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Protective and anti-arrhythmic effects of dauricine and verapamil on acute myocardial infarction in anesthetized dogs

ZHU Jie-Quan, ZENG Fan-Dian, HU Chong-Jia
(Department of Clinical Pharmacology, Tongji Medical University, Hankou 430030, China)

ABSTRACT Dauricine (Dau) 5 mg · kg^{-1} and verapamil (Ver) 0.15 mg · kg^{-1} iv followed by infusions of 0.1 and 0.01 mg · kg^{-1} · min^{-1}, respectively, for 30 min, depressed the elevated coronary venous blood LDH and CPK after LAD occlusion. Dau produced antagonistic effects on acute myocardial ischmia-induced ventricular ectopic activities (VE) and ventricular tachycardia (VT). The incidences of VE and VT in Ver group and ventricular fibrillation (VF) in both groups tended to descend. The results suggested that Dau and Ver produced marked protective effects on myocardial infarction and antagonized the acute ischemic arrhythmia.

KEY WORDS dauricine; verapamil; myocardial infarction; lactate dehydrogenase; creatine kinase; anti-arrhythmia agents

Dauricine (Dau) relaxed the vascular-smooth muscles[1,2], depressed the myocardial contraction force[3], increased the coronary and myocardial blood flow[3], and reduced the myocardial infarct size in 24 h after acute coronary occlusion in rats[4]. We have confirmed that Dau inhibited the thromboxane A_2 (TXA_2) formation and platelet aggregation[5]. These effects of Dau might be related to its inhibition of calcium influx across cellular membrane. The present study was to assess the effects of Dau on the release of enzymes and K^+, and on the arrhythmia following experimental acute myocardial infarction in anesthetized dogs.

MATERIALS AND METHODS

Experiments were performed on 24 adult mongrel dogs of either sex weighing 12 ± *s* 2 kg. The dogs were anesthetized with iv sodium pentobarbital 30 mg · kg^{-1} and the respiration was artificially maintained by positive pressure ventilation with room air. The right femoral vein was cannulated for infusion of saline and drugs. The polygraph (SJ-61) was used to record and monitor lead II EKG. The left anterior descending coronary artery (LAD) was occluded just distal to the first diagonal branch by the two-stage occlusion procedure[6].

The blood samples were taken from the coronary vein before and 15, 30, 60, 120, 240 min after LAD occlusion and centrifuged for separating the serum. Lactate dehydrogenase (LDH) and creatine phosphate kinase (CPK) in serum were measured by spectrophotometer (751-G)[7,8] and K^+ concentration was measured by flame photometer (HG-3). The effects of drugs on arrhythmias induced by LAD occlusion were evaluated according to the procedure described by Ribeiro *et al*[9].

Dau, provided by the Faculty of Pharmacy of Tongji Medical University, was dissolved in distilled water. The pH was adjusted to about 6.7. Ver injection solution was made by Knoll AG, Germany.

The dogs were divided into 4 groups. Three groups received saline 1 ml · kg^{-1}, Dau 5 mg · kg^{-1}, and Ver 0.15 mg · kg^{-1}, respectively as a bolus injected into the right femoral vein 5 min before LAD occlusion, followed by infusions of saline 0.5 ml · kg^{-1}, Dau 0.1 mg · kg^{-1}, and Ver 0.01 mg · kg^{-1} · min^{-1}, respectively, for 30 min. In the fourth (sham ligation) group, LAD was not occluded during operation.

Group means were compared by *F* test

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and the incidences of arrhythmias were analyzed by exact probability test.

RESULTS

Effects of Dau and Ver on LDH and CPK release The coronary venous blood LDH level rose from 5 170 ± 840 IU · L^{-1} before infarction to 7 050 ± 840, 8 810 ± 1 250, 9 870 ± 1 030, 12 440 ± 2 720, and 13 420 ± 1 720 IU · L^{-1} at 15, 30, 60, 120, and 240 min respectively after infarction, while CPK activity rose from 43 ± 11 IU · ml^{-1} to 130 ± 32, 145 ± 47, 241 ± 76, 292 ± 87, and 322 ± 75 IU · ml^{-1}, respectively. Dau and Ver depressed the elevated coronary venous blood LDH and CPK at 60, 120, and 240 min after coronary occlusion ($P<0.01$) (Fig 1).

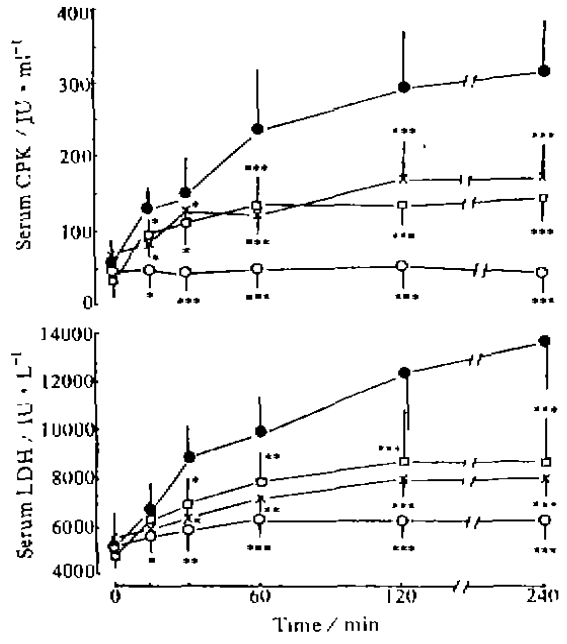

Fig 1. Effects of sham ligation (○, $n=4$), saline (●, $n=6$), dauricine (×, $n=5$), and verapamil (□, $n=5$) on release of CPK and LDH in coronary-ligated dogs. $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* saline.

Effect of Dau and Ver on ischemia-induced change in coronary venous blood K^+ concentration After LAD ligation, the coronary venous blood K^+ concentration increased markedly from control value 4.2 ± 0.8 to 9.1 ± 2.3 mmol · L^{-1} at 30 min after coronary occlusion in the saline group, from 4.4 ± 0.4 to 8.2 ± 1.3 mmol · L^{-1} in Dau group, and from 4.5 ± 0.5 to 7.8 ± 0.3 mmol · L^{-1} in Ver group.

Effects on arrhythmia induced by LAD occlusion During the LAD occlusion period, ventricular ectopic (VE) occurred in all of the 9 dogs (100%) in saline group, 3 of 6 (50%) in Dau group, 3 of 5 (60%) in Ver group, yet did not occur in sham occlusion group. The accumulated numbers of VE within 2 h after LAD occlusion was significantly lower in Dau and Ver groups than saline group. VT appeared in 5 of 9 dogs (55%) in saline group and 1 of 5 (20%) in ver group, but none in Dau group. Ventricular fibrillation (VF) was found in 4 of 9 dogs only in saline group at 2, 4, 10, and 20 min after LAD occlusion, among which 3 of them died and one recovered from VF by electric defibrillation. No VF occurred in Dau and Ver groups.

DISCUSSION

The present study showed that Dau, similar to Ver, inhibited the release of LDH and CPK following LAD acute occlusion. The results suggested that Dau produced significant protective effect on acute myocardial infarction in dogs, just as in rats[4].

Ischemia-induced intracellular calcium overload is one of the important factors leading to myocardial necrosis and enzyme release, which is susceptible to calcium antagonists[10]. The increases in TXA_2 formation and platelet aggregation were also involved in myocardial ischemia and infarction[11]. Dau could inhibit calcium influx across membrane and depress the contractility of myocardium and vascular smooth muscles. It is possible that Dau

exerted its protective effect on acute myocardial ischemia by inhibiting calcium influx across the myocardial membrane and by limiting the intracellular calcium overload, decreasing the myocardial O_2 consumption, increasing the coronary blood flow, improving the myocardial blood supply, and inhibiting the TXA_2 formation and platelet aggregation.

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蝙蝠葛碱和维拉帕米对麻醉犬急性心肌梗死的保护及抗心律失常作用

5.1

朱接全, 曾繁典, 胡崇家 R969.4
(同济医科大学临床药理研究室, 汉口 430030, 中国)

提要 蝙蝠葛碱(Dau) 5 mg · kg^{-1} 和维拉帕米(Ver) 0.15 mg · kg^{-1} iv, 随后分别以 0.1 mg 和 0.01 mg · kg^{-1} · min^{-1} 灌注 30 min, 可明显抑制 LAD 结扎后冠状静脉血中 LDH 和 CPK 升高, 对抗急性心肌缺血引起的 VE, VT. Ver 组 VE, VT 及两给药组 VF 趋于降低. 结果提示 Dau 和 Ver 对急性心肌梗死具有保护及抗心律失常作用.

关键词 蝙蝠葛碱; 维拉帕米; 心肌梗死; 乳酸脱氢酶; 肌酸激酶; 抗心律失常药

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Please contact Istituto di Farmacologia e Farmacognosia, Universitá Degli Studi di Trieste, via S Nicolò 14, 34121 Trieste, Italy.
Phone 040–368343. Fax 040–368808.