Yohimbine is an alkaloid that has been encountered on the streets as an aphrodisiac, hallucinogenic, dietary supplement and erectile dysfunction drug. Yohimbine hydrochloride is an alpha 2-adrenoceptor antagonist, blocking the pre- and postsynaptic alpha-2 adrenoceptors and causing an increased release of noradrenaline and dopamine. An average oral dose of 5–15 mg produces a therapeutic whole blood level range of 40–400 ng/mL. Overdoses leading to neurotoxic effects have been seen with blood concentrations up to 5,000 ng/mL. The laboratories from the Maricopa County Medical Examiner and the Los Angeles County Department of Coroner each encountered a case in which yohimbine was identified in whole blood by means of a liquid–liquid basic drug extraction with detection on a GC–MS. Because validated quantitative methods for yohimbine did not exist at either facility, both agencies referred the blood specimens to NMS Labs, Inc. The reference laboratory analyzed the blood specimens with an LC–MS-MS and determined the quantitative values of yohimbine to be 7,400 and 5,400 ng/mL. Given the absence of other significant positive findings and the substantial yohimbine blood concentrations cited, the respective Medical Examiners determined the cause of death to be acute yohimbine intoxication with the mode being an accident. Yohimbine is a rarely encountered drug in medical examiner casework, and interpretation of the results is difficult to assess toward the cause and manner of death without such case studies being described.

Case Study: Two Fatal Case Reports of Acute Yohimbine Intoxication

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Yohimbine is an indole alkaloid rarely seen in forensic casework that has important implications due to its varied applications (1). It has been approved for use in the USA to treat erectile dysfunction, although its effectiveness has been highly controversial (1). Yohimbine has also been abused on the streets as an aphrodisiac and hallucinogen, while more recently it has gained popularity in the body-building community for its lipolytic and sympathomimetic effects (1). In 1997, the FDA issued a warning against the combined use of yohimbine and caffeine with ephedrine alkaloids, which was done as a response to a number of serious illnesses and injuries, including multiple deaths (2). It was found that yohimbine and other stimulant-like substances increased the likelihood, severity and frequency of adverse effects seen with ephedrine alkaloids, such as renal failure and seizures (2).

Yohimbine is the principal alkaloid derived from the bark of the Pausinystalia yohimbe (formerly known as Corynanthe yohimbe), a West African evergreen (3). Herbal yohimbine extract has been made available in over-the-counter medications and often in dietary supplements (4). However, the manufacturers purified the bark of this evergreen and marketed it as yohimbine hydrochloride (4). This salt preparation is currently prescribed in the USA to treat erectile dysfunction (4). Yohimbine hydrochloride is an alpha 2-adrenoceptor antagonist, blocking the pre- and postsynaptic alpha-2 adrenoceptors (4, 5). Obstruction of these receptors causes an increased release of noradrenaline and dopamine (5). Ephedrine alkaloids also increase the activity of noradrenaline on adrenergic receptors, which is why combination of this alkaloid with yohimbine and caffeine causes excessive serum concentrations of noradrenaline, leading to those aforementioned adverse drug reactions (5). Studies have suggested that oral consumption of yohimbine decreases the risk of experiencing such severe symptoms due to its slower route of absorption (4). Furthermore, it was recommended that yohimbine prescriptions be taken with food, as fasting can lead to increased panic attacks (4). Over the years, use of yohimbine to treat sexual dysfunction has decreased due to the release of sildenafil (Viagra®) and other sexual enhancing substances in the late 1990s (4).

An average oral dose of 5–15 mg produces a therapeutic whole blood concentration in the range of 40–400 ng/mL (1). Overdoses leading to neurotoxic effects have been seen from doses of 200 to 5,000 mg, resulting in blood concentrations up to 5,000 ng/mL (1). One study suggested that the absorption half-time after consuming a 5.4-mg pill is 10 min and the elimination half-life is 36 min (6). Symptoms reported with yohimbine overdose include anxiety, drowsiness, disorientation, tremors and seizures with higher doses (1). A limited amount of literature is available about yohimbine concentrations in blood, and no reports of fatal yohimbine concentrations have been observed.

Yohimbine has a molecular weight of 354.44 g/mol and a molecular formula of C₂₁H₂₆N₂O₃, and its chemical structure is depicted in Figure 1 (7). The nonsalt form is a white powder that can be dissolved in methanol.

Case histories

Case 1: Maricopa County

A 23-year-old male body builder with a history of mixing his own energy and protein drinks in conjunction with steroid use collapsed outside of a fitness center in Gilbert, AZ. Emergency personnel responded after he called a friend stating he ’thought he was dying’ and ’may have put too much caffeine in his energy drink’, though he was known by family to be meticulous in his measurement. He presented to the emergency room with seizures and elevated vitals, and was pronounced dead within hours. Through investigation, jars of yohimbine and caffeine powder were among supplements recovered from the decedent’s residence along with arginine, L-carnitine, beta-alanine and testosterone. Furthermore, the decedent had a medical history of low testosterone and hypogonadism. Notable autopsy findings were cardiomegaly (525 g), pulmonary edema and
congestion. Multiple postmortem samples including vitreous fluid, iliac blood, urine and bile were drawn and sent to toxicology for testing along with hospital admission specimens.

**Case 2: Los Angeles County**

A 37-year-old male was found unresponsive on the floor of his residential bedroom. According to his friends and colleagues, he worked out daily and maintained a very healthy diet. The decedent had been dieting and had lost 15 pounds over 90 days by taking mail order dietary supplements. During the death investigation, numerous pouches of dietary supplements were collected from the kitchen area by the investigator. The autopsy findings were unremarkable, and postmortem specimens of heart and femoral blood, bile, stomach contents and vitreous fluid were collected and submitted for toxicological analysis.

### Methodology

**Case 1**

Volatile analysis to detect methanol (MeOH), ethanol (EtOH), isopropanol (IPA) and acetone was performed on both vitreous fluid and hospital admission serum using an Agilent 7890 Headspace Gas Chromatography/Flame Ionization Detector (HS–GC–FID). Enzyme-linked immunosorbent assay (ELISA) was performed on admission serum with a TECAN Freedom EVO 75 Workstation followed by quantitation of any positives. A basic drug screen, utilizing a chlorobutane liquid–liquid basic drug extraction (with acidic back extraction) and detection occurred on two Agilent systems, GC–NPD and GC–MS. In addition, the pouches of dietary supplements collected as medical evidence by the investigator were also analyzed with a ‘dilute-and-shoot’ method and detection was by an Agilent GC–MS.

**Yohimbine quantitation by NMS Labs, Inc.**

The NMS method is a quantitative measurement of yohimbine in biological specimens with a calibration range of 10–200 ng/mL and quality controls at target concentrations of 25 and 150 ng/mL. After addition of the internal standard tacrine (Sigma), buffered sample is extracted with an SPE technique. The analyte is eluted with organic solvent, which is then evaporated to dryness. The residue is reconstituted in mobile phase and analyzed by high-performance liquid chromatography (HPLC) with fluorescence detection equipped with a Zorbax Stable Bond C-18 column (4.6×150 mm) with a C-8 pre-column. Specimens with quantitative values outside the concentration range are diluted and reanalyzed with an appropriate dilution (Laura Labay, PhD, NMS Labs. Personal Communication, January 2013).

### Results

**Case 1**

Toxicology testing on admission specimens yielded negative results for both the volatile and ELISA screens. The acidic–neutral screen was unremarkable, while the basic drug confirmation revealed the presence of caffeine, diphenhydramine and yohimbine (matches with AAFS, SWGDRG and WILEY libraries). The caffeine and diphenhydramine concentrations were not elevated and were determined to be not relevant to the cause of death. White powder collected from Gilbert PD in a jar labeled ‘Yohimbine’ was also analyzed and compared with the blood results. Due to the limited amount of hospital specimens received and the volume required by the reference laboratory, iliac blood was sent to NMS Labs, Inc. (Willow Grove, PA, USA) for yohimbine quantitation by HPLC. The yohimbine level in the iliac blood was subsequently reported to be 7,400 ng/mL.

**Case 2**

The volatile analysis was positive for ethanol, which included heart blood at 0.05 g%, femoral blood at 0.04 g% and vitreous fluid at 0.05 g%. All the drugs screened by ELISA and the acidic–neutral drugs were negative. Yohimbine was the only drug detected in the basic drug screen requiring a second extraction to confirm. Comparison of yohimbine was made against a known analytical standard and identification was verified through several mass spectral libraries. The heart blood was referred to NMS Labs, Inc. for yohimbine quantitation and was reported to be 5,400 ng/mL.

The complete results of the toxicological analyses for both Maricopa County, AZ, and Los Angeles County, CA, are summarized in Table I.
Yohimbine has a very wide dose range for therapeutic use and pretoxic effects, which may be why many reports of overdoses with adverse effects are not published. As previously indicated, cases of ingestion of up to 3 g have not proved fatal. Table II indicates several cases of yohimbine ingestion and their respective symptoms, along with the two presented case studies for comparison purposes. Unfortunately, in all but one of these cited literature cases, yohimbine concentrations were not measured and correlating concentrations with the observed symptoms and behavior was difficult. However, in one case reported by Giampreti in 2009, the yohimbine level measured in the antemortem blood 3 h post-ingestion was 5,240 ng/mL. The case involved a male who presented to the hospital in an unconscious state and was given diazepam for the recurrent seizures. After it was quickly discovered that the patient had ingested a large amount of the alkaloid, he was administered clonidine, urapidil and labetalol as a preventative measure to counteract the sympathomimetic effects. Due to its short half-life, treating the symptoms allowed the patient to metabolize the drug down from toxic ranges within hours. If the subject in Giampreti had not received medical attention, it is plausible that he may have perished. It is important to note that in the Maricopa case, as well as the Giampreti case, the peak concentration of yohimbine may not have been observed. It is suggested that a peak serum concentration will be observed approximately 1 h after ingestion (6). Therefore, in both the Giampreti and Case 1, yohimbine concentrations may be an underestimation of the actual concentrations.

The two case studies presented had yohimbine concentrations (5,400 and 7,400 ng/mL) greater than that of Giampreti. When interpreting drug concentrations in postmortem case-work, it is important to consider postmortem redistribution as well as plasma/whole blood or central/peripheral blood ratios. Information regarding these factors is not readily available; one must use caution in the comparison of the described cases with each other and with Giampreti. It is interesting to note that both Maricopa County and Los Angeles County detected yohimbine as an incidental finding with their respective basic drug extraction methods. In both the Giampreti and Case 1, yohimbine concentrations were not measured and correlating concentrations with the observed symptoms and behavior was difficult. However, in one case reported by Giampreti in 2009, the yohimbine level measured in the antemortem blood 3 h post-ingestion was 5,240 ng/mL. The case involved a male who presented to the hospital in an unconscious state and was given diazepam for the recurrent seizures. After it was quickly discovered that the patient had ingested a large amount of the alkaloid, he was administered clonidine, urapidil and labetalol as a preventative measure to counteract the sympathomimetic effects. Due to its short half-life, treating the symptoms allowed the patient to metabolize the drug down from toxic ranges within hours. If the subject in Giampreti had not received medical attention, it is plausible that he may have perished. It is important to note that in the Maricopa case, as well as the Giampreti case, the peak concentration of yohimbine may not have been observed. It is suggested that a peak serum concentration will be observed approximately 1 h after ingestion (6). Therefore, in both the Giampreti and Case 1, yohimbine concentrations may be an underestimation of the actual concentrations.

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**Table I**

Toxicological findings by Maricopa County Medical Examiner and Los Angeles County Medical Examiner

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Case 1—Maricopa County</th>
<th>Results</th>
<th>Case 2—Los Angeles County</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Method</td>
<td>Matrix</td>
<td></td>
<td>Method</td>
</tr>
<tr>
<td>Volatiles analysis</td>
<td>GC/FID</td>
<td>Vitreous</td>
<td>Negative for MeOH, EtOH, IPA and acetone</td>
<td>GC/FID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital serum</td>
<td>Negative for MeOH, EtOH, IPA and acetone</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital serum</td>
<td>Negative for barbiturates, benzodiazepines, benzoylcgonine, opiates, methamphetamine, fentanyl and oxycodone</td>
<td></td>
</tr>
<tr>
<td>EIA</td>
<td>ELISA</td>
<td>Hospital serum</td>
<td>Negative for barbiturates, benzodiazepines, benzoylcgonine, opiates, methamphetamine, fentanyl and oxycodone</td>
<td>ELISA</td>
</tr>
<tr>
<td>Acid–neutral screen</td>
<td>SPE → GC–MS</td>
<td>Femoral blood</td>
<td>Unremarkable</td>
<td>SPE → GC–MS</td>
</tr>
<tr>
<td>Basic Drug Screen</td>
<td>LLE → GC–MS</td>
<td>Femoral blood</td>
<td>Unremarkable</td>
<td>LLE → GC–MS</td>
</tr>
<tr>
<td>Yohimbine quantification</td>
<td>HPLC</td>
<td>Iliac blood</td>
<td>Yohimbine of 7,400 ng/mL</td>
<td>HPLC</td>
</tr>
</tbody>
</table>

*Yohimbine quantification performed by NMS.

**Table II**

Previously reported cases of yohimbine intoxication for comparison with the presented cases (adapted from Giampreti et al. [1])

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Yohimbine ingested (g)</th>
<th>Symptoms presented</th>
<th>Yohimbine blood concentrations (ng/mL)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>E2/M</td>
<td>0.2</td>
<td>Anxiety, tremors and hypertension</td>
<td>NP</td>
<td>Friesen et al. (9)</td>
</tr>
<tr>
<td>16/F</td>
<td>0.25</td>
<td>As above plus nausea, headache, rash and dissociative reaction</td>
<td>NP</td>
<td>Linden et al. (10)</td>
</tr>
<tr>
<td>38/M</td>
<td>0.35</td>
<td>Drowsiness, confusion, retrograde amnesia and atrial fibrillation</td>
<td>NP</td>
<td>Verkey (11)</td>
</tr>
<tr>
<td>NR/M</td>
<td>1.8</td>
<td>Unconsciousness, prapism</td>
<td>NP</td>
<td>Vulto and de Smet (12)</td>
</tr>
<tr>
<td>25/M</td>
<td>3</td>
<td>Disorientation, seizures</td>
<td>NP</td>
<td>Halcomb et al. (13)</td>
</tr>
<tr>
<td>37/M</td>
<td>5</td>
<td>Unconsciousness, seizures, hypertension and sinus tachycardia</td>
<td>5,240</td>
<td>Giampreti et al. (11)</td>
</tr>
<tr>
<td>23/M</td>
<td>Unknown</td>
<td>Seizures, hypertension, elevated vitals and death</td>
<td>7,400</td>
<td>Case 1</td>
</tr>
<tr>
<td>37/M</td>
<td>Unknown</td>
<td>None observed—subject found deceased</td>
<td>5,400</td>
<td>Case 2</td>
</tr>
</tbody>
</table>

NP, not performed; NR, not reported.

**Discussion**

Yohimbine has a very wide dose range for therapeutic use and pretoxic effects, which may be why many reports of overdoses with adverse effects are not published. As previously indicated, cases of ingestion of up to 3 g have not proved fatal. Table II indicates several cases of yohimbine ingestion and their respective symptoms, along with the two presented case studies for comparison purposes. Unfortunately, in all but one of these cited literature cases, yohimbine concentrations were not measured and correlating concentrations with the observed symptoms and behavior was difficult. However, in one case reported by Giampreti in 2009, the yohimbine level measured in the antemortem blood 3 h post-ingestion was 5,240 ng/mL. The case involved a male who presented to the hospital in an unconscious state and was given diazepam for the recurrent seizures. After it was quickly discovered that the patient had ingested a large amount of the alkaloid, he was administered clonidine, urapidil and labetalol as a preventative measure to counteract the sympathomimetic effects. Due to its short half-life, treating the symptoms allowed the patient to metabolize the drug down from toxic ranges within hours. If the subject in Giampreti had not received medical attention, it is plausible that he may have perished. It is important to note that in the Maricopa case, as well as the Giampreti case, the peak concentration of yohimbine may not have been observed. It is suggested that a peak serum concentration will be observed approximately 1 h after ingestion (6). Therefore, in both the Giampreti and Case 1, yohimbine concentrations may be an underestimation of the actual concentrations.

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**References**


