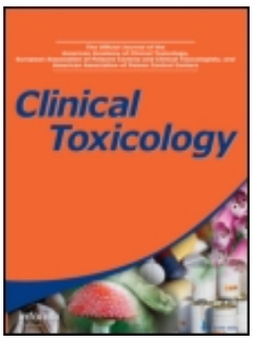

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: http://www.tandfonline.com/loi/ictx20

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To cite this article: Thomas Y.K. Chan (2009) Aconite poisoning, Clinical Toxicology, 47:4, 279-285, DOI: 10.1080/15563650902904407

To link to this article: http://dx.doi.org/10.1080/15563650902904407

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Clinical Toxicology (2009) **47**, 279–285
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ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650902904407

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REVIEW

Aconite poisoning

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Introduction. Aconitine and related alkaloids found in the *Aconitum* species are highly toxic cardiotoxins and neurotoxins. The wild plant (especially the roots and root tubers) is extremely toxic. Severe aconite poisoning can occur after accidental ingestion of the wild plant or consumption of an herbal decoction made from aconite roots. In traditional Chinese medicine, aconite roots are used only after processing to reduce the toxic alkaloid content. Soaking and boiling during processing or decoction preparation will hydrolyze aconite alkaloids into less toxic and non-toxic derivatives. However, the use of a larger than recommended dose and inadequate processing increases the risk of poisoning. *Methods*. A Medline search (1963–February 2009) was conducted. Key articles with information on the use of aconite roots in traditional medicine, active (toxic) ingredients, mechanisms of toxicity, toxicokinetics of *Aconitum* alkaloids, and clinical features and management of aconite poisoning were reviewed. *Mechanisms of toxicity*. The cardiotoxicity and neurotoxicity of aconitine and related alkaloids are due to their actions on the voltage-sensitive sodium channels of the cell membranes of excitable tissues, including the myocardium, nerves, and muscles. Aconitine and mesaconitine bind with high affinity to the open state of the voltage-sensitive sodium channels at site 2, thereby causing a persistent activation of the sodium channels, which become refractory to excitation. The electrophysiological mechanism of arrhythmia induction is triggered activity due to delayed after-depolarization and early after-depolarization. The arrhythmogenic properties of aconitine are in part due to its cholinolytic (anticholinergic) effects mediated by the vagus nerve. Aconitine has a positive inotropic effect by prolonging sodium influx during the action potential. It has hypotensive and bradycardic actions due to activation of the ventromedial nucleus of the hypothalamus. Through its action on voltage-sensitive sodium channels in the axons, aconitine blocks neuromuscular transmission by decreasing the evoked quantal release of acetylcholine. Aconitine, mesaconitine, and hypaconitine can induce strong contractions of the ileum through acetylcholine release from the postganglionic cholinergic nerves. *Clinical features*. Patients present predominantly with a combination of neurological, cardiovascular, and gastrointestinal features. The neurological features can be sensory (paresthesia and numbness of face, perioral area, and the four limbs), motor (muscle weakness in the four limbs), or both. The cardiovascular features include hypotension, chest pain, palpitations, bradycardia, sinus tachycardia, ventricular ectopics, ventricular tachycardia, and ventricular fibrillation. The gastrointestinal features include nausea, vomiting, abdominal pain, and diarrhea. The main causes of death are refractory ventricular arrhythmias and asystole and the overall in-hospital mortality is 5.5%. *Management*. Management of aconite poisoning is supportive, including immediate attention to the vital functions and close monitoring of blood pressure and cardiac rhythm. Inotropic therapy is required if hypotension persists and atropine should be used to treat bradycardia. Aconite-induced ventricular arrhythmias are often refractory to direct current cardioversion and antiarrhythmic drugs. Available clinical evidence suggests that amiodarone and flecainide are reasonable first-line treatment. In refractory cases of ventricular arrhythmias and cardiogenic shock, it is most important to maintain systemic blood flow, blood pressure, and tissue oxygenation by the early use of cardiopulmonary bypass. The role of charcoal hemoperfusion to remove circulating aconitine alkaloids is not established. *Conclusions.* Aconite roots contain aconitine, mesaconitine, hypaconitine, and other *Aconitum* alkaloids, which are known cardiotoxins and neurotoxins. Patients present predominantly with neurological, cardiovascular, and gastrointestinal features. Management is supportive; the early use of cardiopulmonary bypass is recommended if ventricular arrhythmias and cardiogenic shock are refractory to first-line treatment.

Keywords Aconitine; *Aconitum* species; Aconite roots; Herbal medicines; Cardiotoxins; Neurotoxins; Ventricular arrhythmias

Introduction

Aconitine and other *Aconitum* alkaloids are highly toxic cardiotoxins and neurotoxins found in all parts of the plants of the *Aconitum* species (aconite).[1] They are most abundant in the roots and root tubers. In Europe and North America, aconite poisoning usually occurs after the accidental ingestion of the wild plant, *A. napellus* (monkshood, wolfsbane, or devil's helmet). The public may mistake garden and mountain monkshood for some edible plants.[2,3] In Asia, aconite poisoning is much more common because of the continuing use of aconite roots in traditional medicine as analgesic, anti-inflammatory, and cardiotonic agents.[4,5] However, with easy access to, and increased popularity of, herbal medicines in western societies, aconite poisoning can occur anywhere in the world.[6–8]

Received 13 January 2009; accepted 18 March 2009.

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Methods

A Medline search (1963–February 2009) was conducted using the keywords aconite, aconitine, and *Aconitum*. Key articles with information on the use of aconite roots in traditional medicine, active (toxic) ingredients, mechanisms of toxicity, toxicokinetics of *Aconitum* alkaloids, and clinical features and management of aconite poisoning were reviewed. Additional articles were identified from the herbal medicine database of the Prince of Wales Hospital Poison Treatment Centre.

Aconite roots as medicinal herbs

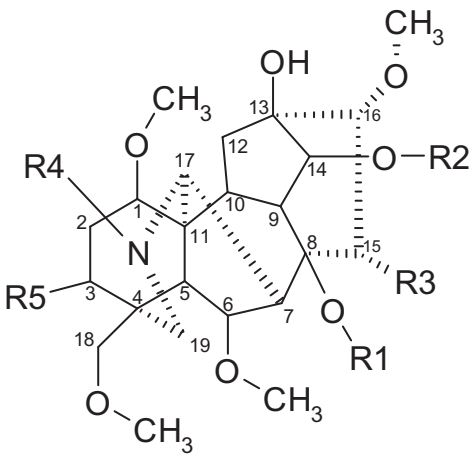
Tincture of aconite (either the whole plant with or without the root tubers, leaves, or the root tubers) has been used to treat pains, agitation, indigestion, and other conditions.[9,10] However, eight drops of a tincture can cause severe poisoning.[10] This is not surprising since wild (i.e., unprocessed) aconite plants are extremely toxic. It is of great concern that numerous websites advocate the use of aconite and describe how aconite tincture may be made.

In India, aconite roots are used by both homeopathic and traditional medicine practitioners. Aconite tincture has been taken orally as an antipyretic, antirheumatic, cardiac stimulant, abortifacient, aphrodisiac, and antihelmintic and used for the treatment of cough, asthma, snakebite, vomiting, and diarrhea.[11] Aconite paste has been used to treat neuralgias.[11] Aconite tincture has been employed topically to relieve gum pain and to enhance the inebriation produced by alcohol.[11,12] Under the Ayurvedia, Siddha, and Unani systems of traditional medicine, aconite roots must first undergo a detoxification procedure before use as anti-inflammatory, analgesic, and cardiotonic agents.[13]

In traditional Chinese medicine, aconite roots are used only after processing, which reduces the alkaloid content by up to 90%.[5] "Chuanwu" (the root tuber of *A. carmichaeli*), "caowu" (the root tuber of *A. kusnezoffii*), and "fuzi" (the lateral root tuber of *A. carmichaeli*) are often used to treat rheumatism, arthritis, bruises, fractures, pains, and other conditions. Soaking and boiling during processing or domestic decoction preparation will hydrolyze aconite alkaloids into less toxic and non-toxic derivatives (see next section). Proprietary medicines containing processed aconite roots are also available as capsules and tablets.

Active ingredients and toxic doses of aconite roots

The principal active (toxic) ingredients in aconite roots are C_{19}-diterpenoid alkaloids, including aconitine, mesaconitine, and hypaconitine (Figure 1).[1,5] Mesaconitine is similar to aconitine in terms of toxicity. Hypaconitine is more potent than aconitine and mesaconitine in blocking neuromuscular transmission.[14] Other *Aconitum* alkaloids may be present or predominant, for example, yunaconitine in the *Aconitum* species from Yunnan and jeaconitine in the *Aconitum* species from Japan.[15,16] Yunaconitine is as toxic as aconitine.[17]



Alkaloids	R1	R2	R3	R4	R5	MW
Aconitine	AC	BZ	OH	CH_2CH_3	OH	645
Mesaconitine	AC	BZ	OH	CH_3	OH	631
Hypaconitine	AC	BZ	OH	CH_3	H	615
Jesaconitine	AC	AS	OH	CH_2CH_3	OH	675
Yunaconitine	AC	AS	H	CH_2CH_3	OH	659

Fig. 1. Chemical structure of major *Aconitum* alkaloids. AC, $COCH_3$ (acetyl group); BZ, COC_6H_5 (benzoyl group); AS, $COC_6H_4OCH_3$ (anisoyl group).

Other aconitine alkaloids and cardiotonic substances may either modulate or contribute to the toxicity of the *Aconitum* species. The cardiotoxicity of lappaconitine is much lower than aconitine and its presence reduces the risk of aconitine-induced arrhythmias.[18] The presence of 6-benzoylheteratisine, 1-benzoylnapelline, and 14-benzoyltalatisamine may cause negative inotropic effects and bradyarrhythmias.[19] These alkaloids are less toxic than aconitine and are inhibitors rather than activators of sodium channels. Aconite roots may contain higenamine (a β-agonist with positive chronotropic and inotropic effects) and coryneine chloride (a dopamine derivative with α-adrenergic effects).[1,20]

The amount of aconitine alkaloids involved is the single most important factor determining whether severe poisoning will occur after the ingestion of *Aconitum* species. The toxicity of different plant parts follows the same order as the alkaloid content, that is, roots and root tubers > flowers > leaves and stems.[1] The *Aconitum* alkaloid contents can vary with the species, place of origin, time of harvest, and, most importantly, the method and adequacy of processing.[5]

In the preparation of aconite tincture, the wild plant is often used without prior processing.[9,10] In addition, as *Aconitum* alkaloids dissolve well in alcohol, aconite tincture may contain a large amount of aconitine alkaloids.[21] When aconite roots are used in traditional medicine, prior processing

should reduce the aconitine and total alkaloid content by as much as 90 and 65%, respectively, because of hydrolysis of *Aconitum* alkaloids to less toxic (e.g., benzylaconine) and non-toxic (aconine) derivatives.[22] The aconitine contents in processed "chuawu" and "caowu" are 0.0041–0.021% and 0.0084–0.034%, respectively.[23] These amounts are much lower than those found in crude "chuawu" (0.137%) and "caowu" (0.199%).[22] However, faulty processing after harvest or during decoction preparation and the use of a greater than recommended dose (e.g., 7–11 g instead of 1.5–3 g) will increase the risk of severe poisoning.[5] The amounts involved are likely to be larger in deliberate ingestion compared to unintentional poisoning due to herbal medicines.[21]

The estimated lethal dose in humans is 2 mg of pure aconitine, 5 mL of aconite tincture, and 1 g of the wild plant.[24] Death has followed the consumption of a decoction made from 10 to 16 g of processed aconite roots.[25]

Mechanisms of toxicity of *Aconitum* alkaloids

The cardiotoxicity and neurotoxicity of aconitine and related alkaloids are due to their actions on the voltage-sensitive sodium channels of the cell membranes of excitable tissues, including the myocardium, nerves, and muscles.[1,5]

Aconitine and mesaconitine bind with high affinity to the open state of the voltage-sensitive sodium channels at site 2, thereby causing a persistent activation of the channels by blocking their inactivation.[19] As a consequence of continuing sodium influx and sustained depolarization, the sodium channels become refractory to excitation. The affinities of aconitine and mesaconitine for the sodium channels *in vitro* correlate with the LD_{50} in rats,[19] suggesting that modulation of sodium channels is responsible for the toxicity of these alkaloids.

The arrhythmogenic effects of aconitine are well recognized. Experimental models of aconitine-induced arrhythmias have long been used to test the efficacy of antiarrhythmic agents.[26] Aconitine can induce ventricular ectopics, ventricular tachycardia, *torsades de pointes*, ventricular fibrillation, and mortality in a dose-dependent manner.[27] The electrophysiological mechanism of arrhythmia induction is triggered activity due to delayed after-depolarization and early after-depolarization.[28] Aconitine binds to sodium channels and prolongs their open state, favoring Na^+ influx into the cytosol. The associated increase in intracellular calcium via Na^+–Ca^{2+} exchange system induces triggered activity. The arrhythmogenic properties of aconitine are also partly due to its cholinolytic (anticholinergic) effects mediated by the vagus nerve.[29]

Aconitine has a positive inotropic effect on the heart by prolonging the sodium influx during the action potential.[30] It has hypotensive and bradycardic actions, which are due to activation of the ventromedial nucleus of the hypothalamus.[31] The latter plays an important role in controlling the autonomic nervous system activity. Neuronal activity of the ventromedial nucleus is associated with suppression of the circulatory system.[32]

The neurotoxic effects of aconitine are mediated through its action on voltage-sensitive sodium channels in axons, thereby blocking neuromuscular transmission by decreasing the evoked quantal release of acetylcholine.[33]

In the guinea pig, aconitine, mesaconitine, and hypaconitine can induce strong contractions of the ileum.[34] A muscarinic mechanism (i.e., acetylcholine release from the postganglionic cholinergic nerve) is suspected since the ileal contractions can be completely blocked by atropine. Contractions of the small intestine may result in abdominal pain and diarrhea.

Toxicokinetics of *Aconitum* alkaloids

The latent period between ingestion of aconite roots and the onset of features may be as short as 10 min,[21] suggesting that aconitine and related alkaloids can be absorbed rapidly by the upper gastrointestinal tract.

The metabolism of *Aconitum* alkaloids is mainly carried out by esterases.[35] Carboxylesterases are located in the endoplasmic reticulum and cytosol of many tissues (particularly the liver microsomes, kidneys, and the gut), where they hydrolyze ester- (e.g., *Aconitum* alkaloids) and amide-containing natural toxins, drugs or chemicals to their respective free acids.[36] Aconitine, mesaconitine, and hypaconitine are hydrolyzed to the much less toxic metabolites, benzoylaconine, benzoylmesaconine, and benzoylhypaconine (Figure 2).[37] Further hydrolysis of these metabolites yields almost non-toxic derivatives, aconine, mesaconine, and hypaconine (Figure 2).

In a woman with rheumatoid arthritis, mild symptoms appeared half an hour after she had ingested an herbal decoction prepared from "chuanwu" 10 g, "caowu" 10 g, and other herbs.[37] In her urine, apart from *Aconitum* alkaloids and their hydrolyzed metabolites, 16-*O*-demethylaconitine and 16-*O*-demethylhypaconitine were present. After the oral administration of aconitine to rabbits, both hydrolyzed (benzoylaconine, aconine) and demethylated (16-*O*-demethylbenzoylaconine, 6-*O*-demethylaconine) metabolites were present in the urine.[38] *In vitro* studies using rat liver microsomes indicated that aconitine metabolism was catalyzed by CYP3A with minor involvement of CYP1A1/2;[39] six metabolites were identified, including three demethylated products.

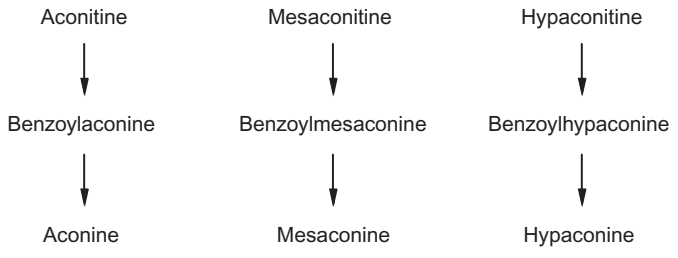


Fig. 2. Hydrolysis of aconitine, mesaconitine, and hypaconitine to the much less toxic (benzoylaconine, benzoylmesaconine, and benzoylhypaconine) and almost non-toxic (aconine, mesaconine, and hypaconine) derivatives.

It can be concluded that *Aconitum* alkaloids are metabolized predominantly through hydrolysis catalyzed by esterases. They also undergo *O*-demethylation and other biotransformation reactions, which are catalyzed by cytochrome P450 (CYP) enzymes, predominantly CYP3A.

A 40-year-old woman died of aconite poisoning 4 h after the suicidal ingestion of aconite roots.[40] The concentrations of jesacontine (the main alkaloid involved) were higher in the urine, kidneys, liver, bile, and ileal contents, compared to the serum. These findings suggest that aconitine alkaloids are eliminated via urine and feces.

In patients who have ingested aconite roots accidentally or deliberately, aconitine and related alkaloids normally became undetectable in blood after 24 h.[41,42] In a 17-year-old man who had ingested *A. napellus*,[41] the blood aconitine concentration peaked (>0.2 μg/L) 9 h later and fell below 0.12 μg/L (the concentration associated with disappearance of ventricular arrhythmias) 18 h later. In a 61-year-old man who ingested an aconite plant accidentally,[42] *Aconitum* alkaloids and their hydrolyzed metabolites were present in much higher concentrations in urine compared to blood. The urine concentration of *Aconitum* alkaloids in the 21st hour sample were much lower than those of the 16th hour sample (aconitine 2.8 vs. 20.2 μg/L, mesaconitine 0.8 vs. 7.7 μg/L, jesaconitine 69.6 vs. 574.4 μg/L), suggesting that the absorption, metabolism, and excretion of these alkaloids can be relatively fast.[42]

A 21-year-old man ingested three homemade *A. napellus* capsules (each containing 237 mg of dried root tuber equivalent to 19 μg of aconitine) in order to sleep.[43] The plasma aconitine kinetics were first order, with an elimination half-life of 3 h. His cardiovascular and neurological symptoms disappeared by the 11th and 13th hour after ingestion, respectively, when the calculated plasma aconitine concentration was 0.65 and 0.45 μg/L, respectively. This case demonstrated a relationship between plasma aconitine concentrations and severity of symptoms.

In five patients with aconitine poisoning (4 men, 1 woman, aged 49–78 years) after the ingestion of aconite roots (n = 4) or leaves (n = 1), the half-lives of aconitine in four of these patients ranged from 3.7 to 17.8 h and the half-lives of mesaconitine in two patients were 2.8 and 5.8 h.[44] The severity of symptoms was affected by both the amount of exposure (i.e., area under the blood concentration–time curve or AUC) and time of exposure (i.e., mean residence time = area under the moment curve from 0 to ∞ divided by AUC).

When aconitine is the principal alkaloid present (e.g., *A. napellus* poisoning), blood concentrations as low as 3.6 μg/L may be considered lethal if not treated.[45] Where several *Aconitum* alkaloids are involved (e.g., "chuanwu" and "caowu" poisoning), the severity of the intoxication and hence the risk of fatality is better explained by the blood concentrations of aconitine, mesaconitine, and hypaconitine.

Given the presence of aconitine alkaloids in high concentrations in the urine and their continued detection in urine up to 7 days after overdose,[35,44] the renal pathway appears to be the most important for elimination.

Clinical features

As can be seen in Table 1, the great majority of patients with aconite poisoning present with a combination of neurological, cardiovascular, and gastrointestinal features.[5,21,45]

The neurological features can be sensory (paresthesia and numbness of the face, perioral area, and the four limbs), motor (muscle weakness in the four limbs), or both. Paresthesia and numbness start in the face and perioral area and spread to the four limbs. Although the muscle weakness is generally mild (grade 5^- power), tetraplegia with grades 0–1 power can occur.[46]

The cardiovascular features include hypotension, palpitations, chest pain, bradycardia, sinus tachycardia, ventricular ectopics, ventricular arrhythmias (tachycardia, *torsade de points*, and/or fibrillation), and junctional rhythm. Ventricular arrthythmias are most likely to occur in the first 24 h and in severe poisoning. Some patients have a raised plasma

Table 1. Demographic and clinical features of aconite poisoning

	Chan et al.[5]	Tai et al.[45]	Lin et al.[21]
Study details			
Study period	1989–1993	1989–1991	1990–1999
Place of study	Hong Kong	Hong Kong	Taiwan
Data source	1 hospital	5 hospitals (ICU)	1 poison center
Demographics			
Sex	11 M, 7 F	12 M, 5 F	9 M, 8 F
Age, median (range), y	(24–81)	56 (9–81)	46 (30–70)
Aconite roots			
Decoction (cured/raw)	18/0	17/0	6/4
Others	0	0	7
Clinical features (%)			
Latent period, median (range), minutes	(18–90)	30 (3–120)	(10–90)
Neurological[a]	94.4	Not available	100
Cardiovascular[b]	83.3	Not available	77.8
Ventricular arrhythmias	11.1	88.2	23.5
Gastrointestinal[c]	72.2	Not available	52.9
Others[d]	33.3	Not available	76.5
Mortality (%)	5.6	11.8	0

[a]Including paresthesia and numbness of face, perioral area, and four limbs, muscle weakness in four limbs.
[b]Including hypotension (systolic blood pressure decreased by >20 mmHg or to <90 mmHg), palpitations, chest pain, bradycardia, sinus tachycardia, ventricular ectopics, ventricular arrhythmias (tachycardia, *torsade de points*, and/or fibrillation), and junctional rhythm.
[c]Including nausea, vomiting, abdominal pain, and diarrhea.
[d]Including dizziness, hyperventilation, sweating, difficulty in breathing, confusion, headache, and lacrimation.

creatine kinase activity without ECG evidence of acute myocardial infarction.[45] Aconite-induced bidirectional tachycardia,[47] atrioventricular dissociation,[10] and pulmonary edema[14] have also been reported.

In contrast to unintentional poisoning due to processed aconite roots (Table 1), ingestion of the wild plant results in even more severe cardiotoxicity because of the huge dose of *Aconitum* alkaloids involved. A 17-year-old man who ingested *A. napellus* with suicidal intent developed ventricular tachycardia and fibrillation, cardiac arrest, and apnea.[41] The ventricular arrhythmias were refractory to 30 direct current cardioversions and antiarrhythmic drugs. He required percutaneous cardiopulmonary support system for 2 days to maintain his cerebral and visceral circulation. He was discharged after 19 days of hospitalization without any neurological deficits.

A 61-year-old man mistook aconite for an edible wild grass.[42] He developed ventricular tachycardia and fibrillation, which lasted 6 h despite direct current cardioversion (193 times in total) and intensive antiarrhythmic therapy. Although sinus rhythm was restored 30 h after admission, he did not regain consciousness and died of hypoxic brain damage on day 6.

A 41-year-old man mistook *A. napellus* for an edible plant.[48] He developed ventricular tachycardia, fibrillation, and cardiogenic shock refractory to treatments. He was supported with percutaneous cardiopulmonary bypass for 1 week. About 3 months later, he was discharged from hospital.

The gastrointestinal features include nausea, vomiting, abdominal pain, and diarrhea. Hyperventilation resulting in respiratory alkalosis is seen in some patients, possibly because of the central effect of aconitine on the medullary center.[5] Other features include dizziness, sweating, a subjective feeling of difficulty in breathing, confusion, headache, and lacrimation.

The main causes of death are refractory ventricular arrhythmias and asystole.[5] Based on the non-selected cases managed in the Prince of Wales Hospital in Hong Kong, the overall in-hospital mortality of aconite poisoning is 5.5%.

Diagnosis

In practice, the diagnosis of herbal toxicity is often based on clinical grounds alone since sophisticated assays for target toxicology screening are not widely available. The diagnosis should be suspected in any patient with a history of consumption of plants or herbal medicines (especially for the treatment of musculoskeletal disorders) who present with a combination of neurological, cardiovascular, and gastrointestinal features (Table 1). Both the herbal residues and written prescriptions of the herbalists should be reviewed to verify the diagnosis and nature of the problem (e.g., use of a larger than recommended dose, dispensing errors, and substitution).[49] If the herbalists' written prescriptions are not available for review, the diagnosis of aconite poisoning should ideally be confirmed by toxicological analysis of herbal residues and biological samples.

In response to the need for clinical or forensic toxicological investigations, chemical analyses for the *Aconitum* alkaloids and their metabolites in biological samples have been developed, using a combination of chromographic and mass spectrometric techniques.[50] Ideally, the assay should cover the key aconitine alkaloids (e.g., aconitine, mesaconitine, and hypaconitine) and the native *Aconitum* species (e.g., yunaconitine in *A. vilmorinianum* of Yunnan and jesaconitine in *A. japonicum* of Japan). As the *Aconitum* alkaloids are prone to hydrolysis after herb processing, decoction preparation, and *in vivo* metabolism, the laboratory assay should cover the metabolites as well. The latter include hydrolyzed compounds (e.g., bezoylaconine, benzoylmesaconine, and benzoylhypaconine) and, if possible, demethylated products (e.g., 16-*O*-demethylaconitine and 16-*O*-demethylhypaconitine.) As the blood concentrations of *Aconitum* alkaloids are generally below the detection limits 24 h after ingestion,[41,42] it is more practical to measure the concentrations of these alkaloids and their metabolites in the urine because of their longer period of detection.[41,42,44]

Management

The management of aconite poisoning is supportive as there is no specific antidote, though atropine is used to treat bradycardia. Immediate attention should be given to the vital functions; hypotension, ventricular arrhythmias, and other potentially life-threatening conditions should be treated immediately. All patients require close monitoring of blood pressure and cardiac rhythm since ventricular arrhythmias may occur during the first 24 h, resulting in sudden deterioration in the patient's clinical condition.

Aconite-induced ventricular arrhythmias are often refractory to direct current cardioversions and antiarrhythmic drugs and pose difficult management problems.[45] As aconitine causes persistent activation of voltage-sensitive sodium channels, class I antiarrhythmic drugs (sodium channel blocking agents) are recommended for the treatment of ventricular arrhythmias.[50] However, in a Hong Kong study of 15 patients with herb-induced aconite poisoning and ventricular arrhythmias,[45] no single agent was uniformly effective. A median of two (range 1–4) antiarrhythmic drugs were given unsuccessfully to 11 patients, including lidocaine in all, amiodarone in five, and bretylium in three. Repeated direct current cardioversion was unsuccessful in 10 patients. Suppression of ventricular tachycardia was finally achieved in nine patients, using amiodarone in five, flecainide in two, procainamide in one, and mexiletine in one. In six patients, non-sustained ventricular arrhythmias spontaneously subsided. Therefore, amiodarone and flecainide are reasonable first-line treatment.[45]

Amiodarone is classified as a class III antiarrhythmic drug due to its potassium channel blocking properties,[51] though it also has sodium and calcium channel blocking properties. Class III antiarrhythmics mainly affect membrane

repolarization.[51] There is prolongation of action potential duration and refractory periods, leading to reduction in membrane excitability of all myocardial tissue. Flecainide is a class 1c antiarrhythmic agent. It is a sodium channel blocker that slows conduction velocity in a wide range of cardiac tissues.[52] There is an increased risk of an arrhythmia after the use of a class 1c agent, an effect that is exacerbated by hypokalemia, which should be corrected if present.

If ventricular arrhythmias and cardiogenic shock are refractory to first-line treatment, it is most important to maintain systemic blood flow, blood pressure, and tissue oxygenation by the early use of percutaneous cardiopulmonary bypass.[21,41,53] These support systems are battery-powered, portable heart-lung machines that can be instituted rapidly.[54] If the need for circulatory support extends beyond 6 h, conversion to conventional extracorporeal membrane oxygenation or a ventricular assist device is recommended.[54,55]

Given the lipid solubility and molecular size (645.7 kDa) of aconitine, extracorporeal techniques are unlikely to be effective in removing circulating aconitine.[45] However, there are case reports of the supposedly beneficial effect of charcoal hemoperfusion in patients with severe aconite poisoning,[21,55] though insufficient clinical and analytical data were provided to support the claims of benefit. Before charcoal hemoperfusion can be recommended for patients with severe aconite poisoning, data on the impact on circulating concentrations of *Aconitum* alkaloids and on the elimination half-life are required.

Prevention

The public should be warned of the dangers of eating the wild plants. When aconite roots are used for medicinal purposes, patients should be educated on the potential hazards from self-treatment and the importance of proper decoction preparation in reducing the amounts of toxic alkaloids. There should be regular measures to promote awareness among herbalists of the dangers of using a larger than recommended dose of aconite roots.[56] Accreditation and registration of the herbalists, registration of the wholesalers and retailers, and listing of processed aconite roots as prescription only herbs will help ensure that only "qualified" persons can prescribe and that only approved companies and shops staffed by certified personnel can trade and dispense these herbs.

Conclusions

Aconite roots contain aconitine, mesaconitine, hypaconitine, and other *Aconitum* alkaloids, which are known cardiotoxins and neurotoxins. They are used in traditional medicine only after processing to reduce the alkaloid content. Life-threatening ventricular arrhythmias can occur after the consumption of aconite roots. The risk is higher with the wild plant, inadequately processed aconite roots, overdose, and tincture preparations. Management is supportive, including treatment of hypotension and ventricular arrhythmias. In refractory cases of ventricular arrhythmias and cardiogenic shock, it is most important to consider early use of cardiopulmonary bypass. The public should be warned of the dangers of eating wild plants and be educated on the potential hazards from self-treatment with aconite roots.

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