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REVIEW

Clinical review of grayanotoxin/mad honey poisoning past and present

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Grayanotoxin is a naturally occurring sodium channel toxin which enters the human food supply by honey made from the pollen and nectar of the plant family Ericaceae in which *rhododendron* is a genus. Grayanotoxin/mad honey poisoning is a little known, but well studied, cholinergic toxidrome resulting in incapacitating and, sometimes, life-threatening bradycardia, hypotension, and altered mental status. Complete heart blocks occur in a significant fraction of patients. Asystole has been reported. Treatment with saline infusion and atropine alone is almost always successful. A pooled analysis of the dysrhythmias occurring in 69 patients from 11 different studies and reports is presented. The pathophysiology, signs, symptoms, clinical course, and treatment of grayanotoxin/mad honey poisoning are discussed. In the nineteenth century grayanotoxin/mad honey poisoning was reported in Europe and North America. Currently, documented poisoning from locally produced honey in Europe or North America would be reportable. Possible reasons for this epidemiologic change are discussed.

Keywords Grayanotoxin; *Rhododendron*; Mad honey; Andromedotoxin

Introduction

Mad honey poisoning is little known outside of Turkey, but it is a well described condition presenting with incapacitating and, sometimes, life threatening bradycardia, hypotension, respiratory depression, and altered mental status. Poisoning occurs when grayanotoxin from the pollen and nectar of certain members of the family *Ericaceae*, especially *Rhododendron* L. species, enters the human food supply as "deli balı" (in Turkish) or "mad honey" (1, 2).

Mad honey poisoning is frequently reported in the Eastern Black Sea region of Turkey (1, 3–5). It was also well described in North America and Europe 100 years ago (6, 7). It is currently rarely reported outside Turkey and even when occurring in Europe the poisoning has been from honey produced in Turkey (8,9). The reasons for the change in distribution of grayanotoxin/mad honey poisoning are debatable.

The pathophysiology, signs, symptoms, clinical course, and treatment of grayanotoxin/mad honey poisoning are well understood. The recognition of this cholinergic toxidrome by a physician practicing in areas where this poisoning is uncommon could be life saving.

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Ancient history

Mad honey poisoning was first described in 401 BC by Xenophon, an Athenian author and military commander (10). In The Anabasis, his report of the campaign against the Persian King Ataxerxes II, he describes an episode of mad honey poisoning which incapacitated his army as they traveled through the Black Sea Region of Turkey (10).

Mad honey was used as a weapon by King Mithradates IV of north-east Anatolia, Turkey against Pompey the Great in 67 BC. On the advice of his chief adviser, the Greek physician Kateuas, Mithradates IV made a tactical retreat leaving mad honey containing honey combs in the path of the advancing Roman troops who consumed the honey. The Romans, thus incapacitated, were easily overcome (10).

Classic works on honey poisoning in the Europe and North America

Grayanotoxin/Mad Honey poisoning was well documented in nineteenth century Europe and North America. A 1999 issue of the British Medical Journal reprinted a 1899 British Medical Journal article which described a typical case of mad honey poisoning. Cases from the United States and Germany were discussed in the same article (7).

In 1896, Kebler reviewed honey poisoning in the United States (6). This review may have been precipitated by the eight cases of honey intoxication which occurred in Princeton, New Jersey, during the preceding year. He also reported earlier studies in his article. According to Kebler, Barton was

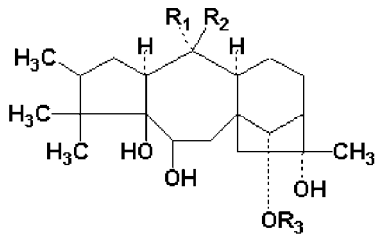
the first American to report the effects of honey intoxication. Barton first read his findings at a meeting of the American Philosophical Society in 1794 and later published his work in 1802. Kebler also quoted the 1853 work of Coleman. Coleman had a series of 14 patients from New Jersey with honey intoxication. In that series one patient died. There was another series in Branchville, SC. In that series there were 23 patients who were poisoned and three died. By 1891, Plugge had examined a number of plants from the *Ericaceae* family and had isolated andromedotoxin in many of them. Andromedotoxin was later shown to be identical to grayanotoxin (11).

What is grayanotoxin?

Grayanotoxins are diterpenes; polyhydroxylated cyclic hydrocarbons that do not contain nitrogen (2). They occur in the nectar, pollen, and other plant parts in some members of the family *Ericaceae* such as *Rhododendron* L. The genus *Rhododendron* is represented by six species in Flora of Turkey (12,2). In Turkey, the commonly found toxic *Rhododendron* species are *Rhododendron luteum* L. and *R. ponticum* L. (12,13) (Fig. 1, Fig. 2). The toxicity of these plants is often attributed to the grayanotoxins included in their flowers. The honey guide is on the upper corolla lobe (sometimes also on the adjacent lobes) and pollinating bees receive pollen on their undersides from the declinate stamens as they alight on the lower lobes (12). In the western United States, toxic *Rhododendron* species are the western azalea (*R. D. Don ex G. Donoccidentale Torr. & A. Gray*), the California rosebay (*R. macrophyllum* D. Don ex G. Don.), and *R. albiflorum Hook*. In the eastern part of North America, the mountain laurel (*Kalmia latifolia L.*) and sheep laurel (*Kalmia angustifolia L.*) are sources of grayanotoxin (2). There are at least 60 different grayanotoxins (14), but the primary toxic compounds are grayanotoxins I and III (4, 14, 15). The common structure of grayanotoxin is given in Fig. 3 (16).

Fig. 1. The purple colored *Rhododendron ponticum* is also known as the "mountain rose".

Fig. 2. The yellow colored *Rhododendron flavum*, also known as *Rhododendron flavum*.



GRAY	R_1	R_2	R_1R_2	R_3
GRAY1	OH	CH_3	-	H
GRAY2	-	-	$=CH_2$	H
GRAY3	OH	CH_3	-	Ac

Fig. 3. Chemical formula of grayanotoxin (16).

How does grayanotoxin get into honey?

When bees ingest nectar containing grayanotoxin, the grayanotoxin, along with the other components of nectar is included in the honey which is produced. The complex sugars in nectar are enzymatically broken down into glucose and fructose in the bees' second stomach (17, 18). The honey is then secreted by the bees into the honeycomb. Here forced evaporation removes water from the honey and concentrates all the components of the honey (19).

Modern experimental work

The role of the central nervous system, vagus nerve, and muscarinic receptors in grayanotoxin poisoning

In animal studies, Onat et al. (20) determined that the respiratory and cardiac effects of grayanotoxin occur within the

central nervous system, rather than at a peripheral site. She evaluated the doses of grayanotoxin needed to produce bradycardia and respiratory depression in rats. Very small doses delivered intracerebroventricularly yielded the same physiologic effects as much larger doses delivered intraperitoneally (20). In the same study, Onat et al. (20) discovered that bilateral vagotomy abolished the bradycardic effect of grayanotoxin. She concluded that the bradycardic effect of grayanotoxin is mediated peripherally by the vagus nerve. In another rat study, Onat et al. (21) observed that atropine, a non-specific anti-muscarinic agent, improved both grayanotoxin induced bradycardia and respiratory depression. AF-DX 116 is a selective M_2-muscarinic receptor antagonist. When she administered AF-DX 116 to grayanotoxin poisoned rats, bradycardia was abolished but respiratory depression was unaffected. She concluded that M_2-muscarinic receptors are involved in the cardiotoxicity of grayanotoxin.

The effects of grayanotoxin at a cellular level

The toxic cellular effect of grayanotoxins is on the sodium channel. The work of a number of researchers was summarized by Maejima et al. (22). They stated that grayanotoxin has three actions on the voltage-dependent sodium channel. First, grayanotoxin binds to the voltage-dependent sodium channel in its open state. Second, the modified sodium channel is unable to inactivate. Third, the activation potential of the modified sodium channel is shifted in the direction of hyperpolarization.

The effects on renal and hepatic tissue and glucose metabolism

High doses of grayanotoxin I administered to rats caused proteinuria and hematuria, but no histologic changes in renal parenchyma. In the same study, transaminases were elevated and there were also significant changes in hepatic central vein dilation, congestion, focal necrosis, inflammatory cell infiltration in the hepatic portal triad and parenchyma (15). In experimentally produced diabetes, grayanotoxin served to normalize blood sugar in diabetic rats (23).

Clinical course of grayanotoxin/mad honey intoxication – A cholinergic toxidrome

The manifestations of grayanotoxin/mad honey intoxication is not a classical cholinergic toxidrome but its may be understood as a cholinergic toxidrome.

Xenophon provides a vivid picture of the clinical manifestations of mad honey intoxication.

> "Here, generally speaking, there was nothing to excite their wonderment, but the numbers of bee-hives were indeed astonishing, and so were certain properties of the honey. The effect upon the soldiers who tasted the combs was, that they all went for the nonce quite off their heads, and suffered from vomiting and diarrhea, with a total inability to stand steady on their legs. A small dose produced a condition not unlike violent drunkenness, a large one an attack very like a fit of madness, and some dropped down, apparently at death's door. So they lay, hundreds of them, as if there had been a great defeat, a prey to the cruelest despondency. But the next day, none had died; and almost at the same hour of the day at which they had eaten they recovered their senses, and on the third or fourth day got on their legs again like convalescents after a severe course of medical treatment." Xenophon (24).

Although less poetic, a letter by Yavuz et al. provides detailed, clinically useful information on the manifestations of mad honey poisoning in their series of 23 patients (4). Their findings are summarized in Table 1. Table 2 summarizes the findings of the larger series of 66 patients reported by Yilmaz et al (5).

Mad honey poisoning has, many but not all, of the symptoms and signs of a cholinergic toxidrome and responds to atropine, as do other cholinergic toxidromes (25). Significant hypotension (mean systolic blood pressures of 70 mmHg) and bradycardia (mean pulse rate of 48 beats/minute) were the

Table 1. Signs and symptoms of grayanotoxin/mad honey poisoning reported by Yavuz et al. (4)

Symptom or sign	Percentage of patient
Hypotension	100
Bradycardia	95
Nausea or Vomiting	91
Sweating	74
Dizziness	74
Impaired consciousness	67
Fainting	30
Burred vision or diplopia	22

Table 2. Quantitative findings in grayanotoxin/mad honey poisoning reported by Yilmaz et al. (5)

Variables	Findings
Age	51.95 ± 14.99 (18–85)
Sex	Male 80.3%
Amount of honey ingested	13.45 ± 5.39 (5–30)g
Time to symptom onset	1.19 ± 0.65 (0.5–3) h
Dizziness	100%
Weakness	100%
Cloudy vision	88%
Nausea	45.4%
Vomiting	31.8%
Syncope	17.6%
Salivation	4.7%
Systolic blood pressure	70.08 ± 14.89 (50–100) mm Hg
Diastolic blood pressure	45.25 ± 12.91 (30–60) mm Hg
Pulse rate	47.96 ± 8.48
Pulse rate less than 60/min	87%
Pulse rate less than 50/min	55.3%

most frequent manifestations (5). These occurred over 90% of the time (4). Diaphoresis, dizziness, and altered mental status were the next most frequent symptoms occurring about 70% of the time (4, 5). Syncope occurred about 30% of the time. Visual symptoms of blurred vision and or diplopia were reported 20–80% of the time (4, 5). Salivation was reported 14% of the time in one series (5). Lacrimation, urination, bronchorrhea and miosis have not been reported (1, 4, 5, 26).

Cardiac dysrhythmias were prominent in the 11 different series and case reports that are summarized in Table 3 (1, 3, 4, 8, 9, 21, 26–30). Either a nonspecific bradyarrhythmia or a sinus bradycardia were reported in about 75% of cases. Heart blocks of varying degrees were present in 25% of patients. Nodal rhythms were present in 11% of patients while 8.7% of patients had a complete heart block and 2.9% had a second degree heart block. One patient had asystole (1.45%). Another patient was reported as having Wolff-Parkinson-White (WPW) syndrome, which is most likely unrelated to the intoxication.

Although reported in animal studies (14, 23), clinically significant alterations in blood glucose, renal, and hepatic toxicity were neither reported nor specifically studied in human case series (1, 4, 5).

Toxic dose and duration of illness

The amount of honey needed to produce toxicity is rather small. The average amount of ingested honey in one report was 13.45 ± 5.39 (5–30 g). Symptoms began one-half to three hours after ingesting the honey (5). Several sources report that the honey has an unusual sharp, biting taste (1, 28).

In untreated cases of severe intoxication, the worst signs and symptoms last about 24 hours. By the end of that time, the patient is alert and vital signs are normal. Complete recovery may takes several more days (6, 24, 26). The exact duration of symptoms has not been carefully documented, but one investigator was able to safely discharge mild cases of mad honey poisoning after 2–6 hours of cardiac monitoring (1). In the modern medical literature there has not been a detailed study of the duration of individual signs and symptoms in severe grayanotoxin/mad honey poisoning.

Treatment

As with other cholinergic toxidromes, treatment with atropine can be life-saving (1, 4, 5, 30).

Although symptoms and signs can be alarming, and sometimes life-threatening, usual supportive care with electrocardiographic monitoring, normal saline infusion and intravenous atropine resulted in no fatalities in 66 cases of mad honey intoxication (5). A number of cases of compete heart block have been recorded (1, 3, 26, 29). One patient required a temporary transvenous pacemaker because of complete heart block (2). One patient developed asystole which was treated successfully with atropine (30). In the unusual case when atropine and intravenous saline are not adequate, Advanced Cardiac Life Support (ACLS) bradyarrhythmia protocols should be considered.

Mortality

In a classic case series from the 1800s, when intravenous atropine and normal saline were not available, there was a significant mortality rate; 1/14 (7%) in one series and 3/23 (13%) in another series (6). There has been no modern report of a fatality from mad honey poisoning (1, 3, 5).

Table 3. Summary of cardiac dysrhythmias occurring in 69 patients from 11 series or case reports

Author	Patients in series	Non-specified brady-arrhythmia	Sinus brady cardia	Nodal rhythm	Wolff-Parkinson-White	Second degree heart block	Complete AV block	Asystole	Honey source
Number of Patients	69	13	37	8	1	1	7	1	69
Percentage		18.8%%	54%	11.6%	1.45%	1.45%	8.7%	1.45%	
Von Malottki and Wiechmann	1		1						Turkish honey
Biberogul et al.	16		8	5	1		1		Eastern Black sea
Yavuz et al.	7		7						Central Black Sea
Sutlupinar et al.	11	11							Black Sea
Gossinger et al.	2	2							Turkish Honey
Dilber et al.	1		1						Eastern Black Sea
Ozhan et al.	19		15				4		Western Black Sea
Kumral et al.	1						1		Eastern Black Sea
Gunduz et al.	8		4	3			1		Eastern Black Sea
Gunduz et al.	1							1	Eastern Black Sea
Onat et al.	2		1			1			EasternBlack Sea

A change in the geographic distribution of human grayanotoxin/mad honey poisoning

The classical medical literature has a number of reports of toxic honey in North America and Europe (6,7). However, all cases of mad honey poisoning in the modern medical literature are from the ingestion of honey produced in Turkey. There are rare anecdotal reports of mild to moderate illness, which possibly represent grayanotoxin/mad honey poisoning in current North American beekeeping and personal web sites (31). Why did this change in the geographic distribution of grayanotoxin/mad honey poisoning occur?

Table 4. Sources of grayanotoxin/honey toxic to humans reported by Adler (34)

Species	Family
Agauria spp.	Ericaceae
Andromeda spp.	Ericaceae
Kalmia spp.	Ericaceae
Rhododendron flavum (Rhododendron luteum)	Ericaceae
Rhododendron ponticum	Ericaceae
Kalmia latifolia	Ericaceae

Cultural factors

Cultural factors are certainly involved. Some Turkish beekeepers purposely harvest mad honey for use as an alternate health product. In Turkey mad honey used in small quantities is widely believed to promote general health, is used as a pain reliever, is used for treatment of abdominal pain and dyspepsia, and is felt to be a sexual stimulant (1). Since the amount of grayanotoxin in mad honey is variable, accidental poisoning from intentional ingestion may occur (32).

Honey production techniques

Although there are large commercial honey packers in Turkey, a significant fraction of honey in the North East of Turkey is sold by individual bee keepers in local markets. This may occur more frequently in Turkey than in North America or Europe. The individual beekeeper's hives produce honey from flowers in a 5 km^2 area around the hives (28). If the area in which the hives are located contains a large number of toxic *rhododendron* species, toxic honey may result. Commercial honey packers receive honey from thousands of hives; therefore, toxin coming from any one hive is diluted (2). Also, the honey sold by an individual bee keeper is often unprocessed. Commercially processed honey is usually heated to retard later crystallization and to kill yeast spores (17). Since grayanotoxin may be heat labile commercial processing of honey with heat may destroy grayanotoxin in honey (33). The amount of heat needed to destroy grayanotoxin is not known with certainty.

Different nectar producing plants?

Grayanotoxin producing plants are not unique to Turkey. Toxic *Ericaceae* are wide spread in North America, Europe, and Asia (2). However, the toxic *Ericaceae* may not be present with great enough density outside of Turkey to produce toxic honey. Sources of honey toxic to humans are given in Table 4 (34). The number of *Rhododendron* spp. growing on the hills and mountains of eastern Turkey is quite impressive. These *Rhododendron* species threaten other commercial plant species (35).

Different bees?

It seems unlikely that the distribution of grayanotoxin/mad honey poisoning is explained by a difference between Turkish honey bees and honey bees in the rest of the world, because historically, the honey bees of Europe and North America were capable of producing mad honey (6,7).

Clinical application

Physicians in North America and Europe would encounter this rarely and that they should ask about foreign travel to Turkey or the ingestion of honey from that part of the world. Clinicians should consider the possibility of grayanotoxin/mad honey poisoning in patients that present with prominent bradycardia, heart blocks, hypotension, and altered mental status. Very likely nausea, vomiting, diaphoresis, dizziness, and prostration will be present. Syncope, blurred vision, and diplopia are possible. Lacrimation, urination, bronchorrhea, bronchospasm, and miosis, if present, would suggest an alternate diagnosis, as these signs have not been reported with grayanotoxin/mad honey poisoning.

Detection of grayanotoxin

The grayanotoxin can be isolated from the suspect commodity by typical extraction procedures for naturally occurring terpenes, especially using methods valid for the lower terpenes (36). Grayanotoxins, as diterpenes which are composed of four isoprene units having a molecular formula as $C_{20}H_{32}$ derived from geranylgeranyl pyrophosphate (GGPP), are less volatile than the sesquiterpenes and require some chromatographic techniques during detections. At the beginning of separation, paper electrophoresis (PE) and thin layer chromatography (TLC) is preferred for class separations. Gas chromatography (GC) and slightly different gas liquid chromatography (GLC) are often required, due to the compounds unstability (oxidize or decompose easily) on heating and having low vapor pressure during analyses. Hence, the compounds require derivatization before the GC or GLC analyses (23). Further identifications is largely based on infrared (IR), nuclear

magnetic resonance (NMR) and mass spectrometry (MS) (33, 36). In recent years, developed liquid-chromatography-mass spectrometry /mass spectrometry (LC-MS/MS) techniques are also in use in detection of the toxins in biological samples (36).

Conclusion

In a patient suspected of having grayanotoxin poisoning, the practitioner should obtain a detailed dietary history. The consumption of unprocessed honey produced and sold by a single beekeeper in an area with an unusually high concentration of toxic *Ericaceae* would be confirmatory. A sample of the suspected toxic honey should be saved for later identification of the pollen and toxin. The documented diagnosis of grayanotoxin/mad honey poisoning in Europe or North America from locally produced honey would be reportable.

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