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Brief Report

Mad honey poisoning

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Abstract Grayanotoxin intoxication, which is mostly seen in the eastern Black Sea region of Turkey, stems from the "mad honey" made by bees from the rhododendron plant flowers. In low doses, this causes dizziness, hypotension, and bradycardia, and in high doses, impaired consciousness, seizures, and atrioventricular block (AVB). This case study was designed as a series of cases of patients (6 women, 2 men) aged between 35 and 75 years. All of the patients' physical examinations revealed hypotension; 4 patients had sinus bradycardia, 3 had nodal rhythm, and 1 had complete AVB. In all patients, except for the patient with AVB, heart rate and blood pressure returned to normal limits within 2 to 6 hours. Two patients were monitored in the coronary intensive care unit. Of these 2, 1 was discharged on the second day. The other was fitted with a temporary pacemaker and was discharged on the third day. All the other patients were kept in for a 6-hour observation period and were then discharged from the ED. To date, 58 such cases have been reported, but we saw 8 patients within 2005. It is commonly seen in the east of the Black Sea region, although cases may occur from all over the eastern Black Sea region of Turkey. So far, no cases of death have been reported, although grayanotoxin causes adverse effects on the cardiovascular and respiratory systems and is therefore of considerable importance.

1. Introduction

Honey from the Black Sea region of Turkey occasionally contains grayanotoxin and causes poisoning. It is believed that this particularly occurs because of the consumption of honey from the eastern part of the Black Sea region, where it is known as "mad honey."

Local people can distinguish that honey from other varieties. It causes a sharp burning sensation in the throat and is thus also referred to as "bitter honey." In 401 BC, the honey found in this area was known to be poisonous [1,2]. Mad honey is used in the Black Sea region as an alternative medicine for the treatment of gastric pains, bowel disorders, and hypertension, and it is also believed to be a sexual stimulant [1]. Given these uses, there has been no decrease in grayanotoxin intoxication cases in spite of this awareness of mad honey.

Mad honey has the potential to cause death if untreated, but since the medical definition of mad honey poisoning in 1983 [3], no fatal cases have been reported in the literature. Complete recovery after hospital admission is normally the rule, because hypotension usually responds to the appropriate

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Table 1 Previous studies of mad honey in the literature to date

Authors	No. of patients	Cardiac disturbance	Blood pressure ≤90 mm Hg	Honey sources
Von Malottki and Wiechmann [3]	1	SB	1	Turkish honey
Biberoglu et al [4]	16	9 SB, 5 NR, 1 WPW + SB, 1 AVB	16	Eastern Black Sea
Yavuz et al [5]	7	7 SB	7	Central Black Sea
Sutlupinar et al [1]	11	7 BA	11	Black Sea
Gossinger et al [6]	2	2 BA	2	Turkish honey
Dilber et al [7]	1	1 SB	1	Eastern Black Sea
Ozhan et al [8]	19	15 SB, 4 AVB	19	Western Black Sea
Kumral et al [9]	1	1 AVB	1	Eastern Black Sea

BA, bradyarrhythmia; SB, sinusal bradicardia; NR, nodal rhythm; WPW, Wolff-Parkinson-White.

fluids, and correction of bradycardia and conduction defects, which usually respond to atropine treatment. However, if people affected in this area rest and their condition does not worsen, they are not usually taken to hospital, and those patients who do go to local hospitals are kept under observation for a few hours and then discharged. The great majority of the cases have been reported from Turkey. To date, a total of 58 cases of mad honey poisoning have been reported in the literature, 1 from Germany, 1 from Austria, and the rest from Turkey, in a total of 8 unpublished papers (Table 1). However, we do not know whether there have been any deaths due to mad honey poisoning before the patient reached the hospital.

Four cases of mad honey poisoning presenting to the Karadeniz Technical University Farabi Hospital Emergency Services, the region's reference hospital for 2005, and 4 cases presenting to the Rize State Hospital are described in this study.

2. Cases

This case study was designed as a series of cases consisting of 8 patients who had eaten mad honey, 6 women and 2 men, aged between 35 and 75 years (mean ± SD, 58.8 ± 16.2). Of the 8 patients with mad honey poisoning, 4 were sent to us from the peripheral hospitals, whereas the rest directly came to us. These patients were admitted to the ED with symptoms of nausea, vomiting, hypotension, and bradycardia in 2005 (Table 2). Patient histories were obtained via researchers, the patients were fully conscious.

Each patient ingested 20 to 150 g of honey, unaware that this was mad honey and believing it to be normal honey, several hours before admission.

2.1. Physical examination

Initial physical examination showed that all patients had bradycardia (pulse 40.9 ± 5.3 [32-48]) and hypotension (systolic blood pressure 81.3 ± 8.3 [70-90] mm Hg, diastolic blood pressure 42.5 ± 7.1 [40-60] mm Hg). In 4 patients, symptoms were comparatively mild because of a slight decrease in blood pressure and sinus bradycardia. In 4 patients, bradycardia was severe, and 1 patient had complete atrioventricular block (AVB). The other 3 had nodal rhythm and were monitored in the ED for 12 hours.

2.2. Treatment

All 8 patients received 0.5 mg of intravenous atropine. Administration criteria were symptomatic hypotension and AVB. Three patients with symptomatic bradycardia and one patient with AVB were given a second dose of 0.5 mg of atropine 5 minutes after the initial dose because heart rate and blood pressure could not be restored. A basal rate of intravenous sodium chloride infusion (100 mL/h) was maintained during follow-up. In all patients, except for the patient with AVB, heart rate and blood pressure returned to normal limits within 2 to 6 hours. Two patients were monitored in the coronary intensive care unit. Of these 2 patients, 1 was discharged on the second day. The other was fitted with a temporary pacemaker and was discharged on the third day. All the other patients were kept

Table 2 Summary of clinical characteristics of patients

Number	Sex M/F	Age	Blood pressure	Cardiac disturbance	Outcome
1	F	40	90/40	SB	Discharged from ED after 2 h
2	F	50	70/40	NR	Discharged from ED after 6 h
3	F	75	70/40	NR	Discharged from ED after 5.5 h
4	F	35	80/40	SB	Discharged from ED after 5 h
5	F	65	80/40	NR	Discharged from ED after 6 h
6	F	75	90/40	AVB	Discharged from the intensive care unit after third day
7	M	55	90/60	SB	Discharged from ED after 4 h
8	M	75	80/40	SB	Discharged from the intensive care unit after second day

Fig. 1 *R ponticum*, called mountain rose.

in for a 6-hour observation period and were then discharged from the ED.

3. Discussion

Beekeeping is a common activity among the local people of the eastern Black Sea area. Native Caucasian bees, which can fly in an area of only about 5 km^2, are used in the traditional method of honey production. Therefore, each variety of honey contains only one valley's flora. Because rhododendrons are long-lived plants, beekeepers know which honey is 'mad.' Honey produced in springtime is more toxic and sometimes contains higher concentrations of grayanotoxin than that produced in other seasons [7].

The specific grayanotoxins vary with the plant species. Not all rhododendrons produce grayanotoxins. There are 5 species of rhododendron in Turkey. *Rhododendron ponticum* (Fig. 1) grows extensively on the mountains of the Black Sea area [10]. Other species of rhododendron and other members of the botanical family Ericaceae, to which rhododendrons belong, may produce the toxins but are not often implicated with the disease. Mountain laurel (*Kalmia latifolia*) and sheep laurel (*Kalmia angustifolia*) are probably the other most important sources of the toxin. Of the 18 forms of grayanotoxins, grayanotoxin I (andromedotoxin) occurs only in Ericaceae plants and contains the compounds responsible for poisoning. These compounds are diterpenes, polyhydroxylated cyclic hydrocarbons that do not contain nitrogen. They are extracted by bees from the leaves and flowers of rhododendron species [2,11].

The grayanotoxins bind to the sodium channels in cell membranes. These compounds prevent inactivation; thus, excitable cells (nerve and muscle) are maintained in a state of depolarization, during which entry of calcium into the cells may be facilitated. All of the observed responses of skeletal and heart muscles, nerves, and the central nervous system are related to the membrane effects [11,12].

The toxic effects of honey poisoning are rarely fatal and generally last for no more than 24 hours. Generally, the disease induces dizziness, weakness, excessive perspiration, nausea and vomiting, sweating, salivation, loss of consciousness, fainting, blurred vision, chills, circumoral and extremity paresthesia, cyanosis, and convulsions shortly after the toxic honey is ingested. Other symptoms that can occur are low blood pressure or shock, bradyarrhythmia, sinus bradycardia, nodal rhythm, Wolff-Parkinson-White syndrome and complete AVB [1,3-9,12].

Cardiac disturbances are the main signs in this poisoning. Onat et al [12] showed thatatropine sulfate alleviated bradycardia attributable to grayanotoxin, and AF-DX 116, a selective M2-muscarinic receptor antagonist, restored heart rate. They suggested that M2-muscarinic receptors were involved in the cardiotoxicity of grayanotoxin [12]. Symptoms of poisoning occur after a dose-dependent latent period of a few minutes to 2 or more hours. The precise amount necessary for a toxic dose is not known. In general, the severity of the honey poisoning depends on the amount ingested. The concentration of grayanotoxin ingested may differ greatly from case to case. As grayanotoxins are metabolized and excreted rapidly, patients generally regain consciousness and feel better within hours, and heart rate and blood pressure usually return to normal within 2 to 9 hours [8]. Our cases monitored in the ED were discharged within 2 to 6 hours. That is why in mild cases, if heart rate and blood pressure are within normal ranges, the patient may be discharged from the ED within the first 6 to 9 hours.

Because of the increasing preference for natural products, intoxication induced by consumption of honey will increase in the future, especially with products bought directly from the beekeeper. The possibility of honey poisoning should be kept in mind in previously healthy patients admitted with unexplained hypotension, bradycardia, and other rhythm disturbances, and patients eating honey from the Black Sea region of Turkey must be examined carefully. Inquiry should be made about the possibility of honey ingestion. In difficult cases, microscopic identification of *R ponticum* pollen tetrads and chromatography for toxins are needed. Close surveillance and symptomatic treatment should be carried out, and physicians should be alert to sudden worsening of bradycardia and progressive conduction disturbances.

Previous studies have stated that patients have been monitored by admission to coronary intensive care units, and in our view, it will be possible for such patients to be treated in EDs with the appropriate means. Thus, the monitoring and admission of patients to intensive care units will be prevented, coronary intensive care units will be prevented from being used for other purposes, and the relevant costs will be avoided. But a series of more cases will be needed for this.

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