

# Mad honey intoxication: what is wrong with the blood glucose? a study on 46 patients

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**Abstract. – OBJECTIVE:** This study was designed to analyze the characteristics of adult patients with mad honey intoxication, with special emphasis on its effects on vital signs and blood glucose levels.

**METHODS:** Patients admitted to the Emergency Department of urban hospital in the Black Sea region of Turkey over the 16-months study period due to mad honey intoxication were included. Patients' demographic and clinical characteristics, including age, sex, systolic and diastolic blood pressure, rhythm at ECG, heart rate, blood glucose levels and clinical outcomes were recorded and analyzed.

**RESULTS:** Forty-six patients with a presumptive diagnosis of mad honey poisoning were recruited. Mean age was 52.2 ( $\pm 17.2$ ). Blood glucose level was normal in 28 cases (60.9%) and high in 18 (39.1%). Systolic blood pressure (SBP) was low in 40 patients (87%) and normal in six (13%). Diastolic blood pressure (DBP) was low in 42 cases (91.3%) and normal in four (8.7%). Mean glucose level in patients with low SBP was 116.1 ( $\pm 52.9$ ) mg/dL, vs. 120.7 ( $\pm 23.0$ ) mg/dL in those with normal or high SBP ( $p = 0.389$ ). Mean glucose level in patients with low DBP was 118.7 ( $\pm 51.4$ ) mg/dL, compared to 96.0 ( $\pm 22.8$ ) mg/dL in those with normal or high DBP ( $p = 0.146$ ). Heart rate was below or equal to 45 bpm in 28 patients (60.9%). Complete (third degree) heart block was diagnosed in one case.

**CONCLUSION:** Mad honey was found not to cause significant decreases in blood glucose levels in humans. Hypotension, bradycardia and related clinical consequences are commonly encountered in patients diagnosed with mad honey or grayanotoxin poisoning.

*Key Words:*

Mad honey, Intoxication, Grayanotoxin, Blood glucose, Hypotension, Bradycardia.

grow in the eastern Black Sea region of Turkey<sup>1</sup>. The symptoms of poisoning from this substance, popularly known as mad or bitter honey, are dose-dependent and appear after a specific length of time. The typical poisoning picture involves findings of digestive system irritation, severe bradycardia and hypotension and central nervous system reaction<sup>2</sup>. A history of honey consumption and clinical findings will suggest grayanotoxin poisoning.

The respiratory effects of grayanotoxin develop through the central nervous system, and the bradycardic effects through vagal nerve stimulation. The bradycardic effect on the central nervous system leads to hypoglycemia by increasing insulin secretion through its effect on the parasympathetic system<sup>3</sup>. There is known to be an exact correlation between mad honey and rhododendron (also known as the forest rose). Rhododendron is a plant cover that can be seen in all continents apart from South America and Africa. But almost all the cases reported involve honeys produced from Turkey, in other words the area along the coast of the Black Sea<sup>1,4</sup>. It is also used in this region as an alternative therapy for gastric-intestinal disorders (gastritis, stomach ulcers and constipation), hypertension, coronary disease and also impotence, since it is thought to enhance sexual performance. It is also used by local people as a traditional treatment for diabetes mellitus, since it is believed to lower blood sugar<sup>2</sup>.

The aim of this study was to analyze clinical findings and blood sugar levels of patients with suspected mad honey (grayanotoxin) poisoning in the eastern Black Sea region of Turkey.

## Introduction

Mad honey poisoning develops with the ingestion of honey containing grayanotoxin and produced from rhododendron flowers, which mainly

## Methods

### *Study Design*

This was a prospective study performed in patients presenting to a Urban State Hospital with

mad honey poisoning between June 2006 and October 2007. Adults patients with clinical findings of mad honey poisoning were included in the study.

### Study Setting and Population

The study was performed at Urban State Hospital in The black Sea region with more than 90 000 emergency department visits yearly.

### Study Protocol

There was a form prepared for the study used in collecting data of patients as a writt and checklist by the first Author.

### Measurements

Patients' blood sugar levels, demographic variables, systolic and diastolic blood pressures, ECG rhythm, pulse rate were all recorded. Blood samples (5 ml) were taken from all patients.

### Data Analysis

Cases' male-female ratio, mean ages, mean blood sugar levels, low, normal and high blood glucose level percentages, mean systolic and diastolic blood pressures, and percentages of hypotensive and normotensive patients' having undergone syncope were investigated. The relationship between subgroups in terms of blood sugar and vital findings was also studied.

SPSS 15.0 was used for statistical analysis of the data obtained. In addition to descriptive statistical methods of analyzing study data (frequency, percent, average, standard deviation), the Pearson chi square test was used in the comparison of qualitative data. The Kolmogorov-Smirnov test was used to examine normal distribution. The Mann-Whitney U test and independent samples *t* test were used for quantitative data between two groups to compare non-normally distributed data between groups. Results were evaluated at a confidence interval of 95% and significance was set at  $p < 0.05$ .

## Results

The study involved 46 cases, aged between 10 and 93, of which 36 (78.3%) were males. Mean age for women was  $59.4 \pm 18.79$ , for men  $50.22 \pm 16.45$  and for the total group  $52.2 \pm 17.2$  (Table I).

Cases' mean glucose level was  $116.7 \pm 49.9$  mg/dL. Glucose level was normal (cut-off point = 70-110 mg/dL) in 28 cases (60.9%) and high in 18 (39.1%). No patient in the study was hypoglycemic.

Cases' mean SBP was  $70.8 \pm 13.4$  mmHg and DBP  $37.8 \pm 14.7$  mmHg. SBP was low in 40 cases (87%); (cut-off point 90 mmHg) and normal in 6 (13%). DBP was low in 42 cases (91.3%) (cut-off point 60 mmHg) and normal in four (8.7%) (cut-off point 60 mmHg, range 60 to 80 mmHg).

Cases' mean heart rate at ECG was  $44.7 \pm 6.0$  beats/min. Complete AV block was determined in one case (2.2%). Heart rate was 45 or below in 28 cases (60.9%) and above 45 in 18 (39.1%). No tachycardic cases were encountered.

Four patients (8.7%) had type II diabetes. These patients had elevated blood sugar levels. Syncope was seen in all 46 cases. Loss of consciousness, lasting for an average 10 min (range 7-13 min), was seen in five cases (10.9%).

Glucose level in the 40 patients with low SBP was  $116.1 \pm 52.9$  mg/dL, compared to  $120.7 \pm 23.0$  mg/dL in the six patients with normal SBP. Glucose levels were statistically equal between the cases with low SBP and those with normal or high SBP ( $p = 0.170$ ). The difference between blood sugar levels in the low SBP group and the groups with normal or high SBP was not statistically significant ( $p = 0.389$ ) (Table II). A similar result was obtained for the DBP groupings ( $p = 0.146$ ) (Table II).

Glucose level in the 40 patients with low DBP was  $118.7 \pm 51.4$  mg/dL, and  $96.0 \pm 22.8$  in the four patients with normal or high DBP mg/dL idi. The difference in glucose levels between those cases with low DBP and those with normal or high DBP was not statistically significant ( $p = 0.214$ ).

Average heart rate at ECG of those cases with blood sugar within normal limits was  $44.14 \pm 6.64$ , compared to  $45.71 \pm 4.91$  for those with high blood sugar ( $p = 0.397$ ) (Table II).

Mean SBP in the subjects with normal blood sugar levels was  $71.03 \pm 12.85$ , compared to  $70.29 \pm 14.51$  mmHg for those with high blood sugar levels ( $p = 0.859$ ) (Table III).

Table I. Patients characteristics.

Male	36 (78.3%)
Female	10 (21.7%)
Mean age, years (mean $\pm$ SD)	$52.2 \pm 17.2$
Pulse beats/min (mean $\pm$ SD)	$44.7 \pm 6.0$ beats/min
Systolic pressure, mm Hg (mean $\pm$ SD)	$70.8 \pm 13.4$ mmHg
Diastolic pressure, mm Hg (mean $\pm$ SD)	$37.8 \pm 14.7$ mmHg
Glucose level mg/dL (mean $\pm$ SD)	$116.7 \pm 49.9$ mg/dL

**Table II.** Normal and high glucose levels relationship among gender, blood pressure and heart rate.

	Gender				Sistolic blood pressure				Diastolic blood pressure				Heart rate	
	Male		Female		Low	Normal/high			Low	Normal/high			min	SD
	n	%	n	%	n	%	n	%	n	%	n	%		
<b>Glucose</b>														
Normal	22	61.1	7	70	26	65	3	50	25	59.5	4	100	44.14	6.59
High	14	38.9	3	30	14	35	3	50	17	40.5	0	0	45.71	4.82

Mean DBP in the subjects with normal blood sugar levels was  $37.93 \pm 16.12$  mmHg, compared to  $37.65 \pm 12.86$  mmHg for those with high blood sugar levels ( $p = 0.951$ ) (Table III).

## Discussion

Ponticum and avium wild plant species from the Rhododendron family grow on the mountains of the eastern Black Sea region in Turkey, and also in the southern Caucasus. Grayanotoxin (andromedotoxin), present in high quantities in honey obtained from the flowers and leaves of these plants, is the agent responsible for poisoning<sup>5</sup>. The toxic effects of grayanotoxin may be ascribed to its blocking the sodium channels on the cell and increasing peripheral vagal tonus. By acting as a cholinergic agent, the toxin thus gives rise to dose-dependent life-threatening conditions, such as hypotension, bradycardia and respiratory depression<sup>6,7</sup>.

Vertigo, nausea, vomiting, lethargy, hypersalivation, diplopia and paresthesia are seen in mild forms of poisoning, while cardiovascular complications such as complete atrioventricular block, sinus bradycardia and hypotension are seen in severe forms. Cardiovascular complications generally resolve completely with intravenous atropine (0.5-2 mg) and saline (100 ml/hour) infusion. In mild poisoning, patients can be dis-

charged in a healthy condition after 2-6 h of cardiac observation. Major symptoms and findings contract within 24 h at the latest in treated severe poisoning<sup>5,8,9</sup>.

Özhan et al<sup>10</sup> determined hypotension (SBP < 90 mmHg) and bradycardia in 15 out of 19 cases presenting to the Emergency Department with mad honey poisoning and complete ventricular block in four cases. Nausea, vomiting, vertigo, sweating and lethargy developed within hours of mad honey ingestion in all cases. In our study, too, syncope was observed in all 46 cases and loss of consciousness in five (10.9%). SBP was low in 40 cases and DBP was low in 42.

A total of 96 cases in 13 different studies of mad honey have been reported in the literature to date. Rare cases developing severe atrioventricular block and asystole requiring pacemaker use have also been reported<sup>5,8</sup>. Full AV block was determined in one case in this study.

In a study on rats, Onat et al<sup>11</sup> administered toxic honey extract intraperitoneally in varying doses and observed dose-dependent hypotension, bradycardia and respiratory depression. The bradycardic effect of grayanotoxin was also shown to disappear with bilateral vagotomy. They concluded that this effect arose peripherally through the vagus nerve. Bradycardia was seen in all the patients in our study for this reason. It is important for health institutions in regions where mad honey poisoning is endemic to be structured

**Table III.** Blood pressure measurement relationship distribution of glucose levels.

Glucose	n	Sistolik blood pressure				Diastolic blood pressure			
		Medium	SD	t	p	Medium	SD	t	p
Normal	29	71.03	12.91	0.18	0.859	37.93	16.77	0.06	0.951
High	17	70.29	14.63	0.18	0.859	37.65	10.91	0.06	0.951

accordingly and for preparations to be made for emergency intervention. For example, temporary pacemaker and intensive care facilities need to be arranged. In-service training for physicians and other health workers in high-risk regions should also address the subject.

Mad honey is widely used in various countries, and also in Turkey, for alternative therapy purposes. The aims behind the use of this kind of honey in alternative therapy has not been fully established<sup>7</sup>.

The effects of grayanotoxin are mediated by the parasympathetic nervous system as a result of M2 muscarinic receptor stimulation. This stimulation is known to increase the secretion of insulin from the pancreas<sup>12</sup>. Oztasan et al<sup>2</sup> showed that grayanotoxin administered to rats orally in the form of mad honey containing grayanotoxin increased insulin secretion by stimulating alpha cells in the islets of Langerhans, and that this caused a fall in blood glucose levels. They also proposed that mad honey containing grayanotoxin might be useful in type II diabetes patients<sup>2</sup>. No hypoglycemia was determined in any of the patients in our study. On the contrary, blood sugar levels were normal or high.

### Conclusions

Hypotension, bradycardia and related clinical consequences are commonly encountered in patients diagnosed with mad honey or grayanotoxin poisoning. It is essential to carry out in-service training of the health care workers in primary care institutions in endemic regions in order to provide the requisite knowledge on the subject. Although it has been emphasized in animal studies that mad honey may have a hypoglycemic effect, it is noteworthy that no hypoglycemic cases were encountered in our study. We think that clinical studies with larger case numbers are needed to investigate the effects of mad honey on blood sugar levels in humans.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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