THE MEDICAL
CLINICS
OF NORTH AMERICA

Metabolic Acidosis: Differentiating the Causes in the Poisoned Patient

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Metabolic acidosis may be a significant consequence of a vast array of toxins. Hence, determining which drugs or toxins might be responsible for metabolic acidosis in a patient with an unknown ingestion, accidental exposure, or exposure from therapeutic drug use can present daunting diagnostic and therapeutic challenges. More importantly, vital cellular functions and metabolic processes become impaired with increasing acidosis [1,2]. Therefore, it is paramount that clinicians recognize the substances that can result in metabolic acidosis so that timely and appropriate therapy may be instituted.

Metabolic acidosis is defined as a process that lowers serum bicarbonate (HCO_3^-) and occurs when H^+ ion production exceeds the body's ability to compensate adequately through buffering or increased minute ventilation. Acidemia should not be confused with acidosis. Acidemia refers to a blood pH less than 7.40. Comprehensive discussion of acid-base disturbances is beyond the scope of this article, and the reader is referred elsewhere for further information [1,3,4].

Approach to the poisoned patient who has metabolic acidosis

Evaluating a poisoned patient may pose numerous challenges to the treating physician. First, patients may present with altered mental status, substantially limiting the ability to take an adequate history. Second, significant clues at the scene suggestive of the nature of the poisoning may

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be absent, may be overlooked by personnel at the scene, or may be inadequately conveyed to health care providers. Third, family members or friends, who are often able to provide critical information, may not immediately accompany the patient to the hospital. The exposure history can be enhanced by specific findings on the physical examination. The patient may have a characteristic toxidrome (eg, anticholinergic, cholinergic, opioid, or sympathomimetic), odor, track marks, or other physical examination clues.

Because many poisoned patients are unable or unwilling to provide an accurate history, laboratory evaluation is essential. Specific diagnostic tests, such as a comprehensive metabolic panel and 12-lead ECG, should be considered. They provide invaluable information regarding end-organ toxicity and may assist with diagnosis and treatment, gauge the gravity of the toxicologic process, and provide insight into potential deterioration in a patient's condition [5]. A quantitative test for acetaminophen, aspirin, carboxyhemoglobin, ethylene glycol, iron, methanol, or theophylline may delineate the cause of an elevated anion gap metabolic acidosis. An arterial blood gas serves as a useful adjunct in differentiating acid-base disturbances; however, serum HCO_3^- remains an important initial diagnostic test, because a depressed level is an early indicator of many metabolic toxins.

The routine use of serum and urine drug screens in the acutely poisoned patient is rarely beneficial. Standard urine drug screens test for a limited number of common drugs, and a negative screen does not exclude toxins as the cause of illness. A positive result on the urine drug screen may confirm exposure to a particular substance, but that substance may not be the cause of the patient's clinical condition. Few institutions have readily available comprehensive toxicology laboratory services, a situation which delays turnaround time for comprehensive drug testing [6]. Furthermore, the results of comprehensive drug screens rarely affect either treatment or outcomes, and often medical decision making is best accomplished through routine diagnostic testing and thoroughly assessing and reassessing the patient's clinical condition [7–9].

Once the comprehensive metabolic panel has been obtained, an anion gap (AG) should be determined using the following equation: $AG = [Na^+] - ([Cl^-] + [HCO_3^-])$. Historically, a normal AG has been defined as 12 ± 4 mEq/L. However, a study by Winter and colleagues [10] suggests that a normal AG should be 7 ± 4 mEq/L, because of an increase in measured chloride from improved instrumentation [11]. Therefore, it is important to recognize that the previously accepted range for the AG may not be suitable with newer laboratory technology. If the ingestion of a toxic alcohol (ie, ethylene glycol, isopropanol, methanol) is suspected, osmolarity should be estimated by the following equation: osmolarity $= 2 \times [Na^+] + [glucose]/18 + [blood urea nitrogen \{BUN\}]/2.8$ [12]. An osmol gap (OG) may then be determined by subtracting calculated osmolarity from measured osmolality (OG $=$ measured osmolality $-$ calculated

osmolarity). Note that osmolarity refers to the number of particles in 1 L of solution (osmoles/L of solution), and osmolality refers to the number of particles per kilograms of solution (osmoles/kg of solution), but the terms are often used interchangeably because they are almost equivalent for body fluids [13].

Classification of toxicants associated with metabolic acidosis

Although there is no ideal way to classify poisons that cause metabolic acidosis, a clinically useful and systematic approach is to differentiate toxins based on whether they are associated with an elevated AG (Boxes 1 and 2) or a normal AG (Box 3). Many medical conditions are also associated with an increased or normal AG metabolic acidosis and should be included in the differential diagnosis. An elevated AG metabolic acidosis occurs when an acid is paired with an unmeasured anion (eg, lactate), whereas a normal AG metabolic acidosis results from a gain of both H^+ and Cl^- ions or a loss of HCO_3^- and retention of Cl^-, preserving electroneutrality. This classification method has several limitations. The AG may be affected by inherent errors in calculation, laboratory anomalies, and numerous non–acid-base disorders and disease states that may disguise an elevated AG or augment a normal AG (Box 4) [14]. Also, a normal AG acidosis may occur with several of the toxins that produce an AG; therefore, a normal AG should not be used to exclude a possible cause of metabolic acidosis [15].

Many common toxicologic and illness-related causes of an increased AG metabolic acidosis may be remembered with the mnemonic MUDPILES (see Box 1). There are however, several other causes (see Box 2) for an elevated AG metabolic acidosis that should not be overlooked. In this author's experience, acetaminophen, amphetamines, carbon monoxide, cocaine, toluene, and valproic acid are toxins commonly encountered in the clinical setting that might contribute to an increased AG metabolic

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Box 1. Toxins and disease states associated with an elevated anion gap metabolic acidosis

Methanol
Uremia
Diabetic ketoacidosis, alcoholic ketoacidosis, starvation
   ketoacidosis
Paraldehyde, phenformin
Iron, isoniazid
Lactic acidosis
Ethylene glycol
Salicylates

Box 2. Drugs and medical conditions not listed in MUDPILES mnemonic associated with an elevated anion gap metabolic acidosis

Acetaminophen
Aminocaproic acid
Amphetamines
Benzene
Carbon monoxide
Catecholamines
Citric acid
Cocaine
Cyanide
Didanosine
Diethylene glycol
Ephedrine
Fluoride
Formaldehyde
Hydrogen sulfide
Ibuprofen
Inborn errors of metabolism
Nalidixic acid
Metformin
Niacin
Nitroprusside
Nonsteroidal anti-inflammatory drugs
Polyethylene glycol
Propofol
Propylene glycol
Pseudoephedrine
Streptozotocin
Sulfur
Theophylline
Thiamine deficiency
Toluene
Triethylene glycol
Valproate
Zidovudine

From Seifert SA. Unexplained acid base and anion gap disorders. In: Dart RC, editor. Medical toxicology. 3rd edition. Philadelphia: Lippincott Williams & Wilkins; 2004. p. 1914; with permission.

Box 3. Drugs and medical conditions associated with a normal anion gap metabolic acidosis

Acetazolamide
Acids (ammonium chloride, calcium chloride, hydrochloric acid)
Cholestyramine
Diarrhea
Hyperalimentation
Magnesium chloride
Pancreatic fistula
Posthypocapnia
Rapid intravenous fluid administration
Renal tubular acidosis
Sulfamylon
Topiramate
Ureteroenterostomy

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acidosis but are not listed in the MUDPILES mnemonic. Recognizing the many toxins associated with an increased AG metabolic acidosis is imperative, because the presence of a profoundly elevated AG may help identify specific causes of the acidosis and have prognostic value [16–18].

The osmol gap may provide additional information in a patient with an elevated AG acidosis who has ingested a toxic alcohol. Although the OG may be increased in the presence of toxic alcohols, several other medical conditions, such as ketoacidosis, renal failure, and shock states, may also increase the measured serum osmolality [19–21]. Toxins that elevate the OG can be memorized with the mnemonic MADGAS (Box 5) [13]. For simplicity, a "normal" OG is considered to be less than 10 ± 6 mOsm/L [22]. However, the use of the "normal" range for the OG has inherent limitations, owing to wide variability of the OG in the population [19,20,23] and potential errors in calculation and laboratory methodology (eg, freezing point depression should be used to measure serum osmolality and not vapor pressure) [24]. Furthermore, the absence of an OG cannot be used to rule out the presence of a toxic alcohol, because patients with a "normal" OG may have toxic and potentially lethal levels of a toxic alcohol [25,26]. Conversely, a significantly elevated OG (> 25 mOsm/L) is a potential indicator of a toxic alcohol ingestion [20].

Other methods of analyzing metabolic acidosis exist, including base excess/deficit and strong ion difference. Base excess/deficit is the quantity of acid or base necessary to restore pH to 7.40 in blood equilibrated at standard conditions [27]; strong ion difference is the apparent difference between entirely dissociated cations and entirely dissociated anions [28]. In a study by Fencl and colleagues [29], the strong ion difference was able to detect acid-base disorders that were missed using the anion gap. However, neither of these

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Box 4. Conditions affecting the anion gap

Increased anion gap
  Carbenicillin
  Dehydration/Diarrhea
  Hypocalcemia
  Hypokalemia
  Hypomagnesemia
  Metabolic acidosis
  Metabolic alkalosis
  Nonketotic hyperosmolar coma
  Respiratory alkalosis
  Sodium penicillin
  Uremia

Decreased anion gap
  Halides (bromine, iodine)
  Hypercalcemia
  Hyperkalemia
  Hyperlipidemia
  Hypermagnesemia
  Hyperparathyroidism
  Hypoalbuminemia
  Hyponatremia
  Lithium intoxication
  Multiple myeloma
  Polymyxin

Data from Salem M, Mujais SK. Gaps in the anion gap. Arch Intern Med 1992;152:1625.

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methods is clinically feasible, because base excess/deficit is prone to missing serious acid-base disorders, whereas the strong ion difference is difficult to calculate and requires additional laboratory testing [29,30].

Mechanisms of toxin-induced metabolic acidosis

Toxin-induced metabolic acidosis arises from increased acid production or impaired acid elimination. Toxins accomplish either of these effects by means of several important and distinct mechanisms. Increased acid production may occur with toxins that (1) are acidic or have acidic metabolites, (2) produce an imbalance between ATP consumption and production, or (3) cause metabolic derangements resulting in the generation of ketone bodies. Underlying impairment of renal function or nephrotoxic compounds may lead to

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Box 5. Toxins associated with an elevated osmol gap

Mannitol
Alcohols: ethanol, ethylene glycol, isopropanol, methanol,
    propylene glycol
Diatrizoate
Glycerol
Acetone
Sorbitol

From Chabali R. Diagnostic use of anion and osmolal gaps in pediatric emergency medicine. Pediatr Emerg Care 1997;13:204; with permission.

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diminished acid elimination and the development of a metabolic acidosis. Some toxins, such as salicylates, may produce metabolic acidosis through a combination of these mechanisms.

Toxins resulting in increased acid production

Toxins that are acids or have acid metabolites

  Metabolic acidosis may result from the ingestion of a substance that is an acid or has an acidifying metabolite. Several alcohols (eg, benzyl alcohol, ethanol, ethylene glycol, methanol) are not acidifying until they are metabolized to acidic intermediates [31]. Ethylene glycol has several acidic metabolites (ie, glycolic acid, glyoxylic acid, oxalic acid); however, glycolic acid is primarily responsible for the metabolic acidosis, whereas formic acid is the metabolite that causes metabolic acidosis from methanol poisoning [32]. Large ingestions of ethanol may produce metabolic acidosis by means of its metabolism to acetic acid. Benzyl alcohol is commonly used as a preservative in intravenous medications. The use of such preparations in neonates has caused gasping respirations, hypotension, hepatic and renal failure, and fatal metabolic acidosis owing to formation of benzoic acid and hippuric acid, the products of benzyl alcohol metabolism [33].

  Salicylates are weak acids that may produce metabolic acidosis through numerous mechanisms. In toxic concentrations, salicylates interfere with energy production by uncoupling oxidative phosphorylation [34] and may produce renal insufficiency that causes accumulation of phosphoric and sulfuric acids [35]. The metabolism of fatty acids is likewise increased in patients with salicylate toxicity, generating ketone body formation. These processes all contribute to the development of an elevated AG metabolic acidosis in patients with salicylate poisoning.

  Caustic agents, both acid and alkali, may cause significant tissue damage after ingestion and produce metabolic acidosis. In some instances of acid

injury, a metabolic acidosis may occur from the absorption of nonionized acid from the gastric mucosa. The ingestion of hydrochloric acid may initially produce a normal AG metabolic acidosis, because both H^+ and Cl^- ions are systemically absorbed and accounted for in the measurement of the AG. Other acids, such as sulfuric acid, may produce an increased AG metabolic acidosis, because the sulfate anion is not accounted for in the measurement of the AG [36].

Toxins affecting ATP consumption and production

Many poisons may interfere with cellular energy production and consumption, resulting in metabolic acidosis. Toxins may disrupt mitochondrial function and subsequent energy production either by uncoupling oxidative phosphorylation or by inhibiting cytochromes of the electron transport chain. Excessive energy consumption may result from toxins that produce a hyperadrenergic state.

Acetaminophen is a readily available over-the-counter analgesic that is commonly ingested or coingested during a suicide attempt and may cause an increased AG metabolic acidosis [37,38]. In fact, a pH of less than 7.30 is used as one of the indicators for a poor prognosis in acetaminophen-induced hepatotoxicity [39]. Although the exact mechanism of acetaminophen-induced metabolic acidosis remains unknown, several animal studies suggest that acetaminophen and its hepatotoxic metabolite N-acetyl-p-benzoquinoneimine inhibit oxidative phosphorylation, which subsequently leads to metabolic acidosis [40–42].

HIV-positive patients taking antiretroviral therapy are at risk for developing lactic acidosis syndrome. Stavudine, zidovudine, and other nucleoside analogue reverse transcriptase inhibitors impair oxidative phosphorylation by inhibiting mitochondrial DNA polymerase γ [43]; this process may result in hepatic dysfunction and steatosis, lactic acidosis, and death [44,45]. Mortality in patients who develop this condition ranges between 25% and 57% [43,46]. Patients who are on chronic antiretroviral therapy may also develop hyperlactatemia without acidosis [47]. Case reports suggest that mortality in patients with lactic acidosis syndrome may be decreased with the administration of carnitine and riboflavin; however, larger studies are required to assess the possible benefit of these therapies [46,48].

Metabolic acidosis is an important consequence of acute valproic acid toxicity, because profound acidosis after massive ingestions confers a poor prognosis [49–51]. Once ingested, valproic acid is extensively metabolized by the liver [52]. The net effect of valproic acid metabolites is depletion of intramitochondrial coenzyme A and carnitine, which inhibits the β-oxidation of fatty acids, impairing ATP production [53]. Carnitine supplementation may help restore β-oxidation to mitochondria, and, in 1996, the Pediatric Neurology Advisory Committee recommended that

carnitine be administered to children with acute ingestions of valproic acid [54]. However, owing to lack of controlled studies, further research is required to evaluate the role of carnitine in valproic acid overdoses.

Historically, the biguanide phenformin is a well-known pharmacologic cause of acquired lactic acidosis (40 to 64 cases per 100,000 patient-years); it was withdrawn from the United States market because of its association with this life-threatening condition [55]. Metformin is another biguanide that became available in the United States in 1995. To date, no clear relationship exists between the therapeutic use of metformin and increased risk for lactic acidosis. Stang and colleagues [55] found the incidence of lactic acidosis in metformin users to be nine cases per 100,000 patient-years, which is similar to the background rate of lactic acidosis in patients with type 2 diabetes mellitus who are not on metformin therapy ($\sim$10 cases per 100,000 patient-years) [56]. Furthermore, most cases of lactic acidosis related to therapeutic metformin use have occurred in the presence of a severe underlying disease state [57], such as renal failure, that could have caused the lactic acidosis. A recent meta-analysis finds no evidence to support the association of metformin therapy with an increased risk for lactic acidosis compared with other hypoglycemic agents [58]. However, metformin does inhibit the electron transport chain by binding to complex I, and the intentional overdose of metformin has resulted in lactic acidosis and even death [59–61].

Several mitochondrial poisons are responsible for a profound metabolic acidosis that may require prompt antidotal intervention. Examples of such toxins include carbon monoxide, cyanide, hydrogen sulfide, iron, methanol, and salicylates. Carbon monoxide, cyanide, hydrogen sulfide, and the metabolite of methanol (formic acid) impair oxidative metabolism by inhibiting complex IV of the electron transport chain [62–64]. Iron and salicylates hinder energy production by disrupting oxidative phosphorylation [34,65]. Following toxicity with these agents, cellular energy stores are quickly diminished, resulting in disruption of critical electrolyte gradients, ATP-dependent processes, and the H^+ ion consumption in the aerobic synthesis of ATP [63]. Furthermore, many of these toxins (eg, carbon monoxide, cyanide, iron) impair tissue perfusion, disrupting aerobic cellular energy production and worsening metabolic acidosis.

Excessive adrenergic stimulation from agents such as amphetamines, caffeine, cocaine, β-2 agonists, ephedrine, phencyclidine, and theophylline may result in hyperglycemia, hypokalemia, leukocytosis, and metabolic acidosis [66–68]. In the presence of catecholamines, β-adrenoreceptor stimulation results in the hydrolysis of ATP and augments cyclic adenosine monophosphate activity within cells, which stimulates $Na^+K^+-ATPase$ and causes K^+ ions to shift intracellularly. Excess catecholamines also stimulate glycogenolysis and the breakdown of fatty acids, resulting in hyperglycemia and metabolic acidosis, respectively. Poisoning with an agent that causes hyperadrenergic stimulation should be strongly suspected in a patient who

has the aforementioned laboratory abnormalities and a sympathomimetic toxidrome.

Special mention should be made of lactic acidosis, because this terminology is misleading and erroneous. When glucose is converted to lactate during anaerobic metabolism to generate two molecules of ATP, net H^+ ions are not produced [69,70]. Other pieces of evidence supporting the concept that lactate does not cause metabolic acidosis include (1) the parenteral administration of lactate causes a rise in pH, because it is hepatically metabolized to HCO_3^-; (2) as many as 25% of patients with an increased AG metabolic acidosis have normal lactic acid levels [17]; (3) lactate levels do not always correlate with the AG [17]; and (4) lactic acid levels may rise without acidosis (eg, with strenuous exercise [71] and the ingestion of ethanol [72]).

Net H^+ ions are produced when ATP is used as a cellular energy source [69]. The electron transport chain then uses the H^+ ions that are generated from the hydrolysis of ATP in the aerobic synthesis of ATP, thus maintaining a normal pH under typical physiologic conditions [73]. However, metabolic acidosis may ensue in the presence of a toxin or other physiologic derangement, resulting in an imbalance of ATP hydrolysis and synthesis. The imbalance of ATP hydrolysis and synthesis is acidifying, not the production of lactate. Lactate should only serve as an indicator of anaerobic metabolism [69,74].

Metabolic derangements causing increased acid production

Certain toxins may induce metabolic derangements, resulting in the increased production of ketone bodies (ie, acetoacetate, acetone, β-hydroxybutyrate). The generation of ketoacids may also occur secondary to uncontrolled diabetes and is a normal response to fasting and prolonged exercise [75]. Alcoholic ketoacidosis (AKA) is a prime example in which toxin-induced (ie, ethanol) metabolic derangements and an acute starvation state result in the production of ketoacids and an elevated AG metabolic acidosis. Patients who develop AKA are usually chronic ethanol abusers who have been binge drinking and develop a gastrointestinal illness (eg, gastritis, hepatitis, pancreatitis) that limits oral intake [76]. The diagnosis of AKA should be considered in a patient who (1) recently binged on ethanol and has had a decrease in ethanol consumption, (2) has a history of vomiting or decreased oral intake, (3) has a blood glucose level of less than 300 mg/dL, and (4) has an elevated AG metabolic acidosis for which other causes have been excluded [77].

Isoniazid (INH) poisoning is characterized by refractory seizures, elevated AG metabolic acidosis, and coma. Survival from acute INH toxicity has been reported in a patient with an arterial pH as low as 6.49 [78]. The mechanism underlying the development of metabolic acidosis in patients poisoned with INH remains unclear. Plausible explanations

include muscular activity from seizures, acidifying INH metabolites, and enhanced fatty acid metabolism that produces ketoacids [79–81].

Toxins impairing the renal elimination of acids

Several substances may cause or exacerbate renal insufficiency. Renal dysfunction may lead to the accumulation of parent compounds or toxic intermediates and contribute to or produce a metabolic acidosis. Renal impairment, whether drug-induced or underlying, may result in uremia. Even in the absence of a toxin that produces metabolic acidosis, the build-up of nitrogenous compounds may cause an increased AG metabolic acidosis by means of impaired ammonia secretion and retention of unmeasured anions [18].

Toluene exposure may lead to a metabolic acidosis as a result of toluene's metabolism to an acidic metabolite, hippuric acid [82]. The chronic abuse of toluene may also result in the development of a distal renal tubular acidosis (RTA), with associated hypokalemia and metabolic acidosis [83]. The mechanism by which toluene induces this RTA has not been fully elucidated. Toluene and hippuric acid are most likely directly toxic to the distal renal tubule [84] and impair H^+ ion secretion. Impaired H^+ ion secretion results in the loss of Na^+ and K^+ ions, incapacity to acidify the urine, and a normal- or increased-AG metabolic acidosis [82,84,85].

Ethylene glycol is not by itself a nephrotoxin [86]. However, once hepatically metabolized, it forms nephrotoxic intermediates. Ethylene glycol–associated renal insufficiency has been attributed to the deposition of calcium oxalate crystals in the renal tubules [87]; however, urinary calcium oxalate crystals are only present in 50% to 65% of patients who have ethylene glycol poisoning [88,89]. Therefore, another mechanism may be responsible for or contribute to ethylene glycol–associated renal insufficiency, and the absence of calcium oxalate crystalluria cannot be used to rule out ethylene glycol poisoning. Ethylene glycol–associated renal dysfunction may exacerbate the metabolic acidosis produced by its metabolites (glycolic acid, glyoxylic acid, oxalic acid).

Propylene glycol is commonly employed as a diluent and preservative in numerous pharmaceutical preparations, including chlordiazepoxide, diazepam, digoxin, esmolol, etomidate, lorazepam, nitroglycerin, phenobarbital, phenytoin, and trimethoprim/sulfamethoxazole. Although it is considered to be generally safe, problems arise with the prolonged or rapid administration of agents containing propylene glycol, especially in patients with renal insufficiency. Cardiac dysrhythmias, hypotension, conduction abnormalities, and death have occurred with the rapid administration of phenytoin, because of the presence of propylene glycol in its intravenous product [90,91]. Patients receiving continuous infusions of propylene glycol–containing sedatives may develop an elevated AG metabolic acidosis and increased osmolality [1]. These metabolic abnormalities resolve quickly once

the offending medication has been discontinued. Because propylene glycol is metabolized to lactate by alcohol dehydrogenase, some authors [92] have proposed this as a mechanism for propylene glycol–induced metabolic acidosis. A study by Morshed and colleagues [93] suggests that the prolonged administration of a propylene glycol–containing medication causes proximal renal tubule damage and subsequent renal dysfunction. However, the concentrations needed to produce renal tubule damage in the study would only occur if very high doses of propylene glycol were administered to a patient.

Treatment considerations for toxin-induced metabolic acidosis

The most important measures in treating toxin-induced metabolic acidosis are to recognize and treat the underlying cause and to provide excellent supportive care, including airway control and fluid resuscitation. Discontinuing the offending agent or agents in a patient who develops metabolic acidosis while taking therapeutic quantities of certain drugs (eg, topiramate, metformin) may be all that is necessary. Many patients who develop a mild metabolic acidosis after an intentional ingestion experience improvement with close observation and supportive care. However, when poisoned patients have progressive worsening of their metabolic acidosis despite supportive care (ie, fluid resuscitation, oxygen therapy), then alternative causes for their metabolic acidosis should be sought. Therapy for specific toxin-induced metabolic acidoses is variable, with some of the more common management strategies discussed in the following section.

Role of buffer therapy

Many clinicians may be inclined to treat toxin-induced metabolic acidosis with a buffer, such as sodium bicarbonate, to increase serum pH. However, this practice should be discouraged. The administration of sodium bicarbonate has not been definitively shown to improve outcomes in patients who have metabolic acidosis, and it can be detrimental in some [74]. Paradoxical intracellular acidosis may occur because of increased production of carbon dioxide [94]. Sodium bicarbonate administration may also impair oxygen delivery to tissues by shifting the oxyhemoglobin dissociation curve to the left [95]. Other methods of alkalinization, such as carbicarb [96] and tris-hydroxymethyl aminomethane (THAM), are not routinely used in the treatment of toxin-induced metabolic acidosis, owing to the scarcity of carbicarb and lack of improvement in patient outcomes with THAM [1].

Patients who may benefit from the use of sodium bicarbonate are those poisoned with agents whose elimination may be increased through alkalinization (eg, salicylates) and those poisoned with drugs that cause

blockade of cardiac Na^+ channels (eg, cyclic antidepressants). Sodium bicarbonate is useful in decreasing tissue levels of salicylates and in facilitating the elimination of salicylates in the urine [97,98]. Hemodialysis should be instituted in those salicylate-poisoned patients who have altered mental status, pulmonary edema, renal failure, severe electrolyte and metabolic abnormalities, or a salicylate level greater than 100 mg/dL after an acute ingestion. Sodium bicarbonate is also effective in treating drug-induced cardiac sodium channel blockade [99]. For cyclic antidepressant–induced cardiotoxicity, 1 to 2 mEq/kg of sodium bicarbonate should be given as an intravenous bolus and repeated as needed until a blood pH of 7.55 is attained [100,101].

Antidotal therapy

Ingestion of a toxic alcohol requires antagonism of alcohol dehydrogenase with ethanol or fomepizole and consideration of hemodialysis in patients who are profoundly acidotic or have had a massive ingestion. Neither ethanol nor fomepizole affects the toxic metabolites of ethylene glycol or methanol. Complications associated with the administration of ethanol include central nervous system (CNS) depression, hypoglycemia, and fluctuating levels due to patient variability in its metabolism. Advantages of fomepizole include ease of dosing, no need for monitoring of serum levels, and lack of CNS-depressant activity. Specific vitamins may be used as adjuvant therapy in ethylene glycol and methanol poisoning. Folate enhances the metabolism of formic acid to carbon dioxide and water, whereas thiamine and pyridoxine help metabolize toxic ethylene glycol intermediates to less toxic compounds [89,102].

Treatment for acute INH toxicity should focus on termination of seizures, reversal of metabolic acidosis, and stabilization of vital signs through supportive measures. INH causes toxicity by diminishing the synthesis of γ-amino butyric acid in the CNS through antagonism of pyridoxine. The antidote for INH-induced neurotoxicity is pyridoxine [103,104]. Pyridoxine rapidly terminates INH-induced seizures, reverses coma, and corrects metabolic acidosis.

Management of patients with cyanide and hydrogen sulfide toxicity is complicated by the nature of these extremely rapidly acting and potent toxins; hence most victims succumb to a rapid death or are moribund with a severe metabolic acidosis on presentation. The cyanide antidote kit containing amyl nitrite, sodium nitrite, and sodium thiosulfate should be considered early in the management of toxicity. Hydrogen sulfide is detoxified when it binds to methemoglobinemia to form sulfmethemoglobin [105]. Several case reports demonstrated improvement in the condition of patients when nitrites were administered soon after exposure to hydrogen sulfide [106–108]. Therefore, sodium nitrite should be considered for patients with suspected severe hydrogen sulfide toxicity.

Summary

Metabolic acidosis may arise from several drugs and toxins through a variety of mechanisms. Differentiating the causes of metabolic acidosis in the poisoned patient is an indispensable skill in clinical practice. Comprehension of toxin-induced metabolic acidosis, combined with a thorough history, physical examination, appropriate use of laboratory tests, and a stepwise approach, should aid the clinician in determining the cause of metabolic acidosis in the poisoned patient. When confronted with such a patient, it is imperative that one administer appropriate antidotal therapy, when necessary, and provide the patient with exceptional supportive care.

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