ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6): 513 - 516
http://www.simm.ac.cn; www.chinainfo.gov.cn/periodical

Dauricine suppressed CsCl-induced early afterdepolarizations and triggered arrhythmias in rabbit heart *in vivo*[1]

XIA Jing-Sheng[2], TU Hong[3], LI Zhen, ZENG Fan-Dian
(*Institute of Clinical Pharmacology, Tongji Medical University, Wuhan 430030*;
[3]*Department of Cardiology, Shenzhen Geneva Cross Hospital, Shenzhen 518029, China*)

KEY WORDS dauricine; action potentials; cesium; arrhythmia

ABSTRACT

AIM: To study the effect of dauricine on CsCl-induced early afterdepolarizations (EAD) and ventricular arrhythmias in rabbits. **METHODS**: Monophasic action potentials (MAP) of the left ventricle of the rabbit heart *in situ* were recorded with MAP recording technique. CsCl 1 - 2 mmol·kg^{-1} iv was used to induce EAD and ventricular arrhythmias. **RESULTS**: CsCl resulted in decrease of MAP amplitude (MAPA, $P < 0.05$) and prolongation of MAP duration at 90 % repolarization ($MAPD_{90}$, $P < 0.01$), QRS, and R-R duration ($P < 0.05$) compared with those before CsCl in the dauricine and control group. CsCl injection induced EAD that appeared within about 30 s and disappeared 5 - 15 min thereafter. EAD always preceded ventricular arrhythmias including ventricular premature beats and paroxysmal ventricular tachycardia. The EAD amplitude (EADA) in the dauricine group (26 % ± 9 % of MAPA) was smaller than that in the control group (52 % ± 5 % of MAPA, $P < 0.05$) and the incidence of arrhythmias in dauricine group (28 %) was lower than that in control group (80 %, $P < 0.05$). **CONCLUSION**: Dauricine exerted an antagonistic effect on EAD and suppressed triggered ventricular arrhythmias by decreasing EADA.

INTRODUCTION

Triggered activity resulting from early afterdepolarizations (EAD) has been proposed as one of the mechanisms responsible for ventricular arrhythmias. Cesium chloride (CsCl) has been widely used in the induction of EAD *in vitro* and *in vivo* to study the mechanisms of arrhythmias and anti-arrhythmic drugs. In previous studies we demonstrated that dauricine, a bisbenzylisoquinoline alkaloid derivative, exerted an antagonistic action to early afterdepolarizations induced by quinidine[1] and delayed afterdepolarizations by many inducers such as phenylephrine, isoprenaline, ouabain, and caffeine[2] in guinea pig papillary muscle. The effect of dauricine on EAD *in vivo* has not been reported. This study aimed to further study the effect of dauricine on EAD and ventricular arrhythmias induced by CsCl in rabbits.

MATERIALS AND METHODS

Drugs Dauricine was a white powder supplied by Dr PAN Xi-Ping (Division of Plant Chemistry of this Institute, M_r 624, mp 103 - 104 ℃, purity > 98 %). It was dissolved in normal saline to 0.5 g·L^{-1}, pH 6.5 - 6.8. CsCl was purchased from Sigma Co and dissolved in normal saline to 0.5 mol·L^{-1}.

Experimental procedure Rabbits of either sex weighing (2.3 ± *s* 0.4) kg, provided by the Experimental Animal Center of Tongji Medical University (Certificate numbers of rabbits and animal house: 19-025 and 19-019), were randomly divided into two groups: (1) dauricine 0.5 mg·kg^{-1}·min^{-1} iv for 24 min; (2) normal saline (NS) 1 mL·kg^{-1}·min^{-1} iv for 24 min. When monophasic action potentials (MAP) and ECG recordings were obtained after intravenous infusion of dauricine or NS, CsCl 1 - 2 mmol·kg^{-1} was administrated into the femoral vein over a 15 - 30 s period. Similar recordings were made after iv CsCl for at least 20 min.

[1] Project supported by the National Natural Science Foundation of China, No 39670834.
[2] Correspondence to Dr XIA Jing-Sheng. Phn 86-27-8369-2628. Fax 86-27-8362-2308. E-mail xiajs@hotmail.com
Received 1998-04-13 Accepted 1998-11-17

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

MAP recording Rabbits were anesthetized with sodium pentobarbital (36 mg·kg^{-1}). The femoral vein was cannulated for injection of drugs. After left sternotomy, the heart was exposed and suspended in pericardial cradle. A quadripolar contact electrode catheter (7F) for pacing and MAP recording (EP Technologies, Sunnyvale CA, USA) was introduced into the left ventricle through a tiny stab wound made in the free wall. The electrode tip was placed against the left ventricular anterior endocardium close to the apex. MAP signals were amplified by a high input impedance, MAP DC-coupled isolated, differential preamplifier (Model 300, EP Technologies)[3]. Together with surface ECG lead Ⅱ, MAP signals were simultaneously displayed on oscilloscope and printed out on 8 channel physiologic recorder (Model RM 6000, Nihon Kohden) at paper speeds of 25 – 100 mm·s^{-1}. The frequency response of the MAP recording system was DC to 5000 Hz.

Definitions and measurement (1) MAP amplitude (MAPA): the potential difference between the diastolic baseline and the crest of the plateau phase. (2) MAP duration at 90 % repolarization ($MAPD_{90}$): interval in seconds from the onset of local activation to the time of 90 % repolarization. (3) EAD: either delay in repolarization or true depolarizations occurring during phase 2 or 3 of the MAP. (4) EAD amplitude (EADA): the difference between phase 4 and the first deviation or the crest of EAD from the smooth repolarization was defined as the percent of MAPA (EADA/MAPA × 100 %). (5) EAD coupling interval (EADCI): the interval between phase 0 of the MAP and the peak or shoulder of the EAD that developed[4-6].

Data analysis Data were expressed as $\bar{x} \pm s$. Statistical comparisons of results were performed with t-test or chi-square test.

RESULTS

Effect of CsCl on MAPA, $MAPD_{90}$, QRS, and R-R duration Before intravenous injection of CsCl, MAPA decreased and $MAPD_{90}$, QRS duration prolonged in the dauricine group *vs* those in control group ($P < 0.05$). CsCl 1 – 2 mmol·kg^{-1} iv resulted in decrease of MAPA ($P < 0.05$) and prolongation of $MAPD_{90}$ ($P < 0.01$), QRS, and R-R duration ($P < 0.05$) compared with before iv CsCl in the dauricine and control group (Tab 1).

Tab 1. CsCl-induced changes of MAPA, $MAPD_{90}$, duration of QRS, and R-R of rabbit heart. $\bar{x} \pm s$. **[a]$P > 0.05$, [b]$P < 0.05$, [c]$P < 0.01$ *vs* control. [e]$P < 0.05$, [f]$P < 0.01$ *vs* before iv CsCl.**

	Group	n	Before	After
MAPA/mV	Control	5	22.7 ± 2.8	17.6 ± 3.2[e]
	Dau	7	17.5 ± 3.6[b]	13.8 ± 4.2[be]
$MAPD_{90}$/s	Control	5	0.18 ± 0.03	0.34 ± 0.04[f]
	Dau	7	0.23 ± 0.06[b]	0.34 ± 0.07[c]
QRS/ms	Control	5	51 ± 8	60 ± 20[e]
	Dau	7	69 ± 23[b]	80 ± 22[ae]
R-R/s	Control	5	0.28 ± 0.05	0.38 ± 0.06[e]
	Dau	7	0.33 ± 0.09[b]	0.45 ± 0.15[b]

Effect of dauricine on EAD and ventricular arrhythmias by CsCl All MAP showed a smooth repolarization with no sign of EAD and no ventricular arrhythmias were present on ECG of all rabbits before CsCl was injected (Fig 1A). CsCl injection induced EAD that appeared within about 30 s and disappeared 5 – 15 min thereafter. EAD always preceded ventricular arrhythmias including ventricular premature beats and paroxysmal ventricular tachicardia (Fig 1B). There was no significant difference of EAD incidence between dauricine and control group ($P > 0.05$). In contrast, the EADA in the dauricine group (26 % ± 9 % of MAPA) was smaller than that in the control group (52 % ± 5 % of MAPA, $P < 0.05$, Fig 1C) and the incidence of arrhythmias in the dauricine group (28 %) was lower than that in the control group (80 %, $P < 0.05$, Tab 2).

Tab 2. Effects of dauricine (0.5 g·L^{-1}·min^{-1} iv × 24 min) on EAD and triggered ventricular arrhythmias in the rabbit heart *in situ*. $\bar{x} \pm s$. **[a]$P > 0.05$, [b]$P < 0.05$ *vs* control.**

	n	EAD Incidence/%	EADCI/s	EADA/%	Triggered/%
Control	5	5/5 (100)	0.20 ± 0.04	52 ± 5	4/5 (80)
Dau	7	6/7 (86)[a]	0.20 ± 0.07[a]	26 ± 9[b]	2/7 (28)[b]

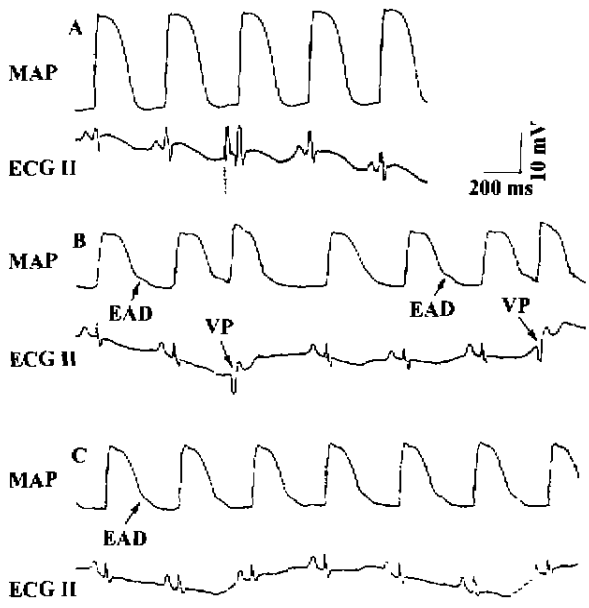

Fig 1. Effect of dauricine on early afterdepolarizations (EAD) and triggered ventricular arrhythmias induced by CsCl in rabbit heart. A) No EAD occurred before iv CsCl. $n = 5$ rabbits. B) CsCl 1 – 2 mmol·kg^{-1} iv-induced EAD and triggered ventricular premature (VP). $n = 7$ rabbits. C) Dauricine 12 mg·kg^{-1} iv pretreatment induced decrease of EAD amplitude and occurrence of triggered ventricular arrhythmias. $n = 7$ rabbits.

DISCUSSION

CsCl has been shown to depolarize the membrane potential and depress the plateau of the action potential[7]. It is primarily a blocker of the inward rectifying potassium current (I_{K1}) and prolongs repolarizaton leading to generation of EAD[8]. In this study, CsCl 1 – 2 mmol·kg^{-1} decreased MAPA and prolonged $MAPD_{90}$, QRS, and R-R duration. The EAD were induced within about 30 s after CsCl injection. Ventricular arrhythmias were always preceded by the development of EAD and occurred only when EAD attained a certain amplitude. This present results are in accordance with those of Takahashi N, *et al*[3] and Di Francisco[9] and suggest that the EAD were closely related to arrhythmias.

EAD may occur when an inward depolarizing current exceeds an outward repolarizing current during phase 2 or phase 3 of the cardiac action potential. Increase of the former or decrease of the latter should facilitate EAD to develop. It was suggested that the currents related to the induction of EAD were mainly slow inward calcium, sodium window current and repolarizing potassium currents. The present data demonstrated that dauricine decreased EADA and reduced the incidence of ventricular arrhythmias triggered by EAD. This may suggest that dauricine has an antagonistic effect on EAD and suppresses triggered ventricular arrhythmias by decreasing EADA. A recent study in guinea pig papillary muscles showed that dauricine could inhibit sodium and calcium currents[10]. This depressant effect of dauricine on EAD could be due to a decrease of the inward depolarizing currents.

ACKNOWLEDGMENTS Thank Prof JING Man-Wen for his encouragement and support to make this study possible and Ms HU Yan for her dedicated technical assistance.

REFERENCES

1 Guo DL, Xia JS, Gu SF, Zeng FD, Hu CJ. Effect of dauricine on early afterdepolarizations and triggered activity induced by quinidine in guinea pig papillary muscle. Chin J Pharmacol Toxicol 1998; 12: 253 – 5.

2 Wang ZX. Antagonisms of dauricine and daurisoline on arrhythmogenic delayed afterpolarization and triggered activity and their electrochemical mechanisms [PhD dissertation]. Wuhan: Tongji Med Univ; 1992.

3 Takahashi N, Ito M, Ishida S, Fujino T. Effects of vagal stimulation on cesium-induced early afterdepolarizations and ventricular arrhythmias in rabbits. Circulation 1992; 86: 1987 – 92.

4 Franz MR. Long-term recording of monophasic action potentials from human endocardium. Am J Cardiol 1983; 51: 1629 – 34.

5 Levine JH, Spear JF, Guarnieri T, Weisfeldt ML, de Langen CD, Becker LC, *et al*. Cesium chloride-induced long QT syndrome: demonstration of afterdepolarizations and triggered activity *in vivo*. Circulation 1985; 72: 1092 – 103.

6 Bailie DS, Inoue H, Kaseda S, Ben-David J, Zipes DP. Magnesium suppression of early afterdepolarizations and ventricular tachyarrhythmias induced by cesium in dogs. Circulation 1988; 77: 1395 – 402.

7 Isenberg G. Cardiac Purkinje fibers: cesium as a tool to block inward rectifying potassium currents. Pflügers Arch 1976; 365: 99 – 106.

8 Zeng J, Rudy Y. Early afterdepolarizations in cardiac myocytes: mechanism and rate dependence. Biophys J 1995; 68: 949 – 64.

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Jun; 20 (6)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

9 Di Francesco D. A new interpretation of the pace-maker current in calf Purkinje fibers.
J Physiol (Lond) 1981; 314: 359-76.
10 Guo DL. Use dependent effects of dauricine and daurisoline on action potential and antiarrhythmic mechanisms [PhD dissertation].
Wuhan: Tongji Med Univ; 1997.

蝙蝠葛碱抑制氯化铯诱发家兔在体心脏早后除极及心律失常[1]

夏敬生[2], 屠 洪[3], 李 真, 曾繁典 (同济医科大学临床药理研究所, 武汉 430030; [3]广东深圳红十字会医院心内科, 深圳 518029, 中国)

目的: 研究蝙蝠葛碱对氯化铯诱发家兔在体心脏早后除极及触发性心律失常的作用. **方法**: 采用单向动作电位记录技术记录家兔在体心脏单向动作电位, 用氯化铯诱发家兔心脏早后除极及触发性心律失常. **结果**: 静脉注射氯化铯 1-2 mmol·kg^{-1}后 MAPA 降低, $MAPD_{90}$, QRS 和 R-R 间期明显延长. 给氯化铯后 30 s 左右出现早后除极, 并由此触发室性早搏和室性心动过速. 蝙蝠葛碱降低早后除极幅度和心律失常发生率. 早后除极幅度对照组为52 % ± 5 %, 蝙蝠葛碱组为26 % ± 9 % ($P < 0.05$). 心律失常发生率对照组为80 %, 蝙蝠葛碱组为28 % ($P < 0.05$). **结论**: 蝙蝠葛碱具有抗氯化铯所致早后除极及触发性心律失常作用.

关键词 蝙蝠葛碱; 动作电位; 铯; 心律失常

(责任编辑 朱倩蓉)

《现代药理实验方法》出版

中国药理学会理事长、中国医学科学院药物研究所张均田教授主编的《现代药理实验方法》已由北京医科大学中国协和医科大学联合出版社于 1998 年 10 月出版, 全书 380 多万字, 分上下册, 29 篇、158 章, 并附有近千幅插图.

此书以介绍现代药理学的新方法和新技术为主旨, 融分子生物学、生物化学、生理学、细胞生物学、免疫学、毒理学、药物化学、计算机及现代仪器分析技术于一体, 按照不同类型(整体、离体、组织培养)、不同层次(整体、组织、细胞、亚细胞和分子水平)分章分节述说.

编者和作者是活跃在各专业领域里的有实践经验的科学工作者, 他们之中有老一辈科学家、年富力强的中年学者以及有才华的青年科学工作者和博士生. 美国、加拿大、澳大利亚、德国和瑞典的一些科学家和华裔学者亦欣然命笔, 加入了编著者的行列.

本书题材广泛, 内容新颖, 能够满足药理学及其他相关学科基础研究工作者的共同需要, 是药理学及其他学科科研人员、高等医药院校教师、高年级学生、硕士生、博士生的重要参考工具书.

本书定价每套 298 元. 欢迎读者购买.

联系地址: 100050 北京市 中国医学科学院药物研究所 新楼 3-27 室 屈志炜 电话: 010-6316-5181