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To cite this article: Shang-Lin Chou, Ming-Yueh Chou, Wei-Fong Kao, David H.T. Yen, Chun-I Huang & Chen-Hsen Lee (2008) Cessation of nail growth following Bajiaolian intoxication, *Clinical Toxicology*, 46:2, 159-163, DOI: [10.1080/15563650701397159](https://doi.org/10.1080/15563650701397159)

To link to this article: <https://doi.org/10.1080/15563650701397159>



Published online: 20 Jan 2009.



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CASE REPORT

Cessation of nail growth following Bajiaolian intoxication

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Bajiaolian (*Dysosma pleianthum*), a species in the Mayapple family (*Podophyllum peltatum*), has been widely used as a traditional Chinese herbal medication for the remedies of snake bite, tumor growth, post-partum recovery, and acne. It has also been used in western medicine, especially topically for various skin lesions. Both oral ingestion and dermal application may result in severe toxicity. The clinical presentations reported after Bajiaolian poisoning include nausea, vomiting, diarrhea, abdominal cramps, tachycardia, orthostatic hypotension, paralytic ileus, urinary retention, hepatorenal dysfunction, leukocytosis followed by leukopenia, thrombocytopenia, prolonged areflexia, prolonged paraesthesia and sensory ataxia, dizziness, fever, memory impairment, hallucinations, paranoia, convulsion, fainting, and coma. There are no previous reports in the literature about the cessation of nail growth as a clinical presentation following Bajiaolian poisoning. We present a case of nail growth that was halted for more than seven years after a single case of Bajiaolian poisoning.

Keywords Bajiaolian; Podophyllotoxin; Nail growth

Introduction

There are four species in the botanic genus of *Dysosma*: *D. pleianthum*, *D. versipelle*, *D. peltatum*, and *D. emodi* (also named *Podophyllum hexandrum*). Bajiaolian (*D. pleianthum*) is the most common species found in China; the May apple (*D. peltatum*) is the most common in western countries. Podophyllotoxin, the major active ingredient of podophyllum and Bajiaolian, was first used medically as a laxative in western medicine during the nineteenth century (1). In 1942, Kaplan introduced podophyllum resin extract for treating verruca vulgaris and condyloma accumulation (2). It is widely used at present to manufacture drugs for the treatment of cancer (particularly small cell lung carcinoma, breast cancer, and testicular cancer) (3–6), genital warts (7,8), psoriasis (9–11), and rheumatic arthritis (12). In HIV infection or other immunocompromised conditions, podophyllotoxin is also effective for oral hairy leukoplakia (13–15). Bajiaolian intoxication has occurred in therapeutic dosage in Chinese herbal medicine (16,17), and as the podophyllum product of topical application

and accidental contact, such as eye exposures or oral ingestion for suicide attempts, in western countries. Podophyllum resin, a keratolytic agent, is strongly irritating to the skin, eyes, and mucous membranes (18). Podophyllum resin is teratogenic by both oral and dermal routes of exposure (19). A large mass of condylomata or the status of pregnancy should be relative contraindications to the use of podophyllum (20,21).

The clinical presentations reported after Bajiaolian poisoning include nausea, vomiting, diarrhea, abdominal cramps, tachypnea, tachycardia, orthostatic hypotension, paralytic ileus, urinary retention, oliguria, hepatorenal dysfunction, leukocytosis followed by leukopenia, thrombocytopenia, prolonged areflexia, prolonged paraesthesia and sensory ataxia, dizziness, fever, memory impairment, visual and auditory hallucinations, paranoia, convulsion, fainting, and coma (1). The peripheral neuropathy usually becomes a hallmark manifestation after the acute stage and tends to persist for several months or years (22,23). In the literature review, discontinuation in nail growth had not been reported after Bajiaolian poisoning. Recognition of unusual presentations of Bojiaolian poisoning would be helpful in making an early diagnosis.

Received 20 December 2005; accepted 11 September 2006.

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Case report

A 48-year-old female prepared and drank pig's brain soup made from an herb blend (without wine) as a treatment for

chronic headache. The soup contained about 15 g of Bajiaolian root that she purchased from an herbal store. About one hour after ingestion, she developed abdominal pain and intractable vomiting and diarrhea. She visited a local clinic where acute gastroenteritis was diagnosed and intravenous fluid was administered. Several hours later, weakness and numbness developed in all four limbs, beginning distally and progressing proximally.

Due to the progression of symptoms and unsteadiness while walking, she was transferred to a local hospital two days later. Upon arrival at the local hospital, she was alert and her vital signs were normal. Neurological examination showed an unsteady gait, impairment of the finger-nose-finger test, and abnormal Babinski's sign, bilaterally. Laboratory data revealed WBC 5610/mm³ (reference 4000–9000/mm³), Hb11.5 g/dL (reference 12–16 g/dL), platelets 127,000/mm³ (reference 150,000–450,000/mm³), BUN 6.6 mg/dL (reference 6.0–27.0 mg/dL), and creatinine 0.8 mg/dL (reference 0.7–1.6mg/dL). Brain CT showed mild brain edema. She was initially admitted with the diagnosis of cerebellar infarct and acute gastroenteritis.

Two days later, the fourth day after the Bajiaolian poisoning, repeated blood examination values were WBC 3860/mm³, Hb12.2 g/dL, platelet 154,000/mm³, aspartate aminotransferase (AST) 63 U/L (reference 0–42 U/L), and alanine aminotransferase (ALT) 71 U/L (reference 0–42 U/L). She was discharged one week later, with a diagnosis of diffuse cerebellar dysfunction and acute gastroenteritis. During the course of her admission, she developed paralytic ileus. Numbness and weakness of the limbs were extended proximally over the area distal to the elbows and hips. After discharge, she still had difficulty standing and could not eat without aid.

One month after poisoning, the woman was transferred to our hospital. She said that she had been unable to stand without aid for about two weeks. Neurologically, she was alert with normal JOMAC (Judgment, Orientation, Memory, Abstract, and Calculation) and intact cranial nerves. Finger-nose-finger test was mildly impaired due to a little bit of intension tremor. Her tandem gait was impaired and wide-based gait was noted. Her muscle power was diffused by weakness (muscle power: 4+), and deep tendon reflex (DTR) was decreased in the upper limbs and absent in the lower limbs. The impairment of position sense, vibration senses, and pin-prick sensation was noted in all four limbs and the Babinski sign was bilaterally down-going. Laboratory data were normal in both cell counts and biochemistries. Nerve conduction velocity (NCV) examination showed generally decreased or absent conduction velocity. EMG showed an active generalized axonal sensori-motor peripheral neuropathy. A diagnosis of polyneuropathy secondary to podophyllotoxin intoxication was based on the patient's history, clinical course, results of investigations, and the patient recognition of the picture and the herbal name of Bajiaolian root; she was discharged in stable condition.

Six and a half years after the Bajiaolian poisoning, we visited her at home to follow-up on her condition. Her muscle

power, Babinski sign, deep tendon reflexes, and sensation to light touch and pin-prick were all normal. However, she had residual deficits in position sense of her fingers and toes. She reported that she was unable to walk well without aid for about three months after the poisoning and regained the ability to ride a motorcycle about six months after the poisoning. At the same time, she told us that her nails stopped growing after the poisoning. She said that she usually had her nails cut about twice a month before the intoxication, but had not needed to cut her fingernails after the poisoning event (Fig. 1). She cut her toenails about every six months. The rate of nail growth declined greatly after Bajiaolian poisoning but no abnormality in hair growth was noted. We visited her again six months and 12 months later (at 7 years and then 7 years and 6 months after poisoning). She claimed not to have cut her fingernails since before the poisoning and they were almost the same length in all three visits (Figs. 2 and 3).



Fig. 1. Photograph displaying the fingernails of the 48-year-old female patient. Bajiaolian poisoning had occurred six years earlier. This patient had cut her thumb nails once a month prior to the intoxication, but had not cut her nails following the intoxication.



Fig. 2. Photograph displaying the fingernails of the 48-year-old female patient. This photograph was taken approximately seven years after her Bajiaolian poisoning. Comparison with Fig. 1 does not reveal any discernable change in fingernail length. The nails had not been cut in the period between the two photographs.



Fig. 3. Photograph displaying the fingernails of the 48-year-old female patient. This photograph was taken approximately 7.5 years after her Bajiaolian poisoning. Comparison with Figs. 1 and 2 does not reveal any discernable change in fingernail length. The nails had not been cut.

Discussion

According to the Annual Report of the American Association of Poison Control Centers, there were 363 exposures to podophyllotoxin between 1997 and 2002 (24–29). Of the 363 cases, the outcomes were attributed to severe effects in two cases (0.55%) and moderate effects in 16 cases (4.4%). Moderate and severe podophyllotoxin poisonings, though unusual, still occasionally occur in the USA.

In our case, the symptoms and signs developed included abdominal pain, vomiting, watery diarrhea, unsteady gait, prolonged sensory ataxia, paralytic ileus, initial leukocytosis and then leukopenia, and abnormality in liver function test. These findings are similar to the previously reported podophyllotoxin poisonings. However, the cessation of nail growth has never been reported in the literature.

The biochemical bases of the toxic effects of podophyllotoxin include inhibition of protein, RNA, and DNA synthesis. It inhibits mitotic activity and results in reduction of H3-thymidine incorporation (30). It binds specifically to tubulin to prevent its polymerization (31), and then blocks cell division by its inhibition of microtubule assembly in the mitotic apparatus (32,33). Different derivatives of podophyllotoxin have different biochemical mechanisms. According to the animal studies by Chang et al., neuronal changes were readily observable after podophyllotoxin poisoning in mice models. Edematous changes of motor neurons of anterior horn were observed in the spinal cord. More serious changes were found in the dorsal ganglion neurons and the nerve fibers in the central and peripheral systems (34). Histopathological examinations showed degenerative changes in the liver, intestine, testis, and pancreas 72 hours after animals had ingested podophyllotoxin (35).

The nail is a durable keratinized structure which continues growth throughout life from nail root (nail matrix) to a free edge distally. It is formed from the matrix as the cell become larger, paler and eventually the nucleus disintegrates (36). The average rate for fingernail growth varies between 1.9 and

4.4 mm/month (37). A reasonable guide for growth rate is 3 mm/month in fingernails and 1 mm/month in toenails (38). Multiple factors, which are divided into systemic and local illness, decrease the rate of nail growth. Systemic factors include old age, malnutrition, fever, and severe illness (i.e., mumps, acute febrile tuberculosis, typhoid and chronic nephrosis) (37–40). Local factors include denervation, including median or ulnar nerve injury (41,42), nail bed injury (43), nail matrix injury (44), sympathetic dystrophy (45), relapsing polychondritis (46), and local infection. Some chemotherapeutic or immunosuppressive agents, such as methotrexate and azathioprine, have also been reported (47) to decrease nail growth.

Nail growth of the patient was reported to be normal for 48 years before Bajiaolian poisoning. The patient had no systemic diseases except chronic headache before Bajiaolian poisoning. She had no local injury over both feet and hands. No chemotherapy or immunosuppressive agents had been used. At the same time, her family that lived with her didn't develop similar presentations of decreasing of nail growth. We were unable to identify any specific events which could have stopped her nail growth. Regardless, the patient's history, clinical course, biochemical and hematologic examinations, and laboratory investigations were consistent with podophyllotoxin intoxication. We therefore infer that the cessation of her nail growth was caused by Bajiaolian poisoning.

According to Chinese herbal dictionaries and textbooks, the recommended dose of Bajianlian ranges from 3 to 60 mg. The rhizomes of Bajianlian contain 2–4% of podophyllum resin, of which approximately 20% is podophyllotoxin. That is 60 to 2400 mg of podophyllum resin or 12 to 480 mg of podophyllotoxin. The minimal reported lethal oral dose of podophyllum resin is 350 mg which is still within the recommended dosage of herbal textbooks. Our patient's ingestion of 15 mg of Bajianlian is within the recommended dosage of the herbal textbooks, but it certainly is a toxic dose and exceeds the minimal lethal dose for a 50 kg person.

Bajiaolian is an unusual poison for most of the physicians in Taiwan. In the initial presentation at the local clinic and the first hospital, although the patient told the physicians that she had used Bajiaolian for chronic headache and a neurologist had even been consulted for her severe neurological deficit, the doctors did not make the connection between the patient's symptoms and signs and the exposure to Bajiaolian. To improve the early diagnosis of Bajiaolian poisoning, understanding its poisoning effects and clinical presentations is important to the front-line clinicians.

Discontinuation of nail growth is a new sequela of Bajiaolian intoxication. The possible mechanisms include inhibition of the mitotic activity of the nail matrix or neuron damage.

Conclusion

We found no previous reports in the literature in which discontinuation of nail growth was a clinical presentation of

Bajiaolian poisoning. The most interesting aspect is that the rate of nail growth declined dramatically after a single dose of Bajiaolian. The long-term effect of Bajiaolian poisoning on the nail matrix is unknown. Further studies on the safe dosage for topical application are necessary. Because Bajiaolian is readily available in herbal stores, public health surveys should be carried out to determine if other cases of Bajiaolian poisoning exist. Careful review of the Bajiaolian doses recommended by Chinese herbal dictionaries and textbooks is necessary to prevent future toxic events.

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