Case Report

Acute Toxicity by Salvia Officinalis: A Rare Cause of Intestinal Sub-Occlusion

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ABSTRACT: Salvia officinalis is a perennial plant commonly used in culinary and medical preparations. Its large intake is usually related to psychiatric disorders (such as pica) and might induce different symptoms (e.g. vomiting, nausea, diarrhoea, salivation, arterial hypertension, tachycardia, vertigo, flushes, cyanosis and convulsions) likely ascribable to pro-cholinergic effects of various constituents. The identification of this toxicity is challenging because of its rarity and possible underlying psychiatric comorbidities. Herein we describe the case of a schizophrenic 56-year-old male admitted to the Emergency Department for abdominal pain and diarrhea resulted in a rare case of acute toxicity by Salvia officinalis.

KEYWORDS: *Acetylcholine; Emergency medicine; Salvia officinalis; Toxicity.*

Introduction

Salvia is the largest genus of plants in the Lamiaceae family, with over 900 species distributed worldwide.

The most common species include S. officinalis (common sage), S. miltiorrhiza (Chinese sage), S. lavandulaefolia (Spanish sage) and S. fruticose (Greek sage).

Some species have nutritional or medical applications, while others (e.g. S. divinorum) contain hallucinogenic compounds [1-2].

S. officinalis is used in culinary and medical preparations.

Since ancient times, it has been traditionally used for the treatment of a wide range of diseases (e.g. dyspepsia, bronchitis, coughs, asthma, memory problems, angina, mouth and throat inflammation and depression).

Also, Salvia leaves are traditionally known for their antioxidant effects and ability to improve memory and delay age-associated cognitive impairment [1].

Salvia is composed by different elements including alkaloids, carbohydrates, fatty acids, glycosidic derivatives, phenolic compounds, poly acetylenes, steroids, terpenes/terpenoids and waxes [3].

Several studies highlighted that the use of Salvia in daily diet is not burdened by severe side effects [3,4-6].

However, in case of prolonged use of ethanolic extract / oil (corresponding to more than 15g of leaves), Salvia might induce different systemic symptoms (e.g. vomiting, nausea, diarrhoea, salivation, arterial hypertension, tachycardia, vertigo, flushes, cyanosis and convulsions) ascribable to pro-cholinergic effects [6-8].

Case Report

A 56-year-old male patient was admitted to the Emergency Department of St. Anna University Hospital of Ferrara, Italy, for persistence of fever, abdominal pain and diarrhea for 7 days unresponsive to loperamide administration.

The medical history was positive for paranoid schizophrenia treated with clozapine, delorazepam, levomepromazine, haloperidol and clotiapine.

At presentation, the patient was alert, partially oriented, collaborative and complained of moderate abdominal pain (NRS=6) associated with diarrhea (about 5 discharges of liquid stools per day).

The vital parameters were: blood pressure 175/110mmHg, heart rate 95bpm, SpO2 99% in ambient air, respiratory frequency 15 acts/minute, body temperature 38°C.

Blood tests showed a mild hyponatremia, moderate hypokalemia and hypochloremia, increased

C-reactive protein and negative procalcitonin (Table 1).

Table 1. Blood values / serum electrolytes

Feature	Value	Normal Values
WBCs (x10^3/µl)	9.0	4.0-11.0
RBCs (x10^6/µl)	4.78	4.50-6.50
HGB (g/dl)	16.2	13.0-18.0
Plts (x10^3/µl)	210	150-450
PT: INR	1.14	0.80-1.20
Creatinine (mg/dl)	1.09	0.50-1.20
Sodium (mmol/L)	132	136-145
Potassium (mmol/L)	2.8	3.5-5.3

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Chloride (mmol/L)	94	98-107
Total bilirubin (mg/dl)	1.09	< 1.20
Direct bilirubin (mg/dl)	0.47	0.00-0.30
Lipase (U/L)	21	< 67
ALT (U/L)	14	< 50
LDH (U/L)	179	< 248
PCR (mg/dl)	21.72	< 0.5

The chest X-ray was unremarkable, while the abdomen X-ray revealed a marked small intestinal distension with air-fluid levels and right colon coprostasis (Figure 1A).

A contrast-enhanced CT scan of the abdomen confirmed air-fluid distension of the entire small intestine (without evident transition points), minimal amount of intra-abdominal fluid and mild coprostasis in the ascending colon (Figure 1B).

The surgical consultation recommended intravenous pharmacological treatment (i.e. metoclopramide 10mg bid; trimebutine 100 mg/die), adequate fluid support (hydro-electrolyte infusion via 2000ml/die of Ringer lactate) and empirical antibiotic therapy with amoxicillin/clavulanic acid (2.2g q.i.d.) along with metronidazole (500mg q.i.d.).

A colonoscopy did not reveal mechanical obstructions.

After psychiatrist consultation, a diagnosis of "pica disorder", due to ingestion of a large amount ("bushes") of Salvia officinalis, was established.

By quitting inappropriate Salvia consumption, the patient's clinical conditions progressively improved with a significant amelioration of the abdominal distension.

The patient was discharged alert and oriented, afebrile and with normal bowel movements (regular evacuation of formed stools).

A written informed consent was obtained from the patient before preparing the paper for publication.

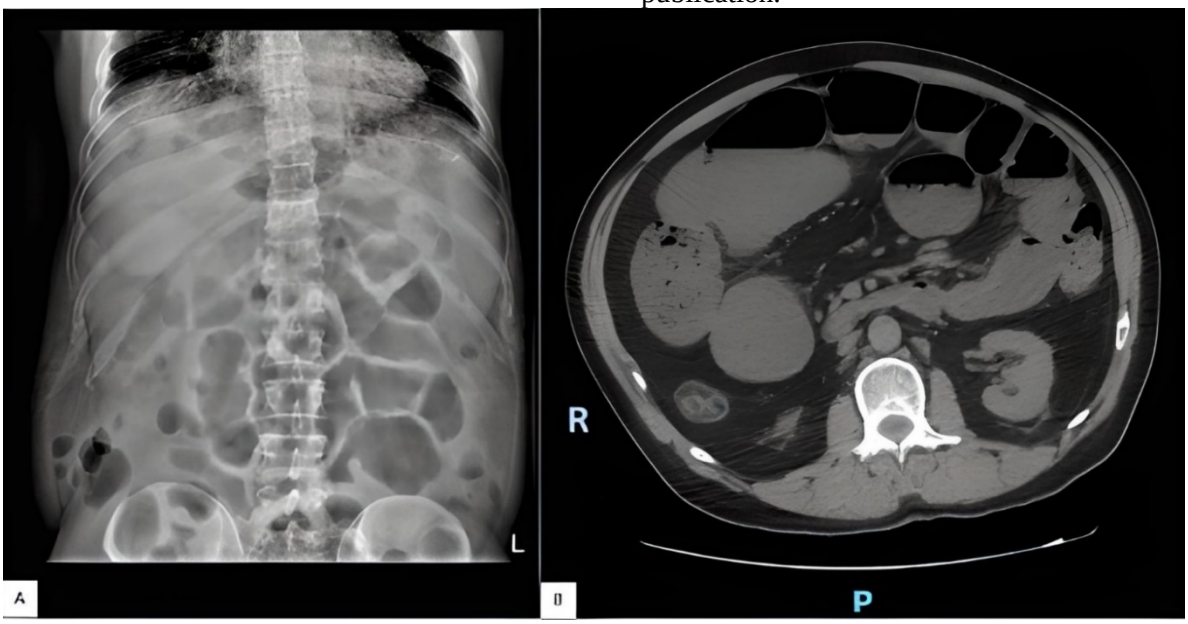

Figure 1: Radiological images showing intestinal sub-occlusion after Salvia ingestion (A: X-ray of the abdomen; and B: contrast-enhanced CT).

Discussion

This case showed an acute abdominal condition associated with the incongruous intake of Salvia officinalis in a psychiatric patient affected by pica.

According to the fifth Diagnostic and Statistical Manual of Mental Disorders (DSM-V), pica is the action of inappropriate ingestion of increasing amounts of non-nutritive and non-food substances that is repeated for a period of at least a month [9].

Pica is mainly observed in children and pregnant women and in certain ethnic populations is culturally accepted and not considered an abnormal behavior.

Pica is usually an isolated disorder, but it can occur in the context of psychiatric diseases (e.g. schizophrenia and/or obsessive-compulsive disorder), with an increased risk of electrolyte disturbances and intestinal obstruction [9].

To our knowledge, there are no reported cases of acute intoxication induced by Salvia officinalis in the literature.

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Its toxic effect is mainly described in cases of chronic use of Salvia extracts.

Salvia leaves are rich of phenolic acids, terpenoids and flavonoids.

However, the distribution of these compounds can vary considerably between

Salvia species. For example, rosmarinic acid and thujone have been reported to be more abundant in S. officinalis than other species.

Animal and human studies confirmed that thujone can exert neurotoxic effects interacting with the γ-aminobutyric acid A receptor, thus causing excitation and convulsions in a dose-dependent manner.

Consequently, the Committee on Herbal Medicinal Products and the European Medicines Agency have recommended an intake of 6mg thujone on a daily basis [1-3].

Salvia has been tested as possible therapeutic compound in several conditions, e.g. Alzheimer's disease, menopausal syndrome, prostate cancer in advanced age, type 2 diabetes mellitus and hyperlipidaemia, because of its anti-β-amyloid peptide mechanisms, antioxidant, antidepressant, anxiolytic, anti-inflammatory properties, neurotrophic actions and cholinergic effects [1,3,4,6-8,10-15].

Indeed, the accumulation of the amyloid-β peptide is a typical feature of Alzheimer's disease and its deposition is considered partially responsible for the cognitive impairment.

For example, Salvia miltiorrhiza has been shown to protect mice from amyloid-β-induced neurotoxicity by inhibiting tumor necrosis factor, interleukin-6 and acetylcholinesterase (AChE) activity [1,4,12].

Furthermore, an excess of free radicals and a reduced antioxidant power can generate an oxidative stress causing tissue/organ, in particular the brain, damage.

An analysis of most common Salvia species (including S. officinalis) confirmed all exhibited significant antioxidant activities as measured by oxygen radical absorbance/scavenging capacities and total phenolic content [1].

However, different patients treated with Salvia species showed several side effects including arterial hypertension, gastrointestinal symptoms (e.g. abdominal pain and diarrhoea) and acneiform rash [1,3,4,6-8,10].

In vitro and *in vivo* studies highlighted that several Salvia species and their derivatives (such as ethanolic extract, phenolic diterpenes, 7-methoxyrosmanol and isorosmanol and rosmarinic acid) are effective AChE inhibitors, thus enhancing cholinergic effects [1,7,10,16,17].

The peripheral actions of acetylcholine (Ach) occurs via the interaction with muscarinic (M1, M2, M3, M4, M5) and/or nicotinic receptors, the latter expressed by muscle (Nm) and neuron (Nn) [18-21].

The main location and related physiological effects of each muscarinic/nicotinic receptor have been summarized in Table 2.

Table 2. Essential features of muscarinic/nicotinic receptors.

Type of Receptor	Receptor	Location	Roles
Muscarinic	M1	Mainly in the CNS and autonomic ganglia including enteric nerves; expressed also in gastric and salivary glands	• CNS excitation (memory and cognitive stimulation, appetite regulation) • Increased gastric secretion
	M2	CNS, heart, smooth muscle	• Cardiac inhibition (chronotropic and inotropic effect, negative, reduction of conduction rate AV node) • Central effects such as tremor and hypothermia
	M3	CNS, smooth muscle, glands, heart	• Increased GI muscle contraction and gastric secretion • Increased gland (lacrimal, salivary, nasopharyngeal, sweat) secretion • Pupil and ciliary sphincter muscle contraction • Bladder detrusor muscle contraction
	M4	CNS	• Inhibition of auto- and hetero-receptor mediated transmitter release in the CNS
	M5	Predominantly expressed in dopaminergic neurons of the *substantia nigra* and ventral tegmental area in the CNS; less detectable in the PNS	• Dilatation of cerebral arteries • Facilitates dopamine release
Nicotinic	Nm	Skeletal neuromuscular junction	• Motor plate depolarization with skeletal muscle contraction
	Nn	Autonomic ganglia including enteric nerves; adrenal medulla	• Depolarization and firing of postganglionic neuron; • Catecholamine secretion

Smooth muscle contraction in various organs is mainly mediated by M3 receptors [19].

The inhibition that Salvia exerts on AChE may induce an exaggerated bioavailability of Ach, which may evoke powerful intestinal smooth muscle contraction (i.e. 'spasm') contributing to abdominal pain and ineffective peristalsis (hence mimicking crisis of intestinal sub-occlusion).

Also, ACh may favor increased secretion via enhancing neurally mediated secretory intestinal reflexes thereby leading to paradoxical diarrhoea which significantly reduces serum potassium levels (and therefore impacting negatively on motility and transit).

Furthermore, the ingestion of Salvia also stimulates M3 receptors distributed on the arterial smooth muscle, thus causing a systemic vascular contraction and therefore hypertension [18-21].

Finally, the nicotinic excitability may have generated nervous system impairment (e.g. tremors, convulsion).

In conclusion, the present case highlighted possible pharmacological effects related to an excessive intake of S. officinalis with many constituents of this plant exhibiting prominent anti-AChE effects.

Although an extremely rare event, Salvia toxicity may occur in subsets of patients especially those with psychiatric disorders (e.g. pica) and evoke different manifestations including abdominal or cardiac abnormalities.

Since there are no antidote, a prompt interruption of Salvia intake, correction of electrolyte derangement and adequate management of gastrointestinal manifestations are crucial to avoid major complications with possible life-threatening consequences.

List of Abbreviations

ACh: Acetylcholine; AChE: acetylcholine-esterase; DSM: Diagnostic and Statistical Manual of Mental Disorders.

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Conflict of interests

None to declare.

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