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LETTER

## “Dead Men Tell Tall Tales”: The Issue of Post-Mortem Redistribution

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The traditional role of the poison center is in poison prevention and managing acute and chronic poisonings and exposure. However, the fact remains that many toxicologists at poison centers are consulted by law enforcement agencies or the medical examiner's office for help with interpreting post-mortem toxicology results. This seems on the surface to be a relatively straightforward task; in reality it can be very complex.

In the early days of post-mortem toxicological analysis, it was thought that a blood level after death was equal to the blood level during life: The person was dead, all cells were dead, no blood circulation or organ perfusion was occurring, and therefore no metabolism was occurring, so the level of a certain drug or toxicant in a dead person's blood reflected what the blood level was at the time of death. However, as our understanding of the perimortem period has increased, we realize that this is not the case. Many factors can affect the post-mortem blood level and one's ability to equate this to an ante-mortem level. The most significant aspect is the phenomenon of post-mortem redistribution.

Post-mortem redistribution (PMR) is an important factor to consider in forensic toxicology. Whether PMR occurs in any given case is dependent on characteristics of the individual drug, as well as the handling of the body, and the specimen col-

lection procedures. This article will present a brief synopsis of the complexities of interpreting post-mortem toxicology tests.

During life, the integrity of the cells in the body depends on intact aerobic cellular respiration, which is performed by the mitochondria. The mitochondria need oxygen to perform this aerobic cellular respiration and produce ATP efficiently. ATP provides the critical energy needed by the cell for the maintenance of many processes, including membrane integrity pumps, like Na-K-ATPase. This pump sends sodium extracellularly and pumps potassium intracellularly. The mitochondrial production of ATP also supplies the energy needed to perform other critical cellular functions like protein synthesis to make enzymes, manufacture cellular structural proteins, and to maintain the nucleus of the cell and nuclear and genetic integrity.

When circulation to the cells stops due to hypoxic/ischemic insult, cells begin to die. Different cells in the body die at different times after ischemic injury. For instance, cells in the brain and CNS die within 3-5 minutes; those of the myocardium after 30-40 minutes; but hepatocytes can live for 1-2 hrs after ischemic injury. Once the ischemic/hypoxic insult occurs, the cells change from aerobic to anaerobic metabolism, and this leads to reduced ATP production, lactate accumulation, and the production of an acidotic cellular pH. As the Na-K-ATPase pump fails due to lack of cellular energy and decreased ATP production, sodium accumulates in cells because the cell can no longer pump it out. The sodium accumulates in cells, drawing water with it, causing the cells to swell. Further swelling intracellularly causes the endoplasmic reticulum to swell, which then causes ribosomes to detach, and hence protein synthesis stops. In addition, the mitochondrial matrix swells, lysosomes leak enzymes, cellular integrity gets destroyed, and the cells die.

Once cells die, their membrane integrity is lost, and the cells leak their contents (drugs, electrolytes, etc) into the extracellular space. With no circulation occurring, the drugs then passively diffuse by concentration gradients from areas of high concentration to areas of low concentration. Drugs that are mainly contained in the cells and tissues during life (ie, those with high volumes of distribution), will diffuse out of the tissues and into the blood after cellular death, and therefore will exhibit this post-mortem redistribution (PMR). In these cases, post-mortem levels in central (cardiac) blood can be several times higher than they were ante-mortem, due to passive diffusion from myocardial cells into blood in the cardiac chambers;

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or diffusion from adjacent lung tissue into the great vessels in the thorax (aorta, IVC, etc). The likelihood that post-mortem samples of blood reflect ante-mortem drug levels will depend on the circumstances of the death and post-mortem sampling, as well as whether PMR is likely to take place.

The characteristics of the drug itself which will influence the likelihood of PMR are the Vd, the pKa, and the lipophilicity. If the Vd of drug or xenobiotic is high, ie a Vd > 1 l/kg, then that drug is distributed more to tissues, and PMR is more likely to occur. The pKa of drug is defined as the pH at which the drug is 50% ionized. A basic drug, ie, pKa >7 will exhibit more PMR. Highly lipophilic drugs are also more distributed in tissues, and are therefore more likely to exhibit PMR

Factors relating to the individual victim also influence whether PMR occurs or the reliability of the post-mortem toxicology results. These other factors which influence post-mortem blood tests are listed below:

1. Age of decedent- older patients have larger Vd due to decreases in protein binding of drugs. Therefore, more PMR may occur in this population
2. Manner of death: trauma, specifically truncal injuries, can cause spillage of intestinal contents and therefore diffusion into contiguous blood and tissues. This is especially important with DWI and MVAs. A victim whose stomach is full of alcoholic beverages can suffer visceral rupture and hence spillage of the alcohol-laden gastric into the peritoneal cavities. In many blunt thoraco-abdominal traumatic injuries, the diaphragm also ruptures, spilling these contents into the chest cavity as well. The alcohol contamination of these body cavities will allow passive diffusion of alcohol into contiguous structures like the heart, aorta, IVC, etc.
3. Conditions of death: aspiration of gastric contents, sea water, etc can cause fluid shifts and dilutions of various drugs.
4. Time since death and conditions of storage of the body - PMR continues for hours, and possibly days after death. Refrigeration can slow this occurrence, and refrigeration as soon as possible after death will decrease the incidence of PMR as well as post-mortem spontaneous hydrolysis of drugs in the blood. Also, the more a body is handled and moved the more blood in central compartments will move. In the cases of DOAs that are discovered an unknown time after death, bystander and then EMS CPR is often performed on bodies that have been dead for some time. This CPR will cause circulation of blood to the periphery from heart and great vessel blood that has experienced PMR, and can make interpretation more difficult.
5. Amount of decomposition/putrefaction- Decomposition can produce certain compounds that were not present prior to death, as well as can metabolize certain drugs after death.
6. Storage of blood after sampling- Spontaneous hydrolysis (non-enzymatic "water-splitting") or enzymes in blood can metabolize drugs after death. For

instance, plasma pseudo-cholinesterases can continue metabolizing cocaine into EME after death, or even in stored blood tubes. Freezing the blood during storage is the best insurance against spontaneous hydrolysis of drugs, and the addition of NaF preservative will inhibit enzymatic hydrolysis. The longer a blood sample is stored, even in optimal conditions, the more drug will break down and therefore the less drug that will be available at the time of analysis. This can be a significant issue in cases where an investigation is re-opened and stored materials are analyzed much later.

7. Site of sampling: Probably the most critical factor influencing whether PMR will be seen is the site of blood sampling, especially for drugs with large Vd and higher pKa's. When heart blood is sampled, the drugs bound in the tissues of the heart muscle diffuse into the blood in the cardiac chambers, and thus will be seen in higher concentrations than they were ante-mortem. In addition, pulmonary tissues harbor an enormous amount of drugs, such that structures contiguous to the lungs (such as the vena cava and the aorta) will be more susceptible to PMR than peripheral blood samples. In addition, the right ventricle is often adjacent to the left lobe of the liver, separated only by thin pleural and diaphragm. High drug concentration in liver tissues can diffuse into the heart chambers. Similarly, drugs in liver tissue can diffuse into the IVC and will falsely elevate these samples. Traditionally, heart blood was the only specimen sampled for post-mortem analysis due to the easy access to a large blood volume. However, it has become increasingly clear that heart blood should be used for initial screening qualitative analysis, and that peripheral blood should be used for quantitation. The preferred sample will be a femoral blood sample, ideally with the vessel ligated proximally, such that back flow from IVC or more central compartments does not occur.
8. Method of blood sampling (i.e. blind thoracic stick) will also influence results, as needle will pass through chest structures and can be inadvertently sampled along the tract of the needle. Also, in severe truncal trauma, a ruptured stomach or intestine can cause spillage into the thorax and abdominal cavities. This will contaminate blind sticks thoracic needlesticks that are commonly done in MVA deaths, especially at the scene by medical examiners (in many small municipalities, the coroner is an elected position and is not a physician. Many times a mortician will perform the sampling at the scene by the blind thoracic sampling technique) This can cause false elevations of drugs, most notably alcohol.
9. Lastly, interpretation of results depends on type of blood tested, since common drug level monitoring in living patients is performed on serum (plasma), and post-mortem testing is typically done on whole blood. Standard reference texts usually give average ranges of blood-to-plasma ratios that will aid in interpretation.

As can easily be seen from this discussion, the results of post-mortem testing must always be interpreted by taking into account the clinical and prescription history in light of the circumstances and the setting where the death took place. In the case of opioids, setting "lethal" post-mortem levels is very difficult, since the range of post-mortem overdose (OD) levels often overlap with those seen in patients on chronic opioid treatment.

The old adage that "dead men tell no tales" should therefore be amended that "dead men can tell tall tales". It is up to the toxicologist to decide which tales to believe.

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## Questions from the Drug Information Center

Contributed by: Pamela Dunn, Pharm.D., Upstate NY Poison Center, Syracuse NY

### Question: What is the mechanism of action of bruxism in Ecstasy (3,4-methylenedioxymethamphetamine or MDMA) users?

Bruxism can be defined as grinding of the teeth, or jaw clenching and is commonly reported in most MDMA users. In fact, they frequently use pacifiers to relieve these effects.<sup>1</sup>

MDMA is a synthetic amphetamine which is widely abused for its ability to produce euphoria and inner peace. It works similar to other amphetamines by releasing catecholamines in the central nervous system, specifically: serotonin, dopamine and norepinephrine<sup>1</sup>. MDMA also binds to reuptake transporters and inhibits catechol removal from the synapse<sup>1</sup>. MDMA is different from the other amphetamines in that it has a much larger affinity for serotonin transporters than other neurotransmitter transporters. In fact it's affinity for serotonin transporters is 10 times greater than that for dopamine and norepinephrine transporters.<sup>2</sup>

MDMA induced bruxism is thought to be a result of the modulation of both dopamine and serotonin. Dopamine is a neurotransmitter involved with movement, emotional response, and the ability to experience pleasure and pain<sup>3</sup>. Antagonizing dopamine in different regions of the brain may result in movement disorders, relief of psychosis, and akathisia<sup>3</sup>. Antagonizing or decreasing dopamine has also been shown to cause bruxism, when administering certain selective serotonin reuptake inhibitors (SSRI's) and/or dopamine receptor antagonists<sup>4</sup>. SSRI's cause a decrease in the dopamine release in the mesocortical tract (dopamine tract which innervates the prefrontal cortex)<sup>4</sup>. It's in the mesocortical tract where serotonin receptors are present on dopaminergic axons and stimulation of these receptors will decrease dopamine release, thereby potentiating movement disorders including bruxism<sup>4</sup>. Similarly, dopamine receptor antagonists may also cause bruxism by antagonizing receptors in the prefrontal cortex<sup>4</sup>.

This mechanism was described by investigators who effectively managed three patients having bruxism with low-dose metoclopramide, 15 mg/day.<sup>4</sup> Metoclopramide is a selective dopamine-2-receptor antagonist that at low-doses binds to presynaptic dopamine-2-receptors. It is speculated that this presynaptic binding inhibited negative feedback and thus restored dopamine regulation in the prefrontal cortex.<sup>4</sup>

Another proposed mechanism responsible for bruxism may be related to the jaw opening reflex (JOR). The JOR is a protective measure used when something is causing strong masticatory forces, in order

to protect the teeth. It's suggested that MDMA's may inhibit this protective response by an as yet undetermined mechanism, although modulation of serotonin and norepinephrine have been implicated<sup>5</sup>. Serotonin has also been proposed to facilitate the JOR as well as lead to an inhibition of the reflex through central serotonergic stimulation<sup>5</sup>. Norepinephrine has two mechanisms on the JOR, either the facilitation by activation of central alpha-1-adrenoceptors or inhibition by activation of alpha-2-adrenoceptors<sup>5</sup>. Studies have demonstrated that serotonin and norepinephrine both have caused an increased activity of trigeminal motor neurons (neurons which control jaw position and movements) as well as an increase in the activation of the masseteric reflex (increase in jaw closing force)<sup>5</sup>. Clonidine, a presynaptic alpha-2-adrenoceptor, has a complete inhibitory response on the JOR. Similar to low-dose metoclopramide, presynaptic alpha-2-receptor agonism results in reduced neurotransmitter release. A study was performed to determine whether MDMA caused inhibition of the JOR in rats and the results showed that there was an inhibition of the JOR, but it was incomplete<sup>5</sup>. It also showed that repeated doses of the drug caused an increase in the inhibitory noradrenergic mechanisms which causes the reflex<sup>5</sup>.

In summary, the mechanism of MDMA induced bruxism is complex and still not fully understood. Current evidence suggests this adverse effect is most likely the result of neurotransmitter modulation, particularly dopamine, serotonin and norepinephrine.

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# FDA Safety Summaries

## **20 mEq Potassium Chloride in 5% Dextrose and 0.45% Sodium Chloride Injection, USP**

Lot number 65-620-FW. A small number of the containers may be incorrectly labeled with a bar code for 5% Dextrose Injection, *December 08, 2008*

## **Innohep (tinzaparin sodium injection)**

(IRIS) study stopped because of an interim finding of an increase in all-cause mortality *December 02, 2008*

## **Starcaps Dietary Supplement Capsules**

Expanded its voluntarily recall due to the presence of an undeclared drug ingredient, Bumetanide. *December 08, 2008*

## **Zhen De Shou Fat Loss Capsules**

Recall, undeclared sibutramine, *November 23, 2008*

## **Phenytoin and Fosphenytoin Sodium**

Potential increased risk of serious skin reactions in Asian patients positive for human leukocyte antigen (HLA) allele, HLA-B\*1502. *November 24, 2008*

## **Benzoyl Peroxide Acne Cream 10%**

recall of all lots of 1 ounce tubes because samples of the products were found to contain bacteria, Burkholderia Cepacia, *November 13, 2008*

## **Bisphosphonates**

FDA issued an update to the Agency's review of safety data regarding the potential increased risk of atrial fibrillation in patients treated with a bisphosphonate drug. *November 12, 2008*

## **Infants' Mylicon Gas Relief Dye Free Drops (Simethicone-Antigas)**

Recall, metal fragments *November 07, 2008*

## **Propafenone HCl Tablets 150 mg, 225 mg, and 300 mg**

## **Isosorbide Mononitrate Extended Release Tablets 30 mg and 60 mg**

## **Morphine Sulfate Extended Release Tablets 15 mg**

## **Morphine Sulfate Immediate Release Tablets 15 mg and 30 mg**

## **Dextroamphetamine Sulfate Tablets 10 mg**

Oversized tablets may contain more than the intended levels of the active drug ingredient *November 07, 2008*

## **Raptiva (efalizumab)**

Highlight the risks of life-threatening infections, including bacterial sepsis, viral meningitis, invasive fungal disease, progressive multifocal leukoencephalopathy and other opportunistic infections *October 16, 2008*

## **Dextroamphetamine Sulfate 5mg Tablets**

Voluntary recall due to the potential presence of oversized tablets *October 15, 2008*

## **Over The Counter Cough and Cold Medications**

Modifying the product labels for consumers of over the counter (OTC) cough and cold medicines to state "do not use" in children under 4 years of age. *October 09, 2008*



## When Does Exposure Become Poisoning: The Case of Methyl Mercury

Gary Myers, MD

Professor of Neurology, Pediatrics, and Environmental Medicine

The popular media and the medical literature<sup>1</sup> are full of statements that our children are being “poisoned” by environmental contaminants. Could this be true or is it simply one interpretation of available data? The term poisoning carries emotional power and suggests serious consequences. However Paracelsus, the father of toxicology, in 1538 wrote “All substances are poisons, there is none which is not a poison. It is the dose that distinguishes a poison from a remedy.” If that is true, how should we define a poison and when should the term be used?

Webster’s International Dictionary<sup>2</sup> offers the following definition for poisoning: a: to injure or kill with poison b: to treat, taint, or impregnate with or as if with poison. Wikipedia gives the following definition to poison<sup>3</sup>: “In the context of biology, poisons are substances that can cause disturbances to organisms,<sup>1</sup> usually by chemical reaction or other activity on the molecular scale, when a sufficient quantity is absorbed by an organism. Legally and in hazardous chemical labelling, poisons are especially toxic substances; less toxic substances are labelled “harmful”, “irritant”, or not labelled at all.” The term “poison” or “poisoning” is not very specific and appears to be used by different writers in varying ways. Many of us were trained to think that “poisoning” is associated with some clinical symptoms. However, this is not the way the term is always used.

For example, in Rochester the Coalition to Prevent Lead Poisoning reports “Last year, over 300 children were poisoned by lead in Monroe County”<sup>4</sup>. They base the statement on the number of children in Monroe County who had a measured blood lead level that exceeded 10  $\mu$ /dL. There have been no clinical cases of lead poisoning reported in Rochester for several years.

Such assertions are usually based on reports of toxicity from epidemiological studies. These studies evaluate sizeable cohorts of children and there are usually no individuals with clinical findings. They measure the exposure, test the children, and then statistically examine the data to determine if there are adverse associations related to the level of exposure. In the case of lead exposure, the assertion is based on reports of an adverse association of exposure with test outcomes at levels below 10 ppm<sup>5,6</sup>.

These epidemiological studies are increasing in number and consequently there are a growing number of reports proclaiming environmental “poisoning”. Such assertions catch the public’s attention, generate concern, and may be important in building the political momentum to remedy the problems of pollution. However, they also generate public fear and the interpretation of the data is often complex. By design, these studies attempt to detect the most subtle difference that can be demonstrated between subjects with varying degrees of exposure. Consequently, they are complex to carry out, easily influenced by inadvertent bias, require control for factors already known to influence development, require complex analyses, and often result in findings that are open to varying interpretations. Even when the results can be confirmed, the impact of the reported statistical association may be of negligible or minimal significance.

Some of the “contaminants” that cause “poisoning”, such as heavy metals, occur naturally in our environment and we are all exposed to them. However, our exposure is often increased by pollution and other anthropogenic measures. These exposures present the population at large and Poison Control Centers with a dilemma: Are the exposures significant enough to constitute “poisoning” and do they deserve our resources and attention? Exposure to methyl mercury (MeHg) from consum-

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ing fish is an example of the larger issue of what constitutes poisoning.

In the 1950s at Minamata Japan a strange illness began<sup>7</sup>. Many causes including infectious etiologies and pollutants were suspected and eventually it was diagnosed as MeHg poisoning. The pollution came from a chemical factory that in 1935 started dumping all of its waste into the local bay. The waste included mercury, manganese, thallium, lead, selenium, iron, and other chemicals. Many of the local people consumed fish and seafood from the bay every day. Fish in the bay had MeHg levels up to 100 times more than seafood sold in the US (50 ppm as opposed to 0.5 ppm). At Minamata some pregnant mothers who were exposed to the contaminated fish and had minimal or no symptoms, but gave birth to children with severe handicaps including cerebral palsy, mental retardation, seizures, and microcephaly. The fetal exposure to MeHg and other pollutants had seriously affected their brain development. There is almost no data on the level of exposure that caused these problems, but pathological studies suggest it was very high. Outside of Japan there have been no confirmed reports of MeHg poisoning from fish consumption. Subsequently, in the 1970s, studies of fetal exposure following an epidemic of MeHg poisoning in Iraq from contaminated seed grain suggested that levels as low as 10 ppm might affect the fetus (Figure 1).

It was known that all fish contain some mercury (Hg) in the form of MeHg and consequently everyone who eats fish is exposed. In addition, with regular fish consumption exposures of 10 ppm and higher can be readily achieved. Since the United Nations estimates that nearly 1 billion people around the world consume fish daily, this was an important issue to investigate.

Finding a population with adequate exposure that could be carefully studied proved to be challenging. Several epidemiological studies were undertaken, but conditions adequate for detecting subtle changes were not always met. Our research team identified a population in the Republic of Seychelles that appeared ideal. Nearly everyone on the island consumes fish daily, but their exposure varies depending upon the amount and species consumed. The Seychelles is a small island nation with a stable, cooperative population and little emigration. The government is socialistic and provides free comprehensive basic health care and education to everyone, so some of the covariates that complicate epidemiologic studies were minimized. We have carried out an observational epidemiologic study of mercury exposure from fish consumption there over the past 25 years. The Seychellois appear to be very healthy and their athletes regularly excel in the Indian Ocean athletic contests. However, we were looking for very subtle differences between subjects with different exposures.

Since clinical experience and experimental studies indicate the developing brain is especially sensitive to the toxic effects of MeHg, we focused on prenatal exposure<sup>8</sup>. We took maternal hair during the prenatal visits and enrolled a cohort of nearly 800 children in 1989. To avoid inadvertent bias in analyses, we designed the study so that subjects and investigators would be blinded to exposures. We additionally specified that all primary analyses would be designed by the research team and

carried out only by biostatisticians in Rochester. We first tested the children when they were 6 months of age and then tested them regularly at intervals. We measured exposure in the mother's hair growing during pregnancy, a biomarker known to correlate with brain levels of exposure<sup>9</sup>. Testing started with global measures of children's cognition and development and as they matured progressed to specialized measures of specific cognitive functions. As the children reached their teens we administered the CANTAB and measured auditory evoked potentials and cardiac measures of autonomic function. This testing is still being analyzed. We have included nearly every test reported by other investigators to be associated with MeHg exposure.

We have found a number of associations between the children's exposure and their development. However, in 20 years of study no clear pattern of adverse associations has surfaced<sup>10</sup>. Indeed, we have found that some test results improve as the children's exposure increases below 10 ppm. This unexpected finding was initially puzzling since MeHg is toxic and Hg has no known function in the human body. However, Hg exposure from fish consumption may differ from other types of exposure in two ways. First, the level of exposure is lower, and second fish contain a host of nutrients that are important for development of the nervous system.

This unusual finding led us to study nutrients and their relation to MeHg exposure in a new cohort. We enrolled 300 mothers in 2001 early in pregnancy and measured iodine, iron, fish consumption, and long chain polyunsaturated fatty acids (LCPUFA). Subsequently, we tested the children on two occasions using the Bayley Scales of Infant Development (BSID). These studies found an adverse association of MeHg with the Psychomotor Developmental Index (PDI) of the BSID. However, it only appeared when the analyses included LCPUFA<sup>11</sup>. Subsequent analyses examining individual and grouped LCPUFA values showed a beneficial association of the PDI with levels of omega 3 fatty acids<sup>12</sup>. The brain is 50% lipid and LCPUFA are important components, so this finding is not too surprising. The human body cannot synthesize adequate LCP-UFA and depends on external sources such as breast milk and seafood to provide these, especially during brain development. Together, these analyses indicate that the benefits of LCPUFA from fish consumption may equal or exceed the detrimental effect of MeHg at the levels of exposure we studied.

Other authors have reported adverse associations with MeHg at exposures lower than those present in the Seychelles<sup>13</sup>. The subjects in that study were exposed to MeHg from consumption of whale meat which also contains polychlorinated biphenyls (PCBs), another toxin. They reported several statistically significant adverse associations of relatively small magnitude. Recently other authors have reported that children whose mothers consume more fish during pregnancy do better on cognitive testing at later ages<sup>14,15</sup>. Unfortunately, their data did not include the measurement of specific nutrients like LCPUFA.

Taken together, our studies and those of others do not provide strong support for an adverse association of MeHg exposure with children's development at the levels achieved by

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**Question: A lactation consultant called the National Lactation Study Center drug information line. She has heard that despite the fact that the American Academy of Pediatrics listed codeine as compatible with nursing, it was no longer considered safe to use acetaminophen with codeine for pain after caesarean sections and to allow mothers to breastfeed. Is this true?**

**Answer:**

The percentage of infants that are being breastfed when they leave the hospital has risen from 60% in 1993 to 77% in 2006 and has finally reached the 2010 target of the US Department of Health and Human Services' Healthy People goal<sup>1,2</sup>. An estimated one third of all infant deliveries nationwide are now done by Caesarean Section. The question of pain management in the post delivery period in a lactating mother has become more common.

Beginning in 1983, The Committee on Drugs of the American Academy of Pediatrics published their statement on "Transfer of Drugs and Other Chemicals into Human Milk" with the last revision in 2001.<sup>3</sup> The National Library of Medicine has developed a fairly comprehensive lacta-

tion data base.<sup>4</sup> Upon review of these resources and Brigg's textbook<sup>5</sup>, there are relatively few reports of adverse reactions in the infants of mothers who are breastfeeding and taking codeine, although sedation has been reported. Of the 100 or so events reported from 1969 through 2002 only half were "probably" codeine related and half were "possibly" related. No event was categorized as "definitely" related. CNS depression was reported in only half the events.<sup>6</sup> Over one third of the events occurred in infants less than 2 weeks of age and over three quarters occurred in infants less than 2 months of age.<sup>6</sup> Only 4 cases of CNS depression were reported in infants over 6 months old and therefore, young infants were thought to be most susceptible.

In January of 2007 Madadi et al.<sup>7</sup> published a case report of an infant death in a breastfed infant whose mother was taking codeine. The infant had become progressively more somnolent and developed difficulty breastfeeding at 7 days of age. On day 13 the infant was found by an ambulance crew to be cyanotic and without vital signs. Resuscitation on site and in the Emergency Department was unsuccessful. In response to this report, the FDA in August

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consuming fish. The data do provide support for the importance of nutrients present in fish for optimum development of children's cognitive abilities.

Methyl mercury is an example of a neurological toxin present in our environment to which everyone who consumes fish is exposed. Fish are a major source of preformed LCPUFA and other nutrients that are important for brain development. The benefits of nutrients from fish appear to counterbalance or perhaps exceed the theoretical risk of MeHg exposure. Exposure to MeHg at the levels achieved by fish consumption does not cause clinical poisoning. However, it is still unclear if there are subtle differences of exposure that can be detected epidemiologically at the levels of exposure resulting from fish consumption. So where should we place the emphasis? Perhaps we should return to the Hippocratic Oath which states "I will prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone."

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Figure 1. From Cox, C, et al. **Dose-response analysis of infants prenatally exposed to methyl mercury: An application of a single compartment model to single-strand hair analysis.** *Environmental Research* 1989; 49; 318-332

2007 sent out alerts to both healthcare professionals and the public of reports of rare but significant CNS depression in infants whose mothers were taking codeine. These effects included apnea, bradycardia, and the death of this 13-day-old breastfed baby.<sup>8,9</sup>

Madadi et al<sup>10</sup> subsequently reported a case-control study of neonatal and maternal toxicity from codeine. Of 72 breastfed infants whose mothers were taking codeine, only 17 infants had signs of CNS depression. These 17 symptomatic infants had mothers whose codeine doses were almost 50% higher than the codeine doses of mothers whose infants were asymptomatic ( $p < 0.05$ ). Mothers of symptomatic infants received 1.62(SD 0.79) mg/kg/day of codeine while mothers of asymptomatic infants received 1.02(SD 0.54) mg/kg/day of codeine. The study found concordance between maternal and infant symptoms of CNS depression. Of the asymptomatic infants, only 5/55 (9%) of the mothers had any CNS depression but of the depressed infants, 12/17 (71%) of the mothers were also exhibiting signs of CNS depression. The clinical effects noted in this study are consistent with the pharmacogenetics of codeine metabolism in humans.

Codeine is a prodrug that is metabolized into morphine by the P450 enzyme 2D6 (CYP2D6). Normally about 10% of the drug is metabolized to morphine. Morphine is eliminated via glucuronide conjugation into either morphine-3-glucuronide (inactive) or morphine-6-glucuronide (M6G) (thought to be at least equipotent to morphine<sup>10</sup>). The transformation of morphine into the active M6G is catalyzed by another enzyme uridyl glucuronosyltransferase 2B7 (UGT2B7). Any genetic variation in CYP2D6 or UGT2B7 could result in the build up of morphine or its active metabolite with resultant CNS depression or the inability to produce concentrations of morphine or M6G adequate to produce analgesia. Patients can be categorized into one of four phenotypes based on their genotype. A patient with 2 nonfunctioning alleles is a poor metabolizer of codeine and would likely produce low amounts of morphine when codeine is administered. A patient with at least one allele with a reduced function is an intermediate metabolizer. A patient with at least 1 functional allele is an extensive metabolizer and a patient with multiple copies of a functional allele is an ultra-rapid metabolizer. Ultra-rapid metabolizers produce higher than average concentrations of morphine when given codeine.

The frequency of ultra-rapid metabolizer genotypes in various ethnic groups ranges from 1% in Scandinavian populations to 10% in Mediterranean peoples to 29% in groups of Ethiopian decent.<sup>11</sup> Cases of adults who are ultra rapid metabolizers of codeine secondary to a duplication of CYP2D6 genes and have developed opioid toxicity with even small doses of codeine have been published.<sup>12, 13</sup> Another study which looked at M6G production from morphine reported that adults who were homogenous for the UGT2B7\*2 allele had higher M6G/morphine ratios than those who were homozygous for the wild-type allele.<sup>14</sup>

The effects of polymorphism in these two enzyme systems may be less pronounced in neonates since in full term neonates, CYP2D6 activity appears to be concordant with genotype at about 2 weeks of age but UGT2B7 activity does not reach adult levels until 2-6 months<sup>10</sup>. Therefore you would expect that mother's phenotypical variation would be more important than the infant's in the situation of a breastfeeding infant exposed to codeine. Two of the seventeen mothers of symptomatic infants in the Madadi study<sup>10</sup> were CYP2D6 ultra-rapid metabolizers in combination with having the UGT2B7\*2/\*2 genotype as compared with none of the mothers among the asymptomatic neonates. Each of these mothers actually consumed 2.1-2.2mg/kg/day of codeine which is equivalent to approximately five Tylenol #3 tablets per day in a 70kg person. One of the infants died and one infant became severely toxic but recovered. Symptoms in these infants were not immediately apparent but became so after 7 days of breastfeeding. One mother of an asymptomatic infant had a CYP2D6 ultra rapid metabolizer in combination with UGT2B7\*2\*1 genotype and took 60mg of codeine a day for a week. The baby at this time, however, was 6 months old and was also receiving formula and solid foods.

While maternal polymorphism in CYP2D6 and UGT2B7 are important determinants in the safety of infants who are breastfeeding while mothers are taking codeine, they are not the only determinants. Doses of codeine over 0.6mg/kg, approximately three Tylenol #3 tablets per day in a 70kg mother, were also associated with infant symptoms. The most severe symptoms were associated with doses over 2mg/kg/day or approximately five tablets of Tylenol #3 per day. Older infants and infants who were not exclusively receiving breast milk were not as likely to be affected. Mothers who reported sedation themselves were more likely to have infants that were also sedated.

If codeine is to be used in mothers who are exclusively breastfeeding, the mothers need to be counseled about using the codeine sparingly and alternating doses with other forms of analgesia such as non steroidal or acetaminophen. Mothers need to be prepared to watch for infant sedation and poor feeding, especially if they themselves become sedated.

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# Adipose Tissue: From Depot Storage to Toxicant Target

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In the clinical research literature of recent years, it's become cliché to note that since the discovery of the fat-produced hormone leptin in 1994, we have gradually discovered that fat is not a mere energy storage depot, but instead, a complex endocrine gland deeply imbedded into the body's energy regulation system.

In toxicology, adipose tissue has been considered for decades to be a depot of another kind -- a convenient and relatively harmless place to store lipophilic toxicants like PCBs and pesticides. The basic story was this: Fat is inert -- therefore toxicants accumulating in fat is no particular threat, and may even be a beneficial sequestering mechanism -- unless, of course, sudden weight loss liberates them back into circulation. My beautiful new copy of Casarett & Doull's Toxicology (2008) unfortunately repeats this mantra.

Meanwhile, the clinical world chants a different, but related, mantra. Traditionally, obesity (and its cousin, type II diabetes) has been seen as resulting from an imbalance of a simple equation: Fat = energy in - energy out. So far, so good, but the crucial corollary to this equation is that diet, physical activity, and good moral fiber are the key to beating these diseases. It is just, they say, elementary thermodynamics.

We should have known it couldn't be that simple. Thyroid disease, for example, clearly affects weight by disturbing metabolic rate and other energy physiology. True -- physical activity would increase energy expenditure and likely help a severely hypothyroid patient -- except for the inconvenient fact that it requires immense willpower in that state to merely stay awake.

The 50,000 year view suggests even more clearly that energy regulation must be complex. Imagine you were designing a mammal for survival in a temperate climate. What are the most basic requirements of the energy system?

First, the system needs to know when energy is needed, and when it isn't. The mammal, of course, can't be too thin, but neither can it be too fat, for it needs to stay agile enough to escape predators and fight successfully for territory and mates. Second, metabolic rate should be adjustable -- greater when energy is plentiful (summer), but throttling back in winter. Third, special conditions such as periodic food scarcity or the onset of fall should ramp up transfer of serum carbohydrates into fat stores to provide additional buffering against starvation. The list goes on.

These functions are almost certainly controlled through a complex mix of neuro and endocrine signaling, the details of which we are only beginning to unravel. But even without the details, it's clear that there are many potential toxicant targets in this system -- some of which are found within adipose tissue.

So, if fat is no longer inert, then concentrating our most persistent and troublesome toxicants within it may have consequences. And given our experimentation with novel lipophilic substances over the last 50 years, we should be watching for evidence of the energy system's disruption, possibly on a large scale.

This we see -- in epidemic proportions. Obesity clearly has many causes, but disruption of functions like hunger, metabolic rate, and fat storage should certainly be on the list.

One epidemiological study, while in no way conclusive, offers a particularly intriguing clue. In 2006, Lee and colleagues published a large cross-sectional study demonstrating a strong association between persistent organic pollutant levels and prevalence of diabetes. These primary results were interesting enough, though not entirely unique. But a figure, buried back near the references offered a stunning, if underplayed, surprise.

Everyone knows obesity and type II diabetes are strongly linked, with obesity a major (though not mandatory) risk factor. In Lee's figure, they revealed that in these data, subjects with high pollutant levels displayed the typical strong association between obesity and diabetes -- but, among the lowest quartile of exposure, there was no association whatsoever. This finding suggests the startling possibility that a substantial proportion of type II diabetes could be caused or exacerbated by environmental toxicants, with obesity either a step on the causal path, or perhaps an independent effect.

Obese people are almost universally blamed for their disease, as a product of overeating and sloth. But long ago, obese hypothyroid patients were also blamed for their obesity -- until we learned to measure thyroid functions. Now we know hypothyroidism is a disease, and when that disease is treated, these "slothful" people miraculously become active and lose weight.

The hypothesis today is that a similar phenomenon, caused by environmental toxicants, is disrupting our energy regulation system. It is a bold hypothesis to be sure, but evidence is accumulating. We now need a concerted investigative effort by researchers and clinicians -- which begins with the cliché that fat is no longer depot storage, and, it follows, the possibility that fat may be a poor place to store some of our most pernicious toxicants.

*Lee, D. et al., 2006. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. Diabetes Care, 29(7), 1638-44.*

# Melamine

Sharon Ternullo, Pharm.D. DABAT

Since 2007 melamine contamination of food products has repeatedly made world news. Melamine has been found as a contaminant of pet foods, candy, infant formula, and specialty drinks made from milk products manufactured from ingredients imported from China. The contamination of pet food manufactured in the United States was reported in February and March of 2007. The source of contamination was melamine that had been added to wheat gluten in China and then exported and used to manufacture pet food world wide. Over 100 brands of pet food were recalled in the United States alone. The confirmed number of animal deaths in the United States was at least 16, with nearly 500 cases of kidney failure. Veterinary organizations estimated the number of pet deaths to be between 2,000 and 7,000 animals and Pet Connections data, based on the self-reporting of pet owners, placed unconfirmed deaths at approximately 4000 dogs and cats.<sup>1,2</sup> In April of 2007 it was determined that “melamine scrap” had been placed in fish and livestock feed and as a result of this addition, melamine contamination was present in eggs shipped from China and pork and chicken produced in the United States but fed contaminated feed imported from China.

In 2008 several Chinese companies were implicated in a scandal involving infant formula with large amounts of melamine added. Melamine powder was purchased and added to pooled, watered-down cows milk and then sold to a Chinese infant formula company. The results were kidney stones and renal failure; especially in young children. Nearly 300,000 children became ill, thousands were hospitalized, and at least 6 infants died.<sup>3,4</sup>

## What is Melamine?

Melamine has a structure that is 66% nitrogen by weight. The nitrogen packed molecule makes melamine useful as a fire retardant in plastics and melamine resin useful in house wares, countertops, fabrics, glues, and flame retardants. As the plastic chars it releases gaseous nitrogen. Most fires are not hot enough to burn nitrogen and therefore melamine is an effective flame retardant and melamine plastics are almost impossible to burn. The product can be manufactured chemically (China is the world’s largest exporter of melamine) and is also a metabolite formed in the body of mammals and some plants from the pesticide, cyromazine.

Because of its rich nitrogen content, melamine was trialed as a fertilizer for crops several decades ago but the slowness of the hydrolysis reactions which made the nitrogen available to the soil precluded its general use. Its use as a non-protein nitrogen source for cattle was also found inferior to other sources of nitrogen due to poor utilizability.

## Toxicity

Occupational exposure to melamine may occur through inhalation and dermal contact with this compound at workplaces where melamine is produced or processed. Chronic exposure in workers can result in eye, skin, or respiratory irritation depending on the route of exposure. Chronic expo-

sure in rodents has had equivocal results in the production of bladder tumors and seems to be carcinogenic in the presence of calculi but there is inadequate data in humans to assess its carcinogenicity. The general population may be exposed to melamine via ingestion of contaminated food. Contamination of food with melamine could occur by several mechanisms: contamination of food with the pesticide cyromazine which can be converted to melamine by the mammal or plant used as the food source, the addition of melamine to nutritional sources of the food source, the decomposition of trichloromelamine used as a sanitizing agent on food processing equipment, or through accidental or deliberate addition of melamine to the final product or one of its components.

Melamine is relatively non-toxic with an acute lethal dose similar to table salt. The LD50 based on rat data is more than 3g/kg. The acceptable standard for human consumption for melamine has been set by the World Health Organization. WHO has set the tolerable daily dose at 0.2mg/kg.<sup>5</sup> However, the combination of melamine and cyanuric acid (melamine cyanurate) has been found to be more toxic than either chemical alone in rodents. In cats and humans the combination of both substances in the diet can lead to acute renal failure. When cyanuric acid and melamine reach the renal microtubules they form melamine cyanurate crystals, which block and damage the renal cells lining the tubules leading to acute renal failure. For foods other than infant formulas, the FDA originally set the tolerable daily intake of melamine at 0.63mg/kg/day but decreased it to 0.063mg daily to apply an additional 10-fold safety factor to compensate for the potential for exposure to the combination of multiple melamine-related compounds. The FDA concluded that “levels of melamine and its analogues below 2.5ppm in foods, other than infant formula, do not raise public health concerns”.<sup>6</sup>

## Chinese Food Recalls

In 2007 a pet food recall was initiated when pet food manufacturers found that their products had been contaminated with melamine and had caused serious illness or death in animals that had eaten them. In March of 2007, the US FDA found granular melamine in pet food which was traced back to the white granular wheat gluten that had been imported from a single source in China. Crystals were also found in the kidneys and urine of affected animals. Later, vegetable protein imported from China was implicated as well. In April 2007 it was determined that “melamine scrap” had been placed into fish and livestock feed so that crude protein analysis of nitrogen content appeared adequate despite using diluted or substandard amounts of protein. As a result of this addition of melamine to animal feeds, contamination has shown up in eggs shipped from China and pork and chicken produced in the United States but fed contaminated feed imported from China.

In 2008, several Chinese companies were implicated in a scandal involving diluted substandard infant formula that

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had large amounts of melamine added to make it appear that the protein content met standards. None of this infant formula was imported to the United States. The widespread scope of the melamine fortification problem has resulted in documented contamination in many varied products worldwide including Chinese-made Cadbury chocolate and several types of Lipton Milk Tea Powder exported from China to Hong Kong. In September and October of 2008 the FDA reported melamine contamination in 27 different products produced abroad and imported to the U.S. that contained powdered milk protein or non-dairy creamer. These included drink mixes, coffee drinks, candies, and snacks.<sup>7,8</sup>

### United States Infant Formula

No Chinese manufacturer of infant formula has fulfilled the requirements to import infant formula to the U.S. Therefore only through members of the Asian Community who have directly imported Chinese-manufactured formulas, would the public have access to any contaminated formula.<sup>7</sup> The FDA has found only extremely low levels of melamine or cyanuric acid in U.S.-manufactured infant formulas. The TDI for infants which includes a safety factor of 1000 fold is 0.063mg melamine/kg/day. The FDA has been collecting and analyzing samples of domestically manufactured infant formula for the presence of melamine and melamine-related compounds. To date, FDA tests have found low levels of melamine in one infant formula sample and low levels of

cyanuric acid in another.<sup>9</sup> The levels are well below 1.0 ppm and the FDA safety assessment of infant formulas asserts that melamine or one of its analogs at concentrations below 1.0 ppm in infant formulas does not raise a public health concern.<sup>6</sup> These amounts are up to 10,000 times lower than the amount of melamine reported in the Chinese-made infant formulas that produced mass illness in infants.

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# FDA Safety Summaries

## **Digoxin, USP 0.125 mg, Digoxin, USP 0.25 mg (Caraco brand)**

Caraco Pharmaceutical Laboratories and FDA notified healthcare professionals of a consumer-level recall of Caraco brand Digoxin, USP, 0.125 mg, and Digoxin, USP, 0.25 mg, distributed prior to March 31, 2009, which are not expired and are within the expiration date of September, 2011. The tablets are being recalled because they may differ in size and therefore could have more or less of the active ingredient. *March 31, 2009*

## **Propafenone HCL Tablets**

FDA and Watson Pharmaceuticals notified healthcare professionals and patients of a recall of Propafenone HCL 225 mg tablets, a drug product used to treat cardiac arrhythmias. The drug is being recalled because some tablets may contain slightly higher levels of the active ingredient than specified. *March 23, 2009*

## **Zencore Plus**

Bodee LLC and FDA notified consumers and healthcare professionals of a nationwide recall of all the company's supplement product sold under the name Zencore Plus. FDA lab analysis of Zencore Plus samples found the product contains benzamidenafil, an undeclared drug product and a PDE5 inhibitor. *March 11, 2009*

## **Transdermal Drug Patches with Metallic Backings**

FDA has evaluated the composition of available patches to determine which of them contain metal components and to assure that this information is included in their labeling. Based on current information from this evaluation, FDA is working with the manufacturers of the following patches to update the labeling to include adequate warnings to patients about the risk of burns to the skin if the patch is worn during an MRI scan. *March 5, 2009*

## **Metoclopramide-Containing Drugs**

FDA notified healthcare professionals that manufacturers of metoclopramide, a drug used to treat gastrointestinal disorders, must add a boxed warning to their drug labels about the risk of its long-term or high-dose use. Chronic use of metoclopramide has been linked to tardive dyskinesia. *February 26, 2009*

## **Zonisamide (marketed as Zonegran, and generics)**

FDA notified healthcare professionals that updated clinical data has determined that treatment with zonisamide, indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy, can cause metabolic acidosis in some patients. *February 19, 2009*

## **Raptiva (efalizumab)**

FDA issued a Public Health Advisory to notify healthcare professionals of three confirmed, and one possible report of progressive multifocal leukoencephalopathy (PML). *February 19, 2009*

## **Xigris (Drotrecogin alfa [activated]) - Early Communication about an Ongoing Safety Review**

FDA is aware of a recently published study, a retrospective medical record review of 73 patients who receive Drotrecogin alfa (activated), marketed as Xigris, indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death (Gentry et al.; Crit Care Med 2009). The study reported an increased risk of serious bleeding events and of death in patients with sepsis and baseline bleeding risk factors who received this product. *February 04, 2009*

## **Ethex Corporation Product Recall**

ETHEX Corporation and Ther-RX Corporation expanded the company's previous recall notices to include prescription prenatal vitamin and iron supplement products. These generic products may have been manufactured under conditions that did not sufficiently comply with current Good Manufacturing Practices. *February 03, 2009*

## **Venom HYPERDRIVE 3.0**

FDA notified consumers not to take Venom HYPERDRIVE 3.0, a product sold as a dietary supplement but containing sibutramine, an undeclared drug product and a controlled substance with risks for abuse or addiction. *January 27, 2009*

## **Clopidogrel bisulfate (marketed as Plavix)**

FDA notified healthcare professionals that the makers of Plavix have agreed to work with FDA to conduct studies to obtain additional information that will allow a better understanding and characterization of the effects of genetic factors and other drugs (especially the proton pump inhibitors (PPIs)) on the effectiveness of clopidogrel. *January 26, 2009*

## Beware of Medication Errors - They Can Happen When You Least Expect it!

Contributed by: C. Nguyen, PharmD candidate, St John's University, A Gupta, MD, Toxicology Fellow, T Caraccio, Pharm.D., Long Island Regional Poison and Drug Information Center

During preparation for sinus surgery, a 43 year old, 70 kg man was intubated, placed on assisted ventilation and sedated with intravenous (IV) propofol. Lidocaine and epinephrine were the next drugs that were supposed to be injected intranasally as local anesthetics. Unfortunately, following the injection, the patient unexpectedly became bradycardic with a heart rate in the 20s. His blood pressure was reported as 110/50 mmHg at the time.

### What is the differential diagnosis?

Bradycardia may be caused by intrinsic cardiac dysfunction, damage to the conduction system, or by the response of normal tissue to extrinsic factors<sup>1</sup>. Patients with bradycardia may develop dizziness, fatigue, weakness, or heart failure. Since this patient had no significant relevant past medical history, the cause of his bradycardia was suspected to be due to an extrinsic factor, such as a medication error.

### What are some common substances that can cause bradycardia?

- Alpha 2 adrenergic agonists such as clonidine and oxymetazoline

- Antidysrhythmic agents (especially type 1a disopyramide, quinidine, procainamide and type 1c: flecainide, encainide, propafenone, lidocaine and phenytoin)
- Cardiac drugs: digoxin, beta adrenergic blockers, non-dihydropyridine calcium channel blockers
- Cholinergic drugs such as physostigmine or neostigmine
- Chloroquine
- Lithium
- Organophosphate insecticides
- Pentamidine
- Plants such as Dogbane, Foxglove, Lily of the valley, Oleander, Siberian ginseng, Squill, Yew berry
- Selective alpha-blockers resulting in reflex bradycardia (ie. phenylpropanolamine)

### What treatment should be initiated at this time?

Management at this time should be the reversal of bradycardia and monitoring of symptoms. Atropine is the first line drug for symptomatic bradycardia. Atropine works by blocking the action of acetylcholine at muscarinic receptors in cardiac smooth muscle to increase heart rate<sup>2</sup>. The adult dose is 0.5 – 1 mg intravenously repeated every 5 minutes up to 3 mg or 0.04 mg/kg<sup>2</sup>.

### What treatment was provided to the patient?

The patient was initially treated with 0.2 mg of IV glycopyrrolate (Robinul®), a drug acting similar to atropine. The FDA supported indications for glycopyrrolate include inhibition of salivation and excessive secretions of the respiratory tract preoperatively, reversal of neuromuscular blockade, control of upper airway secretions, and as an adjunct in the treatment of peptic ulcers. Since no effect was produced by the glycopyrrolate, 0.4 mg of IV atropine was administered. Approximately 5 minutes after this treatment, the patient became hypertensive with a BP of 200/137 mmHg. He was then reparable with IV

## Program Announcements ••

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

**UNY:** The 2009 Toxicology Teaching Day is Scheduled for 11/4/09. Please mark your calendars!!

**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 summer programs

Please call administrative telephone numbers for more information.

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atracurium, a nondepolarizing neuromuscular blocker agent, and further sedated with IV propofol. At this time a pharmacist from the hospital called the Poison Center to seek advice on what additional management would be useful to provide for the patient. A toxicology fellow spoke directly with the anesthesiologist and obtained the following information:

## How did the medication error occur?

Oxymetazoline was poured from the nasal spray bottle into a vial to soak pledgets to be used during the sinus surgery. The error occurred when the oxymetazoline was drawn up into a syringe instead of the lidocaine and epinephrine, and a member of the health care team unintentionally injected 7 ml of oxymetazoline 0.05% intranasally instead of the lidocaine and epinephrine.

## What is oxymetazoline?

Oxymetazoline is a presynaptic alpha-adrenergic agonist of the imidazoline type. Oxymetazoline is available as a nasal spray in a concentration of 0.05% and as ophthalmic solution of 0.025%.<sup>4</sup> The nasal spray is used for the symptomatic relief of nasal congestion while the ophthalmic drops are used for the relief of red eyes due to minor eye irritations. Trade names for oxymetazoline include Afrin<sup>®</sup> Sinus, Mucinex<sup>®</sup> moisture smart<sup>™</sup>, Neo-Synephrine<sup>®</sup> 12 Hour, Visine<sup>®</sup> L.R., Vicks<sup>®</sup> Early Defense<sup>™</sup>, and Duramist<sup>®</sup> Plus.

## What is the mechanism of action?

Oxymetazoline stimulates alpha-2-adrenergic receptors in the arterioles of the nasal mucosa to produce vasoconstriction.

Other agents similar to oxymetazoline are naphazoline, tetrahydrozoline, and xylometazoline. The following table is a comparison of the imidazoline derivatives that are available<sup>4</sup>.

## What is the mechanism of toxicity?

Oxymetazoline's effects are similar to that of the antihypertensive clonidine. It decreases central norepinephrine release by stimulating alpha-2 adrenergic presynaptic receptors in the brain. Hypotension is also augmented by stimulation of imidazoline-specific receptors. Peripherally, imidazoline drugs may agonize alpha-2b-adrenergic receptors, resulting in hypertension. This effect is generally requires high drug concentrations and is generally transient in nature prior to the more typical presentation of hypotension.<sup>5</sup>

## What toxic effects can be produced by the imidazoline derivatives?

The most common *initial* toxic effect reported with oxymetazoline is hypertension. This is usually only a transient effect and is typically followed by hypotension. In children, bradycardia is commonly observed. Decreased respirations, intermittent apnea, and pulmonary edema have also been reported. Some neurological effects that have been reported include headache, nervousness, tremors, and insomnia. Marked drowsiness and mild coma with alternating periods of hyperactivity and thrashing behavior have been reported in children. Nausea and vomiting are possible<sup>3</sup>.

Several case reports on acute and chronic overdoses of the imidazoline decongestants have been published. Mild hypothermia was reported in a patient who ingested an acute overdose of naphazoline<sup>7</sup>. Chronic overdose of the eye drops resulted in acute angle-closure glaucoma in three patients, ultimately resulting in blindness<sup>8</sup>. A man developed acute ischemia of the hand after intra-arterial injection of an unknown amount of 0.05% oxymetazoline which progressed to gangrene

Continued on page 4

Imidazoline derivative	Strength/Dosage form	Adult dose	Onset of action	Duration of action
Oxymetazoline	0.05% nasal spray; 0.025% eye drops	Nasal: 2-3 sprays into each nostril twice daily; Eye: 1-2 drops into affected eye(s) every 6 hours as needed	5-10 min	5-6 hrs
Naphazoline	0.05% nasal spray; 0.012%, 0.025% eye drops	Nasal: 1-2 sprays every 6 hours as needed; Eye: 1-2 drops into affected eye(s) up to 4 times a day	10 min	2-6 hrs
Tetrahydrozoline	0.1%, 0.05% nasal drops; 0.1% nasal spray; 0.05% eye drops	Nasal: 2-4 drops or 3-4 sprays every 3-4 hours as needed; Eye: 1-2 drops into affected eye(s) 2-4 times a day	4-8 hrs	2-3 hrs
Xylometazoline	0.1% nasal spray	2-3 drops or sprays each nostril every 8-10 hours	5-10 min	5-6 hrs



## **Question: What is the incidence of metronidazole-induced peripheral neuropathy and how long does metronidazole induced neuropathy take to resolve?**

**Background:** 30YOF who was prescribed metronidazole 500mg TID by OB/GYN for vaginitis in January. Approximately 4 days after finishing treatment she developed numbness/ tingling in her arms and legs which comes and goes. She has had a computed tomography of head and spine with no significant findings.

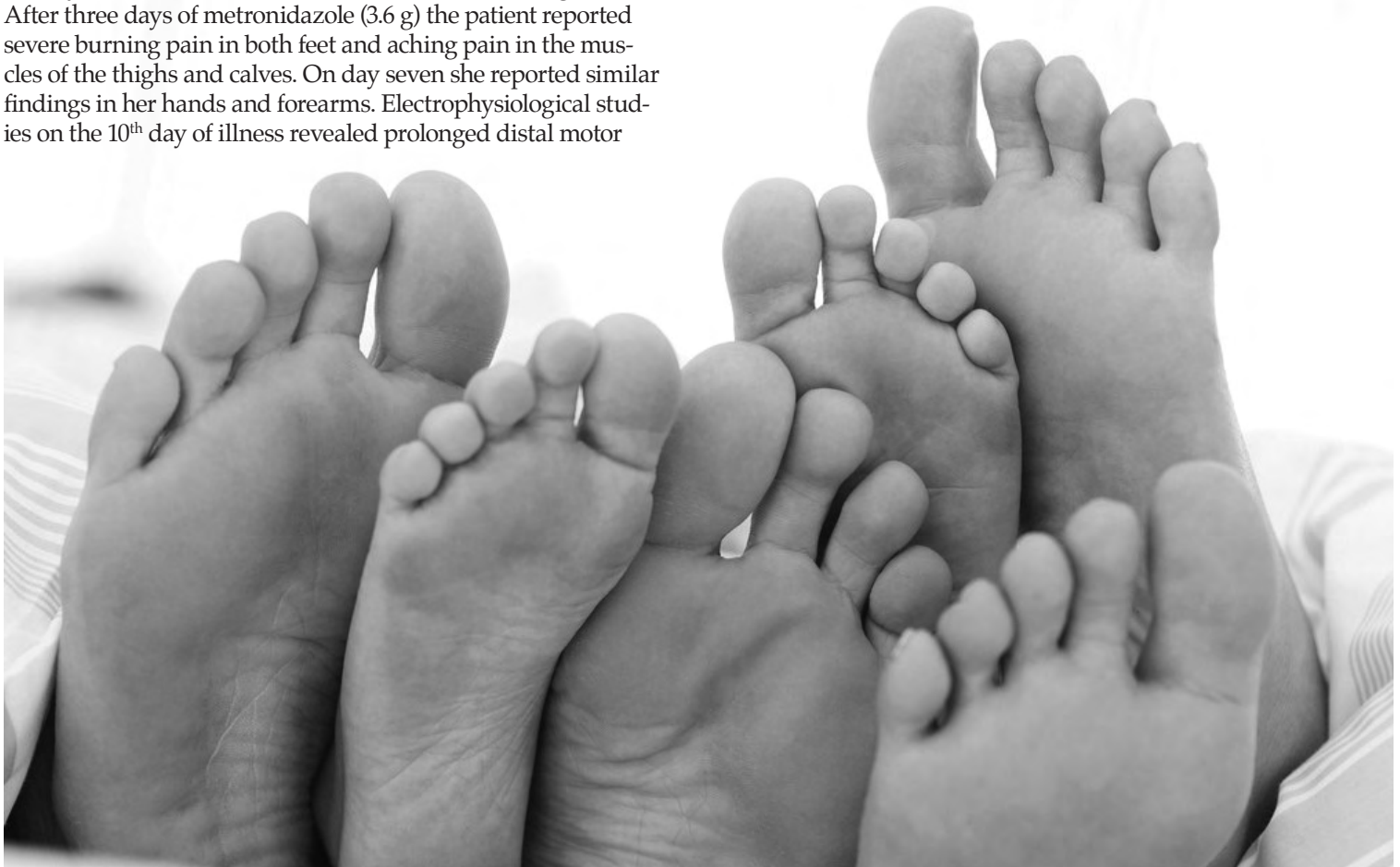
**Answer:** Peripheral neuropathy has been reported as a rare side effect of metronidazole therapy. This usually presents as a predominantly distal sensory polyneuropathy, with patients often complaining of tingling, prickling, burning, in the balls of the feet or tips of the toes. Symptoms and findings are usually symmetric and graded distally and often precede objective motor or sensory signs. Electrophysiologic examination of nerve and muscle, including nerve conduction studies and electromyography are used to diagnose neuropathies. The proposed mechanism for this reaction is not well defined, although animal models suggest inhibition of RNA synthesis may be the cause of observed axonal degeneration.<sup>(1)</sup>

Metronidazole induced peripheral neuropathy has traditionally been associated with high doses of drug given over several months.<sup>(1)</sup> A more recent case report however, describes toxicity in a 45 YOF treated with metronidazole for vaginitis.<sup>(2)</sup> After three days of metronidazole (3.6 g) the patient reported severe burning pain in both feet and aching pain in the muscles of the thighs and calves. On day seven she reported similar findings in her hands and forearms. Electrophysiological studies on the 10<sup>th</sup> day of illness revealed prolonged distal motor

latency of posterior tibial nerve, prolonged distal motor latency and mildly reduced compound muscle action potential amplitude of the peroneal nerve and decreased sensory nerve action potential amplitude of the posterior tibial nerve. The patient was treated with carbamazepine and gabapentin for symptom relief. A repeat nerve conduction study at three months did not show any improvement and the patient remained symptomatic at 24 months. Although a temporal relationship is suggested, cause and effect cannot be clearly established with a case report.

Boyce et al. reviewed the literature of metronidazole-induced peripheral neuropathy (n=33).<sup>(3)</sup> Of those cases, 12 patients continued therapy on the same or lower doses of metronidazole with worsening neuropathy in one, no change in five, and partially improved symptoms in six. Metronidazole was stopped in 21 patients with complete recovery in 11, partial recovery in 7, and no improvement in three. Significant patient variability with regards to susceptibility and resolution of symptoms may be related to genetic variables.

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2. Neurol India. 2005; 53(3):372-3.
3. DCIP, The Annals of Pharmacotherapy. 1990;24(19):19-21.



requiring amputation<sup>9</sup>. Hallucinations have also been reported with therapeutic doses and chronic overuse<sup>10,11</sup>.

Overdose or intoxication from ingestion or excessive topical administration of an imidazoline derivative can also produce miosis, diaphoresis, respiratory depression, pulmonary edema, and coma. Recovery usually is expected in 12 to 36 hours<sup>3</sup>.

Death has not been reported after ingestion, but has been reported after intravenous injection of xylometazoline<sup>3</sup>. Fatal post-mortem concentrations have ranged from 0.14 mcg/mL in the blood to 0.37 mcg/mL in the liver. Death is usually secondary to CNS depression<sup>6</sup>.

## What general management is recommended?

Even when ingested orally, due to rapid absorption from the stomach and quick onset of action, gastrointestinal decontamination is not recommended for  $\alpha$ -2 agonists. Treatment is symptom dependent. As mentioned previously, atropine is indicated for bradycardia. Generally hypertension is transient and does not warrant treatment. In rare instances where hypertension is severe, short acting agents should be used until drug effect wears off. For hypotension, a bolus (20cc/kg) of isotonic fluid should be infused. If hypotension persists, an alpha adrenergic agonist should be used such as intravenous phenylephrine or norepinephrine.

## What parameters should be monitored?

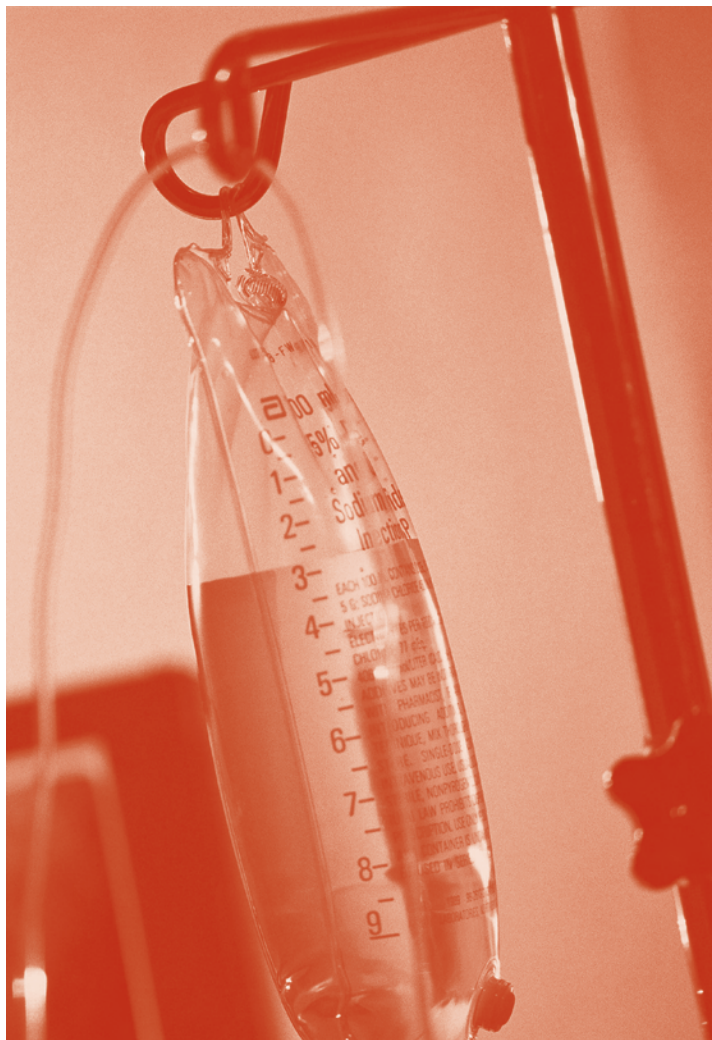
Neither therapeutic nor toxic blood concentrations should be measured because they are not clinically useful. No specific lab tests (CBC, electrolyte, and urinalysis) are needed unless otherwise clinically indicated. Monitor vital signs and mental status. Obtain an ECG in symptomatic patients<sup>3</sup>.

## What was the outcome of this patient?

An hour following the injection of the oxymetazoline, the patient's blood pressure had improved to 117/45 mmHg and his heart rate was in the 70s. No further atropine was required. An hour later the patient's blood pressure rose to 140/69 mmHg. Two doses of enalapril 1.25 mg were given by IV push and he was maintained on D5 NS at a rate of 75 mL/hr. The next morning his blood pressure was reported as 115/73 mmHg with a heart rate of 60 beats/minute. He was rescheduled for his original surgery the following day.

## Comments and suggestions

This case is a prime example of a medication error that could have been prevented. Medication errors are a problem in medicine, which may increase in the future as more medications and dosage forms become available. Hopefully this discussion may serve as a reminder to all health care professionals to be more vigilant with medications in order to help avoid potential errors. All medication errors should be reported to the hospital pharmacy. The Poison Center can serve as an excellent resource for health care professionals to use for advice on these issues.



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# Questions from Monthly Lecture Series at the LIRPDIC

## Tox Questions: General

1. What is the pathognomonic arterial blood gas for a patient with salicylate toxicity?
  - a. Metabolic Acidosis
  - b. Metabolic Acidosis with respiratory compensation
  - c. Mixed primary metabolic acidosis and primary respiratory alkalosis
  - d. Mixed primary metabolic acidosis and primary respiratory acidosis
  - e. Respiratory Alkalosis
2. What is a common pulse oximetry reading in patients with methemoglobinemia?
  - a. 0%
  - b. 50%
  - c. 85%
  - d. 95%
  - e. 100%
3. Which of the following is an indication for hyperbaric oxygen in CO poisoning?
  - a. Any exposure in a pregnant patient
  - b. Headache
  - c. Level above 10%
  - d. Flu-like symptoms
  - e. Loss of consciousness
4. Which of the following drugs should be avoided in a hypertensive emergency caused by monoamine oxidase inhibitors?
  - a. Phentolamine
  - b. Nitroglycerin
  - c. Magnesium
  - d. Beta blockers
  - e. Calcium channel blockers
5. For which ingestion may octreotide be considered an antidote?
  - A. Glyburide
  - B. Metformin
  - C. Pioglitazone
  - D. Insulin
  - E. Sitagliptin
6. Which of the following is true regarding insulin overdose?
  - A. Patients with normal pancreatic function do not get hypoglycemic.
  - B. Patients generally do not need longer than a 6 hour observation time.
  - C. Absorption from SC injection sites is predictable.
  - D. C-peptide levels would be expected to be normal and may help differentiate between insulin and sulfonylurea overdose.
  - E. Octreotide should be administered prophylactically.
7. Which of the following sulfonylureas can lead to SIADH and also be treated with urinary alkalinization?
  - A. Glyburide
  - B. Glimepiride
  - C. Glipizide
  - D. Chlorpropamide
  - E. Nateglinide
8. Which animal was the glucagon-like peptide-1-receptor (GLP-1R) agonists isolated from originally?
  - A. Rattlesnake
  - B. Mongoose
  - C. Black widow spider
  - D. Gila monster
  - E. Wasp
9. Which of the following factors is the MOST important in the development of metformin associated lactic acidosis?
  - A. Presence of heart failure
  - B. Medication interaction
  - C. Dosage
  - D. Renal function
  - E. Age

## Tox Questions: Antidiabetic Agents

5. For which ingestion may octreotide be considered an antidote?
  - A. Glyburide
  - B. Metformin
  - C. Pioglitazone
  - D. Insulin
  - E. Sitagliptin

## Black Box Warning Questions

10. Any drug with a black box warning means the drug cannot be used in pregnancy
  - a) True
  - b) False

Continued on page 6

11. Only a few dozen drugs carry black box warnings  
a) True b) False
12. Methadone carries a black box warning related to potential for cardiac dysrhythmias.  
a) True b) False
13. NSAIDs may cause an increased risk of cardiovascular events.  
a) True b) False
14. Black box warnings laboratory monitoring recommendations are adhered to by most physicians  
a) True b) False
15. Organophosphate nerve agents such as SARIN cause symptoms based upon their deleterious effects on which transmitter system?  
A. Adrenergic  
B. GABA neuro-inhibitory  
C. Noradrenergic  
D. Cholinergic
16. The treatment of choice for a moderate to severe SARIN exposure is  
A. Epinephrine autoinjector, followed by high flow oxygen  
B. Atropine autoinjector, followed by high flow oxygen  
C. Atropine autoinjector, followed by pralidoxime autoinjector  
D. Benzodiazepine autoinjector
17. The treatment of choice for a moderate to severe acute cyanide poisoning is  
A. Sodium nitroprusside  
B. Amyl nitrite  
C. Hydroxycobalamin  
D. Hyperbaric oxygen

**Chemical Weapons and Hazardous Materials**

15. Chlorine gas is considered a medium water soluble inhalation hazard. Which of the following is likely after either a brief but significant or prolonged exposure?  
A. Minimal eye and airway irritation – the water content in the mucous membranes neutralize the toxicant  
B. Potential respiratory failure secondary to acute non cardiogenic pulmonary edema  
C. Minimal coughing and hiccapping – the water solubility draws the toxicant to the trachea before inactivating the toxicant  
D. Nausea and vomiting

Answers: 1. C, 2. C, 3. E, 4. D, 5. A, 6. D, 7. D, 8. D, 9. D, 10. B, 11. B, 12. A, 13. A, 14. B, 15. B, 16. D, 17. C, 18. C



# Clinical Pearls: Antidiabetic Medications

By: Jeanna Marraffa, Pharm.D. DABAT, Upstate NY Poison Center, Syracuse NY

This is intended to serve as an overview for antidiabetic medications with focus on the mechanism, some common culprits and treatment options available.

## Illustrative Case

5 year old male is found with his grandmother's pill container. The grandmother has a medical history significant for diabetes and hypertension. The medications that the child was exposed to were Avandia and Zestril.

The exposure occurred approximately 5 hours prior to the call to the Poison Center. The child was asymptomatic.

**What are some considerations in this case? What would be some possible recommendations?**

Antidiabetic medications that may be involved and need to be considered include sulfonylureas, insulin, biguanides, thiazolidinediones, short acting insulin secretagogues and alpha-glucosidase inhibitors.

Metformin, TZDs and alpha glucosidase inhibitors do not cause hypoglycemia when used alone. The other agents described will produce a nearly identical clinical condition of hypoglycemia.

**Sulfonylureas** include agents such as glyburide, glipizide, glimepiride and chlorpropamide. The pharmacology of sulfonylureas is to stimulate pancreatic secretion of insulin (insulin secretagogues). Because of their mechanism of action, sulfonylureas cause hypoglycemia. Delayed hypoglycemia has occurred and been reported in the literature and due to this, patients exposed to sulfonylureas should be observed for 24 hours with fingerstick monitoring. Treatment of sulfonylurea induced hypoglycemia includes replacement of glucose and octreotide. The replacement of glucose with dextrose may actually stimulate insulin release and will only have a temporary beneficial effect and may, indeed, exacerbate the hypoglycemia. Octreotide is a synthetic analogue of the endogenous hormone somatostatin. Octreotide inhibits insulin release. The dose of octreotide is 50 micrograms SQ and can be repeated every 6 hours.

**Short acting insulin secretagogues** include the agents nateglinide (Starlix) and repaglinide (Prandin). Their mechanism of action is identical to sulfonylureas. Hypoglycemia is anticipated after exposure to these agents. At this point, there is limited experience in regards to overdose and toxicity, and though these agents have different pharmacokinetic profiles when compared to sulfonylureas, the onset and duration of hypoglycemia remains unknown. Until further literature is available, we are treating these agents as sulfonylureas.

**Exogenous Insulin** mimics the physiologic effects of insulin. The insulins are categorized according to their strength and onset and duration of action. There are rapid acting insulins (such as Humalog), short acting insulins (such as humulin), intermediate acting insulins (such as NPH) and long acting insulins (such as Lantus). The onset of action as well as the duration of action of the hypoglycemia is dependent on the type of insulin. For intermediate and long acting insulin, hypoglycemia can be prolonged for up to 24 hours after expo-



sure. For short acting insulin, hypoglycemia will occur within a relatively short time frame (within 30 minutes to 1 hour) and will last for only up to 6 hours. It is imperative to look up the particular type of insulin and its pharmacokinetic parameters. Treatment of exogenous insulin exposure is fingerstick monitoring, glucose either intravenously or orally for hypoglycemia. Octreotide is ineffective for hypoglycemia induced by exogenous insulin administration.

**Metformin** is the only available biguanide in the US. The classic biguanide is phenformin, however, that was pulled from the US market by the FDA due to fatal cases of lactic acidosis. The mechanism of action for metformin is reducing hepatic glucose production and increases glucose utilization in the periphery. Alone, metformin does not cause hypoglycemia. Metformin, though less than phenformin, can cause lactic acidosis and this should be considered particularly in acute overdoses and the setting of anion gap metabolic acidosis.

**Thiazolidinediones (TZDs)** include rosiglitazone (Avandia) and pioglitazone (Actos) and troglitazone (Rezulin). Troglitazone was pulled from the US market by the FDA due to fatal cases of hepatotoxicity. The only two available products are Avandia and Actos. The mechanism of action for the TZDs is activation of the PPAR receptor which subsequently reduce insulin resistance in the periphery (sensitize muscle and fat to the actions of insulin) and possibly in the liver. TZDs alone, do not cause hypoglycemia. A consideration in acute overdose and a definite must in patients on chronic therapy is assessment of liver function tests.

**Alpha glucosidase inhibitors** include Acarbose (Precose) and Miglitol (Glyset). They prevent the breakdown of sucrose and complex carbohydrates in the small intestine prolonging the absorption of carbohydrates resulting in a reduction in postprandial glucose rise. These agents have limited systemic absorption. These agents do not cause hypoglycemia. Toxicity literature is minimal though GI effects are the most likely.

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# TOXICOLOGY

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LETTER

Follow-up from the New York City Poison Control Center  
Consultants' Conference of July 2, 2009

## Hydroxocobalamin for Cyanide Poisoning

Contributed by: Daniel M. Lugassy, MD, Lewis S. Nelson, MD, NYCPCC, New York

### Case Summary:

A 50 year-old man, in cardiac arrest after being pulled out of a building fire, has return of circulation en route to the ED, though he never regains consciousness. During his prehospital resuscitation he receives intravenously at total of 3 mg of epinephrine, 40 units of vasopressin and 1 mg of atropine prior to arrival in the ED. His initial vital signs upon arrival are BP, 110/80 mmHg; HR, 105 beats/min; Temp, 98.0° F; RR, 12/min, intubated on mechanical ventilation; O<sub>2</sub> saturation, 100% on 100% O<sub>2</sub>. Initial laboratory analysis is remarkable for: carboxyhemoglobin, 46%; blood lactate, 11.5 mmol/L; and ABG: pH, 6.9; pCO<sub>2</sub>, 65; pO<sub>2</sub>, 317, O<sub>2</sub> saturation 88%. His physical exam does not reveal significant cutaneous burns, but there is a large amount of carbonaceous material around his mouth and nares. He is treated empirically for cyanide poisoning with 5g of hydroxocobalamin (HCO), with no clinical improvement. About 30 min after its administration his blood pressure is noted to be 220/180 mmHg. Approximately two hours later his blood pressure remains elevated at 185/79 mmHg, for which he receives nicardipine by

intravenous infusion. He subsequently receives hyperbaric oxygen therapy, but on hospital day 7 his care is withdrawn following documentation of brain death. Blood is sent for analysis of the cyanide concentration.

### What is HCO, and what is its use?

The ability of cobalt ion to chelate cyanide has been known for more than one hundred years. HCO, a cobalt containing compound that is a precursor to cyanocobalamin (which is vitamin B12), that contains an OH group in place of a CN group at the cobalt binding site of the molecule. HCO binds cyanide, displacing the OH, to form this vitamin, which is then rapidly eliminated in the urine. Hydroxocobalamin was approved in 2006 by the FDA in the US for the treatment of cyanide poisoning. It is currently marketed as Cyanokit<sup>®</sup>, and is packaged as a lyophilized powder which requires reconstitution with normal saline.

### What are the expected clinical features of cyanide toxicity?

Patients may be exposed to cyanide by several different routes: inhalation, ingestion, dermal, and parenteral. Cyanide inhibits multiple enzymes most importantly mitochondrial cytochrome oxidase (a-a<sub>3</sub> position), causing an arrest of oxidative phosphorylation. This disrupts the ability of electrons to bind to their final acceptor, oxygen, at the terminal end of the electron transport chain. Despite adequate oxygenation of the blood, oxygen cannot be utilized by the tissue, and ATP cannot be produced. As a consequence, cellular hypoxia occurs. A shift toward anaerobic metabolism leads to a metabolic acidosis with an increase lactic acid concentration (>10 mmol/L).<sup>1</sup>

## Program Announcements ••

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

**UNY:** The 2009 Toxicology Teaching Day is Scheduled for 11/4/09. Please mark your calendars!!

**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 summer programs

Please call administrative telephone numbers for more information.

Continued on page 2

Acute cyanide poisoning manifests with rapid onset neurological findings such as headache, anxiety, agitation, confusion, lethargy, seizures, coma, and early tachypnea followed by bradypnea. Cardiovascular effects of cyanide poisoning may initially produce hypertension and bradycardia, followed by hypotension with a reflex tachycardia, although hypotension and bradycardia are the pre-terminal event. The rate of onset is related to the route of exposure, with inhalation of gaseous hydrogen cyanide resulting in nearly immediate collapse, while ingestion of a cyanide salt such as sodium cyanide may not result in clinical effects for 20 minutes.

### Why was this patient treated empirically for cyanide poisoning with HCO?

Fire victims may be exposed to hydrogen cyanide which is liberated from the burning of materials such as wool, plastics, nylon, and polyurethane found in automobiles, carpets, home furniture and appliances. Cyanide poisoning can be difficult to diagnose clinically in fire victims due to the multifactorial nature of smoke exposure and the presence of concomitant traumatic injury and medical conditions (e.g., intoxication). A lactate greater than 10 mmol/L upon arrival in the ED in fire victims without significant burns is a sensitive marker for elevated blood cyanide concentration (and by analogy, cyanide poisoning). But these patients often concurrently suffer from carbon monoxide poisoning, asphyxia, trauma, and thermal injury all of which produce findings that may be indistinguishable from cyanide poisoning.

The patient received HCO in the ED due to his dramatic clinical and laboratory findings (e.g., arrival lactic acid >10 mmol/L). Hydroxocobalamin is a superior choice compared with the traditional cyanide antidote kit (CAK) in this case due to the presence of a significant COHb concentrations. The CAK consists of amyl nitrite, sodium nitrite, and sodium thiosulfate. The nitrites oxidize a small percent of normal hemoglobin to methemoglobin (Hb<sup>3+</sup>), which has a higher affinity for cyanide than the mitochondrial cytochromes. Sodium thiosulfate provides a sulfur moiety for rhodanese, the enzyme that fosters the reaction of sulfur compounds with cyanide to form thiocyanate, a relatively non-toxic and renally eliminated metabolite. In fire victims who may have elevated carboxyhemoglobin, the induction of methemoglobinemia is potentially devastating, as both aberrant forms of hemoglobin inadequately deliver oxygen to the tissues.

Administration of the thiosulfate portion of the CAK may prove beneficial and is often recommended,

although this has not been formally evaluated in clinical trials. Animal data suggests a synergistic effect of sodium thiosulfate and HCO, but the two individual therapies have never been studied head to head.

### Why did this patient develop severe and persistent hypertension?

There are several plausible explanations. Several of the medications administered during the pre-hospital arrest both cause hypertension. However, vasopressin and epinephrine have plasma half lives of 10-20 and 2-5 minutes respectively, and it is unlikely that their effect would last two hours. Atropine should not have a profound effect on blood pressure.

Hypertension is a recognized effect of HCO. This results from the ability of HCO to bind nitric oxide (NO) to form nitrocobalamin. Nitric oxide relaxes vascular smooth muscle tone, causing vasodilation. By scavenging NO, HCO causes vasoconstriction and hypertension.<sup>3</sup>

In healthy volunteers HCO causes a significant elevation in blood pressure. In one such study, intravenous doses of 2.5, 5, 7.5, and 10 g of HCO were randomly administered to 102 subjects alongside a placebo control group of 34 subjects.<sup>2</sup> (Table 1).

In addition to the significant mean increases seen in Table 1, a maximum change in systolic blood pressure of 57 mmHg, and diastolic blood pressure of 52 mmHg was observed. Very little information on the actual duration of these changes was reported.

The authors indicated that the blood pressure “typically” returned to baseline by 4 hours post infusion, but persistent BP elevation in one patient to 166/112 mmHg was noted at 72 hours. Despite these findings the authors concluded that the changes in blood pressure were clinically insignificant. Without further study it is not clear how to apply this data gathered from this small number of patients to the general (e.g., less healthy) population and it may be dangerous to assume that these changes are benign. While an elevation in blood pressure in hypotensive fire victims with cyanide poisoning is desired, the value of HCO in producing this effect or its effect on outcome is not known.

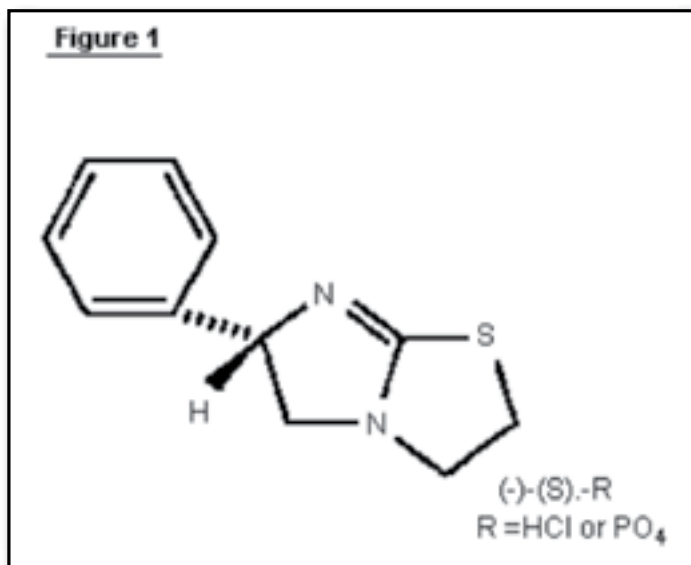
The difficulty in diagnosing cyanide poisoning in a clinically useful timeframe suggests that most patients will be treated empirically. The volunteer studies suggest the potential for severe adverse events in fire victims who are not cyanide poisoned.

*In this case, a serum sample obtained prior to HCO administration revealed no detectable concentration of cyanide.*

# Levamisole as an Adulterant of Cocaine: Its Possible Purpose and Adverse Reactions

Contributed by: Alla Fox, R.Ph., Pharm.D. Candidate, St. John's University, Mary Ann Howland, PharmD., DABAT, FAACT, Clinical Professor of Pharmacy, St. John's University College of Pharmacy and Consultant, New York City Poison Control Center, New York, NY

Levamisole is the levo-isomer of a broad spectrum, highly active anthelmintic agent tetramisole which was introduced in 1966<sup>1,2</sup>. It was widely used in veterinary medicine for the treatment of various pulmonary and gastrointestinal pathogenic nematodes<sup>1-3</sup>.



(Ref. 2)

In 1971 Renoux and colleagues discovered that levamisole possesses immunomodulatory properties in mice via potentiation of T-cell mediated immunity<sup>4</sup>. Further research demonstrated that this compound stimulates T-cell activity and enhances the function of B-lymphocytes and macrophages<sup>4</sup>.

Levamisole has since been extensively studied and utilized for a variety of immunological conditions such as SLE, rheumatoid arthritis, ulcerative colitis, Crohn's disease, and some cancers with minimal success<sup>3,5</sup>. However, it is found to be useful as an adjunct in combination with fluorouracil for the treatment of advanced colon cancer after surgical resection, and was approved for this indication in the United States in 1990<sup>2</sup>. In 2000, the manufacturer of levamisole voluntarily withdrew the drug from the U.S. market due to unfavorable side effect profile. Levamisole is still available outside of the U.S. for veterinary applications<sup>5</sup>.

Recently levamisole has reappeared in North America as an unusual adulterant of cocaine. Illicit drugs such as cocaine are often diluted with various non-pharmacologically and pharmacologically active substances:

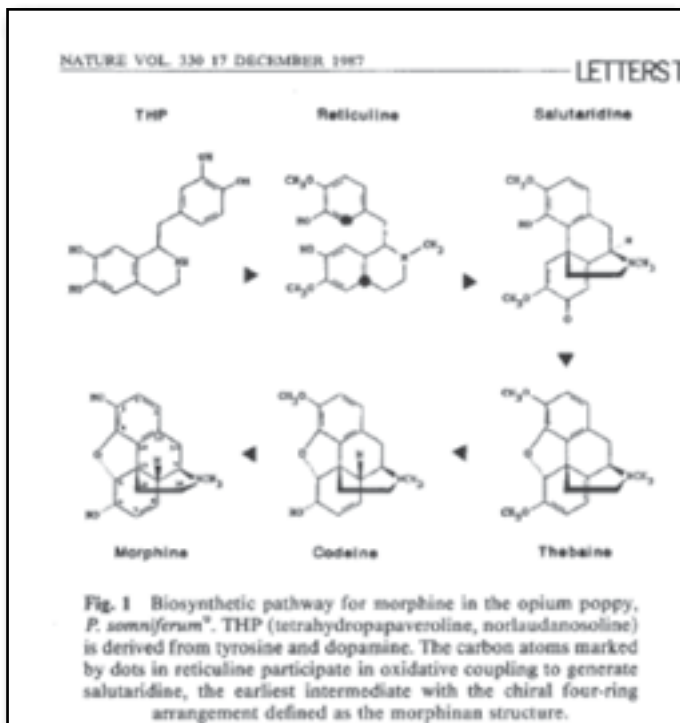
talco, lactose, lidocaine, diltiazem, etc.<sup>7</sup>. These serve simply as bulking agents or may be added because producers believe these substances will enhance the effects of or minimize the side effects of cocaine<sup>6</sup>. It is not clear, however, why a relatively expensive compound like levamisole would be chosen as an adulterant for cocaine.

One hypothesis is that levamisole is used to modulate neurotransmitter effect as an adjuvant to cocaine. This is supported by a study conducted by Spector and colleagues on the ability of levamisole to affect endogenous opiates<sup>8</sup>. This work was based on the extensive body of research conducted earlier by this group of investigators, as well as others, which identified morphine and codeine-like compounds in various tissues of several animal species, such as lower animals and mammals, including primates after levamisole use<sup>8-13</sup>. In addition, there is at least one report of these compounds in human tissues, specifically CSF<sup>12</sup>. The role of these endogenous opiate alkaloids is not completely understood. But the above mentioned studies offer some theories.

For example, Oka et al<sup>9</sup> isolated morphine-like compound (MLC) in the toad skin. They hypothesized that this compound is of endogenous origin, and not from a dietary source, as was proposed by other researchers, since skin was the only organ with detectable MLC concentration. They also theorized that morphine may serve in the regulation of the body temperature of this type of animal because it causes cutaneous vasodilatation<sup>9</sup>. Neri et al concluded that these endogenous opiate alkaloids may function as neuromodulators/ neurotransmitters in CNS of non human primates<sup>13</sup>.

In addition, detection of morphine precursors such as reticuline, salutaridine, thebaine, and codeine lead Spector et al, as well as other researchers, to believe that animal tissues are able to synthesize morphine from antecedent compounds<sup>9,13</sup>. Weitz et al demonstrated the conversion in vivo and vitro of reticuline to salutaridine, a critical step that creates the morphine skeleton structure by rat liver. They hypothesized that this conversion is catalyzed by a specific enzyme, strengthening the argument for the endogenous origin of these MLCs<sup>10</sup>.

Continued on page 4



(Ref. 10)

Spector et al<sup>8</sup> evaluated the ability of immunomodulators, specifically levamisole, to attenuate the severity of a naloxone induced withdrawal syndrome in opioid-addicted rats, via its action on endogenous opiate-like compounds and monoamine neurotransmitters in the brain and peripheral tissues. As part of their investigation, and for the purpose of a control cohort, they also evaluated the effects of levamisole on endogenous morphine-like compounds and monoamine neurotransmitters in opiate-naïve rats<sup>8</sup>.

Following levamisole administration to opiate-naïve rats they performed measurements of the levels of these substances in the brain and peripheral tissues at different time points (0, 15, 30, 60, and 120 minutes). The investigators observed elevated concentrations of endogenous opiate alkaloids and monoamine neurotransmitters in various parts of the body. Endogenous opiate alkaloids were significantly elevated in the lungs, spleen, and colon ( $p < 0.005$ ). Morphine levels were significantly increased ( $p < 0.005$ ) by levamisole in the hypothalamus, hippocampus, brain stem, and cerebellum. Codeine concentrations were significantly increased ( $p < 0.005$ ) in all regions of the brain, except midbrain<sup>8</sup>. The drug did not produce significant changes in the opiate alkaloids concentrations in the cortex and midbrain.

Levamisole administration also produced composite changes in NEPI, DA, and 5HT metabolism. Although levamisole did not alter NEPI levels in most brain regions, it strikingly increased levels of a minor nor-

epinephrine metabolite- normetanephrine (NME) in all brain regions ( $p < 0.001$ ). The researches also observed a modest increase in the concentration of free 3-methoxy-4-hydroxyphenyl glycol (MHPG) – a principle NEPI metabolite in the CNS<sup>8</sup>. A time dependent and regionally distributed increase in DA was also observed in the midbrain, hippocampus, hypothalamus ( $p < 0.05$ ), and cerebellum ( $p < 0.01$ ). DA metabolites 3, 4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were increased in some brain regions as well. Serotonin levels were also augmented by levamisole in a time dependent fashion.

Although changes in concentrations of biogenic amines (NEPI, DA, and 5HT) were observed, Spector et al pointed out that it was not possible to distinguish whether these effects resulted from the direct action of levamisole on metabolism of these neurotransmitters or via its action on endogenous opiate alkaloids<sup>8</sup>.

In summary, this work demonstrates that levamisole increases the levels of endogenous opiate-like compounds in the brain and peripheral tissues, as well as increases the concentration of biogenic amines in the CNS. Whether these direct or indirect effects on the neurotransmitters, specifically DA, are the rationale for the addition of this agent to cocaine is not known<sup>6</sup>.

Cocaine is a central nervous system stimulant, which produces feelings of euphoria, excitement, increased motor activity and a feeling of being energized<sup>14</sup>. Its euphoric properties are primarily due to inhibition of the transporter protein responsible for the reuptake of dopamine into presynaptic terminals of neurons.<sup>14, 15</sup> As a result, increased concentrations of this critical neurotransmitter are found in the synaptic space, and its effects are potentiated<sup>14, 15</sup>. A variety of evidence suggests that dopamine plays a major role in the rewarding effects of drugs of abuse, including cocaine<sup>8, 14, 15</sup>. In addition to dopamine, cocaine blocks reuptake of norepinephrine and serotonin, increasing their presynaptic concentrations as well<sup>15</sup>.

Because levamisole can also increase the levels of DA, 5HT, and to a lesser extent of NEPI, it is plausible to hypothesize that addition of this agent to cocaine can increase its pharmacological effects<sup>6, 8</sup>.

Whatever the rationale for the adulteration of cocaine with levamisole, the prevalence of this agent found during drug seizures across North America and Europe is on the rise<sup>6, 16, 17</sup>. About 30% of the cocaine seized by DEA from July to September, 2008 was tainted with levamisole compared to 11% in Alberta, Canada, from January- October, 2008<sup>6, 18</sup>.

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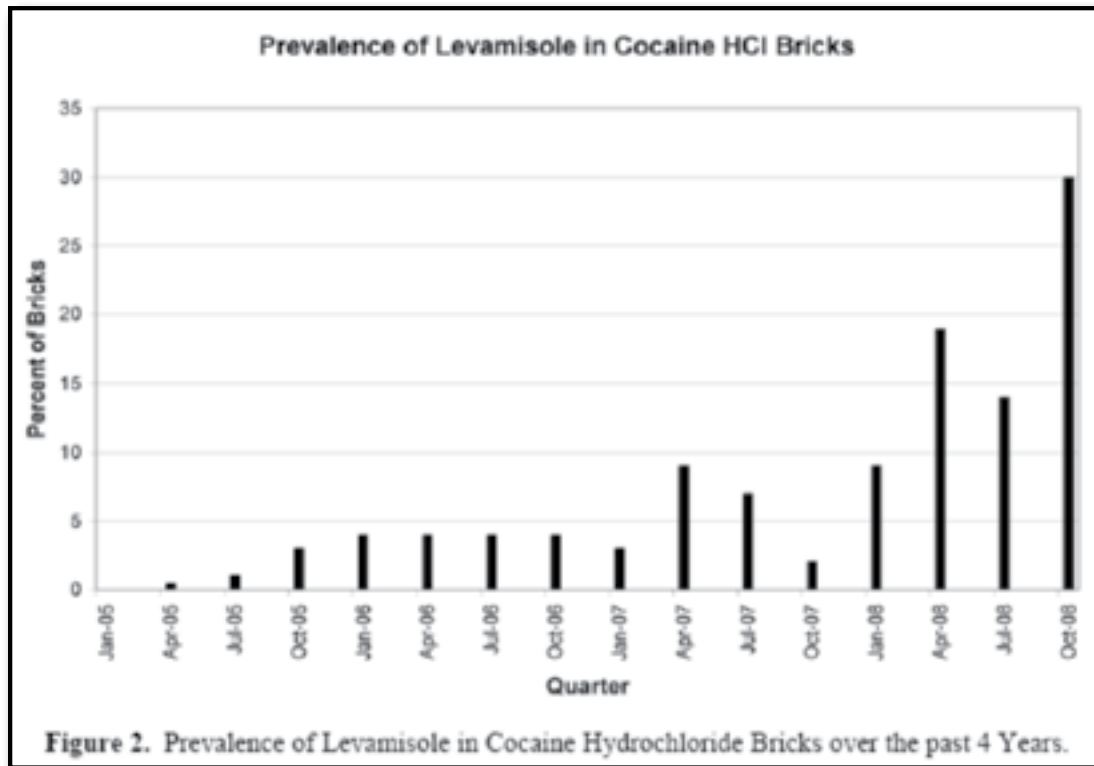


Figure 2. Prevalence of Levamisole in Cocaine Hydrochloride Bricks over the past 4 Years.

The U.S. Drug Enforcement Agency reports that some cocaine originating from Colombian laboratories has been cut with pharmaceutical grade (pure) levamisole since 2003<sup>18</sup>. However, in January of 2008 DEA received a sample of “crack” cocaine for analysis that contained unknown impurities in addition to levamisole. Analysis revealed a presence of two degradation products of levamisole: 6-phenyl-2,3-dihydroimidazo[2,1b]thiazole (about 50% relative to levamisole content) and a trace amount of

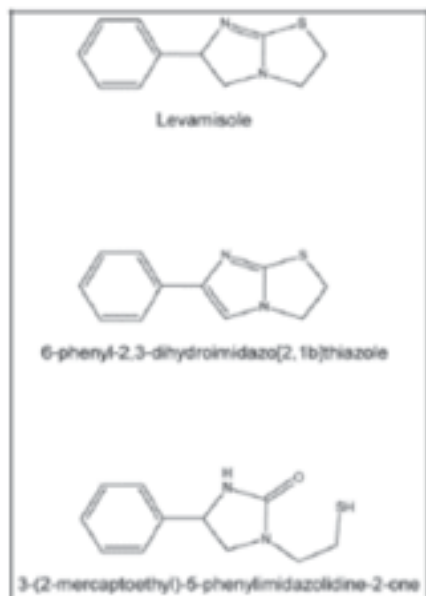


Figure 1.

(Ref 18)

tainted product<sup>6, 16-18</sup>. This drug has an extensive list of side effects such as: nausea, vomiting, diarrhea, anorexia, stomach pains, mouth sores, muscle aches, fatigue, dizziness, headache, skin rashes<sup>3</sup>. The most disturbing side effects are those affecting the immune system: agranulocytosis, leucopenia, and thrombocytopenia, leading to life-threatening infections<sup>3</sup>. Zhu et al<sup>6</sup> described 5 cases in Alberta, Canada, of cocaine abusers who were hospitalized for agranulocytosis, fever, and variety of infections complications. A newsletter of the Alberta Health Services of Canada, reports 39 cases (11 confirmed and 28 probable) of levamisole-

(Ref. 18)

associated neutropenia in cocaine users as of March 31st 2009<sup>19</sup>.

Levamisole exposure in cocaine abusers presenting with unexplained immunosuppressive symptoms is not likely to be confirmed via routine toxicology screening due to its short elimination half-life (0.5-2 hours in the plasma, and about 5.6 hours in the urine)<sup>6,17</sup>. However, Zhu et al and Morley et al report some success with gas chromatography/mass spectrometry (GC/MS) assay and lupus anticoagulant testing<sup>6,17</sup>.

In conclusion, the prevalence of levamisole in the cocaine supply is on the rise. The reason for its addition remains unknown. However, adulteration may be driven by producers’ beliefs that levamisole increases the pharmacological effects of cocaine via its dopamine elevating properties. Clinicians should be on the alert for unusual symptoms in cocaine abusers that may not be attributed to the drug itself or other health conditions. These patient cases should be reported to their regional Poison Control Centers. In addition, confirmatory testing for levamisole is complicated and may not be readily available, making a definitive diagnosis difficult. To complicate the issue further, impurities in the levamisole added to the cocaine may become more prevalent, and their physiological effects are unknown.

Continued on page 6

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## Are there other adverse effects from HCO therapy?

Other commonly recognized adverse effects include chromaturia, skin redness, pustular/papular rash, headache, injection site reaction, lymphocyte count decrease, nausea, chest discomfort, dysphagia, and relative bradycardia. Almost all patients who receive this therapy display this predictable red discoloration of their skin and urine color, which is not surprising given the deep red color of HCO itself. Impressive color images illustrating this effect may be found in the literature.<sup>5</sup> The “color” effects of HCO administration are more than just cosmetic, as several colorimetric laboratory tests may be rendered useless. The most clinically significant interference occurs with cooximetry, in which carboxyhemoglobin measurement, critical information in fire victims, will be inaccurate.<sup>4</sup> Creatinine, bilirubin, triglycerides, cholesterol, total protein, and glucose may be falsely increased, and others such as phosphate, AST, and CK are unpredictably altered. The need to obtain blood for analytical testing before the administration of HCO is essential.

## What protocols currently exist for the use of HCO in NYC?

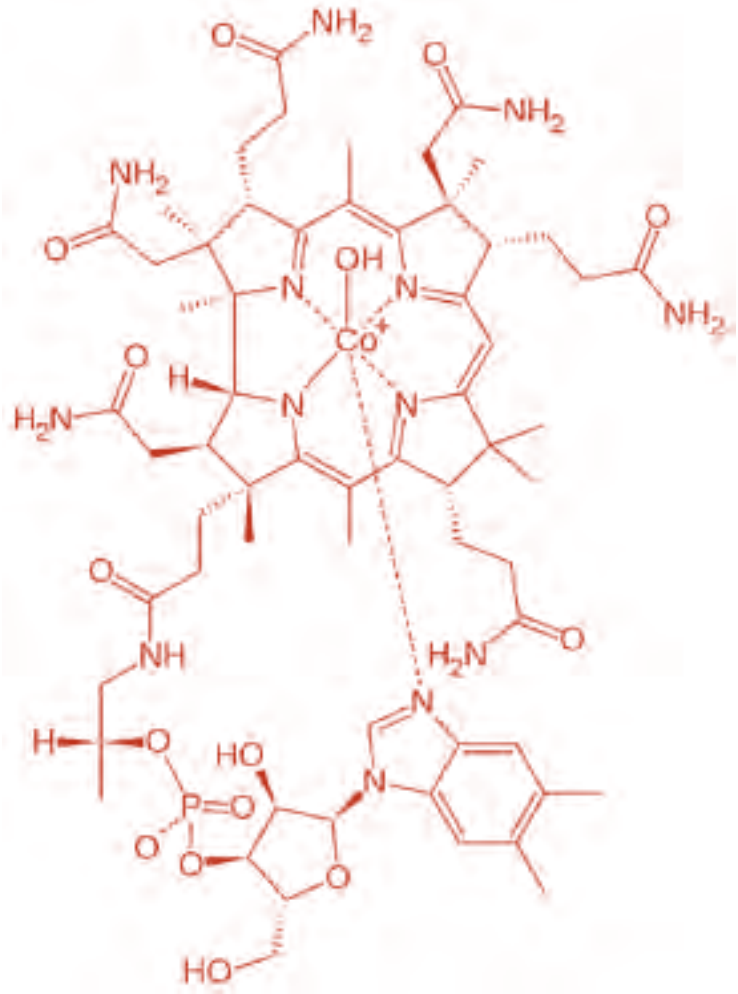
Hydroxocobalamin has gained general acceptance as treatment for presumed cyanide poisoning in fire victims in the pre-hospital setting. FDNY-EMS recently (July 2009) adopted a protocol for this use of HCO. Indication to initiate treatment for suspected cyanide toxicity include patients who after exposure to smoke in an enclosed space demonstrate any of the following symptoms: hypotension not attributable to other obvious causes, altered mental status, coma, seizures, respiratory arrest, or cardiac arrest.

As part of the FDNY-EMS protocol, the following three tubes will be drawn before administration of HCO, a fluoride oxalate whole blood tube (grey), a K<sub>2</sub>-EDTA tube (purple), and a lithium heparin tube (green). The grey tube will primarily be used for the determination of blood cyanide concentration, which cannot be determined after HCO treatment.

In summary, HCO is quickly becoming the therapy of choice for empiric and definitive treatment of patients with cyanide poisoning. Its relatively short history of use and the potential adverse effects make it essential to be cautious with its administration, and to report all such cases to the NYCPCC (or other regional PCC). Further study of adverse effects and outcome benefit should remain a priority.

**Table 1: Mean changes in systolic and diastolic blood pressure in healthy volunteers after 5 g, 7.5 g, and 10 g of HCO<sub>2</sub>**

HCO dose	# of patients	Systolic BP (SD)	Diastolic BP(SD)
5 g	66	22.6 (16.8)	17.7 (9.8)
7.5 g	9	27.0 (10.0)	25.4 (4.7)
10 g	18	25.7 (13.2)	22.6 (10.1)



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