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Case Report

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Diminished Consciousness in a Woman Following an Unsuspected Scopolamine Overdose

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Abstract

Scopolamine is used clinically, but it is also used as a recreational drug and as an incapacitating drug in sexual crimes and robberies. In this paper, the authors report the case of a woman with a diminished consciousness following an unsuspected overdose with scopolamine and review published articles on scopolamine poisoning that included concentrations in biological samples. Scopolamine was identified in the patient's serum and urine samples collected 1 h post-admission to intensive care unit at concentrations of 8.4 ng/mL and 62,560 ng/mL (169,539 ng/mg creatinine), respectively. In non-fatal cases, the median [interquartile range] of serum scopolamine levels was 1.9 [2.1] ng/mL. The serum concentration found in our case would explain the abrupt clinical presentation suffered by the patient. Scopolamine in urine could be detected up to 48 h after admission. This report illustrates that broad toxicology screening, including scopolamine, should be considered when patients with diminished consciousness are attended after ruling out infection or cerebrovascular disease. This can play an important role in identifying this potentially life-threatening etiology.

Introduction

Scopolamine (hyoscine hydrobromide) is the epoxide of atropine; it is used for treating motion sickness, and due to its sedative capacity, it is also used in palliative care. Scopolamine can cause central effects, such as mydriasis, visual hallucinations, agitation and coma. For these reasons, it is also used as a recreational drug. Additionally, the use of scopolamine as an incapacitating drug, in sexual crimes and robberies, has been reported in forensic toxicology (1). Anterograde amnesia, hallucinations and submissive behavior are prominent symptoms in victims of scopolamine-facilitated

crimes (2). We discuss a diminished consciousness in a woman following an unsuspected overdose with scopolamine and review the literature on this topic.

Case History

A 51-year-old woman presented an abrupt alteration of the level of consciousness at home (3:30 a.m.) after going out for dinner. Emergency services found her with bilateral unreactive mydriasis and score 8 in Glasgow Coma Scale. She was intubated and mechanically ventilated and transferred to the reference hospital. There was not known medical history, medical treatment or substance abuse. On arrival to the Emergency Department (5:00 a.m.), the patient appeared to display significant anticholinergic signs and symptoms. Physical examination revealed a blood pressure of 106/56 mmHg, rhythmic cardiac auscultation without murmurs and normal pulmonary auscultation. Neurological examination (under sedation) only revealed unreactive mydriatic pupils. Hematological, biochemical and arterial blood gas laboratory results were within the reference range. Serum ethanol was 0.16 g/L. An urgent computed tomography (CT) perfusion of the head and CT angiography were performed, but no acute intracranial hemorrhage, occlusion in proximal cerebral arterial vessels or notable alterations in the perfusion study were reported.

The patient was transferred to the intensive care unit (ICU) (7:00 a.m.). She persisted with non-reactive mydriatic pupils, was hemodynamically stable without vasoactive support and was afebrile. The patient remained connected to mechanical ventilation. Empirical antibiotic and antiviral treatment were initiated. Electroencephalogram (EEG), electrocardiogram (EKG) and cerebrospinal fluid (CSF) showed no pathological findings. Laboratory testing showed no abnormalities, and urine drug screening immunoassay (DRI®Assay, Abbott Laboratories Inc., North Chicago, IL, USA) was negative. After ruling out ischemic cause of the picture and venous sinus thrombosis, a broad toxicological screening in serum and urine was requested (1 h post-admission to ICU and 4.5 h after alteration of the level of consciousness was detected).

Within a few hours, the patient was conscious and could be extubated. Physostigmine was considered but ultimately not administered as the patient awakened rapidly and had a favorable evolution. Moderately reactive bilateral mydriasis was still present. After 36 h, she was moved to the Neurology Unit. The patient explained that at home, she drank from a bottle her daughter had brought after attending a party. After drinking, the patient fell asleep soundly without responding. She also reported hallucinations. Detailed neurological examination noted the patient to be conscious and oriented, without speech and language alterations. Medium and poorly reactive pupils persisted. The rest of neurological examination was normal. A new blood test with immunology and infectious serology was within the reference range.

From the fourth day of admission, she presented isochoric and normoreactive pupils, without neurological focality. Magnetic resonance imaging study only suggested the possibility of some degree of chronic vasculopathy. Twelve days after admission, she was discharged. The patient granted the authors permission to use her medical records during manuscript preparation.

Methods

Chemicals and reagents

Scopolamine, scopolamine-d_3, β-glucuronidase, N,O-bis(trimethylsilyl) trifluoroacetamide (BSTFA) and trimethylchlorosilane (TMCS) (99% BSTFA with 1% TMCS) and N-methyl-bis (trifluoroacetamide) (MBTFA) were purchased from Sigma Aldrich (Sigma-Aldrich, Barcelona, Spain). Heptane, dichloromethane, dichloroethane isopropanol high performance liquid chromatography (HPLC) grade (LiChrosolv®) solvents and LC–MS grade methanol were purchased from Merck (Merck, Barcelona, Spain). Liquid chromatography–mass spectrometry (LC–MS) grade acetonitrile and ammonium formate were from Scharlau Chemie (Sentmenat, Barcelona, Spain). All other chemicals used were analytical reagents from commercial vendors.

Toxicological analyses

A broad toxicological urine drug screening was performed by gas chromatography (GC)–electron impact–MS non-targeted analysis as described in a previous report (3), using an Agilent HP 7890A/5975C instrument (Agilent Technologies, Santa Clara, CA, USA). Identifications were completed by computer matching against GC–MS library spectra of the National Institute of Standards and Technology (NIST Mass Spectral Library Revision 2017).

Scopolamine quantification in urine samples was performed by GC–MS targeted drug screening, using our routine method (4), which is adapted from Namera et al. (5). Briefly, urine specimens (3 mL) were mixed with β-glucuronidase (5,000 F units/mL in 1.0 M acetate buffer, pH 5.0) and hydrolyzed for 3 h at 65°C. When cold, the hydrolyzed specimen was extracted in a Pyrex tube that contained an organic mixture of solvents (heptane/dichloromethane/dichloroethane/isopropanol, 33.3/25/25/16.7, v/v; 4.5 mL) and buffering salts to give a pH of 9.0 (0.15 g sodium carbonate, 0.15 g sodium bicarbonate and 1.5 g sodium chloride). After stirring the mixture and centrifugation, the organic layer was evaporated to dryness and derivatized using 50 µL BSTFA with 0.1% TMCS at 80°C for 15 min. Two microliters of the extract was injected into the GC–MS. Ion used for quantitation was *m/z* 138. Qualifier ions were *m/z* 94 and 154. Ion 375 (*m/z* for the derivatized parent drug) was used to demonstrate effective derivatization. The method was validated for the analysis of urine samples, including linearity (50–5,000 ng/mL), accuracy [%MRE = 4.2%–(–19.9%)], inter- and intra-assay precision (%CV <10.0%) and endogenous interferences (not detected).

Quantification of scopolamine in serum samples were performed by LC–MS-MS. The HPLC system was an Alliance 2795 Separation Module with an Alliance series column heater/cooler coupled to a Quattro Micro™API triple quadrupole (Waters Corp., Milford, MA, USA). Data acquisition was controlled with Masslynx 4.0 software and processed with Quanlynx software (Waters Corp.). LC–MS-MS conditions were those reported in a previous publication (6). Briefly, chromatographic separation was performed using an Atlantis T3 analytical column (2.1 mm × 50 mm, 3 µm) (Waters Corp.) and maintained at 26°C. A gradient was applied using 2 mM ammonium formate with 0.1% formic acid in water (A) and acetonitrile (B) as mobile phase. Detection was performed in multiple reaction monitoring (MRM) mode, monitoring the following transitions: 304.3 > 138.2 (cone voltage = 34 V; collision energy = 24 eV) and 304.3 > 156.2 (34 V; 16 eV) (quantifying transition is underlined) for scopolamine and 307.3 > 141.3 (35 V; 25 eV) for scopolamine-d_3. For sample extraction, 0.5 mL of serum was mixed with 1.2 mL of ethyl acetate after the addition of the internal standard (50 µL of scopolamine-d_3 at 0.02 µg/mL). Samples were shaken in a rotor for 5 min and subsequently centrifuged at 14,000 rpm. The organic phase was then evaporated to dryness in a TurvoVap LV evaporator (Zymark Corp., MA, USA), reconstituted with 100 µL of 2 mM ammonium formate with 0.1% formic acid/acetonitrile (95:5, v/v)

and 10 µL injected into the LC–MS-MS system. The method was initially developed in hair (6) and adapted and partially validated for the analysis of serum samples, including linearity (0.1–50 ng/mL), accuracy (%MRE = –2.8%–12.0%), inter- and intra-assay precision (%CV < 11.8%) and endogenous interferences (not detected).

Literature search

A literature search was conducted using scientific databases (PubMed, MEDLINE, Scopus, Cochrane Central, Web of Science, EMBASE, Science Direct and reports from international institutions) to review published articles on scopolamine poisoning. The descriptors used were "scopolamine", "Datura", "poisoning", "hallucinogens", "toxicity" and "intoxication". The articles were manually examined, checking on content and checking also for cross-references. Publications were selected, in any language, when included scopolamine concentrations in biological samples. The median and interquartile range (IQR) of serum scopolamine levels were calculated from cases where this concentration was available.

Results

Scopolamine and ibuprofen were identified in the toxicological urine drug screening.

At 1 and 48 h post-admission, scopolamine serum concentrations were 8.4 and <0.1 ng/mL, respectively (Figure 1). At 1, 30 and 48 h, urine scopolamine concentrations were 62,560 ng/mL (169,539 ng/mg creatinine), 199 ng/mL (414 ng/mg creatinine) and 59 ng/mL (93 ng/mg creatinine), respectively.

The literature search resulted in 47 relevant cases to the objective (Table I). In non-fatal cases, median [IQR] serum scopolamine level was 1.9 [2.1] ng/mL (Figure 2). Blood scopolamine levels were only published in two fatal cases (4.8 and 1,890 ng/mL).

Discussion

A high percentage of patients with an altered state of consciousness of unknown origin require intensive care management. Objectives of the neurological examination are to identify lateralizing or focal findings, recognize signs of brainstem dysfunction and define its severity. Brain imaging should be done without delay in comatose patients with unclear diagnoses. Suggested causes of a sudden onset are stroke, seizure and drug overdose. Many toxics can produce coma directly or indirectly. Combinations of physical findings can also characterize toxic syndromes. Supportive care is the cornerstone of the management; however, in some cases, a specific therapy or antidote is beneficial. In this case report, physostigmine was considered. A large retrospective review (7) shown that physostigmine administration to reverse anticholinergic delirium had a good safety profile and often improved or resolved anticholinergic delirium when administered in doses less than 2 mg.

Scopolamine confirmation is complicated in clinical laboratories as analytical instrumentation availability is scarce and because of its short half-life in plasma. Furthermore, LC–MS-MS is required when

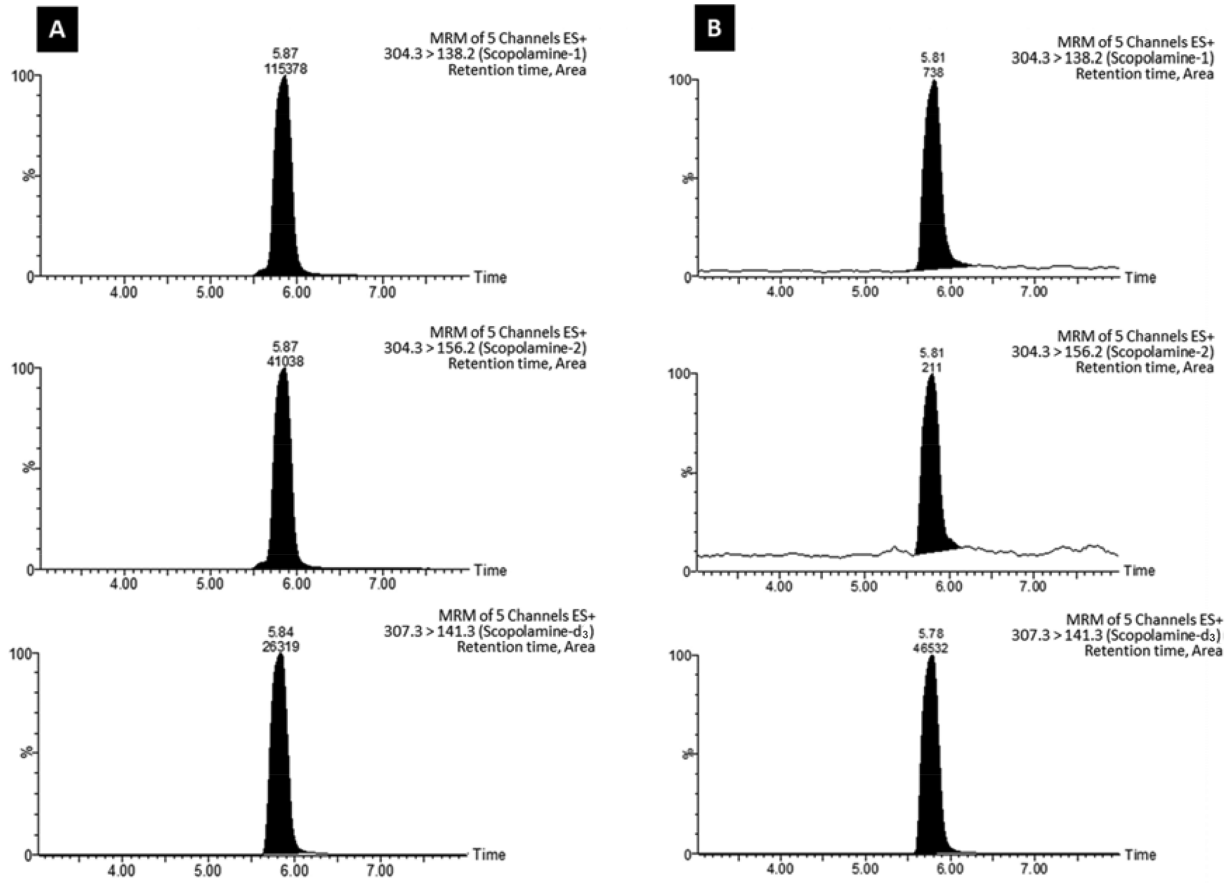

Figure 1. Chromatograms of serum samples obtained at 1 h (A) and 48 h (B) post-admission. Scopolamine concentrations were 8.4 (A) and <0.1 (B) ng/mg. From top to bottom: two MRM transitions for scopolamine (m/z: 304.3 > 138.2 and 304.3 > 156.2) and one MRM transition for scopolamine-d_3 (307.3 > 141.3).

Table I. Scopolamine Concentrations Reported in Biological Matrices and Clinical Features in Poisoning Cases

Case Type	Num.	Outcome	Clinical Symptoms	Time to Sampling (h)	Serum (ng/mL)	Urine (ng/mL)	Other Biological Matrices	Other Toxics	Ref.
Drug-Facilitated Crime									
Robbery	1	Fatal	Unknown (found dead)	Unknown	4.8 (FB)	Not determined	HB: 300 ng/mL SC: 20 mg/kg	Citalopram (FB: 660 ng/mL; HB: 470 ng/mL)	(10)
	2	Fatal	Stomach and digestive pain Unconscious	Unknown	Not determined	Not determined	VH: 5 ng/mL H: Not detected	Methanol (VH: 10 g/L) Atropine + Hyoscyamine (VH: 1 ng/mL)	(11)
	3	Non-fatal	Loss of consciousness Nausea Amnesia	23	0.35 (corrected for $t_{1/2}$: 3.5 ng/mL; $t_{1/2}$:6–7 h)	Detected and metabolites	H (three 1-cm segments): 0.2–0.8 ng/mg	Not detected	(10)
	4	Non-fatal	Amnesia Hallucinations	12	Not determined	Detected and metabolites	Not determined	Ethanol (U: 0.8 g/L) Amphetamine, morphine, codeine, paracetamol and paracetamol metabolites (U)	(10)
Suspected Sexual Assault	5	Non-fatal	Decreased consciousness, mydriasis, confusion, hallucinations, urine retention	24	Not determined	56	Not determined	Not detected	(12)
Children Abuse	6–8	Non-fatal	Not reported	Unknown	Not determined	Not determined	H: 0.3–1.1 pg/mg	Not determined	(13)
Husband Abuse	9	Non-fatal	Clouded confused, incoherent speech, mydriasis, blurry vision gait instability	Unknown (>24)	Not detected	899	Not determined	Not detected	(2)
Voluntary Consumption of Anticholinergic Plants									
Datura	10	Non-fatal	Coma, mydriasis, desaturation, hypotonia When waking up: inconsistency, aggressiveness, hallucinations	9 18	1.2 0.6	132 71	Not determined	Ethanol (S: 1.2 g/L) Benzodiazepines (midazolam), opiates, cannabis, buprenorphine (U)	(14)
	11	Non-fatal	Not reported	Unknown	Not determined	Not determined	H: 14, 43 and 48 pg/mg (three segments)	No determined	(15)

(continued)

Table I. Scopolamine Concentrations Reported in Biological Matrices and Clinical Features in Poisoning Cases

Case Type	Num.	Outcome	Clinical Symptoms	Time to Sampling (h)	Serum (ng/mL)	Urine (ng/mL)	Other Biological Matrices	Other Toxics	Ref.
	12	Non-fatal	Mydriasis, aggressiveness, delirium, hallucinations	12	<1	Not determined	Not determined	Atropine (S: 1.7 ng/mL) Cannabis (U)	(16)
	13	Non-fatal	Agitation, delirium anxiety, hallucinations, disorientation, mydriasis, hyperthermia, tachycardia	2 26 43	1.4 1 <0.1	Not determined	Not determined	Cannabis (U)	(16)
	14	Non-fatal	Not reported	Unknown	2.0	170	Not determined	Not reported	(17)
	15				3.1	300			
	16				3.5	670			
	17				3.2	Not determined			
	18	Non-fatal	Excitation, mydriasis, tachycardia	Unknown	30.6 (at admission) 8.5 (2 h post-admission)	Not determined	Not determined	Atropine (S: 31.3 ng/mL at admission; 6.7 2 h post-admission)	(18)
Datura (Collective Poisoning)	19–26	Non-fatal	Agitation, aggression, hallucinations, dry mouth and skin, mydriasis	20	Not detected (<5 ng/mL)	32.4 to 186.4	Not determined	Atropine (U: 67.1 to 691.7)	(19)
Hallucinogenous Herbal Tea (Collective Poisoning)	27–38	Non-fatal	Hallucinations, aggression, agitation, amnesia, mydriasis, dry skin, tachycardia, hyperthermia, hypotension, collapse, coma, respiratory depression	6	Mean 13 (maximum 50)	Detected scopolamine	GL: Detected	Atropine, harmine (S, U)	(20)
Hallucinogenous Herbal Tea	39	Non-fatal	Disorientation, mydriasis, hallucinations, nervousness, vomiting	12 (approx.)	Not determined	2,407	No	THC-COOH (U 307 ng/mL) Cotinine (U)	(4)
Aphrodisiac Berries	40	Non-fatal	Nausea, vomiting, abdominal pain, agitation, aggression, mydriasis, dry mouth and skin hyperthermia, tachycardia	1	Not detected (<5 ng/mL)	32.7	Not determined	Hyoscyamine (U 539.8 ng/mL)	(21)

(continued)

Table I. Scopolamine Concentrations Reported in Biological Matrices and Clinical Features in Poisoning Cases

Case Type	Num.	Outcome	Clinical Symptoms	Time to Sampling (h)	Serum (ng/mL)	Urine (ng/mL)	Other Biological Matrices	Other Toxics	Ref.
Substitution of Drug in Illicit Users									
Scopolamine Disguised as Rohypnol™ Tablets	41	Non-fatal	Not reported	5	0.45	Not reported	Not determined	Not reported	(22)
	42			3	0.79				
Iatrogenic Poisoning									
Substitution of Hyoscine Butylbromide by Hyoscine Hydrobromide	43	Non-fatal	Difficult communication, loss of motor control, stupor, GCS 9, mydriasis, urinary retention, tachycardia	Unknown (<12)	1.82	76.5	Not determined	Not reported	(1)
	44		General malaise, visual disturbances, hallucinations, dry mouth, confusion, disorientation, mydriasis, amnesia	Unknown (<12)	1.49	320			
Poisoning from Unreported Cause									
Poisoning	45	Fatal	Unknown	Unknown	1890 (B)	Not reported	B: 110 ng/mL L: 360 μg/kg	Not reported	(1)
Poisoning	46	Non-fatal	Not reported	Unknown	210	110	Not determined	Atropine (S 70 ng/mL; U 340 ng/mL)	(23)
Poisoning	47				60	140		Atropine (S 60 ng/mL; U 220 ng/mL)	

B: Blood; BI: Bile; FB: Femoral blood; GL: Gastric lavage; H: Hair; HB: Heart blood; L: Liver; U: Urine; S: Serum; SC: Stomach contents; VH: Vitreous humor.

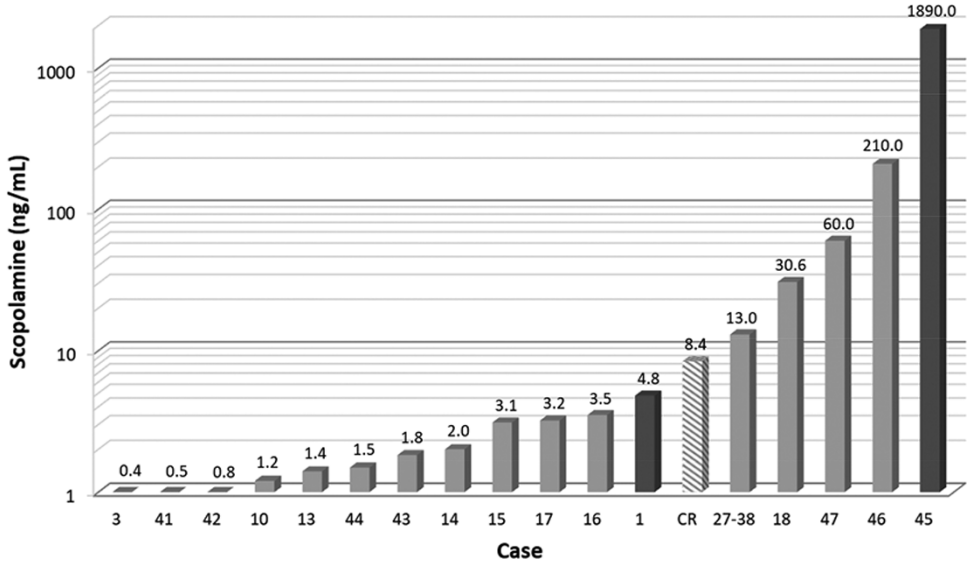

Figure 2. Scopolamine serum concentrations reported in non-fatal and fatal cases (Gray: Non-fatal cases; Black: Fatal cases; CR: Case report).

it is necessary to quantify in serum or hair. Thus, in clinical laboratories in which scopolamine in urine or blood analysis cannot be performed, clinical response to the administration of physostigmine can be a practical diagnosis aid. For these reasons, traditionally the detection of scopolamine has more forensic than clinical value.

Toxicology screening is useful in the diagnosis of unexplained coma. In our case, scopolamine identification in urine was performed only 4 h after the admission to the ICU. This was important in evaluating and managing this case. Meanwhile, the entire clinical management and diagnostic tests continued. The patient was discharge after 12 days, and criminal prosecutions were not initiated. However, toxic effects in the patient described in this case report did not correspond to any of the typical profiles in which the presence of scopolamine has been shown before.

Scopolamine shows longer central effects in comparison to the peripheral effects. High serum concentration measured in the ICU would explain the abrupt clinical presentation that suffered by our patient. Unfortunately, sample volume was not enough to measure serum concentration at admission. Furthermore, retrograde scopolamine concentration is difficult to know due to the high inter-individual variability in all pharmacokinetic parameters (1,8,9).

Even the first urine concentration was higher than those previously reported (Table I). This could explain why scopolamine could be detected up to 48 h after admission.

Conclusion

This report illustrates that broad toxicology screening, including scopolamine, should be considered when patients with diminished consciousness are attended after ruling out infection or cerebrovascular disease. This can play an important role in identifying this potentially life-threatening etiology.

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