November 2018
Issue 33

RPCC Pharmacy Forum

Treatment of Gastroesophageal Reflux Disease with Melatonin

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Special Interest Articles:

- GERD and Melatonin
- Anavip
- Toxidromes

POISON Help 1-800-222-1222

Did you know?

According to JAMA Network Open, many dietary supplements contain active pharmaceuticals that are a threat to public health. For example among 353 sexual enhancement products, sildenafil was found in 166 supplements.

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Gastro Esophageal Reflux Disease, or GERD, is one of the most common upper gastrointestinal tract diseases affecting adults in the United States. According to the American Gastroenterological Association, approximately one-third of the population has GERD. Since GERD is a chronic disease, patients experience significant economic impact due to the expense of its long-term management. Direct costs associated with the disease include costs of over-the-counter and prescription medications, physician office and hospital visits, surgical costs and costs of possible complications, such as Barrett's esophagus, esophageal adenocarcinoma, that may result from the disease. In addition to resulting complications of the disease itself, the occurrence of complications from the long-term use of proton-pump inhibitors, including malabsorption, infections, like C*lostridium difficile*, and drug-drug interactions, is of rising concern. In light of both the economical and physical impacts of GERD, the search for alternative treatment options has been ongoing. Promising research suggests melatonin might be an up-and-coming alternative to traditional GERD therapies.

Melatonin is a hormone that is produced in the pineal gland and aids in the regulation of sleep and wakefulness. Recent studies show that melatonin is not only synthesized in the pineal gland but in the gastrointestinal tract as well where quantities exceed those in the pineal gland, especially after food intake. Melatonin production and its release from the pineal gland remains under photoperiodic control, while its concentration in the gut depends mainly on food intake. It protects gastric mucosa against destructive activity of free radicals in stress-induced ulcers and damage caused by non-steroidal anti-inflammatory drugs (NSAIDs) and other gastric damaging agents. In addition to the protective properties that have been displayed, other studies have demonstrated the inhibitory action of melatonin on secretion of HCL and pepsin. Considering the findings of melatonin's known gut regulatory functions and anxiolytic properties it was hypothesized that melatonin might serve as an effective agent for treating GERD.

To date, several studies have shown efficacy of melatonin in the treatment of GERD. A study conducted at Mansoura University Hospital in Egypt, compared the effects on improvement of symptoms, lower esophageal sphincter (LES) tone, basal acid output (BAO), serum gastrin levels, and gastric pH among four groups of patients. All groups demonstrated overall improvement in GERD symptoms but only those being treated with melatonin, alone or in conjunction with traditional therapies, demonstrated increased LES tone. All groups had significant decrease in BAO, increased serum gastrin and increased gastric pH levels. Treatment of GERD with melatonin, omeprazole, or both was found to be duration dependent. Patients treated with melatonin or omeprazole alone for 4 weeks demonstrated incomplete resolution of symptoms, while those treated with both melatonin and omeprazole for 4 weeks and those treated with melatonin alone for 8 weeks showed complete resolution of symptoms. In head-to-head comparison 175 patients were given standard treatment with omeprazole and 176 patients were treated with a melatonin supplement over a 40-day treatment period. Patients treated with melatonin reported complete regression of symptoms by the end of the study, compared

(*Continued on next page*)

GERD and Melatonin continued:

with only 66% of those treated with omeprazole.

Melatonin is a generally safe supplement. Though a recent study published in the *Clinical Journal of Sleep Medicine* reports an inconsistency in melatonin concentrations with regards to labeling information provided with these products, and this could hinder standardization of dosing, the therapeutic range of melatonin is quite broad and supratherapeutic dosages should not be of significant concern. In one study up to 1 g/day for 25 to 30 days was well tolerated in adults though doses of 3 to 80 mg have shown mild toxicity in pediatric patients. While melatonin may be a safer, more cost-effective alternative to standard GERD therapies and its evidence is promising, whether it can be substituted for omeprazole, especially in pediatric patients and older patients with medically complex conditions, remains unclear at this time.

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PharmD students, Hubbs Bottcher, Hannah Mezler, and Joanna Mitchell taught seniors about medication safety in October at the Pelham Senior Citizen Center.

Hubbs Bottcher spoke to Auburn Daycare in October about being safe in the home and introduced them to **Quills Up- Stay Away!** – a poison awareness program featuring Spike the porcupine.

Anavip® – A New Rattlesnake Antivenom

Hubbs Bottcher, Auburn University PharmD Candidate 2019

According to the CDC, there are approximately 7,000 to 8,000 venomous snake bites annually. In the Southeastern United States specifically, the majority of venomous bites are from copperheads, while the most severe bites are from rattlesnakes. Medical advancements and the introduction of the antivenin CroFab® [Crotalidae polyvalent immune fab (Ovine)] to the market in 2000, has contributed to the decrease in mortality rates from venomous snake bites to as low as five percent. Although CroFab has dominated the market for rattlesnake envenomations, it does not come without its drawbacks. A significant drawback is the drug's short half-life. Considering latent and reoccurrent coagulopathies are common after rattlesnake envenomation, and can lead to life-threatening complications, short half-life is not ideal. Recently, a new antivenin, Anavip [Crotalidae Immune F(ab')2 (Equine)], has been developed that decreases the need for subsequent dosing to ultimately prevent the latent coagulopathy complications that might occur after rattlesnake envenomations.

"According to the CDC, there are approximately 7,000 to 8,000 venomous snake bites annually. In the Southeastern United States specifically, the majority of venomous bites are from copperheads, while the most severe bites are from rattlesnakes."

A prospective, blinded, multicenter, randomized clinical trial comparing rates of latent coagulopathy after Crotalinae envenomations was performed comparing Fab (CroFab) and F(ab')2 (Anavip). Patients were divided into three groups and received F(ab')2 treatment/F(ab')2 maintenance, F(ab')2 treatment/placebo maintenance, or Fab treatment/Fab maintenance. Of these treatment groups, coagulopathy was seen in 29.7% of Fab/Fab group, 10.3% in the F(ab')2/F(ab')2 group, and 5.3% in the F(ab')2/placebo group. There were no serious adverse events related to the study. Patients ranged from 2 to 80 years of age and efficacy was demonstrated in all age groups and demographics. In the patient population less than 10 years old, 15.8% experienced latent coagulopathies. Six extra doses of antivenin were given to the F(ab')2/F(ab')2 group, 11 to the F(ab')2/placebo group, and 18 to the Fab/Fab group. Both F(ab')2 and Fab are FDA approved in pediatric rattlesnake enevomations, but only Fab is approved for copperhead and cotton mouth envenomations.

Not only does this extended half-life lower rates of latent coagulopathy, but it also decreases the number of vials needed to treat a rattlesnake bite and potentially lowers the overall cost of treatment. The treatment dosing for both agents is listed below and may appear very similar, but the costs are actually quite different. According to the manufacturers, CroFab is approximately $3,198 per vial (CroFab Customer Service, personal communication, October 31, 2018) while Anavip is $1,220 per vial (Paul Landes, personal communication, October 31, 2018). It is important to consider the minimum number of vials are not always enough and the total number of vials needed is greatly dependent on initial control specific patient circumstances.

Overall, Anavip appears to have more favorable attributes considering the prolonged half-life, fewer vials needed, and cost-reduction when treating a rattlesnake envenomation. Availability, however, may be a different story. It is important to consider that Anavip is competing with a product that has been on the market for 17 years, so it will take time before it is readily available. Although you may not see Anavip stocked in the emergency departments this year, it is still a noteworthy competitor that is worth considering in snakebite seasons to come. (See following page for tables)

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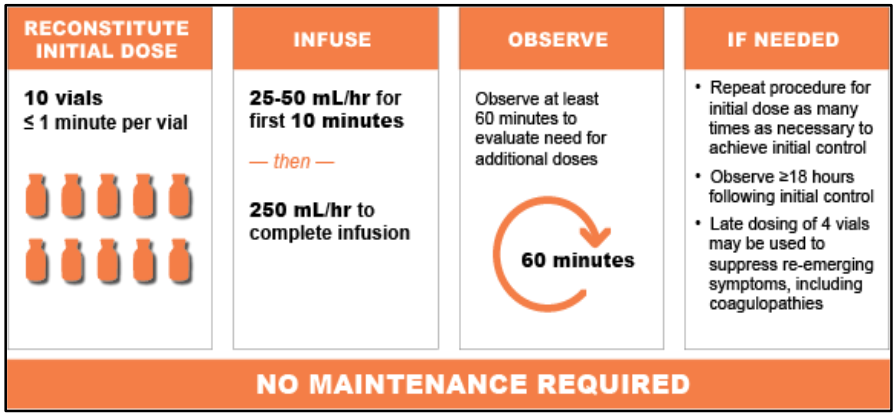
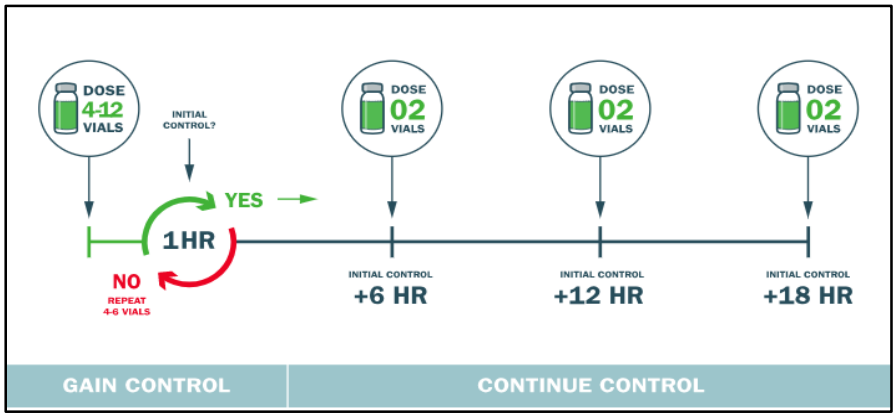
ANAVIP TREATMENT



(https://www.anavip-us.com/)

CROFAB TREATMENT



(https://www.crofab.com/Treatment-With-CroFab/Dosing-and-administration)

	CroFAB®	**ANAVIP®**
	Crotalidae polyvalent immune fab (Ovine)	Crotalidae Immune F(ab')2 (Equine)
FDA Indication	Management of adult and pediatric patients with North American crotalid (**rattlesnakes, copperheads, cotton mouths**) envenomation.	Management of adult and pediatric patients with North American **rattlesnake** envenomation.
Year Approved	2000	2015
Vials Required	-Initial: 4-6 vials (repeat if needed) -Maintenance: three 2-vial doses	-Initial: 10 vials (repeat if needed) -Maintenance: 4 vials (if needed)
Cost		
Reconstitution	18 mL of 0.9% Sodium Chloride Mix by manual inversion Do not shake	10 mL of sterile water Mix by gentle swirling
Adverse Events	(≥5%) Urticaria, rash, nausea, pruritus, back pain	(>2%) Pruritus, nausea rash, arthralgia, myalgia, pain, vomiting
Contraindications	Hypersensitivity to any of its components, papaya, or papain.	None

Serotonin Syndrome vs NMS vs Malignant Hyperthermia

Hannah Metzler, Samford University PharmD Candidate 2019

Serotonin syndrome presents similarly to neuroleptic malignant syndrome (NMS) and malignant hyperthermia. Detailed patient history and thorough physical examination are essential in diagnosis and differentiation of serotonin syndrome. A medication history is necessary to examine the patient's exposure to any causative agents. Although these syndromes present similarly, clinical differences between syndromes do exist and can be used for symptom differentiation, treatment selection and prevention. The chart below includes several parameters that may be helpful for syndrome differentiation.

	Causative agent(s)/Toxicity	**Onset/ resolution**	**Physical examination findings**	**Laboratory values**
Serotonin Syndrome	Serotonergic agents (SSRIs, SNRIs, other Antidepressants, Antipsychotics, tramadol, fentanyl, meperidine, dextromethorphan) Serotonin syndrome has been reported less commonly in overdose of single agents, but usually occurs following interaction of 2 or more pro-serotonergic drugs. Serotonin drug effects may be seen in approximately 30% of patients starting SSRIs.	Within 24 hours of new dose or initiation of new medication/24 hours If patient is taking an MAOI and it is combined with a serotonin uptake inhibitor the reaction can be seen weeks after discontinuation.	1. **Neuromuscular hyperactivity: Hyperreflexia**, **clonus**, ocular clonus, muscle rigidity, akathisia 2. **Autonomic hyperactivity:** Tachycardia, hypertension, diaphoresis, hyperthermia, mydriasis, tremor 3. **Mental status changes:** Agitation, anxiety, confusion, hypomania	No lab values appear very specific for serotonin syndrome but may be present; Elevated WBC, Elevated CK, decreased serum bicarbonate
Neuroleptic Malignant Syndrome	Neuroleptic agents(1st and 2nd generation antipsychotics) NMS occurs in 1% of patients receiving antipsychotics, NMS is more likely to occur with high-potency antipsychotics, but has been reported to occur with virtually every antipsychotic.	Days to weeks/average of 9 days	**1. Mental status change:** agitated delirium or confusion **2. Muscle rigidity (lead pipe)** **3. Hyperthermia** **4. Autonomic instability**: tachycardia, labile or high blood pressure, tachypnea, dysthymias, diaphoresis	Elevated serum CK levels (typically more than 1000 u/L, metabolic acidosis
Malignant Hyperther-mia	Anesthetic agents (halothane, isoflurane, sevoflurane, or desflurane) or succinylcholine The majority of susceptible individuals are completely asymptomatic until exposed to triggering drugs or conditions. The development of MH is dependent upon the dose and duration of the anesthetic.	Within minutes to hours of anesthetic/ 24 hours	**Early signs**: Sinus tachycardia, **hypercarbia**, **masseter muscle rigidity**, generalized muscle rigidity, **Later signs**: hyperthermia, , myoglobinuria, ECG changes related to hyperkalemia, tachypnea	Hyperkalemia, mixed metabolic and respiratory acidosis, elevated $ETCO_2$, (>55mmHG), elevated CK

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