Cleveland Clinic
Clinical Rx Forum
From the Department of Pharmacy

July/August Issue 2014, Volume 2, Issue 4

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Cleveland Clinic
Clinical Rx Forum

From the Department of Pharmacy
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Formulary Information

Drug Interaction with Carbapenems and Valproic Acid

By: Sarah Welch, Pharm.D.

Introduction: There have been several adverse drug events reported in the literature involving the concomitant use of carbapenem antibiotics (e.g., meropenem, doripenem, ertapenem, imipenem-cilastatin) and the anticonvulsant medication, valproic acid (VPA).[1] The interaction between carbapenems and VPA is characterized by significant drops in VPA levels and is observed with all carbapenems. This drug combination can typically be avoided. However, there may be instances when providers wish to continue treatment with both agents, such as in the setting of a central nervous system (CNS) infection in a patient with acute or active seizures. Therefore, it is important to remember that combination therapy is not contraindicated and may be necessary. Furthermore, pharmacists can play a key role in ensuring the safe administration of concurrent therapy.

What is the interaction between VPA and carbapenems? Valproic acid concentrations have been shown to decrease substantially with concomitant administration of carbapenems.[1-5] On average, the addition of a carbapenem rapidly decreases VPA concentrations from 60-80 mg/L to 0-25 mg/L, often within 1 day.[1] In several of these reports, seizure activity was observed, however, VPA levels returned to normal upon discontinuation of the carbapenem. In a retrospective evaluation of patients receiving VPA and a carbapenem, VPA levels were decreased by approximately 73-89%, with the lowest concentrations of VPA occurring between days 4 and 11.[2] Therefore, providers can expect to see a decrease in VPA levels beginning on the first day of carbapenem administration, with lowest levels reached anywhere between days 4 through 11. Valproic acid concentrations typically return to normal

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Removal of REMS Requirements for Rosiglitazone

By: Michael Stanton, Pharm.D.

What is rosiglitazone? Rosiglitazone (Avandia®; GlaxoSmithKline) is a thiazolidinedione (TZD) antidiabetic agent approved by the Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults.[1] It is available as a single entity formulation as well as in combination with metformin (Avandamet®; GlaxoSmithKline) and with glimepiride (Avandaryl®; GlaxoSmithKline).

What events led to the Risk Evaluation and Mitigation Strategy (REMS) requirements for rosiglitazone and the eventual removal of those requirements?

- **In 2006**, GlaxoSmithKline, the manufacturer of Avandia®, submitted to the FDA a meta-analysis containing 42 trials which demonstrated a concern for cardiovascular (CV) risk associated with rosiglitazone; the meta-analysis did not demonstrate a similar risk with pioglitazone (Actos®; Takeda) another TZD.[2]

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between 3 days to 2 weeks after discontinuing the carbapenem.[6] Package inserts for meropenem (Merrem®), doripenem (Doribax®), ertapenem (Invanz®), and imipenem-cilastatin (Primaxin®) all state that if administration with VPA is necessary increasing the VPA dose may not be sufficient to overcome this interaction; therefore, supplemental anticonvulsant therapy should be considered.[7-10]

What is the mechanism of decreased VPA concentration by carbapenems?

Overall, the mechanism of this interaction is unclear.[6] Data suggest that carbapenems cause a decrease in VPA levels through two separate processes which include an increase in glucuronidation and a decrease in enteric hydrolysis**.** Both mechanisms lead to decreases in the plasma concentration of active drug by making the VPA molecule more water soluble, and thus easily excreted through the kidney.[2-3] Other potential mechanisms of interaction include decreased absorption of VPA in the intestines and increased distribution of VPA into red blood cells.[1,3-5]

How should you manage a patient that requires both VPA and carbapenems?

Although it is generally recommended to use an alternative antibiotic when possible, if the provider chooses to continue the use of a carbapenem, the pharmacist can suggest the monitoring of daily VPA levels, beginning the day after the carbapenem is started.[6] Total VPA levels should be recommended as there is not an adequately established free level that correlates with seizure reduction. It is important to note that subtherapeutic levels do not necessitate the addition of other anticonvulsant medications; however if seizure activity is observed, VPA dosage modification and/or additional anticonvulsants should be considered. If VPA is being used for another indication, such as migraine prophylaxis or diabetic neuropathy, monitoring of VPA levels may not be warranted as these indications are not typically dosed by level; however, the provider should be alerted to the interaction.

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- ◊ A separate meta-analysis involving those 42 trials also showed a significant increase in the risk of myocardial infarction as well as an increase in mortality in patients receiving rosiglitazone.[3]

- **In 2007,** the FDA evaluated three large randomized controlled trials (DREAM[4], ADOPT[5], and interim results of RECORD[6]).
  - ◊ With the exception of RECORD, these studies did not evaluate CV risk as the primary endpoint.
  - ◊ After presentation of the data and discussion, the FDA concluded that rosiglitazone increased the risk of cardiac ischemia in type 2 diabetes but the overall risk-benefit profile supported continued marketing in the United States with revised labeling including a boxed warning of this risk as well as a Medication Guide highlighting potential CV risk.[2]
- **In 2009,** the FDA received the completed results of the RECORD trial, which demonstrated no evidence of difference in all-cause mortality with rosiglitazone versus other therapy.[6]
- **In 2010,** a second Advisory Committee meeting asked for a re-adjudication of RECORD as well as the institution of a REMS program for the safe and appropriate use of rosiglitazone in September 2010.[2] The REMS requirements were as follows:
  - ◊ Mandatory certification of health-care professionals
  - ◊ Patients need to be enrolled in REMS program
  - ◊ Restricted access and distribution through certified, specialty pharmacies
  - ◊ A Medication Guide provided with every prescription
  - ◊ Updated labeling limiting the use of rosiglitazone and rosiglitazone-containing products[2]
- **In November 2013**, without a proven risk for CV events over the standard of care shown in this reanalysis of RECORD, and discussion related to difficulty making conclusions due to poor study design in the previously evaluated studies, the FDA decreased the REMS program requirements for the use of rosiglitazone.[7]

What changes were made in the REMs requirements for rosiglitazone?

The following changes to the REMS program for rosiglitazone were made **in May 2014**:

- Product labeling was updated for all rosiglitazone products
- Prescribers are not required to be certified in the REMS program
- Patients do not have to be enrolled in the REMS program
- New patients can be initiated on therapy without restriction
- Rosiglitazone distribution and dispensing are no longer restricted
  - ◊ Pharmacies no longer need to be certified in the REMS program
  - ◊ Patients receiving rosiglitazone can now get their prescription refills from any community pharmacy

Because of the uncertainty surrounding the CV risks, the FDA mandated that GlaxoSmithKline send Dear Healthcare Provider letters and Dear Professional Society letters to educate prescribers about this new information.[8] Information regarding the changes to product labeling and to documents such as these letters can be found at www.rosiglitazonerems.com.

References:

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Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Apremilast (Otezla®)	Phosphodiesterase-4 Inhibitor	Treatment of active psoriatic arthritis	Restriction: Restricted to continuation of home therapy only
Belatacept (Nulojix®)	Selective T-cell costimulation blocker	Prophylaxis of organ rejection in adult patients receiving a kidney transplant	Restrictions: 1) First-line therapy for patients undergoing kidney re-transplantation who have experienced intolerable adverse events (including but not limited to: nephrotoxicity, neurotoxicity, and thrombotic microangiopathies) with CNI or mTOR inhibitor or patients with primary thrombotic micrangiopathy-related end stage renal disease undergoing renal transplantation 2) Second-line therapy for patients who have received a kidney transplant and subsequently experience intolerable adverse events (as previously stated) with a CNI or mTOR inhibitor
Desvenlafaxine fumarate (Khedezla®)	SNRI	Treatment of MDD	Therapeutic interchange from desvenlafaxine succinate (Pristiq®) to desvenlafaxine fumarate The dose conversion from Pristiq® to Khedezla® is 1:1
Dextromethorphan/ quinidine (Nuedexta™)	NMDA receptor antagonist	Treatment of PBA	Restrictions: Restricted to Neurology and Psychiatry for initiation of therapy as a second-or third-line treatment option (after SSRIs and/ or TCAs) There is no formulary restriction for continuation of therapy

CNI=calcineurin inhibitor MDD=major depressive disorder NMDA=N-methyl-D-aspartate PBA=pseudobulbar affect
REMS=Risk Evaluation and Mitigation Strategy SNRI=serotonin norepinephrine inhibitor SSRI=selective serotonin reuptake inhibitor
TCA=tricyclic antidepressant

Formulary Update

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Fidaxomicin (Dificid®)	Macrolide antibacterial agent	Treatment of CDAD	Restriction: Restricted to the Department of Infectious Diseases
Posaconazole (Intravenous) (Noxafil®)	Azole antifungal agent	Prophylaxis of invasive aspergillus and candida infections	Restriction: Restricted to the Department of Infectious Diseases
Short ragweed pollen allergen extract (Ragwitek®)	Allergen extract	Immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis with or without conjunctivitis	Restriction: Restricted to Adult Immunology and Otorhinolaryngology for initiation of therapy in the outpatient setting
Tacrolimus extended-release (Astagraf® XL)	CIN	Prophylaxis of organ rejection	Restrictions: 1) Continuation of home therapy 2) Lung Transplant Service 3) Intestinal Transplant Service

CDAD=Clostridium difficile-associated diarrhea CIN=calcineurin inhibitor

Additions to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Calfactant intratracheal suspension (Infasurf®)	Surfactant	Prevention and treatment of RDS in premature neonates.	Infasurf® replaces Curosurf® as the surfactant of choice
Etanercept (Enbrel®)	TNF blocker	GVHD in pediatric bone marrow transplant patients and for the treatment of idiopathic pneumonia syndrome	Restriction: Restricted to pediatric bone marrow transplant patients with GVHD or idiopathic pneumonia syndrome
Fidaxomicin (Dificid®)	Macrolide antibacterial agent	Treatment of CDAD	Restriction: Restricted to the Department of Infectious Diseases

CDAD=Clostridium difficile-associated diarrhea GVHD=graft-versus-host disease RDS=respiratory distress syndrome TNF=tumor necrosis factor

Formulary Update

Additions to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Ibuprofen lysine injection (NeoProfen®)	NSAID	Treatment of clinically significant PDA in neonates	Restriction: Restricted to Neonatal and Pediatric Intensive Care Units Indomethacin will continue to be the drug of choice for PDA
Meningococcal vaccine (Menveo®)	Vaccine	Prevention of invasive meningococcal disease caused by *Neisseria meningitides* serogroups A,C, Y, and W-135	Restrictions: 1) Patients age 2-23 months with anatomical or functional asplenia. This includes patients with sickle cell disease, complement component deficiency , and those at risk from meningococcal disease outbreaks 2) Pediatric patients <9 months traveling to areas where meningococcal disease is endemic
Posaconazole (Intravenous) (Noxafil®)	Azole antifungal agent	Prophylaxis of invasive aspergillus and candida infections	Restriction: Restricted to the Department of Infectious Diseases
Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract (Oralair®)	Allergen Extract	Immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis	Restriction: Restricted to the Departments of Pediatric Allergy and Immunology and Pediatric Otorhinolaryngology in the Head and Neck Institute Oralair® is NON-formulary for adult patients
Timothy Grass Pollen Allergen Extract (Grastek®)	Allergen Extract	Immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis	Restriction: Restricted to the Departments of Pediatric Allergy and Immunology and Pediatric Otorhinolaryngology in the Head and Neck Institute. Grastek® is NON-formulary for adult patients

NSAID=nonsteroidal anti-inflammatory agent PDA=patent ductus arteriosis

Restriction Changes to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Collagenase clostridium histolyticum (Xiaflex®)	Bacterial collagenase	Treatment of adult men with Peyronie's Disease Treatment of Dupuytren's contracture	Original Restriction: Restricted to hand surgeons in the hospital outpatient setting for adult patients for treatment of Dupuytren's contracture Additional Restriction: Restricted to Urology for the treatment of Peyronie's Disease for outpatient use only Prescribers must meet REMS requirements/certification **(applicable for Peyronie's Disease only)**
Nicardipine (Cardene®)	Calcium channel blocker	Subarachoid hemorrhage-induced vasospasm Blood pressure control in acute ischemic or hemorrhagic stroke	All formulary restrictions have been removed
Prothrombin Complex Concentrate (Kcentra®)	Blood Factor Derivative	Reversal of warfarin-related life-threatening intracranial hemorrhage	Restriction change: Only **staff physicians** may order Kcentra®
Riociguat (Adempas®)	sGC stimulator	Treatment of CTEPH	Restriction change: May be used for initiation of therapy by providers from the Respiratory Institute (including fellows) for CTEPH Prescriber and patient must meet REMS requirements

CTEPH=chronic thromboembolic pulmonary hypertension REMS=Risk Evaluation and Mitigation Strategy
sGC=soluble guanylate cyclase

Restriction Changes to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Melatonin	Dietary Supplement	Treatment of insomnia	Restriction Change: Initiation of therapy is restricted to Child and Adolescent Psychiatry and to the Children's Hospital for Rehabilitation (CC-CHR-Shaker Campus) There is no formulary restriction for continuation of home therapy