

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

LIU Xiao-Lui, MOK Chi-Pui, LEE Ying-Siu, WONG Tak-Ming¹

(Department of Physiology, University of Hong Kong, Hong Kong)

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

Received 1987 Jun 11 Accepted 1987 Sep 4

¹Author for correspondence

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 $t_{1/2}$ in human of about 1 h⁽⁴⁾ and is easily degraded when administered orally. Naltrexone, another pure opiate antagonist with a much longer $t_{1/2}$ 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. Electrocardiograms 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 reper-

fusion. 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 μ l and 1 min, respectively. In the control group 20 μ l 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 previously⁽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

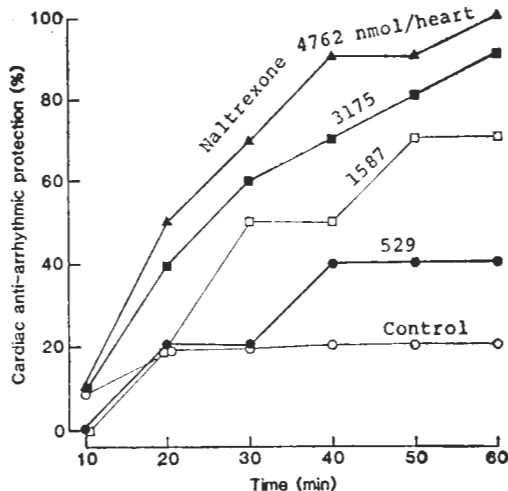


Fig 1. Time course of changes of conversion of ventricular fibrillation to sinus rhythm after administration of naltrexone to the isolated heart, $n = 10$ rat hearts for each dose,

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 CAP₅₀ with 95% confidence limits was 750 (674-836) nmol/heart.

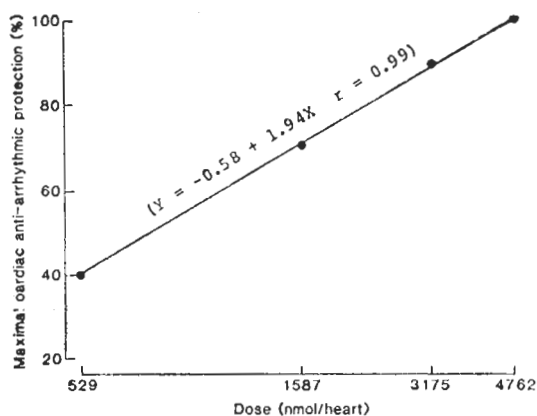


Fig 2. The dose-maximal cardiac anti-arrhythmic protection relationship for naltrexone. $n = 10$ rat hearts for each dose.

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 CAP₅₀ values was found to be comparable to that of naloxone of which, the CAP₅₀ 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.

ACKNOWLEDGMENTS We would like to thank Dr C L Wong for helpful discussions, Dr X D Huang for advice on the Chinese abstract, Mrs Teresa Yuen for typing the manuscript and Mr Steven Lam of the Medical Illustration Unit of the University of Hong Kong for the drawings. The study was supported by a Hong Kong University Grant and the Wing Lung Bank Research Fund. Naltrexone was generously supplied by DuPont Pharmaceutical Co.

REFERENCE

- 1 Wong T M, Lee AYS. Chronic morphine treatment reduces the incidence of ventricular arrhythmias in the isolated rat heart induced by dynorphin₁₋₁₃ or myocardial ischaemia and reperfusion. *Neurosci Lett* 1987; 77 : 61
- 2 Lee AYS, Zhan CY, Mok CP, Wong TM. A cardiac antiarrhythmic screening test using the isolated ischaemic perfused rat heart preparation. *Arch Int Pharmacodyn Ther* 1985; 277 : 217
- 3 Lee AYS, Wong TM. Antiarrhythmic potency of naloxone determined by a screening test using the isolated ischaemic perfused rat heart preparation. *Ibid* 1987; 286 : 212
- 4 Ngai SH, Berkowitz BA, Yang JC, Hempstead J, Spector S. Pharmacokinetics of naloxone in

- rats and in man: basis for its potency and short duration of action. *Anesthesiology* 1976; 44 : 398
- 5 Crabtree BL. Review of naltrexone, a longacting opiate antagonist. *Clin Pharmacol* 1984; 3:273
- 6 Zhan ZY, Lee AYS, Wong TM. Naloxone blocks the cardiac effects of myocardial ischaemia and reperfusion in the rat isolated heart. *Clin Exp Pharmacol Physiol* 1985; 12 : 373
- 7 Wood PL, Charleson SE, Lane D, Hudgin RL. Multiple opiate receptors: differential binding of μ , κ and δ agonists. *Neuropharmacology* 1981; 20 : 1215
- 8 Takemori AE, Portoghese PS. Comparative antagonism by naltrexone and naloxone of μ , κ and δ agonists. *Eur J Pharmacol* 1984; 104 : 101

* * * * *

中国药理学报 1988年1月; 9(1): 40-43

纳曲酮对离体缺血大鼠心脏抗心律失常效能的评估

刘晓雷、莫志培、李应绍、黄德明 (香港大学生理系, 香港)

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(CAP₅₀)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

* * * * *