

## Anti-shock effect of cyproheptadine in rabbit

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**ABSTRACT** Twenty four New Zealand rabbits were equally divided into a cyproheptadine (Cyp) treated group and a control group. Profound hemorrhagic shock was produced by exsanguination via carotid artery until mean arterial pressure (MAP) = 5.3 kPa (40 mm Hg) for a period of 90 min. After given Cyp  $10 \text{ mg} \cdot \text{kg}^{-1}$ , the MAP and central venous pressure (CVP) of the treated group rose obviously ( $P < 0.01$ ) and the mesenteric microcirculation improved markedly. After 1 h, all indices returned nearly to the preshock state. The survival rate 2 h after Cyp increased to 12 ( $P < 0.01$ ) in comparison with the control group (7). The results showed that Cyp, which dilates the vasculature and improves the microcirculation through blocking serotonin  $5_2$  and histamine  $H_1$  receptors, has a beneficial anti-shock effect.

**KEY WORDS** cyproheptadine; hemorrhagic shock; blood pressure; microcirculation

Cyproheptadine (Cyp) is a serotonin and histamine  $H_1$  receptor antagonist. It has been reported that Cyp prevents the pulmonary platelet trapping (PPT) in traumatized dogs<sup>(1)</sup>, and is equally effective in endotoxin-induced adult respiratory distress syndrome (ARDS)<sup>(2)</sup>. Recent investigations indicated that Cyp has anti-inflammatory<sup>(3)</sup>, analgesic, and antipyretic effects<sup>(4)</sup>. The present study was to evaluate the effects of Cyp on the mean arterial pressure (MAP), central venous pressure (CVP), mesenteric microcirculation, and survival rate in rabbits subjected to hemorrhagic shock.

### MATERIALS AND METHODS

Cyp (Changzhou 4th Pharmaceutical Factory); Four track recorder (Type RM-6200,

Nihon Kohden, Japan); Olympus microscope (Model CHS, Olympus Optical Co, Japan). New Zealand rabbits were provided by the Animal Center of this College.

The rabbit was anesthetized with 20% urethane  $1 \text{ g} \cdot \text{kg}^{-1}$  iv and endotracheally intubated in supine position. A catheter full of normal saline containing 0.5% heparin was inserted into the right carotid artery and connected to a four track recorder through a pressure transducer. A venous catheter was inserted into the left jugular vein and connected to a  $H_2O$  manometer to observe CVP. A venous tube was inserted into right femoral vein, ready for infusion of blood, liquid, and drug. Through a lower abdominal median incision a segment of small intestine was gently pulled out, laid onto a box perfused with saline ( $36-38^\circ\text{C}$ ). The mesenteric microcirculation was observed under a microscope.

**Hemorrhagic shock** Heparin  $10 \text{ mg} \cdot \text{kg}^{-1}$  was infused through the venous apparatus for systemic anticoagulation. The blood was rapidly let out to a vessel (5% sodium citrate for anticoagulation *in vitro*) through the arterial pipe of the common carotid artery. When MAP was lowered to 5.3 kPa, the rubber tube was clamped and blood-letting was stopped. When MAP compensatorily rose above 5.3 kPa, it was necessary to let out a small amount of blood so as to lower the MAP to 5.3 kPa. After 4-5 times of blood lettings, MAP was relatively stabilized at 5.3 kPa. The total amount of blood-letting was about  $25-40 \text{ ml} \cdot \text{kg}^{-1}$ . After 90 min, the microcirculatory blood stream tended to stagnate. Thus, a state of profound hemorrhagic shock was produced.

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**Experimental protocol** Rabbits of either sex weighing  $2.2 \pm 0.3$  kg were randomly divided into the treated ( $n=12$ ) and the control ( $n=12$ ) groups. Treated group: After MAP being kept constant at 5.3 kPa for 90 min, a mixed liquid (normal saline and low molecular weight (40 000) dextran, 50% each) was infused  $25 \text{ ml} \cdot \text{kg}^{-1}$  into femoral vein within 25 min. Cyp  $10 \text{ mg} \cdot \text{kg}^{-1}$  was added to the next half of the mixed liquid. After 5 min of infusion, all of the autologous blood was reinfused. One hour later, MAP, CVP, mesenteric microcirculation were observed. Two hours later, the death rate was noted. Control group received the same amount of vehicle.

**Statistical analysis** Data were expressed as  $\bar{x} \pm s$ . Significances were determined by  $t$  test.

## RESULTS

● **MAP** The preshock MAP did not show noticeable difference between the two groups ( $P>0.05$ ). The MAP 1 h after Cyp, the ratio of MAP 1 h after Cyp to normal MAP rose obviously, and the reduction of MAP decreased markedly ( $P<0.01$ ). (Tab 1).

**CVP** The CVP before and 90 min after the induction of shock did not show significant difference between the 2 groups ( $P>0.05$ ). But 1 h after transfusion, the CVP of Cyp treated group rose obviously ( $P<0.01$ ), and recovered to normal more or less. (Tab 1).

**Death rate** In comparison with the control group (42%), the mortality 2 h after Cyp treated group (0%) was significant difference ( $\chi^2=4.042$ ,  $P<0.05$ ).

**Mesenteric microcirculation** As the blood was let out till MAP=5.3 kPa, the mesenteric vessels contracted. After 90 min, the blood flows in the arterioles, metarterioles, venules, and small veins were very slow, even stagnant. Aggregation of red blood cells, extravasation of plasma, and tissue edema gradually occurred. The capillaries in the region involved vanished from sight. After reinfused with the fluid and blood in the control group, the vascular diameters and blood flow velocity slightly increased, a few capillaries reopened, but aggregation of red blood cells and tissue edema were still seen under microscope. In comparison with the normal, it was not apparently improved. In the treated group, as the MAP raised, all arterioles, metarterioles, venules, and small veins dilated, the blood flow velocity obviously increased, the perfusion of tissue improved, the capillaries in the region involved reopened, and edema eliminated. One hour later, the microcirculation, on the whole, returned to normal.

## DISCUSSION

5-HT may cause the vessels contract, microcirculatory stagnation<sup>(5)</sup>, and enhancement of pulmonary pressure<sup>(6)</sup>. Furthermore,

Tab 1. MAP (kPa) and CVP (kPa) before and after shock and after Cyp treatment ( $10 \text{ mg} \cdot \text{kg}^{-1}$ ).  $n=12$ ,  $\bar{x} \pm s$ . \*  $P>0.05$ , \*\*  $P<0.01$  vs control group.

	Group	Before shock	After bleeding	After transfusion	1 h after transfusion	1 h after transfusion / normal(%)	Reduction 1 h after transfusion
MAP	Cyp	$11.74 \pm 1.93^*$		$9.15 \pm 1.65^*$	$9.65 \pm 1.60^{**}$	$82.60 \pm 1.70^{**}$	$2.18 \pm 1.86^{**}$
	Control	$12.44 \pm 1.14$		$8.45 \pm 1.53$	$6.37 \pm 2.63$	$51.80 \pm 2.86$	$6.06 \pm 2.90$
CVP	Cyp	$0.35 \pm 0.04^*$	$0.17 \pm 0.04^*$	$0.33 \pm 0.03^{**}$	$0.32 \pm 0.04^{**}$		
	Control	$0.34 \pm 0.05$	$0.20 \pm 0.03$	$0.26 \pm 0.03$	$0.25 \pm 0.04$		

$\beta$ -endorphin is implicated as a pathophysiologic factor in shock, and 5-HT is the possible mediator of their action<sup>(7)</sup>. Therefore, 5-HT antagonist was useful in shock therapy<sup>(8,9)</sup>. Histamine is another shockgenic factor.  $H_1$  receptor blockers had obvious protective effect in the hemorrhagic and intestinal ischemia shock rats<sup>(10)</sup>. After infusion of Cyp in this experiment, there were early transient drop of MAP and increase of pulse pressure, and widening of mesenteric vascular diameter, suggesting that the drug causes dilatation of vasculature via antagonizing  $S_2$  receptors at the smooth muscle, so the decline of MAP. As the microcirculation improved, the venous stagnation alleviated, the quantity of blood returned to the heart increased, and organ function recovered, MAP obviously rose and remained stable nearly at the level before the shock. At the same time, the respiratory frequency and amplitude were reduced, suggesting improvement of the respiratory function. The results proved that Cyp does have an anti-shock effect, giving an experimental basis for extending the clinical application of the drug.

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## 噻庚啉的抗休克作用

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**提要** 24只新西兰兔被随机分为治疗组和对照组。颈动脉放血至血压(MAP) 5.3 kPa (40 mm Hg)、维持 90 min, 复制晚期失血性休克模型。治疗组给予噻庚啉(Cyp) 10 mg · kg<sup>-1</sup>, 1 h后 MAP、中心静脉压(CVP)明显回升( $P < 0.01$ ), 肠系膜微循环改善, 2 h存活率相应提高( $P < 0.05$ )。结果表明 Cyp 具有良好的抗休克作用。

**关键词** 噻庚啉; 出血性休克; 血压; 微循环 抗休克作用