

Toxicity and Pharmacological Effect of Paeogly Antispastic Capsule for Gastrocnemius Cramps: Fundamental Study

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ABSTRACT

Background and Aim: We have conducted a fundamental study to make a prescription with paeoniflorin (main component of *Paeonia albiflora* Palls) which has sedation effect, antispastic effect, analgesic effect, dilate peripheral vessels, and glycyrrhizin (main component of *Glycyrrhiza uralensis* Fisch) which has analgesic effect, sedation effect, anti-inflammatory effect and to make capsule in order to treat gastrocnemius cramps. Gastrocnemius cramps which are also called nocturnal gastrocnemius cramps or sleep-related gastrocnemius cramps produce pain and disrupt sleep. Most of them can be idiopathic. Vitamin B complex, Vitamin E, diphenhydramine, diltiazem, verapamil, gabapentin, carisoprodol, orphenadrine and other medications are used for gastrocnemius cramps but they are limited in use due to weak evidence for their efficacy and several side effects. **Methods:** Female white rats with 20-25 g in body weight and female wistar rats with 100-120 g in body weight were used as experimental animals and Paeogly antispastic capsule (0.3 g per capsule) which consists of 0.15 g extract powder from *Paeonia albiflora* Palls and 0.1 g extract powder from *Glycyrrhiza uralensis* Fisch in distilled water was used as drugs. To verify the toxicity of Paeogly antispastic capsules, acute toxicity experiment was done with maximum injection method and in subacute toxicity experiment, the drug was administrated with the dose of 160 mg/kg/d for 60 days using sonde, measuring the body weight every 30 days then peripheral blood test and blood biochemistry test, measuring organ index of parenchymal organs at 60th day after administration. To verify the pharmacological effect of the Paeogly antispastic capsules, cramp models were made with subcutaneous injection of strychnine nitrate 0.06 mg/100g, diabetic models were made with injection of 5% alloxan in physiological saline (5 mg/100g). Study group was given Paeogly antispastic capsules (0.3 g) in 6 mL of distilled water 200 mg/kg daily for 3 days using sonde and the control group was given only distilled water. Finally, we did electromyogram in gastrocnemius an hour after administration. **Results:** The maximum injection amount of Paeogly antispastic capsules is 800 mg/kg and no abnormal findings were found in body weight, peripheral blood test, biochemical test and organ index during subacute toxicity experiment. **Conclusion:** Paeogly antispastic capsules fastened the nerve conduction velocity of gastrocnemius in cramp models and diabetic model white rats, shortened the inertia time of M wave.

Keywords: Paeogly antispastic capsules, Gastrocnemius cramps, Toxicity, Pharmacological effect.

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INTRODUCTION

Gastrocnemius cramps which are also called nocturnal gastrocnemius cramps or sleep-related cramps are a common leg disease that can produce pain and disrupt sleep. The most of gastrocnemius cramps are idiopathic and can be accompanied by other disease or conditions. The secondary causes of this disease include structural disorders or leg positioning, neurological disorders, extracellular volume depletion and electrolyte disturbances. In healthy people without neurological

diseases may also suffer from this disease due to muscle fatigue, dehydration, electrolyte disturbances, pregnancy and some diseases including diabetes mellitus, uremia, hepatocirrhosis and certain medications. The mechanism of this disease is abnormal contraction of the gastrocnemius due to unstable depolarization of peripheral neuraxons. The gastrocnemius cramps are also caused by continuous active potentials due to increased permeability of membrane then causing overlap of excitation time of muscles. Vitamin B complex, Vitamin E, diphenhydramine, diltiazem, verapamil, gabapentin, carisoprodol, orphenarine and other medications have been used for treatment of gastrocnemius cramps but their use is limited due to weak evidence for their efficacy and side effects. Thus, we have conducted a fundamental study to treat this disease with prescription of paeoniflorin (main component of *Paeonia albiflora* Palls) which has sedation effect,



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antispastic effect, analgesic effect, dilate peripheral vessels and glycyrrhizin (main component of *Glycyrrhiza uralensis* Fisch) which has analgesic effect, sedation effect, anti-inflammatory effect.

MATERIALS AND METHODS

Female white rats with 20-25 g in body weight and female wistar rats with 100-120 g in body weight were used as experimental animals.

Paeogly Antispastic Capsule

Paeogly antispastic capsule (0.3 g per capsule) which consists of 0.15 g extract powder from *Paeonia albiflora* Palls and 0.1 g extract powder from *Glycyrrhiza uralensis* Fisch in distilled water was used as drugs.

Methods to Verify the Toxicity of Paeogly Antispastic Capsules

Acute toxicity experiment was done with maximum injection amount and in subacute toxicity experiment, the drug was administrated with the dose of 160 mg/kg/d for 60 days using sonde, measuring the body weight every 30 days then peripheral blood test, blood biochemistry test and measuring organ index of parenchymal organs at 60th day after administration.

Methods to Verify the Pharmacological Effect of Paeogly Antispastic Capsules

Cramp models were made with subcutaneous injection of strychnine nitrate 0.06 mg/100 g and diabetic models were made with injection of 5% alloxan in physiological saline 5 mg/100g.

Study group was given Paeogly antispastic capsules (0.3 g) in 1mL of distilled water with the dose of 200 mg/kg using sonde for 3 days and the control group was given only distilled water. Finally, electromyogram of gastrocnemius was done an hour after administration.

RESULTS

Toxicity of Paeogly Antispastic Capsules

Acute toxicity of paeogly antispastic capsules

White rats were given up to 800 mg/kg of Paeogly antispastic capsules but no one died. Thus, the maximum injection amount of Paeogly antispastic capsule is 800 mg/kg.

Subacute Toxicity of Paeogly antispastic capsules

Influence of Paeogly antispastic capsules on body weight of white rats

Table 1 shows body weight of study group and that of control group are not significantly different at 30th day and 60th day after administration.

Influence of Paeogly antispastic capsules on mass of parenchymal organs of white rats

Table 2 showed no significant difference in change of organ indexes between the study group and control group was found.

Influence of Paeogly antispastic capsules on peripheral blood test

Table 3 showed no significant difference in the number of red blood cells, white blood cells, thrombocytes and the amount of hemoglobin was found.

Influence on activity of serum transaminase

Table 4 showed that ALT and AST of the study group have a tendency to decrease compared with the control group but no significant difference was found.

Table 1: Influence of Paeogly antispastic capsules on body weight of white rats ($\bar{X} \pm SE$, g).

Group	Dose (mg/kg)	n	Body weight before Administration	Days after administration(d)	
				30	60
Control	-	7	92.3±3.3	107.6±2.5	133.4±3.2
Study	160	7	96.4±3.2	110.6±1.8	136.9±3.4

Table 2: Influence of Paeogly antispastic capsules on organ index of white rats ($\bar{X} \pm SE$, g/100 g).

Group	Dose (mg/kg)	Liver	Spleen	Heart	Kidney
Control	-	4.78±0.34	0.35±0.04	0.32±0.05	0.58±0.08
Study	160	4.57±0.45	0.34±0.05	0.33±0.06	0.56±0.07

Table 3: Peripheral blood test result ($\bar{X} \pm SE$).

Group	Dose (mg/kg)	n	Erythrocyte (T/L)	Hemoglobin (g/dL)	Leukocyte (G/L)	Thrombocyte (G/L)
Control	-	7	6.45±0.53	13.45±1.85	7.79±0.85	594.54±23.56
Study	160	7	6.92±0.55	14.57±1.95	7.23±0.76	551.27±25.74

Table 4: Influence on activity of serum transaminase ($\bar{X}\pm SE$, Unit).

Group	Dose(mg/kg)	N	ALT	AST
Control	-	7	42.5 \pm 2.41	55.7 \pm 2.57
Study	160	7	45.5 \pm 1.05	57.2 \pm 2.64

Table 5: Influence of Paeogly antispastic capsules on electromyogram of gastrocnemius of cramp models ($\bar{X}\pm SD$, n=8).

Group	Dose (mg/kg)	Nerve conduction Velocity (m/s)	M wave inertia time (ms)
Control	-	39.75 \pm 2.19	5.65 \pm 0.64
Study	400	42.00 \pm 0.76*	5.06 \pm 0.18*

*P<0.05 (comparison with control group).

Pharmacological Action of Paeogly Antispastic Capsules

Influence of Paeogly antispastic capsules on electromyogram of gastrocnemius of cramps models

Table 5 showed that nerve conduction velocity of the study group was significantly faster than that of the control group (study group: 42.00 \pm 0.76m/s, control group: 39.75 \pm 2.19m/s, P<0.05). M wave inertia time of the study group was significantly shorter than that of the control group (study group: 5.06 \pm 0.18ms; control group: 5.65 \pm 0.64ms; P<0.05)

Influence of Paeogly Antispastic Capsules on Electromyogram of Gastrocnemius in Diabetic Models

Table 6 shows that nerve conduction velocity of the study group was significantly faster than that of the control group (study group: 42.88 \pm 1.83 m/s; control group: 39.53 \pm 2.75 m/s; P<0.05) and M wave inertia time of the study group was significantly shorter than that of the control group (study group: 4.71 \pm 0.48 ms; control group: 5.43 \pm 0.61ms; P<0.05)

DISCUSSION

Gastrocnemius cramps are common and frequently unreported to clinicians.^[1,2] Gastrocnemius cramps can be idiopathic (the most common), associated with structural disorders or leg positioning, or related to extracellular fluid volume depletion and electrolyte disturbances. It also may be due to low serum magnesium.^[3-5] For the prevention and treatment of the gastrocnemius cramps, vitamin B complex including B6(30mg/day),^[6] naftidrofuryl,^[7] calcium channel blockers such as diltiazem (30 mg/day), verapamil (120 to 180mg at bedtime) can be used.^[8,9] Vitamin E,^[10] chloroquine phosphate (250 mg daily for two to three weeks, followed by 250-500 mg once per week),^[11] muscle relaxants including carisoprodol and orphenadrine,^[12] gabapentin (600 mg daily with increased doses as necessary)^[13] have been used

Table 6: Influence of Paeogly antispastic capsules on electromyogram of gastrocnemius in diabetic models ($\bar{X}\pm SD$, n=8).

Group	Dose (mg/kg)	Nerve conduction velocity (m/s)	M wave inertia time (ms)
Control	-	39.53 \pm 2.75	5.43 \pm 0.61
Study	400	42.88 \pm 1.83*	4.71 \pm 0.48*

*P<0.05(comparison with control group).

for gastrocnemius cramps with variable success. Meta-analysis of some trials found weak evidence for significant benefit in the frequency or severity of cramping and side effects should be considered. We have conducted a fundamental study to make a prescription with paeoniflorin (main component of *Paeonia albiflora* Palls) which has sedation effect, antispastic effect, analgesic effect, dilate peripheral vessels, and glycyrrhizin (main component of *Glycyrrhiza uralensis* Fisch) which has analgesic effect, sedation effect, anti-inflammatory effect and to make capsule form in order to treat gastrocnemius cramps associated with diabetes and pregnancy with Koryo medicine.

First, according to our study results, when the white rats were given 800 mg/kg of paeogly antispastic capsules, no one died and no influence on body weight and organ index were found. Paeogly antispastic capsules didn't affect the number of red blood cells, white blood cells, platelets and the amount of hemoglobin. In the study group, ALT was 65.5 \pm 1.05 and AST was 87.3 \pm 2.64 with a tendency to decrease compared with the control group but no significant difference was found. Secondly, Paeogly antispastic capsules significantly fastened the nerve conduction velocity of gastrocnemius in cramp model white rats and shortened M wave inertia time.

The results of this fundamental experiment show that Paeogly antispastic capsules can be safely used in treatment of the gastrocnemius cramps and this is mainly by pharmacological effect of paeoniflorin and glycyrrhizin which are natural components. The main component of this capsule is crude drug so no significant side effects may be considered and can be used for many patients with gastrocnemius cramps. But we may need further research for the clinical application.

CONCLUSION

Maximum injection amount of the Paeogly antispastic capsules is 800mg/kg and no abnormal findings were found in body weight, peripheral blood and biochemical test, organ index during subacute toxicity experiment.

The Paeogly antispastic capsules fastened the nerve conduction velocity of gastrocnemius in the diabetic models and shortened the inertia time M wave.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

Nil

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