Effects of Morphine and Pethidine on Coronary Vascular Resistance, Blood Pressure, and Myocardial Infarction-Induced Cardiac Arrhythmias

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SUMMARY

In the present study, the effects of morphine and pethidine on coronary vessel resistance (CPP), blood pressure (BP), and experimental myocardial infarction-induced cardiac arrhythmia were investigated. Both morphine and pethidine induced a fall in CPP and BP and inhibited the cardiac arrhythmia. The morphine effects on CPP and BP were largely blocked by mepyramine. The effects of pethidine, on the other hand, were not blocked by mepyramine, propranolol, or atropine. An interesting dose dependent inhibition of cardiac arrhythmia was observed with pethidine.

Additional Indexing Words:
Morphine Pethidine Coronary vascular resistance Cardiac arrhythmia

MORPHINE and pethidine (meperidine) are commonly used for combating pain and shock in cases of myocardial infarction. However, the precise mechanism(s) by which these agents benefit patients with myocardial infarction is still not known. Both morphine and pethidine are known to produce cardiovascular changes when administered parenterally in normal individuals\(^1,2\) as well as in patients with coronary artery disease.\(^3,4\) In patients with acute myocardial infarction, morphine has been reported to reduce oxygen consumption, left ventricular end-diastolic pressure and cardiac work.\(^5\) However, there are no specific studies concerning the effects of these agents on coronary vasculature. Moreover, cardiac arrhythmias, especially those of ventricular origin, are frequently observed in the post-myocardial infarction...
period. The relative efficacy of possible antiarrhythmic effects of morphine and pethidine has not been studied. Thus, the present study was undertaken to evaluate and compare the effects of morphine and pethidine on coronary vasculature and experimental myocardial infarction-induced cardiac arrhythmias.

Methods

I. Coronary perfusion

The study was conducted on adult mongrel dogs of either sex weighing from 10–15 Kg. The animals were anesthetized with pentobarbitone sodium (30 mg/Kg, i.v.) and maintained on positive pressure artificial respiration. The femoral vein was cannulated unilaterally with a polythene cannula for intravenous (i.v.) injection of drugs. Blood pressure was recorded from the right common carotid artery through a mercury manometer on smoked kymograph paper. The thorax was opened on the left side by removing segments of the 3rd, 4th, and 5th ribs. Internal mammary and intercostal arteries were ligated to prevent hemorrhage. The pericardium was converted into a cradle to expose the heart. The coronary vascular bed was perfused through the circumflex branch of the left coronary artery by means of a constant volume pump (Sigma motor pump). The other end of the tube from the Sigma motor pump was connected to the left carotid artery, which supplied blood for coronary perfusion. The coronary perfusion pressure (CPP) was recorded by a mercury manometer placed between the pump and the heart. The pressure of the blood leaving the pump thus reflects changes in the resistance of the coronary vessels.

Before starting the experiments, the pump was filled with heparinized Ringer's solution. Heparin (1,000–1,500 units/Kg) was administered i.v. to the animals just before the start of the perfusion. The quantity of blood required for normal supply of the myocardium was first determined by trial and error for each animal. The volume of blood (per unit of time) was then adjusted to obtain a perfusion pressure equal to or slightly higher than the systemic blood pressure. The perfusion volume of blood usually varied between 30–40 ml/min in all experiments.

Graded and equipotent doses of morphine (2, 4, and 8 mg/Kg) and pethidine (12.5, 25, and 50 mg/Kg) were injected i.v. and their effects were observed on coronary perfusion pressure (coronary resistance, CPP), systemic blood pressure (BP) and heart rate (HR). The percent change in CPP, BP, and HR as compared to controls, the mean and standard error of the mean were calculated. Moreover, the effects of i.v. pretreatment with the
histaminergic receptor blocker, mepyramine (1 mg/Kg), the β-adrenoceptor blocker, propranolol (0.5 mg/Kg) and the anticholinergic agent, atropine (1 mg/Kg), were also studied on morphine and pethidine induced BP, CPP, and HR changes.

II. Coronary artery ligation (CAL) induced cardiac arrhythmias

Experimental myocardial infarction was produced in adult mongrel dogs of either sex weighing between 8–12 Kg. The animals were anesthetized with pentobarbitone sodium (30 mg/Kg, i.v.) and maintained on positive pressure artificial respiration by tracheal intubation. The chest was opened by an incision in the left fourth intercostal space and the intercostal muscles and pleura were cut. The left lung was reflected and the heart was exposed. A transverse incision was made in the pericardium immediately below the left auricle and the anterior descending branch of the left coronary artery was exposed. Two double threads were passed below the artery, about 1 cm below its origin from the left coronary artery. The anterior descending branch was then ligated in two stages according to the method of Harris and Kokernot.7) Cardiac arrhythmias appeared the next day. Electrocardiogram (ECG, lead II) of the unanesthetized and unrestrained animals was recorded the next day on one channel of a multichannel polygraph (Encardio-rite, India). Graded doses of morphine (2, 4, and 8 mg/Kg) and pethidine (6.25, 12.5, and 25 mg/Kg) were administered i.v. and their effects were observed on CAL-induced cardiac arrhythmias. Percent ventricular ectopics, as compared to total number of beats recorded in 30 sec duration, were determined at different time intervals after drug administration. The mean and standard error of the mean percent ventricular ectopics were calculated at different time intervals. Student's 't' test was applied to determine the statistical significance.

Results

1. Effects of morphine and pethidine on BP, HR, and CPP

In equipotent, graded doses, both morphine (2, 4, and 8 mg/Kg, i.v.) and pethidine (12, 25, and 50 mg/Kg, i.v.) induced an almost dose dependent decrease in BP and CPP. The fall in BP and CPP induced by morphine was of lesser magnitude and duration as compared to that of pethidine (Fig. 1). It is interesting to point out that the pethidine-induced decrease in BP and CPP were of considerable magnitude (30–70 mmHg) and duration (15–20 min).

Morphine (2, 4, and 8 mg/Kg, i.v.) failed to elicit any significant change in the HR, while pethidine, in large doses (50 mg/Kg, i.v.), produced a re-
Fig. 1. Regression lines showing the effects of graded doses of morphine (2, 4, and 8 mg/Kg, i.v.) and pethidine (12, 25, and 50 mg/Kg, i.v.) on systemic blood pressure (BP mmHg) and coronary perfusion pressure (CPP mmHg) in anesthetized dogs. The values represent mean ± S.E.

Fig. 2. Bar diagram showing the fall in blood pressure induced by 8 mg/Kg i.v. of morphine (white bar C) and 50 mg/Kg i.v. of pethidine (black bar C). Mepyramine (1 mg/Kg i.v.) could significantly inhibit the hypotensive effect of morphine (white bar M) without affecting that of pethidine (black bar P).

duction of 10–30 beats/min. No tachycardia was observed in the present study after i.v. injection of morphine or pethidine.

2. Effects of mepyramine pretreatment on the BP and CPP changes induced by morphine and pethidine

The effects of an antihistamine, mepyramine, on the decrease in BP and CPP induced by morphine and pethidine were examined. Pretreatment with mepyramine (1 mg/Kg, i.v.) produced about an 80% blockade of the mor-
3. Effects of propranolol and atropine on the BP and CPP changes induced by pethidine

The effects of i.v. pretreatment with a β-adrenoceptor blocker, propranolol (0.5 mg/Kg), and a cholinoreceptor blocker, atropine (1 mg/Kg), on the decrease in BP and CPP induced by pethidine were also studied. Neither of these agents significantly altered the BP and CPP changes caused by pethidine.

4. Effects of morphine and pethidine on the CAL-induced cardiac arrhythmias

The effects of graded doses of morphine and pethidine, administered i.v. in conscious and unrestrained, coronary artery ligated dogs were studied. The results of these studies are shown in Fig. 3. Intravenous administration of morphine (2 and 4 mg/Kg) failed to elicit any significant effect on cardiac arrhythmia. However, higher dose of morphine (8 mg/Kg) significantly inhibited the ventricular ectopics. This inhibitory effect lasted for a duration of 30 min. On the other hand, the three dose levels of pethidine (6.25, 12.5, and 25 mg/Kg) inhibited the arrhythmia in a dose dependent manner. A dose of 25 mg/Kg of pethidine showed an inhibition of 92.8%, which lasted for more than 90 min.
DISCUSSION

Although morphine and pethidine have been used in cases of myocardial infarction for several years, specific studies concerning their effects on coronary vasculature and cardiac arrhythmias have not been carried out. Considering the importance of these factors in the overall prognosis of such cases, an attempt was made to evaluate and compare the effects of morphine and pethidine on BP, CPP, HR, and CAL-induced cardiac arrhythmias in animal models.

Both morphine and pethidine produced hypotension and a decrease in CPP in anesthetized and artificially respirated dogs. While the effects of morphine were small and transient, the effects of pethidine were more pronounced and prolonged. The hypotensive response induced by morphine was largely blocked by mepyramine, suggesting that the release of histamine is a major mechanism for vascular dilatation. On the other hand, the hypotensive effect of pethidine was not blocked by prior treatment with an antihistamine, β-adrenoceptor blocker or cholinergic blocker, suggesting a direct action on the coronary vasculature. Similar results have been obtained with morphine and pethidine on peripheral arteriolar musculature, where histamine release appears to be a major mechanism for dilatation of the vessels by morphine but not pethidine. Similarly, Nadasi and Zsoter have reported that pethidine (1 mg/Kg, i.v.), given to patients with or without heart failure, significantly increased the blood flow in the forearm and leg while the arterial and venous resistance decreased. This is consistent with the results of the present study. The greater, prolonged decrease in CPP induced by pethidine could be an added advantage over morphine, since an increase in the blood flow to the ischemic area of the heart may help in an early recovery.

Though both morphine and pethidine seem to suppress the cardiac arrhythmias, the antiarrhythmic effect of morphine appears to be less marked. On the other hand, pethidine appears to possess considerable antiarrhythmic activity, which may be an added advantage in cases of myocardial infarction. The antiarrhythmic effects of these narcotic analgesics may be the result of an activation of the opioid receptors, either in the periphery or in the thoracic spinal cord. However, the greater efficacy of pethidine, which also possesses considerable local anesthetic activity, may be due to a non-specific membrane-stabilising effect.

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REFERENCES