ORIGINAL ARTICLE

Chinese herbal medicine–induced anticholinergic poisoning in Hong Kong

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Objective To study the epidemiology, causes, and clinical course of Chinese herbal medicine–induced anticholinergic poisoning in Hong Kong.

Design Case series.

Setting Hong Kong.

Patients All case histories of Chinese herbal medicine–induced anticholinergic poisoning (with laboratory confirmation) recorded by the Hong Kong Poison Information Centre over a 93-month period were accessed for analysis.

Results During the relevant period, 22 clusters of Chinese herbal medicine–induced anticholinergic poisoning involving 32 patients were retrieved. The commonest clinical features were mydriasis (n=32, 100%) and confusion (n=24, 75%). No gastro-intestinal decontamination was performed. None of these patients underwent intubation, defibrillation, cardioversion, pacing, fluid resuscitation, inotropic support or dialysis. Of the 32 patients, 17 (53%) were treated with physostigmine because of confusion, three of whom had previously received intravenous benzodiazepines. No patient could be effectively treated with benzodiazepines alone. There was no mortality, and all the patients were discharged within 3 days. None of them re-attended the emergency department within 1 week of discharge. The commonest cause was the substitution of flos campsis (*Campsis grandiflora*) by the flower of the *Datura* species (7 clusters [32%] in 10 patients).

Conclusion Mydriasis and confusion were the commonest clinical features of Chinese herbal medicine–induced anticholinergic poisoning in Hong Kong. Physostigmine was frequently used in the treatment; benzodiazepines appeared ineffective. The commonest cause was the substitution of flos campsis (*Campsis grandiflora*) by the flower of the *Datura* species.

New knowledge added by this study

- Mydriasis and confusion were the commonest clinical features of Chinese herbal medicine–induced anticholinergic poisoning in Hong Kong.
- Physostigmine treatment was frequently administered, but benzodiazepines appeared ineffective.
- The commonest cause was the substitution of flos campsis (*Campsis grandiflora*) by the flower of the *Datura* species.

Implications for clinical practice or policy

- Anticholinergic poisoning should be considered for patients who presented with confusion and mydriasis after taking Chinese herbal medicines.
- Regarding this form of poisoning, gastro-intestinal decontamination is usually not indicated and it can be safely and effectively managed in accident and emergency departments, thus reducing hospital admissions and conserving resources.

Key words
Cholinergic antagonists; Hong Kong; Medicine, Chinese traditional; Poisoning

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Introduction

The use of Chinese herbal medicine (CHM) is common in Hong Kong. According to the Chinese Medicine Council of Hong Kong, over half of all Hong Kong Chinese are reported to use it either for treating illness or maintaining health, and about 18% of

all medical consultations in Hong Kong involve Chinese medicine practitioners.[1] From time to time, emergency physicians see patients suffering from poisoning induced by CHM, which has not been well studied or commonly reported in the English language literature. The aim of this study was to analyse the epidemiology, causative agents, clinical presentations, management, and outcome of CHM-induced anticholinergic poisoning (AP) in Hong Kong.

香港因服用中藥而導致的抗膽鹼性中毒

目的 研究香港因服用中藥而導致抗膽鹼性中毒的流行病學、成因以及臨床症狀。

設計 病例系列。

安排 香港。

患者 於93個月內因服用中藥而導致抗膽鹼性中毒並獲化驗室確認之個案。個案資料來自香港中毒諮詢中心之資料庫。

結果 研究期間共有22宗群因服用中藥而導致抗膽鹼性中毒的事故，涉及32名患者。最常見的臨床徵狀及病徵為瞳孔放大（32名患者，100%）和神志不清（24名患者，75%）。患者中並沒有進行腸胃道解毒，亦沒有需要插喉、心臟除顫、心臟復律、心臟起搏、快速輸液、強心藥或透析。32名患者中，17人（53%）因神志不清而獲注射毒扁豆素；其中3名患者早已獲注射苯重氮基鹽。單獨注射苯重氮基鹽未能有效治療患者。死亡率為0%。所有患者均於3日內出院。沒有患者於出院後1週內需要再次到急症室求診。最常見的中毒成因是將凌宵花與洋金花混淆而誤服洋金花，共有7宗群事故（32%，10名患者）。

結論 香港因服用中藥而導致的抗膽鹼性中毒的病例中，最常見的臨床徵狀及病徵為瞳孔放大和神志不清。治療中毒個案往往需要使用毒扁豆素，苯重氮基鹽似乎無效。最常見的中毒成因是將凌宵花與洋金花混淆而誤服洋金花。

Methods

Patients who had CHM-induced AP in Hong Kong from June 2004 to March 2012 were eligible for this case series. All case histories of such patients (with laboratory confirmation) recorded by the Hong Kong Poison Information Centre (HKPIC) over the 93-month period were retrieved for analysis. The HKPIC provides a consultation service to all medical and health care workers in Hong Kong, and collects data of poisoning cases reported from all the accident and emergency departments (AEDs) in the ambit of the Hospital Authority. All pertinent demographics, clinical information, management approaches, investigation results, and outcome data were retrieved and analysed.

TABLE 1. The symptoms and signs of Chinese herbal medicine–induced anticholinergic poisoning in Hong Kong

Symptom/sign	No. (%) of patients
Symptom	
Confusion	24 (75)
Dizziness	21 (66)
Nausea or vomiting	10 (31)
Weakness	10 (31)
Blurring of vision	6 (19)
Dysuria	5 (16)
Palpitation	4 (13)
Abdominal discomfort	3 (9)
Chest discomfort	2 (6)
Numbness	2 (6)
Headache	1 (3)
Photophobia	1 (3)
Sign	
Mydriasis	32 (100)
Sinus tachycardia	25 (78)
Dry mouth or skin	20 (63)
Sluggish bowel sound	14 (44)
Hypertension	12 (38)
Palpable bladder	11 (34)
Flushing	8 (25)
Hyperthermia	5 (16)
Agitation	4 (13)
Drowsiness	2 (6)

Results

There were 22 clusters of CHM-induced AP in Hong Kong throughout the study period, which involved 32 patients. The male-to-female ratio was 9:23. The median age was 45 (range, 4-79) years. The median time to symptom onset after taking CHMs was 90 minutes (range, 15 minutes to 9 hours).

The commonest symptomatic features were confusion (n=24, 75%), dizziness (n=21, 66%), nausea or vomiting (n=10, 31%), and weakness (n=10, 31%). The commonest physical examination findings were mydriasis (n=32, 100%), sinus tachycardia (n=25, 78%), and dry mouth or skin (n=20, 63%). Other symptoms and signs were also present (Table 1).

No gastro-intestinal decontamination was performed. No patients underwent intubation, defibrillation, cardioversion, pacing, fluid resuscitation, inotropic support, or dialysis. Three patients (9%) received benzodiazepines; one received 5 mg of midazolam, two (6%) received diazepam (10 and 5 mg + 5 mg + 5 mg). In all, 17 (53%) of the patients, including those who had received benzodiazepines, were given physostigmine and

within 5 minutes their confusion resolved. Nine of these patients were given a single dose of physostigmine with no recurrence of confusion, but in eight others the confusion recurred after a median interval of 2.5 (range, 1-5) hours . The latter patients were given repeated doses of physostigmine (in total, five received 2 doses, two received 3 doses, and one received 4 doses over 12 hours). The physostigmine doses ranged from 0.5 mg to 5 mg. None of these 17 patients was noted to develop a cholinergic crisis or other complication following the administration of physostigmine.

Regarding these 32 patients, 24 (75%) were managed in the AED (13 in the AED's observation ward and 11 in its emergency medical ward). The management sites of these patients are summarised in Table 2.

Of the patients, 10 (31%) were discharged on the same day, 16 (50%) on the next day (day 1), three (9 %) on day 2, and three (9%) on day 3. The mortality rate was 0% and none of them re-attended the AED within 1 week of discharge.

TABLE 2. Where patients with Chinese herbal medicine–induced anticholinergic poisoning were managed

Management/treatment site	No. (%) of patients
Observation ward of the AED*	13 (41)
Emergency medical ward of the AED	11 (34)
Medical ward	4 (13)
Paediatric ward	1 (3)
High dependency unit	1 (3)
Refused hospital treatment	2 (6)

* AED denotes accident and emergency department

TABLE 3. Anticholinergic substances detected in the 32 urine samples

Anticholinergic substances	No. (%) of samples
Atropine	32 (100)
Scopolamine	23 (72)
Anisodamine	20 (63)
Hyoscyamine	13 (41)
Anisodine	4 (13)

All the patients had anticholinergic substances detected in their urine samples; atropine was found in all the samples and other anticholinergic substances in some (Table 3). Among the several causes of CHM-induced AP in our series, substitution of flos campsis (*Campsis grandiflora*) by the flower of the *Datura* species was the commonest (Table 4).

Discussion

The pathophysiology of CHM-induced AP entails competitive blockade of muscarinic cholinergic receptors, which gives rise to the anticholinergic toxidrome. This entails tachycardia, hyperthermia, confusion, dry flushed skin, mydriasis, urinary retention, and decreased bowel sounds. The commonest recognised presentation was confusion, whereas the commonest abnormal physical finding was mydriasis. None of our patients presented with every feature of anticholinergic toxidrome, which means that AP should not be ruled out simply because one or two features were absent. Moreover, it took between 15 minutes and up to 9 hours (median interval, 90 minutes) before symptoms became manifest. All our patients had taken their anticholinergics in the form of a herbal broth; longer latency for symptoms would have been expected had they taken them in the form of tablets or capsules because they dissolve.

No patient underwent gastro-intestinal decontamination, as the risk-and-benefit ratio of such a strategy was considered unacceptable after intake in the form of a herbal broth, from which absorption was likely to have been rapid. Besides, many patients had developed confusion and were not able to cooperate during the procedure. Moreover, this form of poisoning is unlikely to be life-threatening.

Regarding the 17 patients who were treated with physostigmine because of confusion, three had already received intravenous benzodiazepines. Physostigmine is a competitive inhibitor of acetylcholinesterase, the enzyme that degrades acetylcholine. This increases the level of acetylcholine, which enhances activation of the muscarinic cholinergic system. The use of physostigmine in the treatment of AP has been reported in the literature,[2,3] and was already reported

TABLE 4. Causes of Chinese herbal medicine–induced anticholinergic poisoning in this series of patients

Cause	No. (%) of clusters	No. of patients
Substitution of flos campsis (*Campsis grandiflora*) (凌宵花) by flower of the *Datura* species (洋金花)	7 (32)	10
Contamination of *Atractylodes lancea* (蒼朮) with anticholinergic substance	6 (27)	8
Overdose of flower of the *Datura* species (洋金花) itself	3 (14)	4
Contamination of Costus root (木香) with anticholinergic substance	1 (5)	1
Consumption of an unknown herb collected from the countryside	1 (5)	5
Unidentified	4 (18)	4

to be more effective than benzodiazepines as an antidote for such poisoning.[4] Notably, physostigmine directly counteracts the anticholinergic effect whereas benzodiazepines only induce non-specific sedation. Further studies with larger sample sizes are required to compare the effectiveness of physostigmine and benzodiazepines for treating the confusion caused by CHM-induced AP.

None of the patients underwent intubation, defibrillation, cardioversion, pacing, fluid resuscitation, inotropic support or dialysis, and none died. Moreover, 24 (75%) of the patients were managed in the AED, whilst all 32 of the patients were discharged within 3 days; none re-attended the hospital within 1 week of discharge. Such outcomes indicate that in these patients, the degree of poisoning was not very severe. Notably, the clinical outcome of patients managed in the AED did not appear to be worse than in those admitted to the ward. Thus, it appeared that CHM-induced AP could be safely and effectively managed in the AED, which helps to save resources.

All the various anticholinergic substances (atropine, scopolamine, anisodamine, hyoscyamine and anisodine) detected in the urine samples in these patients contain a tropane ring and a basic nitrogen atom in their chemical structure, and are known as naturally occurring tropane alkaloids. They can be found in many plants in the family of Solanaceae, such as Angel's Trumpet (*Datura metel*), henbane (*Hyoscyamus niger*), mandrake (*Mandragora officinarum*), jimson weed (*Datura stramonium*), and deadly nightshade (*Atropa belladonna*). Being antagonist of the muscarinic receptor, they inactivate the muscarinic cholinergic system thus giving rise to the anticholinergic toxidrome.

The commonest cause of CHM-induced AP was the substitution of flos campsis (*C grandiflora*) (凌宵花) by the flower of the *Datura* species (洋金花). Flos campsis (*C grandiflora*) and the flower of the *Datura* species look alike and can easily get mixed up. Flos campsis (*C grandiflora*) is used for the removal of 'blood-heat', 'blood-stasis' and 'wind' (活血通經，涼血祛風), whereas the flower of the *Datura* species is used for the relief of cough, alleviation of pain, and arresting spasm (平喘止咳，解痙定痛). According to the Pharmacopoeia of the People's Republic of China, the dosage of the flower of the *Datura* species should be 0.3 to 0.6 g (daily maximum dose of 1.5 g). Notably, the flower of the *Datura* species, but not flos campsis (*C grandiflora*), contains tropane alkaloids and is specified in Schedule 1 of the Chinese Medicine Ordinance in Hong Kong. According to the latter ordinance, it is an offence to dispense to another person any CHM specified in Scheduled 1, without a prescription from a registered Chinese medicine practitioner. Another source was the contamination of *Atractylodes lancea* (蒼朮) by anticholinergic substances. This herb is purported to remove 'dampness and invigorate the function of the spleen' (健脾去濕) and does not contain tropane alkaloids. Thus, the exact source of contamination remains unclear, but could have been during agricultural procurement, processing, wholesaling, or retailing. Another instance of AP followed intake of the Costus root (木香), which is prescribed for the relief of abdominal pain and to improve digestion. It too is devoid of tropane alkaloids, and so the exact source of the contamination also remains unclear. One other instance followed consumption of an unknown herb collected from the countryside, about which information in the literature is lacking.

Conclusion

Mydriasis and confusion were the commonest clinical features of CHM-induced AP in Hong Kong. Physostigmine was frequently used for treatment and appeared effective, whereas benzodiazepines appeared ineffective. The commonest cause was the substitution of flos campsis (*C grandiflora*) by the flower of the *Datura* species.

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