Chemical profile of blood in fluoride toxicity
III. Plasma fibrinogen levels in rabbit.

A.K. SUSHEELA and Y.D. SHARMA

Fluorosis Research Laboratory - Department of Anatomy
All India Institute of Medical Sciences
New Delhi 110029 (India)

Reçu le 27.6.1980
Accepté le 15.10.1980

Summary

Rabbits in two groups were given different doses of sodium fluoride i.e. low dose (10 mg NaF/kg body weight) and high dose (50 mg NaF/kg body weight). Blood was drawn from both groups on certain specific days after fluoride administration. The two different doses of sodium fluoride gave different response with regards to the fibrinogen levels in blood plasma. It is suggested that administration of low doses of sodium fluoride, induce new bone formation enhancing fibrinogen levels. But in high doses of sodium fluoride, moderate tissue damage results in high levels of plasma fibrinogen.

Key-words: Fluoride, Fibrinogen, Plasma, Rabbit

Profil biochimique du sang dans l’intoxication au fluor
III. Taux de fibrinogène plasmatique chez le lapin.

Résumé

Deux lots de lapins ont été traités respectivement par une faible dose (10 mg/kg) et une forte dose (50 mg/kg) de fluorure de sodium. Le sang a été prélevé dans les 2 groupes dans des délais précis après l’administration de Fluor. Les 2 doses provoquent des réponses différentes pour les taux de fibrinogène plasmatique. On fait l’hypothèse que l’administration de doses faibles de fluore de sodium provoque une formation de nouveaux tissus osseux augmentant le taux de fibrinogène alors que l’administration de doses fortes de fluorure de sodium provoque des dommages modérés à divers tissus qui induisent des taux très élevés de fibrinogène.

INTRODUCTION

Previous reports from our laboratory have dealt with changes in serum glycoproteins and seromucoid in human fluorosis (1). It has also been reported that sodium fluoride in two different doses for long duration (i.e. 10 mg/kg/day and 50 mg/kg/day) gave different response to the total protein-bound hexose and mucoprotein levels of rabbit plasma (2). These studies indicated that marked biological changes occurred in human and rabbit plasma during fluorosis and fluoride intoxication.

FURGUSON (3) studied the effect of low doses of fluoride on serum proteins and a serum enzyme in human subjects and found that the protein pattern did not differ significantly. On the other hand, there are reports on animals (4-6) revealing significant changes in serum proteins like albumin and globulins in fluoride treatment.

Further investigation on the chemical profile of rabbit plasma have been undertaken, to identify specific changes, if any, that would enable to understand the pathophysiology of fluoride poisoning.

MATERIAL AND METHODS

Rabbits in two groups were given two different doses of sodium fluoride. One group was given 10 mg NaF/kg body weight and other with 50 mg NaF/kg, body weight. Sodium fluoride was given through intragastric route at 24 hours interval. Control rabbits were pair fed but deprived off sodium fluoride. Blood was drawn on different days of treatment through occular vein puncture and plasma was separated out.

Plasma fibrinogen was estimated by the procedure of RATNOFF et al (7) as adapted by OGSTON et al (8) & MAHMOOD et al (9). Fibrin was separated out on glass wool after addition of thrombin to the blood plasma. The fibrin thus formed was dissolved in 10 % NaOH and then estimated by Lowry method (10). The values are expressed as mg of fibrinogen per ml of plasma.

RESULTS

The results obtained are depicted in the Bar diagram. It is shown that the plasma fibrinogen content for low dose of sodium fluoride (i.e. 10 mg/kg), compared to normal plasma fibrinogen content, is enhanced. On applying the "t" test to the data, the deviation in the plasma fibrinogen content is highly significant at P value < 0.005 for the period 75, 90 and 125 days. The data obtained for day 10, 15 and 50 was also found to be significant at P value < 0.05. However, the results obtained for plasma fibrinogen on day 25 remained non-significant.

The effect of high doses of sodium fluoride (50 mg/kg) on plasma fibrinogen, reveal a different type of response. Initially on day 15, the plasma fibrinogen level was enhanced compared to the data recorded for normal plasma fibrinogen content. This increase in plasma fibrinogen during the initial period is highly significant at P value < 0.005. Subsequent to this, on day 25 and 50, there is a significant reduction in plasma fibrinogen content. But on day 90 and 125, plasma fibrinogen content was significantly enhanced. This leaves a phase of non-significant reduction on day 75.

DISCUSSION

As fluoride ions have an affinity to combine with calcium in fluoride intoxication, it is known that calcium is being removed from blood stream resulting in low calcium content in blood (11). Calcium ions play an important role in the conversion of prothrombin to thrombin, which catalyses the transformation of fibrinogen to fibrin. During fluoride intoxication, due to loss of calcium, adequate thrombin is not formed (released) thereby leading to an increase of fibrinogen. This seems to be true only in instances where low doses of sodium fluoride have been administered. In this context ROHOLM (12) has stated that small doses of fluoride causes new bone formation (Osteosclerosis) with great demand for calcium. However, NICHOLS et al (13) assume that new bone formation is merely the result of stimulation of parathyroid glands. The other effect of this gland, in low doses of fluoride, is blocking the resorption. Therefore, the new bone formation enhances the demand for calcium resulting in reduction of blood calcium (14-15).
In high doses of sodium fluoride (50 mg/kg), the significant decrease in fibrinogen level on day 25 and 50, may probably be due to the activation of enzymes involved in the catabolism of fibrinogen. It is known that, fluoride deposition at the surfaces of bone near blood vessels stimulate enzymes (16-17). The reduction in fibrinogen can also be explained on the basis of their retention in the extravascular pool (18).

Significant increase in fibrinogen levels, due to high doses of sodium fluoride, on the day 15, 90 and 125 may be due to (a) greater transfer of fibrinogen from tissues to the blood vessels, (b) Inhibition of certain fibrinogenolytic enzymes (17), (c) Tissue injury may take place which releases the humoral factor stimulating fibrinogen biosynthesis. It is known that under pathological conditions the moderate damage of liver and kidney increases fibrinogen levels in blood (19). Fibrinogen levels in blood can also be increased due to hyperthyroidism and increase in ACTH (20-21).

**CONCLUSION**

It is concluded that during administration of low doses of sodium fluoride, new bone formation takes place resulting in low levels of calcium and high levels of fibrinogen in blood circulation. Whereas, in high doses of sodium fluoride, it seems that the inhibition of certain fibrinogenolytic enzymes and moderate tissue damage results in high levels of fibrinogen in plasma.

**Acknowledgement**

We are grateful to the Department of Environment (government of India) for financial support.

**REFERENCES**


COLLOQUES, CONFÉRENCES RÉUNIONS


• Le 4e Symposium Européen organisé par la Société Internationale de Toxicologie, section européenne, aura lieu à Marseille du 24 au 27 juin 1981, avec le programme suivant :
  - Les neurotoxines agissant sur les sites présynaptiques ou postsynaptiques ou sur le système nerveux central.
  - Les neurotoxines affectant le transport des ions.
  - Les toxines cytolytiques et les phospholipases.
  - Les toxines agissant sur la coagulation sanguine et la fibrinolyse.
  - Aspects cliniques des empoisonnements par venins.
L'inscription doit être faite au plus tôt auprès du Professeur ROCHAT, Laboratoire de Biochimie, Faculté de Médecine, Secteur Nord, boulevard Pierre Dramard, 13326 Marseille Cedex 3.

• Fifth biennial international symposium on alcoholism : Scientists from 20 countries gathered in Cardiff, Wales, June 9-13, 1980 for the Fifth Biennial International Symposium on Alcoholism. During the conference, organized by the International Society for Biomedical Research on Alcoholism, outstanding scientists presented their findings in several areas of alcoholism research.

  One topic which generated significant discussion was the search for markers for alcoholism. Marc Schuckit of the University of California School of Medicine in San Diego, summarized and critiqued research towards a means of identifying potential alcoholics even before they start drinking, perhaps by measuring the differences in the way an individual responds to alcohol. He presented evidence that male offspring of alcoholics may have higher circulating levels of acetaldehyde and may have a different subjective response to alcohol after ingestion of this drug as compared with individuals with no family history of alcohol abuse. Marsha Morgan of the Royal Free Hospital in London, on the other hand, critically reviewed the biochemical markers for determining the extent of alcohol use in individuals chronically consuming ethanol and concluded that a battery of tests (e.g. the combined use of serum aspartate transaminase and gamma-glutamyl transpeptidase levels together with the measurement of man corpuscular volume) provided better estimates of man corpuscular alcohol abuse than any single test.

  The aversive factors or rewards associated with alcohol consumption—why some humans and laboratory animals find alcohol a pleasurable experience while others do not—was discussed as were factors that lead to the development of physical dependence on alcohol. Dr. Roy Wise of the Center for Research on Drug Dependence, Concordia University in Montreal, Canada, and Dr. Albert Herz of the Max Planck Institute for Psychiatry in Munich, F.R.G., contributed to this discussion and provided rationale for implicating dopaminergic and enkephalinergic neuronal system of brain in such effects of ethanol.

  The conference included many other internationally known scientists such as 1970 Nobel Prize winner Julius Axelrod, Chief of Pharmacology at Stanford University School of Medicine, who presented work on molecular mechanisms of brain function and discussed how ethanol may affect such function.

  The Symposium was financially supported by international sources, including the U.S. National Institute on Alcohol Abuse and Alcoholism; British and Finnish alcoholic beverage producers’ organizations; the Institute for Prevention of Alcoholism, Switzerland, and a number of pharmaceutical and brewing firms of Japan. This symposium was held parallel to the 26th International Institute on the Prevention and Treatment of Alcoholism which was sponsored by the International Council on Alcohol and Addictions.

  Symposium proceedings will be published in a special issue of the international journals Drug and Alcohol Dependence and Pharmacology, Biochemistry and Behavior.

  Further information about the Symposium or about the International Society for Biomedical Research on Alcoholism can be obtained from Professor Boris Tabakoff, Department of Physiology and Biophysics, University of Illinois Medical Center, P.O. Box 6998, Chicago, Illinois 60680, U.S.A. (Phone: (312) 996-7606).