SWEET BEGINING, TRAGIC END: MAD HONEY POISINING

Case Report

TATLI BAŞLANGIÇ, TRAJİK SON: DELİ BAL ZEHİRLENMESİ

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ABSTRACT

Secondary products derived from plants may contain harmful substances such as honey. The honey contaminated with grayanotoxin, a diterpene, which is a polyhydroxylated cyclic hydrocarbon that doesn't contain nitrogen named "deli bali" in Turkish, which is called "[*sic*] mad honey may cause grayanotoxin toxidrome. It affects multiple systems of the body especially cardiovasculare system in a dose dependent fashion. Herein we present a rewiev of this toxidrome.

Keywords: *mad-honey; grayanotoxin; poisoning.*

ÖZET

Bal gibi bitki kaynaklı besinler beraberinde zarar verici içerikler de içerebilirler. Nitrojen içermeyen polihidroksile siklik bir hidrokarbon olan grayanotoksin içeren ve türkçede 'deli balı' olarak da geçen bal türü garayanotoxin zehirlenme sendromuna yol açabilmektedir. Çoklu organ ve sistemlerde bir çok yan etki ile belirti veren bu zehirlenme sendromu daha çok doz bağımlı bir karakter göstermektedir. Burada bu zehirlenme sendromuna ait bir derleme sunmaktayız.

Anahtar kelimeler: *deli-bal; grayanotoksin; zehirlenme.*

INTRODUCTION

Plants contain numerous compounds, some of which are harmful to mammals, including humans. Secondary products derived from plants, such as honey, may also contain these harmful substances. Secondary products can easily be obtained thus have the potential to affect a substantial amount of people if toxic. Though small amounts can be considered medicinal, the lack of standardization contributes to the toxicity of such products.

Beekeeping is a common source of income in many regions around the world including the Black Sea region. Bees can cover wide areas during foraging however local terrain conditions can restrict bees in such a way that their only source their honey comes from the fauna of a severely limited region(1). This occasionally leads to bees to fauna that contains plants from the Rhododendrons spp., causing the toxins from the plant to contaminate the end product, honey. This phenomenon has also been described in other geographic locations around the world, such as the USA and several European countries where, the local fauna contains either Rhododenron spp. or other spp. from the Ericaceae family.

This toxin is called Grayanotoxin. It is a diterpene, which is a polyhydroxylated cyclic hydrocarbon that doesn't contain nitrogen. The honey contaminated with grayanotoxin is named "deli bali" in Turkish, which is called "(*sic*) mad honey". The correct translation would roughly be "honey for the mad", making the assumption that no person in their right mind would dare eat it. The pathophysiology, clinical course and outcomes, and management of this poisoning are well understood.

From a historical perspective, one of the first reports of mass intoxication was caused by the grayanotoxin. Xenophon wrote in this Anabasis during the expedition of Cyrus in 401 BC near Trebizond (Trabzon, Turkey) In later reports Greek Historian Strabo told of the slain of three squadrons of Pompey's troops who were given honey by the local tribesman (2).

Grayanatoxin

Grayanotoxin is a diterpene. These substances are readily produced by some spp. of the family Ericacea and as such can be found in the nectar, pollen and parts of the plants. The commonly known grayanotoxin producing plants are Rhododendron spp. Rhododendron Luteum and Rhododendron Ponticum, found in the flora of Turkey are the main flowers associated with the grayanotoxin poisoning. In other parts of the world, such as the USA, the causative factors differ with regions such as Rhododendron albiflorum in the western region and Kalmia latifolia in the eastern regions(3). There are approximately 60 known grayanotoxins(4). Though the specific grayanotoxins vary with the plant species, Grayanotoxin 1 (G1) (formerly known as andromedotoxin, acetylandromedol or rhodotoxin) is present in the greatest concentration and is the primary toxic compound.(5) Though Grayanotoxin 3 (G3) is present in minor concentrations it is the most toxic of all grayanotoxins. On average the LD50 of G3 is 0.84 mg/kg compared to that of 1.31 mg/kg for G1 and 26.1 mg/kg for G2 in mice(6).

Grayanotoxins can be classified as neurotoxins. They bind to sodium channels blocking the transmission of the action potential via the voltage dependent activation(7). These compounds essentially prevent inactivation leading to continued maintenance of activation in susceptible cells such as the myocardium or neurons consequently causing the facilitation of entrance of calcium into the cells(8). The increased permeability of calcium in myocardium sensitized by the increase of the vagal tone due to effects on the vagal neurons leads to the common cardiac symptoms(9). When this effect on the vagal nerve occurs on the afferent branches of the heart, grayanotoxin activates the Bezold-Jarisch reflex resulting in bradycardia(10). The typical signs and symptoms on other systems attributable to grayanotoxin poisoning can easily be explained by the toxins effect on the sodium channel on diverse cells.

Mad Honey Disease & Toxidrome of Grayanotoxin

The toxicity of the grayanotoxin is rarely fatal. The onset typically occurs in a dose-dependent fashion within a period of 2 hours(11).Though personal characteristics

such as underlying comorbidities, age and the concentration of grayanotoxin in honey differ, the typical amount of honey consumed before symptom onset is in the range of 5-30g (1-5 tbsp.)(12) Intoxication, if not severe, typically resolves by itself within 24 hours. Typical symptoms associated with grayanotoxin poisoning in humans aren't unlike the cholinergic toxidrome. Though the mechanism of action differs from that of cholinergic poisoning(13). the uninhibited action potential leads to an exaggeration of the parasympathetic activation. Common symptoms include salivation, emesis, circumoral and extremity parasthesias. In more severe intoxication, the degree of muscle weakness depends on the dose ingested. Loss of coordination, impaired consciousness, nausea and vomiting, sweating and blurred vision can also be seen (14). The most severe and alarming symptoms of intoxication are those seen in the cardiovascular system. Grayanotoxins affect the cardiovascular system on a large spectrum, also in a dose dependent fashion. The most common CV effects are significant hypotension and bradycardia. Cardiac arrhythmias can also occur within a large gamut(9). These include mild problems such as extra systoles and, on the other end of the spectrum, full-blown asystole(15,16).Heart blocks, nodal escape rhythms and ventricular tachycardias have all been reported (11).

Grayanotoxin intoxication can be a daunting diagnosis for the clinician because of the acute onset, perturbing symptoms on a large scale and the problems with the confirmation of diagnosis no fatalities have been noted in the modern literature(17).Patients should be given supportive care and monitored overnight for possible acute onset rhythm disturbances(18).Hypotension and - bradycardia typically resolve upon administration of Atropine(11, 14, 18).A review of the literature lists several cases of complete heart block necessitating the use of temporary pacing until the grayanotoxin was eliminated from the body(16, 18).There are also reports of asystole also responding to Atropine.(15) This presentation can be particularly challenging due to the restriction of use of Atropine in the 2010 AHA ACLS guidelines to bradycardia only(19). Thus if a physician suspects the cause of asystole as such, via the possible patient characteristics, geographic location and history, should list grayanotoxin intoxication within the possibilities of differential diagnoses.

There are also reports that grayanotoxin has detrimental effects on renal and hepatic systems, leading to nephrotoxicity and hepatotoxicity in animal studies(20). Although there are no reports that renal or hepatic systems are affected in humans. Grayanotoxins can be detected in the honey using terpene extraction methods such as mass spectrometry or infrared analysis(21, 22).No blood tests or isolation methods exist. As patients generally feel better within 4-9 hours and have complete resolution of symptoms within 24 hours it's unlikely that grayanotoxins have long-half lives, in other words they are metabolized and eliminated rapidly.

CONCLUSION

Black Sea region, characterized by its mountainous terrain and widespread beekeeping, has created niche intoxications. The locally produced "deli bali", contains grayanotoxins, due to the regionally found Rhododendron spp. Even if consumed in minute quantities, grayanotoxin has effects on the cardiovascular system. These may be as mild as extra systoles or be severe as hypotension and asystole. The typical treatment consists of Atropine pro re nata, as indicated by the patients' symptoms, close monitoring and supportive care for a period of 24 hours.

Though the geographical region of typical mad honey production is limited to Turkey, in recent times, physicians should anticipate seeing mad honey poisoning

everywhere. With the advent of the Internet, global trade and the so-called "complementary" medicine; this honey can be imported and exported even to the most unimaginable of places. Thrill seekers, drug addicts or people whose search for exotic taste can only be quenched by the most striking of the honeys may even eat mad honey, fully aware of its poisonous attributes. As Paracelsus once said, the dose makes the poison; although there are no validated health benefits of mad honey, specifically grayanotoxin(23, 24) .As one of the most common acute food related intoxications' in Turkey, mad honey should be treated as a controlled substance for purposes of sale and production.

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