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TOXICOLOGY LETTER

COMPRISING THE LONG ISLAND, NEW YORK CITY, RUTH LAWRENCE, UPSTATE NEW YORK, AND WESTERN NEW YORK POISON CENTERS

A Brief Review of Xenobiotic Induced Hyperthermic Syndromes

Contribution by Nicholas Fusco, PharmD candidate, School of Pharmacy and Pharmaceutical Sciences, SUNY at Buffalo, and Ashley N. Webb, MSc, Western New York Poison Center

Question:

An RN specializing in infectious disease called the poison center concerning a patient who presented with an elevated temperature of 106.6°F, tachypnea, tachycardia, flushed skin, urinary retention, and sluggish pupils. It has been 3 days and the patient is now intubated and sedated with normal vitals but with an elevated CPK of 6100 mg/dl. He had a history of cocaine abuse, no prescribed medications, and had been out with friends the night prior to presentation. After returning home with complaints of feeling ill, he became unresponsive. The treating team has ruled out infection as a cause for his symptoms and wants to know if this may be related to a toxic exposure.

Answer:

Many xenobiotics can result in an imbalance between heat production and heat loss leading to hyperthermia including antipsychotics, serotinergics, sympathomimetics, inhaled anesthetics, and anticholinergics.[1] Hyperthermia in this situation is often accompanied by muscle rigidity and may lead to extensive rhabdomyolysis and hyperkalemia resulting in disseminated intravascular coagulation (DIC), renal failure, coma, and death.[1]

In the hypothalamus, neurons are sensitive to slight changes in core body temperature.[1] The hypothalamus signals the body to dissipate heat through cooling mechanisms such as evaporation, convection, conduction and radiation but impairment of any of these mechanisms results in hyperthermia.[2] Management of hyperthermia is focused on halting excess heat production and enhancing cooling mechanisms. The initial rise in core body temperature results from a hypermetabolic state often from agitation, muscle rigidity, and / or impaired sweating rather than a change in the body's core temperature set point as seen in other disease states.[9] For this reason, antipyretics that target the hypothalamus to reduce the set point are of little value in drug-induced hyperthermia. After the inciting agent has been discontinued, general measures to quickly lower

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core body temperature may include cooling blankets, ice packs placed at the groin, axilla, and neck, cool water misting and ventilation with a fan, and cool IV fluids. More extreme measures may include ice-water submersion, iced colonic peritoneal lavage, and extracorporeal partial bypass.[1,2,9] As the core temperature approaches 38-40° C, active cooling is stopped. Benzodiazepines are employed to combat rigidity and agitation, or shivering induced by active cooling. If benzodiazepines are ineffective, barbiturates are employed to slow the metabolic rate. Ultimately, in extreme cases where agitation and rigidity cannot be controlled, intubation, sedation, and paralysis with a non-depolarizing paralytic (vecuronium, pancuronium…) prevent further heat production from continuous CNS and / or muscle stimulation. In this situation, continuous EEG monitoring will indicate the presence of any seizure activity requiring additional therapy.[9] Core temperature monitoring is imperative as a normal axillary temperature is not always indicative of euthermia in these patients.[1] Although drug-induced hyperthermia is precipitated by a variety of agents, the clinical presentation is similar and appreciation for the differences is critical given the suspected offending agent may alter the choice of therapy.

What is malignant hyperthermia?

Malignant hyperthermia is a rare, pharmacogenetically determined response to inhaled anesthetics and depolarizing paralytics, including succinycholine.[1] It is likely precipitated by ryanodine receptor dysfunction and therefore an inappropriate handling of calcium by skeletal muscle.[2] The elevated calcium uncouples oxidative phosphorylation leading to prolonged, sustained fiber contractions.[2] This hypermetabolic state rapidly depletes stored energy, increases oxygen consumption, and destroys cell membrane integrity.[3]

How do I recognize malignant hyperthermia?

Symptom onset is minutes to hours after administration of the offending agent, characterized by a clinical triad of hyperthermia, lactic acidosis (result of ATP depletion), and diffuse muscle rigidity as well as tachycardia, and tachypnea.[2,3] Laboratory anomalies include elevated serum creatinine kinase and potassium.[3] A family history of, or previous reactions to inhaled anesthetics or depolarizing muscle relaxants should increase suspicion, although 24-50% of patients with malignant hyperthermia may have undergone aesthesis without incident.[2,4] Malignant hyperthermia is rarely seen in exposures less than 15 minutes.[5]

How do I treat malignant hyperthermia?

Stopping exposure to the offending agent is critical and patients should be hyperventilated to compensate for the ensuing acidosis.[2] Sodium dantrolene, a direct skeletal muscle relaxant, is the mainstay of pharmacologic therapy.[2] Dantrolene blocks calcium release from the sarcoplasmic reticulum, reducing skeletal muscle hyperactivity.

What is serotonin syndrome?

Unlike malignant hyperthermia, serotonin syndrome is an idiopathic consequence of excess serotonin agonism at central and peripheral receptors. Toxicity results from excess receptor (5-HT_{1A}, 5-HT_{2A}) stimulation, increased release of serotonin presynaptically, decreased serotonin reuptake, and decreased serotonin metabolism.[6] Symptoms extend from excess adrenergic tone in the CNS and periphery as a result from medications that increase serotonin including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and serotonin reuptake inhibitors (SSRIs). Other not intuitively obvious offenders include dextromethorphan, meperedine, L-dopa, bromocriptine, tramadol, lithium, and linezolid.[3]

MAOIs that inhibit the isoenzyme A are often implicated in serotonin syndrome in combination with other serotinergic agents. While most antidepressants increase serotonin through a decrease in reuptake, MAOIs increase available serotonin in the synapse. There have been cases of serotonin syndrome induced by the MAOI isoenzyme B, deprenyl, but this is likely through a loss of iosenzyme receptor specificity with increasing doses. The hydrazines (phenelzine and isocarboxazid) antagonize GABA in addition to their adrenergic effects increasing the likelihood of CNS excitation and seizures.

Although lithium has been implicated as a cause for serotonin syndrome in combination with other antidepressants, distinguishing lithium toxicity from the hypermetabolic state is difficult. Symptoms of lithium toxicity may include altered mental status, agitation, diaphoresis, hyperreflexia, myoclonus, and fever - all symptoms present in serotonin excess (see below). This is not unexpected as lithium may enhance the release of serotonin or work, possibly, as an agonist at 5HT receptors. When the precipitating agent is unknown, the patient history and a lithium level require careful evaluation.

How do I recognize serotonin syndrome?

The common triad of symptoms include mental status changes, autonomic hyperactivity, and neuromuscular abnormalities and range from barely noticeable to lethal.[6] Progression results in metabolic acidosis, and elevated creatinine, creatinine kinase, and serum aminotransferases followed by DIC.[6] Rapid onset, minutes to

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hours, occurs following excess serotinergic tone. Laboratory tests are not used to confirm the diagnosis, but serotonin syndrome is suspect in the presence of at least three of the following signs / symptoms: mental status changes, tremor, agitation, myoclonus, hyperreflexia, hyperthermia, shivering, ataxia, and / or diarrhea.[1]

How do I treat serotonin syndrome?

Generally self-limiting, serotonin syndrome frequently resolves in 24 – 36 hours after removal of the offending agent. Supportive care will usually suffice, but non-specific serotonin antagonists, chlorpromazine, cyproheptadine, and propranolol, show benefit in several case reports, (although lack definitive evidence for symptom resolution in most cases.[1] Control of agitation and hyperactivity with benzodiazepines, management of autonomic instability, and resolution of hyperthermia with active cooling systems are the cornerstone of care.[3] Intubation and paralysis with a non-depolarizing paralytic should be considered in severe cases to minimize excess muscle contractions. Propofol or barbiturates adjunctively decrease metabolic rate. Chemical restraint is preferred over physical to avoid worsening hyperthermia and rhabdomyopathies.[6]

What is neuroleptic malignant syndrome (NMS)?

NMS is a rare, potentially fatal, idiosyncratic reaction characterized by muscle rigidity, hyperthermia, autonomic instability, and altered mental status.[2] Precipitating agents include high potency neuroleptics, atypical antipsychotics, and some non-neuroleptic medications (metoclopramide, promethazine).[2] Additional contributions are high ambient temperatures, dehydration, underlying brain damage, and dementia.

Several pathophysiologic mechanisms are proposed including dopaminergic antagonism (alteration of the thermoregulatory pathways in the anterior hypothalamus and increasing extrapyramidal hyperactivity) or direct myotoxicity (the mechanism of increased muscle metabolism is unknown).[1] It was recently suggested that sympathetic nervous system (SNS) induced hyperactivity results in skeletal muscle hyperactivity and predisposed individuals may elicit a response under emotional or physiological stress.[3] This is supported by markedly elevated catecholamines in the cerebral spinal fluid of individuals with NMS.[3]

How do I recognize NMS?

NMS occurs twice as often in men than in women and also presents as a triad of symptoms - hyperthermia, encephalopathy, and skeletal muscle rigidity.[1,7] Onset is insidious and symptoms often develop within four weeks of the start of therapy or an increased medication dose. Initial altered mental status, delirium and somnolence, progresse to coma and mutism.[2] Muscle rigidity and motor abnormalities are commonly described as "lead-pipe" and resistant to passive movement.[2] Autonomic instability is indicated by tachycardia, diaphoresis, sialorrhea, pallor, labile blood pressure, and incontinence.[8] Nonspecific, laboratory anomalies include significant elevations in serum creatinine, creatinine kinase, and transaminases in addition to a leukocytosis.[8] Following the use of neuroleptics or the withdrawal of levodopa, a simple dystonia can occur and may be confused for NMS. This can be associated with hyperthermia, tachycardia, diaphoresis, muscle rigidity, and mild rhabdomyolysis, but are differentiated from NMS by their response to centrally acting anticholinergic agents.[1] Up to 30% of patients rechallenged with similar medications may experience symptom reoccurrence.

How do I treat NMS?

Death results from respiratory failure, cardiac dysfunction, aspiration, pulmonary embolism, pneumonia, acute renal failure, or DIC.[2] Early recognition, discontinuation of offending agents, and supportive care are crucial to patient survival.1 Commonly recommended therapies include bromocriptine and dantrolene. Dantrolene, as discussed above, acts peripherally and its efficacy in NMS, an aberration in the CNS, is controversial. Bromocriptine, a centrally acting dopamine analog, relieves central neurologic and autonomic symptoms. Its efficacy in NMS as not been thoroughly documented. All neuroleptic agents should be held for at least two weeks following an event of NMS.[2]

Are there other agents that cause hyperthermia?

Anticholinergic and sympathomimetic toxicity may also manifest a life-threatening hyperthermia. Anticholinergic toxicity resulting from excess blockade of central and peripheral muscarinic acetylcholine receptors is accomplished by antihistamines, belladonna alkaloids, anti-parkinsonion agents, and tricyclic antidepressants.[1] Blockade results in impaired sweating and therefore, a loss of evaporative cooling. The clinical presentation manifests both central toxicity (altered mental status, confusion, agitation, seizures, tremor, myoclonus, hallucinations) and peripheral toxicity (dry mouth / axilla, mydriasis, sinus tachycardia, bowel paresis, and urinary retention).[1, 3] Peripheral symptoms and the absence of muscle rigidity differentiate anticholinergic toxicity from other hyperthermic syndromes.[1]

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Sympathomimetic toxicity results from increased activity of central catecholamines, norepinephrine, dopamine, and serotonin, usually after the administration of monoamine oxidase inhibitors, cocaine, amphetamines, or methamphetamine derivatives.[1] Ecstasy, or 3,4-methylenedioxymethamphetamine, has been increasingly associated with death as a result of sympathomimetic toxicity.[7] Sympathomimetic toxicity impairs cutaneous heat loss through vasoconstriction, impaired behavioral response to intoxication, and increased muscle activity through agitation, seizures, and muscle rigidity (to a lesser extent).[8] The clinical presentation includes agitation, altered mental status, confusion, panic, hallucinations, seizures, and progression to coma.[2] Severely toxic, hyperthermic patients may also develop rhabdomyolysis, renal failure, metabolic acidosis, DIC, and / or cardiovascular abnormalities.[2]

Treatment for both anticholinergic and sympathomimetic toxicity includes removal of the precipitating agent, rapid and aggressive cooling, and benzodiazepine or barbiturate administration for agitation and seizures.[3]

Summary

Hyperthermia is caused by a variety of pharmacologic agents and different mechanisms. Successful treatment hinges on early delineation of the precipitating agent and removal of such, followed by provision of aggressive supportive care. Although many hyperthermic syndromes present in a similar manner, the patient's history and recognition of the differences between each syndrome can potentiate an accurate diagnosis. Most syndromes do not have specific pharmacologic treatments, and treatment remains primarily supportive.

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MANIFESTATIONS OF SEROTONIN SYNDROME[6]

	MILD	MODERATE	SEVERE
VITAL SIGNS	Tachycardia	Tachycardia Hypertension Hyperthermia	Tachycardia Severe Hypertension Hyperthermia
AUTONOMIC	Shivering Diaphoresis Mydriasis	Hyperactive bowel sounds Diaphoresis Mydriasis	Exaggeration of mild / moderate symptoms
NEUROLOGIC	Tremor / Myoclonus Hyperreflexia	Clonus Lower > upper extremities	Muscle rigidity Hypertonicity Clonus
MENTAL STATUS	Confusion	Mild agitation Hypervigilance Pressured Speech	Agitated delirium Seizures

Methylxanthine Toxicity

Zhanna Livshits, M.D., Lewis S. Nelson, M.D.

Case Summary:

A 19 year-old girl with obesity, asthma, hypertension, diabetes mellitus, and depression presents to the Emergency Department with an episode of vomiting, 2 hours after reportedly ingesting 39 tablets of her medication for asthma. This is her twelfth suicide attempt.

The patient's initial vital signs are as follows: BP, 149/74 mmHg; HR, 115 bpm; T, 97.9˚F; RR, 22/min; SpO2 97% RA. She is awake and alert, and physical exam is significant for slightly dilated, reactive pupils (4 mm bilaterally) and diaphoresis. She states that she would allow peripheral IV placement and drink activated charcoal, though she refuses all other interventions. Her initial laboratory evaluation is significant for the following: serum potassium, 3.1 mEq/L; anion gap 12 mEq/L; serum glucose, 104 mg/dL; serum lactate, 0.9 mg/dL; and undetectable acetaminophen and salicylate concentrations. Her ECG demonstrates sinus tachycardia with normal QRS and QT intervals.

A few hours later, the patient states that she feels "jittery," and continues to vomit intermittently despite administration of antiemetic agents. Repeat vital signs are as follows: BP, 150/53 mmHg; HR, 130 bpm; RR, 24/min; SpO2, 97% RA. Her serum potassium concentration decreases to 2.5 mEq/L and serum glucose increases to 189 mg/dL.

Assuming she ingested an "asthma medication," which is the most likely?

The agents used in asthma management include ß2-adrenergic agonists, antimuscarinic agents, corticosteroids, leukotriene antagonists, and, rarely, methylxanthines.

Antimuscarinic inhalational agents, such as ipratropium, typically do not cause significant clinical anticholinergic findings since their systemic absorption is minimal. Corticosteroids produce minimal adverse effects following an acute ingestion. The same is true of the leukotriene inhibitors.

ß2-adrenergic agonists, such as albuterol, produce bronchiolar smooth muscle relaxation. The toxicity from these agents includes vital sign abnormalities, metabolic disturbances, and neuroexcitation. Methylxanthines (MX), such as theophylline, are indirect acting ß-adrenergic agonists and share many clinical similarities to albuterol.

Based on the clinical findings and assuming the history is correct, the patient's presentation is most consistent with either methylxanthine or ß2-adrenergic agonist toxicity. However, albuterol is available only as an inhalational liquid and an oral liquid, not in a solid form, while theophylline is available both in immediate and sustained-release oral solid forms. The sustained release form is far more widely used due to its enhanced pharmacokinetic profile.

Case Continuation

Her initial theophylline serum concentration, at approximately two hours post-ingestion is 37.5 µg/mL, with a peak serum concentration of 65.47 µg/mL. Therapeutic serum concentrations for patients with asthma are 5-15µg/mL

What is the mechanism of action of theophylline?

The commonly available MXs include theophylline (1,3-dimethylxanthine) and caffeine (1,3,7 trimethylxanthine); theobromine (3,7 methylxanthine) is the MX found in chocolate.

MXs are structural analogs of adenosine and function at low concentrations as an antagonist of adenosine at its receptors, which are located on nerve terminals within the autonomic and central nervous systems. As adenosine is a primarily inhibitory neurotransmitter, its antagonism is associated with neuronal excitability. Through adenosine antagonism, MXs indirectly promote the release of endogenous catecholamines such as epinephrine (from the adrenal gland), thereby acting indirectly as both a ß1 and ß2 adrenergic agonist. The adrenergic effects result in increased inotropy and chronotropy from the ß1 agonism, as well as peripheral vasodilatation from the ß2 agonism.

At supratherapeutic doses, methylxanthines also competitively inhibit phosphodiesterase, the enzyme that breaks down cyclic adenosine monophosphate (cAMP). Since ß agonists (e.g., epinephrine) exert their

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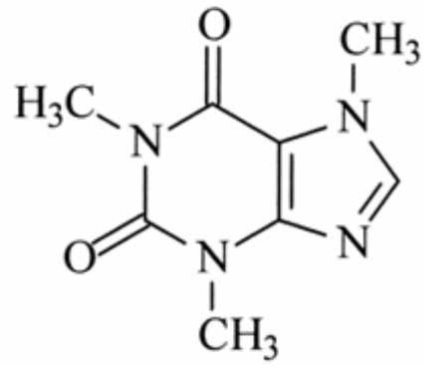
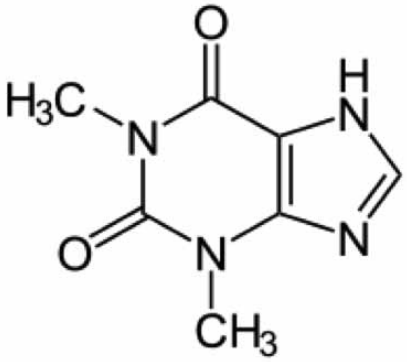
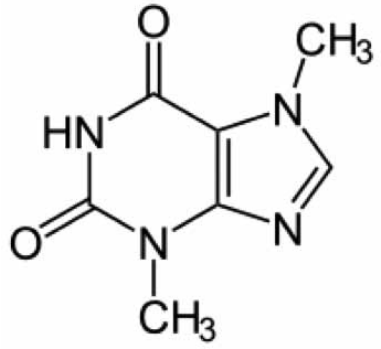


Caffeine
1,3,7-thimethylxanthine



Theophylline
1,3-dimethylxanthine



Theobromine
3,7-dimethylxanthine

effects via elevation of intracellular cAMP concentrations, this inhibition of cAMP metabolism leads to exaggerated ß-adrenergic clinical effects.

What are the clinical signs of MX toxicity?

MXs are associated with multiorgan system effects; of greatest clinical consequence are the cardiovascular and neurological effects. Neurologic findings include anxiety, agitation, tremor, irritability, and seizures; status epilepticus may occur.

The clinical findings in patients with acute theophylline toxicity differ from those noted with chronic toxicity. Patients who are chronically exposed to theophylline may develop significant toxicity following a relatively small increase in dose. The clinical effects following chronic overdose are more subtle, though equally as concerning, as those noted in patients with acute overdose. Furthermore, in patients with equivalent clinical severity following overdose, patients with chronic overdose typically have serum concentrations that are lower than those with acute overdose. This likely is due to a greater tissue burden in patients with chronic overdose.

The combined ß-adrenergic effects produce a characteristic widened pulse pressure, noted as elevated systolic (i.e., inotropy) and reduced diastolic (i.e., vasomotor tone) components (normal is about 40 mmHg). Hypokalemia, hypomagnesemia, hypophosphatemia, hyperglycemia, and metabolic acidosis with an elevated serum lactate concentration also occur. Stimulation of the respiratory center may produce a respiratory alkalosis, and when combined with a metabolic acidosis may simulate salicylate poisoning or sepsis.

Sinus tachycardia is nearly universal in patients with acute theophylline toxicity. The degeneration of sinus tachycardia into more malignant tachydysrhythmias is a common cause of fatality. Tachydysrhythmias include supraventricular tachycardia (common), multifocal atrial tachycardia, atrial fibrillation, premature ventricular contractions, and ventricular tachycardia. The presence of hypokalemia or hypomagnesemia may predispose to the development of dysrhythmias. Myocardial ischemia and infarction may occur. Dysrhythmias should be expected with serum concentration of 40-80 μg/mL in chronically poisoned patients and greater than 80 μg/mL in those with acute overdose.

How does caffeine differ from theophylline?

Although caffeine is widely available, from coffees to energy drinks to nonprescription stimulants, severe caffeine toxicity remains uncommon. The presence of three methyl functional groups enhances caffeine's penetration across the blood brain barrier resulting in exaggerated central nervous system effects.

A generic brewed 240mL (8 oz) cup of coffee contains from 95-200 mg of caffeine. Caffeinated black tea may contain up to 120 mg of caffeine in 240 mL (8 oz). "Maximum strength" caffeine tablets contains approximately 200 mg of caffeine. It is estimated that ingestion of 1 gram of caffeine by an adult or 35 mg/kg may cause acute clinical toxicity, including vomiting, tremor, tachycardia, and confusion. Based on case reports, the lethal dose of caffeine is suggested to range between 150 to 210 mg/kg. Those who ingest caffeine regularly develop tolerance.

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What is the management of patients with theophylline poisoning?

The management of theophylline toxicity includes: laboratory evaluation for the aforementioned abnormalities and theophylline concentration, ECG, gastrointestinal decontamination, cardiovascular and neurological toxicity management, as well as assessment for necessity of enhanced elimination.

Patients with emesis should receive antiemetics followed by a dose of activated charcoal if there are no contraindications (e.g. change in mental status or sedation, active vomiting, co-ingestion of a caustic agent). Whole bowel irrigation may reduce the gastrointestinal transit time of sustained release preparations and should be used liberally. Note that patients who ingest sustained-release theophylline preparations may have a delayed onset and prolonged duration of toxicity.

Hypotension may be managed with isotonic intravenous fluid. Hypotension that is refractory to fluids, likely due to ß2-mediated peripheral vasodilatation, may be managed with α_1 agonists such as phenylephrine or norepinephrine. Hypotension refractory to both intravenous fluids as well as vasopressor agents, may be treated with non-selective ß-adrenergic antagonists such as propranolol or ß1-selective esmolol or metoprolol. Propranolol may lead to bronchospasm in patients with reactive airways diseases such as asthma. Although it seems counterintuitive to administer a ß-adrenergic antagonist to a hypotensive patient, both reduction in vasodilation (ß2) and control of tachycardia (ß1) may both improve hemodynamics and prevent the development of malignant tachydysrhythmia.

Patients with MX-induced SVT should receive intravenous diltiazem. Adenosine is not expected to work since MXs are adenosine antagonists. Electrical cardioversion may not produce sustained effects since the theophylline concentration will not change materially during the short cardioversion interval.

Agitation, seizures, fasciculations, or myoclonus may be abated with a benzodiazepine. Although seizures are due to adenosine antagonism in the brain, there is no role for adenosine in their management. This is due to the inability of adenosine to penetrate the blood-brain barrier, its short half-life, and potential cardiovascular effects (though not a concern in a theophylline poisoned patients as noted above).

There is a prominent role for enhanced elimination in theophylline toxicity. Multiple doses of oral activated charcoal enhance elimination from the serum through gastrointestinal dialysis. Charcoal hemoperfusion, largely a historical technique, has been replaced by hemodialysis which has the added ability to correct electrolyte imbalances. Clearance by modern hemodialytic methods is as good as was previously attained with hemoperfusion.

Indications for hemodialysis include the following:

1. Acute theophylline serum concentration > 90 µg/mL and symptomatic
2. Theophylline serum concentration > 40 µg/mL and
   a. Seizures or
   b. Refractory hypotension or
   c. Ventricular dysrhythmias

Case Management:

Concomitant with a rising serum theophylline concentration, the patient developed progressive sinus tachycardia and hypotension unresponsive to intravenous fluids, requiring a norepinephrine infusion. Potassium and magnesium were repleted. Confusion and agitation required sedation and intubation. Esmolol, a short-acting ß1 antagonist, was considered due to concern for bronchospasm with propranolol, but was not administered. Hemodialysis was recommended though she stabilized before it was initiated. Her theophylline serum concentration trended downward, and she recovered completely. She was subsequently stabilized and transferred to psychiatry.

Conclusions:

Theophylline toxicity, although decreasing in frequency, has devastating effects on the cardiovascular and neurologic systems. The most common reason for fatality is the development of tachydysrhythmia. One must suspect methylxanthine (theophylline, caffeine, and theobromine) toxicity with presence of vomiting, tachycardia with or without tachydysrhythmias, widened pulse pressure, seizures, and metabolic derangements including hypokalemia, hypomagnesemia, hypophosphatemia and/or hyperglycemia. Although gastrointestinal decontamination and supportive

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Complications of Thrombolysis

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Case Summary:

A 88 year-old man with a past medical history of hypertension and paroxysmal atrial fibrillation presented to the emergency department (ED) with a sudden onset of right-sided weakness and difficulty with word-finding. Two hours prior to presentation he was having breakfast with his wife when he suddenly experienced sudden weakness of his right side and his wife noted that he had difficulty speaking.

On physical examination, he was awake and alert. Vitals signs: blood pressure, 141/68 mmHg; pulse, 92 beats/min; respiratory rate, 18 breaths/min; temperature, 98.6°F (37°C). Examination of the head, eyes, ears, nose, and throat was unremarkable. His chest was clear to auscultation bilaterally, and heart examination revealed a regular rhythm with no murmurs. The patient's neurologic exam revealed intact cranial nerves, decreased motor strength and sensation on the right side of the body. His reflexes and cerebellar exam was normal. He was noted to have no dysarthria, but did have a moderate expressive aphasia.

The patient was immediately given 100% oxygen via a nasal cannula; an electrocardiogram demonstrated normal sinus rhythm without ischemia. Initial laboratory studies showed a white blood cell count of 12,000/mm^3, hemoglobin 12 g/dL, hematocrit 36%, and platelets 217,000/mm^3. The initial prothrombin time was 22 seconds (international normalized ratio [INR] of 1).The patient's non-contrast computed tomography of the brain was unremarkable for any acute hemorrhage. The patient was within the 3-hour window for the use of a thrombolytic agent. The neurology "stroke team" evaluated the patient for administration of alteplase (Activase®).

What are the fibrinolytic system and the mechanism of action of tissue plasminogen activator (t-PA)?

The endogenous fibrinolytic system utilizes the enzyne plasmin to dissolve fibrin clots. Plasmin lyses fibrin clots at various locations along their length resulting in fibrin degredation fragments that are eventually cleared by both the liver and kidney. Plasminogen, the precursor to plasmin, is a proenzyme that lacks the ability to degrade fibrin clots, but it is incorporated within the fibrin meshwork. Both endogenous urokinase and tissue plasminogen activator (t-PA) convert plasminogen to plasmin. t-PA is slowly released from damaged endothelium and eventually leads to dissolution of the clot. This can be seen in ***Figure 1.***

What are some roles of fibrinolytic agents and indications?

Thrombolytic agents are used for a variety of conditions that include acute myocardial infarction, thromboembolic disease, and cerebral vascular accident. The ideal thrombolytic would have a rapid onset of action, be fibrin-specific, carry minimum risk for bleeding complications, and be reversible in cases in which therapy is deemed inappropriate. Streptokinase, the first widely used fibrinolytic, is a protein that is secreted by several species of streptococci, that carries a relatively high risk of severe allergic reactions. There are currently three fibrin-specific thrombolytics known as recombinant tissue plasminogen activators (rt-PA) available in the United States: These include alteplase (Activase), reteplase (Retavase), and tenecteplase (TNKase). These available agents differ in regards to their potency, resistance to inactivation by plasminogen activator inhibitor (PAI-I), and specificity to fibrin.

Case Continuation:

Despite some minor improvement in the patient's motor weakness, the patient clearly had difficulty with speech and the neurologist noted an ophthalmoplegia as well. The decision was therefore made to administer alteplase at the standard dose of 0.9 mg/kg with 10% given over a minute and the rest over 60 minutes. However, within 30 minutes of receiving the full dose of alteplase, the patient developed precipitous neurological worsening.

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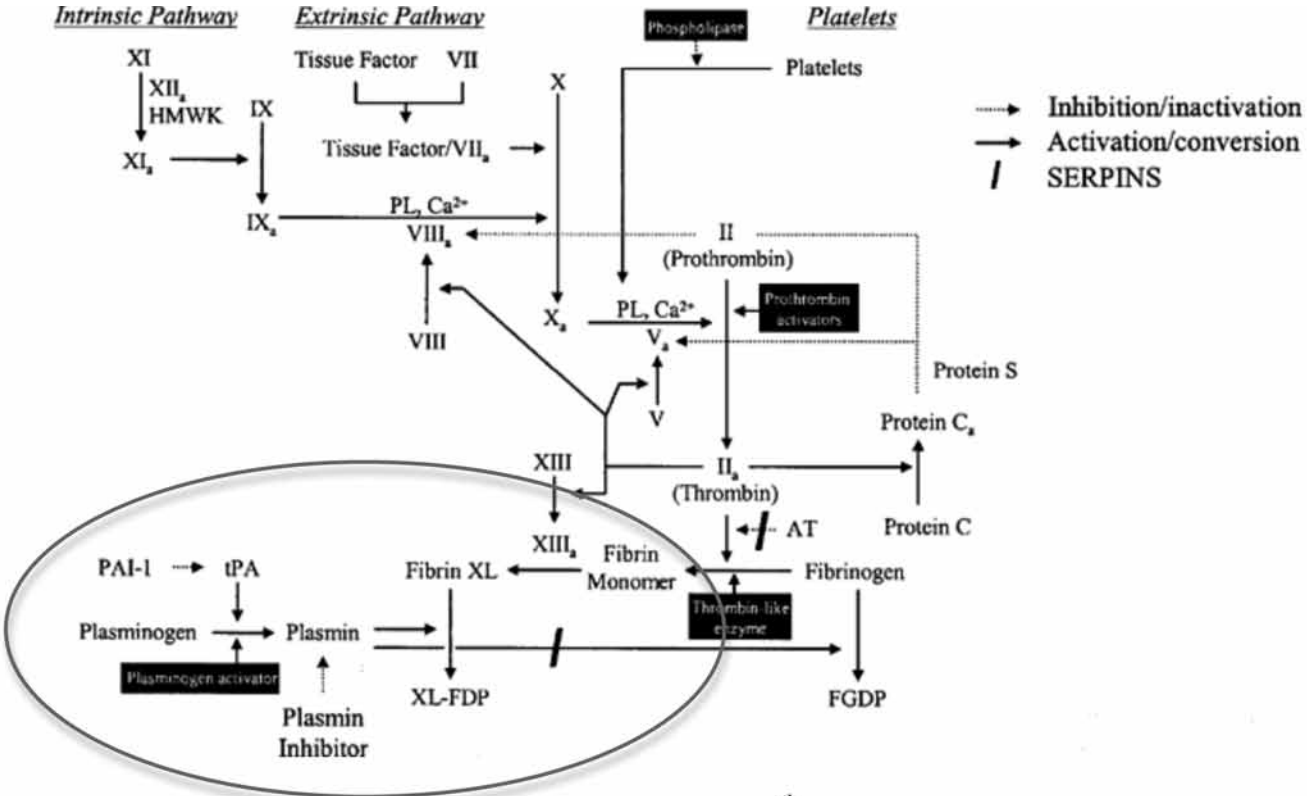

Figure 1: adapted from Goldfrank's Toxicologic Emergencies, 8th Edition (XL = cross linked; FDP = fibrin degradation products)

What are some adverse effects with the use of thrombolytics?

The most consequential adverse effect of the use of thrombolytics is bleeding, in particular intracranial hemorrhage. The incidence of intracranial hemorrhage is similar regardless of the thrombolytic used, with a rate of less than 1%. The incidence of other hemorrhage requiring transfusion is higher with a reported incidence between 5-8%. Given the potential for life-threatening bleeding, there are many contraindications as well as warnings involving the use of these potent agents. Some common contraindications include any history of prior intracranial bleeding, known intracranial neoplasm, and active internal bleeding. An age greater than 75 is also associated with an increased risk of bleeding.

Case Continuation:

The patient became progressively more confused and now demonstrated new left-sided weakness. He immediately underwent a repeat CT of the brain that can be seen in Figure 2. The patient also underwent immediate endotracheal intubation and the neurosurgical service was contacted. At this time the medical toxicology and hematology services were also contacted regarding a possible reversal agent for alteplase.

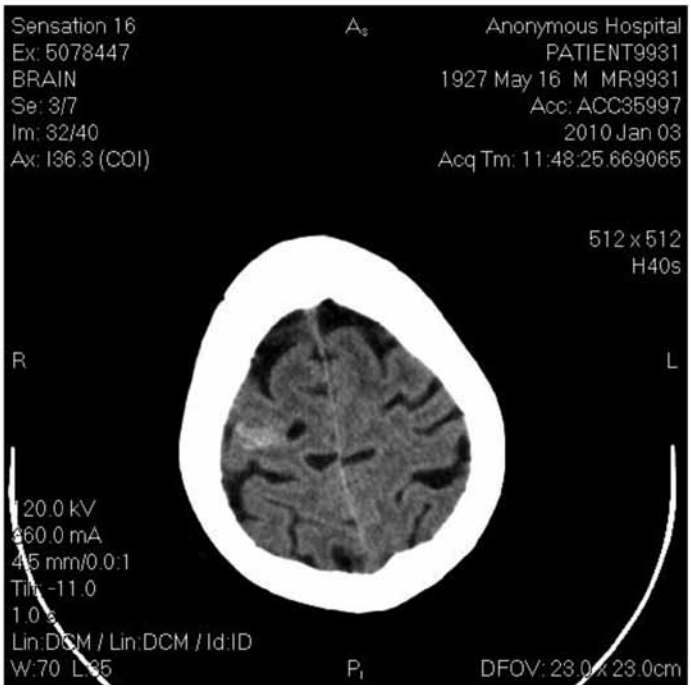

Figure 2: A repeat CT brain reveals a right frontal hemorrhage

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Complications of Thrombolysis

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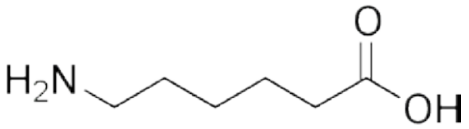
What is the management of thrombolytic-related bleeding complications?

In the event of minor bleeding secondary to thrombolytic use, supportive care is generally sufficient. Patients who develop life-threatening bleeding (i.e. intracranial hemorrhage) typically require aggressive use blood products. The infusion of the thrombolytic (i.e. alteplase is infused over an hour) should be immediately discontinued once a suspected life-threatening bleeding event is suspected; this includes a sudden deterioration in mental status. Many complications are not recognized until after the infusion has been completed.

Platelets should be infused for patients who use aspirin. Fresh frozen plasma (FFP) contains components of the coagulation, fibrinolytic, and complement system. FFP is indicated in the setting of factor deficiencies, massive blood transfusion, and acquired coagulopathy such as warfarin. The role of FFP is not clear with thrombolytic-related bleeding complications. Direct plasminogen inhibitors are another conceptually attractive therapy.

What are direct plasminogen inhibitors and what is its role in this case?



Aminocaproic acid

Aminocaproic acid, also known as Amicar, is an analog of the amino acid lysine. Aminocaproic acid reversibly binds to plasminogen thereby preventing its conversion to plasmin. Aminocaproic acid is primarily used to treat excessive post-operative bleeding, as occurs following liver transplantation.

Aminocaproic acid is available for oral administration (0.25 g/mL of aminocaproic acid with methylparaben 0.20%, propylparaben 0.05%, edetate disodium 0.30%). Each tablet is available as a 500 mg or 1000 mg preparation. It is also available as an intravenous formulation 5 g/20 mL (250 mg/mL).

The recommended dosing for the treatment of acute bleeding due to elevated fibrinolytic activity is 4-5 grams during the first hour of treatment, followed by a continuous infusion at the rate of 1 gm/hour. This is typically continued for about 8 hours or until the bleeding has been controlled. While the use of aminocaproic acid has theoretical benefit in the setting of tissue plasminogen activator-induced bleeds, the action of thrombolytics is typically complete by the time aminocaproic acid is administered.

Aminocaproic acid is generally well-tolerated with common adverse reactions that include nausea, emesis, headache, and myalgia. Perhaps the most feared complication regarding the use of aminocaproic acid is ischemia secondary to hypercoagulability. However, there is no definite evidence that administration of aminocaproic acid results in intravascular clotting; although only case reports support this concern it should not be dismissed.

Another related drug with a similar mechanism of action was aprotinin (Trasylol). This drug was used for excessive post-operative bleeding, particularly in cardiac surgery. Despite the initial apparent success, concerns of safety, including a high rate of anaphylaxis, thrombosis, and mortality, led in 2007 to its withdrawal.

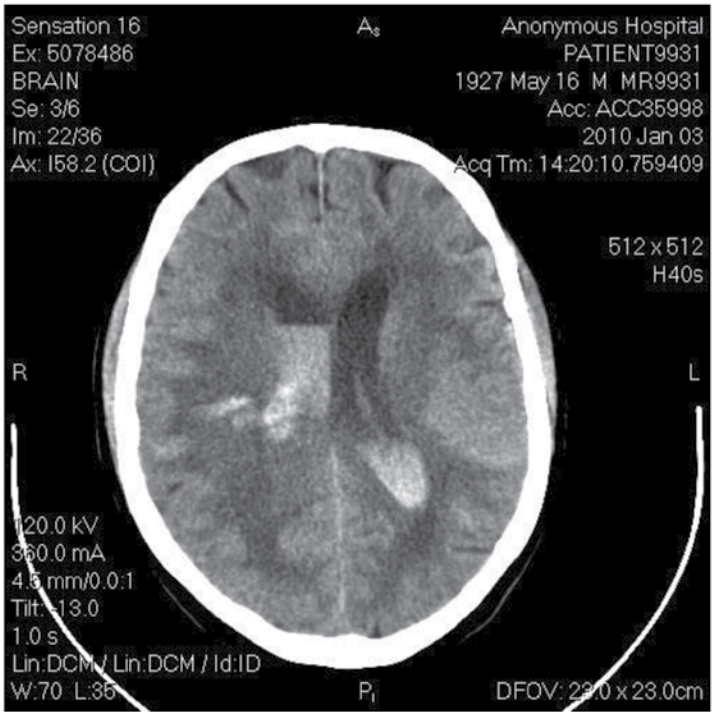


Figure 3: Another CT brain reveals worsening hemorrhage with extension into the intraventricular system and midline shift

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Complications of Thrombolysis

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Case Conclusion:

Upon discussion with both the hematology and toxicology service, the patient was given 4 units of platelets as well as 4 units of fresh frozen plasma. The patient also received aminocaproic acid, 4 grams over the first hour and then 1 gram/hour for 8 hours. Another cranial CT showed extension of the hemorrhage ***(Figure 3)*** after which an intracerebroventricular shunt was placed. Despite maximal supportive care, the patient was made comfort measure only given the poor prognosis and expired 24 hours later.

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Methylxanthine Toxicity

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management are crucial, hemodialysis is an effective method of managing severe toxicity.

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