ACUTE POTASSIUM DICHROMATE POISONING: AN OVERVIEW

NS Neki, Amritpal Singh, Gagandeep Singh Shergill, Amanpreet Kaur

Author's affiliations

NS Neki, Professor; **Amritpal Singh,** Senior Resident; **Gagandeep Shergill**, Postgraduate Student: Department of Medicine, Government Medical College & Guru NanakDev Hospital, Amritsar, Punjab-143001:
Amanpreet Kaur,Consultant Gynaecologist, Civil Hospital, Fatehgarh

Abstract

Potassium dichromate is commonly used chemical in various industrial and laboratory operations. It is highly toxic compound which normally proves fatal when ingested orally as its fatal dose is very small. Its oral ingestion occurs accidently, or knowingly with suicidal intention. Because of high fatality rate, it is of utmost importance to start treatment at the earliest. Treatment is mostly supportive and symptomatic, but there are many other treatment modalities employed by various clinicians and reports of saving the patient from certain death are there with these modalities. This article intends to review all the treatment options available at hand of an emergency doctor in case of a potassium dichromate poisoning.

Keywords:

Acute Potassium dichromate poisoning, dichromate poisoning, management of dichromate poisoning

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Correspondence:

Dr. N.S. Neki, Professor,
Dept. of Medicine, Govt. Medical College
& Guru Nanak Dev Hospital, Amritsar, Punjab, 143001 .
Email:drneki123@gmail.com, Phone: 09501029128

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Introduction

Hexavalent chromate (Cr^{+6}) in the form of potassium dichromate (sodium dichromate and ammonium dichromate are also used) is commonly used chemical in various industrial and technical laboratory operations like Commercial applications of chromium compounds include tanning trivalent chromate (Cr^{+3}), corrosion inhibition, plating, glassware-cleaning solutions, wood preservatives, screen printing (Cr^{+6}), manufacture of safety matches, metal finishing (Cr^{+6}), and the production of pigments (Cr^{+3}, Cr^{+6})[1]. So exposure to this highly toxic compound is an occupational hazard. Chronic chromate poisoning is a well known industrial hazard[2], but acute poisoning because of potassium dichromate ingestion is rare[3]. But some authors have different opinion, according to them, this is a toxin which may be more prevalent than previously thought because of its use in traditional medications and lowest reported lethal dose is as small as 0.1gm[4]. Acute exposure to dichromate is usually due to oral ingestion, it can also occur due to absorption from a scalded/burned skin due to chromate itself resulting from the spillage of the liquid dichromate, or from inhalation of dichromate (chromic acid) aerosols[5] but inhalation of fumes or dust mostly causes chronic toxicity[6]. Some other causes of acute poisoning from dichromate salts has also been reported. In a study[7], seven cases of dichromate poisoning after the use of purgative solutions obtained from 'nyanga' (traditional township healers) are reported. One patient consumed the purgative orally, the other six used as rectal enema, all patients presented in established renal failure requiring dialysis. In another case reported, a 2-year child developed symptomology of acute potassium dichromate poisoning following a foreign body impacted in nose after six days of impaction[8]. Oral ingestion is usually accidental, suicidal ingestion is rare[8]. But some others differ, acute potassium dichromate poisoning is observed more often as a result of suicidal intent than as an accidental occurrence (they appear to be right as in reports reviewed by the author of this review, nearly half of the cases reported are of suicidal attempts). A case of 18-year old female has been reported, who in a bet with fellow student, consumed few grams of potassium dichromate from her lab[9]. In yet another important report, a 2-year child developed acute renal failure following chewing match-stick heads[10]. So poisoning from dichromates can occur by various routes and in various setups of circumstances, this is important in preventive aspects of the poisoning in general and poisoning from dichromates in particular. In following sections of the article, we will visit the chemistry of dichromates related to its medical implications, pathophysiology and clinical picture resulting from acute poisoning and management.

Relevant Chemistry

In potassium dichromate (also in other chromate compounds), the toxic component is ionic form of chromium (chromate). Chromium exists in a series of oxidation states from -2 to +6 valence. The most important stable states are 0 (elemental metal), +3 (trivalent), and +6 (hexavalent). The health effects of chromium are primarily related to the valence state of the metal at the time of exposure. Trivalent (Cr^{+3}) and hexavalent (Cr^{+6}) compounds are thought to be the most biologically significant.

Cr^{+3} is an essential dietary mineral in low doses. It is required to potentiate insulin and for normal glucose metabolism. Cr^{+3}deficiency has been associated with maturity onset diabetes mellitus, cardiovascular disease and obesity. A safe and adequate daily intake for Cr^{+3} in adults is 50 -200 micrograms per day[11]. So trivalent chromate which occurs naturally in chromite ore also, is needed for human body functioning but Cr^{+6} compounds are toxic and carcinogenic. Cr^{+6} is generally considered 1,000 times more toxic than Cr^{+3} [12] and it is this form of chromate that is either used or produced in industrial processes or laboratory applications.

Pathophysiology of Acute Dichromate Poisoning

Following entry of dichromate, may be ingestion, inhalation or dermal route, the dichromate cross the lining epithelia and gains entry into systemic circulation and widely distributed throughout the body. This wide distribution produces complex picture of clinical symptoms which depends upon the route of entry and the organ which is particularly affected in the particular case[9].

In general, with equal solubility, Cr^{+6} compounds are absorbed more readily than Cr^{+3} compounds through all routes of entry, probably because Cr^{+6} readily penetrates cell membranes[13,14]. Due to the actions of stomach acid and other components within the gastrointestinal tract, most of an ingested Cr^{+6}

dosage is converted to Cr^{+3} [15]. This action of gastric action has been considered as first defense against the ingestion of dichromate salts[16]. In humans and animals, less than 1% of inorganic Cr^{+3} and about 10% of inorganic Cr^{+6} are absorbed from the gut; the latter amount is slightly higher in a fasting state[17]. These points are important in management as we will see later. When inhaled, Cr^{+6} is reduced to Cr^{+3} in the lower respiratory tract by the epithelial lining fluid and by pulmonary alveolar macrophages[12]. One study showed that at equivalent numbers of cells, the reducing efficiency of alveolar macrophages by biochemical mechanisms was significantly greater in tobacco smokers than in nonsmokers[18]. So, after Crohn's disease, it is second instance where smoking is actually protective!!

Once absorbed into the bloodstream, Cr^{+6} is rapidly taken up by erythrocytes and reduced to Cr^{+3} inside the red blood cells. In contrast, Cr^{+3} does not readily cross red blood cell membranes, but binds directly to transferrin, an iron-transporting protein in the plasma[12]. Reduction of Cr^{+6} in the red blood cells occurs by the action of glutathione. Since the red blood cell membrane is permeable to Cr^{+6} but not Cr^{+3}, the Cr^{+3} formed by reduction of Cr^{+6} is essentially trapped within the red blood cell. Eventually the diffusion of Cr^{+6}, the reduction to Cr^{+3}, and complexing to nucleic acids and proteins within the cell will cause the concentration equilibrium to change. Regardless of the source, Cr^{+3} is widely distributed in the body and accounts for most of the chromium in plasma or tissues. The greatest uptake of Cr^{+3} as a protein complex is via bone marrow, lungs, lymph nodes, spleen, kidney, and liver. Excretion of absorbed chromium occurs primarily via urine. In humans, the kidney excretes about 60% of an absorbed Cr^{+6} dose in the form of Cr^{+3} within 8 hours of ingestion. Approximately 10% of an absorbed dose is eliminated by biliary excretion, with smaller amounts excreted in hair, nails, milk, and sweat[20]. Clearance from plasma is generally rapid (within hours), whereas elimination from tissues is slower (with a half-life of several days). Doses of Cr^{+6} administered to volunteers were more rapidly eliminated than doses of Cr^{+3}.

As hexavalent dichromate is strong oxidizing agent, so as it enters into different type of cells, under physiological conditions can be reduced by hydrogen peroxide (H_2O_2), glutathione (GSH) reductase, ascorbic acid, and GSH to produce reactive intermediates, including Cr^{+5}, Cr^{+4}, thiylradicals, hydroxyl radicals, and ultimately, Cr^{+3}. Any of these species could attack DNA, proteins, and membrane lipids, thereby disrupting cellular integrity and functions[21] especially damage to mitochondria and lysosomes[22].

On oral ingestion, it leads to damage to gut mucosal cell death and necrosis and further damage of gut wall depends upon the amount consumed. After reaching circulation, it is initially taken up red blood cells where it is oxidized to Cr^{+3}, if large amount enters the RBCs, then intracellular Cr^{+6} concentration increases and damage from Cr^{+6} leads to lysis and hemolysis. Similarly, platelets can be affected, leading to bleeding diathesis or activation of intravascular coagulation. Among major organs, after oral or dermal absorption of Cr^{+6}, the kidney is the main target organ for chromium accumulation, kidney epithelial cells are 10 times more sensitive towards Cr^{+6} than liver epithelial cells and this might explain the known nephrotoxicity in vivo[23]. In kidneys, low doses acting specifically on the proximal convoluted tubules[24] but severe poisoning can lead to acute tubular necrosis and acute renal failure. Acute tubular necrosis may occur as direct injury from dichromates or it may occur following intravascular hemolysis[9].

Large doses of dichromates cause damage to liver cells, necrosis, lymphocytic and histocytic infiltration, and increases in Kupffer cells and if severe enough leads to fulminant hepatic failure[25]. Dichromate can also myocardium leading to hypoxic damage[26] resulting in myocarditis, ventricular arrhythmias and circulatory collapse. Dichromates also exert genotoxic-mutagenic affects also. Previously it was thought to be effect of chronic exposure, but recently, a clinical study reported strong DNA oxidative damage from the urinary samples of the patient who ingested 2 to 3 grams of potassium dichromate in a suicide attempt[27]. Inhalation of large quantity of aerosols can cause local mucosa and parenchyma injury in lungs before causing systemic injury.

Clinical Featues

Within minutes, the direct corrosive action of dichromates leads to irritation in throat, oesophagus, pain abdomen, nausea and vomiting. As the time lapses, gut mucosa more and more inflames and cause dysphasia, dysarthria, bloody diarrhea from direct gut mucosa injury can ensue. GI bleeding can also result from coagulopathy. Perforation can lead

to acute abdomen like picture and circulatory collapse. These relatively early features can cause circulatory collapse and death. If patient survives initial onslaught, intravascular hemolysis leads to anemia, hamaturia and can cause acute renal failure in itself. It manifests as decreased hemoglobin content and hematocrit, and increased total white blood cell counts, reticulocyte counts, and plasma hemoglobin on laboratory testing[9]. Renal failure causes anuria and uremic features. Acute hepatic failure manifest as jaundice, bleeding diathesis or hepatic encephalopathy. Central nervous system manifestations can be due to direct damage from dichromate or due to renal or hepatic failure. Cardiac involvement can cause pump failure resulting circulatory collapse or arrhythmias leading to cardiac arrest.

On inhalation of potassium dichromate compounds, it is highly irritant to mucous membranes causing inflammation of nasal mucosa, hoarseness, cough, bronchospasm and dysnoea. Headache, chest pain, chemical pnemonitis, pulmonary edema and cyanosis may ensue. Lung injury can also occur as a systemic injury target, can cause pulmonary edema leading to dyspnea, cyanosis and respiratory failure because of damage to respiratory membrane.

Systemic symptoms and death have occurred after external burns, with a delay of onset of gastrointestinal symptoms of hours and days. Burns initially resemble first and second degree burns, but extends to subcutaneous tissue within a couple of days[28].

Management

Treatment of acute dichromate poisoning includes supportive measures, attempts to remove as much as possible active form i.e. hexavalent chromate from the body and treatment of complications arising from the systemic toxicity.

Supportive measures[29] include maintenance of airway, giving oxygen by high flow facemask and keeping ready the instrumentation for intubation/tracheostomy and ventilatory support to maintain the necessary oxygen saturation in case obstruction to airflow develops or respiratory failure ensues. Similarly, circulatory support in the form of replacement of blood/plasma loss from GI loss or bleeding from any other site with crystalloids, and ionotropes when needed. Correction of electrolyte imbalance, metabolic acidosis, substitution of blood components as required and prophylactic antibiotics, all are required as in any serious ill patient. It is our theoretical observation that routine use of injectable pantoprazole or other PPIs should be avoided atleast in first 3-6 hours because gastric acid oxidizes Cr^{+6} to Cr^{+3} which is relatively less harmful and rapidly cleared by kidneys. Use of high doses of glucocorticoids has not been mentioned anywhere in the literature reviewed regarding the acute poisoning from potassium dichromate or other dichromates. Theoretically[30], glucocorticoids being suppressants of inflammatory process and decreasing capillary permeability after the initial insult can limit the damage from inflammatory process in the long run. Glucocorticoids also increase the number of RBCs, platelets & neutrophils in circuation that can increase the rate of convertion of Cr^{+6} to Cr^{+3} and reduce the quantity of Cr^{+6} in the target organs. So use of glucocorticoids can be beneficial theoretically, but whether this theoretical benefit gets converted into practical benefit to the patient is matter of speculation yet. Their use depends upon the experience of the attending emergency team.

As dichromate is a corrosive compound, induction of vomiting is not recommended[31]. Gastric lavage with magnesium hydroxide or another antacid might be useful in cases of chromium ingestion. The efficacy of activated charcoal has not been proven[32].

On the theoretical postulate that ascorbic acid can convert Cr^{+6} to Cr^{+3}, it was experimented to use oral ascorbic acid to enhance the clearance of toxic hexavalent chromate but in spite that orally administered ascorbic acid was found to be protective in experimental animals and was reported beneficial in at least one patient after chromium ingestion; however, no clinical trials have been conducted to confirm the efficacy of this treatment[5]. In another study[33], experiments demonstrate the effectiveness of ascorbic acid for the treatment of Cr^{+6} poisoning. Reduction is increased and accelerated by ascorbic acid and the resulting Cr^{+3}-protein complexes are non-toxic and can be excreted with the urine. Early and repeated high i/v doses of ascorbic acid are recommended as the therapy of choice for Cr^{+6} poisoning. In cases of delayed medical treatment, ascorbic acid should be immediately applied orally. But, ascorbic acid administered only within 2 hours can be protective whereas its use after 3 hours is not only anymore seems to be protective, but may even be harmful as after 3 hours much quantity of Cr^{+6} gets sequestered intracellulary. After 3 hours, ascorbic acid produces Cr^{+3} which

generates reactive intermediates intracellularly and Cr^{+3} itself is considered lately more notorious than Cr^{+6} for DNA binding and DNA strand breaks[34,35,36,37].so it appears counter-productive to use ascorbic acid for longer duration. In addition high doses of ascorbic acid risk oxalate nephropathy. Suggested dose for its use 5-10 gm intravaneously within 2 hours[38].

There are favorable reports of therapy with N-acetylcysteine (NAC)[39] NAC can increase the excretion of chromium and also able to reverse the oliguria associated with the toxin[40]. The antioxidant properties of NAC may have theoretical value when there is multi-organ failure, especially liver, from oxidative injury.

The use of dimercaprol, D-pencillamine and DMPS as chelating agent has been suggested in the management of systemic hexavalent chromium poisoning but their efficacy is unproven[31].

Exchange transfusion was effective in reducing blood chromium levels 67% in one case of chromium poisoning, using 10.9 L of blood[41]. But existing evidence does not allow the conclusion that exchange transfusion generally should be employed[31]. Though there are some old reports of trying peritoneal dialysis[3] and hemodialysis[42] at removing chromate from blood in early stages of poisoning when blood concentrations are high, but these modalities and charcoal hemoperfusion do not substantially enhance chromium removal from the body if renal function remains normal.[4,26,43,44] However, if renal failure ensues, hemodialysis may be necessary for management of the renal failure itself; peritoneal dialysis can also be employed for this purpose and both hemodialysis & peritoneal dialysis have been proven life-saving[9,28,31] Lately, plasmapheresis has been advocated in the treatment of severe systemic chromium poisoning[43]. If renal function remains preserved during the course of illness, then sufficient hydration and forced diuresis with either mannitol or furosemide is effective for clearance of chromate from body[45].

Liver transplantation is a treatment option in cases where acute fulminant haptaic failure is prominent feature of poisoning, if other parts of systemic injury are expected to be taken care of, then it is life-saving procedure. Successful liver transplantation has been reported. Although liver failure occurred within 2 days after ingestion, the patient's clinical condition was stable for another 3 days. As soon as he lapsed into coma because of cerebral edema, the decision to perform a LTX was made. At this time, it was assumed that most of the toxin had accumulated in the liver, as serum chromium levels had reduced to 20% of the initial value. The rationale for the delayed transplantation was to avoid damage of the new organ as a result of high serum chromium levels[46].

In case of absorption from skin burns, early excision of the burned tissue is key to decrease the systemic absorption[47]. Topical preparations of ascorbic acid and chelating agents have been tried with variable success. If systemic toxicity occurs, then treatment is similar to management after oral ingestion.

Lethal Dose: Mostly 2-3 gm is considered fatal[22]. Doses as low as 0.1gm can prove fatal[4] and patients consuming quantity higher than fatal dose have also survived. Survival depends upon how much Cr^{+6} reaches in blood stream and ultimately in various cells. All patients with blood chromium dose concentration exceeding 1 mg/100ml died, this level is of prognostic and diagnostic value indicating an ingestion and absorption of the high doses of this metal[45].

Follow up: In patients who are lucky enough to survive, it is important to keep them under follow up for many weeks. Renal and hepatic functions in survived patients can remain depressed for many weeks[48].

Conclusion

Potassium dichromate and other dichromates are strong oxidizing agents and act as corrosive agents locally depending upon the route of entry. Local effects themselves can prove fatal. In addition, they have deadly systemic toxicity affecting liver, kidney, blood cells and myocardium leading to death from multi-organ failure. Early and aggressive institution of treatment aimed at supportive measures, removing the maximum possible quantity of Cr^{+6} from body before entering intracellularly and then management of complications of systemic toxicity can bring out favorable outcome of this poisoning which otherwise proves universally fatal. It is important to educate the workers to reduce its occupational exposure and providing them appropriate protection. Similarly periodic assessment of psychosocial aspects of the persons working with this chemical is equally important to prevent suicide attempts with this chemical.

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