Cleveland Clinic
Clinical Rx Forum

From the Department of Pharmacy
Drug Information Service
(216) 444-6456, option #1

Comprehensive information about medications, biologics, nutrients, and drug therapy

Formulary Information

Cleveland Clinic
Clinical Rx Forum
From the Department of Pharmacy

January/February Issue **2014, Volume 2, Issue 1**

Intranasal Midazolam for the Treatment of Acute Seizures

By: Britany Walls, Pharm.D.

Introduction: Acute seizures in pediatric patients require immediate medical attention and often necessitate drug therapy for seizure control. Prompt control of seizures is important, because prolonged duration of seizures and recurrent seizures increase morbidity and mortality.[1,2] Intravenous (IV) or rectally administered benzodiazepines are first-line therapy for acute seizures with diazepam being one of the most commonly utilized drugs from this class.[3] However diazepam is not a good therapeutic option for intranasal use since it has a relatively short half-life and tends to accumulate with multiple doses leading to brain stem depression, bradypnea, and in rare cases, apnea. Compared to diazepam, midazolam has a slightly longer duration of action and improved safety profile. Other attributes which make midazolam a preferred agent for intranasal administration compared to diazepam are its greater water solubility and lack of propylene glycol and alcohol in its formulation.[2,4,5]

Absorption and Drug Delivery: In order to provide timely cessation of seizures, the method of drug administration must allow for rapid absorption and distribution. Intranasal administration of midazolam makes use of the extensively vascular mucosal tissue of the nasal cavity in a similar manner as diazepam gel (Diastat® AccuDial™) which utilizes the rectal mucosal tissue as a site of absorption.[1,2] An advantage of the intranasal versus the rectal route is direct absorption into the cerebrospinal fluid from the nasal mucosa, thus avoiding first pass metabolism.[6] One disadvantage is that the presence of excess mucous in the nasal passages could decrease drug absorption.[7] Delivery of the drug to the nasal tissue is accomplished

(Continued on page 2)

The Evolving Role of Electronic Cigarettes

By: Jean Bon, Pharm.D. Candidate

Introduction: Despite numerous efforts throughout the years to decrease cigarette use, smoking remains a significant cause of morbidity and mortality in the United States.[1] In 2003, a Chinese pharmacist developed a product that is at the center of the latest controversy in smoking cessation and tobacco harm reduction, the electronic (e)-cigarette.[2] As public health officials debate the utility of e-cigarettes, healthcare providers wonder what to tell patients regarding this new product that is gaining popularity but lacking substantive safety and efficacy data .[1]

What are E-cigarettes? Electronic cigarettes are designed to look like traditional cigarettes, which are referred to as "burn cigarettes".[3] These devices consist of small tubes containing a battery and a microchip that have a red light-emitting diode (LED) on the end to simulate a burning cigarette. A cartridge attached to the tube contains a liquid and a vaporization chamber; this produces an aerosol that the user inhales, a process called "vaping".[4] Included in the e-liquid are propylene glycol, glycerol, and flavorings.[3] This liquid may or may not contain nicotine. When

(Continued on page 3)

(Continued from page 1)

with the use of a nasal dropper or a mucosal atomization device (MAD) that attaches to the end of a syringe. Midazolam injection is drawn up into a syringe and then expelled through the MAD as a fine mist that covers the nasal mucosa.[8]

Efficacy: Time to seizure cessation is the most important primary measure of efficacy for acute seizures. Multiple randomized trials of intranasal midazolam have shown a time to seizure cessation of 10 minutes or less.[2,6,7,9,10] Although data are limited, intranasal midazolam has been shown to be at least as efficacious as rectal diazepam.[4,10,11] When compared to IV benzodiazepine use in the emergency department (ED), intranasal midazolam was able to be administered more quickly which resulted in faster seizure cessation from the time of admission to the ED to treatment. A clinical trial demonstrated that intranasal midazolam achieved seizure control faster than IV diazepam when the time needed to establish an IV line was taken into account (3.16 minutes versus 6.24 minutes, respectively).[2]

Safety: Common adverse effects of benzodiazepines regardless of the route of administration include respiratory depression, excess drowsiness, and bradycardia.[1,2] These adverse effects have also been seen with intranasal midazolam as well as tachypnea and tachycardia.[6,10] Intranasal midazolam also causes nasal irritation due to the solution having a low pH.[1] Overall, intranasal midazolam appears to be as safe as IV or rectal diazepam in treating acute seizures.

Dosing and Administration: The current recommended dosing of intranasal midazolam within Cleveland Clinic Children's is 0.2-0.3 mg/kg for infants ≥6 months, children, and adolescents. The maximum intranasal dose is 0.5 mg/kg; not to exceed 10 mg per dose.[12] Midazolam 5 mg/mL, the more concentrated form of the injection, is drawn up into an injectable syringe and a MAD is attached. Half of the dose is administered to each nostril; the maximum volume is 1 mL (i.e., dose=5 mg) per nare.

Conclusion: Intranasal midazolam offers an alternative method of quickly controlling seizures in pediatric patients. The intranasal route of administration has several advantages including a richly vascular surface for drug absorption, direct absorption of drug into the cerebrospinal fluid, and a relatively quick and easy method of administration. The use of intranasal midazolam may be beneficial in many settings such as the ED, in the hospital for patients without IV access, and at home as rescue therapy.

References

1. Humphries LK, Eiland LS. Treatment of acute seizures: Is intranasal midazolam a viable option? J Pediatr Pharmacol Ther 2013;18(2):79-87.
2. Javadzadeh M, Sheibai K, Hashemieh M, Saneifard H. Intranasal midazolam compared with intravenous diazepam in patients suffering from acute seizures: a randomized clinical trial. Iran J Pediatr 2012;22(1):1-8.
3. Sofou K, Kristjansdottir R, Papachatzakis NE, Ahmadzadeh A, Uvebrant P. Management of prolonged seizures and status epilepticus in childhood: a systematic review. J Child Neurol 2009;24:918-26.
4. Midazolam hydrochloride injection, solution [package insert]. Schamburg, Il: APP Pharmaceuticals LLC; March 2012.
5. Diazepam injection, solution [package insert]. Lake Forest, Il: Hospira, Inc; February 2014.
6. Fisgin T, Gurer Y, Tezic T, Senbil N, Zorlu P, Okuyaz C, et al. Effects of intranasal midazolam and rectal diazepam on acute convulsions in children: a prospective randomized study. J Child Neuro 2002;17:123-6.
7. Mahmoudian T, Zadeh MM. Comparison of intranasal midazoam with intravenous diazepam for treating acute seizures in children. Epilepsy Behav 2004;5:252-5.
8. LMA MAD Nasal™. Available from: http://www.lmana.com/pwpcontrol.php?pwpID=6359 Accessed: October 10, 2013.
9. Thakker A, Shanbag P. A randomized controlled trial of intranasal midazolam versus intravenous diazepam for acute childhood seizures. J Neurol 2013;206:470-4.
10. Bhattacharyya M, Kalra V, Gulati S. Intranasal midazolam versus rectal diazepam in acute childhood seizures. Pediatr Neurol 2006;34:355-9.
11. Holsti M, Dudley N, Schunk J, Adelgais K, Greenberg R, Olsen C, et a. Intranasal midazolam versus rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. Arch Pediatr Adolesc Med 2010;164(8):747-53.
12. Lexi-Comp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp.: 2013: Accessed: October 14, 2013.

(Continued from page 1)
nicotine is added, nicotine concentrations vary between 6-36 mg/mL.[3] An average burn cigarette contains approximately 10 to 15 mg of nicotine; it is estimated that 1 to 2 mg of nicotine is systemically absorbed after smoking one cigarette.[5] Different brands of e-cigarettes labeled with the same nicotine concentration can contain varying amounts of nicotine which makes comparisons with burn cigarettes in which the nicotine content is expressed in milligrams per cigarette difficult.[3]

Safety of E-cigarette Vapors: The aerosol produced by e-cigarettes is similar to the artificial smoke used to create special effects in theaters.[3] Both the aerosol and the smoke primarily contain propylene glycol. Two studies examined the effects of the artificial smoke on actors and found mild effects such as airway irritation with significant, prolonged exposure, especially in asthmatics. A third study found mild but persistent pulmonary function changes in theater staff members who were chronically exposed to propylene glycol mist. Despite these findings, the Food and Drug Administration (FDA) has classified artificial smoke generators as "generally considered safe".

Potential Therapeutic Roles for E-cigarettes: There are at least two potential applications for e-cigarettes.[6,7] E-cigarettes can be used as a nicotine delivery device to aid in smoking cessation, or they can be used as a replacement for burn cigarettes in people with no desire to stop smoking. When used as a nicotine delivery device for smoking cessation, tapering amounts of nicotine are added to the cartridge to wean the user from nicotine over time. The primary outcome of a recently published study by Bullen and colleagues was to compare the efficacy of nicotine e-cigarettes with nicotine patches in achieving smoking cessation at 6 months.[6] Adult smokers who wanted to quit were randomized to 16 mg nicotine e-cigarettes, 21 mg nicotine patches, or placebo e-cigarettes without nicotine. Patients in the e-cigarette group took twice as long to relapse as the nicotine patch group (35 days versus 14 days;$p<0.001$). Additionally, mean burn cigarette consumption was significantly lower in the e-cigarette group compared with the nicotine patch group (57% versus 41%;$p=0.002$). Adverse events were minor and were similar between the groups. Because relatively small numbers of patients achieved smoking cessation at 6 months, the authors were unable to detect a clinically significant difference in efficacy between nicotine patches and e-cigarettes.[8] The more controversial role for e-cigarettes is in tobacco harm reduction. It has been shown that the harmful consequences of burn cigarette smoking are caused by tobacco combustion products, not nicotine.[1] If e-cigarettes provide a nicotine delivery device that is as attractive to people as burn cigarettes without exposing them to the toxins and carcinogens in tobacco smoke, the use of e-cigarettes instead of burn cigarettes could have major public health benefits. Polosa and colleagues conducted a study which examined the long-term efficacy and safety of e-cigarettes in adult smokers who were not interested in quitting.[7] After studying 40 participants in a "realistic setting" that allowed them to use e-cigarettes as needed, the investigators were able to conclude that e-cigarettes significantly decreased burn cigarette consumption by ≥50% at 24 months. Common adverse events associated with e-cigarette use were mouth/throat irritation and dry cough. A summation of these e-cigarettes studies is included in Table 1.

Effects on Cardiac and Lung Function: There is considerable debate surrounding claims that e-cigarettes have no health-related consequences. It was announced at the European Society of Cardiology 2012 Congress that e-cigarettes do not adversely affect cardiac function after a small study concluded that e-cigarettes had no acute adverse effects on left ventricular function, blood pressure, and heart rate.[2] However, CHEST published the results of a study involving healthy individuals who smoked e-cigarettes which concluded that 5 minutes of vaping can have detrimental effects on lung function including increases in airway resistance and oxidative stress.[9]

Cleveland Clinic Policy Concerning E-cigarettes: The Cleveland Clinic's non-smoking policy has recently been expanded to include a ban on e-cigarettes.[10] Individuals may not use e-cigarettes on any Cleveland Clinic owned and leased properties, as well as on private property adjacent to Cleveland Clinic facilities. The rationale for this policy is that e-cigarettes may contain nicotine, an addictive and harmful substance, as well as potentially toxic and carcinogenic chemicals. Furthermore, these devices are not FDA-approved for smoking cessation, and there is currently no conclusive scientific evidence that they definitely promote long-term smoking cessation.

Conclusion: The debate surrounding e-cigarettes leads to significant challenges in regulation of these products. The FDA plans to regulate e-cigarettes as tobacco products.[11] More studies are needed to evaluate the safety of electronic cigarettes, as well as to determine their role in smoking cessation and tobacco reduction.

Table 1: Summary of Electronic Cigarette Studies[6,7]

Study	Primary Outcome	Number of Subjects	Results	P value
Bullen et al.	Continuous abstinence from cigarettes for 6 months	N = 657 n=289 e-cigarettes n=295 nicotine patches n=73 placebo	7.3% e-cigarette group versus 5.8% nicotine patch group Quit smoking at 6 month follow-up	p=0.46
Polosa et al.	≥ 50% reduction in burn cigarette per day at 24 months	N=40	16/40 (40%) Had sustained 50% reduction or smoking abstinence at 24-month follow-up	p<0.002

References

1. Polosa R, Rodu B, Capponnetto P, Magia M, Raciti C. A fresh look at tobacco harm reduction: the case for the electronic cigarette. Harm Reduction Journal 2013 10:19. Available from: http://www.harmreductionjournal.com/content/10/1/19. Accessed: October 31, 2013.
2. Nainnoglan, L. Electronic cigarettes don't adversely affect cardiac function. Medscape 2012 August 25. Available from: http://www.medscape.com/viewarticle/769793 Accessed: October 28, 2013.
3. Bertholon JF, Becquemin MH, Annesi-Maesano I, Dautzenberg B. Electronic cigarettes-a short review. Respiration, September 24, 2013. Available from: http://www.ncbinlm.nih.gov/pubmed/24080743 Accessed: October 29, 2013.
4. Kelland K, Hirschler B. No smoke, plenty of fire fuels e-cigarettes. Medscape 2013 June 13. Available from: http://www.medscape.com/viewarticle/805767 Accessed: November 25, 2013.
5. Benowitz NL, Henningfield JE. Reducing the nicotine content to make cigarettes less addictive. Tob Control 2013;22:i14-i17.
6. Bullen C, Howe C, Laugesen M McRobbie H, Paraq V, Williman J et al. Electronic cigarettes for smoking cessation: a randomized controlled trial. Lancet, September 7, 2013. Available from: http://www.thelancet.com/journals/lancet/article/PIISj0140-6736(13)61842-5/ Accessed: October 31, 2013.
7. Polosa R, Morjaria JB, Caponnetto P, Campagna D, Russo C, Alamo A et al. Effectiveness and tolerability of electronic cigarette in real life: a 24 month prospective observational study. Intern Emerg Med, July 20, 2013. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23873169 Accessed: October 31, 2013.
8. Hajek P. Electronic cigarettes for smoking cessation [Comment]. Lancet, September 7, 2013. Available from: http://www.thelancet.com/journals/article/PIIS0140-6736(13)61534-2/fulltext Accessed: October 31, 2013.
9. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly G, Bahrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. Chest 2012;141(6):1400-6.
10. Electronic cigarettes now prohibited under non-smoking policy. Available from: http://portals.ccf.org/strategyforum/StrategyMessaging/Tabid/12427/ArtMID/32255/ArticleID/3611/Electronic–cigarettes-now-prohibited-under-Non-Smoking-Policy.aspx Accessed: January 16, 2014.
11. Benowitz NL, Goniewicz ML. The regulatory challenge of electronic cigarettes [Viewpoint]. JAMA 2013;310(7): 685-6.

Formulary Update

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Alglucosidase alfa (Lumizyme®)	Enzyme	Enzyme replacement therapy for use in patients 8 years and older with late (non-infantile) onset Pompe disease	Restriction: Department of Hematology/Oncology for outpatient use and those patients enrolled in the Lumizyme ACE REMS program
Aripiprazole extended-release injectable suspension (Abilify®Maintena™)	Antipsychotic Agent	Treatment of schizophrenia	Restriction: Department of Psychiatry for continuation of therapy
Canagliflozin (Invokana®)	Antidiabetic Agent	Treatment of type 2 diabetes mellitus	No restrictions
Intravenous golimumab (Simponi® Aria™)	Antirheumatic Agent	Treatment of rheumatoid arthritis	Restriction: Department of Rheumatology for the treatment of rheumatoid arthritis for outpatient use only
Liposomal vincristine (Marqibo®)	Antineoplastic Agent	Treatment of Philadelphia chromosome-negative ALL	Restriction: Department of Hematology/Oncology for outpatient use at Main Campus only (due to prep-aration requirements)
Oral copper gluconate	Mineral	Copper deficiency	No restrictions

ALL=Acute Lymphobastic Leukemia REMS=Risk Evaluation and Mitigation Strategies

Formulary Update

Addition to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Intranasal midazolam (Versed®)	Benzodiazepine	Seizure Control	Dose is 0.2 to 0.3 mg/kg using the 5 mg/1 mL concentration of the injection drawn up into a syringe. A MAD is attached to the end of the syringe and then half (1/2) of the dose is administered into each nostril. The maximum dose is 5 mg (volume= 1 mL) per nostril (for a total maximum dose of 10 mg=2 mL).

MAD=mucosal atomization device

Restriction Change to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Intravenous acetaminophen (Ofirmev®)	Analgesic	Pain Control	Restriction change: Staff Pediatric ENT physicians may prescribe IV acetaminophen Pediatric ENT residents may not prescribe IV acetaminophen

ENT=Ears, Nose, and Throat IV=Intravenous

Formulary Update

Restriction Changes to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Albumin 5%	Colloid	Plasma Volume Expander	Restriction Change: Restricted to the ORs and ICUs Pediatrics and apheresis (M12) are still permitted to use albumin 5% New restrictions will help facilitate appropriate utilization
Hydroxyethyl starch solutions	Colloid	Plasma Volume Expander	Restriction Changes: Hextend® restricted to the ORs Hespan® restricted to plasmapheresis Restriction changes are due to patient safety reasons outlined in the FDA's warning letter: http:www.fda.gov/biologicsbloodvaccines/safetyavailability/ucm358271.htm
Insulin detemir (Levemir®)	Insulin	Treatment of Diabetes	All restrictions have been removed

FDA=Food and Drug Administration ICU=Intensive Care Unit OR=Operating Room