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CYANOTIC METHEMOGLOBINEMIA CAUSING SELECTED TOXICANTS: A BRIEF ACCOUNT

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ABSTRACT

Disorders of haemoglobin leading to cyanosis include carboxyhemoglobinemia, sulfhemoglobinemia and methemoglobinemia. Methemoglobinemia occurs when iron molecule in haemoglobin is oxidized from the ferrous to ferric state. Haemoglobin can no longer bind oxygen in oxidized state, resulting in decreased oxygen availability in tissue. Cyanosis unresponsive to oxygen, is the hallmark of methemoglobinemia. Agents producing methemoglobinemia have been discussed in this paper.

Keywords: Haemoglobin, methemoglobinemia, toxicity

INTRODUCTION

Haemoglobin, in which the iron molecule is oxidized from the normal ferrous state (Fe^{2+}) to the ferric state (Fe^{3+}) is called methemoglobin. Methemoglobinemia is the clinical condition in which more than 2% of haemoglobin (the normal amount) has been oxidized.

PATHOPHYSIOLOGY

- A methemoglobin molecule cannot carry oxygen. Methemoglobin also increases the affinity of normal haemoglobin for oxygen, which results in reduced ability of normal haemoglobin to release oxygen. This further reduces oxygen delivery to the tissues.
- Normally, the NADH methemoglobin reductase reduces methemoglobin back to haemoglobin; however, this pathway is overwhelmed, when large amounts of methemoglobin are produced. NADPH methemoglobin reductase, another enzyme, also reduces a small amount of methemoglobin under normal conditions; but this enzyme system can only be accelerated when supplied with an exogenous electron carrier, such as methylene blue.
- Elevated methemoglobin levels can be produced by oxidising agents, deficiency of NADH or NADPH methemoglobin reductase, and by oxidative stress in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

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EPIDEMIOLOGY

Toxic effects are usually mild to moderate. In the elderly population, there is a higher incidence of comorbid diseases that may increase methemoglobin toxicity. Death occurs in untreated cases wherein methemoglobin levels are greater than 70%. Most causes are secondary to adverse medication reaction, recreational abuse of amyl nitrites(poppers) or therapeutic misadventure.

RISK FACTORS

Deficiencies in NADPH or NADH methemoglobin reductase, G6PD deficiency or the heterozygous form of haemoglobin M, may lead to methemoglobiniemia. Foetal haemoglobin is oxidized to methemoglobin more easily than normal haemoglobin; patients with underlying pulmonary disease, heart disease or anaemia develop symptoms at lower methemoglobin levels.

SIGNS AND SYMPTOMS

Symptoms are related to decreased oxygen delivery to tissues and often correlate with methemoglobin concentration. Cyanosis that is unresponsive to oxygen therapy and of non-cardiac and non-pulmonary aetiologies, is suggestive of methemoglobinemia.

Vital signs: Tachycardia and tachypnea are common. Hypotension may develop in severe methemoglobinemia.

Dermatologic: When methemoglobin concentrations exceed 1.5%, cyanosis occurs. Cyanosis is typically more brown than blue in colour.

Cardiovascular: In severe cases, dysrhythmias may occur. Cardiac arrest and myocardial infarction have been reported. Hypotension may be due to nitrates and related compounds that are vasodilators, in addition to causes of methemoglobinemia.

Pulmonary: Shortness of breath and acute respiratory arrest have been reported.

Hematologic: Blood may have a chocolate brown colour. Hemolysis is associated with methemoglobin.

Neurologic: At high methemoglobin concentrations, lethargy, confusion, syncope, seizures and coma may develop.

LABORATORY TESTS

- Methemoglobin level should be determined.

Normal methemoglobin level is less than 2%. With 15% to 20% methemoglobin, cyanosis is present, and patient is asymptomatic. With 20% to 45% methemoglobin; anxiety, headache, dizziness, fatigue, syncope, & dyspnoea occur. With 45 to 55% methemoglobin; CNS depression occurs. With 55% to 75% methemoglobin; coma, seizures, dysrhythmias, and shock occur. With more than 70% methemoglobin, death may occur, if the condition is untreated.

- Blood colour: blood with methemoglobinemia has a characteristic chocolate brown colour.

TREATMENT

Supportive care with appropriate airway management is important. Specific treatment should be initiated while supportive care continues. In severe cases, methylene blue should be administered. Many patients with mild methemoglobinemia require only humidified oxygen and removal of the oxidizing agent.

Decontamination: Gastric lavage should be performed in paediatric or adult patients for large ingestion presenting within first hour of ingestion or if serious effects are present. One dose of activated charcoal (1-2g/kg) should be administered if there is a substantial ingestion.

Antidotes: Specific antidote for methemoglobinemia is methylene blue.

METHYLENE BLUE

Indications: Methemoglobin level above 20% to 25% and increasing even if the patient is asymptomatic. Symptomatic patient with any elevation of methemoglobin level. Patient with cyanosis that does not correct with 100% oxygen administration. Any evidence of cardiac or CNS hypoxia.

Contraindications: Allergy to methylene blue. Known G6PD deficiency or NADPH methemoglobin reductase deficiency.

Method of Administration: Dose is 1 to 2 mg/kg of 1% solution intravenously over 5 minutes; clinical improvement should be apparent shortly there.

Potential Adverse effects: Hemolysis in patients with G6PD deficiency. Paradoxical worsening of methemoglobinemia with extremely large doses of methylene blue (cumulative dose greater than 7 mg/kg).

Ascorbic Acid: It works very slowly and is not recommended; it is used in cases of NADH deficiency.

ADJUNCTIVE TREATMENT

For life threatening methemoglobinemia refractory to methylene blue therapy or in patient with severe G6PD deficiency, exchange transfusion and hyperbaric oxygen are rarely used.

Use atropine to correct hypotension related to bradycardia. Patient should receive 10 to 20 ml/kg 0.9% saline. Vasopressor may be added if needed.

SELECTED TOXICANTS CAUSING METHEMOGLOBINEMIA

BROMATES [1]

Introduction

Bromate-containing permanent wave neutralizers was ingested in suicide attempt by a professional hairdresser. Commercial bakeries use bromate salts to improve bread texture, and for some explosives, bromates are the components of the fusing material. In one reported epidemic of bromate poisoning, bromate-contaminated sugar was the cause of poisoning.

Toxic dosage & Mechanism of Toxicity

Serious poisoning is caused by the acute ingestion of 200-500 mg of potassium bromate per kilogram. Ingestion of 2-4 oz of 2% potassium bromate solution cause serious toxicity in children.

The bromate ion is toxic to the cochlea, causing irreversible hearing loss, and also is nephrotoxic. In the stomach, bromates are converted to hydrobromic acid, causing gastritis. Bromates are strong oxidising agents which oxidizes haemoglobin to methemoglobin.

Clinical presentation

Within 2 hours of ingestion, victims develop GI symptoms, including vomiting, diarrhoea, and epigastric pain, which is accompanied by restlessness, lethargy, coma and convulsions. An asymptomatic phase of a few hours may follow before renal failure develops. Within 1-2 days of ingestion, anuria is apparent; Tinnitus and irreversible sensorineural deafness occur between 4 and 16 hours after ingestion in adults, but deafness is delayed for several days in children. Hemolysis and thrombocytopenia have been reported in some children. And methemoglobinemia has been reported.

CHLORATES [2]

Introduction

Some matchstick heads contain potassium chlorate as a component, barium chlorate is used in the manufacture of fireworks and explosives. In commercial agriculture, sodium chlorate is a major ingredient in some weed killers and other chlorate salts are used in dye production. Chlorates are more likely to cause intravascular hemolysis and methemoglobinemia in comparison with bromate intoxication.

Toxic Dosage & Mechanism of Toxicity

The minimum toxic dose is estimated to range from 1g in infants to 5g in older children. The adult lethal dose is probably closer to 20-35 g.

Chlorates are potent oxidizing agents. Also these attack sulfhydryl groups, particularly in red blood cells and the kidneys. Chlorates cause intravascular hemolysis as well as methemoglobin formation. Renal failure is caused by a combination of direct cellular toxicity and hemolysis.

Clinical presentation

Within a few minutes to hours after ingestion, abdominal pain, vomiting, and diarrhoea may occur. Coagulopathy and hepatic injury have been reported. Methemoglobinemia is common. Over 1-2 days after ingestion, massive hemolysis, hemoglobinuria and acute tubular necrosis may occur.

DAPSONE [3]

Introduction

Dapsone is an antibiotic used for treatment of malaria, leprosy, and *Pneumocystis carinii* pneumonia. The immune-suppressant and anti-inflammatory effects of dapsone make it

valuable for the treatment of some rheumatologic and rare dermatologic disorders.

Toxic Dosage & Mechanism of Toxicity

Chronic daily dosing of 100 mg can cause methemoglobin levels of 5-12 %. Persons with glucose 6 phosphate dehydrogenase (G6PD) deficiency, congenital hemoglobin abnormalities or underlying hypoxemia may experience greater toxicity at lower doses. Death has occurred with overdoses of 1.4 g and greater.

The toxic effects are caused by oxidized cytochrome P-450(CYP) dapsone metabolites, which can cause methemoglobinemia, sulfhemoglobinemia, and Heinz body hemolytic anaemia, all of which decrease the oxygen-carrying capacity of the blood.

Clinical presentation

Manifestations of acute dapsone intoxication include vomiting, cyanosis, tachypnea, tachycardia, altered or depressed mental states, and seizures. Methemoglobinemia causes cyanosis and dyspnea. When the methemoglobin level is greater than 15-20%, drawn blood may appear chocolate- brown. Because of the long half-life of dapsone and its metabolites, methemoglobinemia may persist for several days. Hemolysis may be delayed at the onset, 2-3 days after acute overdose.

DINITROPHENOL [4]

Introduction

Dinitrophenols have been used as fungicides, insecticides, herbicides, and chemical intermediaries and are used in some explosives, dyes, and photographic chemicals.

Toxic dosage & Mechanism of toxicity

Ingestion of 1-3g of dinitrophenol is considered lethal.

Dinitrophenols uncouple oxidative phosphorylation in the mitochondria. Substrates are metabolized, but the energy produced is dissipated as heat instead of producing adenosine triphosphate (ATP). There is an increase in the basal metabolic rate, placing increased demands on the cardiorespiratory system. Dinitrophenols oxidize haemoglobin to methemoglobin.

Clinical Presentation

Acute exposure causes irritation of the skin, eyes, and upper respiratory tract. Systemic absorption may cause headache, vomiting, weakness and lethargy. With severe or fatal poisonings, profound sweating, hyperthermia, tachycardia, tachypnea, convulsions, and coma have been reported. Cardiovascular collapse or hyperthermia is usually the cause of death. Dinitrophenol may also induce methemoglobinemia, liver and kidney failure.

Chronic exposure may present in a similar manner and in addition may cause weight loss, GI disturbances, weakness, flu-like symptoms, fevers and night sweats, contact dermatitis, and aplastic anaemia.

LIDOCAINE [5]

Introduction

The class 1B antidysrhythmic agents include lidocaine, tocainide, xylocaine, and mexiletine. Lidocaine Hcl (viscous gel (2%- 4% lidocaine)) is used as a topical anaesthetic.

Toxic Dosage & Mechanism of Toxicity

Toxicity has occurred after ingestion of 5-10 mg/kg of lidocaine.

Antidysrhythmic class1B agents depress phase IV depolarization of the cardiac action potential by producing a blockade of the fast inward sodium channel. This slows propagation of impulse conduction through myocardial tissue. Toxicity may develop with therapeutic doses.

Clinical Presentation

Restlessness is the first sign of toxicity. CNS effects typically develop before dysrhythmia. Toxicity due to intravenous lidocaine is immediate. Bradycardia and hypotension occur after serious ingestion. Miosis and tinnitus occur with lidocaine at high doses. Cardiovascular effects range from nodal bradycardia to third-degree atrioventricular (AV) block and asystole occurs. Apnoea and respiratory depression may occur in a serious overdose. Methemoglobinemia hematologic effect in lidocaine toxicity. Neurologic effects include restlessness, confusion, irritability, dizziness, seizure and coma.

METOCLOPRAMIDE [6]

Introduction

Metoclopramide is a synthetic chemical. Metoclopramide reduces the inhibitory effect of dopamine in gut motility, and in about 10-30% of patients, may induce extrapyramidal signs (ranging from a Parkinson-like syndrome to tremors and agitation). It is an antiemetic.

Toxic Dosage & Mechanism of Toxicity

Nine children aged one month to nine years who received doses of 5 to 50 mg of metoclopramide were hospitalized; and they recovered. No lethal dose of metoclopramide has been reported.

When administered in high doses, these (metoclopramide) substituted benzamide prokinetic agents block 5-hydroxytryptamine (5-HT3) receptors in the gastrointestinal motor system. In the GI tract, metoclopramide enhances acetylcholine release and sensitizes muscarinic receptors. It stimulates gastric emptying. Also, metoclopramide antagonizes the inhibitory effect of dopamine receptors located in the smooth muscle of the GI tract. Within CNS, it also exerts an antidopaminergic effect, resulting in extrapyramidal adverse effects.

Clinical presentation

In Overdose: Overdose in young children, produce intermittent opisthotonos, increased muscle tone in the limbs, facial grimacing, oculogyric crisis, agitation, strabismus, nystagmus, seizures, cyanosis of the extremities, and cogwheel rigidity. Torticollis and opisthotonus are the most common extrapyramidal manifestations of overdose. Intravenous use has resulted in bradycardia and total heart block.

In Chronic use: Methemoglobinemia, extrapyramidal symptoms, dystonic reactions with sudden death after high dose IV metoclopramide have been reported.

MOTH BALLS[7]

Introduction

Mothballs are used to repel moths, and other insects, and small animals. The active ingredient in mothballs is paradichlorobenzene or naphthalene.

Toxic Dosage & Mechanism of Toxicity

Toxic dose: One naphthalene mothball can produce haemolysis in Glucose 6 phosphate Dehydrogenase (G6PD) deficient children.

Paradichlorobenzene: Methemoglobinemia and red cell haemolysis have been reported. Hepatotoxicity has been reported following chronic exposure.

Naphthalene: It is readily absorbed and can cause toxicity. Gastrointestinal distress may occur shortly after ingestion. Hemolysis and methemoglobinemia may occur 1 to 5 days after ingestion. Toxicity is usually delayed for several days as naphthalene is metabolized to a potent haemolytic agent called α-naphthol.

Clinical presentation

Acute effects: No toxicity from a single mothball. Large ingestion may result in fever, nausea, vomiting, abdominal pain, and diarrhoea 24 to 48 hours later. In severe cases, lethargy and seizures develop. Signs of hemolysis include pallor, weakness, haemoglobinuria, jaundice, and cyanosis.

Chronic effects: Aplastic anaemia, hepatic necrosis, and jaundice may occur.

NITRATES AND NITRITES [8]

Introduction

Organic nitrates (eg, isosorbide dinitrate, and isosorbide mononitrate, nitroglycerin) are widely used as vasodilators for the treatment of ischemic heart disease and heart failure. Bismuth subnitrate and silver nitrate are used in antidiarrheal drugs and in topical burn medications respectively. Sodium and potassium nitrate and nitrite are used in preserving foods.

Toxic Dosage & Mechanism of Toxicity

Nitrates. The adult lethal oral dose of nitro-glycerine is 200-1200 mg. Massive doses are required to produce methemoglobinemia.

Nitrites. Ingestion of 15 ml of butyl nitrite produced 40% methemoglobinemia in an adult. Adult lethal oral dose of sodium nitrite is 1g.

Nitrates and nitrites both cause vasodilation, which can result in hypotension. Nitrates relax veins at lower doses and arteries at higher doses. Nitrites are potent oxidizing agents. Oxidation of haemoglobin by nitrites result in methemoglobinemia.

Clinical Presentation

The most common adverse effects of nitrates and nitrites are headache, skin flushing and orthostatic hypotension with reflex tachycardia. Workers or patients regularly exposed to nitrates may develop angina or myocardial infarction**.** Methemoglobinemia is most common

after nitrite exposure; Use of sildenafil and other selective phosphodiesterase inhibitors (tadalafil, vardenafil) can prolong and intensify the vasodilating effects of nitrates, causing severe hypotension.

PHENAZOPYRIDINE [9]

Introduction

Phenazopyridine hydrochloride, has, in overdose, produced methemoglobinemia, hemolytic anaemia, and acute renal failure. Phenazopyridine hydrochloride is a synthetic azo dye. Phenazopyridine exerts an analgesic effect on the mucosa of the urinary tract and is used to provide symptomatic relief of pain, burning, urgency, frequency, and other discomforts resulting from the irritation of the lower urinary tract mucosa.

Toxic Dosage & Mechanism of Toxicity

As little as 50mg/kg of oral phenazopyridine has produced human toxicity and as little as 600 mg/d in adults with renal impairment has caused cyanosis.

Fatal dose: One patient ingested 2000 mg of phenazopyridine with prior renal dysfunction, developed further renal failure, and died of a pulmonary embolism.

In phenazopyridine overdose, progressive oliguric renal failure has been found to occur. This may be due to a direct toxic effect of the drug on the renal tubules. Hemolysis may follow ingestion of either phenazopyridine or aniline alone. Methemoglobinemia follows phenazopyridine oxidation of haemoglobin iron (Fe^{2+} to Fe^{3+}).

Clinical Presentation

Methemoglobinemia may occur usually with hemolytic anemia. Methemoglobinemia may follow a therapeutic dose of phenazopyridine in glucose 6 phosphate dehydrogenase (G6PD) deficient patients, and those with functional renal impairment. Non-oliguric acute renal failure usually is associated with methemoglobinemia and hemolysis. Hypersensitivity hepatitis, rhabdomyolysis and aseptic meningitis have been reported.

PHENOL AND RELATED COMPOUNDS [10]

Introduction

Phenol (carbolic acid) is a potent germicidal agent. Phenol is now most commonly found in topical skin products (eg, Campho-phenique contains 4.7% phenol) and is also used cosmetically as a skin-peeling agent. Creosote, creosol, cresol, cresylic acid, hydroquinone, eugenol, and phenylphenol, are the other phenolic compounds.

Toxic Dosage & Mechanism of Toxicity

The minimum toxic and lethal doses have not been well established. Phenol is well absorbed via ingestion, inhalation and skin application.

A. **Inhalation**: The level considered immediately dangerous to life or health (IDLH) is 250 ppm.
B. **Skin application:** Cardiac arrhythmias occurred after dermal application of 3 ml of an 88% phenol solution. Solutions of more than 5%, are corrosive.

C. **Ingestion:** It has been reported that as little as 50-500 mg is fatal among infants. Deaths have occurred after adult ingestions of 1-32 g of phenol.

Phenol disrupts the cell wall, denatures protein, and produces a coagulative tissue necrosis. Systemic absorption may result in cardiac arrhythmias and CNS stimulation. Dinitrophenol and hydroquinone may induce hemolysis and methemoglobinemia**.**

Clinical Presentation

Inhalation. Vapours of phenol may cause respiratory tract irritation and chemical pneumonia. Severe tracheobronchitis may be caused by smoking clove cigarettes (clove oil contains the phenol derivative eugenol).

Skin and eyes. Topical exposure of the skin may produce a deep white patch that turns red, after which the skin stains brown. If concentrated phenolic compounds meet eyes, irritation and severe corneal damage may occur.

Ingestion usually causes diffuse corrosive GI tract injury. Systemic absorption may cause seizures, coma, hypotension, arrythmias and respiratory arrest.

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