



## Program Announcements ••

**Ruth A. Lawrence:** Monthly conference: every 4 weeks on Thursdays (11 am to noon), and every 4 weeks on Tuesdays (10 am-11 am).

**UNY:** Our Twelfth Annual Toxicology Teaching Day will be held on November 5, 2008 at the Genesee Grand Hotel in Syracuse. Please mark your calendar!

**NYC:** Consultants Case Conference • The first Thursday of the Month from 2-4pm

Our annual "An Intensive Review Course in Clinical Toxicology" will be held on March 13th and 14th 2008 at the NYC Poison Control Center.

**Target audience:** Physicians, Pharmacists, Nurses, Nurse Practitioners, Physician Assistants, medical/pharmacy/nursing students are welcome to register.

Anyone interested in registering can email Maria Mercurio-Zappala at [mmercuri@health.nyc.gov](mailto:mmercuri@health.nyc.gov) for more information.

**Long Island Regional Poison and Drug Information Center Toxicology Teaching Conferences 2008**

Pre-Registration is required. Please contact Mr. Denis Jao at 516-663-2650 to register.

Both Telephone and Televideo broadcasts will be available.

**Target Audience:** Physicians, Pharmacists, Nurses, Nurse Practitioners, Physician-Assistants, Laboratory technicians, EMS staff, medical/nursing/pharmacy students and other healthcare professionals.

Times for ALL Conferences are: 12:15 PM-1:45 PM

**Tuesday, January 22, 2008**

**TOPIC:** *An Update on Carbon Monoxide Poisoning and Hyperbaric Oxygen*

**Speaker:** Dr. Scott Gorenstein, Winthrop University Hospital

**Tuesday, February 26, 2008**

**TOPIC:** *Sports Toxicology*

**Speaker:** Dr. Mark Su, Toxicology Consultant, Long Island Regional Poison & Drug Information Center; Winthrop University Hospital, and Attending Physician, North Shore University Hospital Emergency Department

**Continued on page 2**

Please call administrative telephone numbers for more information.

## Caustic Exposure

*Contributed by: Christine Stork, Pharm.D. DABAT, Upstate New York Poison Center, Syracuse, NY*

### Case Report:

A 36 year old male presents to the emergency department (ED) after ingestion of an acid containing cleaning substance. He has vomited several times and continues to vomit in the emergency department. The pH of the product is determined to be between pH 0 to pH 1. The patient is seen, evaluated, and fluids and anti-emetics are initiated. On physical examination, vital signs include: blood pressure; 136/62 mmHg, heart rate; 85 beats per minute, respiratory rate; 18 breaths per minute and temperature (unknown). Pulse oximetry oxygen saturation was 100% on room air.

### What are the important considerations in the initial care of patients after caustic exposure?

As in most cases after toxin exposure, careful attention to airway, breathing and circulation are paramount. The time prior to and early after arrival to the emergency department provides opportunity to mitigate toxicity with focused efforts on decontamination.

The care of patients with corrosive exposures may differ depending on the identity of the substance, the relative

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## Toxicology Advice Centers ••

**Administrative Phone Numbers** - To obtain a consult in your area, call 1.800.222.1222.

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716.878.7871 • <http://wnypoison.org>

**Ruth A. Lawrence NY Poison Center (FL)**

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**Upstate New York Poison Center (UNY)**

315.464.7078 • [www.upstatepoison.org](http://www.upstatepoison.org)

**New York City Poison Control Center (NYC)**

212.447.8152

**Long Island Poison & Drug Info Center (LI)**

516.663.4574 • [www.LIRPDIC.org](http://www.LIRPDIC.org)

pH, and type of tissue injury expected. Fortunately, in the *initial* management, they are all similar in that limitation of contact time and decontamination are the mainstay of minimizing toxicity. After contact exposure to external skin and eyes, patients should be copiously irrigated with the closest available irrigation solution, most commonly water or normal saline. In select circumstances, where the corrosive agent is not soluble in water or normal saline, such as in the case of phenol, high molecular weight poly ethylene glycol solutions provide a viable alternative.

After *oral ingestion* of corrosives, as described in the reference case, additional considerations limit the viability of decontamination. Specifically, corrosive agents cause injury to the oral cavity and esophagus during ingestion so attention should focus on minimizing the potential for vomiting thereby reducing the risk for additional contact with the caustic. Additionally, the benefit of neutralizing acids and alkalis is largely diminished by the generation of heat and gas which may potentiate tissue injury. Large acid ingestions may benefit from guided placement of a nasogastric tube in an attempt to remove residual acid, although accomplishing such may be technically difficult due to the risks of perforation. Patients ingesting fluoride containing substances such as hydrofluoric acid and ammonium bifluoride should receive oral calcium or magnesium containing substances if possible.

After *ocular exposure* to a corrosive agent, irrigation should occur with an isotonic solution. This should continue until a near normal ocular pH is obtained. Many patients find this process more comfortable using ocular anesthetics and Morgan Lens technology.

## What determines what a “caustic” is and the potential for caustic injury?

A caustic, typically characterized as an acid or alkali, is any substance that causes tissue injury on contact primarily through the mechanism of accepting (alkali) or donating (acid) a proton. Notably, non-acid/ alkali substances are also well known causes of tissue injury and are also thereby given the name caustics. For example, concentrated hydrogen peroxide can create a significant oxidative stressor with resultant tissue damage.

For strong acids and alkalis the extent of toxicity is determined by multiple factors including, the duration of contact, ability to penetrate tissues, pH, concentration, and volume of exposure. Although even when these variables are known, it is often difficult to define the corrosive capacity of a given chemical substance. The titratable alkaline reserve (TAR) was developed and is used to explain these differences in relative toxicity. The TAR is the amount of a neutralizing compound needed to bring the tissue exposed to a caustic back to a physiologic pH. It is important to note that in the case of weak acids, such as hydrofluoric acid and ammonium bifluoride, the majority of the tissue injury seen is the result of fluoride penetration and binding to available calcium and magnesium with subsequent cell dysfunction and death.

## What types of injury do acid and alkali corrosives produce?

Tissue exposure to an alkaline compound, such as sodium hydroxide (NaOH), results in the tissue penetration of the dissociated  $\text{OH}^-$  ions causing a liquefactive necrosis. The liquefactive necrosis results in protein dissolution, collagen destruction, fat saponification, cell membrane emulsification, transmural thrombosis, and cell death. An alkali eye exposure can rapidly form corneal epithelia defects and the alkali will eventually deeply penetrate the eye.

Alternatively, tissue exposure to an acidic compound, such as hydrochloric acid, results in liberation of a  $\text{H}^+$  ion which creates acidic stress to tissue sited and results in coagulation necrosis and eschar formation of exposed tissue.

## What signs and symptoms are common after corrosive exposure?

Tissue necrosis following exposure to a caustic can occur within minutes. The longer the contact time with the tissues, the greater the risk for increased area of necrosis. Ingesting a corrosive agent can result in severe pain of the lips, mouth, throat, chest, or abdomen. Oropharyngeal edema and burns may cause rapid airway compromise, which may or may not present with drooling. Paradoxically, some acidic exposures can be relatively anesthetizing in nature and are not associated with significant discomfort.

Medical management after ingestion of these substances is guided by the degree of tissue injury. Unfortunately, it is often difficult to gauge the degree of tissue injury that has occurred and warrants more invasive diagnostic testing. The presence or absence of oral cavity injury is not predictive of esophageal or gastric injury. This is especially problematic in children which require general anesthesia for endoscopy. Based on findings by Crain et al., standard practice dictates that children exposed to *alkaline* corrosives with two of the following findings, vomiting, drooling and stridor, are at risk for significant esophageal injury (grade II/ III) and should be scoped. After *unintentional* alkaline exposure in a patient who is tolerating oral fluids and without two of the noted findings, significant injury to

## Program Announcements ••

Continued from page 1

Tuesday, March 25, 2008

**TOPIC:** *Environmental Toxicology*

**Speaker:** Dr. Kathy Ferguson, Toxicology Fellow and Attending Physician, North Shore University Hospital Emergency Department

**Location:**

New Life Conference Rooms B&C  
Winthrop-University Hospital  
259 First Street  
Mineola, Long Island, New York 11501

Continued on page 3

the esophagus and stomach is not expected. In contrast, *all* non-alkali caustic exposures require empiric endoscopy as do *all* intentional caustic exposures.

## What are the important management strategies?

After decontamination (if possible) and initial patient stabilization, management should strive to limit the extent of tissue injury and to mitigate long term effects. Patients presenting after exposure to large amounts of caustic agents are best managed surgically, preferably prior to perforation and subsequent sequelae.

Symptomatic patients with non-life threatening presentations can be supportively managed according to endoscopic findings. Patients with Grade I injury generally do well with supportive management alone. Patients with Grade II non-circumferential injuries also do well, but the clinical course may be prolonged. Patients with Grade II circumferential lesions of the esophagus are at risk for the formation of stricture and long term sequelae. In this group, scar tissue forms as part of the healing process which can provide for obstruction and also an increase in risk for esophageal cancer. The use of corticosteroids in these patients is a consideration, however, the lack of evidence of clear benefit, increased infection risk and long course required preclude its routine use. Alternatively, intraluminal stents hold promise in animal and human models in the prevention of esophageal occlusion during healing. Stents may also prevent the formation of strictures, although there are risks of delayed wound healing demonstrated in animal models.

## Are there any newer potential therapies after ocular exposure?

Diphoterine is an amphoteric irrigation solution that can return ocular pH to the physiologic range after exposure.

The amphoteric nature of Diphoterine allows it to bind to either an acid or an alkali. In addition diphoterine is hypertonic and may promote the extrusion of H<sup>+</sup> and OH<sup>-</sup> ions. In a study comparing healing time in grade I and II ocular alkali burns, the healing time of corneal scarring was shorter with Diphoterine compared to a physiologic solution. The clinical importance of this time change and use in grade III and IV burns is unclear at this time.

## Case resolution

Endoscopic evaluation found first degree lesions of the esophagus and stomach. The patient's symptoms resolved over the next several hours and the patient was transferred for a psychiatric evaluation.

## Select References:

- Crain EF, Gershel JC, Mezey AP. *Caustic ingestions – symptoms as predictors of esophageal injury.* **Am J Dis Child** 1984;138:863-5.
- Hoffman RS, Howland MA, Kamerow HN, Goldfrank R. *Comparison of titratable acid/alkaline reserve and pH in potentially caustic household products* **Clin Toxicol** 1989;27:241-61.
- Berkovits RN, Bos CE, Wijburg FA, Holzki J. *Caustic injury of the esophagus. Sixteen years' experience and introduction of a new model esophageal stent.* **J Laryngol Otol** 1996;110:1041-5.
- Karnak I, Tanyel FC, Buyukpamukcu N, Hicsonmez A. *Combined use of steroid, antibiotics and early bougienage against stricture formation following caustic esophageal burns.* **J Cardiovasc Surg** 1999;40:307-10.
- Salzman M, O'Malley RN. *Updates on the evaluation and management of caustic exposures.* **Emerg Med Clin N Am** 2007;25:459-76.

**Table 1 - Common corrosives**

Acids	Alkalis	Non-acid/alkali
Hydrochloric acid – HCL (toilet bowel cleaner, “muriatic acid”, industry)	Sodium Hydroxide – NaOH (drain openers, oven cleaners, industry)	Hydrogen peroxide (30%) (hair relaxers, industry)
Acetic acid (hair neutralizers, industry [photography])	Potassium Hydroxide – KOH (industry)	Podophyllum (pharmaceuticals)
Hydrofluoric acid – HF (glass etching, graffiti remover, computer chip industry)	Potassium Iodide (pharmaceuticals, industry)	
Sulfuric acid (drain openers, industry)		
Phenol (antiseptics)		
Mercury Chloride (antifungals, preservatives)		

# FDA Safety Summaries

<http://www.fda.gov/medwatch/safety/2007/safety07.htm#chronological>

Desmopressin Acetate (marketed as DDAVP Nasal Spray, DDAVP Rhinal Tube, DDAVP, DDVP, Minirin, and Stimite Nasal Spray)

Myfortic (mycophenolic acid) Delayed-Release Tablets

Encore Supplement Tablets

Chantix (Varenicline)

Avandia (rosiglitazone maleate) Tablets

Cefepime (marketed as Maxipime)

Erythropoiesis Stimulating Agents: Aranesp (darbepoetin alfa), Epogen (epoetin alfa), and Procrit (epoetin alfa)

Trasylol (aprotinin injection)

CellCept (mycophenolate mofetil)

Aprotinin Injection (marketed as Trasylol)

Provigil (modafinil) Tablets

Viagra (sildenafil), Cialis (tadalafil), Levitra (vardenafil), Revatio (sildenafil)

Byetta (exenatide)

Charantea Ampalaya Capsules and Charantea Ampalaya Tea by FullLife Natural Options, Inc.

Hydrocodone in Unapproved Prescription Products

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Times for ALL Conferences are: 12:15 PM-1:45 PM

**Wednesday, April 2, 2008**

**TOPIC:** *Environmental Toxicology*

**Speaker:** Dr. Kathy Ferguson, Toxicology Fellow, Long Island Regional Poison & Drug

Information Center at Winthrop University Hospital and North Shore University; Emergency Department

**Tuesday, April 22, 2008**

**TOPIC:** *Neurotoxicology*

**Speaker:** Dr. Louis Trombetta, St John's University College of Pharmacy & Allied Health Professions

**Tuesday, May 27, 2008**

**TOPIC:** *Antidotes: How to Use Them*

**Speaker:** Dr. Howard Greller, Toxicology Consultant, Long Island Regional Poison & Drug

Information Center at Winthrop University Hospital, and North Shore University Hospital; Attending Emergency Department

**Continued on page 2**

Please call administrative telephone numbers for more information.

## Transdermal Medications for Systemic Use

*Contributed by: Sharon Ternullo, Pharm.D. CSPI, DABAT  
Coordinator Drug Information Services Ruth A. Lawrence  
Poison and Drug Information Center, Rochester, NY*

### Case Report:

#### Background

Since scopolamine became the first FDA approved drug utilizing a transdermal delivery system for motion sickness in 1981, technology has been evolving to allow the transdermal route to be used for a more varied assortment of drugs with fewer side effects. Since 1981 the FDA has approved more than 35 transdermal patch products. In 2001 the transdermal market approached \$1.2 billion and was based on only 11 molecules.<sup>1</sup> There are currently at least 16 FDA approved drugs delivered transdermally for systemic use on the market (Table 1 on page 2).

#### Skin Physiology

The skin is the most accessible organ of the human body and also the body's primary biological barrier. The skin's uppermost layer, the stratum corneum, reaches a depth of only 10% of the skin's depth but contributes more than

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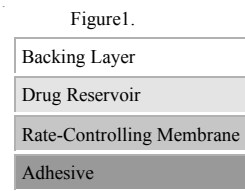
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**Table 1. Currently Available Transdermal Patches for Systemic Effects**

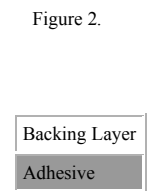
Generic Drug	Brand Name	Strengths/ Release Rate	Application Frequency	Manufacturer	Total Drug Content per Patch	Release Mechanism
Clonidine	CatapressTTS	0.1,0.2,0.3,mg/24hr	7 days	Boehringer Ingelheim	2.5,5,7.5mg	membrane
Estradiol	Alora	0.025,.05,.075,.1mg/24hr	7 days	Watson	0.77,1.5,2.3,3.1mg	matrix
	Climara	.025,.0375,.05,.06,0.75,.1mg/24hr	7 days	Bayer	2,2.85,3.8,4.55,5.7,7.6mg	matrix
	Estraderm	0.05,0.1mg/24hr	3-4 days	Novartis	4mg,8mg	membrane
	Vivelle-Dot	0.025,.0375,.05,.075,.1mg/24hr	3-4 days	Novartis	0.39,585,.78,1.17,1.56mg	matrix
Estradiol/ Norethindrone	CombiPatch	0.05/.14mg/24hr, 0.05/.25mg/24hr	3-4 days	Novartis	0.62/2.7mg, 0.51/4.8mg	matrix
Estradiol/ Norelgestromin	Ortho Evra	20ug/150ug/24hr	7 days	Ortho-McNeil	0.75mg/6mg	matrix
Fentanyl	Duragesic	12.5,25,50,100ug/hr	72 hours	Ortho-McNeil	1.25,2.5,5,7.5,10 mg	membrane
Lidocaine	Lidoderm	35mg/12 hr	12 hr/day	Endo	700mg	membrane
Methylphenidate	Daytrana	10,15,20,30mg/9hr	9 hr/day	Endo	27.5,41,3,55,82.5mg	matrix
Nicotine	Habitrol	7,14,21mg/24hr	16-24 hr/day	Novartis	17.5,35,52.5mg	matrix
	Nicoderm CQ	7,14,21mg/24hr	16-24hr/day	Sanofi/Aventis	36,78,114mg	membrane
Nitroglycerin	Nitro-Dur	0.1,.2,.3,.4,.6,.8mg/hr	12-14hr/day	Key	20,40,60,80,120,160mg	matrix
	Mini-tran	0.1,.2,.4,.6mg/hr	12-14hr/day	Graceway	Approx 8.6,17,34,51.4mg	membrane
Oxybutynin	Oxytrol	3.9mg/24 hr	3-4 days	Watson/Pharma	36mg	matrix
Rotigotine	Neupro	2,4,6mg/24hr	24hr	Schwartz	4.5,9,13,5mg	matrix
Scopolamine	Transderm- Scop	1.0mg/72hr	3 days	Novartis	1.5mg	membrane
Selegiline	Emsam	6,9,12mg/24hr	24 hr	Bristol Meyers/ Squibb	20,30,40mg	matrix
Testosterone	Androderm	2.5,5mg/24hr	24 hr	Watson	12.2,24,3mg	membrane

80% to its permeability barrier<sup>2</sup>. The stratum corneum consists of protein-filled corneocytes that are embedded in a lipid matrix. The cells are arranged in a brick like manner where the channels can be envisioned much like the mortar around the bricks in a brick wall. This arrangement means that to penetrate the stratum corneum, molecules must follow a route of high tortuosity between corneocytes and through the lipid matrix. The result is that despite the stratum corneum having a thickness of only about 10 microns, the actual path that a molecule must diffuse through to cross the membrane may be up to 50-fold greater.<sup>3</sup> Since pores are small enough to only permit the passage of molecules that are smaller than a millionth of a millimeter<sup>2</sup> and hair follicles in the skin only make up 0.001% of the skin's surface area, neither route is a clinically significant means of drug absorption systemically.<sup>3</sup>

to some degree. The delivery system or vehicle must be capable of retaining a sufficient quantity of drug to provide therapy for the desired time frame, but it must also give up the compound readily to the stratum corneum. The two main delivery systems in use at this time are the membrane-controlled and the matrix systems. Schematics of both delivery systems are shown below (Figures 1. and 2.).<sup>5</sup>



Membrane-controlled System



Matrix-controlled System

## Benefits of Transdermal Delivery of Medications

Transdermal delivery potentially improves patient compliance when compared with oral therapy. This has been studied most extensively with oral contraceptives.<sup>4</sup> There is also an advantage of increased bioavailability by avoiding the first pass effect and acid inactivation or generally poor absorption in the GI tract of drugs that are generally hydrophilic. For drugs with short biological half lives and narrow therapeutic windows, continuous release transdermal systems eliminate the need for multiple daily doses to maintain therapeutic levels and minimize adverse effects by eliminating systemic peaks in drug levels.

## Current Technology

The main concept behind current transdermal patches is that liquids in direct contact with the skin can be absorbed

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# Program Announcements ••

Continued from page 1

Tuesday, June 10, 2008

TOPIC: *Cardiac Toxins*

Speaker: Dr. Nima Majlesi, Toxicology Fellow, Long Island Regional Poison Center & Drug

Information Center at Winthrop University Hospital and North Shore University; Emergency Department

Location:

New Life Conference Rooms B&C  
Winthrop-University Hospital  
259 First Street  
Mineola, Long Island, New York 11501

The first transdermal patches on the market incorporated the reservoir/membrane technology. The membrane-controlled system consists of four layers: the backing, the drug reservoir where drug is stored, the membrane which controls the rate at which drug enters the skin, and an adhesive layer that attaches the patch to the skin. The drug diffuses from the reservoir through the rate controlling membrane and then passes through the adhesive to the skin. The release rate is a constant and must be maintained at a level below the skin's saturation limit. Patches incorporating a reservoir and membrane will deliver a steady drug flux across that membrane as long as there is an excess of drug in the reservoir.

In a matrix system, the adhesive serves as the reservoir for the drug and the adhesive for the patch. The drug is dissolved or suspended in a polymer matrix with the adhesive and is present on the skin in combination with the adhesive layer. In this design the drug is delivered to maintain the skin's saturation and therefore the diffusion of the drug is dependent on the skin's absorption rate. When the amount of drug in the patch falls below the saturation of the skin, the rate of drug delivery will gradually diminish. Matrix devices are typically characterized by a decreasing drug flux with time as the matrix layers closest to the skin are depleted of drug and drug in layers further away from the skin begin to diffuse. For most well designed matrix patches, however, the release rate does not significantly affect the rate of drug absorption over the recommended lifetime of the dosage form. Drug-in-adhesive transdermal patches are a major focus of research because of the challenges in integrating adhesive drugs and excipients into a single elegant system and achieving stability of the product and optimal performance of both the drug and the adhesive throughout the intended wear period. Despite these challenges, the matrix system is the workhorse of the current transdermal technologies.

## Limitations in Transdermal Systems

Since the skin is an effective barrier against the majority of drugs, unless the delivery device is made unacceptably large or the natural skin permeation rate of the drug is increased, the drug diffusion across the skin is inadequate for clinical purposes. Since work began in this field serious research of candidate drugs has been carried out only on molecules where there are strong indications for transdermal use. These criteria include drugs with small molecular size, a short half life, rapid inactivation by the liver, rapid degradation by the gastrointestinal tract, problems with oral administration, high in vivo skin diffusion, and high drug potency. The existing patches on the market are limited to low molecular weight drugs that are hydrophilic and are able to diffuse through the stratum corneum. The top molecular weight of a transdermally absorbed drug in a portable patch currently is less than 500 daltons. The lower permeability of higher molecular weight drugs has been a limiting factor. For patient compliance and economics, patch sizes much larger than 50cm are unlikely to be

useful.<sup>6</sup> Smaller and less conspicuous patch designs to increase comfort and privacy are desirable but size is often limited by the amount of drug that can be incorporated and delivered by a given system and therefore only drugs that are of relatively high potency and therefore require very small daily dosages are currently on the market in a transdermal dosage form. Adhesive failure still occurs when skin becomes wet or sweaty which is a problem in patches designed for 24 hour wear. The greatest shortcoming is skin irritation secondary to adhesives, the drug itself, and the traumatic removal of the patch.

## Acute Toxicity of Patches

As previously described, the drugs contained in patches at this time are limited to drugs that are potent in small amounts and highly diffusible through the skin. In order to maintain a consistent release rate of drug, a transdermal patch must contain a surplus of active drug to drive the diffusion into the stratum corneum. Many patches contain 20-30 times the amount of drug that will be absorbed during the time of application and therefore, at the time of removal, most patches will contain at least 95% of the total amount of drug initially placed in the patch.<sup>7</sup> The combination of a potent drug and the excess amount of drug required in the dosage form makes the potential for toxicity significant. However toxicity is expected acutely from only a handful of the patches on the market today. The estrogen, contraceptive, and testosterone patches have minimal potential for acute toxicity from the drug and should be handled as any other foreign body if ingested orally. Of currently available patches only clonidine, fentanyl, lidocaine, methylphenidate, nicotine, nitroglycerin, oxybutynin, scopolamine, rotigotine, and selegiline could be expected to produce acute toxicity in certain circumstances. Toxicity from these patches would follow the course expected from any other exposure to the drug contained in the patch and treatment would also be similar.

There is limited information on acute toxicity from transdermal patches but injury can occur in several ways. Profound bradycardia, slurred speech, and disorientation has been reported from the intentional ingestion of a 0.2mg clonidine patch containing 5mg of clonidine.<sup>8</sup> Accidental application to the oral mucosa or sucking on a discarded clonidine patch in infants and toddlers has resulted in bradycardia, hypotension, sedation, gasping respirations, and miosis; all typical of clonidine toxicity. Resolution of the symptoms took 12-16 hours after the patches were removed.<sup>9,10,11</sup> Anticholinergic toxicity with delirium and blurred vision has been reported 12 hours after the application of a transdermal patch in a 6 year old.<sup>12</sup> The delays reported in the above cases and prolonged time till resolution are consistent with the fact that most patches gradually saturate the skin underneath with drug and this dermal reservoir will release drug for several hours after the patch is removed and the skin below it cleaned. This will also result in a lag between the exposure and the development of clinical symptoms of toxicity as the systemic release



Contributed by: Sharon Ternullo, Pharm.D, CSPI, DABAT, Ruth A. Lawrence Poison and Drug Information Center, Rochester, NY

### Question:

A dentist called the Drug Information Center regarding a 55 year old male patient on whom he just did multiple tooth extractions. The dentist is having difficulty stopping the bleeding from the site. He was aware that the patient was on warfarin but the bleeding is out of proportion to that normally seen in this situation. He remembers that the patient's last INR was less than 3 but cannot remember the exact number. The dentist obtained a history before the surgery and the patient only mentioned warfarin, Zoloft, and atorvastatin. Now the patient indicated that he is on all of the following medications and nutritional supplements:

Warfarin 3mg, 1 p.o qd  
Evening primrose oil, 2gm bid  
Ginkgo, 120mg bid  
Fish oil capsules, 3gm bid  
Zoloft 150mg, 1 p.o qd  
Enteric coated aspirin 325mg, 1 p.o qd  
Atorvastatin 20mg, 1 p.o qd  
Lisinopril 20mg/hydrochlorothiazide 12.5mg, 1 p.o qd

The dentist is enquiring if there are any drug interactions that could be causing this abnormal bleeding.

### Answer:

#### Background

A drug interaction is defined as the pharmacological result, either desirable or undesirable, of drugs interacting with themselves or with other drugs, with endogenous chemical agents, with components of the diet, or with chemicals used in or resulting from diagnostic tests. Interactions can be divided into pharmacokinetic interactions that are often associated with significant changes in a drug's plasma concentration, onset of action, half-life or other pharmacokinetic parameters and are associated with changes in absorption, distribution, or elimination. Pharmacodynamic interactions are usually related to the interacting drug's ability to produce a change in a patient's response to a drug without changing the drug's pharmacokinetic properties. Traditionally prescription and over-the-counter drugs have been the focus of studies that identify and quantitate the significance of drug interactions.

According to the National Center for Complimentary and Alternative Medicine (NCCAM), a dietary supplement can be a vitamin, a mineral, an herb or other botanical, an amino acid, or other such substances or their constituents.<sup>1</sup> Beginning in the early 1990s the market for nutritional supplements increased, especially after the US Dietary Supplement Health and Education Act of 1994 was passed. Currently an estimated one in four persons taking prescrip-

tion medication also take a dietary supplement.<sup>2,3</sup> Some supplements have demonstrated pharmacologic action with the potential to produce therapeutic results. Even supplements that do not have a documented pharmacologic action can affect the absorption, metabolism, and disposition of other drugs. Nutritional supplements, in general, are not studied and their potential for interacting with other drugs and nutritional supplements is not clearly defined.

#### Patient case

In this particular case, the patient was taking<sup>5</sup> other medications known, in addition to warfarin, to have antiplatelet or anticoagulant activity. Only one of these medications was a prescription drug. The increased risk of bleeding due to combination therapy with aspirin and warfarin has been well documented.<sup>4</sup> In a study including 534 patients, bleeding that required a blood transfusion or hospitalization was three times more likely in patients receiving warfarin and aspirin (500 mg/day), than in patients receiving warfarin and 400 mg per day of dipyridamole or in patients receiving warfarin alone.<sup>5</sup> In small doses, it appears that aspirin can cause gastric erosion and inhibit platelet function. In larger doses, aspirin can exhibit a hypoprothrombinemic response that is likely additive with the effect produced by coumarin derivatives.

This patient was also on Sertraline (Zoloft). The selective serotonin reuptake inhibitors (SSRI) may have additional antiplatelet effects in patients already receiving aspirin, and the combination of an SSRI and aspirin may increase the risk of gastrointestinal bleeding. Multiple retrospective case-controlled studies have reported statistically significant associations between concurrent SSRI and aspirin therapy and the risk of gastrointestinal bleeding. Concurrent therapy with a combination of aspirin and an SSRI increases the risk of gastrointestinal bleeding between 2 and 7 times.<sup>6,7,8,9</sup> Currently the data is insufficient to determine differences in risk by individual SSRI or by the dose of SSRI administered. Since serotonin enhances platelet aggregation, and since platelets can not synthesize serotonin, transporter-mediated uptake from blood is required for maintenance of normal intra-platelet serotonin concentrations. Inhibition of platelet uptake of serotonin from blood by SSRIs may lead to a gradual depletion of platelet serotonin and consequently to impaired platelet aggregation. Considering the number of studies and reports suggesting an association between combined SSRI and aspirin use and bleeding, and a plausible mechanism to support an association, it seems reasonable to recommend increased monitoring for bleeding in patients receiving this combination.

Evening primrose oil, ginkgo extract and fish oil are all nutritional supplements that have been advocated for varied conditions. Ginkgo has been advocated for dementia and various cognitive disorders. Fish oil has been recommended for hyperlipidemias, hypertension, and other

Continued on page 5



disorders. Evening primrose has been advocated for osteoporosis, menopausal symptoms, PMS, dermatitis and other chronic disease states.

Evening primrose oil, which contains gamma-linolenic acid (GLA), could have anticoagulant effects<sup>10</sup>. Theoretically, taking evening primrose oil with other anticoagulant or antiplatelet drugs might increase the risk of bruising and bleeding but cases in the literature and study of the issue are lacking.

Spontaneous bleeding has been of the most concerning potential side effects associated with ginkgo. There are several published case reports linking ginkgo to episodes of minor to severe bleeding but causality has not been proven since in most cases there were other risk factors for bleeding present such as concomitant medications, advanced patient age, cirrhosis, or recent surgery. In most cases, bleeding occurred after chronic use for several weeks or months. These reports include intracerebral bleeding, intraocular bleeding, and bleeding post various surgeries including: laparoscopic surgery, total hip arthroplasty.<sup>11</sup> In one case, an elderly man experienced nose bleeds and ecchymosis following use of ginkgo. The bleeding stopped when ginkgo was discontinued and recurred when the ginkgo was resumed.<sup>11</sup> It has been suggested that ginkgo has to be taken for at least 2-3 weeks to have a significant effect on platelet aggregation.<sup>12</sup> It should be used cautiously in patients taking anticoagulants or antiplatelet drugs.

High doses of fish oil seem to have antiplatelet effects but might not be as potent as aspirin in inhibiting platelet function. Theoretically, combining fish oil with herbs and supplements or drugs with antiplatelet or anticoagulant activity might increase the risk of bleeding in some people<sup>13, 14, 15</sup> however, conflicting research suggests that taking fish oils 3-6 grams/day does not significantly affect INR when use in patients taking warfarin.<sup>16</sup> Other conflicting research suggests fish oils do not have additive antiplatelet effects when combined with aspirin<sup>15</sup>. It would be prudent, however, to monitor patients taking fish oils who are on other drugs with antiplatelet or anticoagulant effects.

This patient was taking aspirin along with lisinopril and hydrochlorothiazide. This combination has the potential for an oppositional or antagonistic drug interaction. Aspirin inhibits prostaglandin formation via its inhibitory effect on the enzyme cyclo-oxygenase. Angiotensin-converting enzyme inhibitors at least partially mediate their therapeutic effects via vasodilating prostaglandins. Doses of aspirin as low as 300mg per day have been shown to interfere with the antihypertensive effects of enalapril, whereas 100mg doses did not appear to have an effect.<sup>17</sup> The interactions of non-steroidal anti-inflammatory agents decreasing the diuretic effect of the hydrochlorothiazide and increasing blood pressure by this mechanism and by sodium and fluid retention is speculative with respect to aspirin.

The only pharmacokinetic interaction between this patient's medications is one that involves the Cyp3A4 enzyme system. Sertraline (Zoloft) has some moderate ability

to inhibit the Cyp3A4 system and atorvastatin (Lipitor) is a substrate that is metabolized by this system. This could theoretically increase the risk of side effects associated with atorvastatin such as myalgia or increasing liver enzymes. This patient did not appear to have symptoms of toxicity from atorvastatin.

## Summary

Although nutritional supplements are considered safe and natural by many individuals, in some situations, they can interact with each other, medications, and disease states to produce unwanted or distorted clinical effects in patients taking them. Patients should be encouraged to disclose any nutritional supplements that they are taking and medical professionals should monitor them accordingly.

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# SPI CORNER:

## Carbon Monoxide Exposure in Pregnancy

Contributed by: Paul Dengler SPI, CPNP, Ruth A. Lawrence Poison and Drug Information Center, Rochester, NY

### Case Report:

A primiparous woman, 37 weeks gestation, presented to the ED by ambulance with a report of Carbon Monoxide (CO) exposure. Her symptoms included headache, nausea, vomiting, and lethargy. Pt received oxygen en route to ED, and her carboxyhemoglobin (COHb) level on arrival was 14.3%. CO was detected in the home from faulty ductwork with CO level of 300 PPM. No fetal movement felt in 24 hours. Decreased variability and bradycardia present on fetal monitor. The patient was sent for an emergency C-section. APGAR scores were 2 at one minute and 7 at five. There were no spontaneous respirations. Chest compressions, resuscitation and intubation were required. The fetal COHb level was 33.0% from arterial cord blood. Treatment with O<sub>2</sub> was given in the Neonatal Intensive Care Unit. Symptoms included apnea and posturing. Seizures were present on EEG and an MRI showed cortical changes to the brain. The infant was discharged to home on day 7. He was being treated with Phenobarbital and was no longer having seizures, but his developmental prognosis was poor.

### Discussion:

CO is a colorless and odorless toxic gas created as a byproduct of incomplete combustion. Portable heaters, faulty furnaces, vehicles, and fireplaces are possible sources of CO. CO is preferentially bound to hemoglobin (Hb) and to any hemeoxygen transporting protein. This results in decreased oxygen carrying capability and subsequent tissue hypoxia. The relative affinity of Hb for CO is 200-250 times that of oxygen in adults and 172 times in infants.<sup>1</sup>

Symptoms of mild exposures to CO toxicity are often described as flu like. These include headache, dyspnea, fatigue, nausea and dizziness. Symptoms of more severe exposures also include syncope, confusion, focal neurological deficits, tachycardia and hypotension, disorientation, ventricular dysrhythmias, myocardial ischemia, pulmonary edema, seizures, coma, and death.<sup>2</sup>

Maternal COHb levels do not always correlate with maternal symptoms and do not predict fetal outcome. Fetal Hb has higher affinity for oxygen and does not allow oxygen dissociation into tissues as readily as adult Hb. Hypoxia can occur in the fetus at relatively low maternal levels. The fetal COHb level may be 2 to 3 times higher than mother's and takes longer to clear. In acute exposure the fetal level will lag behind the mother's. Fetal CO elimination half life is 3.5 times longer than maternal half life.<sup>3</sup> Oxygen therapy should be started on any mother with symptoms of CO toxicity. Hyperbaric oxygen (HBO) should be considered for maternal symptoms of toxicity or signs of fetal distress and should be given prior to delivery. Fetal heart

tones should be checked on every pregnant woman with a history of CO exposure. When evaluating CO exposure in a pregnant patient, do not rely solely upon maternal COHb levels to gauge fetal risk. Examine the mother for symptoms, especially neurological and check fetal heart tones. For treatment start high flow O<sub>2</sub> immediately and continue for an extended time. Call your local Poison Control Center for guidance and for consultation on the indications for HBO.

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## FDA Safety Summaries

### "Blue Steel" and "Hero" Dietary Supplement Products

These products contain undeclared substances similar in chemical structure to sildenafil, the active ingredient in an FDA-approved prescription drug for ED. March 25, 2008

### B. Braun Heparin Sodium in 5% Dextrose and 0.9% Sodium Chloride Injection Solution

Nationwide recall of Heparin Sodium USP active pharmaceutical ingredient (API) because of a heparin-like contaminant. March 21, 2008

### Tiotropium (marketed as Spiriva HandiHaler)

Boehringer Ingelheim and FDA notified healthcare professionals that ongoing safety monitoring has identified a possible increased risk of stroke in patients who take Spiriva. March 18, 2008

### Erythropoiesis Stimulating Agents: Aranesp (darbepoetin alfa), Epopgen (epoetin alfa), and Procrit (epoetin alfa)

Changes to the Boxed Warnings/WARNINGS: Increased Mortality and/or Tumor Progression section of the Aranesp and EPOGEN/PROCRIIT labeling to update information describing the results of two additional studies showing increased mortality and more rapid tumor progression in patients with cancer receiving ESAs. March 07, 2008

### Prezista (darunavir)

FDA issued a new "Information for Healthcare Professionals" sheet highlighting the addition of hepatotoxicity information to the WARNINGS section of prescribing information for Prezista. March 21, 2008

Continued on page 8

of the drug does not occur until the skin sites are saturated. Inadvertent overdose by children or animals can be avoided by careful disposal of patches. Patches should be folded in half and the adhesive sides should be stuck together. They should be placed deep in trash so that animals and children cannot access them.

Damage to a transdermal patch, especially a membrane controlled patch, can result in poor control over the release rate of the drug. The recent recall of Duragesic 25ug/hr patches was due to the suspicion that the patches may have had a cut along one side of the drug reservoir within the patch which could result in the possible release of fentanyl gel. This release of fentanyl could expose patients or caregivers directly to fentanyl gel on the skin and absorption unregulated by the membrane within the patch. Because of the separate nature of the drug reservoir in a membrane-regulated patch, the drug is more easily accessible and potentially abusable. Duragesic transdermal patches have a reservoir of dissolved drug in a solvent and have been reported to be baked, scraped, and otherwise modified in order to obtain a soluble supply of fentanyl to administer by an alternate route, subsequently resulting in toxicity.<sup>13,14</sup>

Intentional or unintentional misuse of the patches, such as applying more than 1 patch at a time either has also been reported to result in nicotine toxicity.<sup>15</sup> This has also been reported for fentanyl patches and the potential exists for intentional abuse of clonidine patches in this manner.

## Summary

The transdermal route has several advantages for potent hydrophilic drugs with short half lives, minimal bioavailability, and low molecular weights. Toxicity from transdermal patches has been reported and is generally handled the same as toxicity secondary to other routes of exposure to the same drug. The onset and resolution of symptoms may be delayed due to the reservoir of drug in the skin under the patch. Decontamination consists of removing the patches from the skin and cleaning the site underneath

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Continued from page 5

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## Long-Acting Hydrocodone-Containing Cough Product (marketed as Tussionex Pennkinetic Extended-Release Suspension)

FDA informed healthcare professionals of life-threatening adverse events and death in patients, including children, who have received Tussionex Pennkinetic Extended-Release Suspension (Tussionex). March 11, 2008

## Unapproved Over The Counter Drugs Marketed for Prevention and Treatment of STDs

FDA advised healthcare professionals and consumers that the Agency issued Warning Letters to six U.S. companies and one foreign individual for marketing unapproved and misbranded drugs over the internet to U.S. consumers for the prevention and treatment of sexually transmitted diseases (STDs). The products are marketed under the names Tetrasil, Genisil, Aviralex, OXi-MED, Imulux, Betamannan, Micronutrient, Qina, and SlicPlus.

## Aspire36, Aspire Lite Dietary Supplements

Palo Alto Labs and FDA notified consumers and healthcare professionals of a voluntary nationwide recall of two dietary supplements, Aspire36 and Aspire Lite. The products were recalled because they were found to contain Aildenafil in trace amounts and Dimethyl sildenafil thione, an analog of Sildenafil, a drug used to treat erectile dysfunction. February 28, 2008

## Tamiflu (oseltamivir phosphate)

Roche and FDA informed healthcare professionals of neuropsychiatric events associated with the use of Tamiflu, in patients with influenza. February, 2008

## Spiriva (tiotropium bromide inhalation powder) Capsules; Foradil (formoterol fumarate inhalation powder) Capsules

FDA informed healthcare professionals and consumers of the correct way to use Spiriva and Foradil inhalation powder capsules. FDA and the American Association of Poison Control Center's (AAPCC) National Poison Data System have received many reports of patients swallowing Spiriva and Foradil capsules rather than placing the capsules in the inhalation devices. February 29, 2008

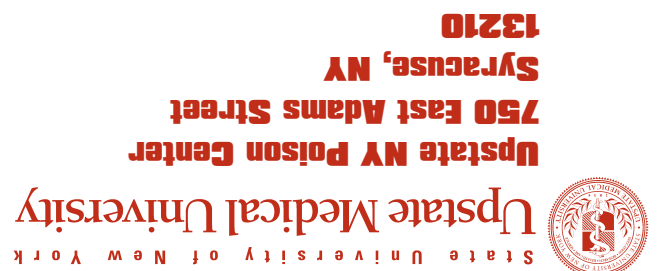
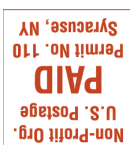
## Tysabri (natalizumab)

Biogen Idec, Elan and FDA notified healthcare professionals of reports of clinically significant liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose of Tysabri. February, 2008

## Avandia (rosiglitazone maleate)

FDA and GlaxoSmithKline notified pharmacists and physicians of a new Medication Guide for Avandia (rosiglitazone maleate). February, 2008

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## Program Announcements ••

**Ruth A. Lawrence:** Monthly conference: every 4 weeks on Thursdays (11 am to noon), and every 4 weeks on Tuesdays (10 am-11 am).

**UNY:** Our Twelfth Annual Toxicology Teaching Day will be held on November 5, 2008 at the Genesee Grand Hotel in Syracuse. Please mark your calendar!

**NYC:** Consultants Case Conference • The first Thursday of the Month from 2-4pm

### Long Island Regional Poison and Drug Information Center Toxicology Teaching Conferences 2008

Pre-Registration is required. Please contact Mr. Denis Jao at 516-663-2650 to register.

Both Telephone and Televideo broadcasts will be available.

**Target Audience:** Physicians, Pharmacists, Nurses, Nurse Practitioners, Physician-Assistants, Laboratory technicians, EMS staff, medical/nursing/pharmacy students and other healthcare professionals.

Times for ALL Conferences are: 12:15 PM-1:45 PM

## Acute Ingestion of Unknown Drugs

*Contributed by: Sojin Chon, Pharm. D. Candidate, St John's University, T Caraccio, Pharm.D., DABAT., Long Island Poison and Drug Information Center, Mineola, New York*

### Case Report:

A 55 year old woman was brought to the emergency department (ED) after being found unresponsive to verbal or painful stimuli. EMS reported that the patient had a seizure at home and was hypoxic when found. The past medical history was unknown but a history of intentional ingestion of unknown types of medications at an unknown time was given by family. Upon examination, she was noted to have frank rigidity of the extremities with bruises on her chin. Blood pressure was 86/48 mmHg and heart rate was 170 beats per minute. Her pupils were fixed and dilated. The urine toxicology screen was positive for benzodiazepines only. Her initial laboratory results are shown below:

RANGE	LEVEL
Na [138-145 mEq/L]	140
K [3.7-5.2 mEq/L]	5.8*
Cl [96-107 mEq/L]	100
CO2 [23-33 mEq/L]	26
Glucose [73-107mg/dl]	124*
BUN [5-21 mg/dl]	16
Creat [0.4-1.2 mg/dl]	0.9
Calcium 8.6-10 mg/dl]	9.5
Anion gap [8-12 mEq/L]	14*
T Protein [6.2-7.6 gm/dl]	8.2*
Albumin [3.5-4.8gm/dl]	4.8
T Bilirubin [0.3-1.2 mg/dl]	0.5
SGOT/AST [0-41 IU/L]	34
SGOT/ALT [0-45 IU/L]	17
CPK [0-422 IU/L]	111
Troponin [<3.1 mcg/L]	<0.02
PT [10-13.8 sec]	12.1
INR [0.7-1.2]	1.0
Acetaminophen mcg/ml	78
ASA mg/dl	<1.0
Ethanol mg/dl	<10

Please call administrative telephone numbers for more information.

Continued on page 2

## What Drugs/Substances Can Cause A Coma? <sup>1</sup>

- Opioids
- Cholinergic agonists
- Benzodiazepines
- Neuroleptic/dopamine agonists
- Barbiturates
- Sedative-hypnotics
- Clonidone, tetrahydrozoline
- Tricyclic antidepressants
- Anticonvulsants
- Carbon monoxide, cyanide, hydrogen sulfide
- Ethanol
- Methanol
- Ethylene glycol
- Isopropyl alcohol
- Hydrocarbons
- Diphenoxylate
- Ethchlorvynol

## How Should A Comatose Patient Be Treated?

Establish airway and vital signs. Administer oxygen to a hypoxic patient. Place on a cardiac monitor.

Treat adult patients with a depressed level of consciousness and respiratory depression with naloxone 2 mg IV. In cases of suspected synthetic opioids doses of up to 10 mg may be required to elucidate a response.

Administer thiamine 100 mg IV to patients with an altered mental status who are thought to be thiamine deficient such as chronic alcoholics.

Administer dextrose 0.5-1.0 g/kg IV to a patient without focal findings.

## What Drugs/Substances Can Cause Seizures? <sup>1</sup>

- Stimulants
- Antidepressants
- Neuroleptic agents
- Antihistamines
- Anticholinergics
- Cholinergics
- Narcotics - select
- Antidysrhythmics
- NSAIDs – mefenamic acid
- Salicylates
- Isoniazid
- Theophylline
- Withdrawal from ethanol, benzodiazepines

## How Should A Patient With A Seizure Be Treated?

Control seizures initially with a benzodiazepine IV. Lorazepam or diazepam may be given initially, repeated every 5-10 minutes as needed.

If seizures persist, barbiturates such as phenobarbital or propofol should be considered. Drug and toxin related causes of seizures rarely respond to phenytoin and in select cases may exacerbate cardiotoxicity and for this reason is typically forgone in overdose seizure cases.

Unresponsive seizures also should be considered for empiric pyridoxine therapy as well. Although relatively uncommon, pyridoxine is a specific antidote for isoniazid, gyrometrium mushroom and other hydrazines causing seizures. In these cases, the toxin inhibits the formation of gamma amino butyric acid which is necessary for benzodiazepine and most barbiturate activity. Administration of the depleted cofactor results in a synergistic response with GABAergic therapy. The dose is gram per gram of a known drug ingested for a maximum of 5 grams and 5 grams in unknown cases.

## How Should A Patient With Rigidity Be Treated?

Drug related causes of rigidity vary with the most common differential diagnosis including serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia and lithium overdose. Malignant hyperthermia is caused by select triggering inhalation anesthetics and succinylcholine and in unknown presenting patients can be excluded due to the relative lack of potential exposure. Fortunately, knowing the remaining potential causative agent is rarely required for an adequate evaluation and treatment plan.

Problems affiliated with rigidity in order of increasing toxicity include hyperthermia and subsequent rhabdomyolysis, renal failure, denaturing of proteins, multi-system organ failure, disseminated intravascular coagulopathy and death. Therefore, aggressive management of the rigidity should occur using benzodiazepines and barbiturates/propofol if necessary with careful monitoring of core temperature, creatinine kinase measurement, serum creatinine and urine output. If hyperthermia occurs, active cooling using ice water immersion and/or mist and fan techniques should be employed rapidly.

## Case Update

Further investigation by the patient's family indicated that the patient had ingested up to 42 tablets of tramadol and 57 tablets of hydrocodone/acetaminophen. The strengths of the medications were unknown. Of note, tramadol is implicated in cases of serotonin syndrome.

## What Is Tramadol (Ultram®) And How Does It Work?

Tramadol HCl is an opioid analgesic that exerts its effect by inhibiting norepinephrine and serotonin reuptake. Tra-

Continued on page 3



madol also binds to the  $\mu$ -opiate receptors. This alters the perception and response to pain by inhibiting the ascending pain pathways. Its indications for use include cancer pain, moderate to moderately severe chronic pain, dental pain, and moderate to moderately severe pain. It is also sometimes used as an adjunct to anesthesia.

## Summary Of Case Reports Of Tramadol Overdose

In a prospective series of 71 cases of tramadol overdose, 47 of which were single ingestions, a reported dose of 500 milligrams was the lowest amount associated with the development of seizures, respiratory depression, tachycardia, agitation or hypertension. Coma developed in some patients after reported ingestion of 800 mg.<sup>2</sup>

Recurrent seizures were reported in a 61-year-old woman secondary to a reported overdose of 1.5 grams of tramadol. The patient was found at home unresponsive 5 hours post-ingestion and had several short-lived clonic seizures, with the last occurring 10 hours post-ingestion. The patient recovered following supportive therapy.<sup>3</sup>

A retrospective study of tramadol exposures included 51 children aged 5 years or less, with reported ingestions ranging from a taste to 300 mg. Of these children, only 8 had any symptoms: 7 (13.7%) developed sedation, one of these also developed agitation and tachycardia, and one child vomited.<sup>3</sup>

Up to 400 mg of tramadol was ingested in a fatal suicide attempt in a 30-year-old woman. Death was attributed to tramadol, alprazolam and alcohol, which were taken concurrently.<sup>4</sup>

Death was reported in a 23-year-old woman following the ingestion of approximately 2.65 grams of tramadol, which was identified as the sole cause of death.<sup>5</sup>

## What Is Hydrocodone/Acetaminophen (Vicodin®) And How Does It Work?

Hydrocodone/acetaminophen is composed of two different analgesics. Hydrocodone is an opioid analgesic and antitussive that blocks pain perception by binding to  $\mu$  and  $\kappa$  opiate receptors within the neuronal membranes of synapses in the cerebral cortex. This results in an inhibition of the flow of pain sensations.

Acetaminophen is a non-opioid analgesic and antipyretic. Acetaminophen inhibits the synthesis of prostaglandins in the CNS and peripherally blocks pain impulse generation. Hydrocodone/acetaminophen is indicated for the relief of moderate to severe pain.

## What Are The Toxic Effects And Clinical Presentation Of Opioids And Acetaminophen?

**Opioids:** Central nervous system and respiratory depression, hypoxia, mild hypotension, miosis, and mild gastric hypomotility. Apnea, shock, ARDS, dysrhythmias, rhabdomyolysis, and anoxic encephalopathy may occur with severe overdose.

**Acetaminophen:** nausea, vomiting, hepatotoxicity, hepatic failure. Acute renal failure is less common. Coma, metabolic acidosis, myocardial injury, and ARDS are also possible with severe overdose.

## What Kind Of Baseline Evaluation Should Be Done For Acetaminophen Toxicity?

A 4 hour post-ingestion acetaminophen plasma concentration should be obtained and plotted on the nomogram, and repeated in two to four hours.

## What Is The Proper Treatment Of Acetaminophen Toxicity?

**Acetylcysteine:** Administer N-acetylcysteine (NAC) if there is a toxic acetaminophen plasma concentration plotted on the rumack matthew nomogram or a level will not be available within 8 hours of ingestion.<sup>6</sup>

## What is the dose of NAC?

**Oral** - 140 mg/kg as a loading dose, 70 mg/kg every 4 hours for 72 hours as maintenance.

**IV** - 150 mg/kg NAC in 200 mL D5W over 60 minutes, followed by 50 mg/kg in 500 mL D5W over next 4 hours, then 100 mg/kg in 1000 mL D5W over next 16 hours. (please note that the amount of D5W is different in those under 40 kg)

## Are There Specific Opioid Therapies?

Naloxone, a competitive non-selective opioid receptor antagonist reverses opioid effects including respiratory depression. A typical dose is 2 mg IV, which may be repeated as needed. In opioid-dependent patients, administer 0.2 mg IV and repeat as needed to reverse effects without precipitating acute withdrawal.

Pre-oxygenation should be utilized in peri-apneic patients to mitigate the risk for acute lung injury.

Continued on page 6

# Cardio Drug Questions

## 1. Which of the following BEST describes the arrhythmias caused by cardioactive steroids?

- Supraventricular tachycardia (SVT) is common
- Sinus tachycardia is a sign that the patient is poisoned
- Rapid atrial fibrillation needs to be treated with digoxin specific Fab fragments in a patient on chronic digoxin therapy
- Premature ventricular contractions are the most common dysrhythmias
- Bradycardia is uncommon

## 2. Which of the following presentations would best differentiate a patient with digoxin toxicity vs. a calcium channel blocker ingestion?

- Altered mental status
- Hypoglycemia
- 3rd degree AV block
- Hypokalemia
- Renal failure

## 3. A patient presents to the emergency department with an acute ingestion of a cardioactive steroid. The patient is currently found to have altered mental status and is found to have ventricular tachycardia. What is the BEST choice for treatment?

- Wait for the level; you don't know if the patient really took it
- Start multiple dose activated charcoal
- Empirically give 5 vials of digoxin specific Fab
- Empirically give 10 vials of digoxin specific Fab
- Treat the patient with amiodarone 150 mg IV over 10 minutes

## 4. When should a patient be administered high dose insulin/euglycemia therapy?

- Any patient with an acute cardioactive steroid ingestion
- All calcium channel blocker overdoses
- All Beta adrenergic antagonist overdoses
- Any patient with a calcium channel blocker or Beta blocker induced bradycardia which has not been responsive to standard therapy.
- Only after transvenous pacing has been attempted and despite use, pacing was not able to capture

## 5. A 79-year-old female (60 kg) presents to the emergency department with lethargy and vomiting. The patient is taking digoxin for atrial fibrillation. Currently, her EKG is a normal sinus rhythm at 70 bpm with intermittent ventricular ectopy. The patient is found to have a digoxin level of 3.0 ng/mL. The potassium is 2.5 mEq/L (3.5-5.0 mEq/L). The patient has a BUN of 25 mg/dL and creatinine of 1.2 mg/dL. What should be the first course of treatment?

- Atropine 1 mg IV should be administered due to increased vagal tone.
- 2 vials of digoxin specific Fab should be administered.
- Potassium replacement should be performed initially
- Nothing; the patient does not have signs of digoxin toxicity.
- IV hydration with normal saline should be the only therapy required.

Answers: 1 - D; 2 - A; 3 - D; 4 - D; 5 - C

# FDA Safety Summaries

## Antipsychotics, Conventional and Atypical

FDA notified healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis. June 16, 2008

## Morphine Sulfate 60 & 30 mg Extended Release Tablets

Additional lots of morphine sulfate 60 mg extended release tablets, and specific lots of morphine sulfate 30 mg extended release tablets, were recalled due to the possible presence of oversized tablets. June 13, 2008

## Tumor Necrosis Factor (TNF) Blockers (marketed as Remicade, Enbrel, Humira, and Cimzia)

FDA issued an Early Communication About an Ongoing Safety Review to inform healthcare professionals that the Agency is investigating a possible association between

the use of Tumor Necrosis Factor (TNF) blockers and the development of lymphoma and other cancers in children and young adults. June 04, 2008

## Viril-ity Power (VIP) Tablets

International Pharmaceuticals, Ltd. and FDA notified consumers and healthcare professionals that the company is recalling all supplement products sold under the brand name of Viril-ity Power (VIP) Tablets. The product is being recalled because one lot was found to contain a potentially harmful undeclared ingredient, hydroxyhomosildenafil, an analog of sildenafil. May 29, 2008

## Mommy's Bliss Nipple Cream

FDA informed consumers not to use or purchase Mommy's Bliss Nipple Cream, marketed by MOM Enterprises,

Continued on page 5

Inc., because the product contains potentially harmful ingredients that may cause respiratory distress or vomiting and diarrhea in infants. Potentially harmful ingredients in the product are chlorphenesin and phenoxethanol. May 23, 2008

## **Xiadafil VIP Tablets**

FDA alerted consumers and healthcare professionals not to buy or use Xiadafil VIP Tablets sold in bottles of 8 tablets (Lot #6K029) or blister cards of 2 tablets (Lot# 6K029-SEI). Xiadafil VIP Tablets contain hydroxyhomosildenafil, an analog of sildenafil, the active ingredient in Viagra, an FDA approved prescription drug for ED. May 27, 2008

## **Solodyn (minocycline HCL) Extended Release Tabs 90 mg**

Medicis and FDA notified healthcare professionals of the recall of lot numbers B080037 (Exp: 12/09) and B080038 (Exp: 12/09) of Solodyn Extended Release Tablets. The product was recalled because one of the bottles contained Azasan (azathioprine tablets) 75mg instead of Solodyn 90mg Tablets. May 16, 2008

## **Mycophenolate Mofetil [MMF] (marketed as CellCept) Mycophenolic Acid [MPA] (marketed as Myfortic) Inosine Monophosphate Dehydrogenase Inhibitors (IMPDH) Immunosuppressants**

FDA is aware of reports of infants born with serious congenital anomalies, including microtia and cleft lip and palate, following exposure to mycophenolate mofetil (MMF) during pregnancy. May 16, 2008

## **Cardinal Alcohol-Free Mouthwash**

Hydrox Labs issued a voluntary recall of another lot of Alcohol-Free Mouthwash because samples of the product tested were positive for Burkholderia cepacia (B. cepacia). May 16, 2008

## **Enbrel (etanercept)**

Amgen and Wyeth Pharmaceuticals informed healthcare professionals of revisions to prescribing information for Enbrel including serious infections leading to hospitalization or death that have been observed in patients treated with Enbrel. March 14, 2008

## **Digitek (digoxin tablets, USP)**

Actavis Totowa LLC notified healthcare professionals of a Class I nationwide recall of all strengths of Digitek. The product is being recalled due to the possibility that tablets with double the appropriate thickness may contain twice the approved level of active ingredient. April 25, 2008

## **Herbal Science International, Inc. Dietary Herbal Supplements**

Herbal Science International, Inc. and FDA informed consumers and healthcare professionals of a nationwide recall of twelve dietary supplements that contain ephedra, aristolochic acid or human placenta because they may present a serious health hazard to consumers. April 10, 2008

## **CellCept (mycophenolate mofetil) Myfortic (mycophenolate acid)**

FDA informed healthcare professionals that the Agency is investigating a potential association between the use of CellCept and Myfortic, medicines used to prevent organ rejection, and the development of progressive multifocal leukoencephalopathy (PML), a life-threatening disease. April 10, 2008

## **Neupro (rotigotine transdermal system)**

Schwarz Pharma informed healthcare professionals and patients of the recall of Neupro, a transdermal delivery system worn on the skin and used to treat early stage Parkinson's disease, at the end of April 2008, because of the formation of rotigotine crystals in the patches. April 8, 2008

## **Exubera (insulin human rDNA origin) Inhalation Powder**

Pfizer informed healthcare professionals and patients of updated safety information in the WARNINGS section of prescribing information for Exubera, a short-acting insulin you breathe in through your mouth using the Exubera inhaler. There have been 6 newly diagnosed cases of primary lung malignancies in clinical trials among Exubera-treated patients, and 1 newly diagnosed case among comparator treated patients. April 9, 2008

## **Cubicin (daptomycin for injection)**

Cubist Pharmaceuticals, Inc. informed healthcare professionals that a potentially significant impurity, 2-mercaptobenzothiazole (MBT), has been isolated from reconstituted Cubicin stored in with ReadyMED elastomeric infusion pumps. Cutaneous exposure to MBT has been associated with dermal sensitization, and chronic administration of MBT to laboratory rodents has been associated with an increased risk of certain tumors. April, 2008

## **Heparin Sodium USP Pre-Filled Syringes**

Covidien notified healthcare professionals of a voluntary recall of certain lots of Heparin Sodium USP because two lots of the product acquired by Covidien had a heparin-like contaminant. March 28, 2008

## **Relenza (zanamivir)**

GlaxoSmithKline informed healthcare professionals of changes to the WARNINGS AND PRECAUTIONS sections of prescribing information for Relenza regarding information from postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who are receiving neuraminidase inhibitors, including Relenza. March, 2008

## **Total Body Formula, Total Body Mega Formula**

FDA notified healthcare professionals and consumers that the Agency's final analysis of certain flavors of "Total Body Formula" and "Total Body Mega Formula" detected hazardous amounts of chromium in addition to selenium. May 01, 2008



## Case Reports Of Hydrocodone/Apap Overdose

A plasma acetaminophen concentration should be determined after intentional ingestions or with known ingestions of 200 mg/kg or more <sup>6</sup>

Following an acute overdose, persistently elevated acetaminophen serum concentrations over several days may occur due to slow intestinal motility from the opiate effect, extended release formulations, or from bezoar formation. In a single case after an unknown quantity of acetaminophen-opiate combination products, persistently elevated acetaminophen serum concentrations occurred as follows: <sup>7</sup>

HOURS POST-INGESTION	ACETAMINOPHEN SERUM CONC.
1	72.4 mcg/mL
4	83 mcg/mL
10	88 mcg/mL
17	116 mcg/mL
26	75.1 mcg/mL
31	52.6 mcg/mL
40	24.8 mcg/mL

In a prospective, randomized, crossover study, 10 healthy volunteers were given either 5 grams of acetaminophen, or 5 grams of acetaminophen plus 0.5 mg/kg of oxycodone. The acetaminophen plus oxycodone combination delayed and reduced absorption of acetaminophen (a 27% lower AUC, a 40% lower maximum acetaminophen concentration, and a 68% longer  $t_{max}$ ). <sup>8</sup>

Patients with cirrhosis of the liver do not appear to be at enhanced risk for developing hepatotoxicity and may actually produce toxic metabolite at a diminished rate. <sup>9</sup>

In a series of 11,195 cases of suspected acetaminophen overdose, there were 50 deaths of adult patients. In 28 of these cases, death could be definitely or probably attributed to acetaminophen. Mortality was significantly higher in patients who received NAC more than 16 hours post-ingestion than in those who received NAC within 16 hours. <sup>10</sup>

## Discussion Of Case

The patient was admitted, sedated with propofol and lorazepam IV and ventilated. The patient received intravenous n-acetylcysteine therapy phenylephrine IV for support of low blood pressure. She progressed to multi-organ failure two days post-admission. The peak PT was 47.6 seconds and peak INR was 6.5 on day two post-admission. On day four, her liver transaminases peaked with an AST of 2641 U/L and an ALT of 2977 U/L. The patient developed hyponatremia with a sodium level of 128 mEq/L. During

this time the serum total bilirubin and creatinine reached peaks of 3.4 mg/dL and 4.8 mg/dL, respectively. She developed generalized muscle rigidity, non-reactive pupils and expired seven days post admission. It is unclear if the temperature and other measures of hyperthermia sequelae were addressed. Autopsy results are pending.

## FYI: Lidocaine Update

### Drug Information Topical Lidocaine Toxicity

*Contributed by: Sojin Chon, Pharm. D. Candidate, St. John's University, T Caraccio, Pharm D., DABAT., Long Island Poison and Drug Information Center, Mineola, New York*

### Can Lidocaine Produce Toxicity?

Lidocaine is an amino amide used as a local anesthetic. It comes in various forms, including a subcutaneous injection, many topical preparations, and a transdermal patch. While many believe these agents to be relatively safe, they are not immune to side effects and toxicity. It is important to realize that while lidocaine is safe when used properly, there have been many instances of cardiotoxic and neurotoxic adverse events reported. <sup>1-10</sup>

Lidocaine blocks the sodium ion channels required for the initiation and conduction of neuronal impulses by decreasing ionic flux through the neuronal membrane. The penetration of lidocaine through intact skin will produce an analgesic effect but is not sufficient to produce a complete sensory block. It may produce erythema, edema, or an abnormal sensation at the application site. When lidocaine topical systems are used appropriately, systemic effects are unlikely due to the small amount of lidocaine absorbed.

### Lidocaine Toxicity

Toxicity may occur after ingestion, topical use, or parenteral administration.

Toxicity may result from an excessive dose, mistaken drug identity, enhanced drug absorption, inadvertent intravascular injection, altered protein binding, slowed redistribution and/or elimination.

Initial effects following an overdose include mild hypertension and tachycardia, light headedness, mild agitation, and confusion. In severe cases, this may progress to seizures, coma, respiratory depression, bradycardia, ventricular dysrhythmias and asystole. Lidocaine rarely produces methemoglobinemia. Transient apprehension, confusion, disorientation, and panic and psychotic reactions may occur.

Mild toxicity may occur with therapeutic drug levels. Plasma concentrations of 5 to 10 mg/L are associated with marked CNS toxicity. <sup>2</sup>

Plasma levels of 8-12 mg/L can be associated with seizures. <sup>3</sup> Drug levels above 15 mg/L have been reported in fatal cases. <sup>4</sup>

Which formulations of Lidocaine are available in a Topical form and have any produced toxicity?

Continued on page 7

1. **EMLA<sup>®</sup>** – Eutectic Mixture of Lidocaine and Prilocaine – is a topical mixture of local anaesthetics. It contains 2.5% each of lidocaine and prilocaine and is available over the counter in the U.S.<sup>5</sup>

A healthy 23 year old man presented to a hospital with acute confusion. EMLA<sup>®</sup> cream had been applied to his chest, abdomen, and back prior to laser hair removal treatment. Approximately 45 minutes later, he complained of weakness, nausea, vomiting, was confused, disoriented, talkative, and experienced a brief loss of consciousness following by a frontal headache. Two hours after the onset of the episode, the patient's condition resolved completely. The CSF tested positive for lidocaine at a significant level of 1 mg/L which corresponds to a toxic serum concentration of 12.5-16 mg/L.<sup>5</sup>

A 21 month old girl who received EMLA<sup>®</sup> experienced seizures and respiratory depression. The serum level of lidocaine was 16.8 mg/L.<sup>5</sup>

2. **DentiPatch<sup>®</sup>** – The DentiPatch lidocaine transoral delivery system is indicated for mild topical anesthesia of mucous membranes in the mouth. It contains 46.1 mg of lidocaine (20% concentration). The onset of action is as early as 2.5 minutes after application, and the patch can be left in place for up to 15 minutes.<sup>6</sup>

The risk of CNS toxicity is very low, but it can be precipitated by the co-administration of other CNS depressant medications, such as meperidine or chloral hydrate.<sup>6</sup>

3. **Xylocaine Viscous<sup>®</sup>** – Lidocaine HCl oral topical solution is indicated as a topical anaesthetic for irritated or inflamed mucous membranes of the mouth and pharynx. The usual adult dose is one tablespoonful. For use in the mouth, the solution should be swished around in the mouth and expelled. For use in the pharynx, the undiluted solution should be gargled and may be swallowed. This dose should not be administered at intervals of less than three hours, and not more than eight doses should be given in a 24-hour period. The maximum recommended single dose should not exceed 4.5 mg/kg or a total of 300 mg.

Lidocaine plasma concentrations greater than 5 mg/L have been reported to result in toxic symptoms. Ingestion of 5 to 25 mL of 2% viscous Xylocaine (lidocaine) has resulted in seizures in children. An 11-month-old male infant developed seizures and a plasma lidocaine concentration of 10 mg/L, following the application of 2% viscous lidocaine to his gums 5 to 6 times daily for a week.<sup>8</sup>

Toxicity was observed in a 22-year-old man during daily use of 240 mL viscous lidocaine for a severe tongue ulcer. His serum lidocaine concentration was 6.7 mg/L.<sup>9</sup>

4. **Lidoderm<sup>®</sup>** – is used to relieve the pain of post-herpetic neuralgia, which is also referred to as post shingles pain. Lidoderm<sup>®</sup> patches should be worn for no more than 12 hours a day. No more than 3 patches should be applied at one time. Patches may also be cut into smaller sizes prior to removal of the release liner.

Toxicity may occur with “therapeutic” drug levels, particularly in patients with low serum protein levels who have increased levels of free (non-protein bound) drug.<sup>10</sup>

For information on how to manage Lidocaine toxicity please consult your Regional Poison Center.

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## Ziagen (abacavir) Videx (didanosine)

The FDA issued an Early Communication about recent findings of The Data Collection on Adverse Events of Anti-HIV Drugs Study. Data analyses from this study indicate a higher risk of heart attack in patients infected with HIV-1 who were taking Ziagen (abacavir) or Videx (didanosine) as part of their drug therapy. March 27, 2008

## Regranex (becaplermin) Gel

FDA informed healthcare professionals that a Boxed Warning was added to prescribing information for Regranex that describes an increased risk of death from cancer in patients treated with three or more tubes of Regranex compared with those patients who did not use the product. June 06, 2008

## Singulair (montelukast)

FDA informed healthcare professionals and patients of the Agency's investigation of the possible association between the use of Singulair and behavior/mood changes, suicidality (suicidal thinking and behavior) and suicide. March 27, 2008

## Toxicology Advice Centers ••

**Administrative Phone Numbers** - To obtain a consult in your area, call 1.800.222.1222.

**Western New York Poison Center (WNY)**

716.878.7871 • <http://wnypoison.org>

**Ruth A. Lawrence NY Poison Center (FL)**

585.273.4155 • [www.FingerLakesPoison.org](http://www.FingerLakesPoison.org)

**Upstate New York Poison Center (UNY)**

315.464.7078 • [www.upstatepoison.org](http://www.upstatepoison.org)

**New York City Poison Control Center (NYC)**

212.447.8152

**Long Island Poison & Drug Info Center (LI)**

516.663.4574 • [www.LIRPDIC.org](http://www.LIRPDIC.org)

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## Case: DRESS Syndrome

*Contributed by: Daniel Lugassy, M.D., Medical Toxicology Fellow, Lewis Nelson, M.D., Director, Fellowship in Medical Toxicology, New York City Poison Control Center, NY, NY*

### Case Report:

A 63 year-old Chinese woman presents to the emergency department (ED) complaining of a rash that started two days earlier, as well as fever and decreased appetite. She has a history of mixed connective tissue disorder, hypertension, diabetes, and psoriatic arthritis. She completed a course of azithromycin about one week ago for an upper respiratory infection. Due to the persistence of symptoms her doctor prescribed clotrimazole lozenges and trimethoprim-sulfamethoxazole two days prior to arrival. In addition to these medications above, she takes numerous medications daily for her chronic conditions, which her husband states he will bring to the hospital later.

Upon initial physical examination, she was awake, alert and oriented. Vital signs were: blood pressure, 119/55 mmHg; heart rate 92 beats/minute; respiratory rate 18 breaths/minute; and temperature 99.8° F. A diffuse blanchable maculopapular rash was noted on upper and lower extremities, chest, and abdomen. No rash was present on her palms or soles and there was no mucosal involvement. Scleral icterus and mild abdominal tenderness were the only other significant exam findings.

Initial pertinent laboratory results were as follows: Complete blood count: white blood cell count, 12,300 cells/mm<sup>3</sup>; and an absolute eosinophil count of 861 cells/mm<sup>3</sup>. Chemistry: sodium 124 mEq/L, potassium 5.2 mEq/L, chloride 106 mEq/L, bicarbonate 10 mEq/L, blood urea nitrogen 38 mg/dL, creatinine 1.6 mg/dL, glucose 277 mg/dL. Hepatic studies: AST 1,063 IU/L; ALT 604 IU/L; alkaline phosphatase 1425 IU/L, total bilirubin 7.3 mg/dL; direct bilirubin 5.3 mg/dL; albumin 3.4 gm/dL.

## Program Announcements ••

**Ruth A. Lawrence:** Monthly conference: every 4 weeks on Thursdays (11 am to noon), and every 4 weeks on Tuesdays (10 am-11 am).

**UNY:** Our Twelfth Annual Toxicology Teaching Day will be held on November 5, 2008 at the Genesee Grand Hotel in Syracuse. Please mark your calendar!

**NYC:** Consultants Case Conference • The first Thursday of the Month from 2-4pm

**Long Island Regional Poison and Drug Information Center:** Please look for our fall programs

Please call administrative telephone numbers for more information.

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# FDA Safety Summaries

## **Statin drugs and amyotrophic lateral sclerosis (ALS)**

An FDA analysis provides new evidence that the use of statins does not increase incidence of amyotrophic lateral sclerosis (ALS), a neurodegenerative disease often referred to as “Lou Gehrig’s Disease.” *September 29, 2008*

## **Epoetin alfa - Early Communication about an Ongoing Safety Review**

FDA has been made aware of preliminary safety findings from a clinical trial conducted in Germany investigating the use of epoetin alfa to treat acute ischemic stroke. The clinical trial utilized doses of epoetin alfa that were considerably higher than the doses recommended for the treatment of anemia as described in the FDA-approved labeling for the product. Over a period of ninety days after the start of the trial, there were more deaths in the group of patients who received epoetin alfa compared to patients who received the placebo (16% versus 9%). *September 26, 2008*

## **Ammonul (sodium phenylacetate and sodium benzoate) Injection 10%/10%**

Ucyclyd Pharma, Inc. informed healthcare professionals of the detection of particulate matter in the Ammonul Injection product. *September 15, 2008*

## **Tarceva (erlotinib)**

OSI and Genentech notified healthcare professionals that cases of hepatic failure and hepatorenal syndrome, including fatalities, have been reported during use of Tarceva, particularly in patients with baseline hepatic impairment. *September 12, 2008*

## **Phosphocol P 32 (Chronic Phosphate P 32 Suspension)**

Covidien and Mallinckrodt Inc. informed healthcare professionals of important new safety information in prescribing Phosphocol P 32. Phosphocol P 32 is approved for the intracavitary instillation for the treatment of peritoneal or pleural effusions caused by metastatic disease. Phosphocol P 32 may increase the risk for leukemia in certain situations. *August 29, 2008*

## **Infant Formula Manufactured in China**

FDA issued a Health Information Advisory to consumers and healthcare professionals regarding milk-based infant formula manufactured in China. The Chinese manufactured infant formula may be contaminated with melamine. Melamine artificially increases the protein profile of milk and can cause kidney diseases. *September 20, 2008*

## **Rituxan (rituximab)**

Genentech informed healthcare professionals of revisions to prescribing information for Rituxan regarding a case of progressive multifocal leukoencephalopathy (PML) leading to death in a patient with rheumatoid arthritis who received Rituxan in a long-term safety extension clinical study. *September 2008*

## **Tumor necrosis factor-alpha blockers (TNF blockers), Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab)**

FDA notified healthcare professionals that pulmonary and disseminated histoplasmosis, coccidioidomycosis, blastomycosis and other opportunistic infections are not consistently recognized in patients taking tumor necrosis factor- $\alpha$  blockers (TNF blockers). *September 4, 2008*

## **Tysabri (natalizumab)**

FDA informed healthcare professionals of two new cases of progressive multifocal leukoencephalopathy (PML) in European patients receiving Tysabri monotherapy for multiple sclerosis for more than one year. *August 25, 2008*

## **Ezetimibe/Simvastatin (marketed as Vytorin) Simvastatin (marketed as Zocor) Ezetimibe (marketed as Zetia)**

FDA informed healthcare professionals that the Agency is investigating a report from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial of a possible association between the use of Vytorin and a potentially increased incidence of cancer. *August 21, 2008*

## **Vivitrol (naltrexone)**

FDA informed healthcare professionals of the risk of adverse injection site reactions in patients receiving naltrexone. *August 12, 2008*

## **Simvastatin Used With Amiodarone**

FDA notified healthcare professionals of the risk of muscle injury, rhabdomyolysis, which can lead to kidney failure or death, when simvastatin is used with amiodarone. *August 08, 2008*

## **Viapro 375mg Capsules**

EG Labs, LLC, notified consumers and healthcare professionals not to buy or use Viapro 375mg Capsules because one lot of the product was found to contain a potentially harmful undeclared ingredient, thio-methisosildenafil, an analog of sildenafil, a FDA approved

Continued on page 3

product used to treat erectile dysfunction in men to enhance sexual performance. *July 23, 2008*

## **Erythropoiesis Stimulating Agents (ESAs) - Epoetin alfa (marketed as Procrit, Epogen), Darbepoetin alfa (marketed as Aranesp)**

Changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated. *August 7, 2008*

## **Mitoxantrone Hydrochloride (marketed as Novantrone and generics)**

FDA reminded health care professionals who treat patients with mitoxantrone about recommendations that left ventricular ejection fraction (LVEF) be evaluated before initiating treatment and prior to administering each dose of mitoxantrone. *July 29, 2008*



## **Abacavir (marketed as Ziagen) and Abacavir-containing Medications**

FDA informed healthcare professionals that serious and sometimes fatal hypersensitivity reactions (HSR) caused by abacavir therapy are significantly more common in patients with a particular human leukocyte antigen (HLA) allele, HLA-B\*5701. *July 24, 2008*

## **Sodium Polystyrene Sulfonate Suspension**

Roxane Laboratories, Inc. informed healthcare professionals of the recall of two lots of Sodium Polystyrene Sulfonate Suspension, USP, 15 g/60 mL Unit dose bottles (NDC 0054-0165-51; lot 856396A Exp April 2010, and lot 856693A Exp May 2010), a product used to treat hyperkalemia. A sample of one of the affected lots tested positive for a strain of yeast, which could potentially affect immunocompromised patients. *July 14, 2008*

## **Avastin (bevacizumab)**

Genentech, Inc. informed healthcare professionals of reports of several cases of microangiopathic hemolytic anemia (MAHA) in patients with solid tumors receiving Avastin in combination with sunitinib malate. *July 11, 2008*

## **Herceptin 440 mg Vials and BWFI Diluent**

Genentech informed healthcare professionals that an increased number of complaints were received regarding damaged and broken vials of Herceptin 440 mg and BWFI (bacteriostatic water for injection) diluent. *June 28, 2008*

## **Fluoroquinolone Antimicrobial Drugs**

FDA notified healthcare professionals that a BOXED WARNING and Medication Guide are to be added to the prescribing information to strengthen existing warnings about the increased risk of developing tendinitis and tendon rupture in patients taking fluoroquinolones for systemic use. *July 08, 2008*

## **Rize 2 The Occasion Capsules Rose 4 Her Capsules**

Jack Distribution, LLC, announced a nationwide recall of all lot numbers of the company's supplement products sold under the brand names Rize 2 The Occasion and Rose 4 Her. Lab analysis by FDA of samples of random lots found the product contains a potentially harmful, undeclared ingredient, thiomethisosildenafil, an analog of sildenafil, the active ingredient of a FDA-approved drug used for erectile dysfunction. *July 28, 2008*





Contributed by: Nicholas Steidl, Pharm.D., Clinical Toxicology Fellow, Upstate NY Poison Center, Syracuse NY



### **Question: Is multiple dose activated charcoal (MDAC) effective in the setting of salicylate poisoning?**

#### **Background:**

A 17 y/o male presented with nausea and tinnitus 12 hours following an overdose on aspirin. He was subsequently started on bicarbonate to achieve serum and urine alkalinization and MDAC to enhance excretion of salicylate. A question on the utility of MDAC in this situation and with salicylate poisoning in general arose.

#### **Summary:**

While there is a potential theoretical benefit of MDAC in the setting of salicylate overdose the evidence is inconclusive and clinical benefit has not been proven. There is no role for late administration of MDAC at 12 hours and there is insufficient evidence to recommend its routine use in early presenters.

#### **Answer:**

There are several reasons that MDAC is employed in certain poisoning cases. It may be useful in cases where there is the potential for ongoing absorption and the amount of drug exceeds the binding capacity of a single dose of charcoal. While in most cases salicylates are rapidly absorbed there are some situations in which absorption may be prolonged. Salicylates are known to cause pylorospasm and enteric-coated formulations can form concretions in the stomach.<sup>1</sup> In large overdoses maximal peak concentrations may not be reached for 4-6 hours. In cases such as this there is a theoretic benefit to administration of MDAC.

MDAC is also indicated for use when the drug ingested undergoes significant entero-hepatic recirculation. Salicylates and their metabolites are primarily eliminated in the urine and only trace amounts are eliminated in the feces or by other routes. Therefore there is almost no capacity for entero-hepatic cir-

ulation and MDAC will not cause benefit from this mechanism.<sup>1</sup>

In addition the use of MDAC may facilitate reverse diffusion of drug from the circulation into the gastrointestinal tract by binding drug in the gut, setting up a concentration gradient. This is referred to as "gut-dialysis."<sup>1</sup> In a pig model MDAC had no effect on clearance of 300 mg/kg IV aspirin demonstrating that this effect is not significant with salicylates.<sup>6</sup>

While theoretic benefit exists, trials in humans have exhibited mixed results. Mayer et al. studied 9 patients in a crossover trial in which he gave 2880 mg aspirin followed by 25 g AC at 4, 6, 8, and 10 hours and compared it to control. There was no significant difference found in the AUC between the groups (control: 2320 ± 501 mg/Lh vs. MDAC: 2040 ± 454 mg/Lh, NS).<sup>2</sup> Similarly, Ho et al. evaluated the administration of 55 g AC at the same time intervals after administration of 1300 mg aspirin in a crossover study of 6 patients and found no significant differences in AUC.<sup>3</sup> A notable limitation of these studies is that the dosing allowed cannot simulate toxic ingestions.

In contrast, Kirshenbaum et al. did a similar evaluation in a crossover study of 10 patients and found a potential benefit. They gave 2880 mg aspirin followed by 25 g MDAC in the same dosing schedule as the previous trials. They observed a significant decrease in the AUC of 9% ( $p < 0.05$ ) in the MDAC group as well as an 18% decrease in urinary excretion ( $p < 0.01$ ).<sup>4</sup> While statistically significant it is important to note that this effect is small and of questionable clinical significance, however the potential for a greater benefit in the overdose setting exists.

Barone et al. also showed a potential benefit of MDAC after administration of twenty-four 81 mg aspirin tablets. They compared urinary excretion of salicylates in a four-limbed crossover study of 10 vol-

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### **Question:** Should a patient experiencing priapism with trazodone refrain from alpha-blockers?

#### **Answer:**

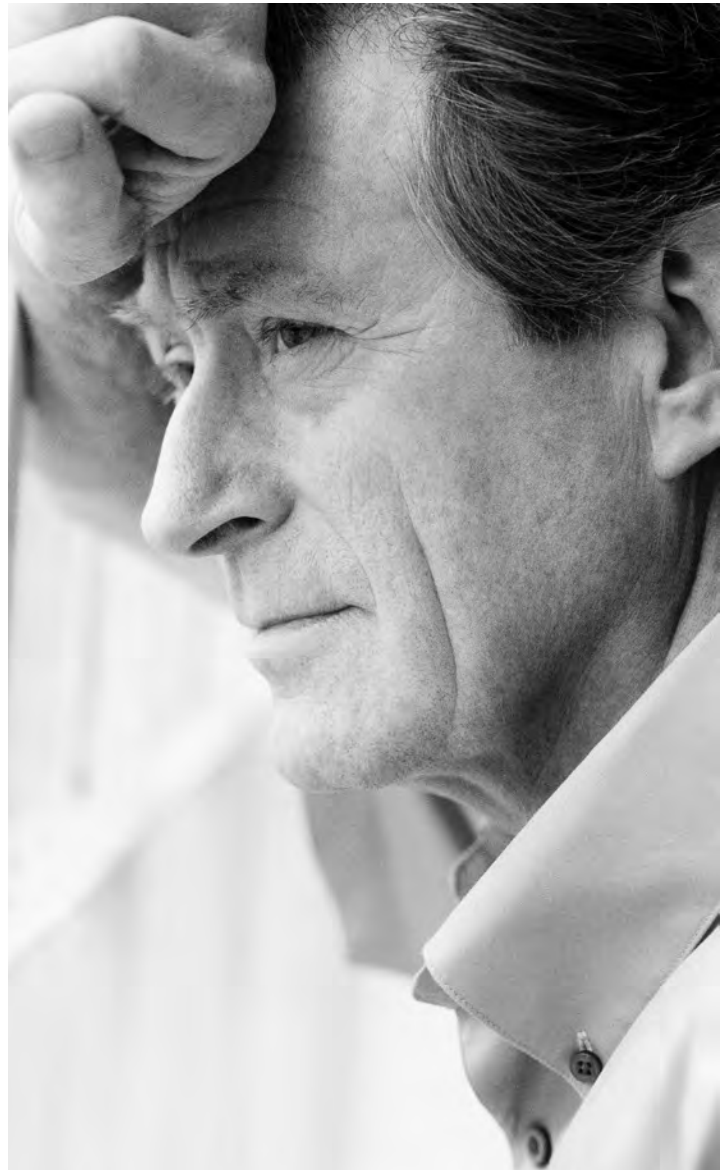
Trazodone is triazolopyridine derivative that works as a selective inhibitor of neuronal serotonin uptake and also has peripheral serotonin antagonist and alpha-adrenergic antagonist effects<sup>1</sup>. It has been used in the United States since 1982 as an antidepressant with minimal anticholinergic effects<sup>1</sup>.

Since trazodone has a sedative property, it is commonly used as a sleeping agent at a low dose. Other common adverse effects of trazodone include anorexia, blurred vision, sweating, weight changes, orthostasis, dizziness, headache, memory impairment, insomnia, and gastrointestinal effects, including nausea, vomiting, diarrhea, and dry mouth<sup>2</sup>. Rare, serious side effects include arrhythmias, hyper- or hypotension, hemolytic anemia, leukocytosis, methemoglobinemia, and seizures<sup>2</sup>. One of the more common, but extremely painful serious complications associated with the use of trazodone is priapism.

During the period from 1982 to 1988, at least 20 cases of priapism with trazodone therapy were reported. These occurred in patients ages 24 to 60 who were taking standard doses of 100–600 mg per day for a duration ranging from 6 days to 4 weeks<sup>1</sup>.

Priapism is an uncommon condition that causes a prolonged and often painful erection, which occurs without sexual stimulation. In one-third of the cases, the cause of the disorder is unknown<sup>3</sup>. The remaining cases are caused by an associated condition, including sickle cell disease, pelvic tumors, pelvic infections, leukemia, genital trauma or spinal cord trauma and medications or recreational drugs<sup>3</sup>. Associations have been demonstrated between ischemic priapism and many medications with alpha-adrenergic blocking activity or central serotonin-like activity<sup>1</sup>. Alpha-adrenoceptor antagonism is the most likely mechanism; constriction of the blood vessels supplying erectile tissue is prevented and detumescence does not occur. Prazosin is the drug most frequently associated with priapism<sup>3</sup>.

Surprisingly, there is no study directly correlating not using alpha blockers in patients that have experienced trazodone induced priapism. The physician, however, may choose to keep a patient off alpha blockers because if they take trazodone and experience priapism, it is most likely due to the alpha-blocking



activity of this drug. Therefore, any additional alpha-blockers thereafter should be avoided because the alpha-blocking activity is higher in direct alpha-blockers than in trazodone, and priapism will become a serious risk and complication for this patient.

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## Case: DRESS Syndrome

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### What clinical syndrome should be considered in this case?

This patient appears to be having a severe adverse cutaneous drug reaction that included abnormalities of bone marrow, liver and renal function. Together these form the basis for the DRESS syndrome, an acronym for “drug rash with eosinophilia and systemic symptoms.” DRESS syndrome is commonly accepted to include previously described drug hypersensitivity syndromes such as for anticonvulsant or sulfonamides syndrome.

### How does one make the diagnosis of DRESS syndrome?

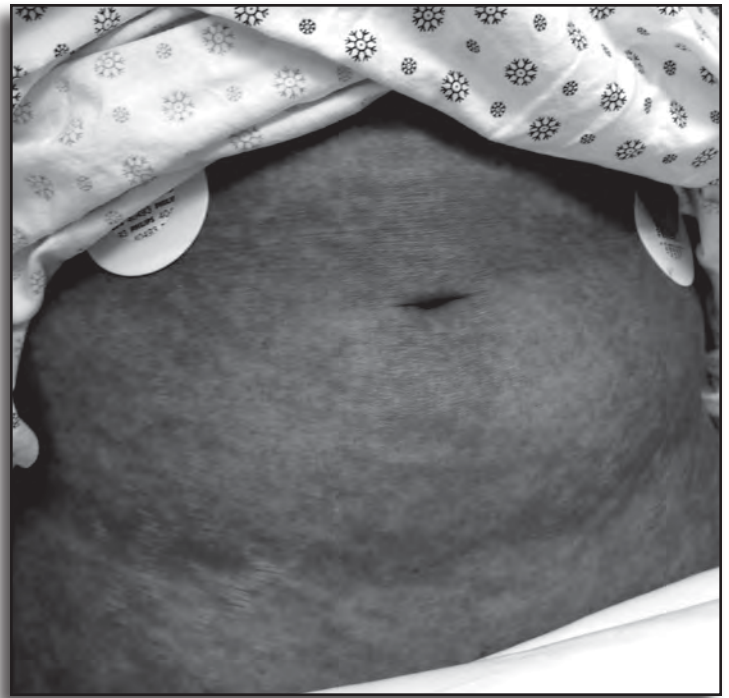
The triad of rash, fever and internal organ involvement are the key features in making this diagnosis. It is usually seen 2-8 weeks after the initiation of a new drug or within a day of re-exposure. The rash, which can vary in appearance and severity, is most commonly morbilliform (measles-like). The eruption of the rash often precedes or coincides with the development of a fever and non-specific findings including malaise, pharyngitis, facial edema, and lymphadenopathy.

DRESS may be clinically indistinguishable from other cutaneous syndromes such as Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Kawasaki disease, Still’s disease, and bacterial infections. SJS/TEN, a life threatening cutaneous drug rash, differs from DRESS in that SJS/TEN features prominent mucosal involvement, target lesions, and epidermal necrosis leading to skin sloughing.

The diagnosis of DRESS requires the presence of eosinophilic infiltration of the internal organs. This most commonly manifests as acute hepatitis, and can progress to fulminant hepatic failure. Interstitial nephritis, encephalitis, pneumonitis, and thyroiditis are also relatively common. Internal organ involvement is determined initially through laboratory analysis, which should include renal, hepatic, and thyroid studies. The initial studies of bone marrow activity (e.g. CBC with differential) demonstrate atypical lymphocytes and eosinophilia.

### Which medications have been observed to cause DRESS syndrome?

Anticonvulsants and sulfonamides have been the most common drugs reported to cause DRESS syndrome, with an incidence ranging from 1 in 1,000 to 1 in 10,000 exposures. Some of the other drugs implicated in this syndrome include: phenytoin, carbamazepine, phenobarbital, lamotrigine, minocycline, dapsone, allopurinol, nevirapine, and abacavir.



### Case Continuation:

The patient’s husband brought to the hospital a large bag of medications including the following: acetylsalicylic acid, allopurinol, folic acid, gemfibrozil, glipizide, lansoprazole, leflunomide, metformin, simvastatin, and valsartan. The prescriptions came from several different pharmacies and physicians. The patient had only taken two or three doses of trimethoprim-sulfamethoxazole before her symptoms began, and further investigation by calling several of her primary care physicians and pharmacies revealed that she had never previously used this drug, making this an unlikely etiologic factor. Allopurinol was initiated six weeks prior to presentation, making it the most likely cause of DRESS syndrome in this patient.

### What is the mechanism of DRESS syndrome?

The exact cause of DRESS is unclear and for each drug a different mechanism may exist. Most proposed mechanisms infer an unwarranted immunological response to the drug itself or its metabolites. For example, various endogenous enzymes create active metabolites from aromatic anticonvulsants that are thought to be detoxified by epoxide hydroxylase. If this process is faulty these metabolites may induce an auto immune response by creating neoantigens to which the immune system responds. Evidence also suggests that active human herpes virus 6 infection may also play a role by interfering with the removal of toxic drug metabolites.

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## How is DRESS syndrome treated?

Nothing is more important to reducing morbidity and mortality than rapid recognition of DRESS syndrome and immediate cessation of all potential offending agents.

Corticosteroid treatment to suppress the inflammatory eosinophilic involvement of the skin and internal organs remains controversial for several reasons. Viral activation may play a role in the cause of DRESS syndrome and there are concerns that systemic corticosteroids may enhance this process. Corticosteroids do not seem to have an outcome benefit in similar diseases such as in SJS/TEN, likely due to the increased septic complications associated with the presence of mucocutaneous lesions. But complications of DRESS syndrome are more commonly due to internal organ derangement rather than cutaneous effects. Despite the lack of randomized control trials and the potential harm, systemic corticosteroids are typically recommended and many patients seem to respond favorably.

## Question from...

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unteers after administration of 0, 1, 2, and 3 doses of 50 g AC separated by 4 hours. They found that 3 doses of AC showed a significant reduction in % urinary excretion as compared to control, 1 and 2 doses (49.2 vs. 91.0, 68.3, and 65.9% respectively,  $p < 0.01$  for each).<sup>5</sup> Unfortunately data on serum concentrations was not gathered which is a limitation as effects on absorption were not directly measured. In addition clinical significance in the effect on outcome cannot be surmised.

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IV N-acetylcysteine is used to treat DRESS syndrome related hepatitis, given its proven nonspecific beneficial role in a variety of other causes of fulminant hepatic failure. But this therapy remains unproved and controversial, with benefit suggested in some case reports and possibly an increased rate of anaphylactoid reactions in others.

Although DRESS is typically due to a specific drug, other drugs in a similar class, such as the aromatic anticonvulsants (i.e. phenobarbital, phenytoin, carbamazepine), may cause a similar reaction in an affected individual. Therefore patients who survive DRESS syndrome need specific education and ongoing medication reconciliation to prevent exposure to other potential offending agents.

Evidence has linked genetic components to several medications that are known to cause DRESS syndrome, therefore counseling family members must be a part of treatment. It has been described that in patients of Chinese descent there is a very strong association with HLA-B\*5801 allele and DRESS syndrome caused by allopurinol. This patient is an immigrant from China.

## Case Conclusion:

Shortly after presenting to the ED, the patient became obtunded and an ABG showed: pH,7.1; pCO<sub>2</sub>, 30 mmHg; pO<sub>2</sub>, 62 mmHg; bicarbonate, 9 mEq/L. Her initial clinical course was complicated by respiratory failure requiring intubation, fulminant hepatic failure, refractory hypotension requiring vasopressors, and renal failure requiring hemodialysis. She was given a course of IV N-acetylcysteine, and IV corticosteroids. After two weeks her liver and renal failure improved dramatically, but she suffered from several hospital related septic complications. Her family was educated on the potential for a genetic link.

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