensary, New Orleans Pharmacy Museum, New Orleans, LA. Photo: Dean Elbe

Poly-Vi-Sol and Tri-Vi-Sol Product Change

The vitamin A content in Poly-Vi-Sol and Tri-Vi-Sol has been reduced from 1500 international units (IU) per mL to 750 IU per mL. This change was made to reduce the risk of infants exceeding the tolerable upper limit (TUL) of vitamin A from all sources. The Institute of Medicine recommends a TUL for vitamin A of 600 micrograms (2000 IU) per day. Link to Table of Dietary Reference Intakes (DRI)

Pancuronium Discontinued by Manufacturer

After more than 2 years on backorder, pancuronium has now been discontinued by the manufacturer. Other neuromuscular blockers available at Children's and Women's Health Centre include rocuronium, atracurium, cisatracurium, and succinylcholine. Programs who have been using alternate neuromuscular blockers during the pancuronium shortage are advised to continue to do so.

Congratulations to Dr. Mary Ensom on the Publication of Her 500th Paper

Dr. Mary Ensom, Professor of the Faculty of Pharmaceutical Sciences and Distinguished University Scholar at UBC, a Senior Associate Clinician Scientist at CFRI, and a Clinical Pharmacy Specialist at the Children's and Women's Health Centre of BC, has achieved **the remarkable milestone of the publication of her 500th paper**. She has contributed immensely to research in clinical pharmacokinetics and pharmacodynamics, pharmacogenetics and pharmaceutical outcomes evaluations, among other areas, and has been recognized with numerous prestigious national and international awards.

That she has published over 500 papers is a testament to her dedication, perseverance, passion, and willingness to collaborate and encourage others to contribute to clinical improvements via research.

With heartfelt congratulations, we applaud Mary's exceptional accomplishments and her continued inspiration and mentorship to both her colleagues and students!

Research, Education & Awards

Karen Ng, BScPharm, PharmD, BCPS

Research

Burgess S, Mabasa VH, Chow I, **Ensom MHH**. Evaluating Outcomes of Alternative Dosing Strategies for Cefipime: A Qualitative Systematic Review. Ann Pharmacother 2015;49:311-22. doi: 10.1177/1060028014564179 Abstract

Wang EHZ, Bolt JL, **Decarie D**, Semchuck W, **Ensom MHH**. A Study of Dabigatran Stability in 3 Clinically-Relevant Environments: Manufacturer's Blister Pack, Unit-Dose Packaging, and Community Pharmacy Blister Pack. Can J Hosp Pharm 2015;68:16-21. Full Text

Egan G, **Ensom MHH**. Measuring Anti-Factor Xa Activity to Monitor Low Molecular Weight Heparin in Obesity: A Critical Review. Can J Hosp Pharm 2015;68:33-47. Full Text

Kanji S, Hayes M, Ling A, Shamseer L, Chant C, Edwards DJ, Edwards S, **Ensom MHH**, Foster DR, Hardy B, Kiser T, La Porte C, Roberts J, Shulman R, Walker S, Zelenitsky S, Moher D. Reporting Guidelines for Clinical Pharmacokinetic Studies. The ClinPK Statement. Clin Pharmacokinet 2015; 54: 783-95. doi:10.1007/s40262-015-0236-8 Abstract

Pawluk SA, Roels CA, Wilby KJ, **Ensom MHH**. A Review of Pharmacokinetic Drug-Drug Interactions with the Anthelmintic Medications Albendazole and Mebendazole. Clin Pharmacokinet 2015; 54: 371-83. doi: 10.1007/s40262-015-0243-9. Abstract

Reardon J, Lau TTY, **Ensom MHH**. Vancomycin Loading Doses: A Systematic Review. Ann Pharmacother 2015; 49: 557-65 doi: 10.1177/1060028015571163 Abstract

Rainkie D, **Ensom MHH**, **Carr RR**. Pediatric Assessment of Vancomycin Empiric Dosing (PAVED): a Retrospective Review. Pediatric Drugs 2015; 17: 245-53. doi: 10.1007/s40272-015-0122-8 Abstract

Kiang TKL, Wilby KJ, **Ensom MHH**. A Critical Review on the Clinical Pharmacokinetics, Pharmacodynamics, and Clinical Trials of Ceftaroline. Clin Pharmacokinet 2015 May 5. [Epub ahead of print] Abstract

Marra F, **Ng K**. Controversies around epidemiology, diagnosis and treatment of *Clostridium difficile* infection. Drugs 2015; 75: 1095-118. doi:10.1007/s40265-015-0422-x Abstract

Bridging The Gap: An Oak Tree Clinic Interdisciplinary Outreach Approach to HIV Care at Alouette Correctional Centre for Women in BC. Pick N, Friesen K, **Quaia C**, Paquette T, Slater A, Kestler M, Krell S, Moody C, Mervyn L, Feder D, Murray M. Poster presentation at 4th International Workshop on HIV & Women, January 13-14, 2014.

Awards

Mary Ensom was one of only 4 individuals to be inducted into the **Inaugural Class of the Hall of Distinguished Alumni**, University of Kentucky College of Pharmacy (March 2015) Link to Story

Editor's Corner

There have been significant changes in some of our distribution channels since we resumed publishing, and we continue to work to make sure everyone has access to our content. If you did not automatically receive a copy (or notification of where you can download a copy) of this newsletter, please contact one of the editors at the email addresses listed below. For those of you who may have missed our Winter 2015 issue, the newsletter has been posted on the UBC Department of Pediatrics website.

Pharmacy Informer Editorial Board