The Role of the Nephrologist in Management of Poisoning and Intoxication: Core Curriculum 2022

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Poisoning is a common problem in the United States. Acid-base disturbances, electrolyte derangements, or acute kidney injury result from severe poisoning from toxic alcohols, salicylates, metformin, and acetaminophen. Lithium is highly sensitive to small changes in kidney function. These poisonings and drug overdoses often require the nephrologist's expertise in diagnosis and treatment, which may require correction of acidosis, administration of selective enzyme inhibitors, or timely hemodialysis. The clinical and laboratory abnormalities associated with the poisonings and drug overdoses can develop rapidly and lead to severe cellular dysfunction and death. Understanding the pathophysiology of the disturbances and their clinical and laboratory findings is essential for the nephrologist to rapidly recognize the poisonings and establish an effective treatment plan. This installment of *AJKD*'s Core Curriculum in Nephrology presents illustrative cases of individual poisonings and drug overdoses and summarizes up to date information on their prevalence, clinical and laboratory findings, pathophysiology, diagnosis, and treatment.

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

In 2019, the American Association of Poison Control Centers (AAPCC) recorded over 2.1 million cases of human exposure to poisons. Although emergency physicians, hospitalists, and toxicologists manage many of these poisonings, the nephrologist is often necessary to manage severe acid-base disorders, electrolyte abnormalities, or kidney dysfunction. Further, hemodialysis can be an important component of treatment, facilitating effective removal of the parent toxin and injurious metabolites.

In this installment of *AJKD*'s Core Curriculum in Nephrology, we discuss the pathophysiology, diagnosis, and treatment of acute and chronic poisonings encountered by the nephrologist. These include toxic alcohol poisoning (methanol, ethylene glycol, diethylene glycol, propylene glycol, and isopropanol), salicylate intoxication, metformin-associated lactic acidosis, severe acetaminophen (paracetamol) poisoning, and lithium poisoning.

Additional Readings

➢ Ghannoum M, Nolin TD, Lavergne V, Hoffman RS; EXTRIP Workgroup. Blood purification in toxicology: nephrology's ugly duckling. *Adv Chronic Kidney Dis.* 2011;18(3):160-166. ★ESSENTIAL READING

➢ Gummin DD, Mowry JB, Beuhler MC, et al. 2019 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 37th annual report. *Clin Toxicol (Phila.)* 2020;57(12):1220-1413.

➢ Nelson LS, Howland MA, Lewin NA, et al. eds. *Goldfrank's Toxicologic Emergencies.* 11th ed. McGraw-Hill; 2018.

Toxic Alcohols

Case 1: Family members discover a 35-year-old man in his garage confused and poorly responsive. Paramedics find a suicide note and an open jug nearby. In the emergency department, he appears inebriated, with tachypnea, tachycardia, and blood pressure of 120/60 mm Hg. His blood chemistry values reveal the following concentrations: serum sodium ($[Na^+]$), 136 mEq/L; potassium ($[K^+]$), 3.2 mEq/L; [total CO_2], 10 mEq/L; and chloride ($[Cl^-]$), 100 mEq/L. The calculated serum osmolarity is 290 mOsm/L, and the measured serum osmolality by freezing point depression is 350 mOsm/kg H_2O.

Question 1: What would be your next step(s) in managing this patient?
a) Normal saline infusion at 150 mL/h.
b) Infusion of sodium bicarbonate 150 mEq added to 1 L of 5% dextrose in water at 150 mL/h.
c) Fomepizole at 15 mg/kg intravenously.
d) Obtain ethylene glycol and methanol results before selecting treatment.
e) Both (b) and (c).

For the answer to the question, see the following text.

Epidemiological Features

The prevalence of toxic alcohol poisoning varies greatly from compound to compound. In the 2019 AAPCC report, isopropanol was the most frequent cause of toxic alcohol poisoning (16,000 cases reported) followed by ethylene glycol and methanol. Diethylene glycol was a rare cause, but outbreaks may occur in developing countries without

strong pharmaceutical regulatory oversight. The prevalence of propylene glycol intoxication is unknown, but it is likely to be infrequent. The intoxications occur through different means, as summarized in Table 1.

In adults, methanol intoxication and ethylene glycol intoxication may develop after ingestion of adulterated liquids with a toxic alcohol substituted for ethanol. Methanol intoxication also occurs with ingestion or inhalation of automotive windshield-washer fluid or fuel-line antifreeze. Adults typically ingest ethylene glycol (antifreeze) in a suicide attempt. In children, most methanol and ethylene glycol ingestions unintentionally result from exploratory behavior.

Isopropanol intoxication is generally the consequence of ingesting rubbing alcohol, hand sanitizer, or various industrial products. Intoxication also occurs by inhalation or absorption through dermal or rectal routes.

Diethylene glycol intoxication can occur sporadically after ingestion of automotive brake fluids or industrial products. However, it most frequently occurs in outbreaks, particularly in children who have ingested consumer products or oral medications containing diethylene glycol improperly used as a diluent in lieu of propylene glycol. The earliest epidemic of diethylene poisoning due to contamination of drugs occurred in the United States in the 1930s, and it spurred the establishment of the US Food and Drug Administration (FDA). Outbreaks have subsequently occurred in several countries outside the United States including South Africa, India, Bangladesh, Haiti, and Panama. Children may be at higher risk than adults because of their smaller body surface area.

Propylene glycol intoxication may occur in the hospital setting with high-dose infusions of relaxants such as lorazepam or diazepam, both of which contain 40% propylene glycol. Propylene glycol is also the principal ingredient of automotive antifreeze products marketed as being "nontoxic" or "environmentally friendly." The actual prevalence of propylene glycol intoxication is unknown, but it is likely uncommon.

Pathogenesis

Except for isopropanol, the injurious effects of the toxic alcohols primarily result from accumulation of their toxic acid metabolites. Figure 1 illustrates the metabolism of the toxic alcohols. Alcohol dehydrogenase (ADH) is critical to the process, catalyzing oxidation of the toxic alcohols. This produces aldehydes (aside from acetone produced by metabolism of isopropanol) that then undergo further oxidation by aldehyde dehydrogenase to form carboxylic acid metabolites: methanol produces formic acid, ethylene glycol forms oxalic and glycolic acid, diethylene glycol forms 2-hydroxyethoxyacetic acid and

**Table 1.** Clinical and Laboratory Features of the Toxic Alcohols

Alcohol	MW (Da)	Change in Serum Osmolality	Common Sources	Common Clinical Features	Notable Laboratory Features	Half-life, h −EtOH	Half-life, h +EtOH
Methanol	32.04	3.09 mOsm/L per 10 mg/dL of alcohol	Windshield washer fluid, carburetor cleaner, octane boosters, racing fuels, adulterated ethanol ("moonshine")	Abdominal pain; decreased vision, blindness; rarely, Parkinson-like features	Osmolal gap; HAGMA	14-30	43-96
Ethylene glycol	62.07	1.60 mOsm/L per 10 mg/dL of alcohol	Antifreeze, engine coolants, deicing fluids	Inebriation, AKI	Osmolal gap, HAGMA, calcium oxalate crystalluria, elevated lactate with point-of-care analyzer	2-6	17-18
Isopropyl alcohol	60.10	1.66 mOsm/L per 10 mg/dL of alcohol	Rubbing alcohol, hand sanitizers	Inebriation, depressed sensorium, abdominal pain	Osmolal gap, acetonemia, spurious increase in creatinine (Jaffe reaction)	NA	NA
Propylene glycol	76.09	1.31 mOsm/L per 10 mg/dL of alcohol	Diluent in parenteral medications, "nontoxic" automotive antifreeze	Liver or kidney disease may increase likelihood of more severe toxicity	Increased osmolal gap; lactic acidosis; rarely, AKI	1.4-3.3	17
Diethylene glycol	106.12	0.9 mOsm/L per 10 mg/dL of alcohol	Automotive brake fluids, hydraulic fluids, adulterated liquid medications	Abdominal pain, nausea/vomiting, acute pancreatitis, AKI	Osmolal gap, HAGMA, AKI	4-6	Unknown

Abbreviations: AKI, acute kidney injury; +EtOH, with coingested alcohol; −EtOH, without coingested alcohol; HAGMA, high anion gap metabolic acidosis; MW, molecular weight; NA, not applicable.

A Metabolic Pathways of Toxic Alcohols
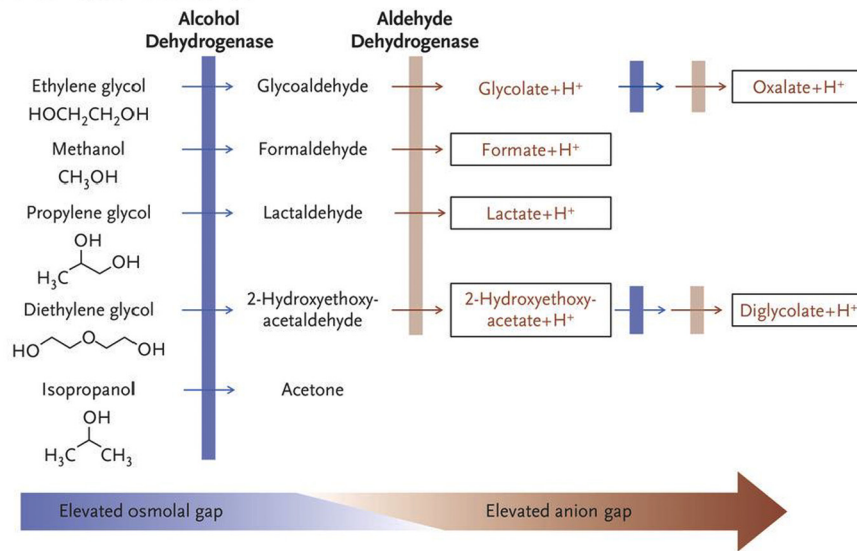
B Time Course of Changes in the Osmolal and Anion Gaps
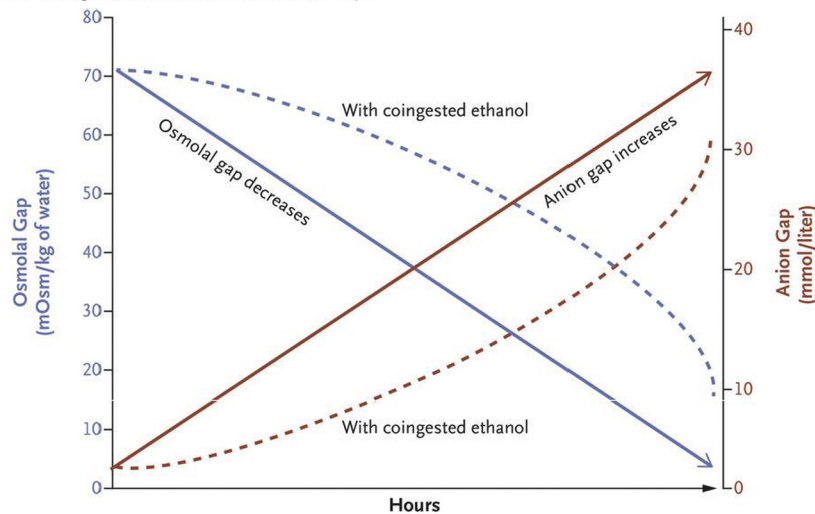
Figure 1. (A) Metabolic pathways of toxic alcohols. Alcohol dehydrogenase catalyzes the first oxidation of the toxic alcohols and is an important target for antidotal therapy. The enclosed boxes highlight the putative toxic metabolites. Methanol is metabolized to formic acid, ethylene glycol to oxalic and glycolic acid, diethylene glycol to 2-hydroxyethoxyacetic acid and glycolic acid, and propylene glycol to D-lactic and L-lactic acid. (B) Time course of changes in the osmolal and anion gaps with and without coingested ethanol. An increased osmolal gap is prominent early owing to the accumulation of the un-ionized alcohols. As metabolism proceeds, the osmolal gap declines with the formation of ionized metabolites. Conversely, the serum anion gap is lowest before the alcohol is metabolized and increases with the formation of ionized metabolites. The time course of these changes in both parameters varies among the alcohols. They typically evolve over several hours to over a day. Coingested ethanol impedes metabolism (dashed lines) and delays the onset of the high anion-gap acidosis. Original graphic ©2018 Massachusetts Medical Society; reproduced with permission of the copyright holder from Kraut & Mullins, 2018 (*N Engl J Med*. https://doi.org/10.1056/nejmra1615295).

diglycolic acid, and propylene glycol forms D-lactic and L-lactic acid.

The onset of toxicity after exposure to the toxic alcohols depends upon the rate of metabolism and the presence of coingested ethanol (Table 1). Coingestion of ethanol, the natural substrate of ADH, can markedly delay production of the toxic metabolites, making their recognition difficult. Spurious increments in blood lactate can occur in ethylene glycol poisoning due to glycolate interfering with the

lactate measurement when point-of-care instruments are used.

Clinical Features

To varying degrees, alcohols—particularly ethylene glycol and isopropanol—produce some inebriation. Accumulation of their toxic metabolites produces organ dysfunction. Methanol intoxication frequently impairs vision and can produce permanent blindness in some cases. Pulmonary

dysfunction, abdominal pain, coma, and, rarely, Parkinson-like symptoms can occur. The clinical abnormalities usually evolve over 6 to 24 hours, but coingested ethanol can delay the toxic effects. Rarely, neurologic sequelae may occur days or weeks after exposure.

Ethylene glycol metabolism forms glycolic acid and then oxalate crystals. Glycolic acid is the principal cause of acidosis. Oxalate crystals produce organ dysfunction including acute kidney injury (AKI). Cranial nerve damage, sometimes delayed for days, can also occur. Typically, the signs and symptoms develop in a characteristic fashion: neurologic dysfunction develops within the first 12 hours, followed by cardiac and pulmonary dysfunction in the next 12 hours, and AKI at 48 to 72 hours after exposure. However, dysfunction of all 4 organ systems can occur concomitantly. Coingested ethanol delays the accumulation of toxic metabolites and the appearance of clinical abnormalities.

Isopropanol intoxication depresses the sensorium and can cause respiratory dysfunction, cardiovascular collapse, acute pancreatitis, and hypotension-induced lactic acidosis. Serum isopropanol concentrations above 500 mg/dL (83 mmol/L) are clinically significant; those in excess of 1,500 mg/dL (250 mmol/L) result in deep coma. The major metabolite acetone can produce a spurious increase in serum creatinine concentration due to its interference with laboratory measurements using the Jaffe reaction.

Diethylene glycol ingestion can cause abdominal pain, nausea, vomiting, diarrhea, acute pancreatitis, altered mental status, hepatic disease, central and peripheral neuropathy (occasionally causing quadriplegia), AKI, and death. The AKI often appears many hours after exposure (8 to 24 hours), may require hemodialysis, and is a major cause of death. Indeed, diethylene glycol poisoning should be excluded in instances in which a cohort of children present concurrently with severe AKI requiring hemodialysis. Coingestion of ethanol can delay toxicity by as much as 48 to 72 hours. Cranial nerve palsies and other neurologic complications can appear several days after exposure.

Propylene glycol intoxication often leads only to an increase in the osmolal gap, but it can cause lactic acidosis and AKI. The predisposing factors are preexisting kidney disease, hepatic disease, or both. Patients receiving a continuous infusion for more than 48 hours of high-dose lorazepam (>10 mg/h), which contains 40% propylene glycol, are at higher risk.

Diagnosis

Because a history of the alcohol ingestion is often lacking, the presumptive diagnosis of toxic alcohol poisoning usually rests on a report of possible exposure in association with the aforementioned symptoms and physical findings and characteristic blood chemistry abnormalities. Chief among them are high serum osmolality and high anion gap metabolic acidosis.

High concentrations of the parent alcohol elevate the osmolal gap (measured osmolality in mOsm/kg H_2O minus the estimated osmolarity in mOsm/L) early in the clinical course. Accumulation of organic acid metabolites increases the serum anion gap as the poisoning progresses. The clinician must understand the utility and limitations of the serum osmolal and anion gaps for the diagnosis of toxic alcohol poisoning.

The normal serum osmolality is the sum of the activity of all the osmotically active particles in the blood. When concentrations are low, the serum osmolarity and osmolality are basically equal. There are a number of formulas to estimate the osmolarity of the blood. The most common is:

Serum osmolarity = $(2 \times [Na^+]) + ([SUN]/2.8) + ([Glucose]/18)$

where serum osmolarity and $[Na^+]$ are in mmol/L and concentrations of serum urea nitrogen (SUN) and glucose are in mg/dL (note that the equation includes factors to convert the non-International System of Units [SI] units usually used in the United States to SI units).

The 2 methods of measuring serum osmolality are freezing point depression and vapor pressure osmometry. Freezing point depression is more reliable. With vapor pressure osmometry, the volatile alcohols can evaporate, leading to a measured serum osmolality that is lower than it should be. If there are no exogenous osmotically active substances, the measured osmolality and estimated serum osmolarity should be essentially equivalent. By contrast, when there are osmotically active substances other than sodium, potassium, urea, and glucose, the measured serum osmolality should be greater than the estimated serum osmolarity (ie, an osmolal gap). But even if no other osmotically active substances are apparent, an osmolal gap averaging 8-9 mOsm/kg H_2O is common. An osmolal gap of less than 10-15 mOsm/kg H_2O is nondiagnostic and does not reliably exclude toxic alcohol poisoning. An osmolal gap of greater than 10-15 mOsm/kg H_2O suggests foreign osmotically active substances in the blood.

The normal osmolal gap reported by various clinical laboratories can vary substantially from 2 to 11 mOsm/kg H_2O. These differences have important clinical implications because the baseline osmolal gap is an important influence on the actual osmolal gap found when alcohols accumulate in blood. Consider the effect of an osmolal gap of 2, 0, 5, and 9 mOsm/kg H_2O baseline osmolal gap on the final osmolal gap noted with accumulation of different alcohols. A methanol or ethylene glycol concentration of 20 mg/dL is a widely accepted threshold for antidotal treatment. If the baseline osmolal gap were low (2 mOsm/kg H_2O), the osmolal gap produced by a concentration of 20 mg/dL will remain below 10 mOsm/kg H_2O. Even if the baseline osmolal gap were 5 mOsm/kg H_2O, only methanol at a concentration of 20 mg/dL will cause the osmolal gap to exceed 10 mOsm/kg H_2O. For diethylene glycol (which has a molecular weight of 106 Da), a

concentration of 20 mg/dL will increase the osmolal gap by just 2 mOsm/kg H_2O. A diethylene glycol concentration above 50 mg/dL would be required to raise the serum osmolality by more than 5 mOsm/kg H_2O.

In addition, as listed in Table 1, each alcohol has a different metabolic rate (the half-life is as short as 8 hours for methanol and 3 hours for ethylene glycol). As a result, if there has been substantial time since ingestion, much of the parent alcohol could have been metabolized to its organic acid metabolite, lowering the serum osmolality and thereby the osmolal gap. Thus, if the baseline osmolal gap is low or even negative, the accumulation alcohol has a high molecular weight, or significant metabolism of the alcohol has occurred, the osmolal gap may be normal. For these reasons, serum osmolal gap alone may not be a sensitive test for detecting exposure to toxic alcohol.

Despite these caveats, serial changes in the osmolal gap reflect changes in the parent alcohol's concentration, particularly during hemodialysis. An osmolal gap ≤10 mOsm/kg H_2O may be one indicator to discontinue therapy.

Disorders other than toxic alcohols such as lactic acidosis, diabetic ketoacidosis, alcoholic ketoacidosis, chronic kidney disease, and sickle cell syndrome may increase in the serum osmolal gap, but it rarely exceeds 20 mOsm/kg. To this point, in one study, 77% of 341 patients from a single hospital with an elevated serum osmolal gap of 14 mOsm/kg or greater had disorders other than toxic alcohol intoxication.

Similar limitations affect in the use of the serum anion gap. Although an elevated serum anion gap is frequently important in indicating that there has been a toxic alcohol exposure, an increase in the serum anion gap can be absent for several reasons.

First, the span of lowest to highest serum anion gap values in a population of normal individuals is about 10 mEq/L. For patients with a baseline serum anion gap at the low end of range, the serum anion gap might remain in the normal range even in the presence of substantial accumulation of the organic acid anions. Also, the magnitude of the serum anion gap will depend on when it is sampled. If blood is sampled early after the toxic alcohol exposure before extensive metabolism of the toxic alcohol, the serum anion gap might be normal. Figure 1 illustrates the typical changes in the falling serum osmolal gap and rising serum anion gap during the course of toxic alcohol exposure.

Many hospital laboratories can perform a "volatile screen" using gas chromatography to detect methanol, ethanol, isopropanol, and acetone but not ethylene glycol. However, this is not a universally available methodology.

Lactate measurements by point-of-care analyzers (using lactate oxidase reaction) will give falsely elevated lactate concentrations in the presence of glycolate (acid metabolite of ethylene glycol). Lactate oxidase does not distinguish between lactate and glycolate, which differ by only 1 methyl group. This is a useful clue in cases of suspected ethylene glycol poisoning. Lactate measurements using lactate dehydrogenase (LDH) are specific for lactate. In hospitals with both methods available, a large difference between the rapid, point-of-care lactate measurement and a lactate measurement by LDH strongly suggests ethylene glycol poisoning.

Automotive antifreeze usually contains fluorescein to detect radiator leaks. Case reports suggest that examination of the urine under ultraviolet light using a Wood's lamp might detect antifreeze exposure. However, other substances in normal urine will fluoresce under ultraviolet light, so this method is highly unreliable.

Oxalate crystals in the urine also suggest ethylene glycol poisoning but may be present in other conditions without ethylene glycol poisoning. The presence or absence of oxalate crystals in the urine does not reliably detect or exclude ethylene glycol poisoning.

Definitive diagnosis of methanol and ethylene glycol uses high performance gas or liquid chromatography. This process is labor intensive, expensive, and not available in most clinical laboratories. Therefore, results can take several hours or even days. Thus, there is an unmet need for simple, quick, and inexpensive tests to detect and measure the toxic alcohols.

One such test to detect ethylene glycol in serum is a modification of a veterinary assay using glycerol dehydrogenase to oxidize ethylene glycol to glycoaldehyde while reducing the cofactor nicotinamide adenine dinucleotide (NAD) to NADH. This has no interference by propylene glycol, ethanol, methanol, diethylene glycol, or fomepizole. It correlates closely with results using gas chromatography, can detect levels as low as 5 mg/dL, and is linear up to 300 mg/dL. This test, available from Catachem, currently lacks FDA approval.

A similar enzymatic test measures methanol in serum samples with alcohol oxidase to convert methanol to formaldehyde and then formaldehyde dehydrogenase to reduce NAD to NADH. The assay is adaptable to most spectrophotometric clinical analyzers, is linear to a methanol concentration of 100 mg/dL (31 mmol/L), and shows no interference from ethanol up to a concentration of 690 mg/dL (a human is usually comatose at 400 mg/dL ethanol). This test, also from Catachem, currently lacks FDA approval.

Treatment

Delayed treatment of toxic alcohol poisoning inevitably results in worse outcomes. Therefore, some experts recommend early treatment when toxic alcohol poisoning is strongly suspected or there is unexplained metabolic acidosis.

Treatment of toxic alcohol poisonings primarily includes antidotal use of fomepizole or ethanol (inhibitors of ADH) to delay or prevent metabolism to their toxic metabolites, and hemodialysis to remove the parent alcohol and its toxic byproducts. Figure 2 shows an algorithm consistent with our approach and recommendations from
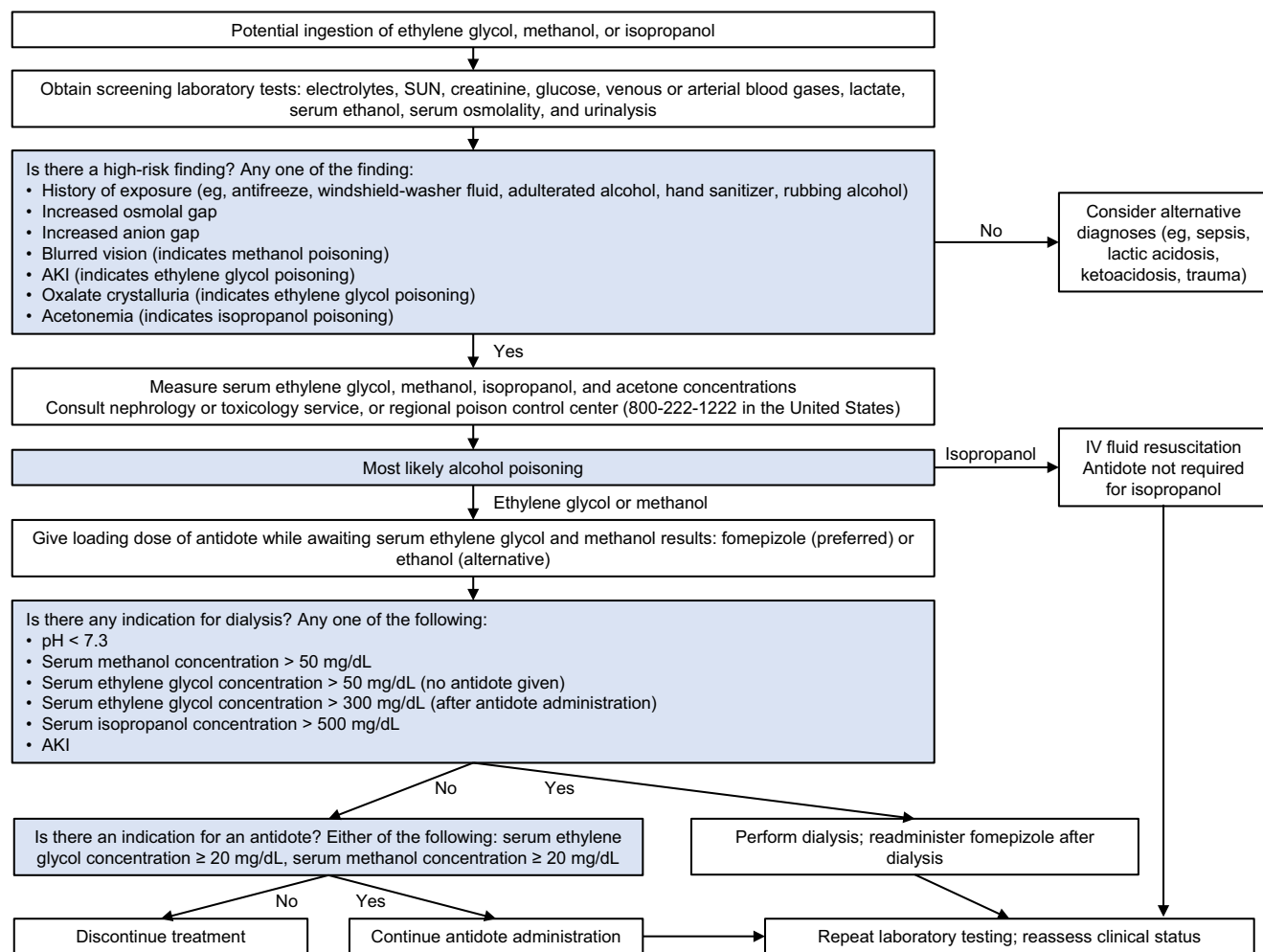
Figure 2. Algorithm for the diagnosis and treatment of methanol, ethylene glycol, and isopropanol intoxications. This algorithm provides an approach to the diagnosis and treatment of the 3 most common poisonings. A similar approach might be useful for diethylene glycol poisoning, although this poisoning is rare. One criterion for dialysis (serum ethylene glycol concentration > 300 mg/dL after antidote administration) reflects the practice of the second author. Conversion factors for methanol, ethylene glycol, and isopropanol in mmol/L, ×0.3121, ×0.1611, and ×0.1664, respectively. Abbreviations: AKI, acute kidney injury; IV, intravenous; SUN, serum urea nitrogen. Original graphic ©2018 Massachusetts Medical Society; reproduced in modified form with permission of the copyright holder from Kraut & Mullins, 2018 (*N Engl J Med.* https://doi.org/10.1056/nejmra1615295).

the literature. Box 1 shows indications for emergency hemodialysis.

Methanol and Ethylene Glycol

Gastric decontamination is usually not helpful because the absorption of methanol and ethylene glycol in the gastrointestinal tract is so rapid. Intravenous administration of base (sodium bicarbonate) corrects metabolic acidosis and increases methanol's ionization to formic acid. This promotes its urinary excretion and reduces its penetration into the optic nerve.

Treatment guidelines recommend an ADH inhibitor when the serum methanol or ethylene glycol concentration exceeds 20 mg/dL (6 mmol/L of methanol or 3 mmol/L of ethylene glycol). Other indications include a high

suspicion of toxic alcohol ingestion with either an osmolal gap greater than 10 mOsm/kg H_2O or metabolic acidosis of unknown cause.

Intravenous ethanol was the major therapy before FDA approval of fomepizole (4-methylpyrazole) 2 decades ago. It remains an alternative, particularly when fomepizole is not available. It is an effective competitive inhibitor of ADH. The target ethanol concentration is 100 mg/dL (22 mmol/L). Ethanol is generally available and inexpensive but requires compounding by a pharmacist for intravenous (IV) use. The serum ethanol concentration requires careful monitoring, so patients usually require hospitalization in the intensive care unit. It may be difficult to discern the degree of inebriation attributable to the toxic alcohol and to the ethanol used as an antidote.

Box 1. Indications for Hemodialysis

Toxic Alcohols
- Ethylene glycol or methanol concentration > 50 mg/dL without ADH inhibitor (fomepizole or ethanol)
- Ethylene glycol concentration > 200-300 mg/dL *with* ADH inhibitor *and* normal kidney function
- Methanol concentration > 70 mg/dL *with* ADH inhibitor *and* normal kidney function
- Isopropanol concentration > 400-500 mg/dL
- Any toxic alcohol: severe acidemia (pH < 7.2) *or* AKI

Salicylate
- Concentration > 7.2 mmol/L (100 mg/dL)
- Concentration > 6.5 mmol/L (90 mg/dL) with AKI or CKD
- Concentration > 6.5 mmol/L (90 mg/dL) after IV fluids, sodium bicarbonate, and potassium
- Concentration > 5.8 mmol/L (80 mg/dL) after IV fluids, sodium bicarbonate, and potassium *and* with AKI or CKD
- Altered mental status
- Respiratory distress or new hypoxemia requiring supplemental oxygen
- pH ≤ 7.2

Metformin
- Lactate > 10 mmol/L
- pH < 7.2
- Shock
- Failure of standard supportive measures (IV fluids, sodium bicarbonate)
- Decreased level of consciousness

Lithium
- Concentration > 5.0 mEq/L
- Concentration > 4.0 mEq/L with AKI or CKD
- Decreased level of consciousness, seizures, or life-threatening dysrhythmias at any lithium concentration
- Estimated time to reach lithium concentration < 1 mEq/L exceeds 36 hours

Acetaminophen
- Concentration > 1,000 mg/L (6,620 μmol/L)
- Concentration > 700 mg/L (4,630 μmol/L) with altered mental status, metabolic acidosis, or elevated lactate

Based on information from www.extrip-workgroup.org and additional readings. Abbreviations: ADH, alcohol dehydrogenase; AKI, acute kidney injury; CKD, chronic kidney disease; IV, intravenous.

Fomepizole is a strong inhibitor of ADH with very high enzyme affinity (8,000 times that of ethanol). It is effective at micromolar concentrations, does not have serious side effects, and patients do not need to be monitored in an intensive care unit. The loading dose is 15 mg per kilogram of body weight and the subsequent maintenance dose is 10 mg/kg every 12 hours. Given that the drug may induce its own metabolism by cytochrome P450 enzymes, the maintenance dose is raised to 15 mg/kg every 12 hours after 48 hours. Because hemodialysis removes fomepizole, patients undergoing hemodialysis should receive it immediately after a hemodialysis session.

Both fomepizole and ethanol are effective inhibitors of ADH, but there is no controlled clinical trial directly comparing their outcomes. In the United States,

fomepizole is the most common antidote to treat methanol and ethylene glycol poisonings. By contrast, outside the United States, fomepizole is less readily available, and ethanol (either IV or oral) is more frequent. Although fomepizole is more expensive than ethanol, fomepizole results in lower mortality and fewer adverse effects. Oral ethanol is an effective first aid treatment until a poisoned patient can reach a hospital with access to fomepizole or hemodialysis.

Methanol and ethylene glycol both have low molecular weights, high water solubility, low protein binding, and small volumes of distribution. These characteristics favor their rapid removal by extracorporeal toxin removal (ECTR).

The Extracorporeal Treatments in Poisoning Workgroup (EXTRIP, www.extrip-workgroup.org) has guidelines for the use of hemodialysis in the treatment of methanol poisoning. They recommend hemodialysis with severe metabolic acidosis, serum methanol concentrations higher than 50 mg/dL (16 mmol/L), deteriorating vital signs despite supportive care, and AKI or problems with vision. Intermittent hemodialysis with a large (>2.1) surface area dialyzer and high-flux membrane is highly effective in the rapid removal of the toxic alcohols. Continuous kidney replacement therapy (CKRT) removes toxic alcohols more slowly but may be safer for hemodynamically unstable patients. Antidotal treatment of methanol or ethylene glycol intoxication without hemodialysis has been reported without adverse consequences. However, fomepizole (without hemodialysis) extends the half-lives for elimination of methanol and ethylene glycol to as long as 71 hours and 16 hours, respectively (these values are only 2.5 and 2.7 hours, respectively, with hemodialysis). Hemodialysis may shorten the total hospital stay but requires more critical care resources. The comparative costs of the 2 treatment strategies (ADH inhibition with or without hemodialysis) varies according to several factors, including absorbed dose of the toxic alcohol, drug costs, cost of hemodialysis, and room costs. Although controlled studies are not available, treatment in children is similar to that in adults.

EXTRIP has reviewed ECTR for ethylene glycol. We expect that a published guideline for ECTR in ethylene glycol poisoning is forthcoming.

Before the advent of fomepizole, any concentration of a toxic alcohols above 50 mg/dL warranted urgent hemodialysis in addition to antidotal treatment. Clinical experience in the 2 decades since the FDA approval of fomepizole has demonstrated that higher hemodialysis thresholds are possible when using fomepizole. This is more clearly true with ethylene glycol, which undergoes renal clearance, but less so for methanol, which has much lower renal clearance and little clearance in exhaled breath. Experts suggest that fomepizole allows a hemodialysis threshold as high as 300 mg/dL for ethylene glycol when acidosis is mild or not present. EXTRIP guidelines indicate a hemodialysis threshold of 70 mg/dL for methanol poisoning treated with fomepizole.

Adjunctive treatments may promote conversion of toxic metabolites to less toxic metabolites. For ethylene glycol poisoning, thiamine and magnesium promote conversion of glyoxylate to α-ketoadipate. Pyridoxine (vitamin B$_6$) promotes conversion of glycolate to glycine. For methanol poisoning, high-dose folic acid or folinic acid (1 mg/kg of either) promotes conversion of formic acid to carbon dioxide and water. No prospective trials show the magnitude of these effects.

Propylene Glycol

Toxicity of propylene glycol is low. If hyperosmolality and lactic acidosis occur, discontinuation of the medication containing propylene glycol and administration of IV fluids are generally sufficient treatment. Fomepizole is generally unnecessary. Hemodialysis may be helpful in significant lactic acidosis with AKI.

Diethylene Glycol

Most experts recommend fomepizole. However, because AKI in patients with this poisoning is often severe enough to produce marked kidney failure, intermittent hemodialysis along with administration of fomepizole is often necessary.

Isopropanol

Generally, supportive measures are sufficient. Intermittent hemodialysis has been recommended when the serum isopropanol concentration is ≥500 mg/dL (83 mmol/L), or if hypotension is present or severe lactic acidosis develops. In contrast to the other toxic alcohols, alcohol dehydrogenase inhibitors are unnecessary.

Review of Case 1

Returning to question 1, (e) is the best answer. Correction of acidemia and inhibition of ADH are both early critical actions. This is true for both ethylene glycol and methanol. It has been suggested that provision of sdoium bicarbonate will increase the urinary excretion of formate and glycolate. Timely ethylene glycol concentrations are seldom available, so critical treatment must precede diagnostic certainty. The garage in the example may have antifreeze (ethylene glycol), windshield washer fluid (methanol), or brake fluid (diethylene glycol, glycol ethers).

Additional Readings

➢ Hassanian-Moghaddam H, Zamani N, Roberts DM, et al. Consensus statements on the approach to patients in a methanol poisoning outbreak. *Clin Toxicol (Phila.)* 2019;57(12):1129-1136.
➢ Kraut JA. Diagnosis of toxic alcohols: limitations of present methods. *Clin Toxicol (Phila.)* 2015;53(7):589-595.
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➢ Kraut JA, Mullins ME. Toxic alcohols. *N Engl J Med.* 2018;378(3):270-280. ★ESSENTIAL READING

➢ Kraut JA, Xing SX. Approach to the evaluation of a patient with an increased serum osmolal gap and high-anion-gap metabolic acidosis. *Am J Kidney Dis.* 2011;58(3):480-484.
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Salicylate Intoxication

Case 2: A 48-year-old man arrives by ambulance after a large dose of unknown medication. In the emergency department, he has altered mental status; blood pressure, 110/70 mm Hg; respiratory rate of 30; heart rate of 130, and temperature of 39°C. He complains of hearing a loud "buzzing" sound. His blood chemistry values reveal the following: [Na$^+$], 135 mEq/L; [K$^+$], 3.1 mEq/L; [total CO$_2$], 12 mEq/L; [Cl$^-$], 102 mEq/L; pH 7.40; and P$_{CO_2}$, 18 mm Hg.

Question 2: Which of the items presented above is most suggestive of salicylate intoxication rather than some other intoxication?
a) Altered mental status
b) Buzzing sound in his ears
c) Hypokalemia
d) Tachycardia
e) Tachypnea

For the answer to the question, see the following text.

Epidemiology

Salicylate intoxication can be either acute or chronic. Acute salicylate intoxication occurs after ingestion of ≥100 to 150 mg/kg salicylate or ingestion of small amounts of methyl salicylate (as low as 5 mL of oil of wintergreen). Rarely, repeated topical use of topical analgesic cream (up to 30% methyl salicylate) may cause serious poisoning. Headache powders (most commonly used in the southeastern United States) provide a rapidly absorbable form of acetylsalicylic acid with caffeine.

The most common source of salicylate poisoning is acetylsalicylic acid or aspirin (the latter is a trade name in some countries but a generic name in others, including the United States). Acetylsalicylic acid undergoes rapid hydrolysis to salicylate in the gastrointestinal tract, liver, and bloodstream. Acute salicylate intoxication most commonly occurs in adults taking salicylates in a suicide attempt or in children after unintentional exposure. US poison centers record approximately 25,000 salicylate exposures annually.

Chronic poisoning is more common in elderly individuals. Preexisting kidney disease or compromise of kidney function produced by the salicylate itself can lead to an increase in blood salicylate concentrations and worsen toxicity.

Pathogenesis

Salicylates directly stimulate the respiratory center of the medulla, producing an increase in both the rate and depth of respiration resulting in respiratory alkalosis. They also uncouple oxidative phosphorylation and inhibit citric acid cycle dehydrogenases, causing a shift in metabolism due to increased glycolysis. This leads to generation of lactic acid and stimulation of hormone-sensitive lipase, leading to increased lipolysis and increased ketone production. Organic acid transporters in the proximal tubule of the kidney excrete these products, which compete for uric acid excretion. The kidney freely excretes only about 10% of unchanged salicylic acid.

Clinical Features

Patients with acute salicylate intoxication can present with confusion, agitation, disorientation that can progress to coma, shortness of breath, and tinnitus (or other hearing disturbances). Physical findings can include hyperventilation, evidence of volume depletion, noncardiogenic pulmonary edema, hematemesis, and petechiae. The latter may result from platelet dysfunction. A chest radiograph can reveal pulmonary opacities. Symptoms and signs can be subtle and insidious and may initially be misattributed to other causes such as sepsis.

When toxicity occurs in individuals taking salicylates for treatment of chronic diseases, there may be no overt evidence of excess ingestion. Agitation, confusion, hallucinations, slurred speech, seizures, and coma appear to be more frequent in those with chronic salicylate poisoning than with acute intoxication. These patients often have a delay in diagnosis of salicylate intoxication. A delay in diagnosis and initiation of therapy may explain, in part, the higher morbidity reported for chronic intoxication than with acute intoxication.

Diagnosis

Prominent laboratory abnormalities include acid-base disturbances. In children, there is often an early, transient respiratory alkalosis followed by metabolic acidosis. In adults, approximately 20% will have respiratory alkalosis alone, and 56% will have combined respiratory alkalosis and high anion gap metabolic acidosis. In both groups, the respiratory alkalosis results from stimulation of the respiratory center by salicylate.

Less commonly, a normal anion gap metabolic acidosis can develop due to excretion of sodium and potassium salts in the urine with subsequent retention of chloride. The normal anion gap metabolic acidosis can also result in a false hyperchloremia due to salicylate interference with the measurement of chloride. The latter effect can rarely cause a negative anion gap. Hypokalemia results from increased losses of potassium in the urine due to increased excretion of the organic acid anions, augmented aldosterone concentrations, and increased distal sodium delivery.

Measurement of salicylate concentration best confirms the diagnosis. Tests for salicylate are simple and generally available in all clinical laboratories.

Treatment

Question 3: Which of the following is true?
a) Hemodialysis is usually necessary only if the salicylate concentration is greater than 100 mg/dL.
b) Tachypnea is a sign of respiratory distress, and the patient requires intubation before considering hemodialysis.
c) Hemodialysis should commence as quickly as possible.
d) Hemodialysis is only necessary if a trial of sodium bicarbonate fails to lower the salicylate concentration.
e) Hemodialysis is only necessary if the serum potassium concentration is high in a salicylate-poisoned patient.

For answer to the question, see the following text.

Aggressive volume resuscitation with normal saline or lactated Ringer solution is important as fluid losses are common. However, once euvolemia is achieved, large quantities of fluid to induce forced diuresis is not recommended. Oral activated charcoal reduces further salicylate absorption when given within 1 to 2 hours of ingestion and may be useful beyond 2 hours if persistently high salicylate concentrations suggest the possibility of a gastric bezoar of acetylsalicylic acid.

Salicylic acid is a weak acid (pKa 2.97), and therefore alkalinization of the blood and urine with IV sodium bicarbonate is important. Alkalinizing the serum decreases salicylate concentrations in the central nervous system. Alkalinizing the urine (target urine pH of 7.5 or greater) will increase excretion of salicylate. Increasing urine pH by 1 unit from 6.5 to 7.5 can triple urinary salicylate clearance. Oral bicarbonate should be avoided because it might enhance gastrointestinal absorption. Because bicarbonate administration can exacerbate any systemic alkalemia present, blood gases should be monitored carefully during therapy. Also, alkalemia can worsen any hypocalcemia, making monitoring of ionized calcium important.

Salicylate-poisoned patients generally present with mild hypokalemia. Potassium replacement (both IV and orally) should accompany sodium bicarbonate administration. This prevents worsening hypokalemia and facilitates urinary alkalinization.

Hemodialysis is the fastest and most effective method of eliminating salicylate from the body. Salicylate has low molecular weight, low volume of distribution, high water solubility, and limited protein binding. Hemodialysis should occur early when indications are present. Delaying hemodialysis increases mortality. Box 1 shows indications for emergency hemodialysis. Absolute indications for hemodialysis include a salicylate blood concentration of 90 mg/dL (6.5 mmol/L), regardless of the presence of signs or symptoms. Other indications for hemodialysis regardless of concentration include altered mental status, decreased kidney function, or acute respiratory distress. Promptly removing the

drug at this stage can limit accumulation in tissue and prevent severe toxic effects. Intermittent hemodialysis is the preferred method, but hemoperfusion and CKRT are acceptable should intermittent hemodialysis not be available or if the patient is hemodynamically unstable.

Observation of the patient with close monitoring of serum salicylate concentrations and blood pH are important until the patient has clinically improved and serum salicylate concentration has fallen considerably.

Review of Case 2

Returning to question 2, the best answer is (b) the buzzing sound in his ears (tinnitus). The other findings are typical of salicylate poisoning but overlap with other conditions such as diabetic ketoacidosis, sepsis, methylxanthine poisoning, and alcoholic ketoacidosis.

The best answer to question 3 is also (b): hemodialysis should commence as soon as possible because delays in hemodialysis can result in a fatal outcome. Tachypnea, altered mental status, and hyperthermia indicate severe toxicity in this patient.

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Acetaminophen (Paracetamol)

Case 3: A 29-year-old woman comes to the emergency department after texting a friend that she had ingested "handfuls" of acetaminophen from a container bought earlier in the day at a "big box" retailer. She arrives approximately 6 hours after ingestion. Her blood chemistry values reveal the following: [Na+], 140 mEq/L; [K+] 3.5 mEq/L; [Cl-], 100 mEq/L; [total CO2], 10 mEq/L; [SUN], 25 mg/dL; serum creatinine concentration ([Scr]), 1.5 mg/dL (134 μmol/L); pH 7.21; and PCO2, 26 mm Hg. Her serum acetaminophen concentration is 980 mg/L (6,500 μmol/L). Her serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are 122 and 115 IU/L, respectively.

Question 4: Which one of the following regarding hemodialysis in acetaminophen overdose is true?

a) Acetaminophen has a high protein binding in the plasma and is not easily dialyzable.

b) Hemodialysis is only indicated if antidotal treatment with acetylcysteine fails to reduce the acetaminophen concentration.

c) Indications for hemodialysis include serum acetaminophen concentration > 900 mg/L (6,000 μmol/L) or the presence of severe metabolic acidosis.

d) AST activity greater than 1,000 IU/L is an indication for hemodialysis.

For answer to the question, see the following text.

Epidemiology

Acetaminophen (paracetamol) is the most frequent pharmaceutical agent involved in human poisonings. It accounts for approximately 5% of the over 100,000 cases reported annually to US poison centers and remains a leading cause of poisoning death (overshadowed only by street drugs such as heroin or illicit fentanyl).

Pathogenesis

The principal toxic effects occur in the liver. Overdoses of acetaminophen saturate the glucuronide and sulfate conjugation pathways, and a larger fraction of the drug undergoes oxidation (mainly by cytochrome P450 2E1 isozyme [CYP2E1]) to N-acetyl parabenzoquinonimine (NAPQI). NAPQI is a potent oxidant that binds sulfhydryl (-SH) groups on intracellular proteins and denatures them, causing hepatocellular injury. Glutathione, an antioxidant sulfhydryl donor, binds NAPQI to prevent cellular injury. This process consumes glutathione, and hepatotoxicity results when NAPQI depletes available glutathione.

Three aspects of acetaminophen poisoning may come to the attention of a nephrologist. The first is severe metabolic acidosis. Extremely large overdoses (eg, >30 g) cause early metabolic acidosis due to mitochondrial dysfunction and impaired oxidative phosphorylation developing well before the hepatic transaminase activities reach their peaks. These cases involve acetaminophen concentrations above 700 mg/L (4,600 μmol/L).

The second is AKI after acute acetaminophen overdose. This occurs in approximately 2% of all acetaminophen overdoses but may occur more frequently in severe overdoses. In most cases, Scr slowly rises to a peak within 1 week of the overdose. Scr gradually returns to normal; patients seldom require hemodialysis.

The third and rarest is high anion gap metabolic acidosis due to 5-oxoproline (pyroglutamic) in a small number of patients with chronic acetaminophen exposure (including therapeutic doses). The actual prevalence of this complication is unknown. Formation of 5-oxoproline reflects disordered glutathione production and metabolism. Most of these cases likely reflect pyroglutamic acidosis due

to inherited enzyme deficiencies or malnutrition. In case of unexplained high anion gap metabolic acidosis (HAGMA) with concern for 5-oxoproline, a reference laboratory that screens newborns for inherited metabolic defects can detect and measure 5-oxoproline. Although some authors have suggested using N-acetylcysteine (NAC) for this problem, supportive care and discontinuing acetaminophen exposure are likely the mainstays of treatment.

Clinical Findings

On the first day after an acetaminophen ingestion, the patient may have nausea and abdominal pain or may be asymptomatic. Rising AST and ALT activities will become apparent on day 2, with peak values around day 3. The international normalized ratio (INR) may rise about 1 day after the rise in AST and ALT. Peak toxicity occurs around day 3 or 4. Severe cases may have hepatic encephalopathy and cerebral edema. AKI with acute tubular necrosis may appear. Following this, patients will either recover or die (unless they receive a liver transplant).

Kings College Criteria for liver transplantation include a blood pH < 7.30 at any time *or* a composite of Scr > 3.3 mg/dL, prothrombin time >100 seconds, and severe (grade III or IV) hepatic encephalopathy. Lactic acidosis and hypoglycemia are sensitive indicators of severe hepatotoxicity. Blood lactate concentrations above 3.0 mmol/L on initial assessment or above 2.5 mmol/L after fluid resuscitation are highly sensitive for acute liver failure.

Diagnosis

Because there are no early signs or symptoms that reliably indicate toxicity, the diagnosis depends upon the serum acetaminophen concentration. The Rumack-Matthew nomogram determines the risk of hepatotoxicity by plotting serum acetaminophen concentration versus time after ingestion for any single serum acetaminophen concentration drawn at least 4 hours after ingestion. If the acetaminophen concentration exceeds the treatment line starting at 150 mg/L (993 µmol/L) at 4 hours, the patient should receive antidotal NAC either IV as Acetadote or orally as Mucomyst.

Treatment

The main therapeutic measures are supportive care and the administration of NAC, which as a sulfhydryl donor directly reduces NAPQI and repletes glutathione.

Severe cases with profound metabolic acidosis and very high acetaminophen concentrations (exceeding 700 mg/L or 4,630 µmol/L) warrant hemodialysis. Acetaminophen is water soluble and has a low molecular weight (151.2 Da), low protein binding, and a low volume of distribution (0.9 L/kg). Hemodialysis removes acetaminophen and corrects acidosis. Intermittent hemodialysis is the preferred modality, but CKRT is acceptable if the patient is hemodynamically unstable or if hemodialysis is unavailable.

Fomepizole, the ADH antagonist used in toxic alcohol poisoning, also blocks CYP2E1, the main enzyme that oxidizes acetaminophen to NAPQI. Case reports and case series suggest that fomepizole may be useful in patients with extremely high acetaminophen concentrations (>700 mg/L or >4,630 µmol/L) with metabolic acidosis.

Review of Case 3

The best answer for question 4 is (c), the indications for hemodialysis include serum acetaminophen concentration > 900 mg/L or the presence of severe metabolic acidosis. One of the major indications for initiation of hemodialysis is a markedly elevated serum concentration of acetaminophen or the presence of a severe metabolic acidosis.

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Metformin

Case 4: *A 63-year-old man comes to the emergency department reporting a headache. The patient has a history of type 2 diabetes mellitus for which he takes metformin and small doses of insulin. He is awake and responsive. His blood pressure is 110/70 mm Hg without orthostatic changes. His blood chemistry values reveal the following: $[Na^+]$, 138 mEq/L; $[K+]$, 3.0 mEq/L; [total CO_2], 8 mEq/L; $[Cl^-]$, 100 mEq/L; [SUN], 25 mg/dL; [Scr], 2.5 mg/dL; pH, 7.15; and P_{CO_2}, 24 mm Hg. His initial lactate concentration is 15 mmol/L. A point-of-care ketone measurement (β-hydroxybutyrate) is 0.5 mmol/L.*

Question 5: Which of the following statements is true?
a) This patient has diabetic ketoacidosis and requires insulin in addition to IV fluid resuscitation.
b) Lactic acidosis only occurs in patients with metformin overdose.
c) Lactic acidosis can develop in patients taking therapeutic doses of metformin.
d) Hemodialysis does not remove metformin.

For the answer to the question, see the following text.

Epidemiology

Metformin is one of the most frequently prescribed diabetic medication in the world and is first-line therapy in the treatment of type 2 diabetes mellitus. Complications appearing in as many as 20% to 30% of patients are not life threatening and usually include nausea, vomiting, and decreased appetite.

Metformin-associated lactic acidosis (MALA) occurs in 3 to 10 cases per 100,000 patient-years. Mortality can be as high as 61% in some cases. Predisposing conditions include hepatic and acute or chronic kidney disease. For this reason, metformin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) of ≤30 mL/min/1.73 m^2 (CKD 4 or 5). Also, clinicians should be cautious in administering metformin to individuals with an eGFR ≤45 mL/min/1.73 m^2 (CKD 3b) or who have potentially unstable kidney function.

Pathogenesis

Metformin inhibits glycerol-3-phosphate dehydrogenase and the glycerophosphate shuttle. This decreases the mitochondrial redox state and increases the cytosolic redox state, reducing conversion of lactate to pyruvate in the cytosol. Also, inhibition of the mitochondrial respiratory chain complex in peripheral tissues augments lactic acid production.

Clinical Findings

Gastrointestinal symptoms are common in patients with metformin-related lactic acidosis, but nonspecific signs may dominate. In severe cases, patients may have serious hemodynamic instability and depressed consciousness. Abdominal tenderness may mimic an acute abdomen. Laboratory findings include elevated lactate concentrations (>5 mmol/L) and acidemia. Because hepatic and kidney disease are predisposing factors, it is common to find evidence of both kidney and liver disease.

Treatment

Treatment includes sodium bicarbonate to treat the acidemia and supportive therapy to stabilize the blood pressure. Mortality approaches 40% with high blood concentrations (above 50 mg/L or 388 μmol/L), but most clinical laboratories cannot measure metformin concentrations. Early hemodialysis is the most effective therapy to remove metformin and to correct the acidosis. Box 1 shows indications for emergency hemodialysis.

Intermittent hemodialysis is effective in hemodynamically stable patients with a drug clearance of 200 mL/min. CKRT is acceptable in hemodynamically challenged patients.

Review of Case 4

The best answer to question 5 is (c), lactic acidosis occurs most often among patients taking therapeutic doses of metformin. Lactic acidosis does not require acute overdose of metformin. Hemodialysis removes metformin and corrects acidosis.

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Lithium

Case 5: A 55-year-old woman arrives to the emergency department via the emergency medical service after neighbors found her with confusion. She had been well until she developed an acute diarrheal illness for the past 2 days. Her basic metabolic panel reveals AKI with a [Scr] of 2.4 mg/dL (compared with 1.2 mg/dL 1 month earlier). Her anion gap is 6 mmol/L (compared with 10 mmol/L 1 month earlier). Further history reveals that she takes lithium carbonate for bipolar disorder and that her psychiatrist increased her dose 1 month earlier.

Question 6: Which of the following statements are true?
a) Forced diuresis with normal saline and IV furosemide is the appropriate treatment.
b) Sodium polystyrene resin (Kayexalate) is effective in removing lithium.
c) The indication for hemodialysis depends solely on the serum concentration of lithium.
d) Central nervous system dysfunction is an indication for hemodialysis regardless of the lithium concentration.

For the answer to the question, see the following text.

Lithium salts were first shown to have benefit in mania and bipolar disorder in 1949 in Australia. Subsequent studies in the 1950s to the 1970s corroborated its use. The exact mechanism of action remains incompletely understood but may involve inositol metabolism or modulation of serotonin release.

Lithium (usually as lithium carbonate) has a very narrow therapeutic range (serum lithium concentration [Li$^+$] usually between 0.6 and 1.3 mmol/L) and is sensitive to modest changes in kidney function. Acute-on-chronic lithium toxicity most often results from AKI from other causes (such as dehydration from diarrhea) or from rapid escalation of the dose. Acute overdose can rapidly produce high lithium concentrations.

Hemodialysis effectively clears lithium, which has a molecular weight of 7 Da. Its volume of distribution is near 1 L/kg. Due to high intracellular concentrations, $[Li^+]$ often rebounds after hemodialysis due to redistribution from the intracellular space.

Indications for hemodialysis depend upon the $[Li^+]$, kidney function, and neurological symptoms. The EXTRIP Workgroup recommends hemodialysis when $[Li^+] > 4.0$ mEq/L or if the patient has a decreased level of consciousness, seizures, or life-threatening dysrhythmias, regardless of the $[Li^+]$. CKRT is an acceptable alternative if hemodialysis is unavailable or inadvisable.

When measuring $[Li^+]$, using the wrong tube produces an unexpectedly high apparent concentration. Green-top tubes (both Kelly green and mint green) contain lithium heparin. The heparin prevents coagulation of blood in the analyzer. Heparin has many negative charges and requires cations to neutralize the charge without interfering with chemistry measurements. Because lithium is an unmeasured cation in the basic metabolic panel, it is the cation used (instead of sodium) to neutralize the charge on heparin in the tubes. If the laboratory uses a green-top tube to measure lithium, the lithium heparin will produce a factitious elevation in the apparent $[Li^+]$. The magnitude of the apparent $[Li^+]$ varies inversely with the amount of blood in the tube, but the range of concentrations overlaps the toxic range. Blood specimens for lithium measurement should go in red-top tubes.

Returning to question 6, (d) is the best answer. Central nervous system dysfunction is an indication for hemodialysis regardless of $[Li^+]$. This is one EXTRIP criterion for hemodialysis. Other EXTRIP criteria include $[Li^+] > 5.0$ mmol/L, $[Li^+] > 4.0$ with AKI, estimated time to $[Li^+] < 1.0$ mmol/L exceeds 36 hours, confusion, seizure, or cardiac arrhythmia.

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