

MAD HONEY POISONING IN MAN AND RAT

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SUMMARY

Grayanotoxins are known to occur in the honey produced from the nectar of *Rhododendron ponticum* growing on the mountains of the eastern Black Sea region of Turkey. Two cases of honey intoxication are presented here. Both patients experienced severe bradycardia and hypotension following ingestion of honey which was brought from Trabzon, Turkey. Microscopical examination of the honey demonstrated *Rhododendron ponticum* tetrades. Anesthetized albino rats were injected intraperitoneally with toxic honey extracts in amounts equivalent to 1 or 5 g honey/kg b.w. Dose-dependent hypotension, bradycardia and respiratory rate depression were observed.

Key words: Grayanotoxins, *Rhododendron ponticum*, intoxication

INTRODUCTION

Grayanotoxins occur in various plants, notably *Rhododendrons*, *Pieris* and *Kalmia* of the botanical family *Ericaceae*. These toxic compounds may be found in leaves, twigs, pollen grain and honey derived from these plants (1). *Rhododendron ponticum* grows extensively in the mountains of the eastern Black Sea area of Turkey (2-4). Ingestion of "mad honey" produced from the nectar of *Rhododendrons* causes several symptoms and signs, including bradycardia, hypotension, cardiac arrhythmias, vomiting, sweating, weakness, blurred vision, respiratory depression, mild paralysis, and convulsions (5-8). The intoxication is rarely fatal and generally lasts for no more than 24 hours. Grayanotoxin I, variously

known as andromedotoxin, acetylandromedol and rhodotoxin, is usually responsible for these symptoms (9-12).

Mad honey intoxication was first reported in 401 BC by Xenophon, who stated that it resulted from the ingestion of honey produced from the nectar of *Rhododendron ponticum* near Trebizond (today's Trabzon), Turkey (12). Recently, Gossinger et al. (6) reported a case of honey intoxication in an individual who had ingested honey brought from Turkey. The most recent report by Biberoğlu et al. (8) describes 16 honey intoxication cases from Trabzon, Turkey.

Although the cardiac toxicity of mad honey in man has been reported since 401 BC (12), there is very little information on the toxic effects of mad honey extracts in experimental animals. In this paper, two cases of mad honey intoxication are presented and the effect of mad honey extracts on the heart rate, blood pressure and respiratory rate of rats is described.

MATERIALS AND METHODS

Extraction of honey:

Rhododendron ponticum I pollens were seen on microscopic examination of the honey obtained from the first patient presented below. Samples of honey were extracted according to the method described by Scott et al. (13). Briefly, 50 g of honey was shaken with 100 ml methanol-water (1:3, v/v) until homogenous. The mixture was adjusted to pH 6.5 with dilute NaOH (0.1 N) solution and then filtered through Whatman no. 46 filter paper. The solution was extracted 5 times

with 150 ml aliquots of chloroform. The combined chloroform extracts were evaporated to near dryness on a steam bath which was maintained at 50°C. The residue was dissolved in 5 ml of warm distilled water (14).

Animal experiments:

Albino rats of both sexes weighing 200-250 g were used. Rats were injected with honey extracts intraperitoneally in constant volumes (0.1 ml/100g b.w.). Stock solution of extract was diluted in order to give appropriate amounts of extracts equivalent to 1 or 5 g honey/kg b.w. (n=17 and 15 respectively). Rats (n=5) injected with nontoxic honey extracts were used as control group.

Rats were anesthetized by Urethane (1.6 g/kg b.w., i.p.). Respiratory rates were counted, and heart rates and rhythms were monitored by ECG (Nihon Kohden). In another group, direct blood pressure recordings were made by carotid artery cannulation via a pressure transducer on a polygraph (Nihon Kohden, Model RM 6100). Following at least two control recordings, toxic or nontoxic honey extracts were injected. The animals were observed for two hours after the injection.

Data are expressed as mean \pm SEM. Statistical analysis was done by Student's paired t-test.

RESULTS

1) Case reports

The first case was a 48-year-old man who developed weakness, dizziness and faintness an hour after ingestion of 2 tablespoonfuls of honey which had been brought from Trabzon, Turkey. He had eaten smaller amounts of the same honey previously without any adverse effects. Shortly after the onset of the symptoms he was admitted to the Marmara University Hospital with a blood pressure of 60/20 mm Hg and a pulse of 34/min-regular. He did not experience nausea, vomiting, sweating or syncope and had no history of cardiovascular disease or symptoms. He had been hospitalized because of schizophrenia in 1970, 1973 and was on salazopyrine 500 mg t.i.d. for the last 5 months due to a probable diagnosis of inflammatory bowel disease. Other than bradycardia and hypotension, the physical examination was unremarkable. Routine laboratory tests including a chest x-ray were normal. An ECG showed sinus bradycar-

dia (25 bpm) and occasional AV nodal escape beats.

The second case was a 74-year-old man with chronic obstructive lung disease of long duration. He developed weakness, dizziness, faintness and also sweating half an hour following ingestion of some honey which had been brought from Trabzon. He had no nausea, vomiting or syncope and was admitted to Marmara University Hospital with a blood pressure of 60/30 mm Hg and a pulse of 35/min-irregular. Apart from chronic lung disease, his past medical history was unremarkable, and he was not on any cardiac drug therapy. Upon physical examination, in addition to bradycardia and hypotension he was barrel chested with sibillant ronchi and coarse rales. The remainder of the physical examination was normal. Routine laboratory tests were within normal limits whilst a chest x-ray revealed mild cardiomegaly, signs of emphysema and reticulonodular opacities over the lung areas. An ECG showed sinus bradycardia (37 bpm), second degree AV block (Mobitz Type I) and incomplete right bundle branch block.

Both of the patients responded dramatically to i.v. saline infusion and i.v. atropine (1-2 mg). Heart rates rose to tachycardic levels (sinus rhythm) and blood pressure normalized within several minutes following atropine administration. The first patient required 0.5 mg atropine every 3 to 4 hours during the initial 18 hours of treatment. The second patient was given only i.v. saline solution following the initial atropine administration. Both patients had a normal heart rate, rhythm and blood pressure within 24 hours of the mad honey poisoning.

2) Animal experiments

Nontoxic honey extracts did not change heart rate, respiratory rate and mean arterial pressure (MAP) throughout the observation period. Toxic honey extracts reduced heart rate, respiratory rate and MAP dose-dependently (Figs. 1, 2 and 3).

The respiratory depressant effect of 1g/kg of toxic honey extract became significant 15 min after injection and reached a maximum of 59.1 ± 6.2 % of the control value at 90 min, whilst that of 5g/kg was significant at 15 min with a maximum of 12.9 ± 2.2 % at 30 min (Fig. 1).

The bradycardic effect of toxic honey extracts also became significant at 15 min and reached its maximum at 90 min with both doses (77.5 ± 2.0 % of cont-

rol value for 1g/kg and 53.5 ± 7.6 % for 5g/kg honey extract) (Fig. 2).

The hypotensive effect of the lower dose of toxic honey extract was significant at 60 min and the maximum effect (65.2 ± 10.4 %) was seen at 90 min. The higher dose caused a more prominent hypotension which started immediately and reached a maximum of 47.8 ± 12.2 % at 60 min (Fig. 3).

All effects of toxic honey extract lasted until the end of the observation period. ECG monitoring of these animals showed increasing sinus bradycardia in all, AV junctional escape rhythms in 4, AV block of 2nd and 3rd degree in one, and occasional ventricular premature beats in one other rat.

Extracts from the honey which caused intoxication in the second patient also led to bradycardia and despiratory rate depression when administered to rats. These effects were similar to those reported above and are not included here.

DISCUSSION

The grayanotoxins are said to be responsible for mad honey intoxication (9). These, particularly grayanotoxin I is found mainly in honey, produced from the nectar of various genera of Ericaceae, notably *Rhododendron*, *Pieris* and *Kalmia* (1,9-12).

All the cases reported previously share the major symptoms and signs with those presented in this paper; namely severe bradycardia and hypotension (5-8). Other common complaints are dizziness, weakness, excessive sweating, nausea and vomiting. Syncope and several types of cardiac dysrhythmias may be observed. In severe intoxication loss of coordination and progressive muscular weakness may develop. Convulsions are reported occasionally. In man, symptoms of poisoning occur after a latent period of a few minutes to a few hours. The intoxication is rarely fatal. Since grayanotoxins undergo rapid metabolism and excretion (15), spontaneous recovery is expected within 24 hours. Administration of parenteral fluid and atropine usually relieve hypotension and bradycardia as seen in our patients.

In the present study, toxic honey was extracted to isolate grayanotoxins (13). The three major toxic effects in rats were respiratory depression, hypotension and sinus bradycardia. Bradycardia and hypotension are also characteristic effects of grayanotoxins in man. Interestingly, respiratory depression in rats was so severe that the respiratory rate fell to even 5-10/min in some animals. In man, respiratory depression only

rarely occurs due to grayanotoxins. This may depend on the amount of toxin ingested or a species difference. Similarly, severe respiratory depression has been reported in dogs (7), in mice (13) and guinea-pigs (3) with severe respiratory depression.

Additionally, in some in vitro studies, a positive inotropic effect of grayanotoxin has been demonstrated (5,16). Moran et al (17) have suggested that grayanotoxins may cause vagal stimulation and blockade of the carotid sinus pressure reflex. Recently, grayanotoxins were demonstrated to bind to sodium channels in cell membranes and prevent inactivation; thus excitable cells (nerve and muscle) are maintained in a state of depolarization (18,19). All of the observed responses of skeletal and myocardial muscle, nerves and central nervous system to the toxin, are reported to be related to the membrane effects (12).

Although the risk of an intoxication with Grayanotoxin honey is highest in areas with Ericaceae-dominated vegetation, namely Turkey, Japan, Brazil, North America, Nepal, British Columbia and parts of Europe (5,12), the increase in travel and trade throughout the world leads to poisonings outside these areas. Some may be ascribed to a search for exotic tastes that can be realized from imported honey. Others may result from the ingestion of unprocessed honey in the quest for natural foods.

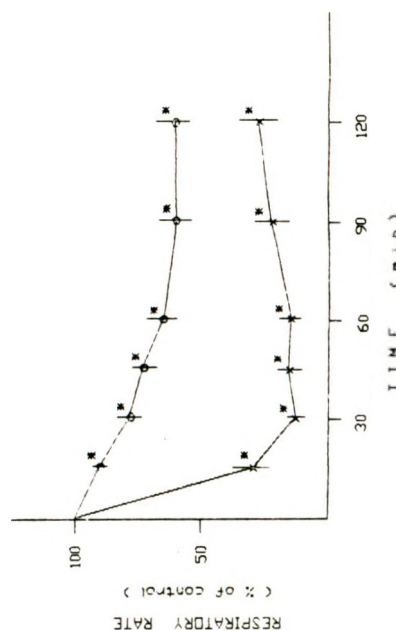


Figure 1: Effect of (o---o) 1 g/kg and (x---x) 5 g/kg of toxic honey extract on respiratory rate in rats. *, significantly different than control ($p < 0.05$).

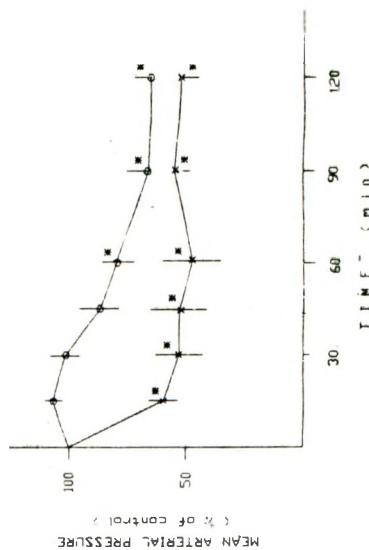


Figure 2: Effect of (o---o) 1 g/kg and (x---x) 5 g/kg of toxic honey extract on heart rate in rats. *, significantly different than control ($p < 0.05$).

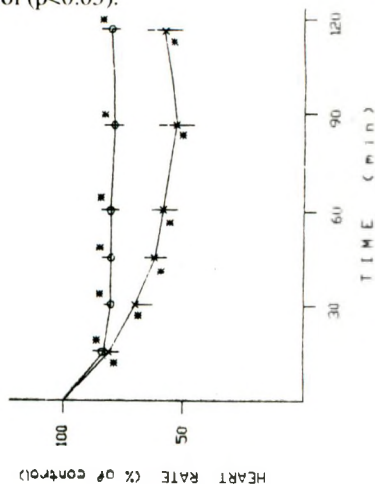


Figure 2: Effect of (o---o) 1 g/kg and (x---x) 5 g/kg of toxic honey extract on mean arterial pressure in rats. *, significantly different than control ($p < 0.05$).

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