SCHEDULED EVENTS:

Emergency Medicine Grand Rounds
Marley Education Center: Sulzle Auditorium
Third Friday of the Month, 11:00 AM

April 17, 1998
May 15, 1998
June 19, 1998

Toxicology Case Conference
CNYPCC, 550 E Genesee Street
Poison Center Conference Room
Every Thursday 10:00 AM – 11:00 AM

PROGRAM ANNOUNCEMENT:

Mark you calendar now for the second annual Toxicology Teaching Day scheduled for October 30, 1998. More information will be coming shortly!

CNYPCC TIDBITS:

1. Which toxin smells like vinyl (new shower curtain)?
2. After a snake envenomation to the hand, the limb should be placed _____ in relation to the heart.
3. Salicylate overdose may manifest as hypoglycemia centrally while maintaining peripheral euglycemia.

TOX TRIVIA:

1. Who are the patron saints of pharmacy and medicine?
2. The mother in the novel "Flowers in the Attic" by V.C. Andrews poisoned her children using _____.
3. Which vitamin is formed when the "antidote" hydroxycobalamin is given to a cyanide poisoned patient?

Case History

Contributed by: Christine M. Stork, Pharm.D., ABAT

TOXIC ALCOHOLS

A 22 year old male presents to the Emergency Department after ingesting a "gulp" of a green liquid located in a Gatorade bottle. A co-worker stated that engine antifreeze was transferred from a large vat into the bottle for convenience. The patient had no significant past medical history and was asymptomatic. Vital signs were remarkable for tachycardia at 105/min. Otherwise, the physical examination was negative. The first laboratory tests received were a measured serum osmolality of 365 mOsm/kg and an ethanol level of 0.00 mg/dL.

What is the differential diagnosis for an increased osmol gap?

The osmol gap is the difference between the calculated osmolarity and the measured osmolality. Osmolarity is calculated through various methods. The most commonly used equation is:

$$2) \frac{Na(mEq/L)}{} + \frac{BUN(mg/dL)}{2.8} + \frac{Glucose(mg/dL)}{18} + \frac{Alcohol(mg/dL)}{"R"}$$

R: ethanol = 4.6, ethylene glycol = 6.4, methanol = 3.2

Sodium is multiplied by 2 because it is assumed that each positively charged sodium molecule will be associated with another negatively charged osmotically active particle. All other coefficients are determined by the gram molecular weights, which determine the amount they contribute to the osmotic load. Any gap between the measured and calculated values is consistent with the presence of uncalculated osmotically active particles. The usual osmolar gap can range from -14 to +10. While a small osmolar gap is not useful to exclude a toxic alcohol ingestion, a very large gap can be quite useful. This patient had a measured osmolality of 365 mOsm. His calculated osmolarity was 310 mOsm/L. Thus, his osmolar gap was 55 mOsm which is much larger than the upper limit of the range. A drug effect of at least 45 mOsm is present, which using the last part of the equation (alcohol/R = osmol gap) could correspond with an ethylene glycol level of (EG/6.4 = 45) 288 mg\dL or a

methanol level of (methanol/3.2 = 45) 144 mg/dL, both of which are highly toxic.

Other patients that may have a high osmol gap include patients with hyperlipidemia, hyperproteinemia, mannitol, other alcohols, alcoholic ketoacidosis, lactic acidosis, and renal failure.

How to patients with toxic alcohol ingestions typically present?

Any alcohol can produce central nervous system (CNS) depression, however, the degree to which each alcohol produces this effect varies according to its molecular size and arrangement. Generally, the larger the alcohol, the greater the CNS depression. For example, methanol will produce less CNS depression at a given serum concentration than ethanol or ethylene glycol.

> *inebriation comparison*
> methanol < ethanol/ethylene glycol<isopropanol

The toxic manifestations of methanol and ethylene glycol such as acidosis, hypotension, end organ damage, and death can be delayed. Ethylene glycol toxicity generally begins to manifest within 4-6 hours, where as methanol toxicity can be delayed for up to 12-24 hours. Coingestion of ethanol will delay the manifestations of toxicity even further. It is important to recognize the possibility of toxicity early, before manifestations have occurred, because the goal of therapy is to prevent potentially irreversible organ damage.

Both methanol and ethylene glycol can cause acidosis through their metabolic by-products. Methanol is metabolized to formic acid which, in addition to producing an acidosis, also damages the optic nerve. Ethylene glycol creates an acidosis largely through metabolism to glycolic acid and produces renal failure by metabolism to oxalate which crystallizes as calcium oxalate in the renal tubules.

Are there any clinical clues to a toxic alcohol ingestion?

There are several quick and easy bedside tests that can be employed to differentiate between toxic alcohols. These tests can prove extremely useful in many situations where rapid alcohol concentrations cannot be obtained.

Methanol toxicity can be assessed through questioning the patient about visual acuity. A patient with methanol intoxication may report snow field vision. Also, funduscopic examination of methanol poisoned patients may show papilledema.

Ethylene glycol toxicity can be assessed by examination of the patient's urine. The presence of calcium oxalate crystals or fluorescence (fluorscene is an additive in some antifreeze preparations) of the urine may provide evidence for exposure.

Isopropanol can be identified because it is a unique alcohol that produces ketosis without concurrent acidosis.

How are patients with toxic alcohol ingestions treated?

Generally, patients with ethanol and isopropanol ingestions can be treated with supportive care with special attention to the airway. Methanol and ethylene glycol poisoned patients, however, require specific interventional therapy because of their propensity to cause severe and permanent organ damage.

The definitive therapy for patients toxic from ingestions of methanol or ethylene glycol is hemodialysis. All alcohols have small molecular weights, low lipophilicity, low volumes of distribution and ionization which make them extremely amenable to extracorporeal removal. Hemodialysis is not without its risks, however, and a level documenting toxicity or clinical signs should be considered when deciding who should be dialyzed. Otherwise asymptomatic patients with methanol or ethylene glycol levels of 25 mg/dL require hemodialysis.

Ethanol therapy can be provided while waiting or deciding on definitive therapy. Ethanol is metabolized by the enzyme alcohol dehydrogenase preferentially over methanol or ethylene glycol. It is important to realize that it is the metabolic products and not the parent compounds that are responsible for systemic toxicity. An ethanol level greater than 100 mg/dL is desired and can be reached through a loading dose (orally or intravenously) of 1 g/kg of ethanol, followed by an hourly dose of 15% of the loading dose. Frequent ethanol concentrations should be obtained and subsequent doses titrated to assure therapeutic levels and protect against toxicity. Ethanol is also removed through hemodialysis and therefore, the dose of ethanol

should be increased by 2-3 times while the patient is being hemodialyzed.

Folic acid can be given to methanol intoxicated patients to help increase metabolism of formic acid to a non-toxic metabolite. Similarly, thiamine and pyridoxine can be given to ethylene glycol toxic patients.

What is Fomepizole?

Fomepizole (Chemical name: 4-methylpyrazole, Brand name: Antizol) was approved for use after ethylene glycol poisoning in December, 1997. It is not unlike ethanol in its ability to competitively inhibit alcohol dehydrogenase and clinical trials have proven it's effectiveness in preventing the formation of the toxic metabolites formed after ethylene glycol and methanol poisoning. The advantages of fomepizole over ethanol include ease of administration, lack of blood level monitoring, and lack of significant adverse effects. However, fomepizole has a significantly increased cost over traditional ethanol treatment and there is no outcome data to suggest that fomepizole is better at treating ethylene glycol or methanol poisoning. As more clinical experience accumulates, the relative role of fomepizole versus ethanol in the treatment of ethylene glycol and methanol poisoning will become more clear.

What if hemodialysis is not available, can I just keep the patient on fomepizole or an ethanol infusion until the drug has renally cleared?

Methanol is excreted almost exclusively through renal elimination. It could take weeks for a patient to eliminate enough methanol not to require hemodialysis, therefore, such a patient should be transferred to a facility that can perform hemodialysis as soon as possible. Ethylene glycol has an increased rate of extrarenal elimination and it may be possible in some circumstances, in a low degree of poisoning (level < 50 mg/dL in a patient with normal renal function), to keep the patient loaded with ethanol or fomepizole for a few days until the ethylene glycol level falls. This option should be considered in cases where it is difficult to transfer patients or where there is a contraindication to hemodialysis.

What is the active ingredient of the new "environmentally safe" antifreeze?

The typical composition of antifreeze is ethylene glycol. Recently, companies have begun to use propylene glycol as an environmentally safe alternative for use in their antifreeze products. Propylene glycol, when ingested, is much less toxic than ethylene glycol. However, there have been case reports of patients developing acidosis and an increased osmol gap after ingesting large quantities of propylene glycol. When evaluating a patient with a antifreeze exposure it is prudent to assume the patient has been exposed to ethylene glycol, until it can be definitively excluded.

This patient was transferred to a facility providing hemodialysis, received hemodialysis within 6 hours of presentation, and had no adverse sequelae. An ethylene glycol level at an unknown point prior to hemodialysis was 240 mg/dL.

References

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Jacobson D, Hewlett TP, Webb R, Brown ST, Ordinaro AT, McMartin KE. Ethylene glycol intoxication: evaluation of kinetics and crystalluria. Am J Med. 1988;84:145-52.

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Sklar AH, Linas SL. The osmolal gap in renal failure. Ann Intern Med.1983;98:481-2.

Brent J, McMartin K, Phillips S et al. 4-methylpyrazole (fomepizole) therapy of ethylene glycol poisoning: preliminary results of the meta trial. (Abstract). J Toxicol Clin Toxicol 1997;35:507.

CNYPCC Tidbits Answers

1. Ethchlorvynol (Placidyl®)
2. Dependant (lower than the heart)

Tox Trivia Answers

1. St. Cosmos and St. Daemon
2. Arsenic
3. Cyanocobalamin (vitamin B-12)

THE "SPI" CORNER

Contributed By: Teesh Guenthner, RN, CSPI

Topic: Olanzapine (Zyprexa (R))

As many of you have suspected, we are receiving an increasing number of calls about the new drug, olanzapine.

Olanzapine is considered an atypical antipsychotic of the thienobenzodiazepine class. It acts similar to other atypical antipsychotics to inhibit the activity of serotonin and dopamine. Olanzapine is a desirable pharmaceutical addition due to its low incidence of extraparametical symptoms and it's demonstrated efficacy in the treatment of both the positive and negative symptoms of schizophrenia.

Olanzapine is well absorbed from the gastrointestinal tract and after therapeutic doses, reaches peak serum concentrations within 6 hours. Food does not appear to effect the rate or extent of absorption. Olanzapine's elimination half-life ranges from 21-54 hours (mean 30 hours).

The most common side effects noted after therapeutic doses of olanzapine include somnolence, agitation, dizziness, and asthenia. Constipation, dry mouth, rhinitis, weight gain, and hepatic enzyme elevations are less frequently reported.

Large doses of olanzapine such as those seen after overdose consistently cause a depressed mental status. Other effects may include nausea and vomiting, hypotension, anticholinergic effects (mydriasis, hyperthermia, tachycardia, dry flushed skin, urinary retention and decreased bowel sounds) and rarely extraparametal symptoms and seizures.

There is no specific antidote available for the treatment of olanzapine overdose. Aggressive supportive measures should include airway management, intravenous fluids, and pressors for the treatment of hypotension. Monitoring parameters include serial ECGs and vital sign assessment. Most patients respond and do well with supportive care alone.

ANTICHOLINERGIC POISONS
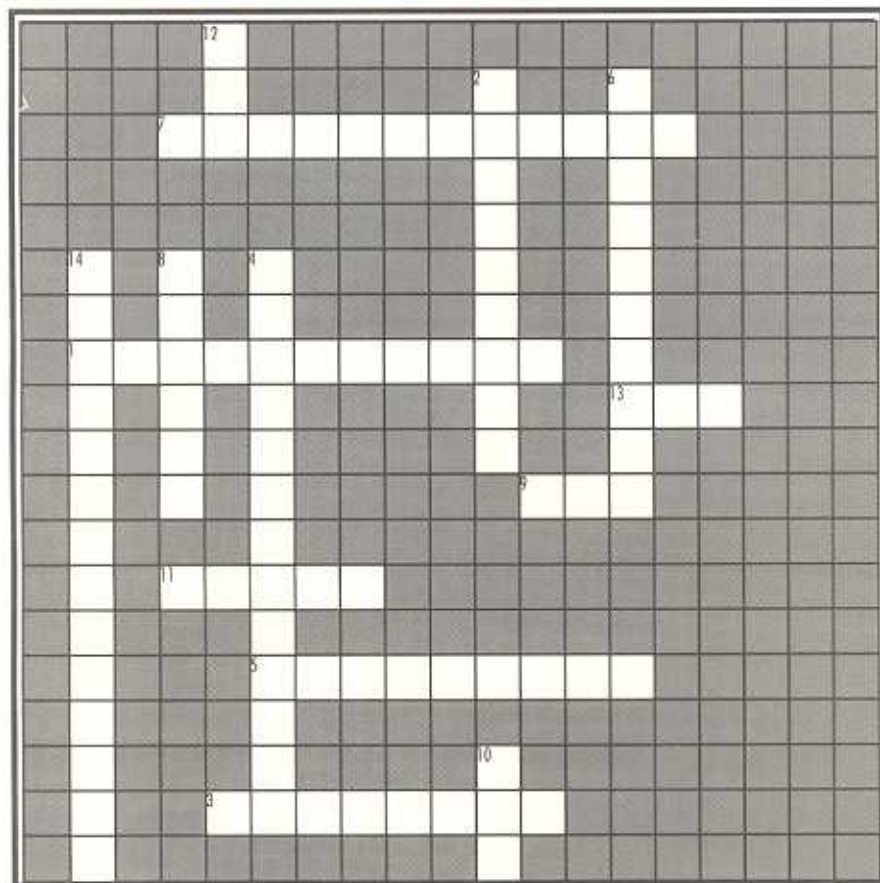
CLUES:

ACROSS

1. Heart Rate Change
3. Clonic Tonic Movements
5. Pupils
7. Temperature Change
9. . . . . as a hatter
11. . . . . as a bat
13. . . . . as Hades

DOWN

2. Urinary . . . .
4. Caustiously use this antidote
6. . . . . bowel sounds
8. . . . . antidepressants
10. . . . . as a beet
12. . . . . as a bone
14. cold and allergy medication

Across: 1. Tachycardia; 3. Seizures; 5. Mydriasis; 7. Hyperthermia; 9. Mad; 11. Blind; 13. Hot Down: 2. Retention; 4. Physostigmine; 6. Diminished; 8. Cyclic; 10. Red; 12. Dry; 14. Antihistamines

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July - canceled
August - canceled
September JB McCabe Visiting
Professorship (Dr. Hoffman)

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PROGRAM ANNOUNCEMENT:

Look soon for the brochure for our second
annual Toxicology Teaching Day scheduled
for October 30, 1998. Please call
315-464-7078 for more information.

CNYPCC TIDBITS:

Last year the Central New York Regional
Poison Control Center managed over
23,000 calls from health care providers and
the general public.

TOX TRIVIA:

Matching – recombinant products and their
source

A. goat   B. equine
C. sheep   D. salmon

1. digoxin FAB fragments
2. crotalid antivenin
3. protamine
4. scorpion antivenin
5. latrodectus (black widow spider)
   antivenin

Case History

Contributed by: Christine M. Stork, Pharm.D., ABAT

TOXIC PLANTS

A 52 year old male presents in the evening to emergency care with symptoms of severe nausea and vomiting, diaphoresis, tingling of the tongue and dizziness. In the afternoon he had eaten soup prepared from "leeks" he had foraged earlier in the day. His vital signs include a systolic blood pressure of 60 mmHg, a pulse of 40/minute, a respiratory rate of 16/minute and a temperature of 99°F taken orally. Abnormal physical examination findings included mild abdominal tenderness, marked diaphoresis, and a confused, but alert mental status. His pupils are 3 mm and reactive. No other abnormalities are noted. The patient receives intravenous glucose and thiamine without effect. An initial ECG shows marked sinus bradycardia and a shortened PR interval. He receives atropine and intravenous fluid, which temporarily increases his heart rate to 70/minute and his systolic blood pressure to 120 mmHg. Over the next 12 hours, the patient remains bradycardic and develops varying degrees of AV block occasionally resulting in junctional escape cardiac arhythmia.

What is the differential diagnosis of toxin associated bradycardia/hypotension?

Toxins that commonly cause bradycardia include calcium channel blockers, beta adrenergic receptor antagonists, digoxin, organophosphates, centrally-active alpha adrenergic agonists (e.g. clonidine), peripherally-active alpha adrenergic agonists (e.g. phenylpropanolamine), antidysrhythmic agents, in addition to drugs that cause electrolyte abnormalities (e.g. hypercalcemia). Hypotension may be caused by digoxin, clonidine, peripherally-active alpha adrenergic antagonists (i.e. phenothiazines, phentolamine/prazosin), direct-acting nitrovasodilators (i.e. nitroprusside), angiotensin converting enzyme inhibitors, angiotensin-2 antagonists, ganglionic blockers, beta-2 adrenergic agonists (e.g. albuterol) and others that decrease perceived intravascular volume. Sedative hypnotics and opioids also can cause small decreases in pulse and blood pressure, but uncommonly produce frank bradycardia or hypotension.

As there is no history of medication use or availability, most of the cardioactive drugs may be removed from the differential diagnosis list. The bradycardia associated with peripheral alpha adrenergic agonists should be associated with hypertension. Since this patient presents with hemodynamic abnormalities associated with eating foraged plants, plant toxicity and organophosphate poisoning should be considered early in the differential diagnosis. The findings of diaphoresis, nausea and vomiting suggest organophosphate poisoning, although the presence of midposition pupils, clear lungs, and no diarrhea or urination make this diagnosis unlikely. Since no common toxidrome sufficiently explains this patient's constellation of signs and symptoms, a focus on identification of the plant ingestion was made.

What toxic plants can result in significant hypotension and bradycardia?

Digoxin-like

The classic plant related cause of hypotension and bradycardia is digoxin, a cardiac glycoside derived from *Digitalis lanata*. Although animal sources of cardiac glycosides exist (e.g. *Bufo marinus*), many more are available from botanical sources. Examples include lily of the valley (*Convallaria majalis; convallotoxin*), purple foxglove (*Digitalis purpurea; digitoxin*), yellow oleander (*Thevetia peruviana*), oleander (*Nerium oleander; oleandrin*) and red squill (*Urginea spp; scillarin*).

Digoxin-like cardiac glycosides act pharmacologically to block the sodium-potassium ATPase on the myocardial cell membrane. This enzyme is responsible for cellular repolarization through the shifting of sodium and potassium, extracellularly and intracellularly, respectively. The result of pump inhibition is increased intracellular sodium, which subsequently inhibits the exchange of extracellular sodium for intracellular calcium. Increased intracellular calcium enhances contractile function and prolongs the action potential. Clinical manifestations of toxicity include nausea, vomiting, hyperkalemia, bradycardia, hypotension, and life-threatening cardiac dysrhythmias

The digoxin immunoassay may cross-react with the other digoxin-like cardiac glycosides. Cross-reactivity is generally unpredictable and these levels cannot be used to gauge the degree of toxicity. Treatment of poisoned patients consists of supportive care with special consideration toward the use of digoxin-specific Fab fragments (Digibind ®). If Fab fragments are used, a higher dose may be required to reverse the cardiotoxic effects of non-digoxin cardiac glycosides as the antibody is specific for digoxin.

Aconitine

Monkshood (*Aconitum napellus*) contains the toxin aconitine. When ingested in sufficient quantity, aconitine results in nausea, vomiting, dysesthesias, hypotension, bradycardia, respiratory failure, and ventricular dysrhythmias. Of interest, aconitine is commonly found in Chinese herbal products, where it is reported to exhibit anti-inflammatory, analgesic and cardiotonic effects. These herbs are touted to increase local blood flow, increase energy metabolism and increase the absorptive activities of the gastrointestinal tract.

Aconite, a C19 – diterpenoid-ester activates voltage sensitive sodium channels. Activation of the excitable membranes of the cardiac, neuronal, and muscle tissues prolongs the influx of sodium into the cell during depolarization. Neuronal channel activation produces paresthesias and weakness. Parasympathetic innervation is responsible for hypotension and bradycardia, while enhancement of the plateau phase of the action potential prolongs repolarization in cardiac myocytes and induces after-depolarizations with triggered automaticity.

Cardiac dysrhythmias are the life threatening consequences of as little as 0.2 mg of aconitine. Treatment is supportive and no uniformly successful antidote is known.

Veratrum

False or green Hellebore (*Veratrum viride*) ingestion can result in a variety of cardiac manifestations including bradycardia, hypotension, decreased PR interval, and other conduction related dysrhythmias. Other associated findings may include paresthesia, nausea, vomiting, altered mental status, and decreased ventilation.

The alkylamines contained in these plants (most notably jervine) bind to membrane lipids to increase sodium conductivity. The interaction of the *Veratrum* alkaloids with the sodium channel is modulated by the kinetic state of the channel. Binding is greatly enhanced while the channel is in the open state. As a result of the sodium channel remaining open, a negative stimulation threshold occurs that enables a repetitive response to a single stimuli. When this occurs, signs and symptoms of toxicity develop.

Treatment after exposure consists of gastrointestinal decontamination, followed by intensive supportive care. Bradycardic patients may benefit from the administration of atropine.

Gryanotoxins

Some examples of plants that may contain grayanotoxin include the death camas (*Zigadenus spp*), azalea (*Rhododendron spp*), rhododendron (*Rhododendron spp*) and mountain laurel (*Kalmia latifolia*). Symptoms may include salivation, lacrimation, rhinorrhea, emesis, weakness, bradycardia and hypotension. Similar to aconite and veratrum alkaloids, grayanotoxins act primarily through activation of the fast sodium channel.

Case Follow-up:

The patient's family obtained the remains of the partially ingested soup and plant. The local forestry school was able to identify the plant as *Veratrum viride* (false hellebore). The patient was successfully managed with supportive care and fully recovered.

What are the other common general classes of plant poisons?

In addition to the cardioactive plant toxins, there are several other major types of toxicity that are typically produced following plant ingestions. That plants are toxic

is not surprising. Many of the pharmaceuticals in use today are derived directly from plants (e.g. digoxin). Some of the common toxicities and the associated plants causing them are listed below.

Anticholinergics

Plants that contain anticholinergic toxins produce a classic anticholinergic syndrome. Symptoms may include altered mental status, hallucinations, dry/flushed skin, dry mucous membranes, dilated pupils, urinary retention and absence of bowel activity. Some examples of plants capable of causing anticholinergic symptoms include Jimson weed (Datura stramonium), deadly nightshade (Atropa belladonna), and henbane (Hyoscyamus niger). Treatment is generally supportive although physostigmine, an anticholinesterase derived from another plant, the Calabar bean, has been used successfully to counteract anticholinergic effects.

Cellular toxins

Colchicine (Colchicum autumnale, Autumn crocus) and podophyllin (May apple, Podophyllum peltatum) cause toxicity by inhibition of cellular division during metaphase. Rapidly dividing cells manifest poisoning first, and produce the profound gastrointestinal symptoms seen after ingestion of these plant toxins.

The cyanogenic compound amygdalin can be found in plants of the Prunus species (apricots, apples, peach, cherry, etc.). Following ingestion, the enzyme emulsin causes the conversion of amygdalin to hydrocyanic acid (i.e. HCN) which is absorbed. Cyanide inhibits cytochrome A_3 in the electron transport chain inhibiting aerobic respiration and producing cellular death.

Abrin (Abrus precatorius, Jequirity pea) and Ricin (Ricinus communis, Castor bean) contain toxalbumins. These toxins are able to gain intracellular access where they act on the 60_s ribosomal subunit to inhibit protein synthesis and, ultimately lead to cellular death. Exposure to these toxins occurs most commonly through the ingestion of intact seeds. However, unless the seed coating is compromised through maceration or grinding, toxicity is unlikely.

Gastrointestinal toxins

A wide variety of plants cause their toxicity through gastrointestinal irritation. Some of the classes below have been identified as being unique in terms of mechanism or findings:

Dumbcane (Dieffenbachia spp), philodendron (Philodendron spp), caladium (Caladium spp), and jack in the pulpit (Arisaema triphyllum) are plants that cause gastrointestinal irritation through the release of water insoluble calcium oxalate crystals. These crystals are contained in a structure that discharges with pressure, such as when chewed. Contact with mucous membranes produces local pain, erythema, irritation and inflammation. Treatment is supportive and airway patency must be carefully assessed.

Poke weed (Phytolacca americana) contains the toxin phytolaccine which produces gastrointestinal irritation. In addition, a mitogen found in the pokeweed plant is responsible for the proliferation of lymphoid cells which causes an abnormally elevated white blood cell count.

Some examples of where Solanaceous alkaloids can be found include the potato, tomato and in other unripe (or green) fruits. The mechanism by which solanine causes toxicity is unclear, but typical symptoms include nausea, vomiting, diarrhea and abdominal pain. Neurologic symptoms including altered mental status and hallucinations have also been reported with some of these plants.

Central nervous system toxins

Several plants contain nicotine like alkaloids. Poison hemlock (Conium maculatum) ingestion was probably responsible for the death of Socrates. Coniine, found in this plant, acts to selectively stimulate nicotinic cholinergic receptors. Typical symptoms may include tachycardia, tremulousness, nausea, vomiting, and dilated pupils. Excess stimulation can lead to seizures and muscle weakness that may progress to depolarizing neuromuscular blockade.

Water hemlock (Cicuta spp) and poison hemlock (previously discussed) have an umble-like structure that may be mistaken in nature for Queen Ann's lace or wild carrot. Cicutoxin, contained in water hemlock produces rapid onset seizures following ingestion. The seizures are often refractory to standard treatment and mortality is not uncommon.

Conclusion

Plant poisoning is a serious problem. This case represents one of the most common means by which plant poisoning occurs. Besides foraging, another common arena in which botanical poisoning occurs is herbal or self-medical treatments. Expertise is often required to differentiate similar looking plants, and amateurs are often fooled into ingesting poisonous plants. If one is not absolutely confident in the identification of a specific plant, it should not be consumed.

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Tox Trivia Answers

1. c
2. b
3. d
4. a
5. b

Contributed By: Carol Sopchak, RN, CSPI

TOPIC: POISONOUS MUSHROOMS

The inability to distinguish toxic from non toxic mushrooms can cause serious poisoning. There are many cases where established mushroom foragers have become seriously poisoned after ingesting what they mistakenly thought to be "safe" or edible mushrooms. The only known universally safe mushrooms are those harvested for sale and these are generally found in supermarkets. There have even been cases where poisonous mushrooms have made their way into specialty store mushroom bins to cause toxicity.

Once a mushroom has been ingested, proper identification is important, but may be impossible to achieve because the mushroom is not available or because the specialized techniques required to properly identify mushrooms are not readily available. Historical and clinical information can help classify the mushroom. Look for specific mushroom group toxidromes and the time of onset of gastrointestinal symptoms, specifically vomiting. Early onset of vomiting, within three to six hours, is associated with the less toxic mushrooms and a good prognosis. Onset of vomiting later than six hours, is associated with mushrooms capable of causing more severe toxicity.

A brief overview of the classes of poisonous mushrooms is as follows:

VOMITING OCCURS 6 HOURS OR MORE AFTER EXPOSURE

Cyclopeptides;hepatotoxic cellular death 1-2 days after exposure

Gyromitrin;seizures (status epilepticus) 12-24 hours after exposure

Orelline; nephrotoxicity 3 - 20 days after exposure

VOMITING OCCURS 6 HOURS OR LESS AFTER EXPOSURE

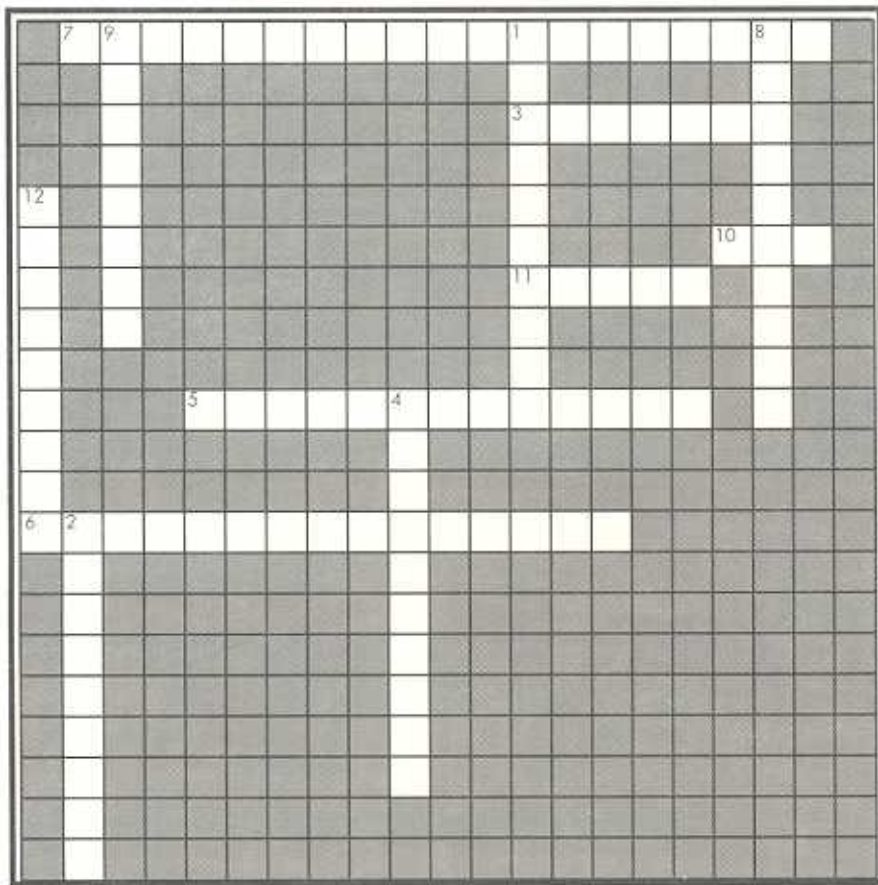Muscarine; acetylcholine-like symptoms (salivation, lacrimation, urination, defecation)

Coprine; disulfiram-like effect when mixed with ethanol

Ibotenic and muscimol CNS (ataxia, lethargy, coma, hallucinations), some anticholinergic

symptoms.

Psilocybin; illusions/hallucinogenic

Gastric-irritants; gastrointestinal irritants

HOLD THE MUSHROOMS, PLEASE!

CLUES:

ACROSS

3. Symptoms occur after alcohol ingestion
5. Symptoms occur greater than six hours
6. "The Death Cap" (2 Words)
7. Gastointestinal symptoms (3 words)
10. Umbrela like expension
11. Underside of mushroom cap

DOWN

1. Mushroom specialist
2. Cholinergic symptoms
4. Take a walk on the wild side
8. Symptoms occur 36 hours to 3 weeks later
9. Confusion, drowsiness, uncoordination
12. Twist and turn

Across: 3. Coprine; 5. Cyclopeptides;
6. Amanita Phalloides; 7. Little Brown Mushroom;
10.Cap; 11. Gills
Down: 1. Mycologist; 2. Muscarine;
4. psilocybin; 8. Orellanine; 9. Ibotenic;
12. Gyrometra

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October 30, 1998 – Toxicology Teaching Day,
University Sheraton Inn
November 20, 1998 – TBA
December 18, 1998 – Best Cases of the Year

Toxicology Case Conference
CNYPCC, 550 E Genesee Street
Poison Center Conference Room
Every Thursday 10:00 AM – 11:00 AM

PROGRAM ANNOUNCEMENT:

Please call the CNYPCC at 315-464-7078 for a registration form for our 2nd Annual Toxicology Teaching Day scheduled for October 30, 1998.

CNYPCC TIDBITS:

1. Calcium channel antagonists are among the leading causes of death due to prescription medications according the American Association of Poison Control Center's Toxic Exposure Surveillance System
2. Approximately 1/3 of Americans use some form of alternative medicine
3. Inhalation abuse is responsible for a significant number of fatalities, particularly in adolescence

TOX TRIVIA:

1. Which toxin is similar to tetanus in terms of mechanism of toxicity?
2. How many types of food botulism are capable of causing disease in humans?
3. A bite from which should not be expected to place the patient at risk for rabies? (a. dog, b. squirrel, c. bat, d. raccoon)

Case History

Contributed by: Christine M. Stork, Pharm.D., ABAT

TOXIC FUMES

Date: January 10, 1998

A 55 year old male is brought to the emergency department after being found obtunded in his home. He lost power during a storm 3 days prior and was not seen in the interim. In the emergency department, he is responsive to verbal stimuli, but confused and only oriented to person. Vital signs include a heart rate of 85/minute, blood pressure of 140/85 mm Hg, temperature of 36 C and respiratory rate of 20/minute (98% saturation). Physical examination with the exception of an altered mental status is non-contributory, ECG is read as normal and blood glucose is read as 120 mg/dL. An arterial blood gas returns at 7.35/45/99 with 99 % saturation on room air. A co-oximeter reading for carbon monoxide is requested and returns at 35% carbon monoxide (hemoglobin saturation 65%)

Epidemiology of ICE STORM '98...

The ice storm of January 1998, among other problems, led to a lack of electricity and heat for several areas in northeastern New York, Canada, northern New Hampshire, northern Vermont and Maine. Carbon monoxide exposures reported to poison control centers increased approximately 9 times over those of a similar period the year previous. As the fall of 1998 and winter of 1999 approach, we should be aware of the circumstances for increased exposure in order to prevent recurrent poisonings:

- Information could not be disseminated via usual routes (television and telephone) due to the long-term lack of electrical and telephone power.
- Questions could not be answered due to the lack of similar mechanisms.
- Heat was lost in cold weather for several days – weeks in some areas prompting the internal use of outdoor heating sources.
- Persons were improperly educated as to the use of generator equipment.

Why was carbon monoxide generated?

Carbon monoxide (CO) is produced through the incomplete combustion of carbon containing materials. Fuels produce

carbon monoxide in varying degrees in direct correlation to the efficiency of burning. For example, methane (natural gas) burns more efficiently and would be expected to produce less carbon monoxide that charcoal briquettes. In these cases, heat sources that burn inefficiently were brought into the home and not properly ventilated. The most common source of carbon monoxide exposure is through house fires.

How does carbon monoxide cause toxicity in humans?

Carbon monoxide (CO) binds to hemoglobin with more than 200 times the affinity of oxygen. This decreases the oxygen-carrying capacity of the blood. CO also causes a left shift of the oxyhemoglobin dissociation curve, preventing the release of oxygen at the tissue. Even one carbon monoxide molecule bound to one site of the hemoglobin tetramer can cause the binding of oxygen to the 3 remaining sites to become tighter. As a result, a CO level of 10% will decrease oxygen delivery more than that seen after a 10% decrease in hemoglobin from anemia.

Carbon monoxide also binds to myoglobin in cardiac tissue and may influence cytochrome oxidase activity resulting in aerobic respiration at the cellular level. The cardiotoxic effects seen after CO exposures are only partially explained by the decrease in oxygen delivery to the heart. CO is also shown to bind to the cytochrome chain in vitro. This binding interferes with aerobic respiration at the cellular level, however, the clinical significance of this is uncertain.

CO is thought to increase free radical formation and lipid peroxidation. This is one of the proposed mechanisms of delayed cerebral edema and delayed neuropsychiatric sequelae seen after CO poisoning.

What are the clinical manifestations of CO poisoning?

The clinical signs and symptoms seen after CO poisoning are nonspecific. As with other asphyxiants, the primary targets are the nervous and cardiovascular systems. High concentrations (>100 PPM) causes death within minutes. At low concentrations, patients complain of nausea, headache, and dizziness. There are no specific findings on physical examination or routine neurologic examination. Neuropsychiatric testing can demonstrate memory loss and more subtle decreases in cerebral function, however, this is operator, patient and situation dependent. As neurologic compromise increases, headache may worsen and complaints of difficulty concentrating and weakness occur. Physical examination includes confusion, ataxia, cognitive deficits, and focal deficits. After severe poisoning, coma and seizures are seen.

Cardiovascular effects occur due to an increased workload to make up for decreased oxygen delivery and direct cardiotoxicity. Cardiac effects seen include palpitations, chest pain, shortness of breath, dyspnea on exertion, tachypnea, and tachycardia. More severe symptoms of ischemia, hypotension and electrocardiogram changes occur after larger exposures or in patients with low amounts of cardiac reserve. Hemodynamic dysfunction may play a role in the development and exacerbation of neurologic sequelae.

The area of greatest concern in the literature is the ability of CO to cause delayed neurologic sequelae. Neurologic consequences of CO poisoning include personality and memory disturbances, a Parkinson-like disorder, mixed motor sensory peripheral neuropathy, and psychiatric disturbances. In select cases, central nervous system globus pallidus degeneration can be seen with CT scan.

How should patients be managed after suspected carbon monoxide poisoning?

Treatment of CO poisoning involves supportive measures and administration of normobaric or hyperbaric oxygen. Oxygen should be administered as soon as CO poisoning is recognized or suspected. Evaluation for suspected CO can be accomplished by venous or arterial measurement with a co-oximeter blood gas analysis. Oxygen shortens the biologic half-life of CO bound to hemoglobin. At room air, the half-life of CO is approximated at 3-5 hours, at 1 ATM and 100% oxygen the half-life is 40-90 minutes and at 2.8 ATM half-life is 20-50 minutes. The implications of the reduction in half-life are unknown.

CO poisoning is also managed using hyperbaric oxygen. Hyperbaric oxygen at 2 or more ATM will increase oxygen delivery and speed CO elimination. Indications for hyperbaric oxygen include altered mental status, neurologic findings, cardiovascular dysfunction, pulmonary edema, severe acidosis, and loss of consciousness. Other criteria for considering HBO include carboxyhemoglobin greater than 25%, history of cardiovascular disease and age older than 60, and pregnancy with symptoms or carboxyhemoglobin level greater than or equal to 15%.

Why do the pulse oximeter and regular blood gas measurements supply inaccurate oxygen saturation?

A pulse oximeter measures two wavelengths of light that most nearly match with the maximal absorbency of oxy and deoxyhemoglobin. Carbon monoxide's absorbency is close to and therefore read as oxyhemoglobin on a pulse oximeter. Therefore, even severely poisoned patients will appear to have normal pulse oximetry readings.

A conventional blood gas machine calculates the oxygen saturation from the amount of dissolved oxygen (pO2) in blood. Since carbon monoxide does not interfere with the amount of dissolved oxygen carrying capacity, this value will be falsely calculated to be normal. Only a co-oximeter, which specifically measures four wavelengths of light corresponding with oxyhemoglobin, deoxyhemoglobin, methemoglobin and carbon monoxide will provide the proper oxygen saturation after carbon monoxide exposure.

Why are pregnant patient and infants at increased risk?

Pregnant patients and infants require special consideration in the setting of CO poisoning.

Increased metabolic demands and minute ventilation

found in these patients increase the dose of carbon monoxide delivered per unit of time. In addition, the fetus and small infant have a significant amount of fetal hemoglobin. Fetal hemoglobin has a greater affinity for CO than hemoglobin, leading to increased effects at a given level in the fetus and infant and a prolonged elimination time. Many times it is difficult to access fetal effects and duration of exposure due to the disparity of CO elimination between mother and fetus. As a result, these patients should receive longer treatment with oxygen and should be considered for hyperbaric oxygen with levels greater than 15%.

Patient follow-up:

This patient received oxygen, was transferred to a tertiary care center for treatment with hyperbaric oxygen. All neurologic signs and symptoms abated and he was able to be sent home with instructions regarding the proper ventilation of his portable generator.

What other toxin is formed when CO is produced during house fires?

Combustion of plastics, polyurethane, wool, silk, nylon, nitrocellulose, polyacrylnitriles, rubber, and paper products lead to the production of cyanide gas. In addition to combustion byproducts, cyanide is found in metalurgy, photo processing, and chemistry laboratories. Cyanide is a chemical asphyxiant that interferes with cellular metabolism by binding to the cytochrome oxidase system and halting aerobic metabolism. The actual binding site is the ferric (Fe^{3+}) ion on cytochrome A3. The manifestations of poisoned aerobic metabolism are lactic acidosis from anaerobic metabolism and decreased oxygen consumption. Although the mechanism of cyanide poisoning is different from that of CO, the clinical manifestations are quite similar. The central nervous system and cardiovascular system are affected most often, but the signs and symptoms are nonspecific. Central nervous system findings include agitation, cephalgia, disorientation, seizures, coma, and death. Cardiovascular findings include tachycardia, bradycardia, and hypertension that progress to hypotension with bradycardia and cardiovascular collapse. There is no method for rapid detection of cyanide. The nonspecific clinical findings and the inability to establish definitive diagnosis rapidly is further complicated by the rapid onset and progression of toxicity requiring immediate treatment. Cyanide should be considered in all smoke inhalation victims with central nervous system or cardiovascular findings. The most practical approach would be to assess for other causes of clinical findings such as CO, hypoxia, and hypoglycemia. If no other explanation can be established, treatment for cyanide should be considered. In smoke inhalation victims with CO poisoning, failure to improve with administration of oxygen may indicate coexistent cyanide and CO poisoning.

Tox Trivia Answers

1. strychnine

2. 5 types (A,B,E,F,G)

3. b

Management of Suspected Cyanide Poisoning

Cyanide poisoning is treated using the "cyanide antidote kit". This kit contains three antidotes; amyl nitrite, sodium nitrite, and sodium thiosulfate, in quantity sufficient to treat two adult patients. The nitrites convert hemoglobin to methemoglobin. Cyanide is attracted to methemoglobin and combines to form cyanomethemoglobin. The sodium thiosulfate provides substrate for the enzyme rhodenase, which combines thiosulfate and cyanide to form a non-toxic compound thiocyanate, which is rapidly excreted in the urine. The major disadvantage of the nitrites is hypotension secondary to vasodilatation.

The most difficult aspect of treating cyanide poisoning in the setting of smoke inhalation is deciding when to initiate treatment. There is no rapid test for the presence of cyanide. Cyanide levels are elevated in 78 - 100% of fire fatalities. In one study, 90% of the fire survivors had cyanide levels greater than 0.1ug/ml. In a fire victim with a CO, inducing methemoglobinemia risks causing a severe decline in oxygen carrying capacity. In this setting, either sodium thiosulfate alone should given or nitrates with thiosulfate only after the initiation of hyperbaric oxygen.

Several other antidotes for cyanide poisoning are being investigated. Dimethylaminophenol (DMAP) is another methemoglobin-forming agent. Red cell stroma-free methemoglobin, dicobalt, EDTA, and hydroxycobalamine are potential antidotes that act by binding cyanide directly. DMAP is currently used in Europe but not approved in the United States. It may have some advantage over nitrites in that it causes less hypotension and induces methemoglobinemia more rapidly. DMAP still has the major disadvantage of decreasing oxygen carrying capacity. Stroma-free methemoglobin has theoretical concerns about obstruction of renal tubules and allergic reactions. Dicobalt EDTA (Kelocyanor) is currently used in Europe but is not approved in the United States. It chelates cyanide and is excreted in the urine. Side effects include allergic reaction, hemodynamic instability, and tachypnea. The most promising new antidote is hydroxycobalamine (vitamin B12), which is eliminated by the urine. Hydroxycobalamine is considered an orphan drug by the FDA and is used in Europe. Side effects include reddish discoloration of the skin, mucous membranes, and urine, increased blood pressure, and anaphylactoid reactions. If hydroxycobalamine proves to have minimal risk, empiric treatment with sodium thiosulfate and hydorxycobalamine may become the treatment of choice.

Suggested reading

1. Mathieu D, Nolf M, Durocher A et al. Acute carbon monoxide poisoning risk of late sequelae and treatment by hyperbaric oxygen. J Toxicol Clin Toxicol 1985;23:315-324.

2. Smith JS, Branson S. Acute carbon monoxide poisoning – 3 years experience in a defined population. Postgrad Med J 1970;46:65-70.

3. Gorman DF, Clayton JE, Gilligan JE et al. A longitudinal study of 100 consecutive admissions for carbon monoxide poisoning to the royal adelaide hospital. Anaes Intens Care 1992;20:311-316.

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TOPIC: HERBALS

What are the implications of the increased use of herbal medications to health care providers? Every day, an increasing amount of information is conveyed to the public regarding herbal therapy in all media sources including; written forms, television and, most recently, the internet. Estimates claim that over 16 million Americans take herbal supplements. Reasons for the use of herbals over conventional medication include psychological comfort of a "natural", an idea that the herbal will have less side effects, and financial (herbals many times are less costly than traditional medications and do not require a prescription).

There are numerous problems related to the use of herbals. Health care providers may not be aware of the patient's use because the patient does not perceive the "natural" product as being a medication so information regarding use is not provided. Even when herbal medication history is provided, the health care provider cannot be assured that the products contain the ingredients that are reported on the label. This because these medication are considered dietary supplements and are not regulated by the Food and Drug Administration. Sometimes this can be dangerous. An example is an herbal preparation containing digoxin that was mislabeled as plantain. Remember to treat the patient not the poison. If there are digoxin like s/s treat like digoxin and get a level - there may be cross-reactivity. Examples of adulterants include a recent case in which kelp was contaminated with arsenic. Other herbals may contain microbials such as fennel that are natural breeding grounds for salmonella. Some herbals have other contaminants the manufacturer considers active ingredients, such as earthworms and tortoise shell.

Many herbal preparations are safe in the right amount and route of administration. Others contain toxic ingredients where patients may experience adverse reactions - even without additives. Remember, when eliciting medication use from patients, to inquire not only about prescription and over the counter pharmaceutical use, but also herbal medications, teas and liniments.

The following are some examples of popular herbal products that can result in serious toxicity:

1. Ginseng Abuse Syndrome: (hypertension, anxiety, diarrhea, and eruptive dermatitis).
2. MaHuang, or Ephedra, or Herbal Ecstasy: (hypertension, tachycardia MI, stroke, and seizures).
3. St. John's Wort: potential for many drug interactions.

HERBALS; REPORTED USES
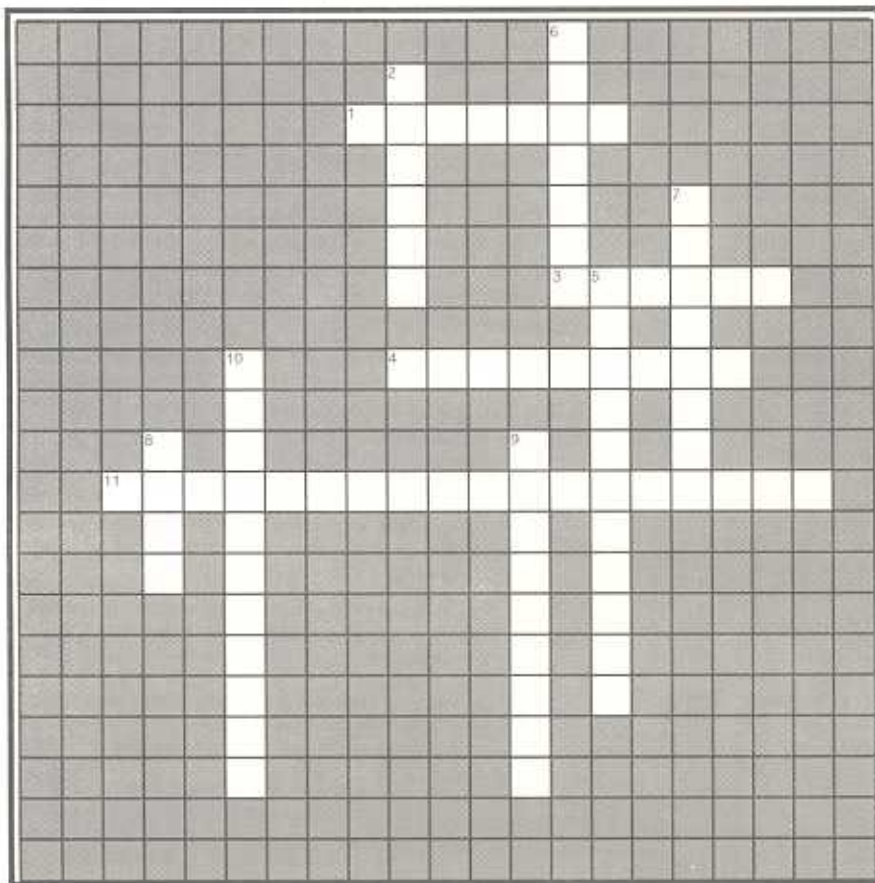
CLUES:

ACROSS

1. Phen of herbal Phen-Fen
3. Anticoagulant
4. Prevent UTI
11. Fat burner ingredient

DOWN

2. Aphrodisiac, Aromatic
5. Antihistamine
6. Increased mental and physical activity
7. Sounder sleep
8. Fountain of youth
9. Cold/flu
10. Antidepressant, Fen of herbal Phen-Fen