การระบาดของโรคอาหารเป็นพิษฮีสตามีนจากการกินปลาทูน่า ในกลุ่มผู้ต้องขังที่ได้ยา Isoniazid รักษาวัณโรค ในเรือนจำจังหวัด จังหวัดสงขลา ประเทศไทย

An Outbreak of Histamine Food Poisoning after Ingestion Longtail Tuna in Prisoners Taking Isoniazid from Songkhla Province Prison, Songkhla Province, Thailand

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บทคัดย่อ

เมื่อ 3 ธันวาคม 2563 เกิดการระบาดของพิษฮีสตามีนในเรือนจำจังหวัด จังหวัดสงขลา ผู้ต้องขัง 19 ราย มีผื่นหลังกินแกงส้มปลาทูน่ามะละกอจากร้านอาหารในตัวเมือง ทีมสอบสวนโรคเข้าสำรวจหาสาเหตุการระบาดของพิษฮีสตามีนโดยวิธีกรณีศึกษาการควบคุมโรคทางระบาดวิทยา พบผู้ต้องขัง 19 คน มีอาการเป็นพิษฮิสตามีน และ 33 คนในกลุ่มควบคุมไม่มีอาการ ทั้งสองกลุ่มมาจากเรือนจำเดียวกัน เป็นวัณโรคปอดและได้ยา Isoniazid (INH) มีการส่งวัดระดับฮีสตามีนในแกงส้มปลาทูน่ามะละกอ วิเคราะห์ลักษณะทางคลินิกของผู้ป่วย 19 ราย เปรียบเทียบกับกลุ่มควบคุมที่ได้กินแกงส้มแต่ไม่มีอาการแพ้ พบว่า 19 (36.5%) ของผู้ต้องขัง 52 คน ที่ได้ยา INH และกินแกงส้มปลาทูน่ามะละกอ มีผื่นที่ผิวหนัง 100% อาการคัน 100% เวียนศีรษะ 94.7% ปวดศีรษะ 78.9% คลื่นไส้ 47.4% อาเจียน 5.3% ท้องเสีย 10.5% และแน่นหน้าอก 42.1% เริ่มเกิดอาการภายใน 40 นาที อาการดีขึ้นทันทีด้วยยาต้านฮิสตามีน ระดับฮีสตามีนที่วัดได้จากแกงส้มปลาทูน่าคือ 10 มก./กก. ซึ่งเป็นระดับที่ต่ำกว่าระดับอันตรายในอาหารคือ 50 มก./กก. เนื่องจากผู้ต้องขังได้รับ INH ซึ่งยับยั้งทั้ง monoamine oxidase และ

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diamine oxidase ลดการทำงานของ histaminase ทำให้เกิดอาการเป็นพิษของฮีสตามีนได้ง่าย การระบาดของพิษ ฮีสตามีนนี้เป็นผลมาจากปฏิสัมพันธ์ระหว่าง INH และปลาที่ มีพิษของฮีสตามีน โดย INH ทำให้พิษของฮีสตามีนเพิ่มขึ้น ดังนั้นผู้ป่วยวัณโรคที่ได้รับ INH ควรหลีกเลี่ยงอาหารที่มีฮิสตามีน เพื่อป้องกันการเกิดอาการแพ้พิษฮีสตามีน

คำสำคัญ: พิษฮีสตามีน ปลาทูน่า ยาวัณโรค

Abstract

On 3 December 2020, an outbreak of histamine poisoning occurred in the Songkhla province prison (SPP), Songkhla, Southern of Thailand. A total of 19 cases were identified. A suspected cause was a Longtail Tuna cooked as a sour curry with papaya delivered from a downtown restaurant. The aim of the study was to investigate the reason for the outbreak of histamine poisoning in the SPP. A case-control study was conducted among 19 cases of histamine poisoning and 33 unmatched controls from the same prison. Both cases and controls were diagnosed with pulmonary tuberculosis (TB) and still receiving anti-tuberculosis drugs. The toxic histamine concentration level in cooked Longtail Tuna sour curry with papaya and clinical characteristics of the 19 cases were measured and analyzed. The characteristics of cases and controls were compared. 19 (36.5%) of 52 prisoners in SPP who consumed the Tuna fish had developed allergic reactions. The manifestation of symptoms was skin rash 100%, itching 100%, dizziness 94.7%, headache 78.9%, nausea 47.4%, vomiting 5.3%, diarrhea 10.5%, and chest tightness 42.1%. The median time from consumption to developing symptoms was 40 minutes. Most prisoners abruptly recovered with antihistamine and symptomatic treatments. All cases were taking isoniazid (INH) as an anti-tuberculosis treatment. The elevated histamine level of 10 mg/kg of tuna was measured in the cooked Tuna. However, the level was still lower than the hazardous levels (50 mg/kg of food). INH suppresses both monoamine oxidase and diamine oxidase, thus decreasing histaminase activity causes more toxic of histamine poisoning. This outbreak of histamine poisoning was a result of the interaction between INH and fish containing histamine at the levels below hazard level. In patients with active tuberculosis especially those who were treated with INH, the drug and food containing histamine should be avoided to prevent histamine poisoning.

Keywords: Histamine food poisoning, Scombridae fish, Isoniazid

Introduction

Histamine is a naturally occurring endogenous substance in the human body that is derived from the decarboxylation of the amino acid histidine (Visciano, Schirone, Tofalo, & Suzzi, 2014a). Histamine may also be present in certain foods containing free histidine or generated by certain bacteria during spoilage and fermentation of fish (Biji, Ravishankar, Venkateswarlu, Mohan, & Gopal, 2016). Histamine-rich foods may cause food intolerance in sensitive individuals while histamine-contaminated fish and fish products may cause food poisoning (Food and Agriculture Organization of the United Nations, 2013). Scombroidae fish family (e.g., tuna, sardines, and mackerel) contains a high concentration of histamine (Hungerford, 2010). Histamine level in these fishes increase when improperly or delayed refrigerated. Histamine can be rapidly produced in fish stored at $\geq$ 20°C (Visciano, Schirone, Tofalo, & Suzzi, 2012). The histamine level in a fresh fish is usually less than 0.1 mg/kg. However, elevated levels of histamine > 200 mg/kg have been reported after fish storage for > 15 hours at 20°C – 35°C. Moreover, histamine is heat-stable, therefore the substance might remain high even after cooking.

Outbreaks of scombroid fish poisoning have become common in many countries because scombroid fish is a species of tropical fish worldwide. This type of food poisoning could have more serious consequences for other populations of fish consumers. European fresh tuna imports increased by 5% per year on average between 2011 – 2015 (Joe Whitworth, 2019). Most outbreaks of histamine poisoning have been associated with fish histamine levels $\geq$ 200 mg/kg and often > 500 mg/kg, although some outbreaks were associated with levels < 200 mg/kg. The hazardous levels were thought to be 50 mg histamine/kg of food or more (Kang et al., 2018). The onset of scombroid poisoning is typically from few minutes to 1 hour (*Scomberesocidae - an Overview | ScienceDirect Topics*, n.d.) following the consumption of histamine-contaminated fish and usually resolved within few hours (Demoncheaux et al., 2012). The clinical characteristics were allergic reactions, including flushing, cutaneous rash or headache dizziness, abdominal cramps, and palpitations. Interactive factors which may increase the severity of histamine poisoning are drugs. In the human body, histamine is primarily metabolized by two enzymes; diamine oxidase (DAO) and histamine-N-methyltransferase (HMT). DAO converts histamine into imidazole acetic acid, which can be conjugated with ribose before excretion in urine (Gagic et al., 2019). Histamine methyltransferase converts histamine into

methylhistamine, which is then converted by monoamine oxidase (MAO) into N-imidazole acetic acid. Altered histamine metabolism has been reported in individuals taking isoniazid and drugs that inhibit DAO or MAO (Kaneko & Ishigatsubo, 2005). Thus, the results were the longer half-life of endogenous and exogenous histamine, which might increase the severity of histamine food poisoning.

Prisons had active tuberculosis prisoners, taking INH. Interaction between INH with other drugs was well recognized by physicians. However, food interaction with INH was less recognized. Unaware of the interaction between INH and food may lead to serious poisoning and fatal allergic-like symptoms. Therefore, we examine and describe the cases of histamine poisoning to raise physician awareness on the possible serious interaction between INH and food.

Objective

To determine the cause of outbreak mimicking food poisoning and analyzed the clinical characteristics of the affected patients in the Songkhla province prison (SPP)**.**

Methodology

A case-control study was conducted among 19 cases of histamine poisoning and 33 controls among prisoners with active tuberculosis in SPP, located in Southern Thailand.

Statistical Analysis

An exploratory analysis was done. The outbreak was described using an epidemic curve on the time scale of hours. Continuous variables were presented using median (IQR). The categorical variable was compared between cases and controls using fisher's exact test.

Ethical statement

Ethic No: SKH IRB 2021-Md-IN3-1005All participants received information about the investigation and their symptoms. This was an emergence foodborne outbreak investigation. Therefore, informed consent was not collected before the investigation. The study design and retrospective chart review were approved by Songkhla hospital.

Results

A total of 19 cases were identified among the 52 prisoners with tuberculosis who had eaten Longtail Tuna fish on 3 December 2020. The attack rate was 19/52 (36.5%). Fifty-two prisoners were included in the case-control study, 19 cases and 33 control cases.

The 19 cases had allergy-like symptoms. The clinical characteristics are rapid onset flushing of face and neck with erythematous patches 100%, itching 100%, dizziness 94.7%, headache 78.9%, nausea 47.4%, vomiting 5.3%, diarrhea 10.5%, and chest tightness 42.1% (Table 1). Whereas the other 33 tuberculosis prisoners had no such symptoms.

The median age of cases was 38 years (26–54 years). All of the prisoners were men. The mean body mass index was 21.5± 2.81 kg/m2 (Table 1). The INH doses for all participants were 300 mg per day. The median duration of INH treatment was 3 months. 63.2% of the cases consumed the whole fish (Table 1).

Table 1 Characteristics of cases longtail tuna fish poisoning in prisoners Songkhla province, Thailand (n=19)

Characteristics	**Cases N (%)**
Sex	19(100%)
Age (Median [IQR])	38.0 [26.0, 54.0]
Body Mass Index (BMI) (Mean (SD))	21.5 (2.8)
Fish consumption	
-Little	7 (36.8%)
-Whole	12 (63.2%)
Clinical manifestations:	
-Flushing	19 (100.0%)
-Itching	8 (42.1%)
-Nausea	9 (47.4%)
-Vomiting	1 (5.3%)
-Diarrhea	2 (10.5%)
-Dizziness	18 (94.7%)
-Headache	15 (78.9%)
-Fever	2 (10.5%)
-Chest tightness	8 (42.1%)

The first cases occurred shortly 5 minutes after 7.30 A.M. after fish consumption. The median time from fish consumption to symptom development was 40 minutes. The epidemic curve showed two consensual peak onset at 7.40 A.M and 8.00 A.M, consecutively (range: 0–110 minutes) (Figure 1).

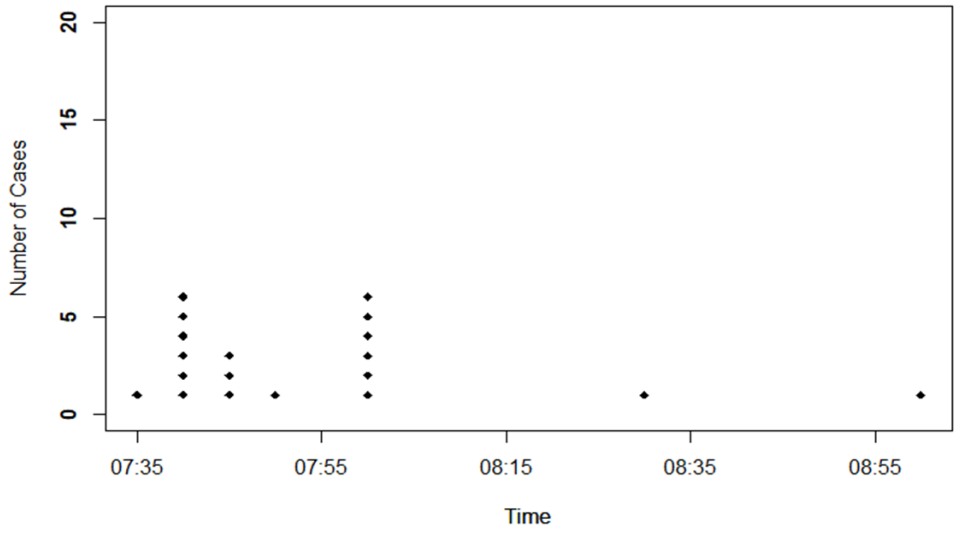


Figure 1 The time before symptom onset of scombroid fish poisoning by 20-minute intervals (n = 19).

There are no significant differences between cases and controls in the aspect of Longtail Tuna consumption, sex, age, body mass index (BMI), and duration of treatment with INH (Table 2).

Table 2 Relationship between consumption of food and illness of prisoner cases and control cases, Songkhla province, Thailand (n=52)

Characteristics	**Case (n=19)**	**Control (n=33)**	**Overall (n=52)**	**P-value**
Sex: Male	19(100%)	33(100%)	52(100%)	NA
Age (median [IQR])	38.0 [26.0, 54.0]	35.0 [22.0, 64.0]	35.5 [22.0, 64.0]	0.813
BMI Mean (SD)	21.5 (2.8)	20.9 (2.7)	21.1 (2.7)	0.480
Fish consumption				
-Little	7 (36.8%)	11 (33.3%)	18 (34.6%)	1.000
-Whole	12 (63.2%)	22 (66.7%)	34 (65.4%)	
INH duration (months) Median	3	4	4	0.052

*P-value from Fisher's exact test

Laboratory investigation

The Longtail Tuna sour curry with papaya was sent to a lab for measuring histamine levels. The level of histamine revealed was 104.38 ug/g which is about 10 mg/kg of food by in-house method AOAC (on 7 DEC 2020, 4 days after outbreak event). Prisoner's serum histaminase and MAO level were not sent for laboratory analysis in this outbreak due to financial limits.

Treatments

Anti-histamine H1-receptor antagonists (chlorpheniramine, hydroxyzine) and local treatment with calamine lotion were given to all 19 cases. Their symptoms improved within 3 hours since the onset of symptoms.

Discussion

In general, histamine food poisoning (HFP) from scombroids fish outbreak had varying attack rate ranged from 5.4% to 30.0% (Kang et al., 2018)(9). The attack rate of this study was 36.5% which is slightly higher than those found in general. This outbreak of histamine poisoning can be explained by the interaction between isoniazid and ingestion of Longtail Tuna sour curry with papaya. Only a few case reports of histamine poisoning after ingestion of scombroid fish were reported in active tuberculous patients (Morinaga, Kawasaki, Hirata, Suzuki, & Mizushima, 1997). The symptoms of histamine allergy such as flushing, itching, dizziness, headache, diarrhea, vomiting, nausea, fever, and chest tightness were observed. The most frequently reported symptoms were dermatological manifestations such as flushing and headache similar to other studies (Miki, Ishikawa, & Okayama, 2005).

In scombroid poisoning, clinical manifestations usually occur within an hour after ingestion of the contaminated meal and last for several hours (Velut et al., 2019). In this outbreak, the time from consumption to the onset of clinical manifestations showed two consensual peaks onset at 7.40 a.m. and 8.00 and onset of symptoms occur in 5 minutes after ingestion of food that very short when compared to the previous study (Miki et al., 2005). However, when compared time to onset of symptoms with non-tuberculosis patients (Velut et al., 2019). Its found that tuberculosis patients with INH did not have a rapid time to onset of symptoms more than other populations on histamine food poisonings. The time between consumption and the onset of symptoms was not related to the amount

of tuna eaten. Histamine food poisoning can sometimes lead to severe cases or death, even among healthy patients (Velut et al., 2019). Therefore, suspected or confirmed HFP should be considered an emergency and confirming the origin of histamine food poisoning should be made an urgent priority. Our study mostly tuberculosis prisoners who had mild symptoms, no severe cases that needed hospitalization or perfusion procedures. As previously (Miki et al., 2005) reported, tuberculosis patients' recovery occurred within 3 hours same as our study. The first-line treatment included symptomatic H1 receptor antagonists as recommended in the literature (Food and Agriculture Organization of the United Nations, 2013), corticosteroid was not generally used same as a treatment in our study.

It is essential to confirm HFP by verifying histamine concentration in the suspected food. In our study, the histamine concentration in the Longtail Tuna sour curry with papaya was 10 mg/kg while the hazard level was 50 mg/kg. For European Union, the critical level of histamine is 100 mg/kg for raw fish. In the United State of America, the critical level is 50 mg/kg (Gagic et al., 2019). In our study histamine concentration was below hazard level probably due to delay food sample for histamine concentration. The sample was frozen stored and sent 4 days after the outbreak. Only one of food sample was sent for measuring histamine concentration. Temperature and storing methods might affect histamine level in the cooked Tuna (Colombo, Cattaneo, Confalonieri, & Bernardi, 2018).

There were few case reports of histamine poisoning after ingestion of tuna fish in tuberculosis patients (Morinaga et al., 1997) (13). In our study, all tuberculosis prisoners had been taking 300 mg of INH per day. The median duration for INH was 3 months. Our study reported possible interactive effects between INH and histamine-containing food. INH can suppress both MAO and DAO, decreasing histaminase activity. The results were the excessive amount of histamine which aggravated the histamine food poisoning outbreaks.

There was no significant difference between cases and control in terms of sex, age, body mass index (BMI), amount of fish consumption**,** and duration of treatment with INH. These results pointed that the allergic reaction may be depending on individual sensitivity through elimination and body regulation to histamine (Visciano, Schirone, Tofalo, & Suzzi, 2014b). Another possible explanation is that histamine levels might be varied between each tuna within the same batch. Therefore, to confirm histamine presence in suspected food, several samples must be analyzed.

Unfortunately, due to the limited financial support, multiple sample testing was not allowed in this study.

There were limitations of this study. Firstly, the cooked Tuna was stored for 4 days before sending for histamine concentration. Secondly, plasma histamine levels, serum MAO and DAO levels were not tested. Lastly, possible bacteria producing histamine cannot be ruled out.

The histamine-containing food such as the Scombroidae fish family e.g., tuna, sardines, mackerel should be avoided in prisoners taking INH. Nevertheless, to prevent a future outbreak in prison, attention should be paid to detect possible interactions between food products and medications for prisoners. This is not limited to only INH but also other drugs that prisoners are taking.

Conclusions

Our study reported the first outbreak of scombroid fish poisoning in tuberculosis prisoners treated with INH in Thailand. This outbreak of histamine poisoning demonstrates the interactive adverse effects between INH and the consumption of fish containing histamine at the levels below the hazard level. In tuberculosis patients, the drug and food containing histamine should be avoided to prevent histamine poisoning.

Suggestion

Further study should examine histamine levels in Tuna during the process of preparing, cooking and packaging techniques of Tuna fish (Colombo et al., 2018). Bacteriological investigations such as bacterial culture should be considered to evaluate possible bacterial contamination. Interaction of INH and antihistamine might be another interesting topic.

For prison, histamine concentration in prisoner's food should be randomly checked, if possible. Crucially, prisoners taking INH should be tested for plasma histamine levels if suspected histamine food poisoning and avoid raw fish, fermented food product.

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Conflict of interest

None declared.

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