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Comparison of anti-arrhythmic activities of valproic acid derivatives in animals

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ABSTRACT The anti-arrhythmic activities of valproic acid derivatives were compared in animal models. The ig LD_{50} of sodium valproate (SV), magnesium valproate (MV) and valpramide (Val) in mice were 904, 966 and 438 mg/kg, respectively.

The efficacies of SV, MV and Val against the arrhythmia induced by iv $BaCl_2$ in anesthetized rats at equitoxic doses were 5/10, 5/10 and 8/10 by ig, and 5/10 7/10 and 10/10 by ip respectively. When the doses of ouabain necessary to induce arrhythmia in anesthetized guinea pigs were increased, the electrical ventricular fibrillation thresholds in anesthetized rabbits were raised and the functional refractory period of isolated guinea pig left atria was prolonged, the effects of MV were all stronger than those of SV.

The anti-arrhythmic activities of magnesium sulfate were weaker than that of SV and MV.

KEY WORDS valproate; anti-arrhythmia agents; magnesium sulfate; pharmacodynamics

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Evaluation of anti-arrhythmic potency of naltrexone in isolated ischaemic rat heart

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ABSTRACT The anti-arrhythmic properties of naltrexone were evaluated by an anti-arrhythmic screening test using the isolated ischaemic perfused rat heart preparation. The maximal anti-arrhythmic effect of naltrexone was attained 60 min after its administration and the potency based on cardiac anti-arrhythmic protection $(CAP)_{50}$ was 750 nmol/heart with 95% confidence limits of 674-836 nmol/heart. The time required to reach the maximal response and the anti-arrhythmic potency were much longer than and comparable to that of naloxone, respectively.

KEY WORDS naltrexone; naloxone; isolated heart; myocardial ischemia; anti-arrhythmia agents

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There is substantial evidence suggesting that endogenous opioid peptides may be involved in cardiac arrhythmogenesis[1]. It is suggested therefore that opiate antagonists may be used as anti-arrhythmic agents. Naloxone, being the first pure opiate antagonist and most commonly used, was naturally the first one to be considered. Its anti-arrhythmic potency was determined with a screening test using the isolated ischaemic perfused rat heart preparation developed by us[2]. It was found to be comparable to those of the prototype anti-arrhythmic agents, namely, lidocaine, quinidine and propranolol[3]. However, naloxone is short-acting with a $t_{\frac{1}{2}}$ in human of about 1 h[4] and is easily degraded when administered orally. Naltrexone, another pure opiate antagonist with a much longer $t_{\frac{1}{2}}$ of 3.9-10.3 h, is more resistant to enzymes in the liver and is twice more potent than naloxone in stopping the development of heroine dependence in humans[5]. It is therefore of interest to determine the anti-arrhythmic potency of naltrexone and compare it with that of naloxone.

MATERIALS AND METHODS

The screening test using the Langendorff techniques in the isolated rat heart preparation described previously by us[2] was employed. Female Sprague-Dawley rats of 210-230 g were used. The rat was decapitated and the heart mounted within 3 min. The heart was perfused with Krebs-Ringer solution at pH 7.4. The perfusion pressure and rate were about 13.3 kPa (10 mm Hg) and 6-8 ml/min, respectively. The heart was kept at 31-32°C. Electrocardiagrams were monitored throughout the experiment with a positive electrode hooked at the apex of the heart and a negative electrode at the aorta.

Immediately after mounting, perfusion was stopped for 10 min followed by reperfusion. Previous studies have shown that ventricular fibrillation (VF) usually occurred 2-15 min after reperfusion[6]. Naltrexone (DuPont) dissolved in Krebs-Ringer solution was injected via an aorta cannula within 1 min after VF had occurred. The volume and rate of injection were 20 μl and 1 min, respectively. In the control group 20 μl of Krebs-Ringer solution was injected. The doses of naltrexone were 529, 1587, 3175 and 4762 nmol/heart.

We have also employed the same method in evaluation of the anti-arrhythmic potency as described previosuly[2]. It was considered to have cardiac anti-arrhythmic protection (CAP) if VF was converted into sinus rhythm after drug administration. The time course of changes of CAP of the naltrexone at different doses were analysed and the times of maximal CAP determined. It was 60 min after medication (see Result). A regression line showing the relationship between maximal CAP and doses was also determined by the least square fit analysis with each dose on regression point representing data from 10 hearts.

RESULTS

Figure 1 shows the time course of

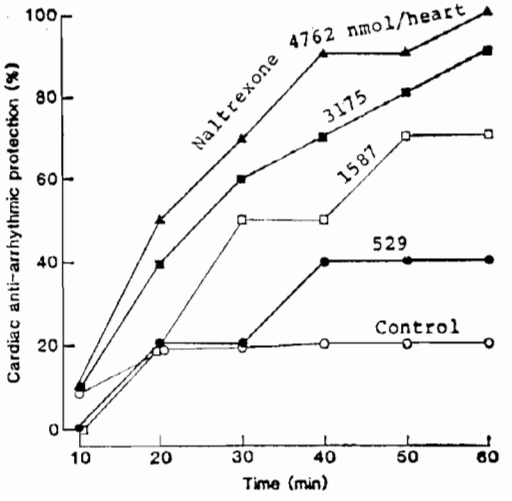

Fig 1. Time course of changes of conversion of ventricular fibrillation to sinus rhythm after administration of naltrexone to the isolated heart. n = 10 rat hearts for each dose.

changes of CAP of naltrexone at different doses. The CAP increased with time and reached a plateau at 60 min after administration of the drug. The response at 60 min was considered as the maximal CAP and used later in the analysis of dose-response relationship.

Figure 2 shows the dose-response (maximal CAP) relationship. The maximal CAP of naltrexone at a dose 4762 nmol/heart was 100%. The CAP_{50} with 95% confidence limits was 750 (674-836) nmol/heart.

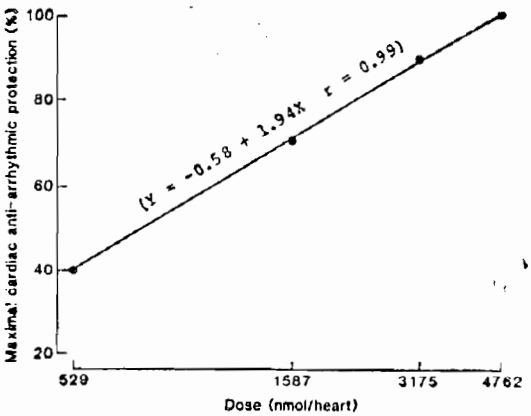

Fig 2. The dose-maximal cardiac anti-arrhythmic protection relationship for naltrexone. n = 10 rat hearts for each dose.

DISCUSSION

The study on the time course of changes of CAP showed that the maximal CAP of naltrexone was attained 60 min after its administration(Fig 1),whereas the maximal response to naloxone was attained 25 min after its administration[3]. The results suggest that naltrexone requires a longer time before it produces its maximal effects. In addition to the difference in duration of action bioavailability and resistance to digestion, this is another difference between naltrexone and naloxone and is important when considering them for use as anti-arrhythmic agents.

In this study, the anti-arrhythmic potency of naltrexone based on the CAP_{50} values was found to be comparable to that of naloxone of which, the CAP_{50} was 818 nmol/heart with 95% confidence limits 646-985 nmol/heart[3]. With receptor binding studies using rat brain membranes the affinity of naltrexone to μ and δ receptors were found to be much greater than that of naloxone whereas the affinity to κ sites of both opiate antagonists were similar[7]. In the guinea pig ileum naltrexone is 3.5 – 5 times more potent than naloxone in antagonizing morphine, a μ-agonist, but they are equipotent in antagonizing ethylketazocine, a κ-agonist[8]. The similar anti-arrhythmic potency of these two antagonists suggests that their anti-arrhythmic action may be due mainly to the occupation of κ receptors.

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纳曲酮对离体缺血大鼠心脏抗心律失常效能的评估

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提要 用离体缺血-再灌流大鼠心脏评估纳曲酮抗心律失常作用的特点。结果显示，纳曲酮的最大抗心律失常于给药后 60 min 出现，半数最大有效剂量(CAP_{50})为 750 nmol/心。纳曲酮抗心律失常最大作用出现时间较纳洛酮迟，而其抗心律失常作用则与纳洛酮相近。

关键词 纳曲酮；纳洛酮；离体心脏；心肌缺血；抗心律失常药

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间尼索地平与尼索地平对麻醉犬的心血管效应

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提要 间尼索地平(*m*-Nis)3 μg/kg iv 降低麻醉犬 SBP 及 HR 弱于等剂量尼索地平(Nis)，两药 1 及 3 μg/kg 降低 DBP 相近。*m*-Nis 3 μg/kg 降低 $IMVO_2$ 与等剂量 Nis 相似；*m*-Nis 1 及 3 μg/kg 增加 ABF，Nis 则无明显影响；*m*-Nis 1 μg/kg 降低 TPR 较等剂量 Nis 强，1 及 3 μg/kg 提高 CI 较 Nis 显著。*m*-Nis 以上剂量降低 VAR 较 Nis 强，降低 CAR 及 FAR 与 Nis 相近。

关键词 间尼索地平；尼索地平；血液动力学；血管阻力；冠状血管；椎动脉；股动脉；肾动脉

1986年6月26日收稿 1987年4月9日接受

尼索地平(nisoldipine, Nis)为近年合成的二氢吡啶类钙拮抗剂，其特点为主要抑制血管平滑肌；Nis 扩张冠脉、增加冠状窦血氧含量比硝苯啶(nifedipine, Nif)强 3-10 倍[1]。Nis 减轻心脏后负荷，又有强大的扩冠作用。可望成为防治缺血性心脏病的有效药物[2]。但 Nis 对光极敏感，可迅速分解灭活；我院药学系有机化学教研室袁风燕等首创合成其同类药物间尼索地平(*m*-nisoldipine, *m*-Nis)，在阳光直射下不起变化，原料价廉易得，合成工艺较简