



CLINICAL PRACTICE ARTICLE

REVISED Strychnine poisoning due to traditional Chinese medicine: a case series [version 2; peer review: 2 approved]

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Abstract

Background: Strychnine poisoning is rare but possibly fatal. The most reported sources of strychnine poisoning include rodenticides and adulterated street heroin. Here we report a case series of an unusual cause of strychnine poisoning – *Strychni semen*, a herb known as “maqianzi” in traditional Chinese medicine (TCM).

Methods: All cases of strychnine poisoning confirmed by the Hospital Authority Toxicology Reference Laboratory (HATRL, the highest-level clinical toxicology laboratory in Hong Kong) between May 2005 and May 2018 were reviewed.

Results: Twelve cases of strychnine poisoning were recorded, and *Strychni semen* was the exclusive source. Ten (83%) patients presented with muscle spasms, and four (33%) developed typical conscious convulsions. The poisoning was severe in two (17%) patients, moderate in three (25%) and mild in eight (58%). No case fatality was recorded. Three (25%) patients were TCM practitioners and two (17%) were laymen who bought the herb themselves without a proper prescription.

Conclusion: The practice of TCM is becoming popular in different parts of the world amid the COVID-19 pandemic. The spectrum of clinical features of strychnine poisoning secondary to *Strychni semen* are similar to those arising from different origins. Eliciting a history of TCM use, apart from exposure to rodenticides and drugs of abuse, may allow timely diagnosis in patients with compatible clinical features. Enhancement of TCM safety could minimize the hazard.

Keywords

Strychnine poisoning, herbal medicine poisoning, *Strychni semen*, Maqianzi

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 2 (revision) 17 Dec 2021		 report
version 1 15 Sep 2021	 report	 report

1. **Jou-Fang Deng**, Taipei Veterans General Hospital, Taipei, Taiwan
2. **Camille Paradis** , Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Tong HF:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Writing – Original Draft Preparation; **Chan CY:** Data Curation, Project Administration; **Ng SW:** Data Curation, Formal Analysis, Investigation, Validation; **Mak TWL:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing

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REVISED Amendments from Version 1

Percentages have been rounded to the nearest integer. The reason for the use of strychnine as a heroin adulterant has been removed in the introduction section. The term “weakness” has been replaced with “stiffness”. HATRL is the only laboratory which provides analytical confirmation for strychnine poisoning in Hong Kong, and such information has been listed in the methods section. The years of clinical presentation have been added in the Table 1. The sentence “We believe that empowering patients ... for decades.” has been removed from the discussion section. In the bibliography, one citation on a study of rodenticide-induced strychnine poisoning has been added, and Clin Toxicol (Phila) has been changed to Clin Toxicol.

Any further responses from the reviewers can be found at the end of the article

Background

Around a century ago, the wide availability of **strychnine as an over-the-counter remedy** for a variety of ailments caused a significant number of deaths, especially in children¹. As such, strychnine has been withdrawn from the food and medicine markets in many countries, and poisoning is now rare. Nowadays, the most reported sources of poisoning include rodenticides²⁻⁴ and adulterated street heroin⁵⁻⁷.

Strychni semen, a herb also known as “maqianzi” in traditional Chinese medicine (TCM), also contains strychnine together with its less toxic analog, brucine. The herb is used for its analgesic, anti-diarrheal, antioxidant, anti-inflammatory, antimicrobial and anti-neoplastic properties^{8,9}. However, it has an apparently narrow therapeutic index – the recommended dosage is 0.3–0.6 g daily according to the Chinese Pharmacopoeia 2015¹⁰.

Strychnine is rapidly absorbed from the gastrointestinal tract and toxicity may occur as soon as 15 minutes after ingestion. By inhibition of glycine receptors at the spinal cord, strychnine overdose causes stiffness and intermittent spasms. Each episode of spasm lasts for around half to two minutes and is easily triggered by emotional distress or even trivial sensory stimuli¹¹. Severe spasms may mimic epileptic convulsions, but there is preserved awareness without post-ictal drowsiness. This typical feature of strychnine poisoning is known as conscious convulsions/spinal seizures¹² and may mimic tetanus, though the latter can be differentiated by a positive history of injury, and a more gradual and protracted course of illness¹³. Severe convulsions may cause rhabdomyolysis and can be rapidly fatal due to respiratory failure¹⁴. Milder symptoms of strychnine poisoning include agitation, palpitations, hyperventilation, dizziness, hyperacusis and paresthesia¹⁵.

Apart from epilepsy and tetanus, acute dystonia and hypocalcemia are the other differential diagnoses of strychnine poisoning. In acute dystonia, muscle contractions are more static. Hypocalcemia also results in numbness and muscle spasms but can be easily differentiated by blood tests¹⁶.

Management of strychnine poisoning is supportive. Activated charcoal may be given if patients present early. Benzodiazepines are used to control muscle spasms, and a dark and quiet environment also helps. Airway intervention and mechanical ventilation can be lifesaving, though succinylcholine must be avoided as it exacerbates muscle spasms¹⁶⁻¹⁸.

Here we report a case series of an unusual cause of strychnine poisoning – *Strychni semen*.

Methods

All cases of strychnine poisoning, which were analytically confirmed by the Hospital Authority Toxicology Reference Laboratory (HATRL), between May 2005 and May 2018 were reviewed. HATRL is the highest-level clinical toxicology laboratory serving all public hospitals in Hong Kong, and it is the only laboratory which provides analytical confirmation of strychnine poisoning in the territory. Clinical records were reviewed to collect the patient demographics, details of exposure, clinical features, pertinent laboratory findings, treatment provided and clinical outcomes.

Diagnosis of strychnine poisoning was confirmed by detection of strychnine in urine, and *Strychni semen* exposure was inferred by the concurrent detection of brucine. Detection of strychnine and brucine was performed by using high-performance liquid chromatography with diode array detection (HPLC-DAD; Agilent 1100 and 1200 LC Systems with DAD) and liquid chromatography-tandem mass spectrometry (LC-MS/MS; Agilent 1100 LC System with Applied Biosystems 4000 QTrap triple-quadrupole mass spectrometer)¹⁹. Wherever available, herbal prescriptions were transcribed and studied, unused herbs were morphologically identified, and analysis of strychnine and brucine was performed on suspicious herbal products.

Results

There were twelve cases of strychnine poisoning confirmed during the study period, and all of them were due to *Strychni semen* (Table 1). Two severe cases are further described to highlight the salient features.

A 55-year-old male (case 5 in Table 1), a TCM practitioner, was woken up by severe wrist pain at night and inadvertently took 19 grams (31 times the recommended therapeutic dosage) of *Strychni semen* instead of another herb. He developed dizziness, hyperventilation, generalized muscle spasms and conscious convulsions 30 minutes later. He attended the accident & emergency department and was hospitalized. Activated charcoal and intravenous diazepam (3 mg) were given, and the symptoms subsided six hours later. However, there was rhabdomyolysis (plasma creatine kinase level 5085 U/L; reference interval 45–235 U/L) and he required prolonged aggressive rehydration. *Strychni semen* exposure was confirmed by detection of both strychnine and brucine in urine. He eventually recovered and was discharged after one week of admission.

A 45-year-old man (case 7 in Table 1) consulted a bone setter for gouty arthritis and was dispensed some herbal powder

Table 1. Summary of patient demographics and clinical features.

Case	Year	Sex	Age (y)	Latent period (hrs)	Symptom duration (hrs)	Stiffness	Spasm	Convulsion	Other manifestations
1 ^c	2005	M	58	0.5	4.5	-	-	-	Agitation, palpitations, dizziness, paresthesia
2 ^b	2005	M	52	0.6	1.0	+	+	-	Not reported
3	2005	F	36	2.0	4.0	+	+	-	Not reported
4 ^b	2006	M	32	0.5	0.5	+	+	-	Palpitations, dizziness
5 ^{a,b}	2006	M	55	0.5	6.0	+	+	+	Dizziness, hyperventilation
6 ^a	2006	F	8	0.5	0.5	+	-	-	Paresthesia
				0.2	1.3	+	+	-	Dizziness, paresthesia
7 [*]	2007	M	45	1.0	7.0	+	+	+	Dyspnea, paresthesia, dizziness, hyperacusis
8 ^{a,c}	2007	F	54	2.0	N/A	-	+	-	Dizziness
				2.0	6.0	+	+	+	Vomiting, dizziness
9	2007	F	36	0.3	3.0	+	+	+	Palpitations
10 ^a	2008	M	49	N/A	3.0	-	-	-	Chest pain, dyspnea
				1.0	3.0	-	-	-	Chest pain, dyspnea, respiratory acidosis
11	2012	F	55	0.5	6.0	-	+	-	Paresthesia
12 ^a	2018	F	48	0.5	3.0	-	+	-	Palpitations, dyspnea
				2.0	3.0	+	+	-	Palpitations, dyspnea

*: Severe poisoning (see text for description)

^a: Recurrent episodes of poisoning

^b: This patient was a TCM practitioner

^c: This patient was a layman who bought the herb from a TCM pharmacy

†: Present

-: Absent

with undisclosed ingredients. One hour after taking the herbal powder, he developed chest discomfort, dyspnea, hyperacusis, generalized muscle spasms, trismus, opisthotonus and conscious convulsions. He was hospitalized and repeated dosing of intravenous diazepam (10 mg in total) was required to control the convulsions. The symptoms lasted for seven hours, but he soon requested early discharge despite medical advice. *Strychni semen* exposure was subsequently analytically confirmed.

The demographics and clinical features of all 12 patients are summarized in Table 1 in chronological order of presentation. Numbers of male and female patients were equal. The median age was 48.5 years (range 8 – 58 years). *Strychni semen* exposure was the exclusive source of strychnine poisoning, and the herb was most commonly used to relieve chronic pain. Four (33%) patients had recurrent episodes of poisoning

before the definite diagnosis was made. Ten (83%) patients presented with muscle spasms, and four (33%) patients developed typical conscious convulsions. One patient (case 10) had transient respiratory acidosis, which resolved spontaneously. Median latent period before symptom onset was 0.5 hours (range 0.2 – 2 hours), and the median symptom duration was 3.5 hours (range 0.5 – 7 hours). Based on a previously published poisoning severity score system²⁰, the poisoning was severe in two (17%) patients, moderate in three (25%) and mild in seven (58%). No case fatality was recorded, and all patients recovered eventually.

Intriguingly, three (25%) patients were professional TCM practitioners (cases 2, 4, 5) themselves. On the other hand, two (17%) were laymen who bought *Strychni semen* without a proper prescription. One was a housewife (case 8) who bought the herb at a Chinese medicine pharmacy and took a markedly

excessive dose (15 times the recommended dosage) of *Strychni semen* based on a misprinted soup recipe in a book borrowed from a public library²¹.

Discussion

Our results showed that *Strychni semen* was the exclusive source of clinically and analytically confirmed strychnine poisoning in Hong Kong during the 14-year study period. In addition, *Strychni semen* poisoning shared a similar spectrum of clinical features with strychnine poisoning due to other causes^{1,11,12,16,17,22}. This peculiarly predominant source of strychnine poisoning in Hong Kong is likely contributed to by the fact that most Hong Kong residents are ethnic Chinese.

Nevertheless, with globalization, immigration and the rising popularity of TCM around the world²³, especially amid the COVID-19 pandemic²⁴, eliciting a history of herbal medicine use, in addition to exposure to rodenticides and drugs of abuse, may be helpful in making the clinical diagnosis of strychnine poisoning. Identifying the source of strychnine poisoning is also important for public health measures.

Unfortunately, obtaining a definite history of *Strychni semen* use can be challenging if the herbal prescription is not disclosed by the TCM practitioner. In our case series, five (42%) patients did not possess such information, which made the diagnosis difficult. We noted that TCM clinics associated with the Hospital Authority and the universities in Hong Kong provide computer-generated herbal prescriptions to their patients. However, this good practice is neither universally exercised nor required legally.

Intriguingly, three patients of our case series were TCM practitioners themselves, who were the learned professionals of this dangerous herb. This illustrates the fact that *Strychni*

semen is a dangerous herb and systematic measures should be introduced to minimize such poisoning events.

Enhancement in TCM dispensing could be an important measure. Among our case series, the TCM dispensers did not prevent the inappropriate dosages of *Strychni semen* from being prescribed by the TCM practitioners. Shockingly, *Strychni semen* was dispensed to two patients (case 1 & 8) who did not bear a registered TCM practitioner's prescription. These sub-optimal practices should certainly be noted and enhanced by the profession. To ensure patient safety, both good prescription and dispensing practices are essential. In the long run, all TCM practitioners and dispensers around the world should be adequately trained, certified and licensed.

Conclusion

The practice of TCM is becoming popular in different parts of the world amid the COVID-19 pandemic. This study serves to remind the profession that strychnine poisoning can result from TCM use. The spectrum of clinical features of strychnine poisoning secondary to *Strychni semen* (maqianzi) are similar to those that arise from different origins. Eliciting a history of TCM use, apart from exposure to rodenticides and drugs of abuse, may allow timely diagnosis in patients with compatible clinical features. Enhancement of TCM safety could minimize the hazard.

Consent

We respected all patients' rights to privacy and protected their identity. The study was approved by the Kowloon West Cluster Research Ethics Committee of the Hospital Authority, Hong Kong (approval number KW/EX-19-002), who waived the need for informed consent as the presented data have been anonymized and de-identified.

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Reviewer Report 04 February 2022

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Camille Paradis 

Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

Thank you very much for your responses and changes to your manuscript, I fully agree with them.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 06 December 2021

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Camille Paradis 

Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

This is a retrospective case series. This work is very interesting since it presents a circumstance of exposure to strychnine by therapeutic error, which is unusual compared to the numerous cases of intoxication in the context of suicidal behavior or other involuntary circumstances. This has implications for the management of intoxicated patients because this circumstance does not raise suspicion of this type of xenobiotic.

For the context, I find that the reason for the use of strychnine as a heroin adulterant is not easy to understand. If it is difficult to explain it quickly, perhaps it would be better to just mention this use, without detailing its origin. The bibliographic reference can remain the same. Secondly, I did not really understand why the term "weakness" was used for the description of strychnine poisoning. Classically, patients present with a state of hyperexcitability with significant rigidity, perhaps you meant to refer to the symptom "coma" by this term? If you change it, consider doing so in Table 1 as well.

Regarding the data shared on your case series, do you have any notion of the amounts of strychnine and brucine found in the urine of your patients? If you have them, it would be a pity not to share them, especially to compare them with the rest of the literature. In addition, it might be interesting to provide the dates of each case of intoxication, perhaps in your table. Actually, you indicate that the use of TCM is increasing, it might be interesting to see how the number of intoxications evolve over the duration of your study.

For the discussion, I really have trouble seeing how you conclude that *Strychni semen* poisonings are the only circumstances of strychnine poisonings in your study location. It is possible that you have other arguments for stating this, but they need to be included in your paper. In particular, you should explicitly state that no center other than HATRL can analytically confirm strychnine poisoning in your study location. In a recently published study by *Paradis et al.*,¹ it is shown that cases of strychnine poisoning still occur through old rodenticide products. Then I find the sentence that starts with "We believe that empowering patients..." perhaps a bit long and I find it difficult to easily understand its purpose.

Finally, two formal remarks. On the bibliography, you specify "Clin Toxicol (Phila)" (2) and "Clin Toxicol" alone (13), check that there is not a clarification to be made on which one is alone. For the expression of all your values as a percentage, it seems to me that for a number of patients <100 you should express your values as integers and not as decimal numbers.

For the conclusion, I find it perfectly appropriate with a clear purpose, its opening is particularly valid.

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Is the background of the cases' history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the conclusion balanced and justified on the basis of the findings?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacy, Clinical Toxicology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Dec 2021

Hok Fung Tong,

Thank you very much for your comments and suggestions on improving the quality of the manuscript. Please kindly find below our responses.

1) For context, I find that the reason for the use of strychnine as a heroin adulterant is not easy to understand. If it is difficult to explain it quickly, perhaps it would be better to just mention this use, without detailing its origin. The bibliographic reference can remain the same.

- The reason has been removed.

2) I did not really understand why the term "weakness" was used for the description of strychnine poisoning. Classically, patients present with a state of hyperexcitability with significant rigidity, perhaps you meant to refer to the symptom "coma" by this term? If you change it, consider doing so in Table 1 as well.

- We replaced the term "weakness" with "stiffness" instead as this should be the more appropriate description, although some patients would describe such symptom as "weak".

3) Regarding the data shared on your case series, do you have any notion of the amounts of strychnine and brucine found in the urine of your patients? If you have them, it would be a pity not to share them, especially to compare them with the rest of the literature.

- Our laboratory did not provide quantitative analyses of strychnine and brucine. Therefore, such information is not available.

4) In addition, it might be interesting to provide the dates of each case of intoxication, perhaps in your table. Actually, you indicate that the use of TCM is increasing, it might be interesting to see how the number of intoxications evolve over the duration of your study.

- We have added the years of clinical presentation in Table 1.

5) For the discussion, I really have trouble seeing how you conclude that Strychni semen poisonings are the only circumstances of strychnine poisonings in your study location. It is

possible that you have other arguments for stating this, but they need to be included in your paper. In particular, you should explicitly state that no center other than HATRL can analytically confirm strychnine poisoning in your study location.

- Being the highest level clinical toxicology laboratory in Hong Kong, HATRL is the only laboratory which provides analytical confirmation for strychnine poisoning locally. For all analytically confirmed strychnine poisoning cases that we have encountered during the study period, they were all due to Strychni semen. Such information is now stated in the methods section.

6) In a recently published study by Paradis et al., it is shown that cases of strychnine poisoning still occur through old rodenticide products.

- We agree that strychnine poisoning can still occur through rodenticides, and have added the citation of this study in the introduction section.

7) Then I find the sentence that starts with "We believe that empowering patients..." perhaps a bit long and I find it difficult to easily understand its purpose.

- We have removed the sentence.

8) Finally, two formal remarks. On the bibliography, you specify "Clin Toxicol (Phila)" (2) and "Clin Toxicol" alone (13), check that there is not a clarification to be made on which one is alone. For the expression of all your values as a percentage, it seems to me that for a number of patients <100 you should express your values as integers and not as decimal numbers.

- We have unified the references as "Clin Toxicol", and have modified the percentages accordingly.

Competing Interests: No competing interests were disclosed.

Reviewer Report 29 September 2021

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Jou-Fang Deng

Division of Clinical Toxicology and Occupational Medicine, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

I am a medical toxicologist having been in practice since 1982. Many years ago, I used to treat

severe convulsion cases related to events of drug abuse, which ended up with a diagnosis of strychnine poisoning confirmed by a clinical toxicology laboratory. However, strychnine poisoning related to the use of traditional medicine is not what I am familiar with, and as it is described in the article, it indeed may potentially occur in our society, in which the practice of traditional medicine is not well regulated.

Strychnine poisoning could be a life-threatening condition, and without appropriate treatment and timely ventilation support, life can disappear quickly. This article has brought up some important points, relevant to both the societies of traditional medicine and western medicine. Since strychnine itself does possess prominent toxicity, to prevent any unnecessary and avoidable poisoning, I would like to propose that the dispensing of strychnine contented herbs should not continue, given its toxic potential.

This article describes a retrospective study of a collection of unusual cases of strychnine poisoning which need to be remembered in general practice as well as emergency settings. This is a very interesting clinical report and is valuable for the clinical doctors. Since it is a well written article, and clearly demonstrates the importance of the history of herb intake in our daily practice, I would recommend that there is no need for any revision.

Is the background of the cases' history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the conclusion balanced and justified on the basis of the findings?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical toxicologist

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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