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Serum Histamine Concentrations of Individuals Consuming Histamine Contaminated Fish

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ABSTRACT. *Although fish consumption is often associated with histamine sensitivity reactions, only a few clinical studies have been carried out on the subject performed in Sri Lanka. Fish exports from Sri Lanka have also been affected in the recent past due to contamination by histamine. Blood samples were taken from humans showing clinical sensitivity to fish consumption, when reported to a selected medical institute of the central region of Sri Lanka. Samples of fish that caused this sensitivity were also collected. Histamine concentration in human blood and fish consumed were estimated using AOAC Fluorometric assay. To determine the mean histamine concentration in normal human blood, 10 ml of 12 h fast blood were drawn from individual volunteers. The mean histamine concentration for a normal human was (150±15) ppm. The plot of the histamine concentration in serum against that in fish showed a significant correlation (r^2=0.76). The concentration of histamine in fish that will not raise the blood histamine level beyond 150 ppm was determined using the regression line. The tolerance concentration of 110 ppm in fish appears to be a reasonable non-hazardous concentration at the point of consumption.*

INTRODUCTION

Histamine poisoning is caused by the ingestion of food that contains intolerable concentrations of this compound. This has been referred as Scombroid poisoning because of the frequent association of this illness with consumption of the scombroid fish such as tuna and mackerel (Otwell *et al.*, 1995). However, non-scombroid types of fish have also been identified to cause the intoxication, including mahi-mahi, blue fish, sardine and herring. In the United States this type of poisoning has been dominated by tuna, mahi-mahi and blue fish (Bjeldance *et al.*, 1978). Symptoms of histamine poisoning

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become evident within minutes to a few hours following consumption of contaminated fish. Initial signs appear with facial flushing, sweating, burning, peppery taste sensations in the mouth and throat, dizziness, nausea and headache. These initial symptoms can advance to urticaria, rash, oedema, diarrhea and abdominal cramps. Severe cases may blur vision and cause respiratory stress. Symptoms usually last for approximately four to six hours and rarely extend to several days. This condition is described as histamine poisoning (Taylor, 1986).

Histamine is an organic compound derived in the body from the amino acid histidine by decarboxylation. Histidine is naturally presents in high concentrations in certain species of fish. The production of histamine is due to the action of histidine decarboxylase enzyme produced by bacteria growing on the fish. The common species of bacteria of the family Enterobacteriaceae responsible for histamine production include *Klebsiella pneumoniae, Morganella morganii* and *Hafnia alvei* (Chen *et al.*, 1989). High concentrations of histamine have been found in fish which has caused intoxications in Sri Lanka (Kottegoda, 1984).

Scombroid poisoning remains one of the most common forms of fish poisoning even in the United States of America and Japan. The patients taking anti-tuberculosis drugs (Isonizid) and those with past histories of atopic diseases such as bronchial asthma and eczema are found to be highly susceptible to histamine (Uragoda, 1978, 1979). The Food and Drug Administration of United States of America considers the presence of 200 ppm as an indication of spoilage in tuna and 500 ppm as an indication of a hazard (Otwell, 1995).

In 1955 two researchers from Japan suggested the toxic dose of histamine to be 600 ppm (Simidu *et al.*, 1955). In Sri Lanka most of the histamine intoxication incidents go unreported. In this study an attempt is made to correlate the histamine concentration found in fish consumed by affected individuals and the serum histamine concentration in their blood with a view to understand the tolerance concentration of this compound for individuals in Sri Lanka.

MATERIALS AND METHODS

Collection of blood and fish samples

The blood samples were collected from the subjects presented to a selected medical institution with sensitivity reactions after consumption of fish. These subjects were clinically examined, histories of the illness were recorded and 10 ml samples of blood were taken from each individual before treatment. Portions of the fish which they had consumed, were also collected. The type of the fish and the duration between the onset of the illness and the consumption of the fish were recorded.

Control samples of blood were drawn (5 ml) from 11 normal volunteers to determine the mean histamine concentration in healthy humans. Blood was centrifuged at high speed to separate serum. Serum was stored in separate glass bottles at -4°C. Samples from fish, which they had consumed were collected from each of the clinically sensitive humans and stored at -4°C pending analysis.

Determination of histamine concentration of fish

Histamine concentrations of fish and blood were measured by AOAC Fluorometric method (AOAC, 1990). Histamine in fish was detected by blending with methanol (35 ml) in mini-blender for 2 min at low speed and maintaining the extract at 60°C for 15 min to enhance extraction. The extract was made to 50 ml with methanol and filtered. The extract (1 ml) was purified by passing through a Dowex ion exchange resin (50-100 mesh) column of 1 cm diameter and 8 cm height eluting with 30 ml of distilled water. The purified extract was made to a final volume of 50 ml with distilled water. The resulting extract (5 ml) was mixed with 10 ml of 0.1 N hydrochloric acid, 3 ml of 1 N sodium hydroxide, 1 ml of 0.1% o-phthalic dicarboxaldehyde and 3 ml of 3.57 N phosphoric acid. The resulting fluorescence was measured using Perkin-Elmer model 203 Fluorimeter with excitation at 350 nm and emission at 444 nm (AOAC, 1990).

Determination of histamine in human blood

Serums separated from 5 ml blood samples were transferred in to a 50 ml volumetric flask made up to the mark with methanol and heated at 60°C in a water bath for 15 min. The extract was purified and histamine

concentrations were estimated as described for determination of histamine concentration of fish.

RESULTS AND DISCUSSION

Serum histamine concentrations in humans

The serum histamine concentrations of the sensitive individuals were found to vary between 200-1100 ppm (IQR of 400) indicating a low dispersion in the middle 50% of the population. In the control group the range was 100-250 ppm with a fairly low variability. The mean serum histamine concentration of the sensitive group was found to be significantly higher ($p=0.001$) than the histamine concentration of the control group (Table 1). Two identified subjects (Figure 1, marked A and B) who showed comparatively low concentrations of histamine had taken anti-histamine tablets. This indicated that the consumption of histamine contaminated fish is a possible cause of high concentration of histamine in the human blood.

Table 1. Serum histamine concentrations of sensitive and control individuals with sensitivity reactions.

Subjects	Histamine Concentration (ppm)	
	Mean (±SE)	Range
Control (11)	150±15	100-250
Sensitive (19)	700±60	300-1100

Relationship between histamine concentrations of fish samples and human serum

The concentration of histamine observed in fish consumed by the sensitive subjects was 1035±386 ppm with a range of 400-1600 ppm. The histamine concentrations in fish showed a linear relationship with the histamine concentration of human serum ($p=0.001$, $r^2=0.76$). The relationship was quantified using the least square principle and the estimated regression model is as follows.

$$H_{hb} = 80.478 + 0.607\, H_f$$

Where, r^2 = 0.76
H_{hb} = Expected histamine concentration in human blood
H_f = Histamine concentration in fish

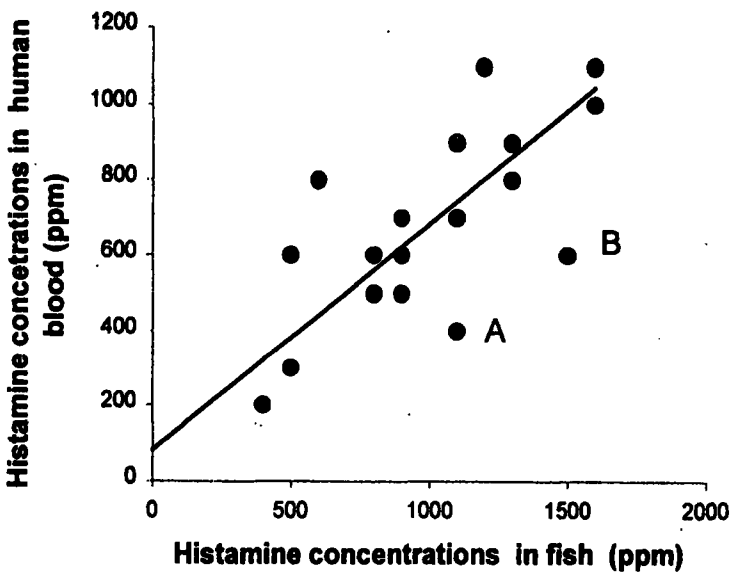

Figure 1. Relationship between histamine concentrations of fish and human serum.

According to the model, each additional part per million of histamine in fish is expected to contribute about 0.6 ppm to human blood up to the concentration 1600 ppm of histamine in fish. The balance 0.4 ppm histamine is ingested may be metabolised in the body. Histamine is metabolised by monoamine oxidase in the gut and liver of humans at the rate of 1.2 mg/kg body weight (Bartholomew *et al.*, 1987).

The intercept of the equation, which is 80 ppm, is the predicted concentration of histamine in human blood when no histamine contaminated fish is consumed. However the estimated mean histamine concentration in serum of the control group is 150 (±15) ppm.

Histamine concentrations in human blood of the subjects who were found with sensitivities after consumption of fish were always higher than the concentrations detected in normal subjects.

Non-hazardous concentration of histamine in fish

Although consumption of histamine contaminated fish raises the histamine concentration in human blood, a non-hazardous concentration of histamine in fish could be predicted.

This non-hazardous concentration would be useful to identify fish, both by type and by concentration of histamine, which will not cause sensitivity reactions in humans. The mean serum histamine concentration of control subjects was found to be 150 (±15) ppm. At this concentration no sensitivity reactions are observed clinically. Therefore, any fish, which will not raise the blood histamine level beyond 150 ppm, could be considered as safe. The concentration of 150 ppm histamine in serum of the subjects corresponds to the histamine concentration of 114 ppm in fish when predicted using the model (Figure 1). This could be considered a reasonably acceptable concentration leading to no sensitivity reactions. The value could perhaps be rounded off to 110 ppm.

This concentration falls within the suggestions of Bartholomew *et al.*, 1987 who carried out a literature search on 250 cases of suspected histamine poisoning. They suggested the following classifications regarding the hazardous nature of histamine in fish.

Histamine concentration in fish (ppm)	Hazardous nature
< 50	normal and safe
50-200	mishandled and possibly toxic
200-1000	unsatisfactory and probably toxic
> 1000	toxic and unsafe

The mean concentration of histamine of marine fish in the Sri Lankan market was found as 140 (±167) ppm (Gunaratne, 1999) with tuna fish showing concentration of the order of the 300-500 ppm. Canned jack mackerel is reported to contain a mean histamine concentration of 119 (±129) ppm (Gunaratne, 1999). In view of the observations on possible sensitivity of individuals, the consumption of tuna fish and canned fish appear to cause a food safety threat. The Food and Drug Administration of the United States of America considers the presence of more than 50 ppm histamine to be an indication of decomposition of fish and 500 ppm as poisonous action level for tuna fish. Our observation too showed that the concentration of 50 ppm of histamine in fish would not cause any clinically visible sensitivity reactions in humans.

CONCLUSIONS

The histamine concentrations of the sensitive group of humans show significantly higher values than that of control groups. A positive correlation exists between histamine concentration of human serum and the fish consumed. The mean serum histamine concentration of normal human was estimated as 150 (±15) ppm. The fish, which will not raise the serum histamine concentration beyond this, could be safe for consumption. Therefore a concentration of histamine less than 110 ppm can be considered non-hazardous for a normal adult consuming fish. Although FDA regulations maintain an additional margin of safety using 50 ppm as the tolerance limit, the Sri Lankan regulations for the histamine concentration in fish for human consumption is 100 ppm, which appears justifiable taking into consideration the level of technology and cold storage facilities available in Sri Lanka.

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