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EXPERIMENTAL WORK AND RESEARCH

Effect of Yuxintong (愈心痛) Capsule on Serum Creatine Phosphokinase Activity and Plasma Endothelin Concentration in Acute Myocardial Ischemic Dogs

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ABSTRACT The protective effect of the traditional Chinese compound medicine Yuxingtong (YXT) in capsule form on the experimental acute myocardial ischemia formation has been studied in dogs. The plasma endothelin concentration and serum creatine phosphokinase activity were measured after coronary occlusion in different medication groups and compared with the saline control group. Results showed that YXT could significantly lowered the plasma endothelin concentration and the serum creatine phosphokinase activity, it suggested that both YXT and diltiazem have the similar protective effect on acute myocardial ischemia and necrosis in dogs.

KEY WORDS Yuxintong capsule, creatine phosphokinase, endothelin, acute myocardial ischemia, dogs.

The traditional Chinese compound medicine Yuxintong (YXT) capsule, consisted of Radix Ginseng, Radix Sanchi, etc. with effects of blood stasis removing, pain relieving and cardiotonic action, was used in treatment of angina pectoris and myocardial infarction.

This experiment observed the effect of YXT on serum creatine phosphokinase (CPK) activity as well as the plasma endothelin (ET) level in acute myocardial ischemic dogs, and compared it with that of diltiazem, a calcium channel blocking agent, aimed at examining the protective effect of YXT against myocardial ischemic injury and providing further basis for clinical application of YXT in treatment of coronary heart disease. The results were as follows.

METHODS

Experimental Animals

Twenty healthy and hybrid dogs, weighing 12 to 18 kg, both male and female were used and divided randomly into 4 groups, 5 dogs in each group. (1) Normal saline control group (Group A, non-medicated); (2) diltiazem group (Group B, 5mg/kg); (3) YXT high-dose group (Group C, 1.0g/kg); (4) YXT low-dose group (Group D, 0.5g/kg).

Medicament, Reagent and Instrument

YXT capsule was provided by The Yanbian Aodong Pharmaceutical Factory of Jilin Province.

Diltiazem was provided by The Yan'an Pharmaceutical Factory of Shanghai.

Pentobarbital sodium was provided by The Shanghai Chemical Reagent Station.

Endothelin-RIA-kit was offered by PLA General Hospital. CPK activity was measured with an automated enzyme analyzer (KONE, made in Finland).

Measurement of ET and CPK Activity

The myocardial ischemic model was produced by ligating the left coronary artery at the middle of anterior descending branch or the end of the maximal oblique branch in barbital-anesthetized (30 mg/kg) open-chest dogs. Fifteen minutes after the ligation, medicine (dissolved in saline, 4ml/kg) was administered

with the same speed intraduodenally to the animals.

Blood samples were collected at 15 min after ligation, and 1, 2, 3 hrs after medication from femoral vein respectively. One part of each sample was provided for serum CPK activity measurement; the other part was treated with chilled EDTA-Na_2 and Atrotonin for anticoagulating and peptidase activity inhibition, and centrifuged immediately at 4℃ to separate the plasma, which was frozen at -20℃ for ET measurement.

The plasma ET was directly measured with radioimmunoassay. Interassay and intraassay coefficients of variation of the RIA kit were less than 15% and 10% respectively; the range of detection was 5 ~ 5120 pg/ml with the sensitivity of 2pg/ml; the antibody exhibited a cross-reactivity of 100% with ET-1, the cross-reactivity with ET-2, ET-3 in this assay were negligible, no cross-reactivity with unrelated peptides such as atrial natriuretic factor 1-28, brain natriureric peptide, vasopressin, angiotensin I and II etc. could be detected.

Statistical Analysis

All results are given as means ± S. Significance of differences was determined using Student's t test, $P<0.05$ was taken as statistically significant.

RESULTS

The level of serum CPK activity detected at 15 min after ligation was 520.26 ± 244.66 IU/L. Changes of serum CPK activity after medication are shown in table 1.

As showed in table 1, the serum CPK activity gradually increased as the time of coronary artery occlusion prolonged. In Group A versus the measurement of 15min after occlusion, the CPK activity increased 41%, 93% and 161% at 1, 2 and 3 hours after medication respectively, which suggested that there was a severe myocardial injury. While the increments were 3.6%, 21.3% and 51.5% ($P<0.05$) in Group B; 13%, 24% and 41% in Group C; and 8.2%, 22% and 35% in Group D respectively. These results suggested the medication led to a reduction in myocardial injury.

Table 1. Effect of Myocardial Ischemia and Medication on CPK Activity ($\bar{x} \pm S$)

Group	n	CPK activity ($IU \cdot L^{-1}$)		
		60min	120min	180min
A	5	819.20 ± 179.16	1122.00 ± 223.46$^{\triangle\triangle}$	1517.00 ± 313.74$^{\triangle\triangle}$
B	5	602.40 ± 102.99*	706.20 ± 121.12**	882.20 ± 276.65$^{\triangle\triangle}$
C	5	658.00 ± 234.98	726.60 ± 110.65**	822.60 ± 183.79**
D	5	630.00 ± 363.81	708.00 ± 387.97	786.00 ± 245.03*

Notes: $^{\triangle}P<0.05$, $^{\triangle\triangle}P<0.01$, compared with the level at 15min after ischemia;
$^{*}:P<0.05$, $^{**}P<0.01$, compared with level of Group A

The level of plasma ET concentration detected at 15 min after ligation was 80.89 ± 21.23 pg/ml, changes of which during the period of myocardial ischemia and after medication are displayed in table 2.

As showed in table 2, the level of plasma ET elevated significantly as the time of occlusion extended and reached a peak at 120 min after occlusion in the control group, whereas in the other 3 groups, it revealed a remarkable decrease after medication with fair dose-dependent and time-dependent correlation.

There were no significant difference between diltiazem group and the two YXT groups.

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Table 2. Effect of Myocardial Ischemia and Medication on ET Concentration ($\bar{x} \pm S$)

Group	n	Plasma ET Concentration (pg/ml)		
		60min	120min	180min
A	5	86.65 ± 18.65	99.47 ± 16,59	94.11 ± 10.92
B	5	73.98 ± 10.79	64.82 ± 13.90**	57.95 ± 14.87**
C	5	71.94 ± 18.12	65.30 ± 19.84*	59.28 ± 7.35**
D	5	73.38 ± 23.20	74.83 ± 13.81*	69.84 ± 13.61*

Note: * $P<0.05$, ** $P<0.01$, compared with level of Group A

DISCUSSION

Endothelin is a novel endothelium-derived vasoactive peptide with potent and persistent vasoconstrictor action. It participates in the pathogenesis of myocardial ischemia, infarction and other cardiovascular diseases. The level of CPK activity reflects the size of myocardial injury and indicates the severity of it. The severer the myocardial injury, the higher the CPK activity[1].

This experiment took serum CPK activity and plasma ET level as indices proved that canine model of acute myocardial ischemia could be made successfully by left anterior descending branch or maximal oblique branch of coronary artery ligation. The serum CPK activity increased persistently during the period of myocardial ischemia, while plasma ET level increased rapidly at 120 min. after coronary artery occlusion and showed a tendency to drop at 180 min. post-occlusionally.

These results indicated that there is no correlation between elevation of serum CPK activity and plasma immunoresponsive ET-1, and it suggested that the increase of the latter might not be relevant to myocardial necrosis itself, but to other vascular events associated with infarction. This result was the same as the conclusion reported by Stewart[2].

It is deduced that plasma ET might be an endogenic pathogenic factor released due to the cardiac ischemia caused by coronary artery ligation. Current studies[3] have shown that both ischemia and hypoxia were the most important factors in release of ET. Hypoxia could cause functional disturbance of endothelial cells of coronary artery and cause a marked increase in the release of ET by these cells, and the ET released could feedback to injure vascular and myocardial tissues, it is a marker of the severity of disease.

Tang reported[4] there was a positive correspondence between infarctional size and plasma ET level in experimental acute myocardial ischemic rats, and application of anti-endothelin serum could reduce the infarctional size, which inferred that ET plays an important role in the regulation of coronary blood flow .

It has been known[5] that calcium channel blocker is an effective inhibitor to the vasoconstriction of ET. Results of the present studies also showed that bothYXT and diltiazem could reduce myocardial cell injury as well as inhibit the leakage of CPK and the release of ET during myocardial ischemia, therefore alleviate the myocardial injury caused by feedback effect of ET. These data suggested that YXT had the same effect as diltiazem, both of them were effective antagonists against ET and cardioprotective agents on acute cardiac ischemia in vivo.

Among the ingredients of YXT, Radix Ginseng could supplement Qi and nourish Yin, regulate the adaptation of organism, enhance the ability of anti-stress and hypoxia tolerance, and improve the myocardial perfusion[6]. Radix Sanchi possesses the effects of removing stasis and relieving pain, its total saponin has been shown to be a selective chronic calcium channel blocker and could efficiently decreases the myocardial oxygen consumption and ameliorate coronary artery circulation[7], and therefore diminishes and delays the injurious

process caused by ischemia. All the ingredients of YXT worked together to play a similar role as diltiazem in cardioprotection during ischemic insult.

The above-mentioned results and relevant data suggested that the mechanism of YXT capsule in protecting the heart from ischemic injury may be associated with its effects on enhancing the anti-stress ability and hypoxia tolerance, improving the myocardial circulation, inhibiting the release of ET and ameliorating its damage to heart, and protecting the myocardial cell membrane.

Thus, the YXT capsule is definitely valuable on prevention and treatment of coronary heart disease.

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Clinical Study of TCM-WM on Aplastic Anemia Complicated with Hepatitis C

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The testing kit of second generation for serum anti-HCV was used in 82 cases of aplastic anemia (AA). The results showed that positive rate was 69.4% (43/62) in the patients of AA with transfusion, this was significantly higher than that in the patients of AA without transfusion. There was no difference of anti-HCV antibody positive rate between chronic AA and acute AA ($P < 0.01$). The anti-HCV positive patients were divided into two groups: PTHC and non-PTHC, there was no statistical difference of their transfusion volume, hemoglobin, white blood cell between these groups. Response rate of AA was lower in anti-HCV positive patients than that in negative patients ($P < 0.05$). Acute, icteric PTHC was liable to bleed and be infected PTHC has been an important complication in patients with AA. The better response was obtained by TCM-WM therapy in the patients.

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