

Mad Honey Poisoning: A Review

Rakesh Gami^{1*} and Prajwal Dhakal²

¹All Saints University, St. Vincent and The Grenadines

²Michigan State University, East Lansing, MI, USA

*Corresponding author: Rakesh Gami, Assistant Professor, Department of Epidemiology, College of Medicine, All Saints University, St. Vincent and The Grenadines, Tel: +1-443-854-8522; E-mail: gamirakesh@gmail.com

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Abstract

Mad honey, which is different from normal commercial honey, is contaminated with grayanotoxins and causes intoxication. It is used as an alternative therapy for hypertension, peptic ulcer disease and is also being used more commonly for its aphrodisiac effects. Grayanotoxins, found in rhododendron plant, act on sodium ion channels and place them in partially open state. They also act on muscarinic receptors. Cardiac manifestations of mad honey poisoning include hypotension and rhythm disorders such as bradycardia, nodal rhythm, atrial fibrillation, complete atrioventricular block or even complete heart block. Additionally, patients may develop dizziness, nausea and vomiting, weakness, sweating, blurred vision, diplopia and impaired consciousness. Diagnosis is made with history of honey intake and clinical presentation. Treatment is symptomatic. Patients presenting with severe hypotension and bradycardia may need prompt treatment with fluids, atropine or even temporary pacing if other measures fail. Although fatalities are rare, poisoning may be hard to recognize and arrhythmias may be life-threatening.

Keywords: Mad honey; Grayanotoxin; Poisoning; Clinical event

Introduction

Honey use in folk medicine dates back to 2100-200 BC. Historically, it has been used for gastritis, peptic ulcer disease, hypertension, wound healing, cold, and diabetes. Modern scientific literature suggest potential health benefits of honey as an antihypertensive [1], antidiabetic, antioxidant [2], hepatoprotective [3], cardioprotective [4], antitussive, anti-bacterial [5], antiviral [6], anti-fungal [7], anti-inflammatory [8], and antitumor [9] agent.

Mad Honey is Different from Common Commercial Honey

It is contaminated with grayanotoxin, which causes intoxication. This grayanotoxin is found in rhododendron plants in various places such as Turkey, China, Tibet, Nepal, Myanmar, New Guinea, Japan, Indonesia, Philippines and North America [10]. Mad honey produced in spring is more toxic and contains more grayanotoxin than that produced in other seasons and has a sharp and biting taste which is irritating to throat [11,12]. Mad honey is used for purposes different than common honey including peptic ulcer disease, hypertension, and as a sexual stimulant. Nowadays, it is being used more commonly for its aphrodisiac effects. Cases of mad honey intoxication are being increasingly reported from all over the world including the western hemisphere and the original source of honey usually tracks back to Black sea region of Turkey or Nepal [13-15]. This suggests widespread use of mad honey indicating its global demand and popularity. However, it should be noted that the commercial honey is safe and even if there is any contamination, the mass production dilutes the toxin quantities.

At the cellular level, these biological toxins act on ion channels and have the capability of modifying the function of these channels.

Grayanotoxin binds the voltage-dependent sodium (Na) channel of excitable cells from the inside of the cell [16] in its open state [17]. The receptor consists of the S6 transmembrane segments of four homologous domains facing the ionconducting pore [18]. The affinity of the grayanotoxin to the Na channel is regulated by two residues (PhePhenylalanine and TyrTyrosine) which respectively control the access and binding of the toxin to its receptor [18]. After binding to the receptors, grayanotoxin prevents inactivation of Na channel and thus, increases the membrane permeability of Na channels and the membrane potential moves in direction of hyperpolarization [18]. Na channels from skeletal muscle are more sensitive to grayanotoxin than those from cardiac muscle [19].

Grayanotoxin also has muscarinic effects. In a study, atropine reversed the bradycardia and respiratory depression due to grayanotoxin, while AF-DX 116, a selective muscarinic-2 (M2) receptor antagonist, only reversed bradycardia but not the respiratory depression. This suggested that bradycardia of grayanotoxin is mediated via M2 receptor but the respiratory effect is not [20]. For the same level of bradycardia and respiratory depression smaller doses of the toxins were required when injected intraventricularly than intraperitoneally; suggesting that the site of action for cardiac and respiratory effects are within the central nervous system. Bradycardia was not observed after bilateral vagotomy suggesting the involvement of the vagal pathways [20].

Different types of grayanotoxin have different effects on the heart. Grayanotoxin I is the main toxin responsible for cardiac manifestations [17,21] and affects both sinoatrial (SA) node and atrioventricular conduction. Grayanotoxin II is less toxic than I and III. Grayanotoxin II suppresses the spontaneous beating of the SA node. It produces an inhibitory action on the electrical activity of the SA node cell by increasing the membrane permeability to Na ions and thus hyperpolarizing the cells. This results in inactivation of the slow inward current. As the slow inward current becomes small, the activation of the outward current may be reduced [22].

Grayanotoxin III is mainly thought to produce arrhythmia. In a study on feline cardiac Purkinje fibers, grayanotoxin III produced either [1,2] low amplitude or repetitive, suprathreshold after potentials within 15 minutes of administration. Increasing stimulation frequency, raising extracellular calcium concentration or lowering extracellular potassium concentration, each of which augments triggered activity, enhanced the production of grayanotoxin III-induced after potentials.

Verapamil (a calcium channel blocker), by raising extracellular potassium concentration, each of which blocks triggered activity, suppressed after-potentials elicited by grayanotoxin III. Thus, grayanotoxin III-induced arrhythmias are the product of triggered activity in the form of oscillatory after-potentials [23] doors. But next day none had died and recovered their senses at the same h and on the third and fourth day they recovered completely after medical treatment” [24].

Mad honey poisoning presents with features of cholinergic toxicity, though not a classic cholinergic toxidrome. The signs and symptoms can seem life threatening but are rarely fatal.

The symptoms generally last less than 24 h as the grayanotoxin is metabolized and excreted within 24 h [25]. With increasing amount of acute ingestion, toxic effects appear to be more severe. Also, grayanotoxin is not homogeneously distributed within honey leading to a different level of intoxication in different patients.

It is reported more in males; the mean age is between 50-60 years. The reason behind the most common age group might be due to its use as a sexual stimulant and also a higher prevalence of hypertension in this age group. The amount of honey needed for intoxication is 15-30 g and symptoms appears with 30 minutes to 4 h [25-30]. The amount of mad honey needed to produce intoxication not only depends on the amount but also on the concentration of grayanotoxin in the honey and the season in which it is produced. The course and severity of clinical symptoms depend on individual sensitivity to the toxin. The symptoms; nausea, vomiting, second-degree heart block and nodal rhythms were more frequent and severe in males than females [31]. Long-term consumption rather than single dose may result in a various degree of desensitization of sodium channel in excitable cells which itself prevents dramatic symptomatic presentation [32].

Author	Total patient	Hypotension	Bradycardia	Fainting or Syncope	Nausea/Vomiting	Sweating	Dizziness
Biberoglu et al. [41]	16	16	0	0	0	0	0
Bostan et al. [27]	33	3	30	4	27	16	26
Chang et al. [14]	15	15	15	46	0	0	0
Gunduz et al. [11]	8	8	8	0	0	0	0
Gunduz et al. [28]	47	0	37	0	0	0	0
Hasan et al. [26]	21	14	0	5	18	18	21
Kati et al. [31]	45	41	42	8	28	5	0
Ozhan et al. [25]	19	16	19	0	0	0	0
Sutlupmar et al. [42]	11	11	0	0	0	0	0
Uzun et al. [43]	46	40	28*	4	0	0	0
Yavuz et al. [44]	23	23	22	5	21	17	17
Yilmaz et al. [29]	66	0	58	12	21	0	66

Table 1: Cardiac sign and symptoms of mad honey poisoning.

The cardiac manifestations of the grayanotoxin are the main reason for hospital admission in mad honey poisoning (Table 1 and Table 2). The most common presenting feature is syncope.

Hypotension and bradycardia are most common physical finding. The stimulation of the afferent cardiac branches of the vagus nerve leads to a tonic inhibition of central vasomotor centers leading to reduced sympathetic output causing bradycardia, peripheral vasodilation, and hypotension. Patients may also present with chest tightness or heaviness and ST changes including ST elevation on electrocardiogram mimicking acute coronary syndrome. This is due to hypotension and bradycardia causing decreased blood supply to coronary artery bed leading to decreased oxygen supply to the

myocardium. Cardiac arrhythmias including sinus bradycardia (commonest), nodal rhythms and atrioventricular block can also occur. This is thought to be due to direct stimulation of afferent vagal nerve fibers causing tonic inhibition of the vasomotor center leading to reduced sympathetic output and vagal inhibition on sinus node function. Another possible mechanism is M2 mediated bradycardia. The degree of bradycardia is dose dependent [17]. Cases of atrial fibrillation, left bundle branch block with extreme QT prolongation, second-degree heart block, and even asystole have also been reported [33,34]. Till date, only one case of paediatric mad honey poisoning has been reported in which the patient presented with sinus bradycardia [35].

Author	Patient in series	Sinus Bradycardia	Nodal/junctional Rhythm	AV block	Wolff-Parkinson-White	Atrial Fibrillation	Second heart block	Brady-arrhythmia
Biberoglu et al. [41]	16	9	5	1	1	0	0	0
Bostan et al. [27]	33	30	0	0	0	0	0	0
Chang et al.(14)	15	8	4	2	0	1	0	0
Gunduz et al. [11]	8	4	3	1	0	0	0	0
Gunduz et al. [28]	47	0	0	1	0	0	0	0
Hasan et al. [26]	21	7	3	0	0	1	0	0
Kati et al. [31]	45	38	2	0	0	0	2 (Mobitz type 1)	0
Ozhan et al. [25]	19	0	0	4	0	0	0	0
Sutlupmar et al. [42]	11	0	0	0	0	0	0	7
Uzun et al. [43]	46	28*	0	1	0	0	0	0
Yavuz et al. [44]	7	7	0	0	0	0	0	0

Table 2: Summary of rhythm disorder of mad honey poisoning from case series/reports (* Heart Rate <45).

Additionally, there may be gastrointestinal as well as neurological symptoms such as dizziness, nausea, and vomiting, generalized weakness, sweating, mental confusion or impaired consciousness, diplopia and blurred vision (Tables 1 and 2). Few patients may also present with excessive salivation. In the central nervous system, neurons maintained at a state of depolarization can result in convulsion. Some study in animal also showed, respiratory depression, liver toxicity (transaminitis, hepatic central vein dilation, congestion, focal necrosis, inflammatory cell infiltration in hepatic portal triad and parenchyma) and renal toxicity (hematuria, proteinuria) and effect on blood sugar [36]. However, no such effects have been noted in human yet.

Diagnosis

The diagnosis of mad honey intoxication is mainly clinical. It should be suspected in any patient without prior heart disease, who presents with hypotension and bradycardia after honey consumption. Grayanotoxin intoxication from intake of other parts of a plant of Ericaceae family: leaves, flower, bark or root also can present with symptoms similar to mad honey intoxication. Mad honey intoxication from commercial honey is rare because commercial honey is collected from many sources, which helps in dilution of the toxin if present in any sample.

ECG should be done to check for cardiac rhythm abnormalities or cardiac ischemia. An ischemic change is more commonly seen in a patient presenting with chest pressure. A coronary angiogram, which is normal in mad honey poisoning, might be indicated to rule out acute coronary syndrome. Estimation of cholinesterase enzyme level in serum can be done to rule out organophosphate poisoning, which has a similar presentation of cholinergic excess. The enzyme level is not affected by mad honey poisoning [37].

There is no widely available commercially laboratory test for the diagnosis. However, detection of grayanotoxin in honey can be done in suspected cases by paper electrophoresis [38] or thin layer chromatography [39]. Gas chromatography and gas liquid chromatography are also used as grayanotoxin is heat labile compound and has low vapor pressure. Other advanced technologies for detection are based on infrared, nuclear magnetic resonance and liquid-chromatography-mass spectrometry. Occasionally, detection of pollen grains of rhododendron flower (which is rich in grayanotoxin) in honey may also provide corroborative evidence for mad honey poisoning.

Treatment

The signs and symptoms of intoxication last for about 24 h if left untreated. Patients then gradually recover their mental status and vital signs although it may take few days for complete recovery.

Mad honey poisoning is usually treated symptomatically. Mild hypotension and dizziness respond to normal saline infusion. Atropine is the treatment of choice for the patient with bradycardia and severe hypotension. The dose required is generally 0.5-2 mg. Antiplatelet therapy is not required in these patients even if they present with acute coronary syndrome because the pathophysiology is decreased oxygen supply to the heart secondary to bradycardia or hypotension and their coronaries are usually clean. In an unusual case which does not respond to atropine and normal saline, temporary cardiac pacing might be indicated until the toxin washed out of the system. Till date, temporary transvenous pacemaker use has been reported in two patients because of complete heart block and asystole [28,40].

In one study, no difference was observed in morbidity or mortality between patients observed briefly in emergency department versus patients admitted for a day. Six-hour monitoring was sufficient for a stable patient and did not require hospital admission [28].

Prognosis

The prognosis of mad honey intoxication is very good, although the presenting symptoms may seem life threatening. Almost every patient responds to symptomatic treatment. No case fatality report has been found in the modern medical literature. But there were few case fatalities in case series from the 1800s AD when atropine and normal saline were not available.

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