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Drug-induced hyperlactatemia

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ABSTRACT

Background: Hyperlactatemia is common in critically ill patients and has a variety of etiologies. Medication toxicity remains an uncommon cause that providers often fail to recognize. In this article, we review several medications that cause hyperlactatemia in either therapeutic or supratherapeutic dosing. When known, the incidence, mortality, pathophysiology, and treatment options are discussed.

Methods: We performed a literature search using PUBMED and Google Scholar for English language articles published after 1980 regarding medication induced hyperlactatemia and its management. Our search string resulted in 798 articles of which 138 articles met inclusion criteria and were relevant to the topic of our review.

Conclusions: Hyperlactatemia is a relatively rare but life-threatening toxicity of various medication classes. Discontinuation of the drug is always advised, and some toxicities are subject to specific antidotal treatment. If there is no apparent medical cause for hyperlactatemia (sepsis, hypotension, hypoxia), clinicians should consider a toxicological etiology.

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Introduction

Hyperlactatemia commonly occurs in critically ill patients and serves as a clinical marker for illness severity and risk of mortality. While sepsis, cardiogenic shock, or hemorrhage are the most common causes of hyperlactatemia [1], a subset of patients have no apparent cause. Clinicians should consider drug-induced hyperlactatemia in this patient group. This article provides an overview of medications associated with elevated lactate concentrations, grouped by their underlying pathophysiology of increased pyruvate production, metabolism to lactate, interference with the lactate metabolism (Cori cycle), inhibition of mitochondrial protein synthesis, inhibition of the electron transport chain (ETC), and uncoupling of oxidative phosphorylation. For reasons of clinical applicability, we include substances that interfere with the lactate assay to produce a false elevation of serum lactate concentrations. Where available, we present incidence, treatment options, and data on morbidity and mortality.

Multiple medications cause hyperlactatemia by interference with cellular energy production. In order to meet the energy demands of cells, glucose undergoes cytosolic glycolysis, an oxygen-independent process that generates pyruvate, adenosine triphosphate (ATP), and reduced nicotinamide adenine dinucleotide (NADH). If oxygen is available to the cell, pyruvate enters the Krebs cycle. Under anaerobic conditions, lactate dehydrogenase (LDH) reduces pyruvate to lactate in order to regenerate oxidized nicotinamide adenine dinucleotide (NAD+), so that glycolysis can continue.

Pyruvate dehydrogenase converts pyruvate to acetyl-CoA that enters the mitochondrial Krebs cycle. The Krebs cycle is a series of enzymatic reactions that produces ATP, guanosine-5’-triphosphate (GTP), NADH, and succinate. NADH donates two electrons to complex I of the ETC. As electrons pass from complex I to complex III and complex IV, each complex transfers hydrogen ions into the mitochondrial intermembrane space. Succinate donates electrons to complex II and contributes to the hydrogen gradient between the intermembrane space and the mitochondrial matrix. The hydrogen ion gradient provides the proton motive force for the production of ATP by complex V.

At physiologic equilibrium, endogenous lactate production occurs at a rate of 20 mmol/kg/day. Metabolism of lactate is centralized in the liver, which oxidizes approximately 70% of lactate via pyruvate to glucose (Figure 1); the remainder undergoes renal excretion. Glucose either re-enters the circulation if energy demand persists, or is otherwise stored as glycogen [2].

Hyperlactatemia results from an imbalance of lactate production and metabolism. The most common medical cause of hyperlactatemia is tissue hypoxia (type A hyperlactatemia) as is the case in severe sepsis, seizure, or trauma. In contrast, most toxicological causes are independent of tissue oxygen availability (type B hyperlactatemia). This distinction is important as both type A and type B hyperlactatemia can present with hemodynamic compromise. A tenuous hemodynamic state is often the cause of type A hyperlactatemia but typically a consequence of type B hyperlactatemia.
Therefore, hemodynamic stabilization does not suffice to resolve drug-induced hyperlactatemia.

Methods

We performed a target search of available English literature on pubmed.gov and scholar.google.com from 1980 to August 2016. Search terms used included medication OR iatrogenic OR albuterol OR epinephrine OR beta-agonist OR propylene glycol OR lorazepam OR barbiturate OR phenobarbital OR lactated rings OR biguanide OR phenformin OR metformin OR oxazolidinone OR linezolid OR eperezolid OR NRTIs OR stavudine OR sodium nitroprusside OR salicylate OR aspirin OR bismuth subsalicylate OR valproic acid OR ethylene glycol OR propofol. We combined each search term with overdose OR hyperlactatemia OR lactic acidosis OR toxicity. Based on our clinical experience, we combined specific medication names with the terms dialysis OR hemofiltration OR extracorporeal removal OR antidote OR management. We screened 798 unique titles for relevancy. Abstracts that pertained to the development, diagnosis, treatment, or prognosis of hyperlactatemia from causes other than medication effect (e.g., sepsis) were excluded. We obtained full-length articles where appropriate and accessible, for a total of 138 articles. We followed citations and incorporated relevant information.

Results

Increased pyruvate production

Stimulation of beta-2 adrenergic receptors leads to mobilization of energy stores. In the adrenergic state, glycolysis, lipolysis, and gluconeogenesis significantly increase above baseline [3]. In the medical setting, administration of beta-2 agonists occurs at supraphysiologic doses and with intent to ease bronchoconstriction rather than meeting metabolic needs. This results in energy supply surpassing energy demand and subsequently high tissue pyruvate concentration [4]. Cells shunt pyruvate to lactate to regenerate the cell’s nicotinamide adenine dinucleotide (NAD\(^+\)) pool.

Of particular clinical importance is hyperlactatemia from beta-agonists in patients with severe acute asthma.

A volunteer study (n = 9) showed a rise in serum lactate concentration from 1.1 to 2.3 mmol/L in the absence of hypoxemia during the intravenous administration of albuterol at 20 μg/min for 30 minutes [5]. Another study of four healthy adults showed lactate increased to 4.3 mmol/L (from 0.8 mmol/L) after intravenous administration of albuterol at 0.7 μg/kg over 90 minutes [6]. This complication occurs in up to 40% of patients [3]. The associated acidemia stimulates the respiratory center and worsens the patient’s hyperpnea [7,8]. Clinicians may interpret this as worsening of the patient’s respiratory status, resulting in more aggressive treatment with beta-agonists. This hypothesized positive feedback loop leads to dynamic hyperinflation, intrinsic positive end-expiratory pressure (auto-PEEP), and ultimately respiratory failure [9].

Treatment of beta-agonist induced hyperlactatemia consists of discontinuing the offending agent if the underlying clinical condition allows. Several case reports describe this phenomenon in patients who received intravenous albuterol. None of these patients received epinephrine, which may be preferred in severe status asthmaticus. While a degree of hyperlactatemia is tolerable with use of beta-agonists for respiratory support, clinicians must be vigilant once hyperlactatemia develops in patients with acute severe asthma [10].

Metabolism of medication to lactate

Propylene glycol (PG) is a dihydroxy alcohol used as a vehicle for hydrophobic medication. While 45% is renally excreted, the remainder is hepatically metabolized by alcohol dehydrogenase and aldehyde dehydrogenase. The final metabolite of this pathway is racemic mixture of D-lactate and L-lactate [11,12]. In patients with both intact renal and hepatic function, serum half-life of PG is approximately five hours [13].

The concentration of PG varies by medication, with up to 80% by volume in the case of intravenous lorazepam (see Table 1). Some pharmaceutical formulations also contain polyethylene glycol, but the majority of toxicity is likely due to PG [11]. There are three distinct risk factors for the development of PG-induced hyperlactatemia: amount of PG infused, renal impairment [13], or small distributive volume (e.g., children < 4 years) [14]. For example, a 54-year-old man developed hyperlactatemia (6.1 mmol/L) three days after he was started on continuous lorazepam infusion (range 5–20 mg/h) for severe alcohol withdrawal. Serum PG concentration measured 810 mg/dL [15]. A 50-year old man mistakenly received lorazepam at 2 mg/min instead of mg/h and

<table>
<thead>
<tr>
<th>Medication</th>
<th>PG volume %</th>
</tr>
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<tbody>
<tr>
<td>Lorazepam</td>
<td>80</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>70</td>
</tr>
<tr>
<td>Diazepam</td>
<td>40</td>
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<tr>
<td>Digoxin</td>
<td>40</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>40</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>40</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>40</td>
</tr>
<tr>
<td>Etomidate</td>
<td>35</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>30</td>
</tr>
<tr>
<td>Esmolol</td>
<td>25</td>
</tr>
<tr>
<td>Chloralazineoxide</td>
<td>20</td>
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</tbody>
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Table 1. Propylene glycol content of common parenteral medications.
within 10 hours developed severe acidosis (pH 6.9), hyperlactatemia (18.6 mmol/L) and had a PG concentration of 659 mg/dL [16]. A retrospective study of critically ill patients (n = 33) found the PG accumulation occurs at lorazeepam infusion rates exceeding 4 mg/h [17]. As such, patients suffering severe alcohol withdrawal constitute the majority of reported cases due to the reliance on large doses of benzodiazepines over the course of their illness [12,17].

An elevation in the serum osmolal gap of more than 10 mOsm/L strongly predicts accumulation of PG [18,19]. Other laboratory findings include presence of an anion gap metabolic acidosis and acute kidney injury [17].

Initial treatment consists of cessation of the offending drug. For patients requiring benzodiazepines, midazolam provides a therapeutic alternative that does not contain PG. The alcohol-dehydrogenase inhibitor 4-methylpyrazole (fomepizole) stops the formation of lactate in the setting of PG toxicity [15,16]. However, PG will remain in circulation with fomepizole treatment, especially in the setting of renal insufficiency. The compound itself has significant toxicity. Animal studies demonstrate an increase in cardiac output vaso activity combined with decrease of sympathetic output [20]. This leads to a decrease of mean arterial pressure and heart rate, to the point of asystole [21,22]. Hence, its role in the treatment of PG toxicity remains unclear [11]. Hemodialysis has been successfully employed to remove PG and correct serum pH, and should be considered in patients with significant toxicity in the setting of hepatic and renal failure [14]. Other toxicity associated with PG includes nephrotoxicity in 21% of patients receiving lorazeepam infusions exceeding 4 mg/h [17] and hyperosmolality [14].

A common medication that directly adds lactate is lactated Ringer’s solution (LR). This crystalloid contains 28 mmol/L of lactate. After fluid administration, 1 L of LR leads to a theoretical increase of 4.6 mmol/L of lactate serum concentration in an average adult if no lactate clearance occurs. No clinical effect was demonstrated in healthy human volunteers (n = 24) who received 1 L of intravenous LR over one hour. No volunteer exceeded a lactate concentration of 2 mmol/L. Lactate concentrations did not rise and remained similar to the control group (1 L of 0.9% sodium chloride solution) [23]. Patients with malignancy may have a higher basal lactate production due to the Warburg effect the preferential use of glycolysis for ATP production by cancer cells. This process alone can exceed hepatic lactate clearance [24]. While there are no human data, a transient elevation of serum lactate concentration occurs in dogs with lymphoma that receive LR. The animals received 4.125 mL/kg/h for six hours, with the highest lactate recorded of 4.2 mmol/L [25]. The effect on critically ill patients without malignancy remains unknown.

**Interference with the Cori cycle**

The Cori cycle is a metabolic pathway that shifts the burden of lactate metabolism from peripheral tissues to the liver. Hepatocytes use lactate for gluconeogenesis, and shuttle glucose back to peripheral tissues. Biguanides such as metformin and phenformin reduce hepatic gluconeogenesis. This aspect of the Cori cycle converts lactate to pyruvate and subsequently glucose in an energy-dependent pathway. The incidence of phenformin-associated hyperlactatemia is approximately 60 per 100,000 patient-years and carries a mortality rate of 50% and can occur at therapeutic dosing (e.g., 30 mg PO BID) [26]. In contrast, metformin-associated hyperlactatemia has an incidence of 3 per 100,000 patient-years [27]. Phenformin was removed from the US market in 1978, but is still available in Italy, Brazil, and China [26]. It has since been identified in multiple Chinese “herbal” preparations in the US [28].

A subtle variation in mechanism of action accounts for this difference in incidence. Phenformin increases lactate production in myocytes and interferes with oxidation of lactate to pyruvate whereas metformin does not affect myocytes and increases oxidation of lactate to pyruvate by 25% but decreases conversion of pyruvate to glucose by 37% [29]. Furthermore, phenformin inhibits complex I of the mitochondrial ETC, thereby hindering hepatocellular ATP production and subsequently gluconeogenesis. Metformin binds poorly to mitochondrial membranes and only exerts this effect at supratherapeutic concentrations [27]. Elevated serum lactate concentrations are common in therapeutic dosing of phenformin [30] but not metformin [31].

Metformin undergoes renal tubular excretion without metabolism. Reduced renal function (e.g., after receiving iodine-based contrast) or overdose increase serum metformin concentrations and place the patient at risk for hyperlactatemia. Other risk factors include hypoxemia, alcohol abuse, liver failure, myocardial infarction, sepsis, and shock [32].

Lactate concentration and acidemia correlate with serum metformin concentration and peak at around six hours in the event of an acute overdose. In 22 cases identified in a literature review, a pH of less than 6.9 or a serum lactate concentrations of more than 25 mmol/L correlated with a mortality of 83%, whereas a peak serum metformin concentration of greater than 50 μg/ml predicted a mortality of 38% [33]. However, a patient survived without sequelae despite a pH of 6.59, lactate concentration of 40 mmol/L, and metformin concentration of 160 μg/ml [34]. A systematic review of a voluntary pharmacovigilance database maintained by Merck Serono (the maker of Glucophage®) failed to demonstrate an association between lactate concentration or serum pH and survivability among a cohort of 56 patients. Inclusion criteria for this study included a blood lactate concentration of >10 mmol/L, an arterial blood pH < 7.0, and a measurable serum metformin concentration. These criteria represent more severe metabolic derangements, yet the overall mortality for this group was 53%. In addition, survival rates are likely underestimated since approximately 1/3 of the patients in this analysis were septic or had multiple other drug ingestions [35]. The overall mortality of metformin-associated hyperlactatemia is likely less than 50%. In fact, a case series of 36 patients with metformin overdose of greater than 3 g had no deaths reported, although this cohort had less severe metabolic derangements than those reported in the previous study [36].

Patients may present with clinical signs of acidosis such as Kussmaul respirations, or feature altered mental status,
abdominal pain, gastrointestinal distress, or hemodynamic instability due to reduced catecholamine-receptor binding at pH measurements less than 6.9 [34]. The clinical appearance in combination with laboratory findings may mimic peritonitis. Several patients underwent diagnostic laparotomies prior to identification of metformin toxicity as the underlying cause [37–39].

Treatment options include crystalloid administration [40], bicarbonate therapy [41], and extracorporeal removal [38]. Continuous venous venous high flow hemofiltration dialysis is the recommended modality for enhanced elimination. Metformin is a small molecule and not protein bound, but has a high volume of distribution (>3 L/kg) [42] which necessitates prolonged treatment sessions (average 15 h, up to 24 h) [38]. In addition to drug removal, enhanced elimination techniques correct the pH imbalance. No data exist regarding the effect of extracorporeal removal on mortality. Suggested indications for hemodialysis include a pH <6.9, lactate >25 mmol/L, metformin concentration >50 mcg/ml, or rapidly deteriorating clinical status [33].

**Inhibition of mitochondrial protein synthesis**

The mitochondrion is a cell organelle found in eukaryotes that facilitates energy production through oxidative phosphorylation. When mitochondria become dysfunctional, cytosolic glycolysis is the only remaining means of ATP synthesis. This organelle is the descendent of an alphaproteobacterial endosymbiont, and thus is phylogenetically related to bacteria [43]. Consequently, some mitochondrial structures closely resemble bacterial structures, as is the case with mitochondrial ribosomes.

**Oxazolidinone antibiotics** such as linezolid and eperozolid are treatment options for drug-resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) [44]. This drug class binds to the bacterial 23S ribosome subunit and prevents assembly of the 30S-50S ribosome complex [45].

Patients with oxazolidinone-associated hyperlactatemia show reduced oxygen consumption and extraction. The underlying cause is a polymorphism in mitochondrial DNA (mtDNA) (m.2706A > G) that encodes the 16S subunit of the mitochondrial ribosome. This polymorphism increases drug–ribosome binding and subsequently inhibits mitochondrial protein synthesis similar to the drug's antimicrobial mechanism of action [46]. A post-mortem muscle biopsy of a patient with linezolid-associated hyperlactatemia showed reduced activity of complexes I, III, and IV of the ETC, all of which are encoded in part by mtDNA. Complex II, entirely encoded by DNA of the cell’s nucleus, was not diminished [47].

In a retrospective cohort study (n = 72), about 3% of patients developed oxazolidinone-associated hyperlactatemia defined as a pH < 7.25 and serum lactate concentration exceeding 4 mmol/L. Onset of toxicity occurred with delay among this group, on average between week 1 and 7 of therapy. This delay likely represents the gradual depletion of mitochondrial proteins in the setting of impaired protein synthesis [48]. While in this study 80% of those who developed hyperlactatemia had either acute or chronic renal failure, this trend did not continue in an analysis by the same authors of 35 cases reported in the literature [48]. In addition, linezolid undergoes hepatic metabolism and does not require adjustment for renal insufficiency [49]. Hyperlactatemia arises as early as four hours after intravenous infusion of linezolid, but this phenomenon has only occurred in a single case report, and the patient rapidly died hours later, so causation is unclear since no other case with similar time course exists [50]. Major risk factors remain unknown, but patients with mtDNA m.2706A > G polymorphism [51] or MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like symptoms) appear susceptible [52]. Presenting symptoms include gastrointestinal distress, tachypnea/hyperpnea, and hypotension. Some patients remain asymptomatic [48].

Treatment of oxazolidinone-associated hyperlactatemia consists of withdrawal of the offending agent, hemodynamic support, and pH correction in severe cases. Renal replacement therapy (RRT) increases lactate clearance by only 3%, but addresses the underlying cause and lowers concentration of the offending drug (approximately 30% reduction in linezolid concentration over 10 hours of hemodialysis) [53]. Linezolid is 31% protein bound and has a volume of distribution of 50 L [54]. The majority of patients improve over 1–15 days after drug discontinuation.

**Nucleoside reverse transcriptase inhibitors** (NRTIs) are a mainstay of HIV therapy. These drugs resemble deoxynucleotides, which the viral reverse transcriptase enzyme uses to produce viral DNA from RNA. Unlike deoxynucleotides, NRTIs lack the 3'-hydroxyl group and cannot form the 5'-3' phosphodiester bond to elongate the DNA chain.

Similar to reverse transcriptase, mtDNA polymerase γ lacks proofreading ability and will incorporate NRTIs into mtDNA [55]. Once mtDNA has incurred significant damage, the organelle can no longer produce components of complexes I, III, and IV of the ETC. As mitochondrial respiration slows, cells switch to anaerobic metabolism leading to significant lactate production.

NRTIs also inhibit β-oxidation of fatty acids. Subsequently, the rate of glycolysis increases to provide pyruvate to any remaining mitochondrial respiration. In turn, upregulated glycolysis increases lactate production. Furthermore, the fatty acids accumulate in the cytosol. Subsequent hepatic steatosis reduces lactate clearance rates [56].

With the exception of abacavir, all NRTIs are associated with hyperlactatemia [57]. Estimates of incidence of hyperlactatemia with acidosis vary widely from 1 to 73.9 cases per 1000 patient-years. Therapy with stavudine and didanosine carries the highest risk for hyperlactatemia, which correspond to their increased affinity for mtDNA polymerase γ observed *in vitro* [57,58].

Risk factors for NRTI-associated hyperlactatemia include reduced creatinine clearance (<70 mL/min), low CD4+ count (<200 cells/μL), and female sex [57,58]. Clinicians should suspect this condition in patients on NRTIs who present with abdominal pain, emesis, or pancreatitis [59,60]. NRTI-associated hyperlactatemia with acidosis has a mortality rate of
40–70% despite maximal supportive care [57]. Death occurs within 1–17 days after diagnosis [61].

L-Carnitine reduces mortality in NRTI-associated hyperlactatemia with acidosis. It serves as a co-factor in the ETC and transports long-chain fatty acids across the mitochondrial membrane, which enhances β-oxidation. Patients should receive 50 mg/kg daily (100 mg/kg daily if on continuous dialysis). This recommendation is based on a small study (n = 6) [61]. The efficacy of serum alkalinization, prostaglandins, and thiamine administration has not been systemically studied. Withdrawal of the offending agent is paramount.

Non-nucleoside reverse transcription inhibitors (NNRTIs), protease inhibitors (PIs), fusion Inhibitors, entry inhibitors, and integrase inhibitors are not associated with hyperlactatemia.

**Inhibition of the electron transport chain**

The ETC is the final biochemical pathway of mitochondrial respiration. It consists of a series of five complexes, of which complex I, III, and IV create a chemical gradient by pumping hydrogen ion into the intermembrane space. Complex V uses the potential energy of the chemical gradient to produce ATP.

**Propofol** is a commonly used sedative-hypnotic for both procedural sedation and for the sedation of ventilated patients. Infusion rates above 4 mg/h and prolonged therapy can cause propofol-related infusion syndrome (PRIS). Onset of PRIS occurs between 20 and 60 hours of continuous propofol infusion in 23% of patients, but is delayed by over 60 hours in 57% of patients [62]. The syndrome is a constellation of hyperlactatemia, metabolic acidosis, rhabdomyolysis, hepatomegaly, hyperlipidemia, and renal failure.

Some patients with PRIS develop dysrhythmias. In an analysis of seven cases, the initial abnormality on electrocardiogram (EKG) was a Brugada-pattern with coved-type elevations of the ST-segment in the precordial leads. The QT interval subsequently lengthened and patients developed ventricular tachycardia followed by recalcitrant ventricular fibrillation [62,63]. Despite withdrawal of the offending drug and maximum supportive therapy, mortality persists at 35% [62].

PRIS develops by several different mechanisms. High doses (3 mg/kg/h in one case report) directly inhibit complex I and IV of the ETC [64]. High dose propofol also uncouples the ETC by altering the structure of F1F0ATPase (complex V). Dissipation of the proton gradient generates heat. The result is a very poor prognostic factor, and patients are at risk of heart failure and sudden death [62].

In vitro studies show that propofol interferes with electron transfer among complex I, II, and III in a dose depended manner. Propofol mimics coenzyme-Q and accepts electrons from the ETC but does not donate electrons to the next downstream ETC complex [64,65]. Furthermore, propofol inhibits carnitine palmityl transferase I, rendering mitochondria unable to import long-chain acylcarnitine esters [66]. Impaired fatty acid metabolism leads to hepatic steatosis and reduced lactate clearance. The degree of hepatic dysfunction as measured by liver function tests and serum ammonia concentration is directly proportional to the duration of drug exposure [62,67]. Prolonged infusion increases the risk for dysrhythmias and can produce Brugada-type EKG. This may be due to proarrhythmic properties of free fatty acids contained in the propofol infusion (10% by weight). A propofol infusion of 1 mg/kg/h will meet a patient’s daily dietary fatty acid requirements, but clinical practice often demands higher doses [66,67]. Lastly, the inability of muscle tissues to metabolize fatty acids leads to rhabdomyolysis.

Critical care providers should diagnose PRIS based on drug exposure history, and laboratory tests indicating hyperlactatemia, rhabdomyolysis, hypertriglyceridemia, and acidemia. Immediate withdrawal of the drug is required, and the clinician must limit additional triglyceride administration (e.g., total parenteral nutrition). In addition to supportive care, coenzyme-Q administration is of theoretical benefit, but efficacy is unproven [64].

**Sodium nitroprusside** (SNP) is a simple molecule of a nitric oxide and five cyanate groups bound to a central iron atom. The desired effect is the release of nitric oxide for the purpose of blood pressure control. The release of the molecule’s cyanate groups produces clinically significant toxicity.

During normal oxidative phosphorylation in the ETC, cytochrome c shuttles electrons from complex III to complex IV (also called cytochrome oxidase or cytochrome a3). Complex IV temporarily accepts the electrons by reducing its trivalent iron moietyies, and subsequently donates four electrons to molecular oxygen. The reduced oxygen ions bind hydrogen ions to form water. Cyanide binds the ferric ion (Fe3+) in complex IV and prevents any further electron transfer [68]. This profoundly inhibits the ETC as oxygen cannot be reduced without the enzymatic activity of complex IV. Subsequently, cells switch to lactate-producing anaerobic metabolism [69]. In addition to hyperlactatemia and acidosis, cellular ATP depletion causes altered mental status, seizures, myocardial infarction, and other signs of organ damage [70].

Thiosulfate sulfurtransferase (“rhodanase”) is the endogenous detoxification system that converts cyanide to thiocyanate. SNP infusion rates generally should not exceed 2 mcg/kg/min as this represents the approximate endogenous metabolic capacity for cyanide [70]. Approximately 50 mg SNP administration suffices to deplete thiosulfate stores, and detoxification fails [70,71]. If the patient needs emergent blood pressure control, rates as high as 10 mcg/kg/min can be administered for several minutes [70,71]. Malnourished patients are at increased risk of toxicity due to lower thiosulfate stores. Furthermore, 98.5% of cyanide is sequestered in red blood cells [72]. Hemolysis due to any reason (e.g., prolonged cardiopulmonary bypass time) increases free cyanide and accelerates toxicity.

Several treatments are available for SNP-associated cyanide toxicity. The concomitant infusion of sodium thiosulfate with SNP delays and blunts toxicity [73–75]. Amyl nitrite, sodium nitrite, and hydroxocobalamin are alternative antidotes should toxicity develop.

In a series of patients with aortic dissection treated with SNP, 11.5% of patients (18/157) who received nitroprusside infusion for blood pressure control developed clinically significant cyanide toxicity. None received prophylactic thiosulfate [76].
Barbiturates inhibit complex I of the ETC in tissue culture [77]. The clinical significance of this is not fully understood. Both a 73-year-old man and 21-year-old woman developed hyperlactatemia after administration of thiopental for refractory status epilepticus (303 mg/kg over 48 h and 840 mg/kg over 150 h, respectively) [78]. However, both patients also developed non-occlusive mesenteric ischemia, which in itself produces hyperlactatemia. It is unclear if tissue necrosis occurred due to impaired mitochondrial function. In healthy individuals, barbiturate administration does not produce clinically measurable effects.

Valproic acid is a widely used antiepileptic and mood stabilizer. It is associated with hepatotoxicity and hyperammonemia at therapeutic dosing. In overdose, valproic acid produces hyperlactatemia and acidosis [79,80]. Mitochondrial complex I and IV were the suspected targets of inhibition [81]. However, the effect on ETC complexes was not consistently reproduced in vitro, depending on the energy substrate used for oxidative phosphorylation [82]. Current data suggest that the metabolite valproyl-CoA inhibits dihydrolipoamide dehydrogenase, an enzymatic subunit of pyruvate dehydrogenase, and thus prevents entry of some energy substrates into the citric acid cycle [83].

Pharmacokinetic data show protein binding of 91.6% at therapeutic dosing, which suggests extracorporeal removal to be of low efficacy [84]. In overdose, drug molecules exceed available protein binding sites and up to 85% of drug remains unbound and therefore dialyzable [85]. Continuous venovenous hemodialysis has been used successfully in the treatment of valproic acid induced hyperlactatemia with acidemia [79,80]. The Extracorporeal Treatments in Poisoning (EXTRIP) workgroup recommends dialysis for a pH of less than 7.1 in the setting of acute valproate toxicity [86].

Multiple antidepressants and mood stabilizers inhibit the ETC in vitro. Porcine mitochondria had reduced oxygen use during exposure to supratherapeutic concentrations of desipramine (inhibition of complex I, IV), amitriptyline (inhibition of complex I, II, IV), imipramine (inhibition of complex I, II, IV), citalopram (inhibition of complex I, II), mirtazapine (inhibition of complex I, IV), olanzapine (inhibition of complex I IV), and venlafaxine (inhibition of complex II, IV) [81].

Clinically, this effect appears to be rare. A 55-year-old man who ingested 6000 mg venlafaxine developed hyperlactatemia (peak 8.6 mmol/L) which resolved with hydration and activated charcoal [87]. A 81-year-old man had been on citalopram 20 mg BID for three weeks was started on linezolid 600 mg BID for osteomyelitis. After 3 weeks of combined therapy, he developed hyperlactatemia (peak 29.1 mmol/L) and died shortly thereafter. It is unclear whether he developed serotonin syndrome (tremor/hyperthermia reported, but no clonus or seizure), experienced linezolid-induced hyperlactatemia, citalopram-induced hyperlactatemia, or any combination thereof [88].

Uncoupling of oxidative phosphorylation

The final step of mitochondrial respiration involves complex V (ATP synthase). This enzyme phosphorylates adenosine diphosphate (ADP) to ATP, using the potential energy stored in the mitochondrial chemical hydrogen gradient created by the ETC.

Poisoning with salicylates such as aspirin and bismuth subsalicylate ("Pepto-Bismol") accounts for approximately 13,000 annual poisonings and 47 deaths in the United States [89]. Salicylic acid is a weak acid (pK < 3.0) which deprotonates at alkaline pH but remains unionized at acidic pH [90].

The ETC produces a hydrogen ion gradient between the mitochondrial intermembrane space (pH 6.88) and mitochondrial matrix (pH 7.78) that serves as the proton motive force for ATP synthesis by complex V [91]. The salicylate ion diffuses down its concentration gradient from the cytosol (pH 7.59) into the mitochondrial intermembrane space. The lower pH in the intermembrane space shifts the equilibrium toward the unionized state, and the salicylate ions bind protons. Unlike salicylate, salicylic acid does not carry a charge and can diffuse rapidly (permeability coefficient 0.7 cm/s) into both the cytosol and the mitochondrial matrix [90]. As these compartments have relatively alkaline pH, salicylic acid deprotonates to salicylate and the cycle repeats.

Salicylate therefore acts as a "proton shuttle" from the mitochondrial intermembrane space to the surrounding compartments. As protons bypass complex V and no longer contribute to ATP synthesis, salicylate effectively uncouples the ETC [90,92]. This process is exothermic and patients may develop hyperthermia [89]. Hyperlactatemia results from increased rates of glycolysis in an effort to meet metabolic demands [93]. In addition, salicylic acid accumulation in the mitochondrial matrix exerts osmotic pressure. The subsequent swelling contributes to mitochondrial dysfunction [94].

Treatment of salicylism takes advantage of the three compartment model (tissue, serum, and urine). Alkalination of a compartment traps salicylate in its ionized form in that partition. Administration of sodium bicarbonate with a goal serum pH of 7.55 and goal urine pH of 8.0 creates a gradient favoring salicylate excretion [95]. Severely poisoned patients (ASA concentration >90 mg/dL, cerebral edema/seizure, acute lung injury, profound acidosis, worsening clinical status) require hemodialysis [95,96].

Laboratory errors in lactate measurement

Intoxication with ethylene glycol (EG) results in anion-gap metabolic acidosis due to metabolism to glycolic acid and glyoxylic acid. Several cases reported describe massive hyperlactatemia (greater 15 mmol/L, as high as 42 mmol/L) measured on point-of-care testing, but near-normal serum lactate concentration in laboratory-based assays [97–101]. In combination with severe acidosis and depressed mental status, a clinician may suspect mesenteric ischemia or other conditions as a cause, delaying diagnosis and treatment for EG toxicity.

Two enzymatic laboratory assays are available to measure serum lactate concentrations. Lactate analyzers either use lactate oxidase (LOD) or LDH. LOD converts lactate to H₂O₂; the resultant colorimetric or amperometric changes are quantified by the analyzer. Glycolate and glyoxylate structurally
resemble lactate and serve as a substrate for LOD, but not LDH. For unclear reasons, amperometric quantification is more susceptible to produce factitious lactate elevation than colorimetry. Most point-of-care lactate assays and blood gas analyzers use LOD and amperometry. Interestingly, the bacterial origin of the LOD affects the accuracy of the assay. Amperometric assays using *Pediococcus* sp. LOD are susceptible to interference, whereas amperometric assays with *Aerococcus viridans* derived LOD are not [102].

The interference with point-of-care assays but not laboratory-based assays can also serve as a diagnostic tool. Patients found to have a "lactate gap" between two assays should be suspected to have EG poisoning [103]. While there is a linear correlation between serum glycolate concentrations and spurious serum lactate concentrations [104], the degree of interference depends on the particular point-of-care assay [102]. Therefore, we cannot recommend the use point-of-care lactate concentrations as a surrogate quantitative marker for these toxic metabolites.

**Discussion**

Hyperlactatemia may result from therapeutic use or overdose of a variety of medications and is easy to overlook. True hyperlactatemia generally portends a high risk of mortality. Clinicians often suspect and investigate common causes of hyperlactatemia such as sepsis or mesenteric ischemia first, resulting in a delay of diagnosis and even unnecessary invasive workup. Therefore, emergency medicine physicians, intensive care providers, and doctors prescribing the medications discussed above should remain cognizant and vigilant of this complication.

The pathophysiologic mechanism of action ranges from pyruvate overproduction, to mitochondrial impairment (Figure 2), or interference with lactate metabolism. It is unclear why some patients develop hyperlactatemia whereas others do not despite comparable medication administration. In addition, patients may develop hyperlactatemia weeks after initiation of drug therapy, as is the case in NRTIs.

Treatment generally includes withdrawal of the offending drug and often includes hemodialysis to remove the toxin and to correct serum pH. Some causative agents are treatable with targeted therapies. Delay or failure of recognition is associated with very poor outcome.

This literature review has certain limitations. The available data are often limited to case reports for a specific drug as a cause for hyperlactatemia rather than large scale population studies or randomized controlled trials. In addition, the true cause of medication-induced hyperlactatemia may go unrecognized and thus underreported. At the same time, clinicians may erroneously attribute hyperlactatemia to medication exposure. Most patients who receive the medications associated with hyperlactatemia are medically complex and potentially critically ill. Therefore, clinicians should consider the conditions outlined above only in parallel to other causes of hyperlactatemia.

**Disclosure statement**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.


