

延胡索碱对家兔心电图的影响及其时、量效关系的观察

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内容提要 本文报告了麻醉家兔分别静注不同剂量的溶于水的延胡索生物碱(碱Ⅰ)和非水溶性延胡索碱(碱Ⅱ)的心电图变化。碱Ⅰ剂量超过2.10~4.20mg/kg后出现心率减慢、QTc明显延长、T波增宽。碱Ⅱ剂量超过14.0~28.0mg/kg时,出现P、QRS波增宽和P-R、QTc延长。实验显示碱Ⅰ与乙胺碘呋酮、碱Ⅱ与奎尼丁对心电图的影响大致相似。二药静注后心电图即刻出现变化,5分钟左右变化最显著,30~60分钟基本恢复。

延胡索 *Corydalis turtschaninovii* Bessfyanhussuo YH Chou et CC Hsü (*C. bulbosa* auct. non DC, *C. yanhusuo* WTWang) 采购自浙江省东阳县。该药经临床研究试用,发现具有抗心律失常作用^①。延胡索主要含多种生物碱,分为季胺和叔胺碱两大类,季胺类生物碱比较易溶于水,叔胺类则几不溶或难溶于水。延胡索总碱中的水溶性成分(简称碱Ⅰ)和水不溶性成分(简称碱Ⅱ)对动物实验性心律失常拮抗作用不同^②。本文旨在明确碱Ⅰ、碱Ⅱ注射液对家兔心电图的影响特点,观察给药剂量与心电图改变及其随时间变化的关系,初步探索药物的作用原理,为临床应用提供依据。

材料和方法

碱Ⅰ和碱Ⅱ注射液由中医研究院中药研究所制作,分别含水溶性延胡索碱2.6mg/ml和水不溶性延胡索碱17.4mg/ml;对照组用蒸馏水加入盐酸,分别调pH与碱Ⅰ、碱Ⅱ注射液一致。

健康灰色成年家兔56只,随机分为14组,体重

1.5~2.5kg,雌雄兼用。20%乌拉坦10mg/kg腹腔麻醉,以针形电极刺入四肢皮下,描记Ⅱ导心电图后,自耳缘静脉2分钟内分组注射完0.26~8.40mg/kg碱Ⅰ、7.0~56.0mg/kg碱Ⅱ和对照液,记录药后0.5、1.5、2.5、3.5、5、10、15分钟的心电图。碱Ⅰ4.2、8.4mg/kg组,碱Ⅱ28.0、56.0mg/kg组和对照组尚记录了其后0.5、1、2、4、6、8、12、24小时的心电图。描记电压1mv=20mm,纸速为50mm/s,处理资料时各减半校正。每段图测量5个心电图单位取均值,取P、QRS、T波的振幅、时间及P-R、Q-T间期和心率,据 $QTc = \frac{Q-T}{\sqrt{R-R}}$ 计算QTc值,以剂量组为单位给药前后、给药组和对照组进行统计比较。

结 果

一、碱Ⅰ对家兔心电图的影响

碱Ⅰ各组分别静注后,心电图T波增宽(圆顶式基底部增宽与ST段融合),心率减慢、QTc延长,P波、QRS波和P-R间期未见明显变化。上述心电图变化随剂量增加改变明显,见表1。

表1 家兔静注不同剂量碱Ⅰ的心电图改变

剂 量 (mg/kg)		家 兔 (只)	心 率 (次/m)		T波时间 (ms)		QTc (ms)	
			药 前	药 后	药 前	药 后	药 前	药 后
碱	0.26	4	261±25	245±25	51±14	59±19	194±8	199±7
	0.53	4	248±26	213±13	50±4	59±5	190±6	193±9
	1.05	4	251±19	245±19	64±9	80±6*	107±6	115±4
	2.10	4	219±14	203±21	59±20	91±15	202±6	243±16
	4.20	4	258±23	230±24*	77±4	112±12*	212±5	244±12
I	6.30	4	250±17	214±16**	61±9	90±9**	207±6	246±9*
	8.40	4	234±12	206±14*	76±6	116±6*	218±9	272±11***
对照液2ml/kg		4	265±12	273±10	76±2	76±2	204±2	207±2

与药前比较 * P<0.05, ** P<0.01, *** P<0.001

心电图改变与给药剂量基本呈平行关系,剂量越大,改变越明显。静脉后5分钟较药前心率减慢、QTc延长、T波增宽的百分率与给药剂量呈线性关系。 x 代表碱Ⅰ剂量(mg/kg), Y_1 、 Y_2 、 Y_3 分别代表心率减慢、QTc延长和T波增宽的百分率,其直线回归方程式为: $Y_1=1.647x+5.683$, $r=0.829$, $P<0.001$; $Y_2=2.576x+4.973$, $r=0.640$, $P<0.001$; $Y_3=6.645x+15.450$, $r=0.769$, $P<0.001$ 。其中心率减慢、T波增宽与剂量高度相关,QTc延长与剂量中度相关。

4.2、8.4mg/kg组和对照组24小时定时记录心电图,

给药组药后即刻出现心电图变化,最大改变在药后5分钟左右,此时两组分别较药前心率减慢12.0%、21.4%,QTc延长15.1%、24.8%,T波增宽45.5%、52.6%,此后上述改变逐渐减轻,40~60分钟基本恢复到药前水平。对照组注射后心电图未见明显改变。

二、碱Ⅱ对家兔心电图的影响

碱Ⅱ各剂量组给药后,心电图主要表现为P波和QRS波时间增宽、P-R间期和QTc延长。上述随剂量增加改变明显,见表2。

表2 家兔静注不同剂量碱Ⅱ的心电图改变 (ms)

剂 量 (mg/kg)		家 兔 (只)	P 波时间		QRS时间		P—R		QTc	
			药 前	药 后	药 前	药 后	药 前	药 后	药 前	药 后
碱	7.0	4	31±4	30±2	39±1	37±2	58±4	62±6	207±6	218±7
	14.0	4	21±3	21±3	36±1	37±1	49±3	55±1*	212±3	226±5*
	28.0	4	24±3	31±3*	34±2	37±2*	52±1	63±2*	201±5	225±4**
	42.0	4	26±5	34±5**	35±3	43±3***	51±6	62±5**	222±6	253±8**
Ⅱ	56.0	4	29±3	38±2**	32±2	40±2*	64±5	79±3*	205±9	231±7**
对照液2ml/kg		4	29±2	30±2	34±2	34±2	58±3	58±3	220±11	² 17±11

与药前比较 * $P<0.05$, ** $P<0.01$, *** $P<0.001$

药后5分钟较药前P、QRS波增宽、P-R和QTc延长的百分率与给药剂量呈线性关系。 x 代表碱Ⅱ剂量(mg/kg), Y_1 、 Y_2 、 Y_3 、 Y_4 分别代表较药前P、QRS波增宽、P-R、QTc延长的百分率,其直线回归方程式分别为: $Y_1=0.741x+(-)4.400$, $r=0.729$, $P<0.001$; $Y_2=0.537x+(-)5.422$, $r=0.894$, $P<0.001$; $Y_3=0.382x+5.914$, $r=0.592$, $P<0.01$; $Y_4=0.138x+5.852$, $r=0.448$, $P<0.05$ 。其中P、QRS波增宽与剂量高度相关,P-R和QTc延长中度相关。

28.0、56.0mg/kg组和对照组24小时定时记录心电图,给药组注射后即刻出现改变,5分钟左右改变最为显著,此时两组分别较药前P波增宽26.3%、31.0%,QRS增宽8.8%、25.0%,P-R延长21.2%、23.4%,QTc延长11.9%、12.7%。此后上述改变逐渐减轻,1小时左右基本恢复到药前水平。对照组给药前后无明显变化。

讨 论

本实验结果显示,碱Ⅰ、碱Ⅱ对心电图有明显不同的影响,其各自具有特征性的心电图波段变化。许多抗心律失常药物对心肌电生理的影响,可以在与心肌动作电位相应的心电图波段上表现出来⁽³⁾。奎尼丁

类药物能引起心电图R-R、P-R、QRS和QTc延长,这与碱Ⅱ对心电图的影响颇为相似;乙胺碘呋酮引起QTc延长、T波变形、心率减慢,与碱Ⅰ对心电图的影响大致相似。是否碱Ⅱ具有奎尼丁样作用,碱Ⅱ具有与乙胺碘呋酮相似的电生理作用及其异同尚待进一步研究。

心电图变化在静注给药后即刻出现,5分钟改变最显著,40~60分钟基本消失。在实验所用剂量范围,给药量与心电图变化基本成平行关系,这为临床用药的剂量和方法奠定了基础,并可望将心电图作为掌握药物药效、毒性的一个指标。

(致谢:碱Ⅰ、碱Ⅱ注射液由中国中医研究院中药研究所化学室、药厂提取制作;中国医学科学院基础医学研究所统计室戎振鹏同志核审统计数据)

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the treatment were observed. It was interesting to note that the patients with cervical radiculo-spondylosis revealed prolonged latent period of SEP and had a significant difference from that of normal control ($P < 0.001$). After manipulation, the neurologic symptoms and signs attenuated or disappeared gradually, and the latent period of SEP recovered to the normal range simultaneously.

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Ultrastructural Study of the Effects of *Bulbus Allii* and Some Other Drugs on *Staphylococcus Aureus*

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This paper reported the ultrastructural changes of *staphylococcus aureus* after the action of *Bulbus allii*, *Taraxacum mongolicum*, *Coptis chinensis* and Penicillinum G at minimal bactericidal concentration (MBC). The results showed that after the action of *Bulbus allii*, the cross wall of the bacterial cell became curved, appeared thick or thin, without consistency, its structure became blurred and masses of high electron density appeared in the cytoplasm, nucleoid stria were rough and tended to form aggregation. Using *Taraxacum mongolicum*, the cell became deformed, the internal structures disturbed, the cell disrupted, the cytoplasm leaked out and the cross wall broken down and blurred. Changes in the cytoplasm and nucleoid were similar to those with *Bulbus allii*. After the action of *Coptis chinensis* at MBC caused similar changes in the cross wall and cytoplasm as with *Bulbus allii*. After administration of penicillinum G, the bacterial cell wall became thickened. Some bacterial cells were enlarged, the cross wall became blunt and appeared umbilicus-like. Changes in the cytoplasm were the same as after action of *Bulbus allii*.

No conspicuous morphological and biochemical changes in *staphylococcus aureus* were found after the medication of these four drugs at minimal inhibitory concentration.

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Effects of Alkaloids of *Corydalis Yanhusuo* on ECG of Rabbits and Observation on Time and Dose Effect Relationship

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This paper reports the ECG changes by intravenous injection of A_1 (the water soluble component of alkaloids of *C. yanhusuo*) and A_{II} (the water insoluble component of alkaloids of *C. yanhusuo*) with different dosage on anesthetized rabbits respectively. Application of A_1 in 7 groups with various dosage (0.26~8.40 mg/kg), showed that the heart rate decreased and ECG changed with an obvious prolongation of QTc and widening of T wave when the dosage was over 2.10~4.20 mg/kg. Application of A_{II} in 5 groups (7.0~56.0 mg/kg) showed that widened P, QRS waves and prolonged P-R, QTc intervals appeared obviously when the dosage reached more than 14.0 mg/kg. These phenomena indicated that ECG changes of A_1 was similar to amiodarone and A_{II} was "quinidine-like".

It has been observed that application of both A_1 and A_{II} displayed ECG changes rapidly by intravenous administration. The maximum effect occurred about 5 minutes after injection. The ECG changes normalized within 30~60 minutes afterward.

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