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An indispensable toxin known for 2500 years: victims of mad honey

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Aim: Mad honey (bitter honey) is a local name for a particular type of honey used in alternative medicine to treat gastric pain, bowel disorders, and hypertension, and as a sexual stimulant in the Black Sea coastal region of Turkey. Grayonotoxin behaves like cholinergic agents and has dosage dependent adverse effects on the cardiovascular system including bradycardia, atrioventricular block (AVB), and arterial hypotension. In this manuscript, we report 37 cases of mad honey intoxication from the western Black Sea region.

Materials and methods: This was a retrospective case series of 37 patients who were admitted to the emergency department of a tertiary center with a history of mad honey intake between June 2003 and June 2010.

Results: Patients consisted of 31 males (83.7%) and 6 females (16.3%). Mean age was 56.17 ± 12.56 and 69.66 ± 11.75 in males and females, respectively. Initial physical examination findings included hypotension in 18 patients, sinus bradycardia in 17, and complete AVB in 5 patients.

Conclusion: Mad honey poisoning is an important, life-threatening issue in the Black Sea region of Turkey. Mad honey intoxication should be considered in the differential diagnosis in emergency cases of bradycardia and hypotension.

Key words: Alternative medicine, grayanotoxin, intoxication, mad honey, middle age

Introduction

Mad honey is used in the Black Sea region as an alternative medicine in the treatment of gastric pain, bowel disorders, and hypertension, and it is also thought to be a sexual stimulant (1,2).

The history of mad honey intoxication is quite old. Xenophon (B.C. 434–354) mentions a disease causing delirium, vomiting, and diarrhea during their stay at the coast of the Black Sea with the Greek Army during their flight from the Persians (3). This first information on mad honey intoxication has gone down in history with the intoxication of 10,000 soldiers at that time.

The majority of studies in the literature on mad honey intoxication have been from Turkey (4). In addition, cases have also been reported from Japan, Nepal, Brazil, North America, and various parts of Europe (5,6). Interestingly, one case reported from outside Turkey included a Turkish patient or one that had visited Turkey (7).

This honey is manufactured from 2 members of the genus *Rhododendron* of plants, i.e. *R. luteum* and *R. ponticum*, in the northern parts of Turkey. Grayanotoxin (GTX) I, also called andromedotoxin, is found only in Ericaceae type of plants and is considered to be the particular species responsible for intoxications (8). Mad honey might cause bradycardia, atrioventricular block (AVB), and arterial hypotension and lead to fetal consequences when left untreated. However, no cases have been reported to lead to death in the literature since the

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hypotension and bradycardia observed in the clinical course of this pathology respond to medical treatment (9). Symptoms have an acute onset and their fading takes longer than 24 h (10).

This honey is a commercial food product produced in the northern parts of this country and consumed in all parts of Turkey, as well as the rest of the world, thanks to improvements in transportation and tourism.

In this manuscript, our objective was to report our experiences regarding the clinical and demographic features of patients diagnosed with mad honey intoxication treated at the emergency department of a tertiary center.

Materials and methods

This was a descriptive and retrospective study. The clinical and demographic features of 37 patients diagnosed with mad honey intoxication at the emergency department of our university hospital between June 2003 and June 2010 were investigated. Descriptive data were examined including age, sex, month of presentation, cause of presentation, pulse, arterial blood pressure, ECG findings, systemic disorders, complaints at presentation, treatments administered, and duration of stay. The study design was approved by Zonguldak Karaelmas University Faculty of Medicine ethical committee on 2 September 2010 (no: 2010/09).

The Statistical Package for the Social Sciences (SPSS 16.0 for Windows) was used for evaluating the data and performing the frequency analysis. Data regarding age, duration of stay, pulse rate, and systolic and diastolic blood pressure were reported as mean ± SD. Quantitative data were given as percentages. Seasonal distribution was evaluated with a chi-square test. $P < 0.05$ was considered significant for the tests.

Results

Thirty-seven patients were admitted to the emergency department with symptoms of nausea, vomiting, hypotension, bradycardia, and syncope between June 2003 and June 2010. The patients consisted of 31 males (83.7%) and 6 females (16.3%). Mean age was 56.17 ± 12.56 and 69.66 ± 11.75 in males and females, respectively. Complaints of the patients at initial presentation are shown in Table 1. Seasonal and monthly distribution of patients is shown in Table 2. A chi-square test was conducted for seasonal distribution and no significant difference was found ($P > 0.05$).

The initial physical examination showed that heart rates were 30 to 112 bpm (mean ± SD: 51.78 ± 17.15 bpm), systolic blood pressures ranged from 40 to 130 mmHg (mean ± SD, 97.4 ± 24.08 mmHg), and diastolic blood pressures ranged from 30 to 80 mmHg (mean ± SD, 56.48 ± 15.62 mmHg).

Medical history of the patients included hypertension in 11, and diabetes mellitus, ulcerative colitis, peptic ulcer, and Parkinson's disease in 1 patient each. Twenty-one of the 22 patients with no concomitant systemic diseases were males and their mean age was 52.42 ± 11.06.

The amount of honey intake was determined from the medical records in 11 patients. This included 1 teaspoonful in 1 patient, 1 coffee spoonful in 6, and

Table 1. Main complaints at presentation.

	n	%
Vertigo	10	27.1
Dizziness	9	24.3
Unconsciousness	3	8.1
Nausea, vomiting	6	16.2
Fatigue	3	8.1
Chest pain	6	16.2
Total	37	100

Table 2. Distribution of cases by season and month.

Season	Month	n	Total	%
Winter	December	-	4	10.9
	January	1		
	February	3		
Spring	March	5	9	24.3
	April	3		
	May	1		
Summer	June	2	9	24.3
	July	3		
	August	4		
Fall	September	7	15	40.5
	October	2		
	November	6		

2 coffee spoonfuls in 3, and the maximum amount of intake was 6 coffee spoonfuls. A 46-year-old male patient with no systemic diseases presented with unconsciousness following 6 coffee spoonfuls of intake.

Physical examination findings on admission included hypotension in 18 (48.6%) patients, electrocardiographically demonstrated sinus bradycardia in 17 (45.9%), and complete AVB in 5. Electrocardiographic characteristics of the patients are presented in Table 3.

One milligram of atropine had been administered to 16 patients. The criteria of atropine administration included presence of symptomatic hypotension, bradycardia, and development of AVB. A second dose of 2 mg of atropine had been administered 5 min after the initial dose in one patient with symptomatic bradycardia and another patient with AVB due to failure to restore heart rate and blood pressure. Overall, patients responded to intravenous saline and parenteral atropine treatments; however, additional dopamine infusion had been necessary in 2 patients. Heart rate and blood pressure returned to normal within 2 to 9 h in 32 patients. All patients were monitored and followed up in the emergency department for 24 h. Basal intravenous sodium chloride infusion (100 cc/h) had been continued until symptoms resolved.

Five patients with AVB were admitted to our coronary intensive care unit. Two of these patients were discharged on the second day of admission and another 2 were discharged on day 1 of administration. A temporary pacemaker was placed in the remaining fifth patient, who was discharged on day 6 of admission.

Discussion

Honey might contain grayanotoxin and cause poisoning. Grayonotoxin behaves like cholinergic agents and has dosage dependent adverse effects on the cardiovascular system including bradycardia, AVB, and arterial hypotension. Grayanotoxins bind to sodium channels in cell membranes, preventing their inactivation and maintaining the cell in a state of depolarization, during which calcium entry might be facilitated. There are 18 known forms of grayanotoxins and grayanotoxin I is responsible for honey poisoning (11).

Most of the literature cases on mad honey have been reported from Turkey. Mad honey intoxication has commonly been seen in the eastern Black Sea region of the country (9,12). However, it should be noted that mad honey intoxication is common in the entire Black Sea region. Ozhan et al. have published a series of 19 cases of intoxication in the western Black Sea region. Other cases have also been

Table 3. ECG findings of the cases.

ECG finding	n	%
SB	17	45.9
AVB	5	13.5
NSR	10	27.1
AF	5	13.5
Total	37	100

SB, sinus bradycardia; AF, atrial fibrillation with low ventricular rate; AVB, complete atrioventricular block; NSR, normal sinus rhythm

reported from the western Black Sea region (8,13,14). In this manuscript, we report 37 cases of mad honey intoxication from the western Black Sea region.

There are studies demonstrating that mad honey poisoning is common in summer in the eastern Black Sea region of Turkey (1,2,15). Contrary to the literature, in our study cases of mad honey intoxication were concentrated in the fall and particularly in September. Rhododendron species in Trabzon and the eastern Black Sea region bloom earlier than those in the rest of the Black Sea region (16). For this reason, while mad honey in Trabzon and the eastern Black Sea region could be consumed in summer, mad honey in western Black Sea region is started to be harvested in August and thus is consumed in the fall. One possible cause for encountering mad honey poisoning cases in the western Black Sea more frequently in the fall could be the presence of the late blooming type of Rhododendron species in the region.

Studies have reported that mad honey intoxication is more common among middle-aged males (17). In our study, honey poisoning occurred 5 times more often in males compared to females. It has been reported that mad honey is used by 40–60-year-old men most commonly to cure sexual dysfunction and increase sexual performance (18). Mean age was 52.42 ± 11.06 in 21 male patients with no concomitant disorders and with a history of mad honey intake. The absence of concomitant pathologies prompted us to think that the motivation for mad honey intake was to increase sexual drive in these 21 patients.

The precise amount of a toxic dose is not known; however, it has been reported in previous studies that 1 teaspoonful (15 g) of toxic honey may cause intoxication. Symptoms have been reported to emerge with the intake of various amounts of mad honey (5–180 g) (2,8,19). Although mad honey intoxication has been reported to be associated with the amount of intake, it is quite difficult to determine the quantity of GTX exposure since the distribution of GTX within honey is not homogeneous (8,20). The amount of intake could not be determined in all patients since this was a retrospective study. Only 11 patients used a spoon to determine the amount of consumption. Although the amount of honey intake determined in our study is compatible with the literature, the exact amount of toxin rather than the honey itself is of importance in these cases.

Mad honey intoxication is a mild form of intoxication that includes dizziness, fatigue, excessive perspiration, hypersalivation, nausea, vomiting, and paresthesia where close monitoring is adequate. However, severe intoxication may lead to life-threatening cardiac complications (11). The intoxication might be severe and mortal in cases of advanced age, high dosage, and concomitant use of anti-arrhythmics including propafenone, quinidine, and procainamide that affect sodium channels (21). The exact drug history could not be obtained in our study due to the retrospective design.

Hypotension and bradycardia are common symptoms in cases of intoxication (17). Similar to the literature, symptomatic sinus bradycardia with hypotension was the most frequently reported mad honey-induced cardiac dysrhythmia in our series. Atrial fibrillation with low ventricular rate (AFLVR) was observed in 5 of our patients whereas it has been

reported in 1 patient in the literature (18). They were determined to have had atrial fibrillation prior to the incident.

Often atropine and intravenous saline administrations prove adequate in the treatment of hypotension and bradycardia. However, vasopressor or transient pacemaker administrations might also be necessary in rare cases that are refractory to the above therapy (22). There were only 3 cases in our study that fitted the definition of refractoriness. A vasopressor agent was administered in 2 of these and a transient pacemaker was inserted in 1.

There is no consensus regarding the duration of monitoring in cases of mad honey intoxication. It has been reported that 2–6 h of cardiac monitoring followed by discharge of the patient should be adequate in cases of mild mad honey intoxication (2). Another study has recommended 6 h of monitoring following the establishment of normal heart rate and blood pressure values in the emergency department (19). Yet another study has reported that clinical improvement was noted at the earliest 7 h following the intake of a toxic substance, complete improvement was obtained only after 23.4 ± 10.5 h, and patients were kept under monitoring in the emergency department for 24 h (8,18). GTX is metabolized and excreted within 24 h of intake (20,23). Heart rate and blood pressure returned to normal within 2 to 9 h in 32 patients. Complete recovery was attained in our patients in a period similar to the cumulative mean recovery period reported in the literature. However, we decided to keep the patients under emergency department monitoring for 24 h following the improvement of symptoms considering the severity of cases and the patient monitoring policy of our department.

Sir William Osler, MD, (1849-1919) mentioned the importance of anamnesis in establishing a diagnosis, with the words "*Listen to your patient, he tells you the diagnosis*" (24). History taking is the most important step towards the diagnosis in mad honey intoxication as in all other diseases. Mad honey intoxication should be considered in the differential diagnosis in emergency cases of bradycardia and hypotension, particularly in middle-aged men, regardless of the geographic region and season.

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