HISTOLOGICAL STUDY OF THE EFFECT OF SODIUM FLUORIDE ON THE OVARY OF ADULT ALBINO RAT AND THE POSSIBLE PROTECTIVE ROLE OF VITAMIN C

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Submitted by
Hassan Abd Elraheem Hassan
M.B.B.Ch
Faculty of Medicine - Cairo University

Supervisors

Dr.Ibrahim Labib Abdalla
Professor of Anatomy
Faculty of Medicine-Cairo University

Dr.Medhat Mohamed Morsy
Assistant Professor of Anatomy
Facutly of Medicine-Cairo University

Dr.Sherif Fahmy Arsanios
Lecturer of Anatomy
Faculty of Medicine-Cairo University

Faculty of Medicine
Cairo University
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Abstract

Sodium fluoride is used in dental products, insecticides, detergents production and in fluoridation of the drinking water. This study was carried out to throw more light on the adverse toxic effect of sodium fluoride on the ovary of adult albino rat and the possible protective role of vitamin C using light microscope. Thirty adult albino rats were used in the this study, divided into three groups, ten being the control group (A), group (B) received sodium fluoride and group (C) received sodium fluoride and vitamin C. Administration of sodium fluoride revealed ovarian follicles with degenerated granulosa as well as Cumulus oophorus cells. The oocytes were distorted and necrosed. Areas of hemorrhage and infiltration of inflammatory and fat cells were observed. On the other hand, concomitant administration of vitamin C and sodium fluoride resulted in reduction of the histological changes in the ovaries induced by fluoride administration.

Key words: Sodium fluoride toxicity- Vitamin C - Ovary

Contents

Page

• Introduction and aim of the work…….. 1
• Review of literature…… 3
- Fluoride…… 3
.Sources and uses of fluoride…… 4
.Absorption, Distribution and Excretion…….. 5
. Toxic effects of fluoride…… 6
-Vitamin C…… 11
. Sources of ascorbic acid……. 11
. Chemistry of ascorbic acid……. 12
. Catabolism of ascorbic acid…….. 13
. Dietary recommendations of Ascorbic acid……. 13
. Physiological functions of Ascorbic acid…… 14
-The ovary…….. 18
. Gross anatomy of the ovary…….. 18
. Histological structure of the ovary…… 19
. The estrous cycle in rats……. 24
• Material and methods……. 28
-Materials……... 28
-Methods…… 29
• Results…… 35
• Discussion…….. 88
• Summary and conclusion…….. 95
• References……. 98
• Arabic summary……. ١

INTRODUCTION AND AIM OF THE WORK

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Sodium fluoride is a white powder, moderately soluble in water. It is usually produced from hydrofluoric acid and sodium carbonate or sodium hydroxide ***(Neumuller, 1981).***

Sodium fluoride is used in steel, aluminium, dental products, glass, glue, detergents, insecticides production and fluoridation of drinking water ***(Hansson and Hellsten, 1994).***

Fluoride is essential trace element that has protective effects against bone mineral loss. It has been tested in several species of laboratory animals, some studies revealed no effects on reproductive function (***Tao and Suttie,1976, Marks et al., 1984 and Collins et al., 2001).*** Other studies in different animal species have provided an evidence for adverse and toxic effects of fluoride on a number of bio-physiological functions, including reproduction ***(Guney et al., 200***7).

Sharma et al., (2007 and 2008) confirmed the works of ***Al-Hiyasat et al., (2001)*** and ***Jhala et al., (2004)*** who reported that exposure to sodium fluoride caused toxic effects on reproductive organs whereas vitamin C treatment ameliorated fluoride toxicity. They stressed that vitamin C has important role in prophylactic treatment of fluorosis**.**

There are contradictory reports regarding the effects of fluoride on reproduction in animals and human and few studies have been published on the histological changes that occurred in the ovary with fluoride administration. These studies are not fully understood and the data are conflicting. Thus, the aim of current study is to clarify the outcome of sodium fluoride exposure on the ovary in order to gain further insight into the reproductive effects of sodium fluoride and the possible protective role of vitamin C.

REVIEW OF LITERATURE

FLUORIDE

In the environment, there are many toxic elements that affect human health. Fluoride is widely spread element that has sufficiently severe toxic effects and is considered as the third most serious air pollutant after SO2 and Ozone ***(Edward, 2001).***

Fluorides are defined as binary compounds or salts of fluorine and another elements. Examples of fluorides include sodium fluoride and calcium fluoride. Sodium fluoride, which is the main source of fluoride ion in diverse applications, is the ionic chemical compound with the formula NaF. It is a white powder and is usually produced from hydrofluoric acid and sodium carbonate or sodium hydroxide ***(Neumuller, 1981 and*** **Agency for Toxic Substances and Disease Registry, ATSDR, 2003*).***

Fluoride has protective effects against bone mineral loss, However, it becomes toxic at higher doses and induces some adverse effects on a number of bio-physiological functions, including reproduction ***(Guney et al., 2007).***

The relationship between environmental fluoride and human health has been studied for over 100 years by researchers from a wide variety of disciplines. Although much is known about the occurrence and health effects of fluoride, problem persist in Third World countries, where populations have little choice in the source of their drinking water and food ***(Ozsvath, 2009).***

Sources and uses of fluoride

Sodium fluoride is used in steel, aluminium, glass, glue, detergents and insecticides production. Dental products such as toothpaste, rinses and topically applied gels contain high concentrations of fluoride ***(Hansson and Hellsten, 1994).***

Fluorine is used as a part of a large variety of drugs including: antipsychotics such as fluphenazine, HIV protease inhibitors such as tipranavir, antibiotics such as ofloxacin and trovafloxacin and anesthetics such as halothane ***(Park et al., 2001).***

Water fluoridation is the controlled addition of fluoride to a public water supply in order to reduce tooth decay. Fluoridated water has fluoride at a level that is effective for preventing cavities, this can occur naturally or by adding fluoride ***(Centers for Disease Control and Prevention, 2001).***

Fluorides occur naturally in the earth's crust where they are found in rocks, coal, clay and soil. Small amounts of fluorides are present in water, plants and animals ***(ATSDR, 2003).***

Fluoride's effects depend on the total daily intake of fluoride from all sources and drinking water is the largest source ***(Fawell et al., 2006).***

Absorption, Distribution and Excretion

Fluorides can pass through the placental barrier. Serum concentration in the mother has a direct relation to that in the fetus ***(Shen and Taves, 1974)***.

The absorbed fluoride is distributed by the systemic circulation to all organs and tissues. Only few minutes after intake, there is a rise in the plasma fluoride concentration and the plasma peak usually occurs within 30 minutes. The level of the plasma peak is proportional to the fluoride dose ingested (***Ekstrand et al ., 1977***).

In adult humans, approximately 50 -75% of an oral dose of fluoride appears in the urine within 24 hours after ingestion ***(Ekstrand et al., 1977 and Spencer et al.,1981).*** Under conditions of relatively constant exposure, urinary excretion correlates well with drinking water fluoride levels and is often used as an indicator of exposure.

In human, the dominating route of fluoride absorption is via the gastrointestinal tract. Airborne fluoride may also be inhaled. Fluoride ions are released from soluble fluoride compounds (e.g. sodium fluoride) (***Spak et al., 1982).***

The absorptive process occurs by passive diffusion and fluoride is absorbed principally from both the stomach and the intestine. Most of fluoride is absorbed as hydrogen fluoride which is formed on contact with gastric acid ***(Whitford and Pashley, 1984)***.

Fluoride is excreted mainly via the urine, in addition, the rest is eliminated through saliva, breast milk, faeces and perspiration ***(Whitford, 1990).***

In humans, approximately 99% of the total body burden of fluoride is retained in bones and teeth ***(Hamilton, 1992).***

Toxic effects of fluoride

The effects of fluoride depend on the dose and exposure time. Some may be beneficial in caries prevention, while others are harmful when optimal prophylactic or therapeutic doses have been surpassed ***(Dabrowska et al., 2006).***

I-General effects

Fluoride apparently interferes with several enzyme systems, including cholinesterase and enzymes involved in glycolysis ***(Augenstein et al.,1991).***

Consumption of fluorides can have a range of acute effects including nausea, vomiting, stomach cramps, diarrhea, fatigue, drowsiness, coma, muscular spasms or even cardiac arrest which is believed to be due to development of hypocalcaemia and /or hyperkalemia ***(Augenstein et al., 1991 and Blodgett et al., 2001).***

Data on acute toxicity in humans is available largely from accidental ingestion of pesticide products containing sodium fluoride. Fatal doses have been estimated to be the range of 2.5-10g in adults but less than 1g can cause severe poisoning ***(ATSDR, 2003)***.

High and prolonged uptake of fluoride leads to skeletal fluorosis which is characterized by osteosclerosis, brittle bone and a higher frequency of fractures and a concurrent calcification of tendons can be painful and restricted movement (***Whitford, 1996***).

Fluoride exposure also induced histopathological changes in liver involving focal necrosis, infiltration of leucocytes and hemorrhagic areas (**Dabrowska and Szynaka, 2000**).

Several epidemiological studies are available on the possible association between fluoride and cancer. It was conclude that there was no evidence to indicate any carcinogenic risk to humans from exposure to fluoride ***(Committee on the carcinogenicity of Chemicals in Food Consumer Products and the Environment (COC), 1990 and WHO, 2002).***

Significant histopathological changes were found in the myocardial tissue as myocardial cell necrosis, extensive cytoplasmic vacuole formation, interstitial oedema, small hemorrhagic areas and hyperaemic vessels ***(Cicek et al., 2006).***

Exerperimently, with sodium fluoride treatment, the lung of albino rat showed alveolar congestion, alveolar cell hyperplasia and necrosis, prominent alveolar septal vessels, epithelial desquamation and macrophages in the alveolar spaces. Additionally, there were inflammatory infiltrations in peribronchial, perivascular, intraparenchymal and respiratory tract lumen. Intraparenchymal hyperaemic vessels were observed ***(Gulsen et al., 2003).***

II-Reproductive effects

The oral administration of fluoride has been reported to produce a number of adverse effects on reproductive organs. In male mice, fluoride administration caused toxic effects including lowered sperm motility with decreased sperm counts and fertility rates ***(Susheela and Kumar, 1991, Chinoy and Sequeira,1992).*** On the other hand, simultaneous administration of fluoride along with ascorbic acid resulted in recovery of all the affected parameters studied ***(Chinoy et al ., 1994).***

In females, occupational exposure to fluoride has been reported to induce abnormal menstruation, increase in the frequency of the miscarriages and pregnancy complications among female workers in fluorine factories ***(Zhang et al., 1993).*** With fluoride treatment, the ovary of albino rabbits exhibited congested the follicles, necrosis of follicular cells with interstitial oedema. The degenerative changes were most pronounced with the concomitant increase in the dose of fluoride, in which complete atrophy of follicles along with oocyte disintegration and marked necrosis of cells accompanied with infiltration of monocytes, lymphocytes and histocytes in interstitial tissue occurred (***Shashi,1990&1994).*** Also, he mentioned that fluoride treatment caused a significant depletion of ovarian DNA and RNA compared to controls. The data indicated that fluoride

inhibited nucleic acid synthesis in the ovary and acts directly on DNA to produce structural changes in ovarian tissue which subsequently confirmed by histopathological examination on control and treated animals.

Al-Hiyasat et al., (2000) investigated the toxic effects of sodium fluoride on reproductive system of adult female Sprague – Dawley rats. They found that the number of the viable fetuses were significantly lower than in the control group with increased total number of resorptions. These results indicated that exposure to sodium fluoride causes adverse effects on the reproductive system and fertility.

Jhala et al., (2004) declared that the ovary showed vacuolization of stroma, atretic follicles and pyknotic follicular cells after sodium fluoride administration**.** They mentioned that sodium fluoride administration revealed a significant decline in protein levels and the activities of 3β- and 17β-hydroxysteriod dehydrogenases (HSDs) in the mouse ovary concomitant with a significant accumulation of cholesterol. The affected ovarian steroidogenesis also correlated with altered histology. Withdrawal of sodium fluoride led to incomplete recovery. On the other hand, supplementation with vitamin C during the withdrawal period led to recovery from induced effects, which were therefore transient and reversible by antidotes. These finding are significant in relation to humans living in endemic regions of high fluoride**.**

Sharma et al.,(2008) found that fluoride administration to rats produced reduction in circulating levels of estrogen, number of litters and fertility rate compared to control rats. However, cholesterol concentrations of ovaries increased significantly. The above altered parameters were restored partially/completely after exogenous feeding with vitamin C. Therefore, vitamin C played important role in reduction of fluoride toxicity.

On the other hand**,** ***Tao and Suttie (1976*****),*** ***Marks et al., (1984)*****,*** ***Collins et al ., (1995)*** **and** ***Heindel et al., (1996)*** reported that no significant difference in reproductive functions of female rats and rabbits when exposed to fluoride. No dose-related behavioural changes, maternal clinical signs or soft tissue variations were noted. They noticed that there were no significant differences between the sodium fluoride groups and control groups in the average number of corpora lutea, implantations, live fetuses, or in the percentage of early and late fetal deaths per litter.