CASE REVIEW ON EFFECTS OF SODIUM FLOURIDE ON LIVER

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ABSTRACT: The process of excessive ingestion of fluoride over a prolonged period is called chronic fluorosis. It endangers the health of humans as well as animals. Sodium Fluoride causes toxic effects when given in high doses. Various cases of effects of sodium fluoride on the liver of various animals are studied. Sodium fluoride caused marked increase in serum transaminases like Alanine aminotransferase, Aspartate aminotransferase and Alkaline phosphatase along with inhibition of activation of antioxidants enzymes, Glutathione peroxidase and superoxide dismutase. NaF stimulates increase in hepatic content of Hydrogen Peroxide (H₂O₂), Nitric Oxide (NO), Protein Carbonyls and Oxidation protein products. It also increases the levels of inflammatory markers (NF-κB, IL-1β, TNF-α). It also causes oxidative stress and necrosis.

Key words: Sodium fluoride, Alanine aminotransferase, Aspartate aminotransferase, alkaline phosphatase, inflammatory markers.

1. INTRODUCTION

Fluoride toxicity is a condition in which there are elevated levels of fluoride ions in body. Sodium Fluoride is an inorganic compound denoted by NaF. It used in very little amount in fluoridation of drinking water in toothpaste, in metallurgy etc... It is also used in various pesticides, insecticides and in glass manufacture [1]. NaF administration has advantages as well as disadvantages [2]. Reasonable level of sodium fluoride has given positive effects on skeleton and teeth whereas high level of sodium fluoride has some toxic effects on the human body like nervous system toxicity, gastrointestinal toxicity and excretory system toxicity [3, 4]. The lethal dose is estimated to 5-10g for humans. Manifestation of fluoride toxicity is described as fluorosis [5]. However, fluoride induced toxicity also effects organs such as kidney, liver, thyroid, brain and testis [6, 7]. Compared to all other fluoride salts Sodium fluoride shows severe toxic effects because of its highly soluble nature and releases more fluoride ions compared to other salts [8]. Studies have proved that fluoride induces Geno-toxicity, Cyto-toxicity, Immune-toxicity, Oxidative Damage and Apoptosis in the liver, kidney, spleen [9, 10]. Studies have also confirmed that excess level of fluoride intake could lead to cellular apoptosis via oxidation injury dependent pathways that result in an increase in lipid peroxidation in cells, thus causing to mitochondrial dysfunction and activation of the downstream pathways [2, 11, and 12].

Fluoride toxicity in animals is multifarious [13]. The trace amount of sodium fluoride is able to alter several enzymes activities and metabolism of soft tissue. Previous studies have shown that fluoride could produce abnormalities in the liver including degenerative and inflammatory changes [14], dilation of sinusoids [15] and hepatic cellular hyperplasia, abnormal functions and metabolism and histopathological changes have been found in different species like sheep, claves and rats by several research groups [16-19]. It causes increase lipid peroxidation in blood and tissues. Active oxygen and free radicals play an important role in fluoride toxicity.

1.1 Side effects of Sodium Fluoride
1.1.1 Tooth Discoloration:
High level consumption of fluoride leads to yellowed or browned teeth.
1.1.2 Tooth Decay:
High intake of fluoridated water can cause weakening of enamel.
1.1.3 Skeletal Weakness
Taking too much fluoride highly impact on skeletal system. It causes
• Weak joints
• Increase the risk of fracture
1.1.4 Neurological Problems
It impacts on the development of the brain in young people. Exposure to fluoride during pregnancy causes poor cognitive outcomes.
1.1.5 High Blood Pressure
Fluoride causes increase in the blood pressure
1.1.6 Seizures
Fluoride does not cause seizures but it increases the risk for patients already suffering from seizure.
2. LIVER
The liver is the largest organ in the body and mainly regulates carbohydrates and lipid metabolism. It is situated under rib cage on right side of abdomen. An altered in hepatic metabolism may result from the disease which causes hepatic dysfunction. The different liver diseases are

- **Hepatic Steatosis:**
  It is most common liver disease occurring around the world. It is also called ass fatty liver disease. It is the condition which occurs due to excessive fat build up in the liver
- **Hepatic Fibrosis:**
  It is also called as fibrotic scarring. In hepatic fibrosis, excessive connective tissue accumulates in liver this tissue represents scarring in response to chronic and repeated liver injury.
- **Hepatocellular Carcinoma:**
  It is the most common primary liver cancer. Main risk factors for hepatocellular carcinoma are HBV and HCV.
- **Acute Liver Failure:**
  It is caused by massive liver cell necrosis. Acute liver injury is often accompanied by metabolic disorders, acidosis and sepsis.

3. EFFECTS OF SODIUM FLOURIDE ON LIVER
Liver is the one of the target organs disturbed by fluorosis. As the very active site of metabolism, the liver is especially susceptible to fluoride intoxicification. Sodium fluoride induces oxidative stress and apoptosis. Oxidative stress is caused due to difference between antioxidants and free radicals. Any reaction, metabolic process, or bodily reaction causes the production of free radicals. In liver free radicals are primarily generated by cytochrome P450 in the mitochondria in endoplasmic reticulum of hepatocytes. Administration of NaF leads to oxidative stress. The Reactive oxygen species (ROS) effects the hepatocytic proteins, lipids and DNA this leads to oxidative stress which results abnormalities in liver by effecting the structure and function of the liver. The abnormalities cause inflammatory, metabolic and proliferative liver disease [2].

4. CASE REVIEW

4.1 Sodium fluoride causes oxidative stress and apoptosis in the mouse liver

**Study Design:** The Study was performed to investigate the effect of sodium fluoride on mouse liver by using western blot method. 240 four-week-old ICR mice were randomly divided. NaF is induced to four groups at different concentration levels (0mg/kg, 12mg/kg, 24mg/kg, 48mg/kg) for a time period of 42 weeks.

**Result:** The results showed that NaF caused oxidative stress and apoptosis. Oxidative stress is accompanied by increasing ROS (reactive oxygen species), malondialdehyde (MDA) levels and decreasing mRNA expression level and activities of superoxide dismutase, catalase (CAT), glutathione (GSH), glutathione peroxidase (GSH-PX), glutathione-s-transferase (GST). NaF induced apoptosis via tumor necrosis factor receptor signalling pathway. Sodium fluoride caused oxidative stress and apoptosis results in the impaired hepatic function which results in the impaired hepatic function which is strongly supported by histopathological lesions and increasing in serum alanine aminotransferase, aspartate aminotransferase and alkaline phosphate activities along with TBIL content [2].

4.2 Fluoride-induced hepatotoxicity is prevented by L-Arginine supplementation via suppression of oxidative stress and stimulation of nitric oxide production in rats.

**Study Design:** Sodium fluoride is induced to male wister rats at concentration of 300mgL⁻¹ along with water alone or cotreatment with L-Arginine at different doses for 7 days. Markers of hepatotoxicity, oxidative stress and antioxidants status were thereafter assessed.

Twenty-eight male wister rats are divided randomly into 4 groups of 7 rats in each group. Thus, were treated with Group A (vehicle control) received only distilled water for 7 days.

Group B (NaF group) rat were exposed to sodium fluoride (300mgL⁻¹) alone in drinking water also for 7 days.

Groups C and D were both exposed to NaF (300 mgL⁻¹) and concurrently with L-Arg at 100mg/kg⁻¹ and 200mg/kg⁻¹ by oral gavage for 7 days.

The rats were sacrificed after a week

**Results:** NaF caused marked increase (P< 0.05) in serum transaminases, alanine aminotransferase (P=0.005), aspartate aminotransferase (P=0.030), alkaline phosphate (P=0.023) along with atrophy of centriLOBular hepatic cords and dilation of sinusoids. More over sodium fluoride stimulated increase in hepatic contents of H₂O₂, nitric oxide, protein carbonyls, malondialdehyde and advanced oxidation proteins. NaF also inhibited the activities of antioxidants enzymes, glutathione peroxidase and superoxide dismutase. However, L-Arg supplementation caused significant alleviation of NaF hepatotoxicity by reducing lipid and protein indices [20].

4.3 Hesperidin Protects liver and kidney against sodium fluoride-induced toxicity through anti-apoptotic and autophagic mechanisms.

**Study Design:** Thirty-five male wister rats that are weighing between 250-280g which are 10-12 weeks old are divided into 5 groups. Each group consists of seven male rats.

The five groups are following

Group I Distilled water was given orally.
Group II was treated with 600 ppm NaF along with distilled water for 2 weeks.
Group III was treated with 200mg/kg body weight administered orally by gavage for 2 weeks.
Group IV was treated with both Sodium fluoride (600ppm) and hesperidin (100mg/kg body weight). NaF is given along with drinking water. Hesperidin, however, is given over the course of two weeks through oral gavage. Group V was also treated with NaF (600ppm) and hesperidin (200mg/kg body weight). NaF is given along with drinking water. Hesperidin, on the other hand, is given orally through a gavage for two weeks.
The rats were sacrificed after 2 weeks.

**Results:** NaF led to liver and kidney damage, which was demonstrated by changes in serum levels of kidney function parameters like urea and creatinine, liver enzyme levels like ALT, ALP, and AST, antioxidant enzyme activities like SOD, CAT, and GPx, and inflammatory marker levels like NF-kB, IL-1, and TNF-. The amounts of autophagic indicators (Beclin-1, LC3A, and LC3B) and apoptotic and anti-apoptotic proteins (Bax, Bcl-2, cytochrome C, p53, and procaspase) expressed in liver and kidney tissues were likewise enhanced when NaF blocked the PI3K/Akt/mTOR pathway. Concurrent HSP and NaF treatment considerably reduces all parameter deviations. [21].

**4.4 Effects of Sodium fluoride on hepatic toxicity in adult mice and their suckling pups.**

**Study Design:** This experiment was carried out on female wister mice. NaF 500 ppm is given along with drinking water from 15 day of pregnancy until 14th day after delivery. All mice were sacrificed on day after parturition. 12 pregnant female rats were divided into 2 groups each group consists of 6 rats.
First group (control animals) were given only distilled water.
Second group was treated with 500 ppm NaF given along with drinking water from 15th day of pregnancy to 14th day of delivery. The mice were allowed to delivery spontaneously 3 weeks after coitus. Within 24 h of birth the number of pups born, their sex and weight are recorded and excess pups removed. All pups (n=96) and their mothers (n=12) were sacrificed on postnatal day.

**Result:** Results had shown that AST and ALT were increased significantly in NaF dams by 33 and 31% and in their pups by 20 and 52% as compared to that of control group. Results also have shown that NaF induced mice had shown significant increase in lipid peroxidation in liver by elevating MDA levels by 49% in mothers and 32% in pups as compared to that of control group. The antioxidant status was significantly lowered in fluoride induced group by 33% and 59% in their pups as compared with control group. In liver NaF has induced degeneration and cell necrosis in pups and their mothers. Infiltration of mononuclear cells occurred in portal canals and particularly in hepatic lobules which were more seen in NaF induced group than in suckling pups [21].

**4.5 Effects of dietary fluorine on histopathological changes in calves.**

**Study Design:** The most susceptible animals to fluorine ingestion are dairy cattle. Four equal sets of twenty male Karan fries calves (6–8 months old) were created. For three months, the calves were fed diets that were 50/50 concentration mixture and green maize, then the ratio was altered to 40/60 for the final 112 months. The mineral blend for groups 1 and 2 is dicalcium phosphate. In contrast, rock phosphate is used in place of it in groups 3 and 4. However, in order to increase the levels of dietary Fluorine, the combination for the 2 and 4 groups contained additional NaF. Thus, the fluorine levels in treatment groups 1 through 4 were 7, 79, 132, and 191 ppm, respectively. Animals used in experiments were sacrificed at the end.

**Result:** Result had shown some alterations in liver and kidney. In liver, structural changes were seen in 3 and 4 groups (132 and 191 ppm). Whereas in 1 and 2 group there was no changes were seen in liver. In group 3 at 132 ppm variable of hydropic degenerative changes, centrilobular necrosis, mononuclear cell infiltration in portal triad areas is visible. In group 4 in 191 ppm changes like periglomerular fibrosis and tubular nephrosis were seen. Results also showed raise in blood pressure [17].

**4.6 Histopathology of fluoride induced hepatotoxicity in rabbits.**

**Study design:** young albino rabbits were divided into groups. The sodium fluoride was induced at different concentrations 5, 10, 20 and 50 mg/kg body weight/day in divided groups respectively for 15 weeks. After the experimental time period the rabbits were sacrificed and evaluated.

**Results:** Results had shown that increasing degree of degenerative changes, hepatocellular necrosis, and hepatic hyperplasia, extensive vacuolization in hepatocytes and centrilobular necrosis in liver. The results also showed Dilation in sinusoids and central veins and swelled with blood associated with small areas of haemorrhages [15].

**5. CONCLUSION**

The study was performed to know the toxic effects of sodium fluoride on liver. From the above studies in literature, it is concluded that sodium fluoride when given in high amount damages the liver by causing oxidative stress and increasing the level of serum transaminases.

**REFERENCE**

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