



Case Report

Severe acute intoxication with yohimbine: Four simultaneous poisoning cases

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ABSTRACT

Yohimbine is an indole alkaloid from the leaves and bark of the *Pausinystalia johimbe* tree that has acquired an enviable reputation in treating erectile dysfunction. This report presents four simultaneous severe poisoning/death cases caused by yohimbine. The test samples comprised the venous blood of four middle-aged men (aged 47–65) who were suspected of poisoning; one of the men died due to ineffective rescue. Ethanol concentration determination and toxicological routine screening were performed using gas chromatography with flame ionization detection (GC-FID) and liquid chromatography-tandem mass spectrometry (LC-MS/MS). A specific LC-MS/MS method was developed to quantify yohimbine, which showed concentrations of 459, 249, and 301 ng/mL in three poisoned blood samples and concentrations as high as 5631 ng/mL in the deceased. Moreover, the deceased's autopsy ruled out death from trauma and previous illness, and no other common toxic components were detected in his blood. Therefore, yohimbine poisoning appears to be the most likely cause of death. As a type of alkaloid that can be employed in the treatment of clinical diseases and additives for supplements, the danger of yohimbine should be of widespread concern in society.

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1. Introduction

Yohimbine is a natural indole alkaloid that is extracted from the leaves and bark of the yohimbine tree *Pausinystalia johimbe*, which belongs to Rubiaceae, mainly grows in West Africa, Cameroon and Congo, and has a long history of use as an aphrodisiac in African countries [1,2]. Pharmacological studies have confirmed that yohimbine is a highly potent antagonist of presynaptic and postsynaptic α 2-adrenoreceptors within smooth muscles and blood vessels [3]. It is generally believed that by selectively blocking α 2-adrenoceptors in the locus ceruleus in the brain, sympathetic nerves are excited to increase the release of norepinephrine and dopamine, which can relax vascular smooth muscle, increase peripheral parasympathetic tension and reduce sympathetic tension [4,5]. Studies have shown that yohimbine has a significant effect on the treatment of male erectile dysfunction and is considered an effective drug for improving impotence [3,6]. Alkaloids also dilate peripheral blood vessels, lower blood pressure, have anti-inflammatory effects and can be utilized for

the clinical treatment of atherosclerosis and rheumatism [7]. Yohimbine has also gained popularity in the bodybuilding community due to its lipolytic and sympathomimetic effects for fast weight loss and bodybuilding supplementation [8].

Currently, yohimbine is clinically utilized as a prescription drug with its main dosage forms in powder and tablets, and is also available for purchase on the Internet as an herbal supplement and oral liquid [9]. With increased research, dose-related side effects in clinical applications have been reported. The adverse effects of yohimbine include gastrointestinal distress, hypertension, tachycardia, manic reactions, bronchospasm, palpitations, insomnia/anxiety, chills/cold/shivering, sweating, flushing, and headaches, which can be attributed to its central adrenergic activity [3,9]. Previous studies have reported several adverse cases caused by taking yohimbine [10]. According to the FDA Center for Food Safety and Nutrition (CFSAN), 275 cases of poisoning caused by dietary supplements were monitored in San Francisco within a year (2006), and yohimbine products accounted for 18% of supplement-related symptomatic cases [11]. Since the drug has not yet been subjected to scientifically rigorous human clinical trials and safety assessments, a few death cases related to yohimbine have been published.

This study reports four simultaneous cases of poisoning/death caused after yohimbine consumption.

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2. Case reports

The following four cases co-occurred in Liangshan County, and the four poisoned/deceased persons were all working/retired employees of a local hospital.

Case 1: A 47-year-old male hospital staff member took approximately 4–5 g of a drug powder at the work unit with three other colleagues. After taking it for 1–2 hours, the man developed flushing, sweating, headache, nausea, and vomiting (the vomit was stomach contents with no coffee-like substances and bile). After 10 h of medication, the above symptoms had not improved significantly, and he was then sent to the hospital's emergency department and transferred to the nephrology department for rescue. After admission, the four blood coagulation indexes and the electrocardiogram were checked urgently. The patient was diagnosed as acute drug poisoning with sinus tachycardia. Upon inquiry, the patient denied other long-term drug or medical history. Via treatment, the patient's poisoning symptoms improved significantly, and he was discharged after three days.

Case 2: A 55-year-old male hospital staff member took approximately 4–5 g of the above drug with the patient in case 1 and two other colleagues at the work unit. After taking the drug, the symptoms were similar to those of the patient in case 1, who was sent to the hospital at the same time and was similarly diagnosed as acute drug poisoning with sinus tachycardia. The subsequent test and treatment were the same as the above patient in cases 1. The patient stated that he had a history of type 2 diabetes (fasting blood sugar of 8 mmol/L), hypertension (level 3, high risk), and chronic hepatitis B for many years.

Case 3: A 65-year-old male hospital retiree took approximately 4–5 g of the above drug with the patients in cases 1 and 2 and one other colleague at the work unit. The symptoms of poisoning were similar to those in the above two cases. The patient was also sent to the hospital for rescue 10 h after taking the drug, and the subsequent test and treatment were the same as the above two patients in cases 1 and 2. The patient denied other long-term drug or medical history.

The above three patients' specimens were all collected immediately from the median cubital vein after admission to hospital and then anticoagulated and stored at -20°C for further toxicological analysis.

Case 4: A 55-year-old male hospital staff member took a traditional Chinese medicine with the patients in the above three cases at the work unit. According to the information, the above three poisoned persons described that the man gathered them and provided a drug (powder) named yohimbine, which can increase sexual function. The drug was repurchased by him from the Internet. It was known that the man was an active physician in a local hospital with a medical background. Unlike the other three poisoned persons, who dissolved approximately 4–5 g of powder in water and drank it, the man swallowed the drug at an unknown dose to pursue the drug effect. Subsequently, the man developed the above-mentioned symptoms, such as nausea and vomiting, and called an ambulance 10 h later to be sent to the hospital for rescue. Unfortunately, the man died en route to the hospital. After the incident, a detailed autopsy and dissection of the deceased were completed three days after death, and 10 mL femoral venous blood was collected during the autopsy and stored at -20°C until assayed.

An autopsy of the deceased was performed three days postmortem. External examination revealed no lesions other than an old surgical scar with a length of 6.5 cm on the skin at McBurney's point on the right abdomen. The autopsy showed congestion and edema of the internal organs, especially acute pulmonary congestion, pulmonary edema, and focal pulmonary

hemorrhage in the lungs. The autopsy ruled out death from trauma and previous illness.

3. Material and methods

3.1. Chemicals and reagents

Yohimbine was purchased from Cerilliant (Round Rock, USA). Proadifen and aprobarbital were obtained as gifts from the Institute of Criminal Science and Technology, Public Security Bureau of Jining City (Jining, China). 6-Acetylmorphine-D3 was supplied by Sigma-Aldrich (Merck KGaA, Darmstadt, Germany). Ethanol (HPLC grade) was purchased from Cerilliant (Round Rock, USA). Both tert-butyl alcohol (ACS grade) and boric acid (ACS grade) were obtained from CNW (Shanghai, China). Ethyl ether (AR grade) was supplied by Hushi (Sinopharm Group Co. Ltd., Shanghai, China). Both methanol and acetonitrile (HPLC grade) were purchased from Merck (Darmstadt, Germany). Ammonium acetate (HPLC grade) and formic acid (AR grade) were supplied by Fluka Chemical Co. (Bruchs, Switzerland). Ultra-purified water was filtered through a Milli-Q Advantage Elix Essential 3.5.10.15 system (Merck KGaA, Darmstadt, Germany). A standard stock solution (1 mg/mL) of yohimbine was prepared in methanol and stored in the dark at a temperature below 4°C . Working solutions at levels of 1.0 and 10.0 $\mu\text{g/mL}$ were prepared daily when needed.

3.2. Blood samples

Blank human blood samples from donors were provided by the Jining City Blood Station (Jining, China). The samples were tested and drug-free and used to create spiked blood samples to validate the analytical procedure. The test samples comprised the venous blood of the poisoned/deceased who were suspected of yohimbine poisoning. All blood samples were collected into vacuum blood collection tubes that contained 2.7% EDTA- K_2 and stored at -20°C before analysis.

3.3. Analytical methods

3.3.1. Ethanol (EtOH) concentration determination

EtOH concentration in blood was determined using gas chromatography with flame ionization detection (GC-FID) (7890B-7699A, Agilent Technologies, Santa Clara, CA, USA). The experiment was set up in two parallels, and each 500 μL of blood was employed as a test sample. The internal standard (I.S.) was tert-butyl alcohol (TBA). The calibration range was 10–300 mg/100 mL with a 1 mg/100 mL detection limit.

3.3.2. Routine screening of common drugs

Routine screening for the identification and quantification of common drugs and toxins in blood samples was performed using a Shimadzu high-performance liquid chromatography (HPLC) system (LC-30A, Shimadzu Corp., Kyoto, Japan) coupled with a 5500 QTRAP mass spectrometer (Applied Biosystems Sciex, Foster City, CA, USA) with an electrospray Turbo spray interface using a Kinetex[®] Biphenyl 100 Å column (100 \times 3.0 mm, 2.6 μm , Phenomenex, Torrance, USA). The experiment was set up in two parallels; each 100 μL of blood was mixed with 10 μL I.S. (proadifen and aprobarbital mixed standard solution, 10 $\mu\text{g/mL}$ in methanol) and 890 μL deionized water before liquid/liquid extraction using ethyl ether. After mixing the preparation for 10 min and centrifuging briefly (4000 r/min, 5 min), the nonaqueous (organic) supernatant was evaporated to dryness at 60°C under nitrogen gas. The residue was dissolved in 200 μL of methanol and injected into the liquid chromatography-tandem mass spectrometer (LC-MS/MS) system.

HPLC analysis of the column was performed at a temperature of 40 °C. Experiments used 5 mmol/L ammonium acetate buffer mixed with 0.1% formic acid as eluent A and acetonitrile as eluent B at a flow rate of 0.3 mL/min. The elution program started at an initial composition of 55% B and then increased to a composition of 95% in 4 min and was held for 2 min. Eluent B was ramped to 20% in 6.1 min and held for 4 min before returning to the starting conditions in 10 min. The injection volume was set to 2 μ L.

The MS/MS instrument system was operated using electrospray ionization (ESI) in both positive and negative modes. The detection conditions were previously optimized to afford the highest relative intensity: an ion spray (IS) voltage of 5500 V and a source temperature of 550 °C were applied. The curtain gas (CUR) was 30 psi, the ion source gas 1 (GS1) was 45 psi, and the ion source gas 2 (GS2) was 30 psi. The method was utilized in multiple reaction monitoring (MRM) mode. Specific kinds of drugs and MRM parameters are shown in Table S1.

3.3.3. Yohimbine quantitative analysis

For yohimbine quantification, 6-acetylmorphine-D3 (10 μ g/mL in methanol) was used as the I.S., and the extraction procedure was the same as detailed in Section 3.3.2. After vortex mixing, centrifugation, and evaporation, the residue was dissolved in 1 mL of methanol and injected into the LC-MS/MS system. The injection volume was 2 μ L. Chromatographic separation was achieved over a 10 min run time on a Kinetex® Biphenyl 100 Å column (100 \times 3.0 mm, 2.6 μ m, Phenomenex, Torrance, USA). The elution program started at an initial composition of 10% B, increased to a composition of 90% in 7 min, and held for 1 min. Next, eluent B was ramped to 10% in 8.2 min and held for 2 min before returning to the starting conditions in 10 min. The MS/MS instrument system was operated using ESI in positive mode. Precursor ions, product ions, retention times (Rts) and the optimum turning parameters (declustering potential (DP), collision energy (CE), and collision cell exit potential (CXP)) for yohimbine and I.S. are shown in Table 1.

Validation of the described method was performed according to Meng et al. [12] and Peters et al. [13]. A procedural blank (one laboratory blank, one control blank spiked with I.S. only, and one standard-spiked matrix sample) was run before the samples as a standard and internal quality controls (QC). Specificity was confirmed based on spiked samples ($n = 6$) from different sources. No significant endogenous interfering peaks were noticed at the Rt of yohimbine. The linearity was calculated using the I.S. method, in which the linear calibration range was 1–200 ng/mL, with a determination coefficient $r \geq 0.999$. The detection limit (LOD) and limit of quantitation (LOQ) were 0.05 and 0.1 ng/mL, respectively. For the validation of accuracy, precision, stability, recoveries, and matrix effects, three levels were evaluated: low (5 ng/mL), medium (50 ng/mL), and high (200 ng/mL). The accuracies was within $\pm 15\%$ at all concentration levels ($n = 6$). The intraday ($n = 6$) and interday ($n = 18$) precisions were $<7\%$ and $<8\%$, respectively, for the three concentrations. The recoveries were $>90\%$ at three levels, which indicates the method's satisfactory extraction efficiency. The blood matrix showed no obvious influence on the detection, as the

matrix effects at the three concentrations were within $\pm 10\%$. The carryover was assessed by placing one control blank immediately after every high concentration sample (200 ng/mL) in each accuracy and precision run. There was no significant carryover during method development, with peak areas below 0.07% yohimbine ($S/N < 18$) and 0.45% I.S. ($S/N < 2.0$) in carryover blank samples. Autosampler stability was tested by reinjecting calibration standards at each concentration after a residence time in the autosampler of approximately 24 h. The deviations of standard samples did not exceed $\pm 13\%$ of the controls. The dilution effect was tested on two different dilutions, 1:2 and 1:10, with triplicate samples. The biases of the recalculated concentration and the CV were below 5% and 8% for the two dilutions.

4. Results

Using the GC-FID method, no ethanol content was detected in the four poisoned/deceased patients' blood. Systematic screening using LC-MS/MS of four submitted blood samples revealed the presence of yohimbine. The total ions current of yohimbine and I.S. in the blood of the four poisoned/deceased persons are shown in Fig. 1. The Rt for yohimbine was 7.48 min and was 6.12 min for I.S.. The quantitative analysis results showed that yohimbine concentrations in the three poisoned patients' blood were 459, 249, and 301 ng/mL. The yohimbine concentration for the deceased was 5631 ng/mL.

5. Discussion

Previous poisoning cases indicate that sinus tachycardia and QT interval prolongation may present as yohimbine consumption [8,9]. These symptoms are consistent with the clinical diagnosis of the three poisoned patients in the cases. The three patients showed varying degrees of flushing, sweating, headache, nausea, and vomiting after taking yohimbine and were initially diagnosed as acute drug poisoning with sinus tachycardia. The deceased's forensic pathological diagnosis showed congestion and edema of internal organs, especially acute congestion, pulmonary edema, and focal hemorrhage in the lungs. Previous autopsy reports regarding death caused by yohimbine are very limited. Gicquel et al. [14] reported the case of a 30-year-old woman who died after mistaking a mislabeled powder that contained reserpine, ajmaline, and yohimbine. The autopsy showed congestion of the internal organs and pulmonary edema. Anderson et al. [15] reported a 23-year-old male bodybuilder with a history of steroid abuse who died due to yohimbine. Notable autopsy findings were cardiomegaly, pulmonary edema, and congestion. Yohimbine can mediate erection-inhibiting impulses in the central nervous system, enhancing erection through hormonal changes, increased blood flow, and smooth muscle relaxing properties. The autopsy data suggest that the violent death after initiation of such alkaloids was due to the severe relaxation of vascular smooth muscles and the extremely accelerated local blood flow velocity, which caused adverse effects on the cardiopulmonary circulation and eventually led to congestion and edema of internal organs.

Table 1
MRM parameters and Rts of compounds.

Compound	Precursor ion (m/z)	Product ion (m/z)	DP (V)	CE (eV)	CXP (V)	Rt (min)
yohimbine	355.2	144.1 ^a	190	38	16	7.48
	355.2	212	190	31	16	
6-acetylmorphine-D3	331.3	165 ^a	116	54	16	6.12
	331.3	211.1	116	36	16	

^a Served as a quantitative ion.

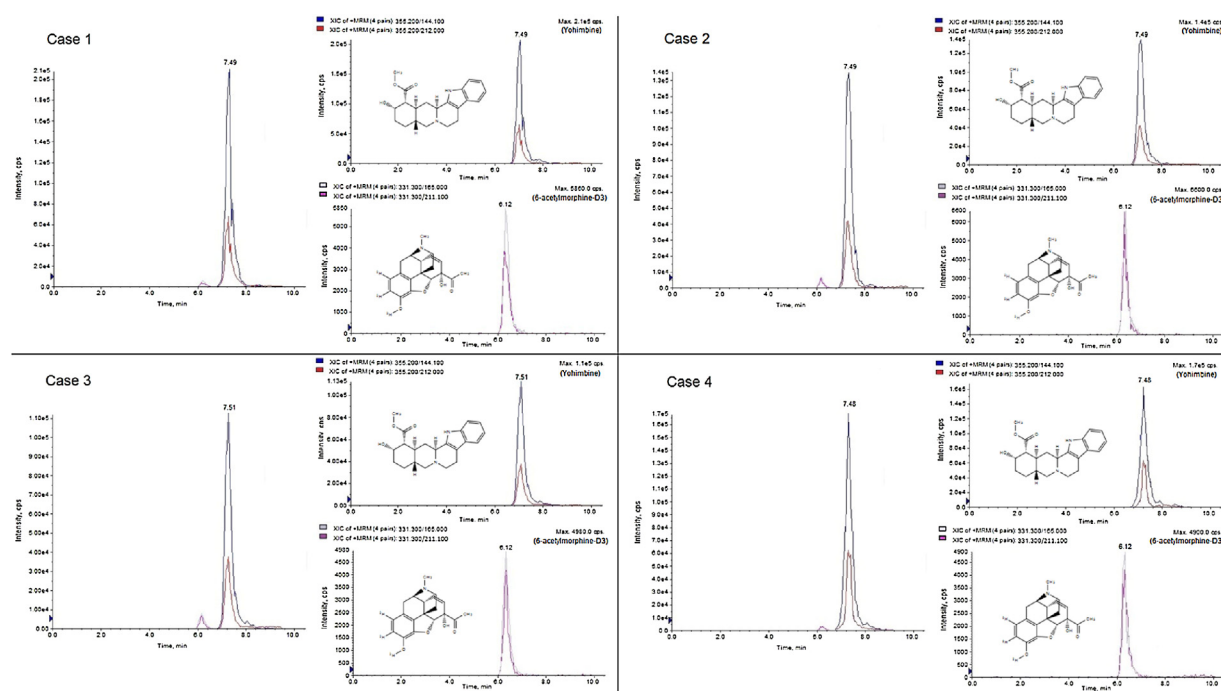


Fig. 1. LC-MS/MS total ions currents of yohimbine and 6-Acetylmorphine-D3 used as I.S. of the poisoned/deceased blood samples.

Clinically, normal human concentrations in the blood observed after consumption of yohimbine at therapeutic doses ranged between 50 ng/mL and 300 ng/mL [16]. However, there are no accurate toxicity data on the toxic or lethal dose range of yohimbine to humans. Gicquel et al. [14] reported that the concentration of yohimbine in deceased patients' blood was 98.2 ng/mL. Although the concentration was within the normal therapeutic dose range, the deceased simultaneously took two other drugs (ajmaline and reserpine), and the synergy between the drugs had an adverse cardiovascular effect. Anderson et al. [15] reported two fatal acute yohimbine intoxication cases, with respective concentrations of 7400 ng/mL and 5400 ng/mL in the blood. Giampreti et al. [8] reported a case of severe yohimbine poisoning. A 37-year-old man vomited, convulsed, and became unconscious after taking an herbal medicine that contains yohimbine. The man was sent to the hospital for rescue and awoke after 12 h. The concentration of yohimbine in the serum was 5240 ng/mL after taking medicine for 3 h. Currently, the maximum blood concentration of acute yohimbine intoxication is discussed in a fatal case report by Drevin et al. [16], who detected 8000 ng/mL yohimbine in the blood of a 27-year-old male bodybuilder with a history of yohimbine and steroid abuse.

In this case, the LC-MS/MS method for detecting yohimbine was fully validated in whole blood. Moreover, the method was also verified to be suitable for the quantitative detection of yohimbine in human urine and bile samples, in which the average recovery rates were both >80%, with the same LOD of 0.05 ng/mL. Since deuterated yohimbine was not available at the time of this experiment, 6-acetylmorphine-D3 was utilized as an I.S.. The concentrations of yohimbine after taking the drug for 10–11 h in the three poisoned patients were higher than or near the treatment threshold. Previous studies have shown that according to the pharmacokinetics of orally administered yohimbine in humans, its oral bioavailability presented significant variability, ranging from 7% to 87% (mean value was 33%) [17]. Different bioavailability is mostly due to a hepatic first-pass effect or incomplete absorption from the gastrointestinal tract. The different results of the three poisoned cases are inferred to be

related to variable bioavailability. In this study, the intake of yohimbine in the three poisoned patients was approximately the same, and the interval of the blood sampling time was less than half an hour. However, the levels of yohimbine in the blood of the three patients were not consistent. The difference was presumed to be related to the poisoned person's health, whose maximum value was found in the healthiest 45-year-old male in Case 1. The poisoned patient with liver disease in Case 2 had the lowest yohimbine content in his blood due to the possible decreased bioavailability of drug extraction in the liver. Yohimbine quantification of the deceased in Case 4 was carried out on femoral blood at a 5631 ng/mL concentration. Since the dose of yohimbine ingested by the deceased was unknown before his death, the comparison between his oral bioavailability and the above three poisoned persons was not carried out. This result is similar to the detected concentration in the fatal case of yohimbine reported previously. The autopsy did not identify other apparent pathological damages, except for internal organ congestion and edema. Therefore, yohimbine poisoning appears to be the most likely cause of death. Because of the case's clear process and timely sampling after the incident, the concentration of yohimbine in other organs of the deceased was not measured. Note that the occurrence of yohimbine redistribution long after death cannot be excluded. Therefore, for more complicated cases, in addition to timely sampling, the determination of such alkaloids and metabolites in the blood, organs, or other body fluids should be compared to accurately acquire the toxic dose and pharmacokinetic characteristics of yohimbine in humans.

6. Conclusion

This report described four simultaneous cases of yohimbine poisoning, the dangers of which should not be underestimated. By comparing the concentrations of yohimbine in the blood of three poisoned patients, the results showed that the oral bioavailability of yohimbine is variable and possibly related to the users' health. It is indicated that the dosage of the drug should be individualized and administered carefully when yohimbine is used orally as a

supplement or for clinical indications. The study provided more clinical and postmortem symptoms of yohimbine poisoning and toxic/lethal doses in human blood for such alkaloids that are rarely encountered in forensic toxicology practice.

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical permission was granted through the Science and Ethics Committee of Jining Medical University. Informed consent was obtained from each individual's family in this study.

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CRediT authorship contribution statement

Lei Zhu: Writing - original draft, Methodology, Investigation. **Xiao Han:** Resources. **Jun Zhu:** Supervision. **Le Du:** Software, Validation. **Li Liu:** Data curation. **Wenjing Gong:** Writing - review & editing, Formal analysis, Funding acquisition, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.forsciint.2021.110705>.

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