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

Cleveland Clinic
Clinical Rx Forum
From the Department of Pharmacy

March/April Issue **2016, Volume 4, Issue 2**

Sugammadex: Is the Third Time the Charm?

By: Jamie Eckardt , Pharm.D.

Background: Sugammadex (Bridion®; Merck & Co., Inc.), a novel agent for the reversal of neuromuscular blockade (NMB) with rocuronium or vecuronium, was previously denied approval by the Food and Drug Administration (FDA) twice; the first time was in 2008 and then more recently in April of 2015. Denial was due to concerns about hypersensitivity/anaphylaxis and cardiac dysrhythmias.[1] This injectable product is currently sold in over 50 countries worldwide.[2] Sugammadex, a modified γ-cyclodextrin, is the first selective relaxant-binding agent that has been shown to rapidly and completely reverse the effects of the neuromuscular blocking agents rocuronium and vecuronium.[3] Currently, the most common NMB reversal regimens include acetylcholinesterase inhibitors (e.g., neostigmine, pyridostigmine, and edrophonium) given intravenously in combination with antimuscarinic agents (e.g., atropine and glycopyrrolate).

Pharmacokinetics: Cyclodextrins have a lipophilic interior and a hydrophilic exterior surface. As a result, these drugs are used as hydrophilic carriers for hydrophobic drugs. Sugammadex selectively binds to the free rocuronium molecules with a high affinity. It encapsulates or chelates this free molecule thereby inactivating it.[4] The resulting complex is then eliminated from the body. The structural similarity of rocuronium and vecuronium allows sugammadex to also encapsulate vecuronium. Sugammadex demonstrates linear pharmacokinetics over the dosing range of 1-16 mg/kg/dose.[4] Its steady state volume of distribution is ~11-14 L. There is no apparent metabolism and excretion is primarily unchanged drug in the urine. Its elimination half-life is 1.8 hours.[3,4]

Therapeutic Efficacy: Efficacy of sugammadex 2mg/kg has been shown

(Continued on page 2)

Incretin-based Therapies and the Risk of Pancreatic Disease

By: Meghan Wilson, Pharm.D.

Introduction: Incretin-based therapies are a class of medications used to treat type 2 diabetes mellitus (T2DM). Incretins are peptide hormones released by the small intestines in response to eating meals.[1] These hormones increase insulin secretion and decrease glucagon secretion. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are two known incretins. The two classes of incretin-based medications are dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. Dipeptidyl peptidase-4 inhibitors bind the enzyme DPP-4, which is responsible for inactivating circulating incretins. As a result, DPP-4 inhibitors lead to increased levels of active GLP-1 and GIP. The DPP-4 inhibitors include alogliptin (Nesina®), linagliptin (Tradjenta®), saxagliptin (Onglyza®), and sitagliptin (Januvia®).[2] The GLP-1 receptor agonists have a different mechanism of action as they bind to GLP-1 receptors on the pancreas and thereby mimic the actions of

(Continued on page 3)

(Continued from page 1)

in a pivotal trial comparing sugammadex to neostigmine 50 mcg/kg plus glycopyrrolate 10 mcg/kg for the reversal of rocuronium 0.6 mg/kg and vecuronium 0.1 mg/kg.[5,6] This study was a multi-center, randomized, active-controlled, parallel-group, safety-assessor-blinded trial with the rocuronium treated group reported separately from the vecuronium treated group. Subjects were randomly assigned to receive rocuronium or vecuronium for intubation and either neostigmine/glycopyrrolate or sugammadex for reversal of neuromuscular blockade. The primary endpoint was the time from administration of reversal agent to the recovery of a TOF (train-of-four) ratio of 0.9.[5,6] In the rocuronium group, mean time to reversal with sugammadex was significantly faster than with neostigmine, 1.5 minutes versus 18.6 minutes, respectively.[5] Mean time to recovery of TOF ratio of 0.9 in the vecuronium group was 6.6 times faster with sugammadex versus neostigmine, 2.7 minutes versus 17.9 minutes, respectively.[6]

Safety: Pooled data from phase I-III placebo-controlled trials demonstrated the following adverse events with an incidence greater than placebo and greater than 2%: vomiting, pain, procedural hypotension, chills, back pain, QTc prolongation, and abdominal pain.[1,7] Data analysis of 56 clinical trials conducted in Europe and the United States was performed by the FDA, including scrutiny of European post-marketing reports from a safety database, the Merck Adverse Event Reporting and Review System (MARRS), to evaluate the true risk of serious adverse reactions/events.[7] This detailed investigation by the FDA provided evidence that sugammadex is associated with hypersensitivity reactions, including anaphylaxis, with an estimated frequency of less than 0.1%. The FDA also required further clinical trials designed to analyze the effect of sugammadex on the QT/QTc interval. These three studies found no evidence of clinically relevant QT prolongation. Dysguesia is uncommon at recommended doses; however this is the most frequent adverse event at higher doses.[4] Adverse events in patients who received neostigmine plus glycopyrrolate included dry mouth, anxiety, and prolonged neuromuscular blockade; this is an incidence of at least two times that of sugammadex.[4]

Approval Status: On November 6, 2015, the FDA's Anesthetic and Analgesic Drug Products Advisory Committee voted unanimously to approve sugammadex for the reversal of neuromuscular blockade induced by rocuronium or vecuronium.[1] On December 15, 2015, suggamadex received final FDA approval.[8]

Formulary Status: Sugammadex was added to the CCHS Formulary in March 2016. It will be available for use in early May 2016.

References

1. Brown, T. FDA Panel Backs Sugammadex for General Anesthesia Reversal. Medscape. Nov 06, 2015.
2. Aniskevich A, Leone BJ, Brull SJ. Sugammadex: a novel approach to reversal of neuromuscular blockade. Expert Rev Neurother 2011;11(2): 185-98.
3. Martindale: The Complete Drug Reference, Lexi-Drugs Online, Hudson, OH: Lexi-Comp Inc.;2015: November 6, 2015.
4. Yang LP, Keam SJ. Sugammadex: a review of its use in anaesthetic practice. Drugs 2009;69(7):919-42.
5. Blobner M, Erikson LI, Scholz J, Motsch J, Della Rocca G, Prims ME. Reversal of sugammadex compared with neostigmine during sevoflurane anesthesia: results of a randomized controlled trial. Eu J Anaesthesiol 2010;27:874-81.
6. Khuenl-Brady KS, Wattwil M, Vanacker BF, Lora-Tamayo JI, Rietbergen H, Alvarez-Gomez JA. Sugammadex provides faster reversal of vecuronium-induced neuromuscular blockade compared to neostigmine: a multi-center, randomized, controlled trial. Anesth Analg 2010; 110:64-73.
7. NDA 22225: Sugammadex Injection. Food and Drug Administration Anesthetic and Analgesic Drug Products Advisory Committee Meeting: http://www.fda.gov/downloads/AdvisoryCommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM470718.pdf. Accessed: February 23, 2016.
8. FDA approves Bridion to reverse effects of neuromuscular blocking drugs used during surgery. Available from: http:/www.fda.gov/NewsEvents/NewsroomPressAnnouncements/ucm477512.htm. Accessed: February 17, 2016.

(Continued from page 1)

endogenous GLP-1.[3] The GLP-1 receptor agonists consist of albiglutide (Tanzeum®), dulaglutide (Trulicity®), exenatide (Byetta®), and liraglutide (Victoza®).[2] In addition to the indication for T2DM, liraglutide (Saxenda®) is also indicated for use in chronic weight management.

Safety Warnings and REMS: In 2007, the U.S. Food and Drug Administration (FDA) released a statement regarding 30 reports of pancreatitis associated with exenatide, leading to the addition of acute pancreatitis risk to the product's labeling.[4] Similarly, the FDA released a medication safety communication for sitagliptin in 2009 concerning 88 post-market case reports of acute pancreatitis associated with sitagliptin and sitagliptin/metformin (Janumet®).[5] As a result, labeling of all DPP-4 inhibitors now includes warnings about pancreatitis. Following these safety communications, an examination of the FDA's adverse event reporting database also found these agents were associated with pancreatitis and pancreatic cancer. Pancreatitis was reported over six times more frequently with sitagliptin or exenatide when compared to the control drugs of rosiglitazone, repaglinide, nateglinide, and glipizide.[6] For pancreatic cancer, the reported event rate was 2.9 times greater with exenatide and 2.7 times greater with sitagliptin when compared to the controls. Currently, all GLP-1 receptor agonists except exenatide have Risk Evaluation and Mitigation Strategy (REMS) programs to communicate the potential increased risk of pancreatitis. These REMS programs do not recommend initiating therapy in patients with a known history of pancreatitis. There are no REMS programs associated with the use of DPP-4 inhibitors.

Follow-up Studies: A retrospective cohort was designed to evaluate the potential association between DPP-4 inhibitors and pancreatic cancer through review of Medicare claims data between 2006 and 2011.[7] The incidence of pancreatic cancer after starting a DPP-4 inhibitor was compared to the incidence after starting sulfonylureas (SU) and thiazolidinediones (TZD). ICD-9CM codes for pancreatic cancer were used to identify the primary outcome. The median follow-up was 10 months. The adjusted HR for pancreatic cancer was 0.62 (95% CI 0.41-0.94) for DPP-4 inhibitors compared to SU and 0.97 (95% CI 0.65-1.43) for DPP-4 inhibitors when compared to TZD. The results suggest that there is no short-term increased risk of pancreatic cancer with the use of DPP-4 inhibitors relative to SU or TZD. Additionally, in recent prospective trials examining the cardiovascular effects of DPP-4 inhibitors, specifically saxagliptin and alogliptin, the incidence of pancreatic cancer did not differ between agents and placebo.[8,9] The median duration of therapy for these trials were 2.1 years and 18 months, respectively. The association of pancreatitis with exenatide was also evaluated in a retrospective cohort using claims from a US healthcare database.[10] The study included patients who had a claim for a new antidiabetic medication on or after June 1, 2005. The primary outcome was the first occurrence of acute pancreatitis as identified by ICD-9 CM codes. The incidence rate of acute pancreatitis in the exenatide arm was not significantly different from the control group (p=0.9383). The mean time for follow-up was 1.4 years for the exenatide group.

Bottom Line: Based on the current evidence, it seems there is no short-term risk of pancreatitis and pancreatic cancer with the use of DPP-4 inhibitors and exenatide. Long-term studies are needed to evaluate the risk beyond 2 years of use with these agents.

References

1. Haluzik M, Mraz M, Svacina S. Balancing benefits and risks in patients receiving incretin-based therapies: Focus on cardiovascular and pancreatic side effects. Drug Saf. 2014;37: 1003-10.
2. Lexi-Comp Online, Lexi-Drugs Online, Hudson, Ohio: Lexi-Comp Inc.; 2016: February 2016.
3. Verspohl EJ. Novel therapeutics for type 2 diabetes: Incretin hormone mimetics (glucagon-like peptide-1 receptor agonists) and dipeptidyl peptidase-4 inhibitors. Pharmacol Ther. 2009;124(1):113-38.
4. Food and Drug Administration [Internet] United States: Byetta (exenatide) October 2007; 2007. Available from: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm150839.htm. Accessed: January 5, 2016.
5. Food and Drug Administration [Internet] United States: Information for Healthcare Professionals – Acute pancreatitis and stiagliptin; 2009. Available from: http://www.fda.gov/Drugs/DrugSafetyPostmarketDrugSafetyInformationforPatientsandProvidersDrugSafetyInformationforHeathcareProfessionals/ucm183764.htm. Accessed: October 15, 2015.
6. Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. Gastroenterol. 2011;141(1):150-6.
7. Gokhale M, Buse JB, Gray CL, Pate V, Marquis MA, Sturmer T. Dipepetidyl-peptidase-4 inhibitors and pancreatic cancer: a cohort study. Diabetes Obes Metab. 2014;16:1247-56.
8. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369 (14):1317-26.
9. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Barkis GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369 (14):1327-35.
10. Wenten M, Gaebler JA, Hussein M, Pelletier EM, Smith DB, Girase P, et al. Relative risk of acute pancreatitis in initiators of exenatide twice daily compared with other anti-diabetic medication: a follow-up study. Diabetic Med. 2012; 29:1412-18.

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Daratumumab (Darzalex®)	Monoclonal Antibody	Relapsed/refractory Multiple Myeloma in patients who have failed at least three lines of therapy which must have included a PI and an IMID or who are double-refractory to a PI and an IMID	Restriction: Restricted to the Department of Hematology and Medical Oncology for outpatient use only.
Elotuzumab (Empliciti®)	Monoclonal Antibody	Relapsed/refractory Multiple Myeloma in patients who relapsed after one to three prior therapies	Restriction: Restricted to the Department of Hematology and Medical Oncology for outpatient use only.
Naloxegol (Movantik®)	Gastrointestinal Agent	Opioid-induced Constipation	Restriction: Restricted to patients currently on opioid therapy who have failed two other scheduled treatments (e.g., not PRN) and were administered laxatives for 48 hours.
Perampanel (Fycompa®)	Anticonvulsant	Seizures	Restriction: Restricted for initiation of therapy to Neurology and Epilepsy; there are no restrictions for continuation of home therapy.
Ryanodex® (Dantrolene sodium 250 mg/vial)	Skeletal Muscle Relaxant	Malignant Hyperthermia	Ryanodex® replaces Dantrium® (dantrolene sodium 20 mg/vial) in the malignant hyperthermia carts. Dantrium® will remain on formulary for post-crisis management and treatment of neuroleptic malignant syndrome.
Sugammadex (Bridion®)	Selective Relaxant Binding Agent	Reversal of rocuronium and vecuronium	Comment: Should not be used in patients with renal failure.
Trabectedin (Yondelis®)	Antineoplastic Agent	Metastatic or unresectable liposarcoma or leiomyosarcoma in patients who have received a prior anthracycline-containing regimen	Restriction: Restricted to the Department of Hematology and Medical Oncology and the Department of Gynecological Oncology for patients with metastatic or unresectable liposarcoma or leiomyosarcoma for outpatient use only.

IMID= Immunomodulatory agent PI=Proteasome Inhibitor PRN=As needed

Modifications to Restrictions on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Modifications**
Haloperidol (Haldol®)	Antipsychotic Agent	Delirium/Agitation	Modification: Patients receiving more than a single dose of IV haloperidol (i.e., order is for repeating doses or a decision is made to continue use after a one-time dose) require telemetry monitoring to assess for QT interval prolongation and arrhythmias. However, no telemetry monitoring is necessary for Palliative Care/Hospice patients.
Kcentra® (Prothrombin Complex Concentrate)	Blood Factor	Warfarin reversal in life-threatening ICH Non-warfarin related refractory coagulopathic bleeding	Modification: Kcentra® restrictions now include use in non-warfarin related refractory coagulopathic bleeding associated with cardiac surgery under the following criteria: 1) Evidence of diffuse microvascular bleeding 2) No evidence of major surgical bleeding necessitating return to CPB 3) Reasonable effort to treat coagulopathy by blood products (e.g., two units pooled platelets, eight units of FFPs and 20 units of cryoprecipitate) 4) Samples for lab investigations should be sent for documenting coagulopathy (e.g., TEG, coagulation profile with platelet count).

CPB=Cardiopulmonary Bypass FFP=Fresh Frozen Plasma ICH=Intracranial Hemorrhage IV=Intravenous TEG=Thromboelastogram

Deletions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
IV Allopurinol (Alloprin®)	Xanthine Oxidase Inhibitor	Management of Hyperuricemia	Other therapies available
Antihistamine Ophthalmic Drops	Antihistamine	Seasonal Allergic Conjunctivitis	If a patient or prescriber wants to continue therapy during an inpatient admission, the patient can use their own supply, or the antihistamine ophthalmic drops (i.e., ketotifen) can be obtained from our Ambulatory Pharmacies.

IV=Intravenous

Therapeutic Interchanges on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Modifications**
Doxylamine*	H_1 Antagonist	NVP	When Diclegis® (doxylamine/pyridoxine) 10 mg-10 mg is ordered, it will be automatically substituted with doxylamine 12. 5 mg and pyridoxine 12.5 mg.
ICS	Respiratory Agent	Asthma COPD	Changes in Therapeutic Interchange: For ICU patients: All ICS will be interchanged to aerosolized budesonide (equipotent dose). Non-ICU patients will continue to be interchanged to mometasone (Asmanex®).
ICS/LABA	Respiratory Agent	Asthma COPD	For ICU patients: All ICS/LABA will be interchanged to aerosolized budesonide (equipotent dose) plus scheduled aerosolized albuterol (if the patient is not already receiving scheduled albuterol or ipratropium/albuterol). For non-ICU patients: All ICS/LABA will be interchanged to fluticasone/vilanterol (Breo-Ellipta®) (equipotent dose).

COPD=Chronic Obstructive Pulmonary Disease ICS=Inhaled Corticosteroids ICU=Intensive Care Unit
LABA=Long-acting Beta Agonist NVP=Nausea and Vomiting of Pregnancy
*Doxylamine was added to the CCHS Adult Formulary in order to be utilized for this therapeutic interchange.

Changes in Formulations on the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Rationale for Change in Formulation**
Aerosolized Epoprostenol Products	Prostacyclins	Pulmonary Hypertension	Veletri® will replace Flolan® as the aerosolized epoprostenol product, since Veletri® has longer stability (stable for 7 days if refrigerated) and thus may be stored in the Pyxis machines for greater accessibility.
Bendamustine (Bendeka®)	Antineoplastic Agent	CLL Non-Hodgkin Lymphoma Hodgkin Lymphoma	Bendeka®, a ready-to-dilute solution with a short infusion time of 10 minutes, will replace both Treanda® liquid formulation, which is no longer commercially available, and Treanda® lyophilized powder, which requires additional compounding and infusion time. Restriction: Restricted to the Department of Hematology and Medical Oncology.
Oral Antiepileptics	Antiseizure Agents	Seizures	Will stock generic formulations of all oral antiepileptic agents with the exception of brand Dilantin® and Carbatrol®. A preferred generic manufacturer and an alternative generic manufacturer were selected for each of the antiepileptic agents.

CLL=Chronic Lymphocytic Leukemia

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restiction/Comments**
Blinatumomab (Blincyto®)	Antineoplastic Agent	Relapsed /refractory Acute Lymphoblastic Leukemia	Restriction: Restricted to the Department of Pediatric Hematology/Oncology and BMT for relapsed or refractory acute lymphoblastic leukemia patients who are ineligible for enrollment onto clinical trial.
Perampanel (Fycompa®)	Anticonvulsant	Seizures	Restriction: Restricted to the Departments of Pediatric Neurology and Pediatric Epilepsy for initiation of therapy. Continuation of therapy is not restricted.
Ryanodex® (Dantrolene sodium 250 mg/vial)	Skeletal Muscle Relaxant	Malignant Hyperthermia	Ryanodex® replaces Dantrium® (dantrolene sodium 20 mg/vial) in the malignant hyperthermia carts. Dantrium® will remain on formulary for post-crisis management and treatment of neuroleptic malignant syndrome.
Vedolizumab (Entyvio™)	Monoclonal Antibody	Moderate-to-Severe Ulcerative Colitis or Crohn's Disease	Restiction: Restricted to the Department of Pediatric Gastroenterology for outpatient use in adolescent patients (age ≥ 12 years) with moderate to severe ulcerative colitis or Crohn's disease who have failed at least one TNF blocker.

BMT=Bone Marrow Transplant TNF=Tumor Necrosis Factor

Deletions to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal/ Comments**
IV Allopurinol (Alloprin®)	Xanthine Oxidase Inhibitor	Management of Hyperuricemia	Other therapies available
Antihistamine Ophthalmic Drops	Antihistamine	Seasonal Allergic Conjunctivitis	If a patient or prescriber wants to continue therapy during an inpatient admission, the patient can use their own supply, or the antihistamine ophthalmic drops (e.g., ketotifen) can be obtained from our Ambulatory Pharmacies.

IV=Intravenous

Changes in Restrictions in the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Modification/Comments**
Acetaminophen IV (Ofirmev®)	Analgesic	Pain Control Patent Ductus Arteriosus	Include Hospitalists for the continuation of therapy initiated in the PICU. All other restriction criteria must be met.
Tocilizumab (Actemra®)	Monoclonal Antibody	Cytokine-release Syndrome	Include the Department of Pediatric Hematology/Oncology and BMT for the management of: Cytokine-release syndrome following chimeric antigen receptor-modified T-cell therapy (CART) or blinatumomab.

BMT=Bone Marrow Transplant IV=Intravenous PICU=Pediatric Intensive Care