Pharmacy Informer

Children's and Women's Health Centre of BC, Department of Pharmacy *Spring 2016*

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 C&W PTN has been busy updating and renewing its medication policies. The following new or updated policies & procedures have been approved and are posted on the C&W intranet:

All **Automated Dispensing Cabinet** policies have been updated support workflow with the new automated dispensing cabinets.

Complementary and Alternative Products (CAM) has been reviewed. Patients at Women's Hospital can sign a waiver if they would like to self-administer CAM. The administration of CAM to children is not permitted except in palliative care. Additional clarification has been added that this policy does not include cannabinoids or medicinal marijuana.

The **Hazardous Drug** policy was updated to include the expanded list of medications that are now considered low-risk hazardous drugs by the National Institute for Occupational Health and Safety. In order to safely provide medications to patients while protecting the worker, handling procedures have been revised.

There is a new **Independent Double Check** policy that describes the detailed procedure that must be used for high alert medications.

All **Narcotics and Controlled Drugs** policies have been updated to comply with Health Canada requirements and to support workflow with the new automated dispensing cabinets.

2. Formulary Changes:

Mannitol 20% has replaced mannitol 25% as the concentration that is stocked in clinical areas and resuscitation kits. Mannitol 20% is less likely to crystallize at room temperature compared to the higher concentration, which frequently required warming to dissolve the crystals.

BioGaia (Lactobacillus reuteri) for prevention and treatment of infectious diarrhea and antibiotic-associated diarrhea was reviewed. Study results for the treatment of infectious diarrhea were inconsistent and of questionable clinical relevance to our population. Studies for the other indications were not available. Therefore, the Committee recommended against addition to formulary at this time.

3. Parenteral Drug Manual:

The Parenteral Drug Manual is undergoing a major update in preparation for the move to the Teck Acute Care Centre. The major change includes removal of existing geographical restriction and addition of restrictions based on monitoring requirements for the medication. Other changes are removal of dosing information and linking to the Drug Dosage Guidelines and addition of dilution guidelines. (continued…)

4. Medication Backorders:

We continue to face medication shortages and the Pharmacy Department continues to monitor supplies and usage.

Clobazam tablets are on backorder and in short supply in the community. We are working with prescribers on a strategy to allocate supply appropriately and plan for a potentially prolonged backorder.

Nitrofurantoin tablets are currently on backorder. We are conserving tablets for compounding suspensions. Nitrofurantoin 100 mg capsules are available for larger doses.

Droperidol injection has been discontinued by the manufacturer. Women's Hospital has updated the post-operative nausea and vomiting order set to make use of alternative medications.

Paraldehyde is no longer available in Canada. The Pharmacy Department has obtained a supply from the Health Canada Special Access Programme.

5. Pre-printed Orders:

The following C&W pre-printed orders have been approved since November 2015:

APS Dexmedetomidine Infusion in Oncology;
APS, PICU, ONC Hydromorphone Infusion;
APS, PICU, ONC Hydromorphone Infusion in Overweight Patients;
APS Continuous Epidural Analgesia Term Infants Less than 3 Months;
APS Continuous Epidural Analgesia Greater than 3 Months;
ED Fever in Infants Less than 60 Days of Age;
Asthma;
GYNE Post-Anesthetic Recovery Room;
NEPH Kidney Transplant Admission Pre-op;
Kidney Transplant Post-op PICU;
Kidney Transplant Post-op Ward;
NEURO Continuous Midazolam for Seizure Control;
OB Gestational Hypertension and Proteinuria Ante-Partum;
Gestational Hypertension and Proteinuria Post-Partum;
PED Inpatient Asthma Admission;
Clostridium Difficile;
PICU Acute Peritoneal Dialysis;
Continuous Renal Replacement Therapy;
Severe Burns (over 25% BSA);
Severe Sepsis or Septic Shock;
Rheumatology Rituximab Administration;
OB Post-operative Nausea and Vomiting;
Intermediate Nursery Admission;
Intravenous Cyclophosphamide (Non-Oncology);
Intravenous Sedation for Patients Greater than or Equal to 12 Months

In This Issue:

Benzodiazepines for Seizure Rescue in Children

Elaine Wong, BScPharm, ACPR
Reviewed by: Dr. Linda Huh, Division of Neurology

Prolonged seizures have traditionally been defined as seizures lasting longer than 5 minutes. They appear to have a low probability of spontaneous cessation[1-5] and may result in negative outcomes such as neuronal injury.[6] Pharmacoresistance may also occur with prolonged seizures[7-9], which complicates treatment by having to use either higher doses or multiple agents, both increasing potential for adverse effects. Due to these reasons, children who are at risk of prolonged seizures may be prescribed seizure rescue medications such as benzodiazepines.

Benzodiazepines bind to the gamma–aminobutyric acid A ($GABA_A$) receptor and potentiate the influx of chloride via ion channels, promoting depressive effects on the central nervous system.[10] Commonly used agents in the acute management of prolonged seizures are intravenous diazepam and lorazepam, however intravenous access can often be challenging, particularly in the pediatric population. The time required to gain intravenous access can cause significant treatment delays, and as a result there has been much active research investigating the use of non-intravenous routes of benzodiazepines in the treatment of acute prolonged seizures.

Initial research of non-intravenous routes began with rectal diazepam in a suppository form[11] as the rectal tissue is highly vascularized and allows for rapid absorption. Further studies indicated that alternative dosage forms such as a gel or a solution have shown improved efficacy and safety[12-13]; however, these alternative forms still rely on rectal administration which is often cumbersome and less socially acceptable, especially for older children. This has prompted further research into alternative routes in order to improve patient quality of life.

Currently, buccal and intranasal midazolam have gained popularity in the pediatric population. Much like rectal tissue, the oral and the nasal mucosa are also highly vascularized and allow for rapid absorption. Most studies have shown that intranasal and buccal midazolam are either equivalent or superior to rectal diazepam with respect to both efficacy and ease of administration, with similar rates of adverse events.[14-20] The choice between intranasal and buccal may depend on preference of the patient and their families as well as patient specific conditions such as rhinorrhea or excessive salivation that may hinder medication delivery.

Based on this current available evidence, the recommendation for seizures lasting longer than 5 minutes is to use intranasal or buccal midazolam at 0.2 to 0.3 mg/kg/dose (maximum 10 mg). Since midazolam is not currently marketed in Canada for intranasal or buccal use, the 5 mg/mL injectable formulation of midazolam solution is used. If the intranasal route is prescribed, an attachment of a nasal atomizer is recommended. For patients who are at ongoing risk for prolonged seizures, midazolam may be prescribed for outpatient use and families of patients should be given appropriate instructions including when to give, how to draw up the correct dose from vials or ampoules, and appropriate technique for administration to the patient. For more information on teaching and administering intranasal or buccal midazolam, please refer to the following documents:

- Buccal midazolam patient handout
- Intranasal midazolam patient handout

Due to inadequate studies in infants < 3 months of age, rectal diazepam may be preferable to intranasal and buccal midazolam. The recommended dose of rectal diazepam is 0.5 mg/kg/dose (maximum 10 mg). In hospital, the 5 mg/mL injectable formulation of diazepam solution is used with an attachment of a tube for rectal administration. Like midazolam, for patients who are at ongoing risk for prolonged seizures, diazepam may be prescribed for outpatient use and families should be given appropriate instructions as listed above. A rectal gel form of diazepam is also commercially available in pre-loaded in syringes of 5 mg and 10 mg for easier administration, however the significantly higher cost should be considered and discussed with families of patients prior to being prescribed. For more information on teaching and administering rectal diazepam, please refer to the following documents:

- Rectal diazepam patient handout
- Rectal diazepam gel (Diastat®) patient handout

When a patient is newly prescribed intranasal or buccal midazolam, a test dose is not routinely required as single, optimal doses of intranasal or buccal midazolam generally have a low risk of respiratory depression. In certain circumstances, however, a test dose may be considered in patients with:

- Previous history of respiratory depression with a benzodiazepine
- Previous adverse reaction to a benzodiazepine
- High risk for respiratory compromise as determined by the prescribing physician
- Compromised respiratory function

For more information, please see the newly approved BCCH benzodiazepine seizure rescue and test dose guidelines.

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What's the "Right Dose" of Amoxicillin for Community Acquired Pneumonia?

Jennifer Kendrick, BScPharm, ACPR, PharmD
Reviewed by Katie Haubrich, BScPharm, PharmD

Amoxicillin is the antibiotic of choice for non-severe community acquired pneumonia (CAP) according to local and international guidelines. Both the Infectious Diseases Society of America and the Canadian Pediatric Society (CPS) recommend high-dose amoxicillin (90 mg/kg/day and 75-90 mg/kg/day respectively) in their 2011 guidelines.[1,2] In 2015, the CPS updated its guideline and the recommended amoxicillin dose was revised to 45-90 mg/kg/day.[3] In a recent commentary, Rajapakse et al. (2016) reviewed their Streptococcus pneumoniae susceptibility rates in Calgary, Alberta and suggest that routine high-dose amoxicillin is unnecessary in their region.[4] They further suggest that other Canadian communities review their susceptibility rates and reconsider routine high-dose amoxicillin for CAP.

What are our resistance patterns like?
The 3-year cumulative antibiogram at BC Children's Hospital published in 2013 reported that 78% of S pneumoniae isolates were susceptible to penicillin, based on meningitic breakpoints (susceptible if MIC ≤ 0.06 mcg/mL). The next antibiogram is expected to report penicillin breakpoints for non-meningitic infections (susceptible if MIC ≤ 2 mcg/mL). A preliminary look at the 2015 S. pneumoniae isolates found that all 56 isolates were susceptible to penicillin for non-meningitic infections, with 86% of isolates susceptible for meningitic infections. Though these isolates indicate low S.pneumoniae resistance locally, there are other considerations when recommending amoxicillin dosing for CAP.

What is the clinical evidence for amoxicillin dosing in CAP?
Hazir et al. (2007) compared amoxicillin 90 mg/kg/day vs. 45 mg/kg/day, both divided three times (TID) a day, in children age 2–59 months with non-severe CAP.[5] In screening patients for inclusion, the investigators used the World Health Organization definition of pneumonia, which is based on respiratory rate. Approximately 40% of the 876 children enrolled had wheezing on exam and received salbutamol nebulized. Amoxicillin therapy was stopped at day 3 in more than 95% of children. Treatment failure, defined as worsening pneumonia or danger signs, occurred in 7 (1.6%) patients in each group. Although the authors concluded that non-severe pneumonia can be treated effectively and safely with a 3-day course of standard dose amoxicillin, some limitations make this make it difficult to apply the results to our population in Canada. Since only 6.8% of children included had radiographic evidence of pneumonia and a number of children were treated for wheezing, the study was likely underpowered to detect a difference in any outcomes.

There are no comparative effectiveness trials in North America for high vs. standard-dose amoxicillin for CAP. Trials comparing amoxicillin to other oral antibiotics for CAP used a variety of dosage regimens from 25-90 mg/kg/day divided twice daily (BID) to three times daily (TID).[6]

In the absence of clinical evidence, is there any pharmacokinetic data to guide amoxicillin dosing in CAP?
Fonseca et al. (2003) compared amoxicillin 45 mg/kg/day divided TID to 50 mg/kg/day divided BID in 62 children age 3–39 months with non-severe pneumonia.[7] They drew serum concentrations immediately pre-dose and at 2, 5, and 8 hours post-dose on days 1 and 3. The mean (SD) percentage of the dose interval where amoxicillin was above the MIC of 2 mcg/mL was 62.2 (22.4)% and 50.7 (20.4)% in the TID and BID groups respectively. However, there was variability in the group and 25.8% and 58.1% of children in the TID and BID groups had serum concentrations below the MIC of 2 mcg/mL for at least half of the dosing interval. Time above MIC of 40% or more of the dosing interval is commonly considered a predictor of successful clinical outcomes for beta lactam antibiotics such as amoxicillin.[8]

Additional consideration must be given to the antibiotic concentration achieved at the site of the infection. There is very little information about amoxicillin penetration into the lung. In a small study of 15 healthy adults, median lung epithelial lining fluid concentrations were only 13% of plasma concentrations at 1–2 hrs after the dose.[9] Unfortunately, we do not have information about amoxicillin exposure over the dosing interval in the lung. Using mathematical modelling, Bradley et al. (2010) predict that for children with susceptible S pneumoniae CAP given amoxicillin 90 mg/kg/day divided TID, there is a 90% chance that the time above MIC would be above 40% at the site of infection and a 95% chance of cure.[10] If the amoxicillin dose was divided BID instead, there would only be a 65% chance of reaching the MIC target.[10]

What are the pharmacists recommending?
Although low S. pneumoniae resistance rates at BCCH would suggest that standard-dose amoxicillin may be adequate for the treatment of CAP, the paucity of clinical evidence, variable amoxicillin pharmacokinetics, and limited penetration to the site of infection suggest otherwise. Therefore, the pharmacists at BCCH continue to recommend high-dose amoxicillin (80-90 mg/kg/day) divided TID, with a usual maximum dose of 1000 mg per dose.

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Ivacaftor/lumacaftor (Orkambi®): A New CFTR Modulator

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Background

Cystic fibrosis (CF) is a fatal genetic disease characterized by a defective or deficient chloride protein channel called cystic fibrosis transmembrane conductance regulator (CFTR).[1,2] There is currently no cure.[1] However, in the past several decades, advances in medicine have improved the median age of survival up to 50.9 years.[1,2] Phe508del is the most prevalent CFTR mutation with approximately 45% of the CF population homozygous for the mutation, and approximately 90% heterozygous.[3-5] Past attempts to target the Phe508del mutation with lumacaftor monotherapy, have not proven to be successful.[6] Combination use of CFTR modulators ivacaftor and lumacaftor (Orkambi®) has recently been approved by Health Canada for use in CF patients who are homozygous for the Phe508del mutation.[7]

Proposed Mechanism of Action[4,5]

Lumacaftor is a CFTR corrector that acts by increasing the processing and folding of Phe508del CFTR, thereby increasing the amount of CFTR at the cell membrane. Ivacaftor is a CFTR potentiator that acts by improving the opening ability of defective CFTR channels at the cell membrane. Together, ivacaftor and lumacaftor increases the amount of functioning CFTR at the cell membrane.

Clinical Evidence

Boyle, et al. conducted a phase II, prospective, double-blind, placebo controlled multicenter randomized trial comparing ivacaftor 250 mg every 12 hours plus incrementally increasing doses of lumacaftor to each other and to placebo in a total of 159 patients with homozygous phe508del CFTR and 27 patients heterozygotes.[4] These CF patients included were at least 18 years old and had a FEV_1 of > 40%. In patients homozygous for Phe508del CFTR, the only dose shown to be statistically significant for absolute change in percent predicted FEV_1 compared with placebo over 56 days was the lumacaftor 600 mg once daily and ivacaftor 250 mg every 12 hours dosing regimen, with a 5.6% ($p = 0.013$) absolute difference. Other dosing regimens with higher or lower doses of lumacaftor were not statistically significant. Interestingly enough, only the lower doses of lumacaftor, 200 mg once daily and 400 mg once daily, showed a statistically significant benefit over placebo in the Cystic Fibrosis Questionnaire – Revised (CFQR) at day 56. No differences compared to placebo were seen in the CF patients with heterozygous phe508del CFTR for any clinically relevant outcome. Statistically significant decreases in mean sweat chloride concentration were reported to be -12.6 mmol/L in only the dosing group receiving lumacaftor 200 mg once daily and ivacaftor 250 mg every 12 hours regimen, compared to placebo. Significant limitations to the study include the lack of clinical outcomes, heavy involvement of Vertex Pharmaceuticals, small sample size, only including adult patients, and excluding complex patients with significant comorbidities from the study.

Initial success with combination ivacaftor and lumacaftor seen in the study by Boyle, et al. lead to the two largest CF phase III trials to date. These were nearly identical, with pooled results being conducted. The TRAFFIC and TRANSPORT trials by Wainwright, et al. were prospective, double-blind, placebo controlled, multicenter randomized trials.[5] Included patients (N = 1108) were clinically stable, at least 12 years old, homozygous for phe508del CFTR, FEV_1 % predicted of 40-90%. Two dosage regimens were compared against each other and placebo, ivacaftor 250 mg twice daily plus lumacaftor 600 mg once daily or ivacaftor 250 mg twice daily plus lumacaftor 400 mg twice daily. The difference between lumacaftor-ivacaftor and placebo in the primary outcome, mean absolute change in the FEV_1 % predicted from baseline to week 24, was statistically significant and comparable for both dosages, at 2.6% ($p < 0.001$) and 4.0% ($p < 0.001$), respectively. Results for secondary outcomes can be found in Table 1. Of particular note both doses of lumacaftor had significantly reduced pulmonary exacerbations. *(continued on page 5…)*

Table 1. Secondary Outcome Measures In Lumacaftor Randomized Controlled Trials[5]

Compared to placebo	Lumacaftor 600 mg OD (95% CI)	Lumacaftor 400 mg BID (95% CI)
Absolute change in predicted % FEV1	3.3 (2.3 - 4.3)	2.8 (1.8 - 3.8)
Relative change in predicted % FEV1	5.6 (3.8 – 7.3)	4.8 (3.0 – 6.6)
Absolute change in BMI	0.28 (0.15 – 0.41)	0.24 (0.11 – 0.37)
Absolute change in CFQ-R	3.1 (0.8 – 5.3)	*2.2 (0.0 – 4.5)*
OR number of patients relative ≥ 5% FEV1	2.9 (2.1 – 4.0)	2.2 (1.6 – 3.1)
Pulmonary exacerbations rate per 48 weeks – Placebo = 1.07	0.80	0.70
Pulmonary exacerbations rate ratio	0.70 (0.56 – 0.87)	0.61 (0.49 – 0.76)

Legend: BMI = Body Mass Index; 95% CI = 95th Percentile Confidence Interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised Score; FEV1 = Forced Expiratory Volume (1 second); OR = Odds Ratio; Values in Green: statistically significant compared to placebo

Ivacaftor/Lumacaftor continued from page 4...

Adverse Drug Reactions

Most common, significant adverse drug reactions compared to placebo:[4,5]

- Dyspnea (14.9%)
- Diarrhea (12.2%)
- Nausea (12.5%)
- Chest tightness (10.8%)
- Upper respiratory tract infection (10.0%)

Rare, potentially severe adverse events:[8]

- Increased blood pressure, decreased heart rate
- Worsening of liver function, including hepatic encephalopathy
- Elevated transaminases
- Cataracts

Orkambi® Dosing and Administration[8]

Adults and pediatric patients ≥ 12 years old: Two tablets (each tablet containing lumacaftor 200 mg/ivacaftor 125 mg) taken orally every 12 hours with fat containing food.

Drug Interactions[8]

Ivacaftor is a major CYP3A substrate, weak inhibitor of CYP3A4, and inhibitor of CYP2C9. Lumacaftor is not extensively metabolized prior to elimination, and is a major inducer of CYP3A4. The net effect expected in the combination of both ivacaftor and lumacaftor is CYP3A4 induction. For recommended dosage adjustments, please refer to the product monograph.

Orkambi® is currently, the only therapy approved for CF patients aged 12 years and above who are homozygous for the phe508del mutation in the CFTR gene. Although Orkambi® reached statistical significance for several outcomes in adolescent and older CF patients, the clinical benefit and extremely high costs of combination therapy (estimated cost $249,000 per year) makes its routine use in all CF patients questionable. Further studies are required to create a better understanding for Orkambi® use before use in all CF patients homozygous for Phe508del CFTR can be recommended.

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Pharmacy Awareness Month 2016

Katie Haubrich, BScPharm, PharmD

Happy Pharmacy Awareness Month 2016!

The Children's and Women's Hospital Pharmacy Department celebrated a very successful "Pharmacy Awareness Month" in March, and hosted a number of on-site activities to help bring awareness to the pharmacy profession. You may have noticed our staff wearing matching, bright blue t-shirts which identified us as "***Team Pharmacy***," and hopefully you stopped by our booth in the cafeteria during lunchtime from March 7th-11th. Our display booth highlighted the role of the pharmacy department in drug distribution, ambulatory care, medication safety, clinical pharmacy activities, teaching and research.

Our booth also had fun activities for staff and visitors to participate in, including a "Name the Medication" interactive game and "Fun Facts" quiz with a draw for multiple prizes, including tickets to see a Vancouver Whitecaps soccer game. We also held 2 tours of our pharmacy department for hospital staff (thanks to everyone who participated!) to showcase the activities that occur on a daily basis in order to safely provide medications to all patients admitted to Children's and Women's Hospital. Our department staff also raised awareness of the pharmacy profession on social media; our tweets were compiled using Storify and can be viewed via this link. Thanks to everyone who helped make our "Pharmacy Awareness Month" at C&W a huge success!

Oral Corticosteroids for Acute Asthma Management at BCCH

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The acute management of moderate and severe asthma in the Emergency Department (ED) at BCCH has changed from giving dexamethasone 0.3 mg/kg/dose (max 10 mg/dose) orally once daily for 3 days to 0.6 mg/kg/dose (max 16 mg/dose) orally for 1 dose. For patients who are admitted to hospital, the options are to provide a second dose of dexamethasone 0.6 mg/kg/dose orally 24 hours later or to switch to prednisolone or prednisone 1 mg/kg/dose orally once daily for 5 days.

Dexamethasone has been the oral corticosteroid of choice in the ED for many years due to improved palatability and less vomiting compared to prednisone; however, the optimal dexamethasone dose has not been clear. The dexamethasone dose was initially 0.2 mg/kg/dose orally once daily for 3 days, which was extrapolated from an approximate dose of 1 mg/kg/dose of prednisone. Pharmacologically, dexamethasone given orally may have some benefits over prednisone. It has a therapeutic duration of activity of 36-54 hours compared to prednisone being closer to 12-36 hours. This extension allows for dexamethasone to be given as a one-time dose which would be similar in activity to a 3 day prednisone course.[1,2] Bioavailability of dexamethasone orally has been reported to be between 70-80% and it usually considered to be more palatable than prednisone.[3,4]

A number of ED studies in recent years have been published comparing dexamethasone to prednisone, with a meta-analysis in 2014 showing no difference in ED length of stay, asthma treatments used, and relapse, but less vomiting with dexamethasone.[5] Intramuscular dexamethasone 0.3 to 1.7 mg/kg/dose for one dose has been compared to prednisone or prednisolone 1 to 2 mg/kg/dose for 3 to 5 days.[5] The oral dexamethasone doses that have been studied range from 0.3 to 0.6 mg/kg/dose for one or 2 days (Table 1).[5] The new protocol is in line with a study completed at BCCH by Altamimi et al. (2006) where they compared dexamethasone 0.6 mg/kg/dose orally once to prednisone 1 mg/kg/dose orally daily for 5 days in 134 pediatric patients in a randomized, double-blind, placebo design.[6] Dexamethasone was found to be non-inferior to prednisone with respect to patient self-assessment score return to baseline, severity of asthma at discharge or asthma medication therapy. Mean length of stay was 0.8 hours shorter in the dexamethasone group while return the ED was seen in 6.6% of the dexamethasone group versus 1.8% of the prednisone group, both of which were non-significant. Return visits requiring hospitalization was higher in the dexamethasone group (4 of 67) versus prednisone (1 of 67).[6] A limitation to this study was an inability to enroll the required sample size for non-inferiority. Two other studies compared dexamethasone 0.6 mg/kg/dose orally once daily for 2 days to 5 days of prednisone or prednisolone, one of which was large and adequately powered for the primary outcome of relapse at 10 days.[7,8] Qureshi et al. (2001) found no difference in relapse, hospitalization rate, and symptom persistence; however, there was more vomiting, non-adherence, and missed school in the prednisone/prednisolone group.[7] The most recent study by Cronin et al. (2015) compared dexamethasone 0.3 mg/kg/dose orally once to prednisone 1 mg/kg/dose daily for 3 days in an open-label randomized controlled trial.[9] While there was no difference in their primary outcome of PRAM score at day 4, more children in the dexamethasone group compared to the prednisone group received further systemic steroids within 14 days (13.1 vs. 4.2%; $p<0.05$). Of patients admitted to hospital, further systemic steroid was administered to 50% in the dexamethasone group and 18.9% in the prednisone group.

ED prescribers and pharmacists considered the available evidence and debated which dosing to adopt. While the dose that was studied in the largest number of patients was 0.6 mg/kg/dose once daily for 2 days (total dose 1.2 mg/kg), the group decided against increasing the total dexamethasone from the previous and current practice (total dose 0.6 to 0.9 mg/kg). The group favoured a single-dose regimen, which removes any issues with adherence for children well enough to be discharged from the ED.

The change has sparked a revision of the inpatient management orders as well. An admitted patient being treated for acute asthma will receive 1 subsequent oral dose of 0.6 mg/kg/dose (Max 16 mg/dose) approximately 24 hours after the dose given in the ED. The literature supporting this was the ED studies by Greenwood et al. (2008) and Qureshi et al. (2001), as well as a retrospective cohort study published in 2015 looking at children with non-intensive care admissions for asthma in multiple hospitals.[7,8,10] Length of stay was significantly shorter in the dexamethasone group as 67% had only a 1 day stay versus 60% in the prednisone group.[10] The nature of this database did not allow for doses to be analyzed. Overall, it supports the option of using dexamethasone for in-patients while dosing can be extrapolated from ED trials.[5-9] Prednisone/prednisolone remains an option on the in-patient order set. The new approved order sets for **Pediatric ED asthma** and **Pediatric IP Asthma Admission** can be found on Medworxx (BCCH intranet access required to view). *(continued on page 8…)*

Table 1. Emergency Department Trials Comparing Oral Dexamethasone to Prednisone/Prednisolone

Trial	*Intervention*	*Comparator*	*Patients*	*Outcomes*
Altamimi (2006) DB RCT N=134	Dexamethasone 0.6 mg/kg/dose PO x 1 (Max 18 mg/dose)	Prednisone/Prednisolone 1 mg/kg/dose PO BID x 5 days (Max 30 mg/dose)	Age 2-16 yrs (median 5 yrs), history asthma, acute exacerbation (median PIS 6)	**1°:** median days for PSAS return to baseline **2°:** PEFR, PIS at ED discharge, time to ED discharge, hospitalization, salbutamol treatments, return to ED, PIS on day 5
Greenberg (2008) DB RCT N=89	Dexamethasone 0.6 mg/kg/dose PO daily x 2 days (Max 16 mg/dose)	Prednisone 2 mg/kg/dose PO once (Max 80 mg/dose), then 1 mg/kg/dose PO BID x 4 days (Max 30 mg/dose)	Age 2-18 yrs (median 6.8 yrs), history asthma, acute exacerbation (median PAS 7)	**1°:** relapse at 10 days **2°:** emesis
Qureshi (2001) OL RCT N=533	Dexamethasone 0.6 mg/kg/dose PO daily x 2 days (Max 16 mg/dose)	Prednisone/Prednisolone 2 mg/kg/dose PO once (Max 60 mg/dose), then 1 mg/kg/dose PO daily x 4 days (Max 60 mg/dose)	Age 2-18 yrs (mean 6 yrs), history asthma, acute exacerbation (22% mild, 56% moderate, 22% severe)	**1°:** relapse at 10 days **2°:** hospitalization, emesis, adherence, symptom persistence, missed school/work
Conin (2015) OL RCT N=226	Dexamethasone 0.3 mg/kg/dose PO x 1 (Max 11 mg/dose)	Prednisolone 1 mg/kg/dose PO daily x 3 days (Max 40 mg/dose)	Age 2-12 yrs (mean 6 yrs), history asthma, acute exacerbation (mean PRAM 4)	**1°:** mean PRAM at day 4 **2°:** PRAM at ED discharge, ED LOS, hospital admission, unscheduled healthcare provider visits for asthma, further steroids

Legend: DB = double blind; ED = emergency department; OL = open-label; LOS = length of stay; PAS = pediatric asthma score; PIS = pulmonary index score; PRAM = pediatric respiratory assessment measure; PSAS = patient self-assessment sheet; RCT = randomized-controlled trial

Intravenous Procedural Sedation and Analgesia on the Ward: Policy Update 2016

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Procedural sedation may be administered in order to reduce anxiety and pain associated with diagnostic and therapeutic procedures. For children admitted to non-critical care areas, administration of procedural sedative and analgesic agents has previously been restricted to oral and intranasal routes. In some patients, single doses of oral or intranasal sedation agents may be insufficient to provide the required level of sedation. Providing procedural sedation may also become challenging in patients who do not tolerate administration of either oral or intranasal medications. In response to these concerns, new hospital guidelines (as of February 2016) have been introduced to allow for the use of select intravenous (IV) agents for procedural sedation on the ward. In order to perform IV procedural sedation, residents and physicians practicing outside of critical care areas must meet a number of required competencies, including maintaining PALS certification, completing a mandatory training course and demonstrating their knowledge in a written and practical exam. *(See updated policy on Medworxx)*

What is Procedural Sedation and Analgesia?

Procedural sedation is an intentional, drug-induced decrease in the level of consciousness, which is achieved through the administration of sedative or dissociative agents, with or without analgesic agents.[1] This induces a controlled state which allows patients to tolerate unpleasant procedures while maintaining cardiorespiratory function, improving both the patient and health care provider experience.

What are indications for procedural sedation and analgesia in children?

Procedural sedation alone may be used prior to diagnostic imaging such as MRI or CT. Procedural sedation with analgesia may be used for painful diagnostic procedures such as lumbar punctures or sexual assault exams, and before painful therapeutic procedures such as laceration repairs, foreign body removal, fracture or dislocation repairs and with burn dressings. Medications for procedural sedation and analgesia may be administered orally (PO), intranasally (IN) or intravenously (IV).

What are contraindications against the use of procedural sedation and analgesia in children?

Procedural sedation should not be performed in children with pre-existing risk factors for complications during sedation. This includes patients with difficult airway syndromes such as Pierre-Robin syndrome or Trisomy 21, where intubation may be challenging if required, and patients with gastroesophageal reflux disease (GERD) or delayed gastric emptying, who may have an increased risk of aspiration while sedated.[1,2]

Children under the age of 6 months should not undergo procedural sedation without the guidance of an experienced anaesthetist. Young infants have lower absolute lung volumes and higher oxygen consumption, putting them at increased risk of rapid hypoxemia with respiratory depression.[2] Considering this risk, the use of procedural sedatives and analgesics is restricted on the ward to children greater than 6 months of age for PO and IN sedation, and to greater than 12 months of age for IV sedation.

Pharmacologic Options for IV Sedation on the Ward:

For patients between 12 months and 9 years of age, ketamine has been recommended as the suggested IV agent for procedural sedation on the ward. Due to the increased risk of emergence phenomenon in older children, midazolam +/- fentanyl have been suggested for children greater than 9 years of age. The complete order set may be viewed via Medworxx. See Table 1 for a review of the dosing, pharmacokinetics and unique characteristics of these agents.

Patient Monitoring during IV Procedural Sedation:

Guidelines for monitoring pediatric patients undergoing procedural sedation have been published by the American Academy of Pediatrics (AAP).[3] Largely based on the AAP guidelines, our in-hospital monitoring guidelines for IV sedation mandate continuous heart rate, respiratory rate and oxygen saturation monitoring while the child is sedated. Vital signs and arousal score must be documented at regular intervals while the patient receives the sedation and throughout the procedure. Monitoring for and documentation of any adverse effects associated with the sedation and analgesic medications is required. Monitoring may only be discontinued once the patient returns to their pre-sedation level of consciousness. Monitoring parameters are outlined in detail in the posted policy on Medworxx. (BCCH Intranet access required) *(continued on page 8…)*

Table 1: Agents for IV Procedural Sedation and Analgesia per Hospital Guidelines

IV Medication	Class	Suggested Age Group for Use	Procedural Dose	Administration	Onset/ Duration	Advantages	Disadvantages
Ketamine (Ketalar®)	General dissociative anaesthetic	12 months to ≤9 years of age	0.5-1 mg/kg/dose (Maximum 75 mg/dose)	Administer IV undiluted over more than 1 minute	Onset: 1 minute Duration: 10-15 minutes	• provides good analgesia, amnesia and anxiolysis • not associated with respiratory depression	• high incidence of minor side effects such as nausea, vomiting, hallucination • risk of emergence phenomenon (particularly in older children)
Midazolam (Versed®)	Benzo-diazepine	>9 years of age	0.1 mg/kg/dose (Maximum 4 mg/dose)	Administer IV undiluted over 2-3 minutes	Onset: 2-5 minutes Duration: 10-20 minutes	• provides amnesia & anxiolysis • no pain on IV injection • rapid onset, short duration of action • reversible with flumazenil	• NO analgesia provided • risk of respiratory depression (particularly when used in combination with other agents)
Fentanyl (Sublimaze®)	Opioid	>9 years of age	1 mcg/kg/dose (Maximum 50 mcg/dose)	Administer IV undiluted over 1-3 minutes (or may dilute to a more convenient volume)	Onset: 1 minute Duration: 30-45 minutes	• rapid onset of action • provides excellent analgesia • reversible with naloxone	• provides no amnesia and minimal sedation • high risk of respiratory depression particularly in infants <3 months old

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Research, Education & Awards
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Research

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Awards

Erica HZ Wang, Jennifer L Bolt, **Diane Decarie**, William Semchuk, and **Mary HH Ensom** received the CSHP – BC Branch Publication Award (category: Original Research Article) at the CSHP – BC Branch Annual General Meeting in Vancouver on Nov 21, 2015: "Stability of Dabigatran Etexilate in Manufacturer's Blister Pack, Unit-Dose Packaging, and Community Pharmacy Blister Pack. Can J Hosp Pharm 2015; 68: 16-21." Full Text

Kyle Collins, Mary Ensom, Dan Rainkie, and **Roxane Carr** received the Canadian Society of Hospital Pharmacists Pharmacotherapy Best Practice Award for the project "Assessment of Pediatric Vancomycin Empiric Dosing" at the CSHP Professional Practice Conference in February 2016 in Toronto.

Pharmacy Informer Editorial Board