

Full Length Research Paper

# Clinical study of the effects of baicalin on arrhythmia induced by aconitine poisoning

Gui-Lin Xiao<sup>1</sup>, Chun-Hu Zhang<sup>2\*</sup>, Guo-Dong Liu<sup>1</sup>, Fa-Yi Liu<sup>1</sup>, Zhao-Yan Liu<sup>1</sup>, Sui-yu Hu<sup>2</sup>,  
Xi Huang<sup>2</sup> and Yi-Qiang Jin<sup>2</sup>

<sup>1</sup>Department of Emergency of Xiangya Hospital, Central South University, Changsha, Hunan 410008, P.R. China.

<sup>2</sup>Institute of Integrated Medicine, Key Unit of State Administration of Traditional Chinese Medicine of the People's Republic of China, Xiangya Hospital, Central South University, Changsha, Hunan 410008, P.R. China.

Accepted 19 October, 2010

To investigate the effects of baicalin on arrhythmia, induced by aconitine poisoning sixty acute patients with aconitine poisoning were studied and randomly enrolled into two groups: the experimental group and the control group, according to the number given to the patient when he/she was admitted to the hospital. Odd numbers were used as experimental groups, while even-numbered patients were used as control. Patients from the control group were treated using conventional methods. Patients from the experimental group were treated with baicalin as the sole antiarrhythmic medication. At the same time, the reasons for taking the aconite roots, the clinical features, management, and possible treatment mechanism were noted. The clinical outcome of the baicalin on the patients in the experimental group was significantly better than that in the control group. For patients in the experimental group, flutter in all patients disappeared within 15 min and sinus bradycardia disappeared within 12 h; all clinical symptoms improved after  $25.2 \pm 9.7$  min and blood pressure reached the normal level within 30 min. For patients in the control group, it took more than 24 h for arrhythmia to disappear,  $1764.1 \pm 664.4$  min for the clinical symptoms to be alleviated and over 27 h ( $p < 0.01$ ) for the blood pressure to reach the normal level. Our study indicated that baicalin injection was efficacious in treating aconitine poisoning induced arrhythmia.

**Key words:** Aconitine, poisoning, baicalin, arrhythmia.

## INTRODUCTION

Herbs from the genus *Aconitum L.*, such as Chuanwu (*Aconitum carmichaeli* Debx.), Caowu (*Aconitum Kusnezoffii* Reichb.) and Fuzi (*A. carmichaeli* Debx.) are widely used in clinic in China and other East Asian countries as analgesic, antirheumatic and neurological medications. Aconitine is the main active ingredient in the medicinal plants, *Aconitum L.* The lethal oral dose of aconitine for humans is estimated to be 1 to 2 mg (Hong-Gui et al., 2005; Chih-Chuan et al., 2004; Zhaohong et al., 2006; Shorong-Shii et al., 2005). Eliminating the toxicity of aconitine in the process of aconitum is required. However, due to the lack of controllable toxicity

standard in the process of medicinal herbs, patients may present signs and symptoms typical of aconitine poisoning after excessive ingestion.

Aconitine poisoning frequently occurs in Asian countries as well, mainly due to the accidental ingestion, and sometimes aconitine is used as suicidal or homicidal poisons (Angela, 1998). Based on our clinical observations, aconitine can affect cardiac muscles and central nervous system, causing flutter and fibrillation, as well as the symptoms of central nerve system. Patients with aconitine poisoning may present one or more of the following symptoms: systemic paralysis, nausea, vomiting, dizziness, palpitation, hypotension, arrhythmia, shock and coma. Currently there are no specific antidotes for aconitine poisoning except the conventional medications, such as atropine, dopamine, isoptin, and so on. The treatment outcome is oftentimes not satisfactory due

\*Corresponding author. E-mail: [chzxysm@yahoo.com](mailto:chzxysm@yahoo.com). Tel: +86 0731 84327222, +86 0731 84327338.

to the long period of treatment (Angela, 1998; Yong et al., 2001; Jan-Zu, 1999).

Baicalin ( $\beta$ -D-Glucopyranosiduronicacid or 5,6-dihydroxyflavone, yellow crystal fine powder) is one of the main active ingredients extracted from the traditional Chinese medicine *Scutellaria baicalensis* Georgi (Chinese name: Huang Qin). It has a wide range of pharmacologic effects, especially in the aspects of anti-inflammation and anti-oxidation (National Administration of Traditional Chinese Medicine, 1998: 1686-1688; Jie et al., 2005).

In the theory of Traditional Chinese Medicine, the herb of genus *Aconitum* L., such as Chuanwu (*A. carmichaeli* Debx.), Caowu (*A. Kusnezoffii* Reichb.) and Fuzi (*A. carmichaeli* Debx.) is "hot", and the herb Huangqi (Baicalin is its main ingredients) is "cool", on the basis of Traditional Chinese Medicine, when the body have the febricity disease, we can use the "cool" herb to make the body equilibrium. Therefore Baicalin is also widely used in Chinese Medicine to treat common flu caused fever. The study of Baicalin on experimental arrhythmia indicated that Baicalin can alter the membrane transport of  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$  ions (Chang-Han et al., 2002).

Our previous animal studies suggested that baicalin possessed significant curing effects on arrhythmia induced by aconitine poisoning (National Administration of Traditional Chinese Medicine, 1998: 1686-1688). In this paper, clinical characteristics and symptoms of sixty aconitine poisoning patients receiving either conventional or baicalin treatment were discussed. Data from this study provide new insights for developing new efficacious therapeutics for aconitine poisoning.

## MATERIALS AND METHODS

### Patients

Sixty patients with acute aconitine poisoning, due to improper usage of aconitine-containing Chinese herbal medicine for rheumatic arthritis, were admitted to our hospital from 2003 to 2006. The experimental group was consisted of 18 males and 12 females, with ages spanning from 25 to 74 years old (mean age =  $47.9 \pm 11.8$  y/o). Diagnosis and treatment was taken between 30 min and 21 h with a mean time of  $7.5 \pm 3.1$  h after the ingestion. The control group was consisted of 15 males and 15 females, with ages ranging from 16 to 68 years old (mean age =  $45.8 \pm 13.1$  y/o). Diagnosis and treatment was taken between 30 min and 19 h with a mean time of  $8.1 \pm 2.1$  h. Drugs that caused aconitine poisoning, symptoms and the cardiographs of all patients were listed in Tables 1, 2 and 3, respectively ( $p > 0.05$ ).

### Diagnostic criteria

All 60 patients suffering from aconitine poisoning met the following diagnostic criteria (People's Republic of China Ministry of Health Guide, 1993): (1) Patients became sick only after taking aconitine-contained herbs; (2) Aconitine was confirmed by checking the residue of the herbs which taken by the patients; (3) Patients presented cardiovascular, neurologic, and/or other symptoms that were typical of aconitine poisoning; (4) The electrocardiographs

showed arrhythmia; (5) Yellow coating on the tongue, which determined by the Chinese Medicine doctor.

### Clinical and biochemical monitoring

The symptoms and biochemical parameters of the two groups were monitored for more than 48 h. Clinical observation and examination included consciousness, breathing rate, blood pressure, pulse rate, stool and urine frequency and appearance, sensibility, alimentary tract and cardiograph. Biochemical parameters consisted of blood routine analysis, urine routine analysis, the renal and liver function panel, and cardiac muscle enzyme activity.

### Treatment

Before treatment, all the patients or their guardian had to sign the consent form. All patients were laid on the bed, supplied with oxygen and received transfusion immediately. Urinary catheters were used in unconscious patients. Different transfusion fluid and treatment reagents were applied to patients in two groups. For the experimental group, 300 ml baicalin (450 mg dissolved in distilled water) was given to the patients through intravenous infusion, followed by 500 ml Ringer's solution or 500 ml, 5% glucose solution (containing 10 ml of 10% KCl and 1 g of vitamin C). All these were given daily at a rate of 3 ml/min (60 drops/min). Baicalin (Approval No. Z20043425), manufactured by the Second Pharmaceutical Company of Harbin, is a clinical drug approved by Chinese National Drug Administration. Clinical studies conducted in this paper were approved by the Ethics Committee of the Chinese Clinicians. Patients were informed about the drug and participations were voluntary.

For the control group, patients orally took 250 ml of 20% mannitol in order to purge the bowel of stool. In addition, patients who were admitted to the hospital within 6 h of aconitine poisoning had to wash out stomach by induced vomiting (stimulate the throat). Patients were then transfused with 500 ml of Ringer's solution or 500 ml of 5% glucose solution (containing 10 ml of 10% KCl). At the same time, patients were administered one or more of the following drugs according to the clinical symptoms: diazepam and phenobarbital (for delirium and convulsion, 3 cases), metaraminol and dopamine (for low blood pressure, 5 cases), atropine (for bradycardia or Atrioventricular block, 2 cases), verapamil (for premature supraventricular beat or supraventricular paroxysmal tachycardia, 3 cases), Lidocaine or propafenone (for ventricular extrasystoles or ventricular paroxysmal tachycardia 13 cases) and isoproterenol (Torsades de pointes, 7 cases).

### Evaluation of baicalin efficacy

The treatment outcome was classified into 4 categories based on the following criteria. (1) Full efficacy: all clinical symptoms disappeared and cardiogram became normal; (2) High efficacy: most of the clinical symptoms disappeared and most of the cardiogram data changed back to normal; (3) Low efficacy: part of the clinical symptoms improved and part of the cardiogram data became normal; the frequency of the premature beat or flutter decreased more than 50%; (4) No efficacy: none of the clinical symptoms improved and the cardiogram was still abnormal. The treatment outcome was examined 12, 24 and 48 h after patients were admitted to the hospital.

### Statistical analysis

All parametric data were analyzed with the Kruskal-Wallis  $\chi^2$  test.

**Table 1.** Comparison of drugs that caused aconitine poisoning in the two groups.

Group	n	Radix aconite	Aconitum kusnezoffii	Radix aconite lateralis preparata	Monkshood root
Experimental	30	13	11	16	3
Control	30	10	11	17	4

Compared with the control group,  $p \leq 0.05$ .

**Table 2.** Comparison of the symptoms between the two groups.

Group	n	Nervous system						Digestive system				Circulation system			
		Acmeesthesia	Eye mistiness	Vertigo	Delirium	Tic	Coma	Urinary Incontinence	Nausea	Vomiting	Abdominal pain	Diarrhea	Palpitation	Low blood pressure	Arrhythmia
Experimental	30	30	23	30	12	9	6	13	8	3	5	4	30	13	30
Control	30	30	21	30	13	9	1	10	8	4	5	4	30	10	30

Compared with the control group  $p \leq 0.05$ .

The rank data were analyzed by Ridit tests. Fidelity rates were compared by using a Mann-Whitney U test. The correlation was considered significant when  $p < 0.01$ .

## RESULTS

### Comparison of general efficacy

Most of the clinical symptoms from the experimental group patients disappeared and majority of the cardiogram data went back to normal within 12 h. The overall efficacy rate was 96.7% after 48 h. But in the control group it was only 3.3 or 73.3% at 12 or 48 h after treatment, respectively. The difference between two groups was statistically significant ( $p < 0.01$ ) (Table 4).

### Comparison of the recovery of arrhythmia

Compared with the control group, patients from the experimental group recovered much faster from arrhythmia. First, the symptoms of premature beats in 25 patients disappeared within 15 min, the shortest recovery time was 5 min and the longest was 15 min (Average =  $6.1 \pm 3.1$  min). Second, the symptoms of auricular flutter and auricular fibrillation disappeared in 8 to 30 min after treatment (Average =  $17.8 \pm 4.3$  min). Third, the symptoms of sinus bradycardia and/or auriculo-ventricular block disappeared relatively slower, but still within 12 h. As a comparison, patients in the control group did not show any improvement on the above listed

symptoms after 12 h. Only 3 patients recovered in 24 h, 12 patients recovered between 24 to 48 h and the other 15 patients recovered in more than 48 h.

### Comparison of other clinical symptoms

(1) Patients from the experimental group completely recovered from acmeesthesia (sensation of pin prick), nausea and vomiting simultaneously after 10 - 90 min (mean =  $25.2 \pm 9.7$  min). While in the control group, it took 16 - 48 h ( $1764.1 \pm 664.4$  min) to have those symptoms relieved. (2) The low blood pressure in 13 patients in the experimental group reached normal level within 30 min (mean =  $15.7 \pm 4.2$  min) without using any other cardiovascular medications. It took 27 - 48 h for 12 patients in the control group to have the low blood pressure to be normal, in addition to the usage of isoproterenol oral administration. (3) 74% of patients in the experimental group were discharged from the hospital within 48 h (mean =  $50.1 \pm 4.4$  h), while no patient in the control group was able to leave hospital in the same time frame (mean =  $107.2 \pm 21.2$  h). These data demonstrated significant differences between the recovery process of the experimental and control groups ( $p < 0.01$ ).

## DISCUSSION

Aconitine is one of the diterpenoid alkaloids which can damage the cardiovascular and nervous systems upon overdose. Aconitine-induced arrhythmia is the result of

**Table 3.** Comparison of the cardiographs between the two groups.

Group	n	premature beat		Paroxysmal tachycardia				Torsades de pointes	Fibrillation Auricular	Flutter Auricular	Block	Bradycardia Sinus
		Multifocal	Multiple	Supraventricular	Ventricular	Ventricular	Supraventricular					
Experimental	30	23	25	21	25	20	15	9	13	5	5	2
Control	30	20	26	21	26	17	10	7	10	7	2	0

Compared with the control group  $p \leq 0.05$ .

**Table 4.** Comparison of the treatment outcome between the two groups.

Group	Time (h)	n	Full efficacy (n/%)	High efficacy (n/%)	Low efficacy (n/%)	No efficacy (n/%)	Overall efficacy (n/%)
Experimental	12	30	28/93.3*	1/3.3	1/3.3	0/0	29/96.7*
	24	30	29/96.6*	1/3.3	0/0	0/0	30/100*
	48	30	29/96.6*	1/3.3	0/0	0/0	30/100*
Control	12	30	0/0	1/3.3	7/23.3	22/73.3	1/3.3
	24	30	2/6.7	5/16.7	13/43.3	10/33.3	7/23.3
	48	30	6/20	16/53.3	5/16.6	3/10	22/73.3

Compared with the control group, \* $p \leq 0.01$ .

double effects of aconitine on the heart. First, aconitine can stimulate the vagus nerve and induce the dysfunction of cardiac transmission system, such as sinoatrial (SA) node inhibition and atrioventricular transmission blockage, which leads to arrhythmia. Second, aconitine may act directly on ventricular myocytes, which can affect the flow of  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$  and cause arrhythmia. When aconitine acts on ventricular myocytes, it can open the  $\text{Na}^+$  channel on the cells membrane and accelerate the influx of  $\text{Na}^+$ . The  $\text{Na}^+$  channel can then be easily stimulated which in consequence induces repeatable discharges and facilitates membrane depolarization (Kelkot, 2006; Fu et al., 2007). As a result, cardiac muscle has an increased frequency in the transposal rhythm. High doses of aconitine can also significantly increase intracellular  $[\text{Ca}^{2+}]$  oscillations, decrease extracellular  $\text{K}^+$  current, increase depolarization frequency and induce the retard agitation. Therefore, the arrhythmia caused by aconitine poisoning is variational, fast acting and fatal. Studies have shown that the toxicity of aconitine comes from the diester linkage and the acetyl group. Without the acetyl group, aconitine becomes phenylacetyl aconitum original alkaloid (PAOA) and the toxicity decreases to 1/1000. PAOA can be further decomposed to aconitum original alkaloid (AOA) and phenylacetic acid. Compared with aconitine, the toxicity

of AOA decreases to 1/2000 to 1/4000.

The body can absorb and metabolize aconitine rapidly. It can be easily absorbed through the alimentary tract or broken skin and mainly be excreted by the kidneys and through saliva. When a low amount of aconitine enters the body, it is rapidly detoxified by the liver, and finally excreted slowly through urine and saliva. However, when the liver could not decompose all the aconitine, it can either act on the heart and induce serious arrhythmia, or act on the nervous system and lead to nervous system dysfunction.

In this study, after patients were given baicalin for treatment, all the symptoms of arrhythmia and dysfunction of nervous system disappeared. Baicalin could have changed the permeability of the ion channels (such as  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Ca}^{2+}$ ) on the membrane of myocytes and improved arrhythmia. Baicalin has been reported to play important regulating roles on the nervous system. For instance, baicalin can restrain the excited vagus and sedate the central nervous system. Baicalin can especially regulate the process of excitement and inhibition in the cerebral cortex, which could be one of the mechanisms that baicalin quickly relieves arrhythmia and improves neurological symptoms. With baicalin treatment, the symptoms of patients improved and aconitine was degraded and discharged through normal

metabolism. Our data has demonstrated that baicalin is significantly more efficacious in treating aconitine poisoning-induced arrhythmia than the conventional medications. The mechanisms of how baicalin works on arrhythmia are still yet to be tested.

Life-threatening arrhythmia can occur after the consumption of aconite roots. The risk is higher with large doses or inadequately processed aconite roots. With increasing popularity of herbal medicines, herb-induced aconitine poisoning has slowly appeared in Western countries. There is still no effective antidote for this extremely dangerous poison. Baicalin injection has been widely used in various diseases due to its safety, availability, low cost and simplicity in the clinical applications. Our data in this study suggested that baicalin has a special curative effect in aconitine poisoning-induced arrhythmia. Further studies on the clinical studies of baicalin against aconitine poisoning will be conducted, aiming to develop an effective therapeutics for aconitine poisoning.

## ACKNOWLEDGEMENTS

The work was supported by the National Natural Science Foundation of China (No.30801506) and was partly supported by fund for Key Unit of Traditional Chinese Medicine Gan of SATCM and HuNan Administration of Traditional Chinese Medicine (No. 222203).

## REFERENCES

- Hong-Gui Z, Ying S, Ming-Yu D, Yu-Juan C, Da-Fang Z, Han-Qi Z (2005). Separation and identification of Aconitum alkaloids and their metabolites in human urine. *Toxicol.* 46(5): 500–506.
- Chih-Chuan L, Thomas YK, Chan Jou-Fang D (2004). Clinical features and management of herb-induced aconitine poisoning. *Ann. Emergency Med.*, 43(5): 574-579.
- Zhaohong W, Jiao W, Junbo X, Ye H (2006). Quantitative determination of diterpenoid alkaloids in four species of Aconitum by HPLC. *J. Pharm. Biomed. Anal.*, 4: 1031–1034.
- Shorong-Shii L, I-Min L, Mei CL, Juei-Tang C (2005). Comparison of the antinociceptive action of crude Fuzei, the root of Aconitum, and its processed products. *J. Ethnopharmacol.*, 99(3): 379–383.
- Angela A (1998). The effects of aconitum alkaloids on the central nervous system. *Progress Neurobiol.*, 56: 211-235.
- Yong X, Yan H, Li W (2001). Treated Experience on 6 Cases of Cardiac Arrhythmia Caused by Aconitine Poisoning. *Chinese J. Pract. Internal Med.*, 21(1)40.
- Jan-Zu L (1999). First Aid of Cardiac Arrhythmia Caused by Aconitine Poisoning. *J. Internal Intensive Med.*, 5(1)34-35.
- National Administration of Traditional Chinese Medicine (1998). *Chinese Materia Medica*(ShangHai: ShangHai Science and Technology Publishing, pp. 1686-1688.
- Jie X, Xiaoyan C, Dafang Z (2005). Stability of baicalin in biological fluids *in vitro*. *J. Pharm. Biomed. Anal.*, 39(3-4):593–600.
- Chang-Han O, Ji-Liang W, Ji C (2002). Anti- Practical Cardiac Arrhythmia Effects of Baicalin. *J. Xianyang Univ. Med.* (1993), 16(1): 7-10.
- People's Republic of China Ministry of Health Guide. Lines of New Chinese Med. Clin. Res., (□): 91-93.
- Zhu-Y, Zhen-Hui J, Xiao-Dong Y (2007). Progress in Studies on Chemical Constituents and Pharmacological Functions of Aconitum L. Plants. *J. YunNan Agric. Univ.*, 22(2): 293-298.
- Kelkot AA (2006). Antiarrhythmic activity of a membrane-protecting agent Sal'magin in rats with aconitine-induced arrhythmias. *Bull. Exp. Biol. Med.*, 142(2): 209-211.
- Fu M, Wu M, Wang JF, Qiao YJ, Wang Z (2007). Disruption of the intracellular Ca<sup>2+</sup> homeostasis in the cardiac excitation-contraction coupling is a crucial mechanism of arrhythmic toxicity in aconitine-induced cardiomyocytes. *Biochem. Biophys. Res. Commun.*, 354(4): 929-936.