Toxicity of ingested formalin and its management

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Formaldehyde is a physiological intermediary metabolite taking part in many biological processes in the body. It is a constituent of many items of daily use, including foods. It is also used in medicine for the treatment of some conditions. A 40% solution of formaldehyde in water is known as formalin. Formalin is irritating, corrosive and toxic and absorbed from all surfaces of the body. Ingestion is rare because of alarming odour and irritating effect but documented in accidental, homicidal or suicidal attempts. Ingestion can lead to immediate deleterious effects on almost all systems of the body including gastrointestinal tract, central nervous system, cardiovascular system and hepato-renal system, causing gastrointestinal hemorrhage, cardiovascular collapse, unconsciousness or convulsions, severe metabolic acidosis and acute respiratory distress syndrome. No specific antidote is available. Treatment of toxicity is supportive care of the various organ systems. Multidisciplinary approach is required for proper management. Human & Experimental Toxicology (2000) 19, 360–366.

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Introduction

Formaldehyde is a water-soluble, colourless, pungent, irritating and highly reactive gas. Forty percent solution of formaldehyde in water is known as formalin.\(^1,2\) In medicine, formalin is used in the preservation of surgical specimens, for the treatment of uncontrolled intravesical hemorrhage\(^3,4\) and radiation-induced hemorrhagic proctitis\(^5-10\) and cystitis, and to prevent hydatid cysts dissemination.\(^11\)

It is also a physiological intermediary metabolite in mammals. The endogenous formaldehyde is rapidly metabolised to formate or enters the one-carbon pool via tetrahydrofolate.\(^1\) Formate, as the sodium salt, is one of the simplest endogenous forms of carbon in man and is the intermediate in many anabolic and catabolic reactions. Formate or formaldehyde has been shown to be involved in single carbon transfers from many essential amino acids including glycine, histidine, tryptophan and serine and in the synthesis of purines, pyrimidines, methionine and cholase.\(^12\) The tetrahydrofolate acid pathway is the primary means through which the above metabolism occurs. Once formate has entered into the one-carbon unit pool, numerous reactions occur that direct formate to various other pathways including the citric acid pathway where it can be utilised for energy need, releasing carbon dioxide and water.\(^13\)

Metabolism and excretion

The metabolic sequence of formaldehyde is identical in all mammalian species. It is rapidly metabolised to formic acid by several enzyme systems, including the formaldehyde dehydrogenase (FDH) complex distributed in several tissues, or a hydrogen peroxide/catalase system (Figure 1). FDH is involved specifically with the oxidation of formaldehyde and has been identified in human liver and erythrocytes. FDH is also involved in the release of formate by cleavage of the thio ester with glutathione. The efficiency of formate metabolism by catalase has been strongly linked to the hepatic concentration of tetrahydrofolate. In vitro studies with human tissue have also shown that functionally related aldehyde dehydrogenase and catalase, which are not dependent on glutathione, are both capable of converting formaldehyde to formate.\(^13\)

In humans and monkeys, formic acid is slowly metabolised to carbon dioxide and water by an enzymatic reaction, which depends on folate. Folate

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is an essential vitamin found in fresh fruits and vegetables and is the building block of tetrahydrofolate. The rate of conversion of formic acid to carbon dioxide and water is approximately 50% more rapid in the rodents liver than in primates. The relatively slow metabolism of formic acid to carbon dioxide and water in humans leads to accumulation of formic acid, which results in metabolic acidosis. Excess formate that is not utilised metabolically will be eliminated in the urine.\textsuperscript{13}

\textit{In vitro} experiment with human blood showed that formaldehyde is quickly oxidised to formate after its transport in erythrocytes. Since formaldehyde can be handled so effectively not only by the liver but by the blood as well, the rapid disappearance of formaldehyde from the blood can be understood. A study using monkeys who were given a rapid intravenous administration of formaldehyde reported that it has a plasma half-life of approximately 1.5 min.\textsuperscript{14} During the disappearance of formaldehyde, a corresponding rapid increase in the plasma levels of formic acid was observed.\textsuperscript{13} Whereas formaldehyde has a very short residence time in plasma, the half-life for circulating formic acid is 90 min.\textsuperscript{13} In an experiment with a monkey who received intravenous infusion of several concentrations of sodium formate, the results indicated that the plasma half-life for formate appears dose-related, at least at high dose levels, but shows signs of becoming constant at lower dose levels. Similar low dose levels could be experienced during workplace exposure.\textsuperscript{15}

Elimination kinetic data on formate in man have been supported in two studies. In one study, the average plasma half-life in 11 volunteers, who were given an intravenous specified dose of formate, was 55 min.\textsuperscript{13,16} Another study reported that the plasma half-life was 45 min when 3 g of formate was given orally to one individual, while in a second individual, the plasma half-life was 46 min after intake of 4.4 g of sodium formate.\textsuperscript{13} In this study, 11 volunteers were given a 1 g and a 2 g oral dose of formate on two occasions and urine samples were collected for the periods 0–6, 6–12 and 12–24 h. It was found, under the conditions of this study, that after the two doses were given, the output of formic acid in urine over the 24-h collection period was 1.9 times and 2.6 times greater than normal, respectively. The increased amount of eliminated formate in the urine, however, represented only 2.2% and 3.3% of the formic acid dose, leaving the remainder unaccounted for. Elimination was rapid in each regimen and 80% and 90% of the increased elimination occurred within 6 h of the administration. This study indicates that large bolus doses of formate result in large, rapid increase in the urine concentration. A much smaller elevation in the baseline formic acid concentration was, however, noticed when the smaller dose of formate was administered.\textsuperscript{13,16}

More recent research indicates that while high plasma concentration of formaldehyde is removed rapidly, a trace baseline concentration frequently, or nearly always, exists. An average of 2.24 and 2.61 \(\mu\)g formaldehyde per gram of venous blood was reported in rats and humans, respectively. When human volunteers were exposed to 1.9 ppm of formaldehyde for a period of 40 min, the blood concentration was not elevated significantly.\textsuperscript{17} These baseline concentrations and the rate kinetics for formaldehyde removal suggest that formaldehyde is replenished constantly by \textit{in vivo} processes, but that the removal process is capable of maintaining plasma concentration in equilibrium at low concentrations. In the above studies, urine or plasma formate concentrations were not measured and it is not known from these studies if urine formate concentration was elevated after inhalation of formaldehyde. The high variation in blood formaldehyde concentration observed within the human volunteers and lack of response to exposure, however, would discourage the use of blood samples for measuring formaldehyde exposure.\textsuperscript{13}

**Toxicity**

High intake of carbohydrate or protein-rich food is believed to increase formate output through the urine.\textsuperscript{13} Formic acid occurs naturally in animals and in most plants.\textsuperscript{14} In addition, some foods and beverages have been reported to contain small amounts of formic acid. Formic acid is added intentionally to some foods as a flavor adjunct.\textsuperscript{13}
Formaldehyde presence has also been reported in popular soft drinks as well as in beer at a concentration of approximately 8 mg/kg. Since formaldehyde can arise from many sources, there always appears to be a certain amount of it in the blood. Endogenous or background levels of formic acid in blood vary from 0.07 to 0.4 mmol/l. A deficiency in any of the essential biochemical components in the tetrahydrofolic acid pathway will reduce the proportion of serum formate metabolised to carbon dioxide and water. Animal studies have shown that nutritional deficiencies in folic acid and vitamin B<sub>12</sub> result in an accumulation of formic acid in the blood and elevated excretion of formate in the urine. This imbalance can be corrected by dietary supplementation resulting in a return to a lower urine formate concentration. Formaldehyde forms Schiff’s base with plasma proteins, which is metabolised into formic acid (an oxidative product of formalin) and is responsible for all its harmful effects. Formic acid is an inhibitor of enzymes like hexokinase and the cholinesterase. It also inhibits succinate oxidation and anaerobic glycolysis and thus affects the normal physiological functions of the liver. Formic acid is also considered to be a sufficient inhibitor of mitochondrial cytochrome oxidase to produce histotoxic hypoxia so that a significant part of the acid load results from hypoxic metabolism.

In minimal concentration, formaldehyde is non-toxic to humans, but exposure to higher concentration may result in severe toxic effects. Following systemic absorption, formaldehyde is oxidised to formic acid by enzyme FDH in the liver and in erythrocytes. Normal blood level of formic acid in human ranges from 0 to 12 mg/l. Urine formic acid levels range from 0 to 27 mg/l, although absolute toxic levels are not known. Investigators have demonstrated that ingestion of 120 ml of 37% formaldehyde (commercial formalin) resulted in formic acid level as high as 500 mg/l. Dietary intake, nutritional status, and smoking may be confounders that can affect the levels of formaldehyde in the blood.

A number of reports have documented the toxic effects of formaldehyde exposure via different routes because it is absorbed from all surfaces of the body. Formaldehyde exposure can occur in various ways. It is a constituent of cigarette smoke and car exhaust fumes. The exposure occurs mostly in autopsy rooms, surgical pathology laboratories, and renal dialysis units. Skin sensitivity to formaldehyde can result from contact with clothing and facial tissues finished with formaldehyde resins. Formaldehyde can also be released from resins used as bonding agents in plywood and chipboard materials employed extensively in mobile homes. Skin hardening, cracking, and bleeding have been reported with its contact. Animal studies have shown that formaldehyde is both mutagenic and carcinogenic in several experimental systems, raising concern about chronic human low level exposure. Although epidemiology studies are underway, no definitive assessment of human risk is available. The exposure levels are low but there are mounting evidence from work in both man and animals that adverse effects of formaldehyde can arise at levels well below 1 ppm.

Most studies have investigated the effects of formaldehyde vapours. Symptoms following low dose formaldehyde inhalation include mild irritation of the respiratory tract and mucus membranes, higher doses may cause respiratory symptoms of various degrees and severity, extending from transient asthmatic episodes through asthma and pneumonitis, culminating in acute respiratory distress syndrome. Bronchoscopy is advised for early diagnosis of pulmonary complications. Industrial exposure to formaldehyde can cause a reduction in ventilatory capacity. The mechanism of the effect of formaldehyde on airways is not clear; it may be due to direct irritant action, but sometimes it may be a hypersensitivity reaction also. Since formaldehyde is a highly reactive, water-soluble chemical, formaldehyde gas is absorbed primarily in the upper respiratory tract. However, formaldehyde could migrate to remote tissues and affect them by direct and indirect mechanism. Formaldehyde that contacts body tissues reacts with amino acids, protein, nucleotides, and nucleic acids. The reaction of formaldehyde with small molecules such as amino acids and nucleotides produces labile conjugates. These may carry formaldehyde to tissues that are remote from the respiratory tract. It is possible that the changes in various organs, such as liver, kidney, and hemopoietic tissues that develop after formaldehyde is inhaled, reflect such a process.

The use of formalin therapy is successful in controlling intravesical hemorrhage and hemorrhage of radiation proctitis. Acute toxicity and death following the use of formalin for instillation in intravesical hemorrhage have been reported. The attributing factors of death were severe metabolic acidosis because of formic acid production and acute renal tubular necrosis leading to anuria. The complication rate is high with prolonged or repeated use of high concentration of formalin. In animal experiments, it has been shown that minimal contact time helps to ensure that only the hemorrhagic mucosa will be affected by formalin and therefore decreases the complication rate. Constant exposure to formalin causes serum formic acid to reach toxic levels.
levels within 15 min after instillation. Blood levels appear to peak prior to removal of formalin, indicating that the tissue may become fixed by formalin, preventing further absorption through the mucosa despite continued exposure. Urine formic acid levels also become elevated in these animals within 15 min, but the result was inclusive as kidney failure occurred in some of the animals. The results of these experiments have shown that instillation of 4% neutral buffered formalin for treatment of radiation-induced hemorrhagic proctitis using a series of aliquots for 60-s intervals appears to be safe and preferable to constant exposure over an extended time. A case of rectal formalin instillation is documented in medical literature when a patient accidentally received a 100 ml enema of 10% formalin. The patient experienced sharp abdominal pain and was misdiagnosed initially as non-specific chronic colitis. The condition was recognised later, which resolved with treatment within 2 months.

The medical literature is replete with cases of ingestion of acids and alkali and the complication thereof. Ingestion of formalin is rare because of its strong irritating effect and alarming odour, but there are many reports where ingested formalin toxicity has been documented because of accidental, suicidal or in homicidal attempts. The pH of formalin (the soluble form of formaldehyde) is neutral and thus cannot be classified as either an acid or alkaline substance. However, the corrosive effects of formaldehyde on gastrointestinal tract are similar to that caused by the ingestion of both acid and alkali. Acids are believed to lead to a coagulation necrosis of the contacted area with formation of a protective eschar, limiting their absorption. Alkaline ingestion, however, can lead to liquefaction necrosis with intense inflammation and saponification of mucous membrane, submucosa, and muscularis layer of area of contact. Ingestion of formaldehyde may cause burning in the mouth and esophagus, nausea and vomiting of tissue and blood, or coffee ground material, abdominal pain, and diarrhoea. Besides gastrointestinal effects, ingested formaldehyde can also cause liver and kidney damage leading to jaundice, albuminuria, hematuria and anuria, acidosis and convulsions or central nervous system depression, and lead to unconsciousness and death resulting from cardiovascular failure. However, the occurrence and the severity of each adverse effect depend on the exposure dose, which is related to the chemical concentration, exposure frequency, exposure duration, average body weight and time period of exposure. The fatal dose of formaldehyde in human is about 60–90 ml.

Once absorbed into the bloodstream, formaldehyde is converted to formic acid within 90 s, which can rapidly necrose cells in the liver, kidneys, heart, and brain. Formic acid can be excreted through the kidney as sodium salt or further oxidised to carbon dioxide and water. The half-life of formic acid is reported to be 90 min. Formic acid levels can accumulate in high concentrations as rapidly as 30 min after ingestion. Local gastrointestinal effects are due to the necrotic effect of formaldehyde on mucous membranes. Early gastrointestinal damage from formaldehyde includes ulcers and perforations, whereas stricture formation is the most common late complication. Dysphagia occurring several weeks after ingestion is indicative of esophageal stricture. This occurs in 6–20% of caustic ingestion and, contrary to prior opinion, is now believed to occur in exposure to both acidic and alkali solutions. Early satiety, weight loss, and progressive emesis suggest an evolving gastric outlet obstruction. Acute symptoms of dysphagia and hoarseness resolve without treatment. Fibrosis, which is induced by caustic ingestion, continues, on the average, for up to 3 months. Thus, it is not uncommon to see stricture occurring weeks to months after the ingestion of caustic substances. According to the experiments of all published cases, the time frame of stricture onset from ingestion, in cases of formaldehyde poisoning, appears to be 2–4 weeks.

The formalin-induced corrosive damage of gastrointestinal tract depends upon the duration of contact between formalin and the gastrointestinal tract. Esophageal burns with formalin is rare because of the rapid passage through esophagus. If present, it may be probably due to ingestion of high concentrations and large amounts and persistent vomiting, which exposes the esophagus to formalin repeatedly. The presence of methanol in formalin (as an added preservative to prevent polymerization of formalin), which causes pyloric spasm, may result in remaining in contact with the gastric mucosa for a longer time leading to extensive lesion. Some patients also show corrosive lesions in the jejunum, ileum and in colon because formalin passes into the lower part of gastrointestinal tract with time and more surface area is available for contact but absorption is slowed down as time passes because tissue becomes fixed.

Methanol is added (5–12%) in formalin solution to prevent polymerization. Thus, methanol toxicity may be present with formalin. Methanol is metabolised in humans and monkeys by liver alcohol dehydrogenase in a rate-limiting step to formaldehyde. Methanol toxicity is caused by its metabolite, formaldehyde, and formic acid. The oxidation of methanol to formic acid leads to a buildup of reduced NAD (nicotinamide adenine dinucleotide), which results in reduction of pyruvate to lactate. The accumulation of formic and lactic acids causes
metabolic acidosis with an increase in anion gap two to three times of normal.\textsuperscript{13}

\textbf{Signs and symptoms of toxicity}

Signs of formalin toxicity are unconsciousness and coma. Other signs of toxicity may be restlessness, drowsiness, extreme tachycardia, tachypnea and anuria.\textsuperscript{3} Metabolic acidosis, which develops in formalin toxicity, is probably due to high concentration of formic acid and hyperlactatemia secondary to circulatory shock.\textsuperscript{1,3} Ingested formalin may cause liver and kidney damage, leading to jaundice, albuminuria, hematuria and anuria, acidosis and convulsions or central nervous system depression and cardiac failure.\textsuperscript{33} Early gastrointestinal damages due to formalin are ulcers and perforations, whereas stricture formation is the most common late complication.\textsuperscript{33}

Endoscopy is the preferred method for determining the degree and extent of injury, but is difficult to perform in acute condition due to fear of perforation. The degree of corrosive burn can be graded endoscopically from grades I to IV as follows: grade I injury — superficial burn; grade IIA injury — hemorrhagic eroding blisters, superficial ulcers, exudate; grade IIB injury — similar to grade IIA, but lesions are circumferential; grade III injury — multiple deep, brownish, black or grey ulcers; and grade IV injury — perforation. Grades I and IIA usually resolve without sequelae, whereas grades IIB and III have a high incidence of eventual stricture formation.\textsuperscript{33}

Another major complication of toxicity is acute renal failure because of acute tubular necrosis. Many case reports have been published where renal failure occurred, but it is not clear whether it is due to toxic effects of altered plasma constituents secondary to reaction with formaldehyde or due to severe circulatory shock.\textsuperscript{1}

\textbf{Treatment}

There are no antidotes. So the treatment is supportive. Since formaldehyde is corrosive, dilution of stomach contents with milk or water as a first aid measure is recommended. This may be followed by charcoal (1 g/kg) or 1% ammonium carbonate and a mild saline catharsis.

Ingestion of formaldehyde can cause a reduction in body temperature. So adequate steps should be taken to keep the patient warm. Vital signs and serial blood counts should be monitored. Signs of gastrointestinal hemorrhage are watched for. Electrolytes, acid base disturbances and kidney function also need close monitoring.

Pharmacological gastric suppression can be the initial treatment of caustic-induced stricture in an attempt to decrease pyloric inflammation and prevent further scarring. Corticosteroids are no longer believed to be of great value in decreasing further stricture formation. Generally, the definitive treatment is surgical, which consists of the removal of the damaged gastric areas. A temporary jejunostomy often allows the patient to regain strength diminished secondary to malnutrition. Elective surgery, consisting of gastroduodenostomy or gastrojejunostomy, can then be performed when the patient is more stable.\textsuperscript{33}

Extreme tachycardia is a prominent feature of formalin toxicity.\textsuperscript{11} Circulatory collapse due to decreased cardiac output may also occur because of severe metabolic acidosis. Vasopressors are ineffective and do not improve cardiac function and may even precipitate cardiac dysrhythmia, irreversible hypotension and cardiac arrest.\textsuperscript{3} Catecholamine, which is required to manage the circulatory shock, probably aggravates the problem by decreasing the renal blood flow by its direct action and secondarily by its inability to raise the blood pressure and to perfuse the kidney in severe acidosis. Treatment must be started at the appearance of the first sign of circulatory collapse. Hypotension should be treated with fluids, sodium bicarbonate and vasopressors. Sodium bicarbonate is essential not only for the effectiveness of the vasopressor but also to prevent the penetration of undissociated form of formic acid into cerebrospinal fluid and in decreasing plasma formate level.\textsuperscript{3} Ethanol therapy also slows down methanol metabolism into formate.\textsuperscript{5,35}

Deteriorating vital signs are indicators for dialysis, but the literature does not contain adequate case studies to guide the treatment. Hemodialysis is usually performed to manage acute tubular necrosis and to remove formalin metabolites, but it is not required in all cases if the patients are maintaining adequate urine output. However, the option of hemodialysis should be kept in mind even in cases with good urine output where the responses to alkali treatment are incomplete or delayed because methanol, formic acid and formate are all dialysable substances.\textsuperscript{1} If the hypotensive shock is responding to alkali treatment, the patient can be successfully managed with forced diuresis also.

Skin, eyes and respiratory tract toxicity should be looked for and appropriately managed. If patient loses consciousness, airway and ventilation must be supported. Ethanol, which has greater affinity for alcohol dehydrogenase, may be given as a component of
therapy to prevent methanol from adding to the formic acid load.\textsuperscript{21,27,35}

Conclusion

Ingestion of formalin in significant amount usually has fatal consequences. Cause of death may be multifactorial because of deleterious effects on all systems of the body so multidisciplinary approach is required for management.

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