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GENERAL UROLOGY
Review

Toxic effects of formaldehyde on the urinary system

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ABSTRACT

Formaldehyde is a chemical substance with a pungent odor that is highly soluble in water and occurs naturally in organisms. Formaldehyde, when taken into organisms, is metabolized into formic acid in the liver and erythrocytes and is then excreted, either with the urine and feces or via the respiratory system. Formaldehyde is widely used in the industrial and medical fields, and employees in these sectors are frequently exposed to it. Anatomists and medical students are affected by formaldehyde gas during dissection lessons. Because full protection from formaldehyde is impossible for employees in industrial plants using this chemical and for workers in laboratory conditions, several measures can be implemented to prevent and/or reduce the toxic effects of formaldehyde. In this review, we aimed to identify the toxic effects of formaldehyde on the urinary system.

Key words: Formaldehyde; toxicity; urinary system.

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Biochemical features of formaldehyde

Formaldehyde (FA) is a colorless and highly water-soluble aldehyde that exists in the natural structures of organisms and is widely used due to its chemical properties. CH_2O (FA) is a highly reactive substance due to its strong electrophilic properties, and it can change from a solid or liquid into the gaseous form at room temperature. Its pure form has a characteristic pungent odor and is an irritant to the respiratory tract. A 37% solution of formaldehyde in water is known as formalin, whereas the polymerized solid form is called paraformaldehyde. The liquid form of FA, which is produced by the oxidation of methanol, is generally expressed in milliliters (mL), whereas the gas form is expressed in parts per million (ppm).[1-3]

Formaldehyde, which is inevitably taken into organisms in an exogenous manner, is also endogenously present in organisms. Exogenous intake commonly occurs through the skin and digestive system and mostly via the respiratory system. Orally, it is ingested in fresh water, sugar, coffee, fruits and vegetables, drugs and the protective additives in some foods. It can be inhaled in cigarette smoke, in smoke due to the combustion of wood or liquid-based fuels, in the exhaust of vehicles with burning fossil fuels and in the fumes of paints used for surfaces and furniture. In the medical field, employees in anatomy, histology and pathology laboratories are affected by FA, which is used especially as a solution for embalming and fixation.[4,5] In humans, glycine and serine are the most important sources of endogenous FA. Additionally, N-methyl amino acids and sarcosine can be converted into FA via oxidative demethylation by specific enzymes. Endogenous tissue levels range from 3 to 12 ng/g and, of this proportion, 40% occurs in the free form.[6] FA, which has a very short half-life (t1/2=1.5 min), is metabolized into formic acid in the liver and erythrocytes, with a reaction catalyzed by formaldehyde dehydrogenase (FDH) enzymes after FA is taken into body, regardless of the manner (respiratory, oral, i.p. or i.v.) of intake. FDH requires glutathione as a co-factor during this reaction. Thus, as the FA concentration increases, the blood glutathione level decreases. The depletion of glutathione, an anti-oxidant, increases the toxicity of FA. FA enters the mono-carbon (C1) pool of cellular metabolism via binding to tetrahydrofolic acid; as such, it can participate in the structure of macromolecules, such as nucleic acids.[7-13] FA exists at varying levels in cells, but it cannot be stored in the body. It is excreted either in the feces or urine as formic acid or via the

respiratory tract as carbon dioxide. It is completely eliminated within a few days.[14,15]

Formaldehyde uses

In industry, FA is used in constructive insulations, dyes and plastics, textiles and the wood and plywood industries, and it is present in concrete and plaster, glass frames, fire extinguishers, platinum electrodes, cables, rubber, furniture, carpet and wallboards.[11,16] Although we might fail to realize it, human beings have also been affected by FA, which plays an important role in the chemical products that are part of our routine daily activities. It is present in liquid-based home cleaning agents, deodorants, toothpaste and cosmetic products, steam disinfectants and other disinfectants, ink, photographs, cartoons, paper and adhesives.[11,12]

In the medical field, FA is mainly used in laboratories. Fixation and long-term storage of cadavers and organs are achieved using FA pools. FA is also used during the tissue fixation stage in histology and pathology laboratories. In addition, it is used in dental coating materials, in the treatment of persistent cystitis and as a protective agent in some drugs. Furthermore, hemodialysis solutions contain formalin.[17-22] Formalin causes air pollution because it exists in the exhaust of diesel vehicles, in fuel oil, in gasoline and in natural gas, and it is released after the burning of trees and firewood. It has been reported that cigarette smoke also contains FA; thus, both active and passive smokers are affected by FA via inhalation.[23-25]

Effects of formaldehyde on organisms

FA has diverse effects on individuals. Some individuals experience no discomfort from FA, even if exposed to moderate levels, whereas very low levels of FA can affect others. However, there is a close relationship between FA dose and affected organ damage. Low doses (0.05 ppm) of FA exposure can affect the eyes, nervous system and upper respiratory tract, whereas higher doses (5 ppm) of FA exposure can result in lower respiratory tract damage. In cases of very high doses of FA exposure, death can occur.[14] The toxic doses and diseases related to those doses are provided in Table 1. FA, which causes an increase in cytotoxic effects by compromising the intracellular balance, has a strong tendency to combine with proteins, nucleic acids (DNA and RNA) and unsaturated fatty acids by non-enzymatic processes. These combinations result in inflammatory reactions, allergic reactions, cytotoxicity, necrosis and mutagenic and carcinogenic effects by developing denaturation in proteins. Moreover, free oxygen radicals are increased in the tissues affected by FA, and this increase accelerates the processes (apoptosis or necrosis) that cause cell death. FA exhibits antimicrobial activity, and it performs a fixative function in non-viable tissues.[26-28]

It has been reported that FA has toxic effects on the skin, respiratory system, nervous system, gastrointestinal system and urinary system, as well as allergic effects. In addition, there are available data in the literature regarding the symptoms and side effects of FA on several systems (Table 2).[29-34]

Effects of formaldehyde on the urinary system

The toxic effects of formaldehyde occur in several systems of the body, and both experimental and clinical investigations have attempted to elucidate the toxic effects of formaldehyde on the urinary system. In a study conducted in workers with occupational FA exposure, it was found that there was a significant increase in the incidence of renal cancers among these employees. It has been observed that acute tubular necrosis can develop due to the edematous obstruction or acute renal failure caused by the intravesicle formalin used for the treatment of chronic hemorrhagic cystitis.[35-38] It was found that acute renal failure developed following hypotension in an individual who ingested 150 mL of liquid formalin to commit suicide.[39] In a study in alcoholic patients, it was demonstrated that methanol, which metabolizes into FA and formic acid, causes tubular necrosis of renal tissue, subsequently resulting in renal failure.[40]

Experimental studies have demonstrated the toxic effects of FA on the urinary system. It was found that FA administered orally to rats caused mucosal ulcers, necrosis, hemorrhage and perforation in the gastrointestinal system and, subsequently, the development of metabolic acidosis, circulatory failure, hematuria, anuria and renal papillary necrosis.[41] It was observed that exposing renal cell cultures from monkeys to FA resulted in depression of RNA synthesis and failure of DNA transcription-termination.[42] Sub-chronic inhalation of FA affects the main metabolic pathways, by which glucose participates in altering the activities of glucose-6-phosphate dehydrogenase (G6PD), lactate dehydrogenase (LDH), malate dehydrogenase (MDH) and hexokinase (HK) enzymes.[43] In another experimental study, in which the FA dose used to treat saprodonti in dentistry

Table 1. Minimal formaldehyde concentrations affecting humans

Formaldehyde Toxicity	Formaldehyde Concentration (ppm)
Neurophysiologic effect	0.05-1.05
Respiration air threshold	0.05-1.0
Ocular irritation	0.05-2.0
Upper respiratory tract irritation	0.1-25
Lung and lower respiratory tract effects	5.0-30
Pneumonia and pulmonary edema	50-100
Death	≥100

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Table 2. Systems in which toxic effects of formaldehyde are commonly observed and their symptoms

Affected System	Involved Organ	Symptom
Urinary System	Kidney	Glomerular Degeneration Acute Tubular Necrosis Tubular Dilatation
	Bladder	Edematous Obstruction Hematuria
Respiratory System	Nose	Nasal Pruritus and Congestion Nasal Cavity Cancer
	Respiratory Tract	Wheezing, Coughing
	Lung	Asthma, Pneumonia
Central Nervous System	Central Nervous System	Behavioral Disorders, Headache
		Convulsions, Sleep Disorders
	Cancer	Glioblastoma Multiforme Astrocytoma
Hematopoietic System	Blood Cells	WBC ↓ IgG ↑, CD4/CD8 ↑ Leukemia
Reproductive System	Teratogenic Effects	Cycle disorders Spontaneous abortion Low birth weight
		Anomalies in the sperm head Implantation and number of alive fetuses ↓
	Mutagenic Effects	DNA breaks gene mutations

was given to rats, it was demonstrated that urea and creatinine levels, which are significant indicators of renal function, were increased.[44] In our studies on rats, we observed several findings indicating histopathological and biochemical alterations in renal tissue, which occurred due to FA exposure. It was observed that systemic application of FA impaired glomerular patterns and thickened tubular and glomerular basal membranes. Additionally, it was found that systemic application of FA caused congestion of the intratubular vessels, vacuolization and dilatation in distal tubules.[45] In another study, it was found that FA application led to glomerular and tubular degeneration, tubular dilatation and congestion.[46] These histopathological changes, observed in renal tissue, clearly demonstrate that FA has severe nephrotoxic effects. Again, it was also found that glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) activities were significantly decreased in the same rats.[45,46] This finding suggests that FA caused oxidative injury by impairing anti-oxidant defense mechanisms in the kidneys. It was observed that levels of MDA, another parameter used in the detection of oxidative injury, were significantly increased as a result of FA application[45,46]. Increases in MDA levels indicated that FA led to lipid peroxidation in renal tissue; thus, oxidative injury occurred. Spanel et al.[47] showed that FA is a potential biomarker of bladder and prostate cancer. Yang et al.[48] suggested that formaldehyde leads to bladder cancers. In a final report on carcinogens by the National Toxicology Program, it was reported that higher levels of formaldehyde exposure caused kidney cancers.[6] In contrast, Homma et al.[49] observed no statistically significant increases in bladder cancers after 15 formalin treatments administered over 30 weeks.

Consequently, the toxic effects of FA have been clearly shown by clinical and experimental studies. It is inevitable that we are exposed to the effects of FA in our daily lives due to our home environments and the food that we ingest, as well as exhaust, smoke and the pollution caused by the usage of natural gas, the burning of wood and coal and the inhalation of air. In addition, the effects of FA are intensively experienced during embalming and dissection in histology, in pathology and anatomy laboratories and in dialysis units. To protect healthcare providers and students, appropriate and sufficient physical conditions and air conditioning systems are needed.

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