Relationship between serum aconitines level and clinical features of aconite poisoning

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Aconitum plants (Ranunculaceae family) are as extremely dangerous plant that contains various toxic di-ester di-terpene type Aconitum alkaloids, such as aconitines (aconitine, mesaconitine, hyperaconitine and jesaconitine), primarily concentrated in the roots. Aconitines are well known for acute and highly toxicity in the causation of severe arrhythmias leading to death. We documented life-threatening intoxication in thirteen patients after accidental aconite poisoning. All patients developed characteristic symptoms of aconite poisoning within 15-30 minutes after intake of roots or leaves. These patients revealed arrhythmia including a ventricular tachycardia (VT) and ventricular fibrillation (VF) and 1 patient of them died. We examined relationship between serum aconitines concentration and disappearance of arrhythmia in five patients of thirteen patients. Serum concentration of aconitines at the time of disappearance of arrhythmia in these patients was within 0.5-1.5 ng/mL, despite the fact that time required for the disappearance exhibited large interindividual variability (5.5-16 h). It suggests that serum concentration of aconitines is important for treatment to arrhythmia of aconite poisoning patient. Therefore, our results seem to be the useful information in the future treatment for the patient of aconite poisoning.

Key words aconite poisoning, arrhythmias, lidocaine.

Introduction

Aconitum plants are widely distributed across Northern Asia and North America. They contain within their tissues highly toxic di-ester di-terpene type Aconitum alkaloids. The toxicological action of aconite poisoning is attributed to the di-ester di-terpene type Aconitum alkaloids. The most cases of aconite poisoning have been occurred in Japan, Taiwan and China. On the other hand, aconite poisoning is extremely rare in Europe and in the United States. The root of aconite has been well used as an important component of Chinese prescriptions called “Chinese herbal medicine” for more than 2000 years and is now well known as natural medicine throughout the world. Many pharmacological studies of aconitines have been reported and the toxicity of these molecules is known based on their action on sodium channels in excitable membranes. In Japan, the common causes mistaken ingestion of aconite instead of edible wild plants, and aconite is sometimes used as homicidal or suicidal agents. Various toxic symptoms are observed in aconite poisoning. Characteristic symptoms of intoxication include nausea, vomiting and generalized paresthesia due to parasympathetic activation and sensory nerve ending stimulation. Intoxication requires strict surveillance and treatment is mainly symptomatic, although hemoperfusion, cardiopulmonary bypass (CPB), percutaneous cardiopulmonary support (PCPS) and intravenous magnesium have been successfully used. Symptoms of intoxication appear during the first hours after the ingestion. Fatal arrhythmia such as ventricular fibrillation (VF) in aconite poisoning may lead to death. Therefore, an understanding of arrhythmias caused by aconite poisoning is important.

Ito et al. have reported that aconitines were distributed in the tissue, such as kidney, liver, heart, and lung in a suicidal case of aconite ingestion. Moritz et al. have shown that the calculated half-life of aconite was 3 hours. Moreover, relationship between serum concentration of aconitines and urinary excretion of aconitines is important in clinical care of patients. Thus, although the establishment of these parameters in aconite poisoning is important for management of patients, little is still known. In the present study, we demonstrated clinical features, and relationship between serum concentration and the disappearance of aconite poisoning-induced arrhythmias in the thirteen patients.

Materials and Methods

Thirteen patients with aconite poisoning were admitted to the Emergency and Critical Care Center at Iwate Medical University from 1997 to 2005. In these patients, the following items were investigated in the medical records: the time of ingestion, ingested plant parts, reason for ingesting aconite, toxic symptoms, type of arrhythmia, method of treatment, and outcome after treatment. Information of the time of ingestion, ingested plant parts and reason for ingestion were obtained from the patients or their family.

Aconitines such as aconitine, jesaconitine, mesaconitine

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and hyponicotine were analyzed by liquid chromatography mass-spectrometry according to the method reported by Fujita et al.\textsuperscript{17} Briefly, 1 mL of serum or urine was mixed with 2.5 ng of mesaconitine (internal standard) and 2 mL of 0.025% (v/v) ammonia solution. The mixture was applied to an Extrelut NT3 column (Merck, Darmstadt, Germany) and the column was left to stand for 15 min at room temperature. Aconitines were then eluted with 15 mL of diethyl ether. The eluate was evaporated to dryness under a stream of nitrogen gas in a heat block at 40 °C, and dissolved in 0.2 mL of the mobile phase.

Liquid chromatography (LC) was performed on a Waters2690 instrument (Waters, Milford, MA, USA). Separation was achieved using an XTerra RP18 column (150 × 2.1 mm i.d., 3.5-μm particle size; Waters, Milford, MA, USA) protected by a guard column (10 × 2.1 mm i.d.) containing the same packing. The injection volume was set to 20 μL, and the mobile phase was a mixture of 0.1% (v/v) formic acid in acetonitrile and 0.1% (v/v) formic acid in aqueous solution (24:76, v/v), with a flow rate of 0.2 mL/min. The column temperature was maintained at 40 °C.

Mass spectrometry (MS) was performed on a Micromass ZMD 4000 instrument (Waters, Milford, MA, USA) operating in the electrospray ionization positive ion mode. The MS parameters were as follows: capillary potential, 3.0 kV; cone voltage, 60 V; ion source temperature, 120 °C; drying gas temperature, 350 °C; and nitrogen gas flow rate, 350 L/hr. Measurements were carried out in the selected ion monitoring mode, and the m/z values of the monitoring ion were 646 for aconitine, 616 for hyponicotine, 676 for jesaconitine, 632 for mesaconitine and 683 for methyllycaconitine (internal standard).

The serum or urine concentrations of aconitines in patients were obtained from the sum of the serum or urine concentrations of alkaloids such as aconitine, jesaconitine, hyponicotine and mesaconitine. For the calculated serum concentration of aconitines at the point of disappearance of the arrhythmia, the serum concentration was the value at which time of disappearance of the arrhythmia was substituted for the regression line. Regression analysis was performed using the concentration-time data points; serum concentration of aconitines was plotted logarithmically against time after ingestion, and a concentration-time curve for serum was obtained. The time of ingestion of aconite plant was shown as 0 h.

Results

Total of thirteen patients were admitted to our Emergency Department 1.5-8 hours after ingestion of aconite plants. There were nine males and four females, and their ages ranged from 40 to 78 years (median 54.8). None of the thirteen patients had a history of ischemic heart disease or cardiac arrhythmias. Nine patients ingested aconite roots or leaves as suicide, and four patients mistakenly ingested aconite leaves instead of edible wild plants. The symptoms and signs of poisoning were similar in thirteen patients. Patients developed a combination of neurologic (n=7), gastrointestinal (n=11), cardiovascular (n=13) and peripheral nervous system disorder (n=12). Nausea vomiting, hypotension, chest pain and numbness of labial or extremities were particularly common symptoms and these symptoms occurred in the most patients. Profiles of patients with aconite poisoning are summarized in Table 1.

Fatail arrhythmia such as ventricular tachycardia (VT) and ventricular fibrillation (VF) in aconite poisoning is an important symptom and may lead to death. Arrhythmia of cardiovascular symptom occurred in all patients. Patients 1, 2 and 3 occurred VT and VF, and these arrhythmias were resistant to treatment with lidocaine and electrical cardioversion. These patients required PCPS due to unstable hemodynamics. Patient 1 required additional CPB. Patients 4, 5 and 6 occurred non-sustained ventricular tachycardia (NSVT). The arrhythmias in these patients were treated with lidocaine. The patients 4 had effective, but patients 5 and 6 had no effective. Patients 7-11 developed premature ventricular contraction (PVC) and were also treated with lidocaine. The arrhythmias in patients 7, 8 and 10 were suppressed by lidocaine. The electrocardiogram of patient 12 showed accelerated idioventricular rhythm (AIVR). Patients 11 and 12 were only treated with fluid therapy and these patients were recovered from arrhythmias without treatment of lidocaine. Electrocardiograms of patients 3 are shown in Fig.1. Patient 13 developed complete atrioventricular block (C-AVB), and then was treated with a temporary pace maker. All patients were not treated with atropine, because these patients did not develop bradycardia. Typical twelve lead electrocardiograms of VF on aconitine-induced poisoning are showed in Fig.2.

We next examined relationship between serum aconitines concentration and disappearance of arrhythmia. We obtained samples of serum and urine from five of the thirteen patients. Serum concentration of aconitines in patients 3, 4, 5, 11 and 12 decreased and mostly disappeared at 30-60 hours. On the other hand, urinary excretion of aconitines increased in a time-dependently manner and reached a peak at 20-35 hours. The decrease of serum concentration showed correlation with the increase of urinary aconitines excretion in the observed five patients. The time courses of serum aconitines concentration and urinary aconitines excretion are shown in Fig.3. We collected samples from five patients after arrival at the hospital, and then measured aconitines concentration of serum and urine. At that time, serum concentration of aconitines in patients 3, 5 and 11 were 1.71, 3.49 and 4.69 ng/mL, respectively. On the other hand, serum concentration of patients 4 and 12 were 0.65 and 0.96 ng/mL, respectively. These serum concentrations of aconitines showed the value that was substituted for the regression line on arrival at the hospital. Serum concentration of aconitines and the time of disappearance of arrhythmia in patients 3, 4, 5, 11 and 12 were 0.91 ng/mL (15.75 h), 0.54 ng/mL (10.75 h), 0.96 ng/mL (9.5 h), 1.51 ng/mL (15 h) and 0.89 ng/mL (5.5 h), respectively.
Table 1. PROFILES OF THIRTEEN PATIENTS WITH ACONITE POISONING

<table>
<thead>
<tr>
<th>Patient/sex/age</th>
<th>Ingested plant parts</th>
<th>Time of aconite poisoning</th>
<th>Gastrointestinal symptom</th>
<th>Cardiovascular symptom</th>
<th>Peripheral nervous system disorder</th>
<th>Type of arrhythmia</th>
<th>Method of treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/41</td>
<td>L</td>
<td>Apr.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>VT, VF, Arret, Tdp</td>
<td>Survival</td>
</tr>
<tr>
<td>2/M/41</td>
<td>R</td>
<td>Jun.</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>VT, VF</td>
<td>Death</td>
</tr>
<tr>
<td>3/M/53</td>
<td>R</td>
<td>Nov.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>VT, VF, Tdp</td>
<td>Survival</td>
</tr>
<tr>
<td>4/M/49</td>
<td>L</td>
<td>Apr.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>NSVT</td>
<td>Survival</td>
</tr>
<tr>
<td>5/M/58</td>
<td>R</td>
<td>Aug.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NSVT</td>
<td>Survival</td>
</tr>
<tr>
<td>6/M/71</td>
<td>R</td>
<td>Nov.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>NSVT, AF</td>
<td>Survival</td>
</tr>
<tr>
<td>7/F/46</td>
<td>R</td>
<td>Mar.</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>PVC</td>
<td>Survival</td>
</tr>
<tr>
<td>8/F/40</td>
<td>L</td>
<td>Apr.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>PVC</td>
<td>Survival</td>
</tr>
<tr>
<td>9/M/54</td>
<td>R</td>
<td>Sep.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>PVC</td>
<td>Survival</td>
</tr>
<tr>
<td>10/F/60</td>
<td>L</td>
<td>May.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>PVC, AIVR</td>
<td>Survival</td>
</tr>
<tr>
<td>11/M/69</td>
<td>R</td>
<td>Mar.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>PVC, AIVR</td>
<td>Survival</td>
</tr>
<tr>
<td>12/F/78</td>
<td>R</td>
<td>Sep.</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>AIVR</td>
<td>Survival</td>
</tr>
<tr>
<td>13/M/52</td>
<td>L</td>
<td>May.</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>PVC, PAC, CAVB</td>
<td>Survival</td>
</tr>
</tbody>
</table>

I. means leaves. + : The toxic symptom was developed.  
R means roots. - : The toxic symptom was not developed.  
Abbreviations: VT, ventricular tachycardia; VF, ventricular fibrillation; Tdp, tordse de points; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contraction; AIVR, accelerated idioventricular rhythm;  
PAC, premature atrial contraction; and CAVB, complete atrioventricular block.
Fig. 1. The electrocardiogram of patient 3 (5h., 8h., 10h. and 24h. after ingested). The electrocardiogram of patient 3 showed fatal arrhythmias such as ventricular fibrillation at 8 h. Then, the symptom of arrhythmias was improved with decreasing of serum concentration of aconitines. Abbreviations: VT, ventricular tachycardia; and VF, ventricular fibrillation.

Fig. 2. Typical twelve-lead electrocardiogram in the patient 3 showed.
Fig. 3. Time courses of serum aconitines concentration and urinary aconitines excretion in patients 3, 4, 5, 11 and 12 after aconite plants intake. Arrows indicate the time of disappearances of arrhythmia.
Discussion

In the present study, we have performed in order to investigation relationship between serum aconitines concentration and the disappearance of aconite poisoning- induced arrhythmias. The very low margin of safety between therapeutically and toxic doses underlines the danger of aconitines use for therapeutic purpose. Severe poisoning has been reported after ingestion of as little as 0.2 mg aconitine or consumption of decoctions prepared from prescriptions containing 6 g of cured Aconitum rootstocks.31 The latent period between the ingestion of aconite roots or leaves and the onset of symptoms can be as short as 15 minutes in the most patients, suggesting that aconitines can be rapidly absorbed by the upper gastrointestinal tract. Our patients invariably developed a combination of nausea vomiting, hypotension and chest pain and tachyarrhythmia. Hyperventilation resulting in respiratory alkalosis was observed in a few patients. Aconite-induced poisoning toxic symptoms in all patients showed similar results with previously reported,1-4,7,10-14,16 and all patients developed arrhythmias such as VT, VF and PVC.

The most important pathway in excretion of aconitines appears to be via the kidney and the continuous detection of aconitines in urine after intoxication.6 The excretion pathway of aconitines in the human liver is not clear. Indeed, absorption, distribution, metabolism and elimination interfere on the ingested dose, leading to inter-individual variation of serum concentration. Therefore, deterioration in renal function and the decreased cardiac output may lead to delay in excretion of aconitines and a corresponding increase in half-life. Serum concentration of aconitines was measured in five of the thirteen patients, although the total dose of aconitines ingested was not measured. The analysis of aconitines in the other eight patients has not performed, because we had not established the method of analysis for aconitines when the eight patients arrived at our hospital.

Serum concentration of five patients decreased, whereas urinary excretion of aconitines revealed peak at 20-30 hours. The observed five patients showed correlation between the decrease of serum aconitines concentration and the increase of urinary aconitines excretion, and the ventricular arrhythmias disappeared with the decrease of serum aconitines concentration. Serum concentration of aconitines at the time of disappearance of arrhythmia in these patients was within 0.5-1.5 ng/mL, despite the fact that time required for the disappearance exhibited large interindividual variability (5.5-16 h). It seems likely that the disappearance of ventricular arrhythmias depends on serum aconitines concentration.

Serum concentration of aconitines in patients 3, 5 and 11 was higher than that of patient 4. The patient 4 ingested only leaves of the plant in five patients who measured serum aconitines concentration. The content of aconitines in roots is higher than that of stems and leaves, and concentration of aconitines in roots are about 300 times than in leaves.18 Therefore, these results suggest that serum concentration of aconitines in the patient 4 reflects low content of aconitines in leaves. Serum concentration of aconitines in the patient 12 who ingested roots was lower than that of aconitines in patients 3, 5 and 11 who ingested roots. The content of aconitines varies according to growth region, season and species.19-22 It seems, therefore, that serum concentration of aconitines in the patient 12 may be influenced with these variables.

Fluid replacement, gastric irrigation or antiarrhythmic drugs are generally performed in aconite poisoning. However, the therapeutic protocol of the arrhythmias in aconite poisoning is not established yet. Class I Na channel blockers such as lidocaine are reasonable first-line antiarrhythmic drugs. However, it seems unlikely that the effect of lidocaine expect aconite poisoning-induced arrhythmias in all patients. Moreover, cardioversion is observed with often the resistance to aconite poisoning patients and unlikely to be effective.14,11,12,14 PCPS has been reported to improve survival in aconite poisoning patients with hemodynamically unstable arrhythmia that is refractory to treatment with antiarrhythmic drugs and electrical cardioversion.11,12,14 PCPS is generally used the resistance patient. We also observed that PCPS had effective in our resistance patients. Lidocaine that is useful for aconite poisoning-induced ventricular arrhythmia was ineffective in patients 1, 2, 3, 5 and 6 who developed VT. Patients 2, 3, 5 and 6 had ingested aconite roots, and patient 1 had ingested a lot of aconite leaves. On the other hand, lidocaine had effective in the patient 4 who ingested aconite leaves and developed NSVT. Lidocaine was effective in all patients who developed PVC. Our findings suggest that lidocaine may be used against PVC aconite poisoning-induced in ventricular arrhythmias following ingestion of aconite roots or leaves, and the effect of lidocaine may be influenced by serum concentration of aconitines. Moreover, lidocaine may be used against NSVT following ingestion of aconite leaves. When we administer with lidocaine to patients, the information such as serum concentration of aconitines is important as rescue management of patients. To our knowledge, this is the first report that determines the relationship between serum aconitines level and the disappearance of ventricular arrhythmias. These results suggest the useful information in the future treatment for aconite poisoning.

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References


