Mad Honey Sex: Therapeutic Misadventures From an Ancient Biological Weapon

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Study objective: "Mad honey" poisoning occurs from ingestion of honey produced from grayanotoxin-containing nectar, often in the setting of use as an alternative medicine. This study is designed to assess the clinical effects, demographics, and rationale behind self-induced mad honey poisoning.

Methods: The study consisted of 2 components: a standardized chart review of the signs, symptoms, and treatment of patients with mad honey ingestion, treated in our emergency department between December 2002 and January 2008; and a cross-sectional survey of a convenience sample of beekeepers specializing in the production and distribution of mad honey.

Results: We identified 21 cases. Patients were overwhelmingly men (18/21) and older (mean [SD]), 55 [11] years. Local beekeepers (N=10) ranked sexual performance enhancement as the most common reason for therapeutic mad honey consumption in men aged 41 through 60 years. Symptoms began 1.0 hour (SD 0.6 hour) after ingestion and included dizziness, nausea, vomiting, and syncope. Abnormal vital signs included hypotension (mean arterial pressure 58 mm Hg [SD 13 mm Hg]) and bradycardia (mean 45 beats/min [SD 9 beats/min]). Seventeen patients had sinus bradycardia and 2 had junctional rhythm. Nine patients were treated with atropine; 1 patient received dopamine. All patients were discharged 18 to 48 hours after admission.

Conclusion: A dietary and travel history should be included in the assessment of middle-aged men presenting with bradycardia and hypotension. A mad honey therapeutic misadventure may be the cause rather than a primary cardiac, neurologic, or metabolic disorder. [Ann Emerg Med. 2009;54:824-829.]

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INTRODUCTION

Background

"Mad honey" is honey purposely derived from grayanotoxin-containing nectar of *Rhododendron ponticum*, a member of the Ericaceae family with particularly high concentrations of grayanotoxin. The ancient Greek general Xenophon published the first account of mad honey intoxication in 401 BC after his soldiers feasted on wild honeycombs in Asia Minor near the Black Sea.[1] All of Xenophon's soldiers recovered. Three hundred years later, the Roman general Pompey was not so fortunate. In 67 BC, his men were deliberately poisoned with grayanotoxin-contaminated honey, and 3 Roman cohorts (1,440 soldiers) were slaughtered by enemy forces while intoxicated.[2] The population of Roman citizens is estimated to be 1,250,000 during the time of Christ; the current population of the United States is more than 300,000,000. To place the massacre in a modern perspective, the same ratio of US military deaths would be approximately 345,600.

Along the Black Sea region of modern Turkey, mad honey is produced and marketed as an alternative medicine by beekeepers armed with a knowledge of local plant flora and familiar with the behaviors of native Caucasian honeybees.[3]

Importance

Grayanotoxin-containing plants are native to ecosystems throughout the world, including Japan, Nepal, Brazil, and parts of Europe.[3,4] There are a number of toxic species native to the United States. Of particular importance are *R occidentale*, *R*

Editor's Capsule Summary

What is already known on this topic

In certain communities, "mad honey"—honey made from plants containing high concentrations of grayanotoxin—is consumed for alleged medicinal purposes.

What question this study addressed

This single-site retrospective chart review assessed demographics, clinical effects, and treatment in 21 mad honey ingestions.

What this study adds to our knowledge

Mad honey poisoning most commonly involved middle-aged men and was manifested by nausea, vomiting, blurred vision, weakness, perioral paresthesia, bradycardia, hypotension, and syncope. Patients appeared to respond well to administration of atropine and were discharged 18 to 48 hours after admission.

How this might change clinical practice

Physicians should consider this toxin when treating patients who present with bradycardia and hypotension and are from regions with grayanotoxin-containing nectars.

macrophyllum, and *R albiflorum*, species found in a wide swath of North American territory from British Columbia to Oregon and southern California.[4] The majority of published cases of mad honey poisoning occur in Asia Minor.[4] The popular use of mad honey for self-treatment of disease has resulted in a series of grayanotoxin-poisoned patients presenting to our emergency department (ED) of Gazi University Hospital, Ankara, Turkey.

Goals of This Investigation

The primary goal of this study was to describe the clinical and demographic features of adults poisoned by a mad honey therapeutic misadventure. A secondary goal was to formally assess and rank the clinical reasons behind mad honey self-treatment. We explored reasons why older men predominate in symptomatic mad honey ingestions. To our knowledge, this is the first formal investigation into the rationale behind traditional mad honey treatment after centuries of use and abuse of this ancient folk medicine.

MATERIALS AND METHODS

Study Design

This study consisted of 2 components: a retrospective case review and a cross-sectional survey of a convenience sample of mad honey beekeepers.

Setting

The case series portion of the investigation was conducted at an urban university teaching hospital with 35,000-40,000 ED visits annually. The authors extracted clinical data from ED and inpatient medical records. The data collection methodology followed all ethical principles, as outlined in the Declaration of Helsinki.[5]

The survey portion was performed during a 680-mile excursion from our ED based in Ankara to the Trabzon Province, the classic area of mad honey production.

Selection of Participants

Case records of symptomatic patients treated for acute mad honey poisoning in our tertiary care university ED between December 2002 and January 2008 were reviewed. Patients' medical records were identified "tagged" (prospective convenience sampling) by authors based at Gazi University Medical Center. After the study period was completed, the records were pulled for a standardized retrospective chart review.

Patients presenting with bradycardia, hypotension, nausea, vomiting, or near syncope were questioned about recent dietary or medicinal ingestions. Patients of any age admitting to the consumption of grayanotoxin-contaminated honey shortly before ED presentation were included. Patients with a coingestion or an alternative diagnosis were excluded from study. Alternative diagnoses were ruled out by history, physical examination, observation, and laboratory analysis.

We formally surveyed local beekeepers who produce and market mad honey to the general public as an alternative medicine (reasons for ingestion were not documented in the medical records). The area selected for seeking out mad honey beekeepers was the Turkish province of Trabzon, a diminutive but historically important area comparable in size to Rhode Island. The 90-km expedition was planned and executed on the northern slopes of the Pontus Mountains, known to have a rich concentration of *R ponticum*, the main grayanotoxin source for mad honey. The search for beekeepers was conducted in the vicinity of the Zigana Pass, an ancient route through the Pontus Mountains taken by Xenophon and his soldiers.[6] This region was selected because it is "ground zero" for beekeepers in the production and distribution of mad honey.

Methods of Measurement

Case series demographic data, clinical symptoms, vital signs, and treatments administered to mad honey patients were recorded. Other causes (cardiac, neurologic, metabolic) were ruled out as alternative diagnoses of clinical presentations. We extracted specific elements of mad honey presentation, including demographics, symptom onset time, ED presentation time, vital sign measurements, medications administered, and recovery period. The vital signs recorded for the study were the initial vital signs recorded in the ED triage area. Subsequent vital signs were reviewed to accurately record the period required for full recovery. "Recovery time" was defined as the

Table 1. Combined clinical features of mad honey to date.

Author	Cases	Sex	% Male	Age, y, Mean	HR, Mean	Systolic Blood Pressure, mm Hg, Mean	Rhythm	Honey Ingestion, g, Range	Recovery Time,* Mean
Present series	21	18 M, 3 F	85.7	55	45.1	78.6	17 SB, 1 AF, 2 JR, 1 LBBB	50–300	23.4 h
Yilmaz[9]	66	53 M, 13 F	80.3	51	47.9	70	66 SB	5–30	24 h
Yavuz[11]	23	21 M, 2 F	91.3	7 mo–61 y (Range)	NA	NA	14 SB, 7 JR, 2 AVB	10–25	24–48 h (Range)
Ozhan[12]	19	12 M, 7 F	63.2	40	41	78	15 SB, 4 AVB	30–180	24 h
Biberoglu[13]	16	14 M, 2 F	87.5	41	NA	NA	12 SB, 3 JR, 1 AVB	50	24 h
Sütlüpinar[14]	11	11 M	100	36–58 y (Range)	NA	NA	11 SB	5–100	1–5 Days (range)
Gunduz[7]	8	2 M, 6 F	25	58	40.9	81.3	4 SB, 1 AVB, 3 NR	20–150	18.5 h
Gossinger[15]	2	2 M	100	NA	NA	NA	2 SB	NA	24 h
Dilber[16]	1	1 M	100	NA	NA	NA	1 SB	NA	24 h
Kumral[17]	1	1 M	100	56	38	NA	1 AVB	NA	24 h
Von Malottki[18]	1	1 M	100	49	38	90	1 SB	NA	24 h
Gunduz[19]	1	1 M	100	60	NA	NA	Asystole	NA	NA
Akinci[20]	1	1 M	100	66	35	70	1 SB	NA	NA
Summary	171	138 M	80.7	49	44.6	73.4	144 SB, 12 JR, 9 AVB 6 (other)	5–300	23.5 h

M, Male patient; *F,* female patient; *SB,* sinus bradycardia; *AF,* atrial fibrillation with low ventricular rate; *JR,* junctional rhythm; *LBBB,* left bundle branch block; *NA,* numeric data not available; *AVB,* complete atrioventricular block; *NR,* normal sinus rhythm.
*Recovery time=time from ED presentation to normalization of signs and symptoms.

time required for complete resolution of mad honey symptoms and return to normalization of vital signs. The authors extracted the data by using a standard form. The investigators were not blinded to the history of mad honey ingestion.

In the survey portion of the study, mad honey beekeepers were asked the question, why do customers purchase your (mad) honey? They were provided with a set of 6 predetermined answers; the final (sixth) answer was the open-ended "other," for which beekeepers were asked to elaborate. The beekeepers were asked to assign a rank between 1 and 6 for the selected answers medical illnesses commonly used to purchase mad honey (including "other"). The 5 predetermined medical conditions chosen for the survery were culled from mad honey literature: diabetes (treatment of hyperglycemia or related complications), gastrointestinal (ulcers, gastritis, other discomfort), hypertension, sexual (impotence, dysfunction, performance enhancement), and arthritis.[4,7,8]

We asked beekeepers the same question with identical answer sets for both sexes and 3 age groups, young, defined as aged 21 to 40 years, middle-aged, defined as aged 41 to 60 years, and elderly, defined as aged 61 to 80 years, to determine whether the various groups self-medicated with mad honey for different reasons. The aim was to explore reasons why middle-aged men are overwhelmingly represented in mad honey case reports. The lead author administered the survey as an interview. Self-administration of the survey was not possible because most beekeepers do not have formal education; many are illiterate. The "head beekeeper" was interviewed at 10 separate mad honey beekeeper operations. The standardized survey was designed in consultation with the University of Michigan Center for Statistical Consultation and Research. Summary data, including mean, SD, and median rank were used for presentation of data acquired from both arms of this study.

RESULTS

Characteristics of Study Subjects

During the 6-year study period, 205,150 patients were treated in our ED. We identified 21 symptomatic patients who admitted to mad honey ingestion during the designated case review period. No patient had an alternative diagnosis. The average patient age (mean [SD]) was 55 (11) years (range 41 to 86 years) and most (85.7%) were men (Table 1). No pediatric patients presented with mad honey poisoning during the observation period. Virtually every patient presented with bradycardia and complaints of dizziness. Presenting complaints also included nausea, vomiting, sensation of motion, blurry vision, weakness, diaphoresis, perioral paresthesia, chest pain, near-syncope, and syncope. The amount of honey ingested by poisoned patients was extremely variable, ranging between 50

Table 2. Clinical features of mad honey poisoning.

Patient number	Age	Sex	Symptom time, h	ED arrival time, h	Recovery time, h	MAP mm Hg	Systolic blood pressure,mm HG	Pulse rate, beats/min	Atropine, mg	Deaths
1	52	M	2.5	4	24	73	100	54	0	0
2	52	M	1	2	24	60	80	50	0	0
3	66	M	1.5	2	24	40	60	32	0.5	0
4	46	M	0.5	4	18	50	70	58	0	0
5	50	M	0.5	2	24	67	80	35	1	0
6	70	F	1	2	48	50	70	51	0	0
7	59	F	1.5	3	36	47	60	48	1*	0
8	47	M	1	4	24	57	70	46	0	0
9	60	M	1	3	24	60	80	49	0	0
10	45	M	0.5	4	48	63	90	30	1	0
11	50	M	0.5	2	24	37	50	30	1	0
12	45	M	1	4	24	60	80	45	0	0
13	49	M	0.5	4	24	50	80	42	1	0
14	50	M	1	2	18	80	120	40	1	0
15	76	M	2	4	24	87	120	47	0.5	0
16	86	M	1	1.5	24	70	90	42	1	0
17	63	M	1.5	5	12	60	80	59	1	0
18	41	M	1.5	2	12	47	60	45	1	0
19	67	M	0.5	1.5	12	40	60	38	1	0
20	51	M	0.5	2	11	47	60	55	0	0
21	45	F	0.5	3	7	70	90	50	0.5	0
Summary, mean (SD)	55 (11)	18 M, 3 F	1. (0.5)	2.9 (1.0)	23.4 (10.5)	58 (13)	79(19)	45(9)	0.4(0.4)	None

MAP, Mean arterial pressure.
*Dopamine infusion.

and 300 g (Table 1). Symptoms began promptly (mean [SD]) 1.0 (0.6) hours after consumption of grayanotoxin-contaminated honey (range 0.5 to 2.5 hours) (Table 2). Patients presented to the ED 2.9 hours (SD 1.1 hours) after ingestion (range 1.5 to 5 hours) (Table 2).

Abnormal vital signs included low initial pulse rates (mean [SD]) of 45 (9) beats/min (range 30 to 59 beats/min) (Table 2). In all cases, the presenting pulse rate was below 60 beats/min. The initial systolic and diastolic blood pressures were 79 mm Hg (SD 19 mm Hg) and 48 mm Hg (SD 3 mm Hg) respectively (Table 2). The presenting mean arterial pressure was 58 mm Hg (SD 13 mm Hg) (Table 2). In all patients, CBC counts, blood chemistries, and cardiac enzyme test results were normal. Two patients had an atrioventricular junctional nodal rhythm, 1 patient had a new left bundle branch block, and 1 patient had atrial fibrillation with a low ventricular rate (Table 1). All bradycardic rhythms resolved within 24 hours. The patients with AV junctional nodal rhythm returned to normal sinus rhythm. However, the patients with left bundle branch block and atrial fibrillation had resolution of bradycardia, but the left bundle branch block and atrial fibrillation continued. We presume those patients had underlying conduction system disease unrelated to mad honey ingestion.

The grayanotoxin-poisoned patients responded to supportive care management. All were treated with intravenous normal saline solution at 100 to 200 mL/hour for approximately 24 hours. Three patients received 0.5 mg atropine intravenous and 10 patients, 1.0 mg of atropine (Table 2). The patients responded to atropine with increased pulse rate and normalization of blood pressure. There was one exception (Table 2); a 59-year-old woman was treated with dopamine after bradycardia and hypotension failed to respond to atropine. Most patients were observed entirely within the ED; however, 4 patients with severe bradycardia and hypotension were admitted to the coronary care unit because of suspected acute coronary syndrome. Patients began to recover as early as 7 hours after ED presentation, with a complete recovery time (mean [SD]) of 23.4 (10.5) hours (Table 2).

Survey responses from mad honey beekeepers are summarized in Table 3 in order of median rank. In men aged 41 to 60 years, treatment of sexual dysfunction was ranked first in importance for mad honey purchase and self-treatment. Beekeepers ranked treatment of gastrointestinal complaints and sexual performance as the first and second most common reasons, respectively, for mad honey consumption by both men and women aged 21 to 40 years and in women aged 41 to 60 years. This ranking was followed by traditional treatment of complications related to diabetes mellitus, arthritis, hypertension, and "other." Self-treatment of upper respiratory symptoms was most frequently cited in the "other" catagory. In the oldest age group (61 to 80 years), treatment of gastrointestinal complaints received the highest rank for mad

Table 3. Illnesses treated by mad honey according to beekeepers.*

Men	Women
21–40 y	
Gastrointestinal	Gastrointestinal
Sexual	Sexual
Arthritis	Diabetes
Other	Arthritis
Diabetes	Other
Hypertension	Hypertension
41–60 y	
Sexual	Gastrointestinal
Gastrointestinal	Sexual
Diabetes	Arthritis
Arthritis	Diabetes
Other	Hypertension
Hypertension	Other
61–80 y	
Gastrointestinal	Gastrointestinal
Diabetes	Diabetes
Arthritis	Arthritis
Other	Other
Sexual	Hypertension
Hypertension	Sexual

*Median rank (descending order) by age group and sex, N=10.

honey purchase by both sexes, whereas treatment for sexual performance decreased to last.

LIMITATIONS

This study contains limitations inherent to convenience sampling and retrospective case series. Investigators used memories of mad honey cases and searched medical records during the designated period. We cannot be completely certain that all mad honey cases were identified because manual searches of medical records are generally inefficient means of identifying records appropriate for study, and the ability to query computer-based databases evolved markedly during the study period. Thus, it is possible that only selected cases of a much larger group were reported in this series.

The therapeutic reasons for honey ingestion were not recorded in medical records. We surveyed the producers and vendors of mad honey because we were unable to ask patients retrospectively for reasons behind mad-honey self-treatment. Also, in Asia Minor it is not culturally acceptable for individuals to openly acknowledge the use of mad honey for sexual purposes, even on direct medical questioning. The survey portion of the study is limited by the potential of selection bias in identification of the beekeepers; the survey may not be reliable or valid in accurately measuring the outcome of interest.

DISCUSSION

An overwhelming number of patients were men and middle aged. The preponderance of middle-aged men has been reported previously,[9] but the reason for this has not been previously elucidated. In the largest mad honey case series to date, Yilmaz et al[9] found that of 66 patients, 80.3% were men with an average age of 51 years ($P<.001$; Z test of proportions). Previous commentary on the male preponderance has observed that the uneven sex distribution of reported cases "was difficult to explain."[9]

Mad honey has assumed a traditional role for the treatment of sexual dysfunction and sexual performance enhancement.[7] The primary ranking given to self-treatment of sexual dysfunction in men in the stratified age group 41 through 60 years is of particular interest, given that this age group is overwhelmingly represented in all reported mad honey case series to date (Table 3). Milligan et al[10] reported that average users of sildenafil (Viagra, Pfizer, New York, NY) for the treatment of erectile dysfunction are 58-year-old men. The average age in the case series reported herein is 55 years. In addition, other medical conditions treated traditionally with honey-contaminated grayanotoxin are diseases known to place patients at higher risk of erectile dysfunction, including diabetes mellitus (including diabetic neuropathy) and chronic hypertension.[8] Older male patients who consume grayanotoxin-contaminated honey for traditional treatment of diabetes mellitus or chronic hypertension would have mad honey immediately available for a situational need to self-treat sexual performance.

In our case series, and in those of patients previously described, symptomatic sinus bradycardia with hypotension is the most frequently reported mad honey–induced cardiac dysrhythmia (Table 3). Our patients generally responded to intravenous saline solution and parenteral atropine, although one patient was treated with dopamine infusion in addition to the above-described therapies. Overall, our patients reached complete recovery in a period similar to the cumulative mean recovery period reported in the literature (Table 3). The mean recovery period is also consistent with Xenophon's original 401 BC report of his mad honey–intoxicated soldiers in that ". . .the next day, no one of them was found dead; and they recovered their senses about the same hour they had lost them on the preceding day."[1]

The natural toxin icon Lampe[4] wrote in 1988 that "cases of mad honey poisoning should be anticipated everywhere," given potential searches for exotic foods such as natural unprocessed honey realized locally from endemic areas or from imported honey products. Turkey, with its unique geographic location, joins 2 continents, Europe and Asia, through Asia Minor. Because of this geographic position, Turkey serves as a biological bridge in the migration of plant species. Easy and rapid transport of foodstuffs has resulted in reports of mad honey poisoning in locations far from the Black Sea region, such as in Germany and Austria.[4] Although mad honey poisoning may affect both sexes and all age groups, the majority of reported grayanotoxin poisonings are in older men. A careful dietary history should be taken for middle-aged men with bradycardia and hypotension. Mad honey ingestion should be included in the differential

diagnosis, in addition to primary cardiac, neurologic, or metabolic disorders.

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