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Eluxadoline and Increased Risk of Pancreatitis

By: Brian Bohn, Pharm.D.

Introduction: Irritable bowel syndrome is a common gastrointestinal (GI) disorder that can be classified as either IBS with diarrhea (IBS-D), constipation (IBS-C), or a mixed bowel pattern (IBS-M).[1] The prevalence of IBS-D worldwide is estimated between 5% to 15% and occurs more commonly in women than in men.[2,3] Since therapeutic options for IBS-D (e.g., loperamide, rifaximin, alosetron) are somewhat limited, eluxadoline, a mixed mu and kappa opioid receptor agonist and delta opioid receptor antagonist which reduces GI motility, was evaluated as a potential treatment for this condition.[1,2] Eluxadoline (Viberzi®; Allergan) gained Food and Drug Administration (FDA) approval for the treatment of IBS-D in May 2015 based on evidence from two randomized controlled Phase III trials, IBS-3001 (a 52-week study) and IBS-3002 (a 26-week study); both studies compared the efficacy of two oral eluxadoline dosage regimens (75 mg twice daily and 100 mg twice daily) with placebo.[4] Results from those studies found that both dosage regimens were superior to placebo in achieving a composite response of ≥ 30% reduction from the average baseline score for worse abdominal pain and a stool consistency score < 5 on the same day for at least 50% of the study period. Although GI ailments (e.g., nausea, constipation, abdominal pain) were the most common side effects in those trials, pancreatitis occurred in five of the 1666 patients (two in the 75 mg group and three in the 100 mg group). Eluxadoline has been associated with an increased incidence of pancreatitis and sphincter of Oddi spasm via increased sphincter of Oddi wave frequency.[2] Therefore, it may be prudent to identify patients with IBS-D who have certain risk factors for pancreatitis such as the absence of a gallbladder or excessive alcohol consumption prior to

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Intravenous Sildenafil for Neonatal Pulmonary Hypertension

By: Erika May Pineda, Pharm.D.

Background: Persistent pulmonary hypertension of the newborn (PPHN) is a condition of increased pulmonary vascular resistance, right-to-left shunting, and severe hypoxemia.[1] It may be idiopathic or associated with a variety of neonatal pathologies (e.g., surfactant deficiency, respiratory distress syndrome).[2,3] The incidence of severe PPHN is 0.2% with a mortality rate between 5% to 10%, even in those treated with appropriate therapy.[2] The primary goal of PPHN treatment is selective pulmonary vasodilation.[4] Inhaled nitric oxide (iNO) is preferred as first-line therapy. However 40% of infants do not respond to iNO; this failure rate has led to a search for other agents to enhance pulmonary vasodilation, including sildenafil.[2] Sildenafil is currently available as oral and intravenous (IV) formulations.[5,6] In neonates, oral sildenafil improved oxygenation and respiratory status while reducing mortality with doses ranging from 1 to 3 mg/kg/dose every 6 hours.[3] The IV formulation of sildenafil (Revatio®;

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initiating eluxadoline.[4] In order to decrease the risk of pancreatitis, a dosage reduction from 100 mg to 75 mg twice daily was recommended in the eluxadoline original prescribing information for patients with a history of cholecystectomy along with various contraindications (e.g., history of pancreatitis, structural pancreatic diseases, pancreatic duct obstruction, consumption of three or more alcoholic beverages a day).[5]

Safety Study: Harinstein and colleagues conducted a retrospective cohort study to further characterize reported episodes of pancreatitis.[6] Patient information was retrieved from the FDA Adverse Event Reporting System (FAERS) including reports from May 27, 2015 through February 15, 2017. A total of 119 cases of pancreatitis were classified as serious adverse events including one death and 75 hospitalizations. Cases were reported more often in female patients, 84% of all cases (n=97). Hospitalization was reported in 63% of cases (n=75). Of patients with dosing data reported (n=83), 71% (n=59) received 75 mg by mouth twice daily and 29% (n=24) received 100 mg by mouth twice daily. Sixty-seven pancreatitis cases were reported in patients with (n=12) or without (n=55) gallbladders. Patients without a gallbladder received the 75 mg dosage more frequently, 78.2% (n=43), with only 9.1% (n=5) receiving the 100 mg dosage. The median time to pancreatitis onset was 1 day after receiving the first dose with 47 patients experiencing pancreatitis after receiving only one to two doses. Twelve patients (18%) had a previous cholecystectomy. A reported fatality occurred in a patient with a history of cholecystectomy, receiving eluxadoline 75 mg twice daily that did not have a history of alcohol abuse. The authors concluded that patients receiving eluxadoline were at risk for developing pancreatitis with the highest risk in patients without a gallbladder, including those who received the 75 mg twice daily regimen.

Drug Safety Communication: Based on results of the Harinstein and colleagues study, on March 15, 2017, the FDA released a Drug Safety Communication reporting the increased risk for pancreatitis with eluxadoline for treatment of IBS-D in patients without a gallbladder.[7] Furthermore, the FDA recommended those patients should no longer be treated with eluxadoline 75 mg twice daily and that history of cholecystectomy should be added as a contraindication in the package insert.[7,8]

Counseling Points: As a part of the FDA Drug Safety Communication, it was recommended that a medication guide explaining the risks of eluxadoline be dispensed with each prescription and reviewed by the patient prior to initiation of therapy.[7] Patients receiving eluxadoline should be instructed to seek immediate emergency care if they develop new or worsening stomach-area or abdominal pain with or without nausea and vomiting. Additionally, they should be aware that these side effects may occur after taking just one or two doses of eluxadoline.

Formulary Status: Eluxadoline is not on the CCHS Formulary.

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Pfizer) was approved by the Food and Drug Administration (FDA) on November 2009 for adults with pulmonary arterial hypertension.[5] However IV sildenafil has also been used off-label for the treatment of PPHN in those unable to take the oral dosage form.[3]

Mechanism of Action: Sildenafil is an inhibitor of phosphodiesterase-5 (PDE-5).[3,4] Phosphodiesterase-5 is located in the smooth muscle of the pulmonary vasculature and is responsible for degrading cyclic guanosine monophosphate (cGMP) which results in pulmonary vasoconstriction. Sildenafil's inhibition of PDE-5 prevents the breakdown of cGMP causing vasodilation of the pulmonary vasculature.

Key Clinical Trial: Darland and colleagues evaluated IV versus enteral sildenafil use in neonates < 1 year old with PPHN.[7] The primary outcome was the occurrence of interventions for hypotension in the IV sildenafil group (n=20) versus the enteral sildenafil group (n=20) within 24 hours of an administered dose. Approximately 30% of patients in the IV sildenafil group required an intervention for hypotension compared with 10% of those in the enteral group (P=0.24). The majority of interventions occurred within 24 hours of initiation of sildenafil. The mean IV sildenafil initiation dose was 0.32 mg/kg/dose with a range of 0.06 to 0.53 mg/kg/dose. There were no interventions when IV sildenafil was initiated at ≤ 0.125 mg/kg/dose. The majority of patients were started on sildenafil every 6 hours (95% in the IV group and 85% in the enteral group). A subgroup analysis of the IV cohort compared patients who required an intervention for hypotension to those without a documented intervention. The intervention group (n=6) compared to the non-intervention group (n=14) had significantly lower mean arterial pressure, systolic and diastolic blood pressure, and significantly greater vasopressor/inotrope use. Most of the patients who converted to IV sildenafil received an IV dose ≥ 50% of their enteral dose. Based on these results, the authors suggested a step-wise IV sildenafil dosing titration protocol as follows: Step 1) 0.125 mg/kg/dose, Step 2) 0.25 mg/kg/dose, Step 3) 0.375 mg/kg/dose, and Step 4) 0.5 mg/kg/dose; each dosing regimen would be infused over 20 to 30 minutes. Upward titration to the next dosing step would be based on the patient's PPHN status and hemodynamic stability. Continuous cardiopulmonary monitoring was recommended at least during the first 24 hours of IV sildenafil administration.

Safety: Hypotension is a frequent side effect of IV sildenafil in newborns.[4,7] Although the FDA issued a warning in 2012 against the use of sildenafil for PAH in children due to the mortality risk associated with high-dose therapy, a FDA communication was released in 2014 indicating that the drug is not contraindicated in pediatric patients and may be used with close monitoring if the benefits of therapy outweigh the risks.[8,9]

Dosing and Administration: At Cleveland Clinic Children's, IV sildenafil is dispensed undiluted as 1 mg/1.25 mL and is administered initially as 0.5 mg/kg/dose over 15 to 30 minutes every 8 hours. The dose and frequency are adjusted based on response and tolerability. The duration of IV therapy is based on clinical improvement and oral intake.

Cost and Availability: Each single-use glass vial of Revatio® injection contains 10 mg/12.5 mL.[5] The average wholesale cost is approximately $251 per vial.[6]

Formulary Status: Intravenous sildenafil is restricted as follows:

1) Neonatal ICU and Pediatric ICU providers (Staff, fellows, NPs, PAs) in consultation with Cardiology and Pulmonology
2) Cardiac Stepdown providers (Staff, fellows, NPs, PAs)
3) Intravenous sildenafil can only be administered in ICUs or Cardiac Stepdown

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Benralizumab (Fasenra®)	Interleukin-5 Receptor Antagonist	Severe Asthma	Restricted to Staff Physicians from the Departments of Allergy/Immunology and Pulmonary/Critical Care Medicine for use in the outpatient setting
Patisiran (Onpattro™)	Anti-Transthyretin siRNA Agent	Polyneuropathy of Hereditary Transthyretin-Mediated Amyloidosis	Restricted to Hematology/ Oncology for adult outpatient use only
von Willebrand Factor (Recombinant) (Vonvendi®)	Blood Product Derivative	von Willebrand disease	Restricted to Hematology/ Oncology

siRNA=Small interfering ribonucleic acid

Removal and Denials to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Calcitonin Intranasal Solution (Miacalcin®, Fortical®)	Hormone	Postmenopausal Osteoporosis	Removed from formulary: Internal Medicine, Critical Care, and Hematology/ Oncology Panels reviewed and decided there was no need for this product on the inpatient formulary. Removal will result in a cost savings.
Angiotensin II Injection (Giapreza™)	Vasoactive Agent	Increase blood pressure in septic or distributive shock	Denied due to high cost and limited safety data
Triamcinolone acetonide extended-release injectable suspension (Zilretta®)	Corticosteroid	Treatment of osteoarthritis knee pain	Denied due to lack of comparative efficacy information, increased cost over existing therapies, and lack of safety and efficacy data for repeat administration

Changes to Restrictions of Medications on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions**
Acetaminophen Intravenous (Ofirmev®)	Analgesic	Pain Reliever	Modified restrictions to include Staff Physicians from Palliative Medicine when all other restriction criteria are met
Denosumab (Xgeva®)	Bone Modifying Agent	Prevention of Skeletal-Related Events in MM	Modified restrictions to include the prevention of skeletal-related events in patients with MM for outpatient use only
Ferric Carboxymaltose Injection (Injectafer®)	Iron	Iron Deficiency Anemia	Modified restrictions to allow use by the Outpatient Blood Management Program
Hypertonic 3% Saline	Hypertonic Agent	Hyponatremia	Modified restrictions to allow peripheral administration of 3% hypertonic saline
Hypertonic 23.4% Saline	Hypertonic Agent	Traumatic Brain Injury	Removed Staff Physician only restriction Modified restrictions to allow APPs to prescribe 23.4% hypertonic saline Hypertonic Saline Guidelines should be followed
Neuromuscular Blockers (e.g., succinylcholine, rocuronium, vecuronium)	Neuromuscular Blockers	Endotracheal Intubation	Modified restrictions to allow APPs to prescribe neuromuscular blocker in ICU-designated areas
Rituxmab subcutaneous injection (Rituxan Hycela™)	Monoclonal Antibody	FL DLBCL CLL	Modified restrictions to include the off-label use for CLL in Medicare patients
Tisagenlecleucel (Kymriah®)	Chimeric Antigen Receptor T-Cell Immunotherapy	DLBCL ALL	Modified restrictions to allow use for the treatment of relapsed or refractory DLBCL after two or more lines of systemic therapy for Hematology/Oncology or Bone Marrow Transplantation

MM= Multiple myeloma APPs=Advanced Practice Providers ICU=Intensive care unit FL= Follicular lymphoma
DLBCL=Diffuse large B cell lymphoma CLL=Chronic lymphocytic leukemia ALL=Acute lymphocytic leukemia

Product Standardizations on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Olanzapine (Zyprexa®) and Ziprasidone (Geodon®) Injection	Antipsychotics	Agitation Psychosis	Both medications will be available across all CCHS EDs as options for the management of acute agitation. Both medications are restricted to Emergency Medicine and Psychiatry.
Recombinant Factor VIII (Advate®)	Antihemophilic Agent	Hemophilia	Advate® will replace Recombinate® as the Formulary Recombinant Factor VIII product for adults. Advate® is restricted to Hematology/ Oncology.

EDs=Emergency departments

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions**
Infliximab Biosimilar (Infliximab-abda;Renflexis®)	Monoclonal Antibody	Crohn's disease	Restricted to outpatients ≥ 6 years of age with Crohn's disease whose insurance mandates the use of Renflexis®. Remicade® will continue to be the preferred infliximab product on the CCHS Pediatric Formulary for both inpatient and outpatient use.
von Willebrand Factor, (Recombinant) (Vonvendi®)	Blood Factor Derivative	von Willebrand disease	Restricted to Pediatric Hematology/ Oncology in adult-age patients (≥ 18 years) with von Willebrand disease

Changes in Restrictions on the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Changes to Restrictions**
Acetaminophen Intravenous (Ofirmev®)	Analgesic	Pain Reliever	Modified restrictions to allow Staff Physicians from Pediatric Gastroenterology or Transplant to prescribe one-time premedication doses for pediatric transplant patients unable to receive oral or rectal forms of acetaminophen
Sildenafil PO and Sildenafil IV (Revatio®)	Phosphodiesterase-5 Enzyme Inhibitor	PPHN	Modified restrictions to: A. IV sildenafil: Use is restricted as follows: 1) Neonatal ICU and Pediatric ICU providers (Staff, fellows, NPs, PAs) in consultation with Cardiology or Pulmonology 2) Cardiac Stepdown providers (Staff, fellows, NPs, PAs) 3) IV sildenafil can only be administered in the ICUs or Cardiac Stepdown B. PO sildenafil: Initiation is restricted to: 1) Neonatal ICU and Pediatric ICU providers in consultation with Cardiology or Pulmonology 2) Cardiac Stepdown providers Continuation of therapy from home is not restricted
Vigabatrin (Sabril®)	Anticonvulsant	Infantile Spasm	Modified restrictions to remove language allowing one-time doses of vigabatrin written by non-certified prescribers for continuation of home therapy during off-hours

IV=Intravenous PPHN=Persistent pulmonary hypertension of the newborn ICU=Intensive care unit NP=Nurse practitioner
PA=Physician's assistant PO=Oral

Removal from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Ceftazidime Injection (Fortaz®, Tazicef®)	Antibiotic	Various Infections	Cefepime (Maxipine®) will be used instead of ceftazidime Ceftazidime was removed from the Pediatric BMT protocols Ophthalmic, intraocular, and nasal ceftazidime products are still on the formulary

BMT=Bone marrow transplant