Newsletter for the TDM and Toxicology Division of AACC

Spring 2013

Therapeutics & Toxins News

Inside this issue:

The Good, the Bad and the Toxic Side of Elements, Part I: Iron

Frederick G. Strathmann, PhD, DABCC (CC, TC)
University of Utah and ARUP Laboratories, Salt Lake City, Utah

In this issue and the next, we'll take a look at two nutritional elements that can also be considered potentially toxic elements. Both are involved in numerous, essential functions throughout the body and play key roles in each other's biology, yet each can become toxic when the body's ability to properly regulate absorption, storage and excretion is compromised. Element 26 (iron) is the last energetically favorable fusion product formed in dying stars while element 29 (copper) is widely used in handrails and doorknobs to reduce the spread of pathogens. Both serve as a reminder that too much of a good thing can sometimes be bad. Up first is a discussion about the good, the bad and the toxic sides of iron.

Logo for Therapeutic and Toxin Newsletter

""The toxicity of free iron is a consequence of its extensive redox chemistry, with the formation of hydroxyl radicals from the non-enzymatic reaction of Fe^{+2} and hydrogen peroxide of significant importance in cellular, oxidative stress ."

Background

Absorption

The healthy body is greatly proficient at retaining and recycling absorbed iron but has no regulated mechanism for iron excretion. As a result, only 1 mg per day is required to replace iron lost in urine, biliary excretions, sloughing of gut cells or menstruation (1). Absorption of iron starts in the gut, with acid hydrolysis of proteins to liberate bound iron and the conversion of ferric iron (Fe+3) to the more soluble ferrous (Fe+2) form. Organic or heme iron is absorbed at a fairly constant rate while inorganic or non-heme iron has a dynamically regulated mechanism for fine-tuning iron absorption that includes a divalent metal transporter (DMT1) at the apical membrane and ferroportin at the basolateral membrane of enterocytes (2).

Distribution

The toxicity of free iron is a consequence of its extensive redox chemistry, with the formation of hydroxyl radicals from the non-enzymatic reaction of Fe^{+2} and hydrogen peroxide of significant importance in cellular, oxidative stress (3). (continue on page 3)

TDM Spotlight: Methotrexate

Brenda Suh-Lailam, PhD
Clinical Chemistry Fellow, University of Utah

Methotrexate (MTX) is an antifolate drug first introduced through clinical trials in the early 1950's and has since been commonly utilized as an antineoplastic agent amongst other uses (1). Other common and trade names for MTX include: amethopterin, Emtexate, Folex, Mexate, Rheumatrex, and Trexall. The antineoplastic capability of MTX is employed in the treatment of a variety of cancers. High-dose MTX (HDMTX), defined as MTX doses ≥500 mg/m^2 is used in the treatment of certain malignancies such as leptomeningeal metastases, systemic non-Hodgkin lymphoma, acute lymphoblastic leukemia and osteosarcoma. Intermediate-dose MTX (50-500 mg/m^2) is used in malignant gestational trophoblastic disease, while low-dose MTX (<50 mg/m^2) is used in the treatment of some malignancies such as acute promyelocytic leukemia, and various nonmalignant disorders such as rheumatoid arthritis (RA), psoriasis and ectopic pregnancies. Intravenous infusions of MTX are usually followed by leucovorin rescue to terminate the toxic effects of MTX. Successful leucovorin rescue, especially in HDMTX therapy, requires urine alkalinization and hydration to facilitate rapid elimination of MTX by the kidneys (2).

"Methotrexate (MTX) is an antifolate drug that is commonly used as an antineoplastic agent"

The utility of MTX lies in its structural similarity to folic acid. It only differs from folic acid by having two modifications that are lacking in the latter, an amino group at position 4 on the pteridine ring and an N-methyl group at position 10 (figure 1, pg. 8). MTX has 3 possible routes of entry into the cell: (i) via the reduced folate carrier (RFC) which is a transporter of naturally occurring folates and leucovorin, (ii) via the folate receptor (FR) by endocytosis, and (iii) via passive diffusion due to high extracellular concentrations of MTX in situations where the tumor cells have decreased or have no transport ability (3-4). Inside the cell, glutamate residues are added unto MTX by the enzyme folyl polyglutamate synthetase (FPGS), through the process of polyglutamation. Polyglutamated MTX (PGMTX) accumulates inside the cell, as it is not easily transported out of the cell thereby prolonging its intracellular effect (figure 2, pg. 9).

The mechanism of action of MTX is by interfering with folate metabolism as it inhibits the key enzymes in this process (figure 2); (i) Dihydrofolate reductase (DHFR) catalyzes the reduction of dihydrofolate (DHF or FH_2) to the functional metabolic cofactor tetrahydrofolate (THF or FH_4) which participates in 1-carbon transfer reactions, essential for the synthesis of purines, thymidine and amino acids. MTX competitively inhibits DHFR due to its higher affinity for DHFR compared to DHF. Inhibition of DHFR prevents the regeneration of THF from DHF, diminishing the intracellular pool of folate cofactors that are required for de novo synthesis of purines and thymidine. Subsequently, termination of purine and thymidylate synthesis results in the interruption of DNA and RNA synthesis and other essential metabolic reactions. This is the main mechanism by which MTX exerts its antineoplastic effects. (ii) Thymidylate synthetase (TS) which catalyzes the synthesis of deoxythymidylate monophosphate (dTMP) from deoxyuridylate monophosphate (dUMP) is also a target of MTX. (continue on page 7)

Iron
(continued from page 1)

Because of this, the regulation of iron transport involves several proteins to sequester iron for storage, excretion or transport, including transferrin (transport) and ferritin (storage). The majority of iron is transported from enterocytes to target organs or cells by transferrin. Iron not immediately required in the synthesis of iron-containing proteins is stored safely after incorporation into intracellular ferritin (1).

Metabolism
During the absorption, distribution and storage processes, iron undergoes several interconversion events between Fe^{+2} and Fe^{+3}. Once delivered to target organs and cells, iron is incorporated into a wide variety of proteins and enzymes, including hemoglobin, cytochromes, peroxidases and other oxidases (4). A majority of recycled iron comes from the breakdown of protoporphyrin IX in senescent erythrocytes in the reticuloendothelial cells of the liver, spleen and bone marrow by heme oxygenase.

Excretion
Iron has no regulated mechanism for excretion. Excess iron absorbed in enterocytes is stored in ferritin and eliminated from the body as the GI mucosal cells are sloughed.

"The three most common causes of chronic iron overload include excess dietary intake, repeated blood transfusions and hereditary hemochromatosis. Regardless of the cause, the pathological consequences of chronic iron overload are analogous."

Pathophysiology of Overload
Acute Toxicity:
Acute ingestion can cause severe gastrointestinal damage leading to increased uptake of iron by non-specific means with distribution and damage to most major organs.

Symptoms
Acute toxicity occurs within hours of ingestion and is often categorized into five clinical stages (5) but is of limited benefit in practical management. Depending upon the severity of ingestion, symptoms can include abdominal pain, diarrhea and vomiting with cyanosis, metabolic acidosis, seizure, coma and cardiac collapse among the more concerning and sever complications.

Causes
For adults, a common cause of unintentional exposure is ingestion of high-dose iron supplements while in children chewable vitamin preparations are of concern. Blister packs and limitations on the number of pills dispensed have dramatically reduced the incidence of iron overload in adults. Similarly, the reduced iron content in children's vitamins has reduced the likelihood of iron toxicity (4). Lastly, patients with renal failure and chronic anemia can be at risk for iron overload from parenteral nutrition.

Treatments
Whole bowel irrigation can be an effective decontamination procedure for acute iron toxicity as absorption to activated charcoal is poor and the efficacy of gastric

Iron
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lavage can be limited due to the poor solubility of iron tablets and their propensity for mass formation. In both acute and chronic iron overload, deferoxamine is the chelator of choice.

Chronic Toxicity:
The three most common causes of chronic iron overload include excess dietary intake, repeated blood transfusions and hereditary hemochromatosis. Regardless of the cause, the pathological consequences of chronic iron overload are analogous.

Symptoms
A hallmark of chronic iron overload is the increased deposition of iron in organs such as the liver and heart. The "classic triad" of bronzing skin, cirrhosis of the liver and diabetes mellitus are present in a subset of individuals with severe iron overload (1). Chronic elevations in iron result in hemosiderosis as ferritin degrades to hemosiderin and excess iron is stored as less chemically active forms of iron. Hemochromatosis is the deposition of excess iron into tissues, often resulting in fibrosis. A growing area of interest is the presence of non-transferrin bound iron (NTBI) in diseases not primarily categorized as iron overload such as alcoholic liver disease, diabetes and end-stage renal failure (6).

Causes
There are numerous categories of hemochromatosis and anemias that lead to chronic iron overload and are categorized as primary (inherited) or secondary syndromes (7). Primary syndromes include HFE (a protein that modulates the expression of hepcidin – discussed later) and non-HFE related hemochromatosis (Type 1), Juvenile Hemochromatosis (Type 2), Transferrin receptor 2 hemochromatosis (Type 3) and ferroportin disease (Type 4). Secondary iron overload syndromes include iron-loading anemias, chronic liver disease, treatment induced and unclassified syndromes such as Aceruloplasminemia, African iron overload or Neonatal iron overload.

"In both acute and chronic iron overload, deferoxamine is the chelator of choice."

Treatments
Phlebotomy remains the most effective and safe treatment for chronic iron overload and continues on a routine basis until serum ferritin is below 50 ng/mL. Careful monitoring of hemoglobin is often warranted if the risk of anemia is high (8). An undesirable side effect of phlebotomy is an increase in NTBI and has been hypothesized as a potential complication for miscellaneous diseases not primarily categorized as iron overload with speculation of the efficacy of oral chelation therapy as an alternative (6).

Lab Testing for Toxicity
Acute:
Acute iron overload is largely a clinical diagnosis, but laboratory testing can be used to determine severity and success of treatment. Serum iron concentration can be useful; however, interferences can confound interpretation during chelation treatment unless an atomization method such as atomic absorption is used.

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One might expect that total iron-binding capacity (TIBC) would be helpful, as iron concentrations less than the TIBC would be less likely to have excess unbound iron. In reality, TIBC has been proven to be inaccurate and falsely elevated in acute iron overdose (9). Anion-gap metabolic acidosis and an elevated lactate may be found in severe ingestions (4).

Chronic:
Serum iron concentration and transferrin saturation and are the most common noninvasive tests for suspected chronic iron overload. In addition, ferritin and markers of acute liver injury such as aspartate aminotransferase can be helpful in determining the need for further clinical intervention. The need for liver biopsies in establishing a diagnosis in iron-overload conditions has been reduced through the development of noninvasive methods such as genetic testing where applicable and imaging analyses. Liver biopsies do remain important in the evaluation of hepatic damage and unclassified genetic causes (10).

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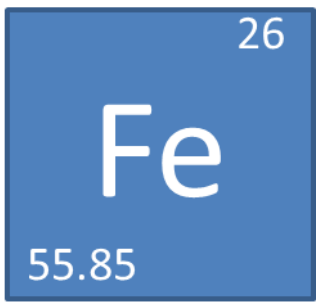
Areas of Interest
Copper plays an important and often overlooked role in iron homeostasis through constant interactions during absorption, transport and iron recycling. As noted above, a genetic lack of ceruloplasmin (Aceruloplasminemia) is a secondary syndrome of iron overload as ceruloplasmin and the associated copper ion cofactor is the major iron oxidation protein (8).

Hepcidin has become a central theme in a majority of the primary iron overload syndromes. Hepcidin, a protein produced predominantly by hepatocytes, counteracts the function of ferroportin by inducing its degradation resulting in a subsequent decrease in circulating iron. The entry of hepcidin into routine clinical assessment has been hampered by analytical obstacles inherent to the protein itself and a lack of harmonization of available assays (11).

For Next Time
The Good, the Bad and the Toxic Sides of Iron and Copper, Part II

Why then, can one desire too much of a good thing?
- Rosalind, from Shakespeare's *As You Like it (1600)*



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"Acute iron overload is largely a clinical diagnosis, but laboratory testing can be used to determine severity and success of treatment."

Methotrexate
(continued from page 2)

The inhibition of TS [which uses methylene-THF (CH_2-FH_4) as a cofactor] by MTX, interrupts thymidine synthesis which is vital for DNA synthesis. (iii) MTX also inhibits the enzymes glycinamide ribonucleotide transformylase (GARFT) and aminoimidazole carboxamide transformylase (AICARFT) which are involved in the synthesis of the purines, adenosine and guanine, using N(10)-formylTHF (10-CHO-FH_4) as a cofactor (figure 2). This results in a deficiency of purines needed for DNA and RNA synthesis. By inhibiting the key enzymes involved in folate metabolism, MTX allows for the depletion of intracellular pools of reduced folates, which are required by normal dividing cells in large amounts to maintain continuous purine and thymidine synthesis. Rapidly dividing malignant cells require reduced folates in even greater amounts as such proliferation is negatively impacted by a decrease in reduced folates. As a result of the depletion of reduced folates, there is cessation of thymidine and purine synthesis, DNA synthesis, and eventually cell death (5).

""By inhibiting the key enzymes involved in folate metabolism, MTX allows for the depletion of intracellular pools of reduced folates, which are required by normal dividing cells in large amounts to maintain continuous purine and thymidine synthesis."

In contrast to the antineoplastic effects of MTX, it is uncertain how the anti-inflammatory effects of MTX are achieved in RA. Several possibilities have been proposed. One school of thought credits these anti-inflammatory effects to increasing extracellular concentrations of adenosine as a result of dephosphorylation of adenine nucleotides by the enzyme ecto-5'-nucleotidase (6-7).

MTX is not selective for cancer cells; as such cytotoxicity also occurs in normal tissue. To improve the safety of MTX, normal cells are rescued from toxicity by providing them with reduced folates, which allows them to bypass the metabolic block initiated by MTX. The form of reduced folate commonly used for this purpose is leucovorin (folinic acid, N5-formyl-tetrahydrofolate, citrovorum factor) (figure 2) (8). Leucovorin selectively rescues normal cells but does not rescue cancer cells; however, this preferential rescue is not well understood. Leucovorin competes with MTX for DHFR binding sites allowing for enzyme reactivation and restoration of reduced folate stores necessary for DNA/RNA synthesis. In the treatment of malignancies, administration of HDMTX by prolonged intravenous infusion is followed by leucovorin rescue within 24 to 36 hours of initiating infusion. Leucovorin rescue is commonly done by administration of 10 mg/m^2 IV or 15 mg/m^2 of leucovorin calcium orally every six hours until serum MTX levels decline to less than 0.05 to 0.1 µmol/L (9). Renal insufficiency causes delayed MTX elimination, to achieve successful rescue in such situations, higher concentrations of leucovorin are needed.

Despite the effectiveness of MTX as an antineoplastic agent, malignant cells can have innate or acquired resistance to MTX. Innate resistance to MTX is illustrated in patients with acute myeloid leukemia (AML) where leukemic cells lack the ability to polyglutamate MTX leads. This makes MTX an unsuitable chemotherapeutic agent for the treatment of AML (10). Several mechanisms of acquiring MTX resistance exist. Resistance can be caused by mutations in the carrier proteins or DHFR enzyme, resulting in either decreased MTX uptake or decreased affinity for MTX respectively. Also, decreased enzyme activity (DHFR or FPGS or TS activities) can result in reduced sensitivity to MTX (11-13).

Methotrexate
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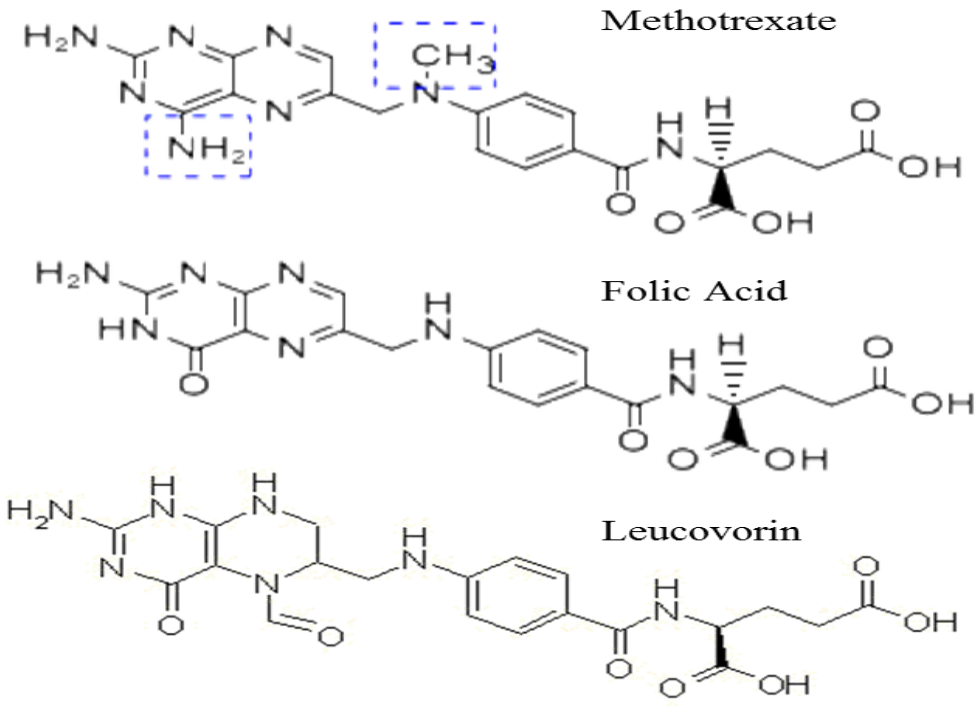
Toxicity due to MTX can occur with both high- and low-dose therapies. The major side effects that result from low-dose MTX therapy are usually not life-threatening, but can result in premature termination of an otherwise effective drug. These side effects include hepatotoxicity, pulmonary toxicity, myelosuppression, and nephrotoxicity (14). On the other hand, patients on HDMTX therapy can develop potentially life-threatening effects, some of which can be associated with the amount of drug and duration of drug exposure. Some of the side effects associated with HDMTX include hepatotoxicity, nausea, vomiting, stomatitis, nephrotoxicity, as well as hematologic, pulmonary, neurologic and dermatologic toxicities (15-16).

To minimize MTX toxicity, plasma MTX concentrations are routinely monitored following HDMTX infusion therapy to determine the rate of drug clearance and the amount of leucovorin necessary for rescue. Routine therapeutic drug monitoring (TDM) of MTX entails monitoring plasma MTX concentrations to very low (<0.05 µmol/L) or undetectable levels. It is, therefore, necessary that an assay for MTX TDM have the ability to detect MTX to very low concentrations. Several commercial immunoassays are available for the quantitative measurement of plasma MTX with varying sensitivities. The most sensitive of these assays has a sensitivity of 0.02 µmol/L (17-18).

""Patients on HDMTX therapy can develop potentially life-threatening effects, which include, hepatotoxicity, nephrotoxicity, nausea, vomiting and neurologic and dermatologic toxicities"

Figure 1: Methotrexate **and leucovorin are structurally very similar to folic acid [figure modified from (19–20)].**



Methotrexate
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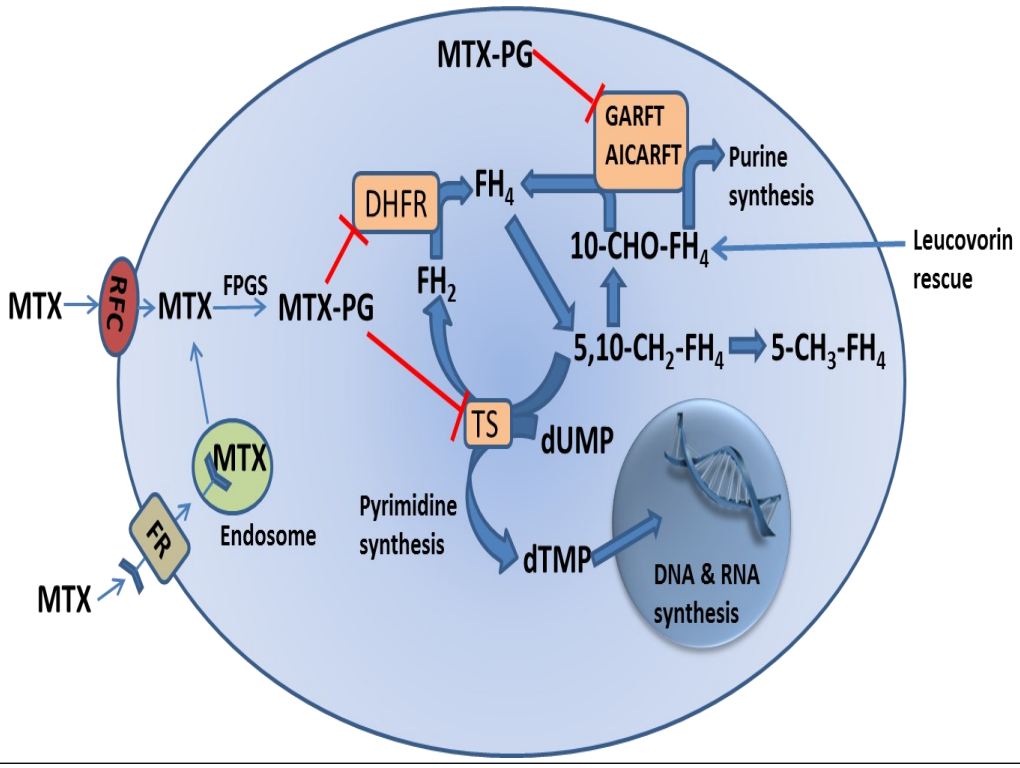
Table 1: Methotrexate Pharmacokinetics (1)

Absorption	Variable
Volume of Distribution (Vd)	0.4-0.8 L/Kg
Oral Bioavailability	~60% (with moderate doses, lower at higher doses)
Peak Plasma Concentrations	1-2 h
Plasma Protein Binding	50-70%
Metabolism	The metabolite 7-hydroxymethotrexate is relatively inactive
Half-life (T½)	5-9 h
Toxic Plasma Concentration	24 h, $>10^{-5}$ molar
Elimination	81% in urine 1% in feces

"To minimize MTX toxicity, plasma MTX concentrations are routinely monitored following HDMTX infusion therapy to determine the rate of drug clearance and the amount of leucovorin necessary for rescue."

Figure 2: Folate metabolism and the mechanism of action of methotrexate.
[MTX-PG = polyglutamated MTX;RFC = Reduced folate carrier; FR = Folate receptor; FPGS = Folyl polyglutamate synthetase; DHFR = Dihydrofolate reductase ; TS = Thymidylate synthetase ; GARFT = Glycinamide ribonucleotide transformylase; AICARFT = Aminoimidazole carboxamide transformylase ;FH_2 = Dihydrofolate; FH_4 = Tetrahydrofolate; 10-CHO-FH_4= N(10)-formyltetrahydrofolate; 5,10-CH_2-FH_4 = 5,10-methylenetetrahydrofolate; 5-CH_3-FH_4 = 5-methyltetrahydrofolate; dUMP = deoxyuridylate monophosphate; dTMP = deoxythymidylate monophosphate]



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"Leucovorin selectively rescues normal cells but does not rescue cancer cells."

UPCOMING MEETINGS OF INTEREST

MIDWEST ASSOCIATION FOR TOXICOLOGY AND THERAPEUTIC DRUG MONITORING (MATT)
Annual Meeting
April 25—26, 2013, Cleveland Clinic, Cleveland, OH
www.midwesttox.org

SOUTHWESTERN ASSOCIATION OF TOXICOLOGISTS
Annual Meeting
May 16-18, 2013, Fort Worth Hilton, Fort Worth, TX
www.sat-tox.org

ASSOCIATION OF CLINICAL SCIENTISTS (ACS)
Annual Meeting
May 22—25, 2013, Omni Parker House Hotel, Boston MA.
www.clinicalscience.org

AMERICAN ASSOCIATION FOR CLINICAL CHEMISTRY (AACC)
Annual Meeting
July 28—August 1, 2013, Houston TX.
www.aacc.org

""TDM/Tox Division lunch meeting will be held on July 29th from 12-2pm."

THE INTERNATIONAL ASSOCIATION OF FORENSIC TOXICOLOGISTS (TIAFT)
Annual Meeting
September 2—6, 2013, Madeira, Portugal
www.tiaft.org

INTERNATIONAL CONGRESS OF THERAPEUTIC DRUG MONITORING & CLINICAL TOXICOLOGY (IATDMCT)
September 21-26, 2013, Grand America Hotel, Salt Lake City, UT.
www.iatdmct.org

THE AMERICAN ACADEMY OF CLINICAL TOXICOLOGY
North American Congress of Clinical Toxicology (NACCT)
September 27—October 2, 2013, Hyatt Regency Atlanta, GA.
www.clintox.org

SOCIETY OF FORENSIC TOXICOLOGISTS (SOFT)
Annual Meeting
October 28—November 1, 2013, Orlando, FL.
www.soft-tox.org

Please contact Dr. Kamisha Johnson-Davis at kamisha.johnson-davis@aruplab.com if you are interested in joining the editorial board or if you have ideas or article contributions for this newsletter.

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DRUGS IN THE NEWS

Recent FDA Approved Drugs

Invokana (canagliflozin)
Treatment: **Type 2 Diabetes**
Approved: March 2013

Osphena (ospemifene)
Treatment: **Dyspareunia and vulvar and vaginal atrophy due to menopause**
Approved: March 2013

Tecfidera (dimethyl fumarate)
Treatment: **Relapsing multiple sclerosis**
Approved: March 2013

Quartette (levonorgestrel/ethinyl estradiol and ethinyl estradiol)
Treatment: **Prevention of contraception**
Approved: April 2013