

Drug Induced Acute Liver Injury

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What is the epidemiology of Acute Liver Failure?

The Acute Liver Failure (ALF) group formed in the late 1990s to study the etiology, management and outcomes of acute liver failure in the United States. The consortium now includes over 23 centers. In 2002 they published findings from the first 308 patients enrolled. Acetaminophen (APAP) was the single most common cause of ALF, over one third of cases, with other drugs or indeterminate being the next two most common etiologies¹. As of late 2009 over 1500 patients have been enrolled (Figure 1). Nearly three quarters of the cases are in females. APAP now accounts for 46% of cases and other drugs and herbal dietary supplements (HDS), another 12%. Indeterminate causes make up 15%². In children drugs account for a smaller percentage of cases of ALF and APAP a lesser number of the drug induced causes. Of 348 children with ALF 14% were due to acetaminophen and 17.5% to other drugs³.

Over half the APAP cases were accidental or unintentional. A study published in 2008 found that 18% of indeterminate cases had APAP-cysteine adducts detected at levels similar to those seen in patients with known acetaminophen hepatic injury. In this group, the pattern of liver injury by liver enzymes as well recovery was very similar to what we see with APAP toxicity, and dissimilar to the other 82% of indeterminate cases without these adducts⁴. This suggests that a significant number of the indeterminate group may be unrecognized acetaminophen poisoning.

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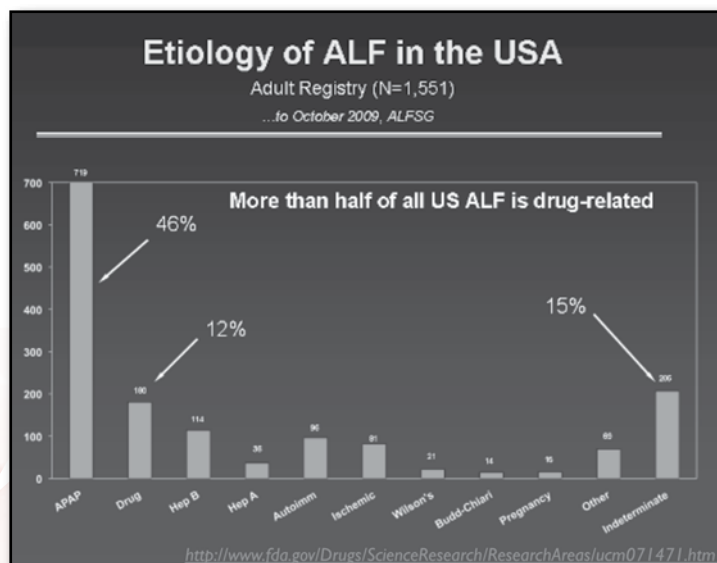


Figure 1

Program Announcements ••

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

UNY: The 2010 Toxicology Teaching Day is Scheduled for 11/3/10. Please mark your calendars!!

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While APAP is the elephant in the room the findings of the ALF group point out the importance of other drugs as the basis for ALF in the United States. Some differences between APAP induced liver failure and other drug induced liver failure include duration of symptoms and outcomes. APAP hepatotoxicity typically runs a very rapid course with either recovery or progression to fulminant hepatic failure within a matter of days to week whereas other forms of drug induced liver failure tend to have a more protracted course that lasts weeks to months. Transplant free survival is better in the APAP group and fewer in the APAP group progress to liver transplant ¹. Similar to adults, in children non-APAP drug induced ALF in children has a poorer prognosis ⁴.

The Drug Induced Liver Injury Network (DILIN) is a consortium of academic medical centers and the NIH enrolling and following cases of drug induced liver injury (DILI) longitudinally. They specifically exclude APAP from their registry. Patients enrolled in this study are not necessarily as ill as those enrolled in the ALF study. Females predominate in this group as well, about 60% of cases. Similar to the non-APAP drug causes in the ALF group, the most commonly implicated drugs responsible for liver injury were antimicrobials and CNS active agents. Of single agents, Amoxicillin-clavulanate (n= 23), nitrofurantoin (n= 13), isoniazid (n=13), and TMP/SMX (n= 9) were the most common antimicrobials. At 6 months after cessation of the suspect drug most patients had recovered, 8% died, 2% were transplanted and 14% had persistent liver test abnormalities ⁵. If we look at what drugs or toxins most often led to liver transplantation in the United States between 1990 and 2002 these were acetaminophen, isoniazid, anti-seizure medications, propylthiouracil and amanita mushrooms ⁶. (Table 2)

Liver Transplantation for Drug Induced Liver Failure in US 1990 to 2002	
	Number
Acetaminophen	124
Isoniazid	24
Propylthiouracil	13
Phenytoin	10
Valproic Acid	10
Amanita mushrooms	9
Herbals	7

Table 2

Total transplants over period 51,741; 492 drug related, above numbers from the 270 who met criteria for emergency liver transplant and felt definitely drug related

Liver Transplan 2004;10:1018-1023

Drugs may cause hepatotoxicity by a number of mechanisms. The drug or a reactive metabolite may directly lead to injury by binding to cellular constituents, leading to acute hepatocellular injury. A drug or metabolite may interfere with bile transport, with the accumulation of bile salts and cholestasis. This may occur within the hepatocyte, such as interference with bile salt export pumps or it may occur in the canaliculi or intrahepatic bile ductules. Cholestasis may be bland, that is there is no hepatic injury otherwise associated with it, or it may be associated with hepatitis and elevations of hepatic transaminases. Drugs that directly affect the mitochondria can result in microvesicular steatosis, lactic acidosis and hepatic injury ⁷.

The immune system plays an integral role in hepatocyte injury. Drug or drug metabolites binding to cellular proteins may create neoantigens. These adducts may ultimately lead to a classic allergic type reaction with antibodies directed towards the adduct, or the neoantigen signals the innate immune system with recruitment of T-cells and other inflammatory mediators that propagate hepatic injury ^{7,8}.

Other cells of the liver may be the target of or participate in liver injury. Damage to the sinusoids may result in veno-occlusive disease. Kupffer cells, the liver's resident macrophages located in the sinusoids may participate in hepatocyte injury through phagocytosis and release of immunomodulators. Activated Stellate cells appear to contribute to the fibrosis associated with some drugs ⁷.

The initial insult may be so severe as to lead to acute hepatocellular necrosis, as might be seen with a massive APAP overdose. In most cases of drug induced liver injury however, the initial insult in and of itself does not lead to acute hepatocellular death but rather, as an "upstream" event, sets off a number of "downstream" responses that may involve inflammatory/ apoptotic pathways, protective pathways, cytokines, chemokines, recruitment of immune cells and gene transcription. The final outcome, either recovery/ adaptation or cell death, depends on the balance of these many events. Mitochondrial integrity and adequate ATP production plays a central role in this process. Failing damaged mitochondria release mediators into the cytoplasm that promote progression to either apoptosis or cell rupture and necrosis ⁸. (Several excellent reviews discuss these processes in detail; *Molecular Interventions* 2010;10:98-110, *Gut* 2009;58:1555-1564, *Current Medicinal Chemistry* 2009;16:3041-3053).

Environmental and genetic variables may confer either increased or decreased risk of hepatic injury. Both

the DILIN registry and the ALF group have a preponderance of females^{1,5}. Besides gender, age, co-ingested drugs, ethanol, preexisting liver disease, nutritional status and obesity may impact the susceptibility to liver injury. Genetic factors besides gender include variants or polymorphisms of CYP p450 enzymes, N-acetyl transferase, antioxidant defense mechanisms, and MHC/HLA phenotype⁹. *Table 3* lists several examples.

acetaminophen	malnourishment
isoniazid	older age, alcohol use, NAT 2 slow acetylator phenotype
methotrexate	alcoholism, obesity
valproic acid	pediatric age group, other antiseizure med use
abacavir	HLA B*5701

Cir 2009;58:1555-1564

Table 3

Most drug related hepatotoxicity is idiosyncratic. Idiosyncratic drug induced liver injury occurs rarely, on the order of fewer than 1 in 100,000 to 1 in 10,000 patients. It is generally not dose related and not predictable. The latency period is on the order of weeks to months. In some cases injury may not manifest until after cessation of the drug, this being a not uncommon scenario with amoxicillin-clavulanate. Some idiosyncratic reactions may have allergic features with fever, rash, eosinophilia, auto-antibodies and a short latency with re-exposure. With cessation of the offending agent recovery is the rule, although full recovery may takes months⁹.

In distinction to idiosyncratic drug toxicity, acetaminophen is known as a predictable hepatotoxin. Toxicity is dose related, occurs with a high incidence if a toxic dose is consumed, and has a short latency to injury. Other examples of predictable hepatotoxins include carbon tetrachloride, iron and the essential oil pennyroyal (pulegone).

What is the classification system of liver injury?

Drug induced liver injury can be classified based on the pattern of liver abnormalities observed; hepatocellular, cholestatic or mixed (*Table 4*). Drugs associated with hepatotoxicity are often associated with a particular biochemical pattern (adapt Navarro table 2006). In general, the degree of elevation of the ALT is not indicative of the extent of liver injury, which may be much worse histologically. Jaundice is a bad prognostic marker in the setting of drug induced liver injury. DILI with a

Hepatocellular pattern:	$ALT \geq 3x \text{ ULN}$ and $[(ALT/ULN)/(ALP/ULN)] \geq 5$
Cholestasis pattern:	$ALP \geq 2x \text{ ULN}$ and $[(ALT/ULN)/(ALP/ULN)] \leq 2$
Mixed pattern:	$ALT > 3x \text{ ULN}$ and $ALP > 2x \text{ ULN}$ and $[(ALT/ULN)/(ALP/ULN)] > 2$ and < 5

ALT: alanine aminotransferase
ALP: alkaline phosphatase
ULN: upper limit normal

Cir 2009;58:1555-1564

Table 4

bilirubin level 3x greater than the upper limit of normal and without biliary tract obstruction or Gilbert's syndrome is associated with a mortality of about 10% and is know as Hy's Law after the hepatologist Dr. Hyman Zimmerman¹⁰.

Examples

1. Direct cell injury due to reactive metabolite.

Acetaminophen hepatotoxicity has probably been studied more than any other type of drug or toxin induced liver injury. The initial insult is well described, the concomitant depletion of glutathione with ongoing metabolism to the reactive metabolite NAPQI, leading to cellular injury and, if the insult is sufficient, ultimately cell death. Centrilobular hepatocytes, with the highest content of CYP 2E1, the enzyme primarily responsible for metabolism to NAPQI, are most susceptible to injury, leading to the pattern of centrilobular necrosis observed. Research over the past several decades has provided further insight into the mechanism of APAP induced liver injury and the complexity of this process. Mechanisms at play include gene translation factors, such as one for the up regulation of glutathione synthesis, the activation of other protective as well as apoptotic pathways, the release of cytokines and chemokines and the recruitment of immune cells¹¹.

Another example of a toxic metabolite leading to hepatic injury is isoniazid. Isoniazid is metabolized by N-acetyl transferase (NAT) in two successive steps, first to acetylisoniazid. Acetylisoniazid is rapidly hydrolyzed to acetylhydrazine which is then acetylated by NAT to diacetylhydrazine, which is non-toxic. Acetylhydrazine may also be metabolized by CYP 2E1 to reactive toxic intermediates that can cause in hepatocyte injury. The slow acetylator phenotype of NAT appears to be associated with an increased risk of hepatotoxicity. Older age is also a recognized risk factor for INH hepatitis¹².

2. Cholestasis

The immunosuppressive Cyclosporin A inhibits the ATP dependent bile salt exporter at the canalicular membrane, leading to cholestasis. Estrogens lead to cholestasis by several mechanisms including decreased uptake of bile salts at the sinusoidal membrane and decreased efflux at the canalicular membrane. The cholestasis seen with these drugs is usually bland, on histology there is no inflammation or necrosis⁹. Other drugs that are toxic to the bile duct epithelial cells may result in a more inflammatory picture of cholestasis. The antifungal terbinafine is an example of this, with a portal inflammatory infiltrate with bile duct damage observed on biopsy¹³. Drug induced bile duct injury may lead to ductopenia and even the loss of bile ducts ("vanishing duct syndrome").

3. Mixed hepatocellular, cholestatic or hepatocellular

Amoxicillin-clavulanic acid (co-amox) rarely leads to liver injury, but given its widespread use is one of the more common drugs to appear in the DILIN registry⁶. Co-amox may cause a cholestatic picture of liver injury with jaundice and itch, or with a mixed cholestatic hepatocellular pattern. Jaundice is the most common presenting symptom. Immune mediated mechanisms play a role in this injury and signs of hypersensitivity, such as fever, rash and eosinophilia are seen in about 40% of patients. The onset of symptoms may not manifest until days to weeks after cessation of the antibiotic¹⁴.

4. Hypersensitivity

The aromatic anticonvulsants, such as phenytoin, phenobarbital and carbamazepine, are a cause of immune mediated hepatitis. Fever, severe cutaneous reactions and eosinophilia are common. Re-challenge results in a prompt recurrence of symptoms. A reactive metabolite is believed responsible. This has been called the Anticonvulsant Hypersensitivity Syndrome.

More generic terms such as reactive metabolite syndrome, drug hypersensitivity syndrome or DRESS syndrome (drug rash, eosinophilia, systemic symptoms) include not only the anticonvulsants but other drugs that may cause a very similar illness. Several of these are allopurinol, sulfonamide antibiotics and dapsone¹⁵.

5. Mitochondrial injury

Mitochondrial injury is another target for hepatocyte injury. Impaired beta oxidation of fatty acids by mitochondria leads to microvesicular steatosis and inadequate ATP production by aerobic pathways leads to lactic acidosis. More severe insult to mitochondrial function or integrity leads to mitochondrial swelling, ly-

sis and the release of mediators into the cytoplasm that activate cell death pathways.

Valproic acid (VPA) is a recognized idiosyncratic hepatotoxin. A more common and benign transaminitis may occur early after the initiation of therapy. Less common is severe hepatic injury that may progress to fulminant hepatic failure. The incidence of this more severe form is higher in children < age 2 years, where it may occur as frequently as 1: 500 to 1:800, especially children on more than one antiseizure medication. This severe form of hepatotoxicity is less common in adults, with an incidence of about 1: 20,000¹⁶.

VPA and metabolites have a number of effects on mitochondrial function. Free acyl CoA and carnitine, essential for the transport of fatty acids into the mitochondria and their subsequent beta oxidation, are depleted by binding with VPA and VPA-metabolites. Total stores of carnitine are also depleted. VPA and VPA-metabolites also appear to interfere with aerobic glycolytic pathways in mitochondria^{16,17}.

Antiretroviral nucleoside analogues inhibit mitochondrial DNA polymerase- γ , inhibiting protein synthesis and mitochondrial replication. As a consequence cells may become energy starved. In hepatocytes this can lead to microvesicular steatosis, hepatitis and cell necrosis. Several of the nucleoside analogues associated with this type of hepatic toxicity include stavudine, didanosine and zidovudine¹⁸.

6. Sinusoidal Injury (Hepatic Venocclusive disease or Sinusoidal Obstruction Syndrome)

The sinusoids course along hepatocytes from the portal vein and hepatic artery towards the central vein. The endothelial cells of the sinusoids are the target of some hepatic toxins and in more severe cases the central vein may be involved as well. This is in a sense a vascular disease. In western countries this was once most commonly the result of myeloablative doses of chemotherapeutic agents, usually in conjunction with radiation, prior to stem cell transplant. The incidence was as high as 20-40% prior to recognition of this disease and dose modifications. Chemotherapy at conventional doses as well as azathioprine and pyrrolizidine alkaloids have all been associated with this disease also. The clinical presentation includes weight gain, jaundice, right upper quadrant pain and hepatomegaly. Portal hypertension and ascites may also be present¹⁹.

Other, delayed toxin induced liver injury includes fibrosis, cirrhosis and tumor transformation.

Toxic Hematemesis

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

Case Summary:

A 38 year-old woman presents to the Emergency Department approximately 9 hours following ingestion of multiple medications in a suicide attempt. She is complaining of sharp epigastric abdominal pain and reports two episodes of hematemesis prior to arrival.

The patient's past medical history is notable for diet-controlled diabetes mellitus, anemia, asthma, and bipolar disorder with previous suicide attempts. She denies using tobacco, ethanol, and/or illicit drugs.

Her initial vital signs are as follows: BP, 141/72 mmHg; HR, 59 beats/min; T, 97.9°F; RR, 20 breaths/min; SpO₂, 100% RA. Physical examination is normal. Her ECG shows normal sinus rhythm, with normal QRS and QT intervals. Her chest and abdominal radiographs are unremarkable.

The initial set of laboratory tests return remarkable for the following: WBC, 32,000/mm³; serum bicarbonate, 11 mEq/L; anion gap, 17 mmol/L; glucose, 275 mg/dL; venous blood gas: pH, 7.24; PCO₂, 37 mmHg; PO₂, 44.1 mmHg; serum lactate, 6.3 mmol/L; total bilirubin, 3 mg/dL with normal LFTs; lipase, 270 U/L; INR, 1.4. The patient has an undetectable serum acetaminophen, salicylate, and ethanol concentrations.

What xenobiotics, taken in overdose, are commonly associated with hematemesis?

The differential diagnosis of profound vomiting with or without hematemesis following the ingestion of a potentially toxic substance includes the following agents:

Table 14: Toxicologic causes of profound vomiting and hematemesis and general mechanism

	Vomiting	Hematemesis
Metals • Lithium • Iron • Mercury • Arsenic • Thallium	<ul style="list-style-type: none"> • Direct mucosal injury • Local stimulation 	<ul style="list-style-type: none"> • Direct mucosal injury
Caustics	<ul style="list-style-type: none"> • Direct mucosal injury 	<ul style="list-style-type: none"> • Direct mucosal injury
Methylxanthines • Theophylline • Caffeine	<ul style="list-style-type: none"> • Local stimulation • Central chemoreceptor trigger zone stimulation 	
Salicylates	<ul style="list-style-type: none"> • Local stimulation 	<ul style="list-style-type: none"> • Direct mucosal injury
Colchicine	<ul style="list-style-type: none"> • Local stimulation 	
NSAIDS	<ul style="list-style-type: none"> • Local stimulation 	<ul style="list-style-type: none"> • Direct mucosal injury
Detergents/soaps	<ul style="list-style-type: none"> • Local stimulation 	
Sympathomimetics • Amphetamine • Cocaine	<ul style="list-style-type: none"> • Elevated intracranial pressure 	
Cardioactive steroids • Digoxin	<ul style="list-style-type: none"> • Central chemoreceptor trigger zone stimulation 	
Anticoagulants		<ul style="list-style-type: none"> • Coagulopathy

Table is partially adapted from Table 25-3; Goldfrank's Toxicologic Emergencies, Eighth Edition

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What is the pathophysiology of iron toxicity?

Although the differential diagnosis is extensive, there was a significant concern for iron toxicity given the patient's history of anemia. Iron is present in many households, largely as a common component of children's and adult multivitamin preparations.

Iron is a transition metal which participates in oxidation-reduction reactions and generates reactive oxygen species. These properties allow it to play an important role in enzymatic reactions, oxygen carrying by hemoglobin, and as a vital component of cytochromes. However, in overdose, the generation of excessive quantities of free radicals leads to damaging effects local to the sites of generation. The free radicals bind to biological membranes and initiate an oxidative cascade, leading to inflammation and membrane destruction.⁷

Iron related membrane toxicity may be localized or systemic. Ingested iron ions irritate the gastrointestinal epithelium, leading to vomiting and hematemesis, and disrupt its barrier abilities. The irritation and breakdown of gastrointestinal epithelium is referred to as local toxicity. Iron then enters the circulation where it is rapidly bound to transferrin. Once transferrin becomes saturated, the "free," or unbound, iron ions distribute throughout the body to various organs, but first pass through the liver, resulting in hepatotoxicity. Once iron enters the circulation, its disruptive effects at the cellular and organ levels are referred to as systemic toxicity.

In addition to the membrane effects, iron disrupts oxidative phosphorylation at the electron transport chain. The inability to utilize the hydrogen ion gradient to make ATP shunts glucose metabolism towards glycolysis, fueling conversion of pyruvate to lactate. Clinically, this includes decreased myocardial and vascular function that contributes to hemodynamic shock. Iron associated coagulopathy may occur independently of hepatotoxicity, and likely occurs due to iron's ability to interfere with thrombin formation and the effect of thrombin on fibrinogen.

What laboratory studies are helpful in determining iron toxicity?

Leukocytosis (WBC >15,000/mm³) as well as hyperglycemia (serum glucose >150mg/dL) may be associated with iron toxicity, presumably due to systemic stress response. Retrospective analysis of patients with a serum iron concentrations of either >300µg/dL or >500µg/dL demonstrated that although more patients in this group developed leukocytosis and hyperglycemia (with

one study demonstrating up to 100% of patients⁵) many patients with serum iron concentrations <300µg/dL also had elevated serum glucose and leukocyte concentrations.¹

It may be challenging to interpret this association, given that iron toxicity is currently defined by both serum iron concentration and the patient's clinical symptoms (not by iron concentration alone). Although serum iron concentration is measured while the ingested iron is in the blood compartment, clinical toxicity only becomes evident when iron distributes to the target organs; this may be associated paradoxically with a fall in the serum iron concentration.

A metabolic acidosis with an elevated anion gap and elevated lactate concentration is a significant finding in a patient with iron toxicity. Protracted vomiting may be associated with electrolyte disturbances such as hypokalemia and hypochloremia. Injury to the gastrointestinal epithelium and subsequent bleeding may lead to anemia. Coagulopathy may manifest with an elevation of prothrombin time (PT) or INR. Hepatic dysfunction may be delayed, typically with a rise in liver function studies in approximately 24-48 hours following ingestion.

Peak serum iron concentration 2-6 hours post-ingestion may serve as a predictor of clinical toxicity. Peak serum iron concentrations between 300µg/dL and 500µg/dL are associated with moderate gastrointestinal injury and mild to moderate systemic toxicity. Peak serum iron concentration between 500µg/dL and 1000µg/dL is a predictor of significant systemic toxicity once iron reaches its target organs. Peak serum iron concentration of >1000µg/dL heralds a concerning risk for morbidity and mortality.

Measurement of total iron binding capacity (TIBC) is not a reliable predictor of iron toxicity. The TIBC concentration is overestimated by the assay with significant iron ingestion.

Furthermore, deferoxamine interferes with TIBC concentration measurement.⁸

Is abdominal radiograph helpful in diagnosing iron ingestion?

The radiopacity of iron on abdominal radiography depends on the preparation (liquid versus tablet) and the concentration of elemental iron.^{6,9}

Various iron preparation have a different percentage of elemental iron.

- Ferrous chloride 28%
- Ferrous fumarate 33%

- Ferrous gluconate 12%
- Ferrous lactate 19%
- Ferrous sulfate 20%
- Carbonyl iron* 98%
- Iron polysaccharide* 46%

*non-ionic preparation

Liquid iron preparations are typically not radiopaque. Similarly, a retrospective review of iron ingestion in children demonstrated that 1 out of 30 children who ingested chewable vitamins had radiographic opacities.⁶

Whereas obtaining a radiograph has potential clinical utility when suspecting that a patient has taken a substantial iron overdose, the absence of radiographic evidence should not eliminate the diagnosis of iron toxicity, especially in children.

What are the clinical signs of iron toxicity?

Although iron toxicity is classically described in stages, the clinical course depends on the amount of iron ingested and may not follow the “classic” timeline.

Patients with early or mild iron toxicity experience gastrointestinal effects, including nausea, vomiting, with or without hematemesis, abdominal pain, and diarrhea, with occasional melena or hematochezia. In many patients these findings wane over several hours and systemic toxicity never occurs. In some however, although the gastrointestinal effects resolve, the patients rapidly progress to develop systemic toxicity, identified by hypotension, tachycardia, an anion gap metabolic acidosis, and/or altered mental status.

If the patient survives, hepatic toxicity may become evident in the days following ingestion. Although rare, gastric outlet obstruction has been reported in 2-8 weeks following the ingestion due to pyloric scarring.

When should one use deferoxamine?

Deferoxamine is derived from the culture of *Streptomyces pilosus*, and chelates ferric iron (Fe³⁺) to form ferrioxamine complex, which is water soluble and excreted by the kidneys. Despite the apparent imbalance in chelation potential (100 mg of deferoxamine binds 8.5 mg of ferric iron³), deferoxamine is clearly effective in the management of patients with serious iron poisoning.

Intravenous administration of deferoxamine should be considered in a patient with hemodynamic instability, altered mental status, or metabolic acidosis regardless of the serum iron concentration, and/or those patients with iron concentration of >500 µg/dL.

It should be initiated at 5 mg/kg/hr and briskly but cautiously escalated to 15 mg/kg/hr, noting that deferoxamine administration is associated with rate-related hypotension.² Intravenous deferoxamine is likely to have the greatest benefit while iron is still in the blood compartment, prior to its distribution to target organs, highlighting the need for early decision-making.

The recommended adult total deferoxamine dose is 6-8 g per day, though this dose is supported by limited science. The pediatric dose is approximately the same. After administering 6 g of deferoxamine, a reassessment of the patient’s hemodynamic status, CNS symptoms and acidbase status is warranted while continuing the deferoxamine infusion. Deferoxamine infusion should be discontinued upon normalization of patient’s clinical status and resolution of metabolic acidosis. Deferoxamine therapy generally should not exceed 24 hours, as longer infusions have been associated with acute lung injury.¹⁰

Desferrioxamine complex may be detected in the urine by noting a urinary color change to what is classically described as “vin rosé”, though most commonly is may be described as dark yellow or rust colored. The color reflects urinary excretion of approximately 10-30 mg of iron over 24 hours.

Do all patients with iron ingestions require hospital admission?

Iron is a powerful emetogenic agent. If the patient has not vomited following iron ingestion, he or she should be observed for several hours in the Emergency Department and does not require a medical hospital admission.

If the patient vomited transiently (up to 3-5 times), has a peak serum iron concentration of <500 µg/dL, no laboratory evidence of metabolic derangement, and normal vital signs and mental status, he or she should be observed several hours in the Emergency Department. If other related issues have been explored, such as suicidality, or a safe home environment for a child, the patient may be discharged.

Any patient with either a peak iron concentration of >500 µg/dL, and any signs of either metabolic, organ, or hemodynamic iron toxicity requires admission to the hospital. Hemodynamically unstable patients, or those with peak serum concentration >500 µg/dL with metabolic disturbances may need an admission to the critical care unit.

An *n*-Butane Canister

Stephanie H. Hernandez, M.D., Anna E. Ringwelski, M.D., Lewis S. Nelson, M.D.

Case Summary:

A 42 year-old man presents to the emergency department (ED) after he is unable to remove an intentionally-placed rectal foreign body. The patient reports the foreign body is a cylindrical butane gas canister that is normally intended for the purpose of refilling a torch. The patient complains of mild rectal discomfort and being able to taste and smell the gas. He denies "huffing" the gas, euphoria, or change in mental status.

A hydrocarbon-like odor emanates from the patient, prompting his placement in an isolated area of the ED for safety. On initial physical examination, he is alert and oriented. Vital signs are: blood pressure, 111/71 mmHg; heart rate, 78 beats/minute; respiratory rate, 18 breaths/minute; and temperature, 97.0° F. His neurologic, cardiac, and pulmonary examinations are normal. His abdomen is non-tender and non-distended, with active bowel sounds. On deep digital rectal exam a solid foreign body is palpable. Stool is without blood and no anal injury is noted.

Laboratory results including basic metabolic panel, complete blood count, and urinalysis are normal. An electrocardiogram demonstrates sinus rhythm with normal QRS and QTc intervals. A supine radiograph of the abdomen demonstrates a non-obstructive bowel gas pattern with air and stool seen throughout the colon. A 12.3 cm x 4.3 cm cylindrical radiopaque foreign body overlies the region of the recto-sigmoid colon (Figure 1). On the chest radiograph no free air or other abnormality is noted.

What is butane and what are its uses?

Butane describes a 4-carbon containing volatile hydrocarbon (boiling point 20.6°C) and typically refers to the unbranched *n*-butane isomer (Figure 2). Methylpropane refers to *i*-butane or isobutane (Figure 3). The canister is filled with compressed *n*-butane gas, which is colorless, and has a pleasant hydrocarbon odor, though stenching agents may be added. Butane is highly volatile, with rapid evaporation from its compressed liquid state (Liquid Petroleum Gas (LPG)). Butane may be found in torches and cigarette lighters, and is also used as a propellant in spray deodorants and room fresheners, and as a refrigerant.

Butane is used as a recreational inhalant. It is usually huffed, or sprayed into a cloth and inhaled. It has a low



Figure 1

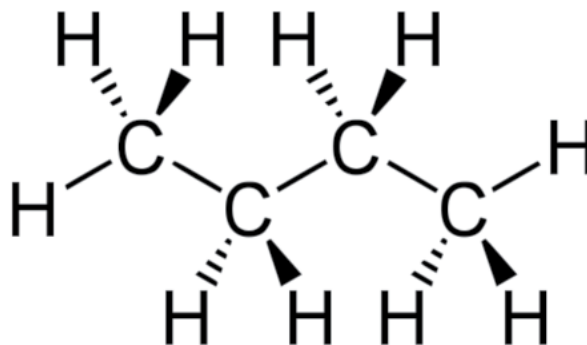


Figure 2: The unbranched chemical structure of *n*-butane C_4H_{10} , butane.

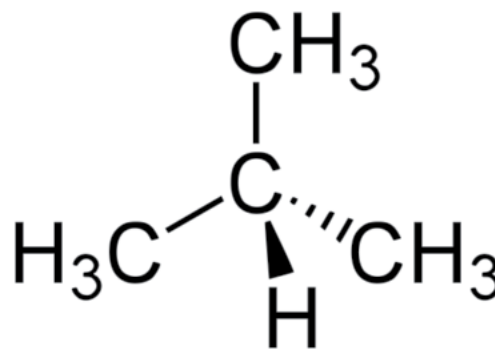


Figure 3: The branched chemical structure of *i*-butane C_4H_{10} , methylpropane.

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blood:gas partition coefficient, 0.019, leading to rapid passage through blood-brain barrier to produce euphoria and sedation. The specific mechanism by which butane and other hydrocarbons produce euphoria is unknown but likely due in large part to nonselective neuronal membrane effects. Unlike halogenated hydrocarbons, butane enhances agonist action on the GABAA receptor only at concentrations that exceed those required to produce anesthesia¹. Thus other receptors or mechanisms are likely involved at concentrations achieved with recreational use.

What are the toxic effects of butane?

Simple asphyxia may result if *n*-butane gas displaces a sufficient amount of oxygen in inspired air, effectively reducing the FiO_2 . This has been reported to occur in butane abuser, including those who abuse for autoeroticism². Rapidly progressive bilateral pulmonary infiltrates occurred in a 19-year-old man following a “fire-breathing” trick in which he filled his oral cavity with butane gas from a cigarette lighter, and exhaled the volatile vapors over an open flame to produce a flame-throwing effect³. Although butane is heavier than air and may have descended the bronchial tree causing chemical pneumonitis, heat injury may have been responsible for this outcome.

Barotrauma, including pneumothorax, pneumomediastinum, and subcutaneous emphysema, may result with huffing butane gas⁴, but is related to the deep inhalation and Valsalva rather than a toxic property of the butane gas.

Patients may sustain cold thermal injury since temperatures as low as -40 °C can be achieved when compressed gasses expand when they are sprayed out of their canister.

For this reason these cans often carry a warning to spray at a minimum distance of 15 cm and not for a prolonged period of time. The cold injury produced to oropharyngeal (or in this case rectal) mucosa if huffing butane gas can be as severe and may require surgical attention⁵. The presence of the leaked butane gas and compromised intestinal mucosa from cold thermal injury places the patient at risk for perforation and subsequent butane gas emboli. Although the use of hyperbaric oxygen therapy for butane gas emboli is yet to be described in the literature, it seems reasonable if time and circumstances permit.

The most frequent life-threatening toxicity from butane gas is myocardial sensitization leading to dys-

rhythmia and death. The consequences of sensitization of the myocardium to catecholamines from huffing solvents has been termed “sudden sniffing death.” In most cases, the inhalant gas alters the delayed rectifier potassium channel and prolongs repolarization, raising both the likelihood that an ectopic beat will occur and simultaneously making the myocardial tissue more favorable for conduction of reentrant dysrhythmias⁶. Although this is more commonly associated with the halogenated hydrocarbons, there are numerous reports of ventricular fibrillation and death following butane huffing^{7,8}. Hypoxia may be involved as well. The dysrhythmia is often preceded by an event that would expectedly cause sudden catecholamine release. One case described a 14 year-old girl being discovered by police huffing butane and developing sudden collapse⁸. Another case described a man huffing butane and suddenly collapsing after running out of his room².

In addition there is a single case in the literature that proposes coronary vasospasm from butane huffing. A 14-year-old boy suffered severe anterior chest pain that lasted for 15 min and subsequently collapsed after sniffing seven canisters of butane. He was found to have extensive anterior myocardial infarction complicated by ventricular fibrillation. Cardiac catheterization revealed patent coronary arteries with severe anterolateral and apical left ventricular wall hypokinesia. It was assumed intense coronary artery spasm had occurred⁹.

Case Continued

Attempts by ED and surgical staff to manually remove the foreign body are unsuccessful using procedural sedation. The patient is offered deep sedation and analgesia in the operating room with the understanding that if transanal removal is unsuccessful, they will need to convert to general anesthesia and laparotomy. The patient refuses to consent.

ED and surgical staff are concerned for the safety of the hospital staff and patient given the presence of a leaking flammable gas. It is considered that the patient may be experiencing central nervous system effects from the volatile hydrocarbon. A psychiatrist finds that the patient’s thought process are illogical and he has paranoid ideations regarding the surgeon’s intentions, and therefore he lacks decisional capacity.

What is the disposition for this patient attempting to elope from the emergency department with an internalized leaking *n*-butane gas canister?

The catecholamine release that could occur when the patient is informed he is going to be involuntarily admitted may predispose him to a life threatening cardiac dysrhythmia. Selection of agents for sedation should be made carefully. Theoretically, agents with the potential to inhibit potassium channels, such as the antipsychotics, should be avoided⁶. Benzodiazepines or other GABA-ergic agents (e.g., propofol) are preferred. Beta-adrenergic antagonists may prevent or treat catecholamine driven dysrhythmias. Propranolol and esmolol have both been used successfully to manage ventricular dysrhythmias following inhalant abuse^{10,11}.

Precautions should be taken in the operating room if removal of the potentially leaking butane canister necessitates conversion to general anesthesia and laparotomy. Use of halogenated inhalational anesthetics should be deferred to avoid further myocardial sensitization. In addition, use of a cautery would be contraindicated due to the flammability of butane.

Case Conclusion

In the operating room deep sedation is sufficient to allow manual removal of the canister. The rectal mucosa appears intact. No further complications are experienced. The following day the patient tolerates food and is discharged.

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Toxic Hematemesis

Continued from page 7

Case Conclusion

The patient receives ondansetron and intravenous fluids for her persistent emesis. Given the presence of systemic toxicity, specifically of metabolic lactic acidosis, deferoxamine therapy is initiated at 5 mg/kg/hr. The serum iron concentration returns at 953 µg/dL.

The deferoxamine dose was escalated to 15 mg/kg/hr with an attempt to chelate large concentration of iron while it was in the blood compartment. The patient's clinical status and acid-base status was reassessed following infusion of 6g of deferoxamine. She improved rapidly and did not require deferoxamine infusion past 24 hours.

She developed a transient transaminitis within 48 hours of ingestion, with peak LFTs AST 605 U/L and

ALT 759 U/L. Her acetaminophen concentration was undetectable and LFTs were normal upon presentation to the Emergency Department. Her INR peaked at 1.5 and subsequently normalized. Following resolution of toxicity, she was transferred to psychiatry.

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Herbal dietary supplements

Over the last several decades there has been an explosion in both the number of herbal dietary substances available in the United States. Of the first 300 patients in the DILIN registry, 33 were using an HDS that may have contributed to their liver injury. 28 were using one or more HDSs, and 5 were using an HDS with a prescription drug⁵. HDSs implicated include proprietary formulations with multiple ingredients such as Hydroxycut and Herbalife products. Traditional Chinese medications, containing a number of different plant or plant extracts have also been implicated. Single agents associated with acute liver injury include green tea extract, pyrrolizidine alkaloids, anabolic steroids and chapparal²⁰.

How is toxin associated liver injury diagnosed?

For most drugs liver toxicity is a rare occurrence. The evaluation of the patient with possible drug related hepatotoxicity should include a careful evaluation for other etiologies. This includes history for heavy alcohol consumption and occupational exposures, imaging studies for signs of biliary tract obstruction or disease, autoantibodies, viral serologies, and tests for metabolic diseases such as Wilson's disease, hemochromatosis and alpha-1 antitrypsin deficiency. A hemodynamic etiology should also be considered if there has been a recent illness with sepsis or shock ("shock liver")⁹.

Interpretation of the results of serologic testing may require expert consultation. Although autoantibodies are associated with autoimmune liver disease they may sometimes be seen with drug induced liver injury²¹. Likewise, DILI may be the cause of deterioration in someone with underlying chronic viral hepatitis.

How is toxin associated liver injury treated?

Recognition and discontinuation of the suspected agent is the most important therapeutic intervention. Beyond that supportive care is the mainstay of management.

The Acute Liver Failure study group is currently studying the use of N-acetylcysteine in non-acetaminophen acute liver failure. Liver failure here is defined as coagulopathy with an INR ≥ 1.5 and encephalopathy. NAC is given over 72 hours intravenously. The schedule is the same as the 21 hour infusion routinely used for acute acetaminophen treatment, with the infusion continued at 6.25 mg/kg/hr to 72 hours. In a report on first 173 eligible patients enrolled and randomized to placebo or NAC they found no improvement in overall survival at 3 weeks with NAC. Fewer patients in the NAC group went on to liver transplant but this did

reach statistical significance. Of note however, transplant free survival was significantly improved in the NAC group, with all this benefit in patients with grade 1 or 2 coma. Patients with grade 3 or 4 coma derived no benefit from NAC. This study includes causes of ALF besides drugs. The subgroup with drug induced liver injury also suggests a benefit with NAC in patients with grade 1 or 2 coma, although the total number of patients is small. Hopefully more data from this study will be forthcoming²².

Carnitine is a benign supplement and may be beneficial in cases of valproate related hepatotoxicity. Although not well studied and mostly confined to case reports, ursodeoxycholic acid has been used for drug induced cholestasis. It may protect hepatocytes and cholangiocytes from adverse effects of elevated bile salts⁹.

Poor prognostic signs with DILI include coagulopathy with encephalopathy. These patients warrant very close monitoring and consideration for liver transplant. Guidelines for liver transplant for non-APAP liver failure differ from those for APAP ALF. The King's College guidelines for non-APAP liver failure (of any etiology) are either a PT time > 100 seconds (INR > 6.5) or any three of age < 11 or > 40 years, etiology is non-A /non-B hepatitis or drug induced liver injury, jaundice of > 7 days prior to onset encephalopathy, PT time > 50 sec. (INR > 3.5), or serum bilirubin > 17 mg/dL⁹.

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