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TOXICOLOGY TODAY

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METHOTREXATE TOXICITY

by Jessica Griffin, PharmD

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Introduction

Methotrexate (MTX) is a folic acid antagonist that is used as an antineoplastic agent and immunosuppressant. It is FDA approved for a variety of solid tumors and hematologic malignancies, rheumatoid arthritis, and psoriasis. Due to its immunosuppressive and anti-inflammatory activity it has also been used for a variety of other diseases such as systemic lupus erythematosus and Crohn's disease. It can be administered parenterally (IM, IV, intrathecal and intra-arterial) and orally.

Pharmacology

Methotrexate inhibits dihydrofolate reductase (DHFR), the enzyme necessary to reduce folate to tetrahydrofolate (FH4). Inhibition of tetrahydrofolate, reduces the synthesis of purines and thymidylate, ultimately leading to an interruption in DNA synthesis, repair, and cellular replication.

Pharmacokinetics

Methotrexate's bioavailability following oral administration is highly variable and dose dependent. Peak concentrations are reached 1-2 hours after an oral dose and 30-60 minutes after an IM dose. Approximately 50% of methotrexate is bound to plasma proteins, mainly albumin, and it has a volume of distribution of 0.4-0.8 L/kg.

Methotrexate is metabolized to methotrexate polyglutamates that also inhibits dihydrofolate reductase. A small amount of the polyglutamates are converted to 7-hydroxymethotrexate, which may accumulate following high dose methotrexate therapy. Methotrexate is primarily renally excreted (80%). The half-life for doses < 30 mg/m^2 is 3-10 hours, but is increased to 8-15 hours for doses > 30 mg/m^2.

Adverse Effects

Methotrexate's adverse effects vary by dose and route but primarily involve normal tissues with rapid cell turnover such as the lining of the gastrointestinal tract, hair, skin, and bone marrow. Common adverse effects include stomatitis, diarrhea, loss of appetite, nausea, vomiting, skin redness, hyperuricemia, and myelosuppression.

Neurologic complications are more likely to occur following intrathecal administration or high dose therapy. Onset of neurologic toxicity can occur anywhere from hours to days after exposure. Neurologic complications include altered mental status, seizures, focal neurologic deficits, and weakness. The exact mechanism is not known. Effects that occur within hours after exposure may suggest a chemical inflammation of the arachnoid and manifest as meningismus with fever, photophobia, and neck stiffness. Long term behavioral disorders or cognitive impairment suggest leukoencephalopathy, which is irreversible. These effects may not manifest until months or years after treatment.

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Monitoring

Serum methotrexate concentrations should be obtained to help guide therapy. Bone marrow suppression may occur within 7-10 days of exposure with recovery generally occurring within 2 weeks. A complete blood count should be monitored accordingly. Liver function should be monitored by checking serum AST, ALT and bilirubin. Renal function should be monitored by obtaining serum creatinine and BUN at18-24 hours and 48-72 hours after MTX dose. A CT scan, MRI, and CSF analysis should be performed if neurotoxicity is suspected.

Treatment

Treatment of an acute methotrexate overdose includes general supportive care, gastric decontamination, and leucovorin. Adequate hydration and alkalinization of the urine can help reduce nephrotoxicity.

Activated charcoal should be considered in patients that present soon after an oral overdose. Multiple dose activated charcoal or *(cont. on pg. 2)*

IN THIS ISSUE

National Poison Prevention Week
March 20-26, 2011

This year marks the 49th anniversary of Poison Prevention Week! The third week in March was officially designated by President Kennedy in 1961 as a time to raise public awareness about the poison problem in the United States. Poison Prevention Week is an opportunity to get involved in spreading the poison prevention message. Help us in observing this important week by visiting our website to access resources that can be used to prevent poisonings in the home and community: www.utahpoisoncontrol.org

(cont. from pg. 1)

Methotrexate Toxicity

cholestyramine has been recommended to interrupt enterohepatic circuation, but limited data are available. These therapies should not be used in lieu of more aggressive therapy with IV leucovorin. Leucovorin (folinic acid/citrovorum factor), used as rescue therapy in patients receiving high dose methotrexate therapeutically, can also be used to treat an inadvertent or intentional overdose. Leucovorin provides the tetrahydrofolate co-factor that is depleted by MTX. It should be used as soon as possible, preferably within one hour, because effectiveness diminishes with time. Doses used for methotrexate rescue therapy are not adequate for an overdose. The initial dose recommended to treat an oral/parenteral overdose is a dose equal to or greater to the dose of methotrexate administered/taken. Methotrexate concentrations may assist in guiding additional treatment, but one should not wait for methotrexate concentrations to begin therapy with leucovorin. An empiric dose of 100 mg/m^2 administered intravenously should be used when the methotrexate dose is unknown. Leucovorin should be administered every 3-6 hours and continued for several days until serum methotrexate concentrations are less than 0.01 mcmol/L. If methotrexate concentrations are not available, continue leucovorin for 3 days or longer depending on renal function. Do not administer leucovorin intrathecally. Oral formulations of leucovorin are available. Patients may be switched to oral leucovorin only if adequate concentrations can be achieved with oral therapy. Hemodialysis has been used in the past, but is not generally recommended.

Summary

MTX is a folate antagonist that causes toxic effects mostly involving rapidly dividing cells such as cancer cells, the lining of the GI tract, and bone marrow. Hydration and urinary alkalinization are important to maintain renal function. Leukovorin should be considered to limit the delayed toxic effects. Patients should be monitored for mucousitis, bone marrow suppression and hepatic and renal injury.

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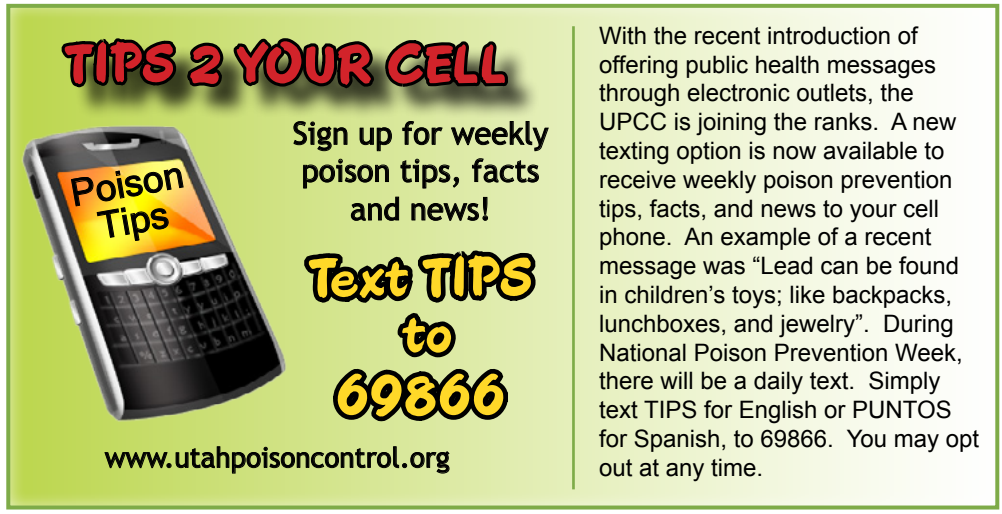

With the recent introduction of offering public health messages through electronic outlets, the UPCC is joining the ranks. A new texting option is now available to receive weekly poison prevention tips, facts, and news to your cell phone. An example of a recent message was "Lead can be found in children's toys; like backpacks, lunchboxes, and jewelry". During National Poison Prevention Week, there will be a daily text. Simply text TIPS for English or PUNTOS for Spanish, to 69866. You may opt out at any time.

M-44 Sodium Cyanide

The United States Department of Agriculture, Animal and Plant Health Inspection Service, Bureau of Wildlife Services would like us to remind you that the M-44 sodium cyanide device is used in Utah. The device is tubular and is placed in the ground with 1.5 inches sticking out of the ground baited with meat. This device is used in specific situations to control coyotes, redfox, gray fox and wild dogs. The purpose of the device is to protect livestock, poultry, and endangered species and to prevent the spread of disease. Although this device is primarily used on private lands, it may also be used on federal land in any county in the state. Areas where it is used are marked with signs. While human exposure to this device would be extremely unlikely, it is important to know that this device contains 91% sodium cyanide. Please report any exposure to this device to the Utah Poison Control Center at (800) 222-1222. We thank you in advance for your assistance.

COLCHICINE TOXICITY

Mike Felten, MD
Emergency Medicine Resident

Colchicine is an alkaloid derived from *Colchicum autumnale* and *Gloriosa superba* that is indicated for gout and Familial Mediterranean Fever. In toxic doses it disrupts the microtubular network by binding with microtubilin. This leads to the prevention of mitosis, cell motility, cardiac myocyte contractility and axonal transport. Colchicine has a narrow therapeutic index and results in many cases of inadvertent overdose. American Association of Poison Control Centers report less than ten serious or fatal cases per year. Peak plasma concentrations occur in two hours and dialysis is not effective due to its large volume of distribution. Toxicity is seen in three phases. The first phase occurs within four to twelve hours and is signified by nausea, vomiting and cholera-like diarrhea. If doses exceed 0.5mg/kg then the second phase occurs within one to seven days and is characterized by multisystem organ failure. Clinical effects include ARDS, cardiovascular shock, dysrhythmias, pancytopenia, metabolic acidosis, rhabdomyolysis and sepsis. There is debate about whether sepsis is a result of pancytopenia or direct neutrophil dysfunction from colchicine. Therapy is mainly supportive. The third phase is characterized by rebound leukocytosis and alopecia if the patient survives. Doses over 0.8mg/kg have been fatal. Due to the severe nature of large overdoses, rapid gastrointestinal decontamination is warranted, often including gastric lavage, if within one hour of ingestion. Serial charcoal administration is often recommended due to colcichine's extensive enterohepatic recirculation. There have been case reports of resolution of sepsis and neutrophil rebound with the administration of G-CSF.

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ACUTE ISONIAZID TOXICITY

Jay Blankenship, MD
Emergency Medicine Resident

Isoniazid (INH) is an antibiotic commonly used for the treatment of Mycobacterium tuberculosis. In toxic doses, INH prevents the formation of pyridoxine by inhibiting the enzyme needed to convert pyridoxine to its active form. Pyridoxine is essential in the production of GABA, an inhibitory neurotransmitter. This results in unopposed excitatory neuron activity causing persistent seizures. INH is quickly absorbed, with symptoms from poisoning often seen within 30 minutes of ingestion. The classic triad of INH poisoning is seizures refractory to traditional treatment, profound anion gap metabolic acidosis, and coma. Other clinical effects include vomiting, slurred speech, dizziness, and tachycardia. Pyridoxine is the antidote and should be dosed 1gm IV for every gram of INH ingested. If the amount ingested is unknown, empirically administer 5 grams IV. Seizures should abate shortly after administration of pyridoxine. If seizures persist, the dose may be repeated. If IV pyridoxine is not available, seizures may be treated with high dose benzodiazepines (often only moderately effective). If PO pyridoxine is available, it may be crushed, mixed in normal saline, and administered via NG tube. IV bicarbonate should be administered for blood pH <7.0. Hemodialysis can be used in patients with renal failure; however, it is not often required due to effectiveness of pyridoxine therapy. If a patient presents within 2 hours of ingestion of a toxic amount of INH, prophylactic administration of pyridoxine is appropriate prior to development of neurological symptoms. The treatment is relatively inexpensive and can prevent the need for ICU admission. Asymptomatic patients should be observed for a minimum of 6 hours.

EXTRACORPOREAL MEMBRANOUS OXYGENATION (ECMO) IN ACUTE CARDIOTOXIC INGESTIONS

Brent Kaziny, MD
Pediatric Emergency Medicine Fellow

Patients that ingest cardiotoxic medications, such as beta blockers and calcium channel blockers, tend to be particularly difficult to manage and result in one of the leading causes of poisoning deaths. These patients can present with severe conduction disturbances that can result in refractory cardiac arrest and/or heart failure. While animal models have proven the effectiveness of cardiopulmonary bypass (CPB) in these ingestions, little research has been done to examine the role of ECMO in humans.[1,2] In 2007, Baud recommended the use of "exceptional therapies," such as ECMO and/or CPB in patients with cardiac arrest or cardiogenic shock not responding to conventional therapies.[3] In 2009, Daubin reviewed seventeen cases over a ten year period and found that 13 of their patients survived to discharge with little, if any, permanent sequelae.[4] While more research is needed, ECMO could play a role in the acute ingestion of cardiotoxic medications that presents stable, but decompensate into refractory shock while being treated at a health care facility.

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3. Baud, et al. Clinical review: Aggressive management and extracorporeal support for drug-induced cardiotoxicity. Critical Care 2007, 11:207.
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TOXINS IN THE NEWS

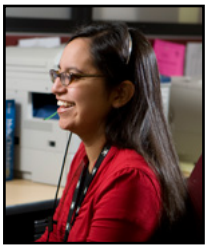
- **Propoxyphene** has been withdrawn from the market due to concerns of cardiac toxicity. The FDA concluded that safety risks outweighed its benefits for pain relief.
- The FDA has notified healthcare professionals and patients that **benzonatate (Tessalon)**, a medication used for cough, can cause tremors, **seizures, coma and death** in overdose. One or two capsules can cause toxic effects in children less than two years of age.

EMPLOYMENT

The UPCC is recruiting for the Assistant Director-Clinical position. This position is a member of the poison center management team and directly supervises approximately 12 specialists in poison information. Licensed pharmacists who meet the position qualifications are encouraged to apply. For additional details, please see our website at www.utahpoisoncontrol.org/employment. Application for the position is made at the University of Utah Human Resource Career page at http://www.hr.utah.edu/careers. (Use keyword "poison" to easily identify the correct job posting.)

MEET THE UPCC STAFF

Poison Information Providers (PIPs)



LISA CHAVEZ joined the UPCC as a PIP in October of 2009. She previously worked as a lab technician for a pharmaceutical company. Lisa was born in Utah and grew up in Arizona and Utah. She enjoys warm weather, music, and a good book. Lisa graduated from BYU in 2008 with a BS in Biochemistry, and is currently studying pharmacy at the University of Utah. Her favorite cases are ones in which she learns something new; she's always impressed by the knowledge of the specialists at UPCC and their willingness to answer any questions.

HEATHER KILLIAN joined the Utah Poison Control Center as a Poison Information Provider (PIP) in August 2009. She is currently a doctor of pharmacy student at the University of Utah and will graduate in May 2011. Following graduation, Heather plans on studying for her pharmacist licensure exams and working while awaiting the birth of her first baby in July. In her free time, Heather enjoys knitting, crocheting, sewing, and blogging. Her favorite follow-up calls are the cases with no effect from exposure and very relieved and appreciative parents.

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*CSPI denotes Certified Specialist in Poison Information.

THANK YOU

The Utah Poison Control Center expresses its sincere thanks to the health care professionals, public health officials and toxicology colleagues that work together to treat and prevent poisonings.

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