

Intravenous administration of cannabis and lethal anaphylaxis

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Abstract

Cannabis allergy appears to be increasing. A 33-year-old woman is reported who collapsed and died shortly after injecting herself with a cannabis solution prepared by pouring boiling water onto plant material. There were no significant findings at autopsy, except for a single recent venepuncture wound in the left cubital fossa. Toxicological examination of the blood revealed low levels of methylamphetamine and amphetamine with tetrahydrocannabinol (Δ^9 -THC) and 11-nor-9-carboxy- Δ^9 -THC, and no opiates. The syringe used by the decedent contained Δ^9 -THC. Serum tryptase levels were markedly elevated ($>200 \mu\text{g/L}$; $N < 12 \mu\text{g/L}$). This finding coupled with the sudden collapse after injecting an aqueous extract of cannabis indicated a likely anaphylactic or anaphylactoid reaction to the extract. Cannabis allergy may occur following handling, inhalation, swallowing or injecting *Cannabis sativa* plants or their products. The possibility of an allergic reaction should therefore be considered at autopsy in deaths where there has been recent contact with cannabis.

Keywords

Cannabis, marijuana, anaphylaxis, plant allergy, serum tryptase

Introduction

This paper reports the unexpected death of a woman who injected a solution containing cannabis. The reported rate of allergies, particularly involving food-stuffs, has increased markedly in a number of communities in recent years. Reactions vary from mild urticaria to full-blown anaphylaxis. The latter is of particular concern, as exposure to a particular antigen may result in an acute, potentially fatal, multi-organ response involving the skin and airways, as well as cardiovascular and neurological systems.¹ The basis is a type I hypersensitivity reaction usually mediated by immunoglobulin E (IgE). Chemicals released from mast cells and basophils result in flushing, itching, angio-oedema, shortness of breath, tachypnoea, arrhythmias, hypotension and an altered conscious state. Less commonly, anaphylactoid reactions occur involving IgG and immune complex complement.¹

Cannabis refers to a variety of preparations derived from the plant *Cannabis sativa* that contains high levels of psychoactive cannabinoids such as Δ^9 -tetrahydrocannabinol (Δ^9 -THC).² It has been estimated that there are between 125 and 203 million cannabis users worldwide, representing 2.8–4.5% of those aged 15–64 years.³ Despite this extensive global usage, however, allergic reactions to cannabis are rarely described, although they are believed to be on the increase.⁴ The following case is reported to demonstrate a significant allergic response to the

intravenous administration of cannabis with a fatal outcome.

Case report

A 33-year-old woman who had been a regular user of amphetamines and cannabis injected herself with a cannabis solution that she had prepared by pouring boiling water into a small plastic bag containing the plant material. Shortly afterwards, she lost consciousness and slumped to the floor. She was noted to be cyanotic with froth in her mouth, and she exhibited shallow breathing with occasional gasping. An ambulance was called and cardiopulmonary resuscitation was commenced by a friend who witnessed her collapse. The resuscitation attempt was continued by ambulance officers without success.

There was a history of epilepsy, stemming from a vehicle accident that resulted in a head injury at the age of 16 years, and more recently a diagnosis of Huntington's disease (her mother had died from this

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disorder seven years previously). She had last used amphetamines approximately 16 hours before her death.

At autopsy, the body was that of a well-nourished Caucasian woman with numerous venepuncture wounds of the arms from attending ambulance officers. These had been circled with marker pen. A single un-circled venepuncture mark was present in the medial aspect of the left cubital fossa. There was no swelling of the face or mucosa of the upper airways. Neuropathological examination of the brain showed focal areas of glial scarring in the right prefrontal cortex and left uncus associated with the previous head injury. There were also changes in the temporal cortex and cerebellum in keeping with the history of epilepsy. Ubiquitinated intranuclear inclusions were present in the neurones of the cerebral cortex and basal ganglia associated with Huntington's disease. The histological finding of eosinophils in the bronchial submucosa, with increased numbers in the spleen, pulmonary capillaries and hepatic sinusoids, indicating the presence of a peripheral eosinophilia, raised the possibility of an underlying allergic disorder. There was no evidence of trauma other than that related to attempts at resuscitation.

Toxicological examination of femoral blood revealed therapeutic levels of paracetamol and lamotrigine (an anticonvulsant), with no alcohol or opiates. There were also non-lethal levels of methylamphetamine and amphetamine consistent with the illicit use of methylamphetamine, with 1 µg/L of THC and 3 µg/L of 11-nor-9-carboxy-THC. The syringe used by the decedent shortly before her collapse contained Δ^9 -THC.

Measurement of serum tryptase levels from femoral blood revealed marked elevation (>200 µg/L; $N < 12$ µg/L). Allergen-specific IgE testing for cannabis was unfortunately not available in our laboratory. However, testing for various fungal organisms (*Aspergillus*, *Alternaria*, *Cladosporium* and *Penicillium*) was negative.

The finding of a markedly elevated serum tryptase level coupled with the history of the decedent's sudden collapse after injecting an aqueous extract of cannabis indicated a likely anaphylactic or anaphylactoid reaction to some component of the extract. As cannabis can be contaminated in vivo or in storage by potentially allergenic moulds, allergen-specific IgE testing for fungi was undertaken, but this was negative. Death was therefore attributed to anaphylactic shock following intravenous injection of aqueous cannabis extract.

Discussion

Adverse reactions to the intravenous injection of cannabis have been very rarely documented in the

literature. Mims and Lee described four cases where cannabis seeds were boiled and the extract then injected.⁵ The victims all developed nausea, vomiting, fever, rigors, diarrhoea and abdominal pain, which progressed to hypotension and hypovolaemic shock with transitory renal failure, rhabdomyolysis and myocardial ischaemia. It was considered that the effects would have been lethal had there not been hospitalisation and treatment.

Other cases from the literature have presented with similar findings,⁶⁻⁹ leading to the coining of the term 'intravenous marijuana syndrome' and the suggestion that it may be related to contamination from cotton filters used to strain the fluid. An allergic component was not thought likely,^{10,11} and the presentations were quite different to the reported case. In a series of six cases of sudden death proximate to cannabis use, the cause of death was considered to be cardiovascular, mediated through β -adrenergic stimulation, possibly with parasympathetic blockade. However, no mention was made of measurements of post-mortem serum tryptase levels, so it is unclear how anaphylaxis was confidently excluded.¹²

The immunological reaction to *C. sativa* is believed to involve a major allergen, non-specific lipid transfer protein (Can s 3), which is also found in tomatoes and plant-food-derived alcoholic beverages, raising the possibility of allergic cross-reaction.^{3,4,13-15} The term 'marihuana connection' for this phenomenon has been proposed.¹⁶ A range of allergic manifestations may occur,² including contact urticaria, a type I hypersensitivity reaction, which was reported in a forensic science technician who was required to handle *C. sativa* plants during her daily work.¹⁷ Inhalation of marijuana has caused allergic rhinoconjunctivitis with nose and eye itching, sneezing, coughing and rhinorrhoea in an atopic patient; the diagnosis was confirmed by a positive skin-prick test.¹⁸ The latter has also been a recognised work hazard for forensic staff handling hashish or marijuana.¹⁹

Rarely, allergic reactions to ingested cannabis seeds have been reported, as in the case of a 44-year-old man who developed generalised urticaria, facial angio-oedema, dysphonia and dyspnoea while eating a meal which contained hempseeds. He responded to adrenaline and antihistamines, and was later positive to skin-prick testing with hempseed.²⁰ A similar response occurred in a 25-year-old male presenting with pruritus, facial oedema and dyspnoea 45 minutes after injecting a mixture of water and crushed marijuana leaves. His symptoms also responded to adrenaline, antihistamines and steroids.²¹

The detection of fatal anaphylaxis at autopsy may be very difficult. For example, no typical macroscopic features were identified in 41% of cases in one autopsy series. This was attributed to the rapidity with which the fatal episodes can evolve.²² An additional

problem with alleged *C. sativa* allergy is that the diagnosis at present ‘generally rests upon skin testing using extracts prepared from macerated buds, leaves or flowers’, with in vitro tests such as the measurement of specific IgE antibodies, flow-assisted basophil activation tests and histamine release tests having ‘not been robustly tested’ and not being predictive of the clinical outcome.^{2,3} It was also noted by these authors that positive laboratory tests might merely be an indication of prior sensitisation to cannabis pollen, and may therefore be of no clinical significance. Hence, the diagnosis in the reported case relied heavily upon circumstantial evidence in combination with the high tryptase level but without specific immunoglobulin elevation. Other authors have suggested, however, that specific IgE determination would have a better diagnostic positive predictive value.²³ The absence of reportable levels of cannabinoids in the post-mortem blood sample in the current case is most likely due to the insolubility of cannabinoids in water. Post-mortem levels of serum tryptase may also be difficult to interpret, as these increase with increasing post-mortem interval and are also elevated in some non-anaphylactic deaths, particularly those due to atherosclerotic heart disease and blunt chest trauma. Levels may also be raised in cases of heroin overdose and are more likely to be higher in blood taken from the heart.²⁴

Another issue that this case raises is the problem of injecting foreign material. A case of a 24-year-old male has been reported where death quickly followed an intravenous injection of *Chan Su*, a traditional Chinese herbal product that is designed to be ingested. It contains highly toxic bufotenine, a tryptamine derivative alkaloid that derives from the secretions of toad skin.²⁵ Injecting any material of uncertain composition is unwise.

This case demonstrates a significant allergic reaction occurring in close proximity to the injection of water steeped in marijuana leaves. Although the autopsy was unremarkable, the high blood tryptase level provided strong supportive evidence for anaphylaxis. Unfortunately, specific IgE tests were not able to be performed. Cannabis allergy appears to be on the increase⁴ and may occur following handling, inhalation, swallowing and injecting *C. sativa* plants and their products. The possibility of an allergic reaction should therefore be considered at autopsy in deaths where there is a temporal association with marijuana use, and appropriate laboratory testing then undertaken. This includes immunological testing for fungal organisms that may contaminate marijuana leaves.

Declaration of conflicting interests

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