

CASE REPORT

Inorganic Arsenic Poisoning Following an Intentional Overdose of Realgar-Containing Niu Huang Jie Du Pian: a Case Report and Literature Review

REX PUI KIN LAM¹, ELLA CHAN², JOE KAI SHING LEUNG², MAN LI TSE³, ZHI XIU LIN⁴

¹Emergency Medicine Unit, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong Special Administrative Region, China

²Department of Accident and Emergency, Pamela Youde Nethersole Eastern Hospital, Hospital Authority, Hong Kong Special Administrative Region, China

³Hong Kong Poison Information Centre, Hospital Authority, Hong Kong Special Administrative Region, China

⁴School of Chinese Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China

Abstract

Background: Niu Huang Jie Du Pian (NHJDP) is a widely used realgar-containing Chinese medicine remedy. Most brands are composed of eight ingredients: Niu Huang (*Calculus Bovis*), Xionghuang (realgar), gypsum (calcium sulphate), Dahuang (*Radix et Rhizoma Rhei*), Huangqin (*Radix Scutellariae*), Jugeng (*Platycodon grandiflorum*), Bingpian (borneol), and Gancao (*Radix Glycyrrhizae uralensis*, licorice root). Most users are not aware that Xionghuang (realgar) contains arsenic disulphide [As₂S₂]. Inorganic arsenic poisoning after therapeutic overdoses has been reported in Chinese literature, but no report of acute, intentional overdose of NHJDP has been published. We report a case of intentional overdose of NHJDP leading to arsenic poisoning.

Case Presentation: A 33-year-old woman ingested approximately 100 tablets of NHJDP bought over the counter, along with her usual antidepressants. She presented with somnolence, agitation, epigastric pain and repeated vomiting, compatible with clinical toxicities of NHJDP reported in Chinese literature. At presentation, blood and spot urine arsenic levels were 440.9 and 7,495 nmol/L, respectively. The patient's condition improved rapidly after admission and chelation therapy was not deemed to be necessary.

Discussion: Despite the self-limiting clinical course, the high arsenic level in the patient's blood and urine raises safety concerns regarding the use of NHJDP in the community. Inconsistencies in the sales regulation of arsenic-containing products, and a lack of product label warning regarding arsenic content, may potentiate inadvertent arsenic poisoning.

Conclusion: Clinician should be aware of the possibility of inorganic arsenic poisoning when treating patients with overdose of Chinese medicine remedies that contain Xionghuang (realgar). Proper product labelling may help reduce inadvertent arsenic poisoning.

Keywords: Acute Poisoning; Arsenic; Drug Overdose; Herbal Medicine; Realgar; Traditional Chinese Medicine

How to cite this article: Lam R.P.K, Chan E, Leung J.K.S, Tse M.L, Lin Z.X. Inorganic Arsenic Poisoning Following an Intentional Overdose of Realgar-Containing Niu Huang Jie Du Pian: a Case Report and Literature Review *Asia Pac J Med Toxicol* 2018;100-3.

INTRODUCTION

Niu Huang Jie Du Pian (NHJDP) is a realgar-containing Chinese medicine, widely used as a remedy. Inorganic arsenic poisoning after therapeutic overdoses has been reported in Chinese literature, but no report of acute, intentional overdose of NHJDP has been published. Here, we report a case of inorganic arsenic poisoning following an intentional overdose of NHJDP.

CASE PRESENTATION

A 33-year-old woman was brought into the emergency department (ED) by her husband at noon. She had been found unresponsive in bed with vomitus at around 9 a.m. that day. Three to four empty packets of NHJDP were found next to her bed. The patient had a history of depression, with multiple suicide attempts. Her current medications included lamotrigine, lorazepam, mirtazapine, olanzapine, pregabalin,

quetiapine, and clonazepam.

On physical examination, she was agitated with a Glasgow Come Score of 12 (E3V4M5). Her tympanic temperature was 36.9 °C, blood pressure 142/82 mmHg, pulse 119 bpm, respiratory rate 18 per minute, and oxygen saturation 97% on room air. Her pupils were 3 mm in diameter, equal and reactive to light. Cardiovascular, chest and abdominal examinations were unremarkable. Spontaneous movements of all four limbs were observed. An electrocardiogram showed sinus tachycardia with QRS 99 ms and QTc 434 ms. Her spot glucose level was normal. Laboratory blood tests showed mild leucocytosis (white cell count 11.90 x 10⁹/L; reference range 3.7-9.3 x 10⁹/L) and hypokalaemia (potassium 3.2 mmol/L; reference range 3.6-5.2 mmol/L). Blood arsenic level was elevated (440.9 nmol/L; reference range <40 nmol/L). Spot urine arsenic level was 7,495 nmol/L, and the arsenic/creatinine ratio was 1,735 nmol/mmol Cr (range reference <68 nmol/mmol Cr). Other

*Correspondence to: Dr. Rex Pui Kin LAM; MD, Emergency Medicine Unit, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Room 512, 5/F, William MW Mong Block, 21 Sassoon Road, Pokfulam, Hong Kong Special Administrative Region, China

Tel: (852) 39179413, Fax: (852) 28162293, Email: lampkrex@hku.hk

Received 01 June 2018; Accepted 24 October 2018

blood tests including haemoglobin, platelet count, renal and liver function tests were unremarkable. Paracetamol, salicylates and ethanol were not detected in the patient's serum (Table 1).

The patient was given intravenous normal saline infusion, and was admitted to the emergency medicine ward for observation. She remained haemodynamically stable, and her GCS improved to 15/15 over the next few hours. Further history was obtained from the patient when she became conscious. She admitted having ingested around 100 tablets of NHJDP bought over the counter, and one packet of each of her usual medications, at around 10 p.m. the night before admission, in order to commit suicide. She complained of epigastric pain and repeated vomiting. She then became drowsy and was not able to recall further details. She denied co-ingestion of other medications and alcohol intake. Since her condition rapidly improved after admission with no evidence of systemic organ toxicities, chelation therapy was not administered. She was transferred to the psychiatric ward after her medical condition was stabilized. She left our hospital, against medical advice, two weeks after admission.

She was followed up by the ED Toxicology Team at two, five, seven and ten weeks after the initial presentation. She remained asymptomatic following hospital discharge. At seven weeks, her blood arsenic level decreased to 246.5 nmol/L. The spot urine arsenic level was 10,963 nmol/L, and the arsenic/Cr ratio dropped to 465 nmol/mmol Cr. At ten weeks, her blood arsenic level decreased further to 41.4 nmol/L. The spot urine arsenic level fell to 71 nmol/L, and the arsenic/Cr ratio returned to normal (44 nmol/mmol Cr), as shown in Table 1. She defaulted all subsequent follow-up

appointments, and therefore subsequent blood and urine tests could not be performed.

DISCUSSION

NHJDP is a popular Chinese medicine remedy. Most brands are composed of eight ingredients: Niu Huang (*Calculus Bovis*), Xionghuang (realgar), gypsum (calcium sulphate), Dahuang (*Radix et Rhizoma Rhei*), Huangqin (*Radix Scutellariae*), Jugeng (*Platycodon grandiflorum*), Bingpian (borneol), and Gancao (*Radix Glycyrrhizae uralensis*, licorice root) (1). It is used in a variety of conditions, such as tonsillitis, gingivitis, oral ulcers, and other inflammatory diseases, to purge "toxic heat" (2).

Realgar (>90% arsenic disulphide [As₂S₂]) is considered to be the most toxic ingredient in NHJDP (3). It is also used in many other formulas, and can be found in 191 patented Chinese medicines, of which 86.9% are oral preparations (4). The traditional custom of drinking realgar wine, and painting children's foreheads and limbs with leftover slurries during the Dragon Boat Festival, has been practiced for many centuries in China to ward off diseases and to drive away evil spirits. However, this practice can result in significant systemic absorption of arsenic (5).

Realgar contains mostly inorganic trivalent arsenic, which is more toxic than pentavalent and organic arsenic. However, the water solubility of arsenic in realgar is low, and the presence of the other herbs (except borneol) in the formula of NHJDP appears to decrease arsenic solubility (6). The extract rates for arsenic in artificial gastrointestinal fluids range from 0.805% to 1.926%, and only 4% is bioavailable for absorption (7, 8). Compared with arsenic trioxide (As₂O₃), realgar is

Table 1. Laboratory findings

	On presentation	At 7 weeks	At 10 weeks	Reference range
Complete blood count				
White blood cells	11.9 x 10 ⁹ /L	6.19 x 10 ⁹ /L		3.7-9.3 x 10 ⁹ /L
Haemoglobin	13.1 g/dL	11.6 g/dL		11.5-15.4 g/dL
Platelet count	262 x 10 ⁹ /L	219 x 10 ⁹ /L		160-420 x 10 ⁹ /L
Biochemistry				
Sodium	142 mmol/L	139 mmol/L		136-145 mmol/L
Potassium	3.2 mmol/L	3.5 mmol/L		3.6-5.2 mmol/L
Urea	4.1 mmol/L	2.3 mmol/L		2.7-7.2 mmol/L
Creatinine	64 µmol/L	53 µmol/L		55-83 µmol/L
Total protein	70 g/L	57 g/L		64-83 g/L
Albumin	43 g/L	36 g/L		35-50 g/L
Total bilirubin	9 µmol/L	6 µmol/L		3-21 µmol/L
Alkaline phosphatase	55 IU/L	49 IU/L		36-105 IU/L
Alanine aminotransferase	12 IU/L	14 IU/L		<49 IU/L
Blood arsenic level	440.9 nmol/L	246.5 nmol/L	41.4 nmol/L	<40 nmol/L
Spot urine arsenic level	7,495 nmol/L	10,963 nmol/L	71 nmol/L	N/A
Spot urine creatinine	4.3 mmol/L	23.6 mmol/L	1.6 mmol/L	N/A
Urine arsenic/creatinine ratio	1,735 nmol/mmol Cr	465 nmol/mmol Cr	44 nmol/mmol Cr	<68 nmol/mmol Cr

Table 2. Reported adverse drug reactions of Niu Huang Jie Du Pian in Chinese Literature

Organ System	Adverse Drug Reactions
Respiratory System	Dyspnoea, productive cough
Nervous System	Lethargy, somnolence, agitation
Gastrointestinal tract	Nausea, vomiting, abdominal pain, diarrhoea, gastrointestinal irritation
Liver	Reversible rise in liver enzymes
Urogenital System	Haematuria, cystitis
Haematological System	Thrombocytopenia
Skin	Hyperkeratosis, skin pigmentation, Steven-Johnson Syndrome
Others	Allergic reaction, anaphylaxis, withdrawal symptoms

100-fold less toxic (the LD₅₀ for arsenic trioxide is 33 to 39 mg/kg, compared to 3.2 g/kg for realgar, both in mice) (9). It is also far less toxic than sodium arsenite and arsenate (10).

Acute overdose of trivalent arsenic can cause significant systemic toxicity. Arsenic has a high affinity for the sulphhydryl groups. It inhibits pyruvate dehydrogenase and various important cellular enzymes. It decreases citric acid cycle activity, gluconeogenesis, fatty acid oxidation, cellular glucose uptake, and glutathione synthesis. Arsenic also affects cardiac repolarization currents, causing QT prolongation and ventricular dysrhythmia (11). It is not known whether these toxic effects would occur in acute NHJDP overdose, since there is a paucity of published literature. Most of our current understandings of its toxicities come from adverse drug reaction (ADR) reports published in Chinese, which mainly involve cases of chronic therapeutic overdose. The reported clinical toxicities of NHJDP are summarised in Table 2 (12).

According to the Pharmacopoeia of the People's Republic of China, the daily recommended oral dose of NHJDP is two to three pills, two to three times per day (1). Our patient took more than 10 times this dose. Assuming that each pill contains 4.7 to 28 mg of arsenic and the bioavailability is 4%, the total amount of arsenic absorbed was estimated to be 18.8 to 112 mg (7, 8). The patient's spot urine arsenic level at presentation was 7,495 nmol/L (561.38 µg/L), which exceeded the CDC's cut off point of >50 µg/L for inorganic arsenic poisoning (13). The clinical presentations, including somnolence, agitation, epigastric pain and vomiting, were compatible with NHJDP poisoning, but the concomitant overdose of multiple medications made it difficult to attribute toxic effects to NHJDP alone.

Fortunately, the clinical course in this case was mild and self-limiting, and the patient recovered without chelation therapy. However, the high arsenic level in the patient's blood and urine raises safety concerns regarding its use in the community. Our patient did not know that NHJDP contained arsenic, despite the fact that Xionghuang was listed as an ingredient on the product label. This case exposed inconsistencies in the sales regulation of realgar in the community. In Hong Kong, realgar belongs to Schedule I Chinese Medicine, which can only be purchased in licensed retail shops with a prescription issued by a

registered Chinese medicine practitioner (14). Interestingly, realgar-containing NHJDP can easily be bought over the counter in many groceries and community pharmacies, without a prescription. Although not every brand of NHJDP contains realgar, most brands which do contain realgar do not alert customers to the arsenic content in their product labels and inserts. Whilst acute intentional overdose on the whole is rare, inadvertent arsenic poisoning can occur after chronic misuse (12).

CONCLUSION

In summary, we have reported a case of inorganic arsenic poisoning due to an intentional overdose of NHJDP. Inconsistencies in sales regulation, and a lack of warning of the arsenic content, may potentiate inadvertent arsenic poisoning. Clinician should be aware of the possibility of inorganic arsenic poisoning when treating patients with overdose of Chinese medicine remedies that contain Xionghuang (realgar). Proper product labelling may help reduce inadvertent arsenic poisoning.

Conflict of interest: None to be declared

Funding and support: None

REFERENCES

1. Pharmacopoeia of the People's Republic of China. Beijing: Chemical Industry Press, China; 2010.
2. Wu J, Shao Y, Liu J, Chen G, Ho PC. The medicinal use of realgar (As₄S₄) and its recent development as an anticancer agent. *J Ethnopharmacol* 2011;135:595-602.
3. Pharmacopoeia of the People's Republic of China. Beijing: Chemical Industry Press, China; 2010.
4. Li Y, Wang D, Xu Y, Liu B, Zheng Y, Yang B, et al. Use status and metabolism of realgar in Chinese patent medicine. *J Ethnopharmacol* 2015; pii: S0378-8741(15)00236-6.
5. Zhang YN, Sun GX, Huang Q, Williams PN, Zhu YG. A cultural practice of drinking realgar wine leading to elevated urinary arsenic and its potential health risk. *Environ Int* 2011;37:889-92.
6. Xu Z, Yu S, Huang K. Influence of the different components in Niu Huang Jiedu tablets on solubility of arsenic in realgar. *China J Biochemi Pharmaceutics* 2009;30:121-3.
7. Jin P, Kuang Y, Hu X, Zou D. Study on total contents of 20 trace elements in Niu Huang Jiedu tablets and their extract and arsenic speciation in gastrointestinal fluids by ICP-MS.

- Chin J Pharm Anal* 2014;34:985-91.
8. Koch I, Sylvester S, Lai VW, Owen A, Reimer KJ, Cullen WR. Bioaccessibility and excretion of arsenic in Niu Huang Jie Du Pian pills. *Toxicol Appl Pharmacol* 2007;222:357-64.
 9. Liu J, Lu Y, Wu Q, Goyer RA, Waalkes MP. Mineral arsenicals in traditional medicine: orpiment, realgar, and arsenolite. *J Pharmacol Exp Ther* 2008;326:363-8.
 10. Miao J, Liang S, Wu Q, Liu J, Sun A. Toxicology evaluation of realgar-containing Niu-Huang-Jie-Du Pian as compared to arsenicals in cell cultures and in mice. *ISRN Toxicol* 2011:250387.
 11. Munday SW, Ford MD. Chapter 88: Arsenic. In: Nelson LS, Lewin NA, Howland MA, Hoffman RS, Goldfrank LR, Flomenbaum NE, eds. *Goldfrank's Toxicologic Emergencies*. 9th ed. New York, NY: McGraw-Hill; 2011.
 12. Ni J, Zhao K. Literary analysis of the adverse reactions of Niu Huang-Jie Du pill. *Int J Trad Chin Med* 2013;35:295-7.
 13. Centres for Disease Control and Prevention. Case definition: arsenic (inorganic). Available from <http://emergency.cdc.gov/agent/arsenic/casedef.asp>
 14. Chinese Medicine Ordinance – Schedule I Chinese Herbal Medicines. Available from http://www.legislation.gov.hk/blis_ind.nsf/e1bf50c09a33d3dc482564840019d2f4/6d16d74bea4d8e84482567fa00292a69?OpenDocument