Original Article

Effects of dezocine, morphine and nalbuphine on electropain threshold, temperature pain threshold and cardiac function in rats with myocardial ischemia

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Background: Myocardial ischemia (MI) could cause many complications, such as arrhythmia, ischemic cardiomyopathy, which could lead to angina and myocardial infarction. The clinical efficacy of dezocine, morphine and nalbuphine are becoming dominated in China market. This aim of this study was to investigate the effects of dezocine, morphine and nalbuphine on electrical pain threshold, temperature pain threshold and cardiac function in rats with MI.

Methods: A rat model of MI was established by ligating the coronary artery. Rats in the model group were injected with dezocine, morphine, nalbuphine and 0.9% normal saline. The effects of the three analgesics on MI rats were evaluated by comparing the electrical pain threshold, temperature pain threshold, and cardiac function index.

Results: The electrocardiogram revealed that the model of MI was successful. The results of the electrical pain threshold and temperature pain threshold tests revealed that nalbuphine was the most sensitive after medication, followed by dezocine, and the sensitivity of morphine was the lowest. These three drugs reached its peak at two hours after administration. The analgesic effect of dezocine on electrical stimulation was the best, while nalbuphine had the best effect on temperature. The efficacy of dezocine decreased with time, while morphine basically failed at four hours after administration. The peak time of these three kinds of analgesics was selected to detect the cardiac function index in each group. Morphine had the least influence on the cardiac function index of rats, followed by nalbuphine and dezocine.

Conclusions: These results show that the analgesic effect of nalbuphine had the earliest and best effect with the longest duration on temperature, and had less influence and higher safety in the cardiac function test of MI rats. Hence, nalbuphine is a relatively good analgesic for MI patients. The present study provides a database for the selection of analgesics in patients with MI.

Keywords: Dezocine; morphine; nalbuphine; electric pain threshold; temperature pain threshold; cardiac function

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Introduction

Myocardial ischemia (MI) is led by the unbalance between myocardial oxygen supply and myocardial oxygen requirements. Generally, angina is a common complication of MI. Increasing attention has been given to its clinical significance because sudden cardiac death would be caused by the disorder (1).

Several studies have been reported to illustrate difference of pain thresholds between on some pain tests in silent MI and symptomatic MI (2,3). However, few was to be reported about whether the different analgesic could have various influence to pain threshold. Analgesics are a large and diverse group of drugs that selectively inhibit and relieve various kinds of pain, which exact great importance on the postoperative recovery of patients and effect of treatment (4). They are potentially useful for one or more painful conditions by interacting with specific receptors of the central or peripheral nervous system (5). The main analgesics used in outpatient surgery or the treatment of moderate to severe pain are dezocine, morphine and nalbuphine. Anesthetic agents may differentially modulate pain perception (6). Particularly, it has been declared that morphine is a widely used opioid for treatment of moderate to severe pain (7).

Therefore, in the present study, the MI model was established by ligating the coronary arteries of rats. We applied the animal models that combine disease and syndrome, an important tool for pharmacodynamic evaluations, to investigated the effects of dezocine, morphine and nalbuphine on the electrical pain threshold (8), temperature pain threshold and cardiac function were investigated, providing a theoretical basis for the selection of safer and more effective analgesic drugs for patients with MI. We present the following article in accordance with the ARRIVE reporting checklist (available at http://dx.doi.org/10.21037/apm-19-460).

Methods

Experiment model

Experiments [(Healthy male Sprague-Dawley (SD) rats (SPF grade, 10–12 weeks old, and 250–300 g each)] were performed under a project license [license number: SCXK (Jun 2018-004)] granted by Tianjin Second Animal Experimental Center and was approved by institutional of Tianjin Second Animal Experimental Center [SCXK (Jun 2018-004)]. These rats were raised in a professional room with free drinking water and eating food. Room temperature was maintained at approximately 26 ℃ with a humidity of 40–70%, light was provided for 12 hours a day, and the room was well-ventilated.

Reagents and instruments

Main reagent

Ulatan (ethyl carbamate, analytical pure) was purchased from Sigma. The penicillin sodium injection was purchased from North China Pharmaceutical Co., Ltd. The dezocine injection (1 mL:5 mg) was purchased from Yangzijiang Pharmaceutical Co., Ltd. The sodium chloride injection (0.9%) was purchased from Hebei Siyao Group Co., Ltd. The morphine hydrochloride injection (0.5 mL:5 mg) and nalbuphine injection (1 mL:10 mg) were purchased from Hubei Yichang Renfu Pharmaceutical Group.

Main instrument

Electrocardiogram machine, PX9300, Futian, Japan; Neural stimulator, Stimuplex BL-410; Constant temperature water bath, Tianjin Huaxing Scientific Instrument Factory, TBS-5; Ultrasonic cardiograph, Siemens ACUSON Sequoia type 512 (8 mHZ probe); Refrigerator, Haier Co., Ltd.; Electronic balance, Mettler Toledo Instrument Co. Ltd.

Experimental methods

MI modeling

All rats were examined by electrocardiogram before the operation, and the T wave, S-T segment abnormal changes, or abnormal heart rhythms were discarded. Forty rats were randomly selected as the MI group. Then, 20% of urethane (dose: 5 mL/kg) was intraperitoneally injected for anesthesia. The thoracotomy was performed under sterile conditions, and the heart was exposed between the third and fourth ribs. After the operation, the electrocardiogram machine (rated voltage, 10 mm/mv; paper speed, 25 cm/s) was connected to record the changes of the electrocardiogram at different time points. The success of MI modeling was defined as achieving one of the following two conditions: (I) T wave towering and more than half of the R wave; (II) T wave towering and S-T segment displacement. Each rat was intramuscularly injected with 40,000 U/d of penicillin to prevent postoperative infection.

Grouping and administration

The purchased injections of dezocine, morphine and

nalbuphine were prepared into a single dose of 0.5 mL of intravenous injection containing a 5-mg drug dose, and was intraperitoneally injected to these rats. Rats in the MI group were randomly divided into four subgroups, with 10 rats in each group: Mid group, a 2.5-mg/kg injection dose was given at 30 minutes after surgery; Mim group, an injection dose of 2.5 mg/kg of morphine was given at 30 minutes after surgery; Min group, an injection dose of 2.5 mg/kg of nalbuphine was given at 30 minutes after surgery; MI group, the same volume of 0.9% normal saline was injected at 30 minutes after surgery.

Measurement of pain threshold by electrical stimulation

Degreasing was carried out at 1.5–2.0 cm away from the rat tail tip, and the negative electrode of the nerve stimulator was connected to the degreasing site. Then, the positive electrode was connected and fixed at the root of the rat tail, and a 10% KCl solution was added to the junction to increase the electrical conductivity. Percutaneous electrical stimulation (2 Hz, 1 ms) was given to the nerve stimulator to observe the current magnitude, namely, the electrical stimulation tail rejection threshold (mA), which caused the tail rejection of these rats. The interval of the electrical stimulation was five minutes, and the values of five consecutive measurements were taken as the mean value of three measurements. The measurement was immediately conducted after administration, and at 1, 2, 3 and 4 hours, respectively. The percentage change in the tail rejection threshold. by electrical stimulation = (The tail rejection threshold by electrical stimulation after administration – the tail rejection threshold by electrical stimulation before administration)/the tail rejection threshold by electrical stimulation before administration ×100%.

Temperature pain threshold measurement

The water bath temperature was set at a constant temperature of 55 ℃, immerse the area less than 1/3 of the end of the rat tail in the sink, and the time interval from immersion to the appearance of a spin was recorded, namely, the temperature stimulation spin threshold(s). The values of five consecutive measurements were taken as the mean values of three measurements. The percentage change in tail rejection threshold of temperature stimulation = (the tail rejection threshold of temperature stimulation after administration – the tail rejection threshold of temperature stimulation before administration)/the tail rejection threshold of temperature stimulation before administration ×100%. The temperature and pain thresholds were immediately measured at 1, 2, 3 and 4 hours after administration.

Cardiac function index measurement

For both the MI and control groups, at two hours after treatment, two-dimensional Doppler ultrasound cardiography was performed to record the left ventricular systolic and diastolic motion curve, and the left ventricular end-systolic diameter and end-diastolic diameter and respiration rate (RR) interphase, and calculate the heart rate (HR), ejection fraction (EF), cardiac output (CO) and isovolumetric diastolic volume (IRT). CO = Aortic orifice area × systolic aortic velocity × time × HR. Rats were anesthetized with 20% urethane, mean arterial pressure (MAP) was measured, and the hearts of these rats were extracted and weighed to calculate the relative heart weight.

Statistical analysis

All experimental data were expressed as "mean ± standard deviation" ($\bar{x} \pm SD$). SPSS 18.5 statistical software was used for data processing, one-way ANOVA was used for inter-group comparisons, and the LSD (least significant difference) method was used for pairwise comparisons. $P<0.05$ was considered statistically significant.

Results

Electrical stimulation rejection threshold comparison

The electropain threshold values before and after administration are presented in *Table 1*. The response to electrical stimulation at each time point of MI (MI without treatment) was the lowest in the same time period, when compared to the other groups, and the peak was observed in this group at two hours after administration.

The change in the curve for the tail rejection threshold of electrical stimulation is presented in *Figure 1*. The higher the curve value was, the more the pain sense decreased (the threshold value increases). There was no significant difference in the MI group at each time point ($P>0.05$). Nalbuphine has the highest sensitivity, followed by dezocine and morphine. At one hour after administration, this gradually increased with morphine, but remained lower with dezocine and nalbuphine. At two hours after administration, all three drugs reached its peak. The difference between morphine and nalbuphine was not significant, while the decrease in pain with dezocine was the highest. After three hours of administration, the effect of nalbuphine decreased

Table 1 Comparison of electric pain threshold before and after administration (mA, n=10, $\bar{x} \pm s$)

Group	Before dosing	Zero hours after administration (immediately)	End of first hours after administration	End of second hours after administration	End of third hours after administration	End of fourth hours after administration
Mi	0.223±0.034	0.211±0.021	0.309±0.019	0.331±0.016	0.287±0.034	0.324±0.023
Mid	0.241±0.033	0.351±0.048	0.872±0.035	1.345±0.034	0.698±0.021	0.388±0.047
Mim	0.211±0.054	0.283±0.023	0.678±0.025	1.121±0.046	0.488±0.038	0.216±0.038
Min	0.252±0.032	0.456±0.054	0.963±0.046	1.327±0.054	1.005±0.042	0.873±0.056

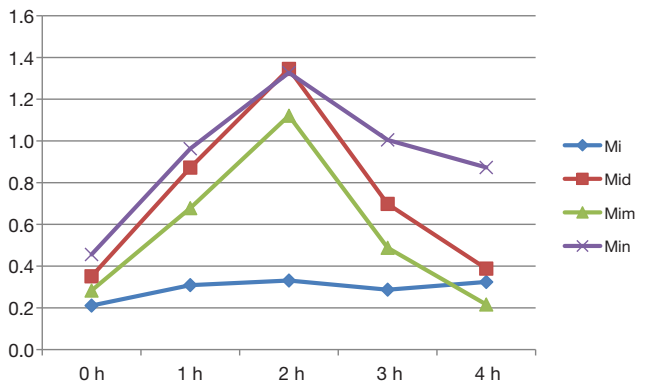

Figure 1 Change curve of tail rejection threshold in electrical stimulation.

the slowest. That is the effect lasted for a long period of time. The effect of dezocine also decreased with time, while the effect of morphine basically diminished at four hours after administration.

Comparison of temperature-stimulated tail rejection thresholds

The temperature pain threshold value before and after administration is presented in *Table 2*. The temperature stimulation response corresponding to each time point of MI was the lowest at the same time period, when compared to the other groups, and the peak value appeared in all groups at two hours after administration. *Figure 2* shows the variation curve for the tail rejection threshold under temperature stimulation. There was no significant difference between the MI group and the other groups at each time point (P>0.05). Nalbuphine had the highest sensitivity, followed by dezocine and morphine. At one hour after administration, the effect of morphine gradually increased, but this was still lower than that of dezocine and nalbuphine. There was no significant difference between dezocine and nalbuphine. At two hours after administration, all three drugs reached the peak value, and ranked in order from high to low, as follows: nalbuphine, dezocine and morphine. After three hours of administration, the effect of nalbuphine lasted for a long time and decreased the slowest. The effect of dezocine and morphine decreased with time, and the decrease trend of morphine was more significant.

Comparison of cardiac function indexes in rats

According to the above results for the electrical pain threshold and temperature pain threshold, the cardiac function indexes of each group of rats were measured at the peak of efficacy, that is, at two hours after administration. The HR, EF, CO, IRT and MAP results are presented in *Table 3*.

The HR comparison revealed that the Mid group had the fastest HR, while the Mim and Min groups had no significant difference, when compared to the MI group (P>0.05). EF was the lowest in the Mim and Mid groups. When compared with the MI group, there was no significant difference in CO between the Mim and Min groups (P>0.05), and the Mid group had the lowest output. IRT increased most significantly in the Min group, but no significant difference was found between the Mim group and MI group. For the MAP comparison, the Mid group presented with the most significant decrease, while the Mim and MI groups had no significant difference.

The hearts of rats in each group were dissected and weighed, and the results for the calculated the heart weight to body weight ratio are presented in *Table 4*. The weight gain in the Mid group significantly increased up to (630.9, 52.3) mg/100 g, but there was no significant difference between the Mim group and MI group.

Discussion

An animal model that combines disease and syndrome is

Table 2 Comparison of temperature and pain threshold before and after administration (s, n=10, $\overline{x} \pm s$)

Group	Before dosing	Zero hours after administration (immediately)	End of first hours after administration	End of second hours after administration	End of third hours after administration	End of fourth hours after administration
Mi	1.33±0.12	2.13±0.21	2.56±0.19	2.78±0.36	2.48±0.34	2.71±0.24
Mid	1.45±0.23	3.51±0.39	7.65±0.28	9.35±0.47	5.89±0.26	3.45±0.67
Mim	1.48±0.45	2.93±0.33	6.56±0.24	8.96±0.54	4.88±0.40	2.45±0.36
Min	1.67±0.48	4.56±0.29	8.93±0.35	11.57±0.46	9.58±0.37	8.73±0.39

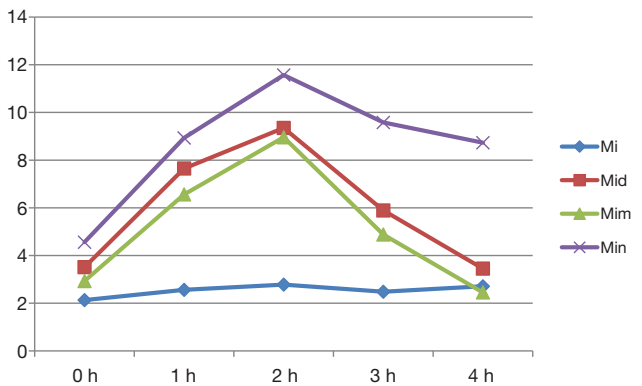

Figure 2 Temperature stimulated tail rejection threshold change curve.

an important method to explore the mechanism of disease occurrence and search for effective treatment methods. The advantages are as follows: (I) on the basis of the disease model, it has good reliability, stability and single factor; (II) it can introduce the time for model construction, and better reflect the law of disease development; (III) it is both macro and micro, and is practical and operational; (IV) it has more restrictions, and many uncertain factors clearer. The disadvantage is that there are great differences between animals and human beings in physiology and biochemistry, which needs to be verified by multiple parties before this can be applied in clinical practice. In the present study, the MI model was established by ligating the coronary artery. In the experiment, the measurement of cardiac function in the MI group confirmed that all indexes in the model group were significantly lower than those in the normal group. Some literatures have shown that severe MI can be induced as long as the infarct area is more than 20% (9,10). However, the disadvantage of this method is that the operation is difficult, and the postoperative mortality can reach more than 50%, which requires skilled operators (11).

Analgesics mainly act on the central or peripheral nervous system, selectively inhibits, and relieves all kinds of pain caused by tissue damage or potential damage, reduces the tension and anxiety caused by pain, and helps patients have a good rest, activity, and diet (12). Opioids have been commonly used as analgesics, but most of these are addictive, and have adverse reactions, such as respiratory depression (13). Therefore, in terms of drug selection, and in addition to its quick effects and good effects, these should also be safe.

Dezocine is a novel opioid receptor-antagonistic analgesic, which has been mainly applied as postoperative, visceral, and carcinogenic analgesics (14-16). In general, the peak value can reach within 10–90 minutes after intramuscular or intravenous injection, with an average terminal half-life of 2.4 hours (17,18). Its advantages mainly include the following: (I) The analgesic effect was similar to or slightly higher than that of morphine, but there were fewer mental dependence and related adverse reactions; (II) it has a capping effect on respiratory depression and so on; (III) it is a receptor agonist or receptor antagonist, and is less addictive (19). The common side effects include nausea, vomiting, sedation, giddiness, anorexia, disorientation, psychedelic, perspiration, and tachycardias (20). So coronary heart disease patients should take it with caution. The most common symptoms of MI were angina pectoris, presenting as paroxysmal and compressive pain in the front of the chest, accompanied by palpitations, shortness of breath, dyspnea, and other symptoms, which were mainly associated with strenuous exercise, mood swings and acute circulatory failure. In the present study, dezocine peaks in 2 hours, and the analgesic effect of electrical stimulation was better. However, for the rat HR, EF, CO, IRT and MAP, and relative heart weight was the most significant. Hence, analgesics should be chosen carefully for safety.

Morphine is a form of opioid drug morphine hydrochloride, a derivative of morphine, is a kind of anesthetic that can relieve acute pain in clinic, and it has a strong analgesic effect (21). It is also used for angina pectoris caused by myocardial infarction.

Table 3 Values of HR, EF, CO, IRT and MAP in each group

Group	HR (Times/min)	EF (%)	CO (L/min)	IRT/RR	MAP (mm Hg)
Mi	441.5±42.8	52.6±8.76	0.066±0.016	0.154±0.034	95.3±15.7
Mid	460.4±38.9	39.6±5.96	0.052±0.034	0.168±0.045	85.6±14.5
Mim	440.3±78.9	51.3±1.34	0.063±0.060	0.160±0.089	92.5±13.9
Min	432.1±35.5	48.8±3.21	0.060±0.040	0.174±0.018	90.4±11.3

HR, heart rate; EF, ejection fraction; CO, cardiac output; IRT, isovolumetric diastolic volume; MAP, mean arterial pressure.

Table 4 The relative heart weight of each group after dissection

Group	Relative heart weight (mg/100 g)
Mi	589.2±71.0
Mid	630.9±52.3
Mim	600.8±67.9
Min	620.3±45.2

Morphine mainly acts on the cerebral cortex, which can inhibit the pain area, respiratory center, and cough center. Morphine is usually injected subcutaneously and intramuscularly, and is absorbed rapidly. Furthermore, 60% of the total morphine can be absorbed within half an hour after injection, and rapidly metabolized to the lungs, liver, spleen, kidney, and other organs. Since morphine acts on opioid receptors in different brain regions, it has strong physiological dependence, and can easy cause addiction. Therefore, patients who need long-term medication should use this with caution. In the present study, morphine had the worst pharmacodynamic sensitivity and short duration, but its main effect was on the brain, and had the least impact on various cardiac function indexes in rats. However, due to its contraindication with use time, morphine has certain limitations.

Nalbuphine is short for nalbuphine hydrochloride injection, and is an opioid receptor agonist—antagonistic analgesic (22). It mainly acts on spinal cord kappa receptors, activates kappa receptors at the spinal cord level and kappa 3 receptors at the upper spinal cord, and is mainly used as relief to severe pain, such as burns, cancer, surgery, kidney, or biliary colic pain (23). It is also often used for myocardial infarction, angina pectoris, pain, etc. Its advantages are as follows: (I) a part of the antagonistic receptor has related side effects, which mainly reduce respiratory depression, nausea and vomiting, itching, and other adverse symptoms; (II) it does not easily increase the load to the heart, and does not increase blood pressure; (III) it has a quick response (5–10 minutes) and long action time (3–6 hours); (IV) it has a low incidence of adverse reactions and high safety, and can be used for postoperative analgesia, and gynecological and pediatric surgery analgesia (24). In the present study, the analgesic effect of nalbuphine was the earliest and longest, and it has the best analgesic effect in terms of temperature. In addition, in the cardiac function test of MI rats, nalbuphine has a small effect and high safety. Therefore, nalbuphine is a relatively good analgesic agent for patients with MI.

Conclusions

The present study provides a certain data basis for the selection of analgesics for patients with MI, but the specific application in clinical practice needs to be verified through multiple approaches, in order to ensure its safety and reliability.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Experiments were performed under a project license [license number: SCXK (Jun 2018-004)] approved by Tianjin Second Animal Experimental Center.

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