Expert Consensus on Wenxin Granule for Treatment of Cardiac Arrhythmias

Heart Rhythm Society of the Chinese Society of Biomedical Engineering, Nao Xin Tong Zhi Committee of the Chinese Association of Integrative Medicine

Key words: Cardiac Arrhythmias; Treatment; Wenxin Granule

INTRODUCTION

Antiarrhythmic drugs remain a critically important component of the approach to therapy of cardiac arrhythmias. Over the past 20 years, despite their antiarrhythmic efficacy in many pathological settings, Class I and III antiarrhythmic drugs have been shown to be associated with the development of proarrhythmias and an increase in the likelihood of causing higher mortality by inducing torsade de pointes ventricular tachycardia and other serious adverse reactions. Consequently, the development of safe and effective antiarrhythmic regimens remains a primary focus of contemporary cardiovascular research.

The clinical application and study of Wenxin Granule have been ongoing for three decades. Numerous studies, including a randomized, placebo-controlled, double-blind, and multicenter trial, have shown that Wenxin Granule is effective and safe for the treatment of cardiac arrhythmias. [1] With respect to the mechanisms of antiarrhythmic action, Wenxin Granule has a clear theoretical basis for the treatment of cardiac arrhythmias underlying traditional Chinese medicine (TCM) and multiple antiarrhythmic mechanisms of actions which have been confirmed by studies using modern clinical and cardiac electrophysiological research techniques.[2-4]

Evidence from basic and clinical researches has been advanced in support of the use of Wenxin Granule for the treatment of cardiac arrhythmias, including atrial and ventricular premature beats. This expert consensus statement was drafted by domestic and foreign experts organized by the “Heart Rhythm Society of the Chinese Society of Biomedical Engineering” and the “Nao Xin Tong Zhi Committee of the Chinese Society of Integrative Medicine” in an attempt to standardize clinical application, to promote in-depth researches into mechanisms underlying Wenxin Granule, and to enhance the evidence base of Chinese medicines. This expert consensus document reviews the available data concerning the use and the mechanism of antiarrhythmic action of Wenxin Granule. We expect this expert consensus to help physicians using both TCM and western medicine to understand the status of the current research and application of TCM antiarrhythmic medicines.

HISTORY OF RESEARCH AND DEVELOPMENT

In the early 1980s, Dr. Yu-Ping Zhou, together with other TCM doctors from Guang’amen (GAM) Hospital affiliated with the China Academy of Chinese Medical Sciences (formerly the China Academy of TCM), initiated the research and development of Wenxin Granule (Heart-stabilizing Granule). The ingredients were finalized as five Chinese herbs: Danshen (Codonopsis root, Radix Codonopsis), Huangjing (Siberian Solomon’s seal rhizome, Rhizoma Polygonati), Sanqi (Pseudoginseng root, Radix et Rhizoma Notoginseng), Hupo (Amber, Succinum), and Gansong (Nardostachys root, Radix et Rhizoma Nardostachys). The composition of this formula was determined under the treatment principle of pattern identification in TCM from the prescriptions of

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Zhigancao Decoction (prepared licorice root decoction) in the book, Treatise on Cold Damage: “Zhigancao Decoction is mainly used in patients with palpitations due to irregular or intermittent pulses,” and from the personal clinical experience of physicians in GAM Hospital. Then, the preparation form of this formula was changed from decoction to granule.

In 1987, Wenxin Granule for the treatment of arrhythmia became a research project of the Institute of Chinese Medical Sciences. In 1991, it was included in “The 8th Five-Year Plan,” the National Key Science and Technology Project of TCM. In 1996, the outcomes were reviewed and approved. In 1995, this product received new drug certification issued by the Ministry of Health of the people’s Republic of China and was officially marketed.

Since then, further in-depth studies on its antiarrhythmic mechanisms of action were carried out at different levels ranging from clinical studies to basic studies and from myocardial tissues to animals. The results confirmed the significant preventive and therapeutic efficacy of Wenxin Granule on arrhythmias induced by aconitine, barium chloride, and epinephrine. Studies on the mechanisms of action then were performed at the cellular and molecular levels. The application of the whole-cell patch-clamp technique proved the followings: Wenxin Granule significantly inhibited sodium, potassium, and calcium channels on myocardial cell membrane in a dose-dependent manner, and it was found to possess activities of Class I, III, and IV antiarrhythmic drugs.

Foreign scholars began to investigate the Wenxin Granule in 2005. Benefiting from the advanced basic research technologies and previously developed equipment, a number of internationally renowned scholars became involved in the study on Wenxin Granule and three important achievements were quickly achieved.

The first is the study conducted by Xue et al. This study confirmed that Wenxin Granule significantly inhibited late sodium currents to reduce early after‑depolarization, delayed after‑depolarization, and T‑wave alternate, thus to prevent and reduce the occurrence of malignant ventricular arrhythmia.

The second is the study conducted by Burashnikov et al. in 2012. This study showed that Wenxin Granule produced atrial‑selective inhibition of peak sodium current (I_{Na,p}) and was thus capable of prolonging postepolarizing refractoriness and prevented or terminated atrial fibrillation induced by acetylcholine and burst pacing. The conclusion was affirmed by a commentary article.

The third is another study conducted by Minoura Y et al. in which Wenxin Granule was found to inhibit the transient outward current I_{to}. Using experimental models of Brugada syndrome generated with the I_{to} agonists (NS5806), Wenxin Granule, particularly in combination with quinidine, was shown to suppress the electrocardiographic and arrhythmic manifestations of Brugada syndrome, with the inhibition rate of 60% and 100% by 5 and 10 g/L Wenxin Granule, respectively, suggesting a therapeutic effect of Wenxin Granule on Brugada syndrome.

In 2010–2012, a randomized, double‑blinded, placebo‑controlled, and multicenter clinical study on Wenxin Granule for the treatment of atrial premature beats and ventricular premature beats was conducted. This study, involving 60 Grade‑III medical institutions in China, was led by researchers at Beijing Fuwai Cardiovascular Hospital and enrolled 2400 participants. The results showed that the total effective rate of Wenxin Granule for the treatment of atrial premature beats and ventricular premature beats was 83.6% and 83.0%, respectively. It was also reported to improve heart palpitations, chest tightness, fatigue, and other symptoms. No proarrhythmia was observed; the incidence of adverse reactions was not statistically different from those of the placebo group.

In summary, recent studies have advanced our understanding of the mechanisms of action of Wenxin Granule and its clinical effectiveness.

**Features of Formula in the Description of Traditional Chinese Medicine**

Wenxin Granule consists of Danshen, Huangjing, Sanqi, Hupo, and Gansong. Among them, Danshen is the “monarch” medicinal herb of this regimen. Characterized by a moderate and nourishing nature with a neutral property and sweet flavor, it supplements the middle energizer, boosts qi (nutrients), tranquilizes the mind, and relieves palpitations. Huangjing is the “minister” herb of this regimen, helping Danshen tonify qi and generate blood; it also has a neutral property and sweet flavor and fortifies the spleen qi to nourish the heart and lungs. The other three ingredients are all assistant medicinal herbs. Sanqi has a slightly bitter flavor and a warm property. It can remove blood stasis, relieve pain, and tonify weakness. Hupo is neutral and sweet with the effects of activating blood, removing stasis, pacifying the liver, and tranquilizing the mind. Gansong is warm and sweet and can relieve depression, remove stagnation, and regulate the liver and spleen qi.

Simple but carefully formulated, this formula has effects of supplementing qi, nourishing yin, tranquilizing the mind, restoring pulses, activating the blood, and removing stasis. Its indication is dual qi and yin deficiency and its stasis pattern manifests as palpitations, shortness of breath, listlessness, dizziness, vexation, insomnia, chest distress, and chest pain.

This formula has the following three features. First, it targets the key mechanism of the qi-yin deficiency pattern in palpitations. Zhong‑Jing Zhang was the first to elaborate on the cause of palpitations as interior deficiency and formulated the Zhigancao Decoction for it. His book, “Essential Prescriptions from the Golden Cabinet”, described the observation of weak and thready radial pulse in palpitations. Based on these findings, palpitations are often
considered to be caused by a deficiency of both *qi* and *yin* with obstructed heart meridians. Wenxin Granule is on target for the treatment of palpitations by supplementing the *qi* and *yin*, tranquilizing the mind, restoring vessels, activating the blood, and removing stasis.

Second, it also protects the spleen and stomach. The Yellow Emperor’s Internal Classic stated, “When food is ingested and then digested in stomach, turbid *qi* will flow to the heart and circulate the essence in the meridians,” therefore fortifying the spleen and stomach that reinforce the heart *qi* and blood. In this formula, Huangjing and Danshen replenish the spleen and stomach.

Finally, this formula regulates both *qi* and blood aspects. The majority of deficiency patterns are often accompanied by blood stasis caused by *qi* deficiency, and insufficient blood in the meridians. Following the TC theory of “blood generating *qi* and *qi* directing blood”, Sanqi and Hupo are thus selected to activate the blood, maintain the blood flow in vessels fluent, and relieve palpitations effectively.

**Pharmacodynamics and Toxicology**

Wenxin Granule has been studied in several models of induced arrhythmias to assess its antiarrhythmic efficacy and potential toxicity. Subsequent researches focused on its effects on ion channels in single cardiomyocytes as well as electrophysiological parameters in isolated cardiac tissues and wedge preparations. In recent years, researches have focused on the selective inhibition of late sodium current and atrial selectivity for fast (peak) sodium current.

**Pharmacodynamic study**

**Inhibition of ventricular arrhythmias induced by aconitine, barium chloride, myocardial ischemia, and reperfusion**

Rats were used as an experimental animal model for the early pharmacodynamic study of Wenxin Granule. Ventricular arrhythmic models were developed using aconitine, barium chloride, and myocardial ischemia-reperfusion methods. Wenxin Granule was administered in progressively higher doses. The results showed that Wenxin Granule could significantly delay the onset arrhythmias, shortened its duration, and also reduced ischemia-reperfusion-mediated arrhythmias.\(^5\)

**Inhibition of isoproterenol-induced ventricular arrhythmias following myocardial infarction**

Wenxin Granule, amiodarone, and placebo were evaluated in rats subjected to ischemia followed by infusion of isoproterenol. Wenxin Granule reduced the development of ventricular arrhythmia when compared with placebo.\(^4\)

**Toxicological study**

**Acute toxicity test**

Mice were given a single-dose of Wenxin Granule by intragastric gavage; the dosing volume was 0.04 ml/g and the dose was 80 g/kg (equivalent to 88.9-fold, the dose for adult patients). During the 7-day observation period after administration, the mice were quiet and ate, urinated and defecated normally with smooth fur. No deaths were reported, suggesting that Wenxin Granule had no significant acute toxicity (unpublished data).

**Maximum dose test**

Mice were given three doses within 24 h by intragastric gavage; the first dosing volume was 0.04 ml/g and the dose was 80 g/kg (equivalent to 88.9-fold, the dose for an adult patient); the second and third doses were 80% of the first dose. During the 7-day continuous observation, the treated mice showed reduced activities and became quiet. Some animals developed diarrhea and recovered within 24 h. No deaths occurred. No other obvious adverse effects were observed (unpublished data).

**Chronic toxicity test**

Mice received 13.3 ml·kg\(^{-1}\)·d\(^{-1}\) of Wenxin Granule by intragastric gavage. The administered dose was equivalent to 40-, 25-, and 10-fold, the clinical dose for adult patients. The control group was given an equal volume of tap water. The treatment lasted for 90 successive days. When compared with the control group, no abnormalities were observed in the Wenxin Granule group, suggesting that it had no significant chronic toxicity (unpublished data).

**Mechanisms of Action**

**Effects on myocardial ion channels**

Domestic and foreign experts used the patch-clamp technique to study the electrophysiological action in individual myocardial cells. The results confirmed that Wenxin Granule inhibited multiple ion channels.

**Sodium channel blockade**

**Inhibition of fast sodium current (I\(_{\text{Na}}\))**

When individual rabbit ventricular myocytes were examined using whole-cell patch-clamp, *Nardostachys chinensis* Batal extract (main ingredient of Wenxin Granule, concentration = 5 and 10 g/L) significantly reduced the peak I\(_{\text{Na}}\) (I\(_{\text{Na, max}}\)) and slowed down the recovery from inactivation, with no change in steady-state activation or reversal potential.\(^9\) Furthermore, in rabbit ventricular myocytes and Purkinje cells, the half maximal inhibitory concentration (IC\(_{50}\)) of Wenxin Granule on fast sodium currents was 10.6 ± 0.9 mg/ml and 13.3 ± 0.9 mg/ml, respectively.\(^10\)

**Inhibition of late sodium current**

Slow inactivated and late reopenings of the sodium channel give rise to late I\(_{\text{Na}}\). Although its amplitude is a small fraction (merely one-thousand) that of the fast sodium current in normal myocardial cells, the late I\(_{\text{Na}}\) is known to increase under various pathological conditions (e.g., hereditary ion channel diseases, ischemia, or heart failure), which would result in prolonged repolarization and increased repolarization heterogeneity, promoting the occurrence of malignant arrhythmias. In recent years, the role of the late sodium current in the pathogenesis of arrhythmia has...
attracted increasing attention.[3] Studies employing rabbit ventricular myocytes and Purkinje cells showed that Wenxin Granule selectively inhibited late $I_{Na}$. The median effective concentration inhibiting late $I_{Na}$ in rabbit ventricular myocytes and Purkinje cells was $3.8 \pm 0.4 \text{ mg/mL}$ and $4.3 \pm 0.5 \text{ mg/mL}$, respectively. Therefore, the concentration of Wenxin Granule needed to inhibit the late sodium current is 2.8–3.1-fold lower than that needed to inhibit the peak sodium current.[4,10]

**Calcium channel blockade**

*Nardostachys chinensis* Batal extract (5 and 10 g/L) inhibits L-type calcium currents and shifts the current-voltage relationship upward without changing its activation potential or reversal potential. The effect is increased with higher concentrations.[9]

**Potassium channel blockade**

Inhibition of slow-activating delayed rectifier potassium current ($I_{Ks}$)

A dose of 5 or 10 g/L *Nardostachys chinensis* Batal extract, the main ingredient of Wenxin Granule, inhibits the $I_{Ks}$ tail current ($I_{Ks,tail}$) by 20.9% and 41.6%, respectively.[9] However, it has no significant effect on the inward rectifier potassium current ($I_{K1}$).

Inhibition of transient outward potassium current ($I_o$)

Wenxin Granule (10 g/L) reduced the $I_o$ peak in ventricular myocytes of adult rats by 57.9%. In canine ventricular myocytes, 5 and 10 g/L of Wenxin Granule decreased the $I_o$ amplitude by 41.9% and 69.8%, respectively. This result was consistent with inhibition of the Brugada wave and polymorphic ventricular tachycardia at the tissue level, suggesting that Wenxin Granule may be effective in the treatment of J-wave syndromes, including Brugada syndrome.[9]

**Effects of Wenxin Granule on myocardial electrophysiological properties**

Effects of Wenxin Granule on ventricular sodium current and conductivity

Low concentrations of Wenxin Granule inhibit late sodium current with little effect on fast sodium current, leading to abbreviation of action potential duration (APD), reduction of T-wave peak-to-end interval (Tp-e, related to the dispersion of repolarization),[4,11] and suppression of early and delayed after-depolarization. Higher concentrations of Wenxin Granule inhibits fast sodium current, leading to mild increase of QRS duration without significant rate dependence, which means very little change in QRS wave duration with varying heart rate, such characteristics are significantly different from Class Ic antiarrhythmic drugs but similar to the class Ib drug lidocaine. The mechanism of action may be related to the quick dissociation of Wenxin Granule from sodium channel proteins.[3]

Characteristics of action on atrial electrophysiology

Because Wenxin Granule inhibits peak sodium current to a greater extent in atrial myocardium than in ventricular myocardium,[8,12,13] consequently, it abbreviates the atrial APD but prolongs atrial effective refractory period, resulting in a significant postrepolarization refractory period, being capable of suppressing atrial arrhythmias.

The atrial-selective inhibition of sodium channel parameters is related not only to the differential electrophysiological properties between atrial myocardium and ventricular myocardium but also to Wenxin Granule-mediated inactivation of sodium channels in atrial myocytes. When compared with ventricular myocardium, a relatively low concentration of Wenxin Granule inhibited the fast sodium current in the atrial myocardium, increasing the diastolic stimulation threshold, decreasing atrial excitability, and thus terminating or preventing the acetylcholine-mediated atrial fibrillation.[3]

**Indications and Clinical Applications**

**Indications**

Wenxin Granule is mainly used for the treatment of complicated atrial premature beats and ventricular premature beats in symptomatic patients with or without organic heart disease. It has some preventive and therapeutic effects on paroxysmal atrial fibrillation.

**Clinical application**

**Atrial premature beats**

It should be noted that the majority of atrial premature beats including frequent atrial premature beats and even atrial bigeminy do not require treatment if the patient has no symptoms. When the symptoms become apparent and affect the hemodynamics or quality of life, treatment can be considered. Clinically, the patients often have a certain degree of anxiety and anxiety-associated systemic symptoms caused by climacteric syndrome or cardiac neurosis. For concomitant atrial premature beats in these patients, Wenxin Granule has therapeutic advantages because it can treat both atrial premature beats and directly or indirectly improves the subjective symptoms.

Results of a single-center study showed that the total efficacy on atrial premature beats was higher with Wenxin Granule than in control group (76.7% vs. 30.0%, $P < 0.05$) but
was similar to that of propafenone (150 mg, 3 times daily) (75% vs. 72%, P > 0.05).[14,15] However, Wenxin Granule had a lower incidence of adverse reactions and weak sinus bradycardia effects.

A multicenter evidence-based medical study in China showed that the total effective rate of Wenxin Granule for the treatment of atrial premature beats was 83.6%. The incidence of adverse reactions was not statistically different from that of the placebo group.[9]

**Ventricular premature beats**
A single-center study showed that the effective rate of Wenxin Granule for the treatment of ventricular premature beats was 68–85%,[16]

A multicenter, randomized, double-blind, parallel, placebo-controlled study showed that the total effective rate of Wenxin Granule to reduce ventricular premature beats and nonsustained paroxysmal ventricular tachycardia was 83%,[17]

**Atrial fibrillation**
In an experimental acetylcholine-mediated model of AF, 5 g/L Wenxin Granule effectively terminated and prevented the development of atrial fibrillation in 100% preparations. Currently, there are no large-scale multicenter study data for the clinical application of Wenxin Granule for the treatment and prevention of atrial fibrillation. Two single-center studies[17,18] have shown that the addition of Wenxin Granule can improve the efficacy of other drugs (including amiodarone and propafenone) in the treatment of patients with paroxysmal atrial fibrillation. For patients with chronic atrial fibrillation, Wenxin Granule in combination with digoxin or metoprolol further decreased the ventricular rate, improved the symptoms, and increased exercise tolerance.[18,20]

**Others**
In the elderly[21] and in patients with hypertension,[22] heart failure,[23] pulmonary heart disease,[24] acute coronary syndrome,[25,26] hyperthyroidism,[27] angina pectoris,[28] menopausal syndrome, and anxiety disorders,[29] Wenxin Granule has been shown to suppress premature beats with a high level of safety profile.

**Improvement of traditional Chinese medical “syndrome”**
In addition to the effective treatment of atrial and ventricular premature beats, Wenxin Granule can significantly improve the specified groups of symptoms or “syndrome” within the scope of TCM. Its indications include qi and yin deficiency and heart blood stasis, complicated with palpitations, shortness of breath, fatigue, dizziness, chest tightness, chest pain, and insomnia to improve a patient’s quality of life.[30]

**METHOD OF ADMINISTRATION**

**Conventional application**
Wenxin Granule is a prescription preparation formula of proprietary Chinese herbal medicines. The packaging specification is 5 g/bag (sugar-free) or 9 g/bag (with sugar). The conventional usage is to dissolve it in boiled water, one bag each time, three times daily, or following medical directions.

**Special application**

**Increased dose**
For patients with serious disease conditions, the dose can be increased to two bags each time, 3 times daily. After the disease condition becomes stable, the treatment can be changed to a conventional maintenance dose.

**Long-term use**
Depending on the disease conditions, long-term application is possible. It was reported that the continuous administration of Wenxin Granule for 6 months and 12 months resulted in satisfactory efficacy without severe adverse reactions.

**Combined application**
Reported are available that Wenxin Granule can be used in combination with amiodarone,[17] digoxin,[19] metoprolol,[20] and propafenone.[18]

**ADVERSE REACTIONS AND TREATMENT**
Wenxin Granule-related adverse reactions include dizziness, nausea, dry mouth, and upper abdominal discomfort. A large-sample study showed that the incidence of adverse reactions in the Wenxin Granule treatment group was 0.5% with no statistical difference from the placebo group. The majority of these adverse reactions require no special treatment; if necessary, drug discontinuance is usually sufficient.[31]

**Precautions**
Patients with severe bradycardia should not use this product; pregnant women should use it with caution.

**CONCLUDING REMARKS**
“Expert consensus on Wenxin Granule for the treatment of cardiac arrhythmias” is the first expert consensus on the antiarrhythmic use of a TCM. This consensus is the outcome of conscientious writing by hundreds of national and international experts from medical universities/colleges, hospitals and research institutes worldwide, thorough discussions at dedicated meetings, seeking opinions of experts from relevant subdisciplines/specialties, and repeated argumentation to ensure scientific, professional, accurate, and practical unity. All participants hope that their efforts will make this consensus highly representative and stand the test of time.

The development, application, and postapplication study of Wenxin Granule are the achievements of a successful integration of TCM and western medicine, which has concentrated the wisdom and expertise of Chinese and foreign experts. Wenxin Granule has multiple electrophysiological actions. The main characteristics include selective block of ventricular late sodium current and atrial-selective block of peak sodium current. Further investigations is needed to determine whether the
concentrations used in basic research studies are consistent with the clinical actions of the drug.

Clinical use of Wenxin Granule showed good efficacy and safety as the first-line therapy of ventricular and atrial premature beats; it can be used either alone or in combination with antiarrhythmic agents used in western medicine. Recent studies also indicated that Wenxin Granule may be of benefit in the treatment of other types of arrhythmias, including atrial fibrillation and Brugada syndrome. An understanding of its mechanism of action and characteristics will continue to enhance its use. Certainly, the accumulation and transformation of study achievements will move the application of Wenxin Granule toward a more standardized, scientific, and accurate direction.

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Effects of table. Clinical observation on wenxin granules for 199 cases of Nardostachys. A multi-center clinical study of the effects

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