Pharmacological effects of Chinese herb aconite (Fuzi) on cardiovascular system

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Abstract
Fuzi (aconite, Radix Aconiti praeparata), a widely used Chinese herb, plays a significant role in the cardiovascular system. This is mainly reflected by Fuzi’s cardiotonic effect, its protective effect on myocardial cells, and its effect on heart rate and rhythm, blood pressure, and hemodynamics. In this article, the pharmacological effects and the corresponding mechanisms of Fuzi (aconite) and its active components on cardiovascular system are reviewed.

INTRODUCTION
Fuzi (aconite, Radix Aconiti praeparata) is the processed tuberous root of Aconitum carmichaeli Debx (Ranunculaceae). Fuzi tastes spicy and sweet, has a hot nature and toxicity, acts on the heart, kidney and spleen meridians and plays a role in saving yang for the treatment of collapse, supplementing kidney yang, and eliminating cold to stop pain. Fuzi (aconite) consists of a variety of alkaloids, such as the diester-diterpene alkaloids, aconitine, hypaconitine, mesaconitine, and higenamine. Aconite also is composed of some lipids, such as fatty acids, phosphatidate calcium, and steroids. It is mainly clinically used for treatment of heart failure, shock and hypotension subsequent to acute myocardial infarction, coronary heart disease and rheumatic heart disease. Along with the repeated application of aconite in clinical practice and studies on pharmacology, its use in the cardiovascular system has been the focus of increasing research. In this article, aconite’s pharmacological effects on the cardiovascular system are summarized.

CARDIOTONIC EFFECT OF ACONITE
Domestic and international research has shown that aconite enhances cardiac contractility and also accelerates myocardial contraction frequency. Rao performed experiments on the heart of toads, frogs, guinea pigs and rabbits in vitro, and showed a cardiotonic effect of aconite decoction, while experiments on the heart of frogs, cats, and dogs in vivo also suggested a mildly cardiotonic effect of aconite. The mechanism of this action of aconite was shown to be related to calcium based on further research.¹

Zuo et al. confirmed a “faint pulse verging on expiry” in a pathological cat model where intravenous administration of aconite water extract could gradually enhance the heart beat. They observed that the heart in this cat model contracted more vigorously with much greater amplitude than that before drug administration, and repeated administration of the drug resulted...
in a stronger effect. However, this effect was different according to the different states in the model. For example, when the heart beat was weak and the extremities were cold, aconite had a positive effect, but it did not show any cardiotonic function when the heart beat was normal. Further experiments indicated that the mechanism of effect of aconite may be related to β1 receptor and α receptor activation in the heart. Xu et al. reported that aconite decoction can antagonize the inhibition of phenobarbital, chloral hydrate and other drugs on the heart of the toad, and it showed a significant cardiotonic effect on the heart of the reserpinized cat model in vivo or in vitro. They concluded that the cardiotonic effect of drugs of this type is not caused by catecholamine release, but by a direct contribution on the heart. Therefore, based on previous findings, aconite has obvious cardiotonic effects on the heart in vitro and in vivo, as well as in the normal and exhausted heart. The effective components of aconite include higenamine, salolacaine, methyl chloride dopamine, and aconite glycosides, and it is likely that there are other undiscovered components.

With regard to the mechanism of the cardiotonic effect of aconite, different explanations have been provided. Aconite achieve this effect through some substances contained in it functions as α receptor and β receptor agonists, and increases intracellular calcium concentrations by activating sodium channels and increasing Na⁺ influx, thereby stimulating reverse Na⁺/Ca²⁺ exchange. A slight decrease in serum Tumor Necrosis Factor - α (TNF-α) and Nitric oxide (NO) levels of adriamycin-induced heart failure in rats by aconite decoction has been shown, suggesting another mechanism of cardiotonic function.

Aconite is widely used in the treatment of heart failure and shock subsequent to acute myocardial infarction, especially for symptoms, such as yang debilitation, a cold body and extremities, and a faint pulse verging on expiry, which also suggest that aconite has cardiotonic and anti-shock effects. Although the purified chemical composition from Fuzi has strong cardiotonic and anti-shock effects, the herb, Fuzi, itself hasn’t been used as a cardiotonic drug in research and in the clinical setting. This may be because of the effect of one the herb’s ingredients, aconitine, which can cause rapid arrhythmia and ventricular fibrillation.

**PROTECTIVE EFFECT OF ACONITE ON MYOCARDIAL CELLS**

It has previously been shown that aconite and its extract can conserve myocardial cells of animal models and clinical patients with heart failure, myocardial infarction, cardiac hypertrophy and other cardiovascular diseases. The explanation of the mechanism of action varies because of different viewpoints.

Huang et al studied a rat model of heart failure induced by adriamycin, and found that aconite decoction could reduce Brain natriuretic peptide and Interleukin-6 levels in serum, protect blood vessels and myocardial cells, and improve heart function. They also showed that the degree of myocardial cell injury was significantly less in the aconite decoction group than that in the heart failure model group which was not given any drug after the heart failure model is successfully made. Fang, et al reported that hyperaonitine at an appropriate concentration of 250 ng/mL reduces apoptosis of myocardial cells induced by H₂O₂. They speculated that its mechanism may be related to a decrease in expression of the apoptosis proteins, caspases 3 and 9, and an increase in cell proliferation activity. Lee et al showed that higenamine protects myocardial cells from ischemia reperfusion injury, and therefore, it significantly reduces myocardial infarct size. They found that administration of higenamine 1 hour prior to ischemic-reperfusion (I/R)-injury greatly decreased the release of cytochrome C, caspase-3 activity, and Bax expression, but it up-regulated the expression of Bcl-2 and HO-1, as well as HO enzyme activity in the left ventricle. These changes could be inhibited by ZnPP IX, an enzyme inhibitor of HO-1. As a result, they considered that HO-1 plays an important role in the protective action of higenamine in I/R-induced myocardial injury.

It has also been suggested that the mechanism of the above function may be due to blocking sodium channels, or protecting the mitochondria of the cells. A previous study investigated the effect of aconite on the vascular extracellular matrix of the aorta in a cardiac hypertrophy rat model induced by thyroxine, and found that the mechanism whereby aconite prevented cardiovascular hypertrophy could be attributed to inhibition of collagen synthesis.

Combined administration with ginger in a heart failure model in the rat, aconite causes a decrease in the epinephrine, atrial natriuretic peptide, and endothelin levels in plasma. Furthermore, on the one hand, a decrease in epinephrine levels can prevent or reduce the toxicity of catecholamines on the heart, reduce myocardial energy demand and curb excessive adrenergic decompensation during heart failure, and on the other hand, a decrease in epinephrine levels can also inhibit renin release.

In addition, the active ingredients of aconite have anti-inflammatory and antioxidant effects, which both play important roles in a variety of cardiovascular diseases. For example, an increased expression of adhesion molecules and inflammatory-induced cytokines was found in the myocardial tissues of patients with cardiovascular disease, indicating that local inflammation of microvascular and myocardial cells is important in the pathological changes of cardiovascular diseases. This also provides a theoretical basis for the protective effect.
of aconite on myocardial cells. The effect of Yi Qi Wen Yang Huo Xue Fang (tonify Qi, warm yang, and promote blood circulation formula) on bone marrow stem cells in patients with myocardial infarction was investigated, and it was found that it can mobilize stem cells, which can reduce myocardial infarct size, suppress left ventricular remodeling, and improve cardiac function.19

As well as the protective effect of aconite on myocardial cells, including inhibiting injury of these cells, it can also mobilize bone marrow stem cells that may migrate into the ischemic myocardium, differentiate into myocardial cells in the myocardial microenvironment to increase the number of myocardial cells directly, and alter necrosis of the myocardium.

EFFECT OF ACONITE ON HEART RATE AND RHYTHM

Aconite can increase heart rate, mentioned as positive chronotropic action, and it also acts on the rhythm of the heart, which antagonizes arrhythmia and results in an arrhythmogenic effect. This may lie in the fact that different components of aconite have different pharmacological effects. The effects of aconite on heart rate and rhythm vary between studies because of different origins, processing methods, extract compositions, animal models, and how individual body reacts upon special circumstances. An aconite decoction can speed up the contraction frequency of the mammalian heart in vitro. However, a large dose of aconite inhibits the heart by slowing the heart rate, which suggests that the effect of aconite on heart rate is dose-related.1 Another study reported that an aqueous solution of aconite in different doses can accelerate the heart rate in a cat model of heart failure, but it did not significantly affect the heart rate of normal anesthetized dogs and cats.6 Zhang, et al. showed that butanol extract, ethanol extract and aqueous extract of aconite all have a preventive effect on ventricular fibrillation induced by chloroform in mice, especially the aqueous extract.20 Wang et al. administrated hypaconitine intravenously to anesthetized rats and observed its effect on electrocardiogram and experimental arrhythmia. They found that a small dose (0.5 mg · kg⁻¹ intraperitoneal injection) of hypaconitine caused anti-arrhythmic effects. Hypaconitine could antagonize aconitine-induced arrhythmia. Therefore, hypaconitine serves as a natural compound type I anti-arrhythmic.21 With regard to the mechanism, it could be related to higenamine up regulating the Adrenergic beta-receptor (β-AR)2223 and electrophysiological properties and ion channels of myocardial cell membranes.12 A previous study suggested that higenamine increases the responsiveness of cAMP in plasma, and affects heart rate through the receptor-G protein-cAMP complex.25 Large doses of higenamine act directly on the β-AR, showing neither synergy nor antagonism with isoproterenol (ISO), suggesting that its up-regulation of myocardial β-AR function may also achieved by affecting the pharmacokinetics of the receptor, subtypes changes, and gene expression.21 Ameri reported that anti-arrhythmia may depend on chemical composition of Fuzi (aconite) having different affinities to various subtypes of the alpha-subunit of the Na+ channel in the brain and heart.21

The dual pharmacological effect of aconite and its extract on heart rate and rhythm determines its different clinical applications. According to the effect of higenamine on bradycardia, it is clinically used to treat sinus bradycardia, sinoatrial block and atrioventricular block, with satisfactory results. Guanfu base A, an active extract ingredient from white aconite, has shown great value in antagonizing supraventricular arrhythmia, improving myocardial ischemia and anti-angina. In spite of the antiarrhythmic effect of aconite, it is also reported that aconite can induce arrhythmia, in which ventricular arrhythmia, sinus tachycardia or bradycardia are common.20,26 but bundle branch block is rare.27 Aconite is often used to create anti-arrhythmic animal models in research because of its arrhythmogenic pharmacological property.28

Diterpenoid alkaloids contained in aconite can induce arrhythmia. Two mechanisms are involved: 1) they have a direct effect on the myocardium causing sodium ion channels in the myocardial cells to open, accelerating the influx of sodium ions, leading to membrane depolarization, increasing automaticity of fast responsive cells, and leading to arrhythmia; and 2) they cause vagus nerve stimulation, resulting in arrhythmia, such as bradycardia.29

EFFECT OF ACONITE ON BLOOD PRESSURE

Reports of aconite’s effects on blood pressure are varied, including some reports that it lowers blood pressure, some studies have shown that it elevates blood pressure initially and then lowers blood pressure later, and some studies consider that it has no significant effect on blood pressure.3 The reason for this discrepancy between studies may be because blood pressure-increasing substances, such as chloride methyladipamine and salsonolin, and blood pressure-decreasing substances, such as higenamine, coexist in aconite. Therefore, different origins and processing methods of aconite may lead to different levels of these components, which then results in varied effects on blood pressure. In addition, aconite’s effect on blood pressure is also related to dose. Gu et al.30 reported the effect of water extract from Sichuan aconite on blood pressure of anesthetized cats. They found that it decreased Blood Pressure (BP) at a
low dose (12.5-50 mg/kg), but showed a three-phase effect at a higher dose (400 mg/kg), with a temporary increase in BP, then an immediate increase in BP, followed by a final decrease in BP. The mechanism is as follows: the effect of increasing BP depends on the direct excitation of α receptors in blood vessels; and the effect of decreasing BP is related to excitement of M receptors and β2 receptors. Furthermore the effects of aconite on BP also indicates the involvement of nervous system, as well as unknown active substances of the cardiovascular system contained in aconite preparations. The water soluble part of aconite can increase femoral arterial blood flow, decrease the pressure of blood vessels, and show mild expansion of coronary vessels. Chong et al. created a vasoconstriction model of rats using phenylephrine or KCl, and they observed a relaxing effect on rat aorta from aconitine, and additionally found that the relaxing effect was concentration-dependent. Niu et al. found that the relaxing effect of aconite decoction on aorta is endothelium-dependent, and related to NO released by the endothelium, instead of receptor-dependent Ca$^{2+}$ channels in cell membranes of smooth muscle or voltage-dependent Ca$^{2+}$. Results of these experiments showed that aconite had a dilatory effect on peripheral blood vessels, and its decoction can significantly expand blood vessels of the hind limb in anesthetized dogs and cats, and increase blood flow. After intravenous administration of aconite, BP of the "faint pulse verging on expiry" pathological model cat rose, but this function was significantly weakened by α-receptor blockers. According to the above results, aconite may play a role in the increase of BP as an α receptor stimulant.

**EFFECTS OF ACONITE ON HEMODYNAMICS**

The effect of aconite on hemodynamics is mainly due to anticoagulant and anti-thrombosis effects, and the active component is mainly higenamine. Aconite has shown therapeutic potential for disseminated intravascular coagulation (DIC) and/or accompanying multiple organ failure. Studies have shown that aconite decoction can extend the time for thrombosis, which indicates that it can inhibit blood clotting and antagonize thrombosis. Higenamine shows inhibitory activity in both human and rat platelet aggregation induced by ADP, collagen and epinephrine. And higenamine had the strongest inhibitory effect on epinephrine-induced aggregation. Anti-thrombotic effects of higenamine have also been observed in both an acute mouse thrombosis model and rat arterio-venous shunt (AV-shunt) model. The oral administration of higenamine increases the rate of recovery from an acute thrombotic challenge in mice and decreases the weight of thrombus formed inside the AV-shunt tube in rats. Higenamine possibly exerts anti-thrombotic effects by blocking α-adrenergic receptors. Higenamine has inhibitory effects on amino acid (AA)-induced platelet aggregation, partly by inhibiting the production of thromboxane A2 from AA, and partly by directly blocking the thromboxane A2 receptor, in addition to previously reported effects on the α2-adrenergic receptor, mostly by directly blocking the thromboxane A2 receptor.

The effect of higenamine on DIC was investigated by using an experimental DIC rat model. The oral administration of higenamine significantly ameliorated a decrease in fibrinogen levels in plasma, an increase in fibrinogen/fibrin degradation product levels, and prolongation of prothrombin time induced by the intravenous infusion of lipopolysaccharide (LPS). Prolongation of activated partial thrombin time and a decrease in platelet count were also suppressed with higenamine. Additionally, an increase in serum aspartate transaminase and blood urea nitrogen levels was prevented with higenamine. These data strongly suggest that higenamine suppresses NO products and induced nitric oxide synthase expression in the experimental DIC model, prevents platelet aggregation, inhibits the formation of intravascular fibrin deposition or thrombosis, and improves blood supply to organs. This indicates that aconitine can protect the heart, platelets and vascular smooth muscle in the DIC rat model induced by LPS. Previous studies have shown that higenamine up-regulates the β-AR, increases responsiveness of cAMP in plasma, and acts directly on the β-AR at a large dose. In addition, aconite polysaccharide extracted from aconite increases hepatic low density lipoprotein receptor and cytochrome P450 1a1-expression and decreases 3-hydroxy-3-methyl glutaryl (HMG)-CoA expression, and lowers cholesterol levels, which are significant factors in the prevention of cardiovascular diseases. In conclusion, aconite has been used for the treatment of many types of diseases, and is especially well known for its pharmacological effects on the cardiovascular system, such as improving heart function, easing ischemia reperfusion injury, resisting arrhythmia, stretching of the arteria coronaria, stabilizing blood pressure, and antagonizing coagulation and thrombosis. These effects are able to be used to treat heart failure, shock due to myocardial infarcts, arrhythmia, DIC state and multiple organ failure. However, most of the pharmacological effects of aconite are dual, such as the effects on cardiac rhythm and blood pressure, which are closely related to the various active components contained in Chinese herbs. The basis of the above-mentioned pharmacological effects of aconite are mostly concerned with the regulation of the neuroendocrine system. For example, aconite acts as an agonist of different subtypes of α and β receptors, as well as affects sodium and calcium ion channels. Furthermore, studies on signal transduction involving NO
and cAMP are also carried out supplementarily. By reviewing the literature in this field, we realized that the following two points should be emphasized. First, because of the close relationship between the pharmacological effects of aconite and the category and dosage of the active components, it is unwise to prescribe aconite alone in clinical application with a large dose. It is highly recommended that aconite is applied when compatible with other herbs, such as ginseng, ginger, ramulus cinnamonami, atracyloides macrophala, tuckahoe, gypressum, and berberine, to ensure clinical safety, and play an efficient role in its pharmacological effects. If a high dose of aconite is required, attention should be paid to observing adverse reactions, so that any adverse effects can be dealt with in a timely manner. Otherwise, it is a good choice to use an extract of an effective monomer aimed at the corresponding pathological response. Second, research on cardiac protection of aconite is still insufficient. Development of science and technology, in particular, intervention technologies, has led to an increasing number of patients surviving from myocardial infarction, which leads to another problem of ischemia reperfusion injury. As a result, further research on the protective effect and application of aconite on myocardial cells and bone marrow stem cell mobilization is required, because it can protect myocardial cells from direct injury, while promoting cardiac cell regeneration.

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