Opium has been used for the treatment of pain since antiquity. The Greek physician, Theophrastus, described its use at the beginning of the third century B.C. Undoubtedly it was used then for the relief of chest pain, but it was not until the beginning of this century, and the description of myocardial infarction as a clinical entity, that opium (or its derivatives) was recognized as a potent analgesic in myocardial infarction (Herrick, 1912).

Morphine was isolated as the active constituent of opium by the German pharmacist Serturiner in 1805, and was first given by injection in this country in 1853. It is a tribute to its efficacy that it is still one of our most widely used analgesics. Diamorphine was synthesized from morphine in 1874, but it was not until recent years that alternative narcotic preparations capable of relieving the pain of myocardial infarction were introduced (pethidine 1939, methadone 1946, pentazocine 1964). A mixture of nitrous oxide and oxygen has been used extensively in Russia for the relief of cardiac pain (Iosava, 1965), but has only recently been used in this country (Kerr et al., 1972) and has not yet gained wide acceptance.

Other preparations have been advocated as suitable analgesics in myocardial infarction. Boland (1940) considered that 100 per cent oxygen relieved cardiac pain effectively. Despite this promising report, oxygen has not been included in a properly controlled trial and clinical experience has not confirmed its analgesic role (Friedberg, 1966). Nichol, Phillips, and Casten (1959) and Enger, Julsrud, and Kirkeby (1963) produced evidence that heparin reduced cardiac pain. However, a double-blind trial performed by Bulpitt (1967) did not confirm their findings.

The ideal analgesic should provide rapid relief of pain without clouding of consciousness or production of unwanted side effects. The analgesics which are currently available may relieve pain but also introduce many unwanted side effects.

**Analgesic efficacy**

Surprisingly little has been written about the ability of drugs to relieve the pain of myocardial infarction. Most of the available information has been derived from studies of other painful conditions. The assessment of pain relief is difficult and particularly so in a complex illness such as myocardial infarction. Keele (1968) has shown a good correlation between the degree of pain, assessed by a simple questionnaire, and the amount of infarcted tissue indicated by the extent of electrocardiographic and enzymatic changes.

Scott and Orr (1969) performed a between-patient double-blind trial comparing the analgesic effects of intravenous morphine 10 mg, diamorphine 5 mg, methadone 10 mg, and pentazocine 30 mg, in relief of cardiac pain. Little difference was found between their respective analgesic potencies. Diamorphine and methadone acted more quickly by producing complete relief of pain in a significantly greater number of patients within 10 minutes. By 30 minutes each drug had produced complete relief of pain in the same proportion of patients. Pentazocine gave the shortest period of pain relief.

Pethidine has not been included in a comparative study of analgesic properties in myocardial infarction but has been shown by Lasagna and Beecher (1954a) in a dose of 75 mg to have the same analgesic effect as 10 mg of morphine.

**Side effects**

**Circulatory effects**

Ideally analgesic drugs should not impair the circulatory status of the patient, but because many of the drugs have circulatory effects much time...
and effort have been spent assessing this important complication.

It has been known for some time that morphine will cause a fall in blood pressure in normal erect subjects, a phenomenon explained by dilatation of the capacitance vessels in the legs (Drew, Dripps, and Comroe, 1946). Thomas et al. (1965) were the first to study the circulatory effects of morphine in patients with myocardial infarction. Though the authors interpreted their findings cautiously, this paper has been widely quoted as evidence of frequent serious haemodynamic effects produced by morphine. When 10 mg morphine was administered intravenously on 15 occasions to 13 patients, 7 had a transient, but clinically insignificant fall in arterial pressure, and one had a persistent fall though cardiac output was maintained. One patient had a dramatic fall in arterial pressure, the systolic pressure falling from 140 to 40 mmHg. The heart rate was initially constant, dropping to 20 a minute only when extreme hypotension occurred. It is notable that this patient had an episode of unconsciousness before the study started, suggesting the presence of haemodynamic instability before morphine was administered.

Subsequent studies have shown little circulatory upset when morphine is used in myocardial infarction. Grendahl and Hansteen (1969), in a double-blind study, found an insignificant fall in arterial pressure when 20 supine patients received 15 mg morphine intravenously. When 5 sitting patients were given 7.5 mg morphine intravenously one patient had a significant fall in arterial pressure, both systolic and diastolic pressures falling by 10 mmHg. In the only double-blind study comparing the haemodynamic effects of intravenous morphine 10 mg and diamorphine 5 mg, Muir (1970) found a small but statistically insignificant fall in arterial pressure with an associated slight rise in heart rate in each group.

It is interesting that though bradycardia is a recognized feature of the dog's response to morphine (Schmidt and Livingston, 1933), this has not been a consistent finding in patients with myocardial infarction (Thomas et al., 1965; Grendahl and Hansteen, 1969; Muir, 1970).

In a search for alternative drugs free from haemodynamic side effects, MacDonald et al. (1967) demonstrated a fall in mean aortic pressure of 5 mmHg when 5 mg diamorphine was administered intravenously to 8 patients with myocardial infarction. Studying the haemodynamic effects of pethidine, Rees et al. (1967) demonstrated a biphasic response when 100 mg was administered intravenously to 8 patients with myocardial infarction. In 7 patients the mean aortic pressure rose by 12 mmHg for 15 minutes, finally falling to a mean level 10 mmHg below control levels 30 minutes after injection. In one patient the mean aortic pressure fell immediately after administration, and 10 minutes after injection was 22 mmHg below the control level.

Controversy exists regarding the circulatory effects of pentazocine. Lal, Savidge, and Chhabra (1969) found that it caused a 16 mmHg rise in systolic arterial pressure and concluded it was suitable for use in myocardial infarction. Caution was expressed by Jewitt, Maurer, and Hubner (1970) who found a mean rise in mean main pulmonary artery pressure of 6 mmHg and 11 mmHg in two groups of patients with myocardial infarction given 30 mg and 60 mg pentazocine intravenously. These findings were confirmed by Rickards, Smithen, and Sowton (1971). Jewitt et al. (1971) later demonstrated a rise in left ventricular end-diastolic pressure (mean control 14 mmHg rising to 22 mmHg) in 5 patients with severe angina undergoing investigation before cardiac surgery, and assumed that this was the reason for the rise in pulmonary artery pressure. However, in a recent study of the effects of pentazocine on the pulmonary circulation of 6 patients with mitral stenosis and 2 with aortic stenosis, Miller and co-workers (1972) found no rise in left atrial or left ventricular end-diastolic pressure, and attributed the rise in main pulmonary artery pressure to increased pulmonary vascular resistance. Nitrous oxide 50 per cent and oxygen 50 per cent has been shown to cause no adverse haemodynamic disturbance when administered to patients with myocardial infarction (Kerr et al., 1972).

Respiratory effects
The respiratory effects of the narcotics have been best evaluated with respect to morphine. Animal studies suggest that, in causing respiratory depression, it acts at many sites in the central nervous system and seems particularly to enhance inhibitory vagal stimuli on the respiratory centres (Ngai, 1961). In normal human subjects intravenous morphine causes a fall in minute ventilation which is maximal between 3 and 7 minutes after injection. The effects of intramuscular morphine are comparatively delayed but of the same degree (Dripps and Comroe, 1945).

Morphine, diamorphine, pethidine, and pentazocine have all been shown to cause mild respiratory changes in patients with myocardial infarction (Thomas et al., 1965; MacDonald et al., 1967; Rees et al., 1967; Lal et al., 1969; Hoel and Refsum, 1969; Muir, 1970; Nagle and Pilcher, 1972). In these patients the $P_{\text{CO}_2}$ rose by 2 to 7 mmHg and
PaO₂ fell by 4 to 9 mmHg. In addition, Lal and colleagues (1969) demonstrated a fall in minute ventilation in patients given comparable doses of morphine and pentazocine. The drugs were given intravenously in each case and produced maximal change in respiration within 10 minutes.

When comparing the respiratory effects of morphine and diamorphine in patients with myocardial infarction, Muir (1970), in a double-blind trial, demonstrated a more prompt rise in PaCO₂ with diamorphine though the final increase was the same. Diamorphine produced a slightly greater fall in PaO₂.

Although morphine and pentazocine were shown to produce similar changes in overall ventilation, morphine produced a rise in the dead space/tidal volume ratio (Vd/VT) and alveolar arterial oxygen gradient (A-a gradient); pentazocine caused a fall in both these parameters (Lal et al., 1969). These changes may have been due to the relative effects of the drugs on pulmonary artery pressure, pentazocine causing a rise (Jewitt et al., 1970) and morphine a fall (Sapru, 1966), with redistribution of pulmonary perfusion and subsequent changes in ventilation perfusion relations.

Recent work suggests, though morphine is a time-honoured remedy in the treatment of left ventricular failure, care should be exercised in its use. A study of the blood gas changes in 46 consecutive patients with varying degrees of left ventricular failure and pulmonary oedema included 11 patients with a PaCO₂ greater than 45 mmHg. These patients did not have more severe pulmonary oedema or greater evidence of chronic airway obstruction than others in the group (Aberman and Fulop, 1972). Nine of the hypercapnic patients received morphine; respiratory depression was severe enough in one patient to require ventilatory assistance.

Another point which could be of more than theoretical interest concerns the administration of a narcotic to patients with cardiogenic shock. The decrease in ventilation may prevent adequate respiratory compensation for a metabolic acidosis; an increase in PaCO₂ with subsequent rise in hydrogen ion concentration could compound a coexisting lactic acidosis (Kirby and McNicol, 1966).

Other side effects
Perhaps the most distressing side effects of the narcotics, from the patient’s point of view, are nausea, vomiting, and dizziness. Though morphine is often considered a prime offender (Douthwaite, 1966), there is good evidence to suggest that this is not the case. When used in equianalgesic doses to treat cardiac pain, it has been shown to have the same incidence of nausea and vomiting as diamorphine, methadone, and pentazocine (Scott and Orr, 1969). In a study comparing the side effects of diamorphine and methadone in young women awaiting minor gynaecological surgery, there was no appreciable superiority of diamorphine over morphine with respect to nausea and vomiting (Dundee, Clarke, and Loan, 1967). Methadone was less emetic than either drug. It has been suggested that the incidence of nausea, vomiting, and dizziness is higher when morphine is given in trial to normal individuals without pain (Christie et al., 1958). Consequently, assessment of the side effects of narcotics in normal people may provide misleading results when considering relief of cardiac pain caused by myocardial infarction.

Comments
When narcotics are given by intramuscular or subcutaneous injection their respective times to relief of pain are not greatly different. In standard doses their analgesic potency is comparatively similar. Heroin has the most rapid action by virtue of its greater water solubility which provides faster access to the circulation (Wright, 1941), and also because of the ease with which its metabolite, 6 mono-acetyl morphine, crosses the blood brain barrier (Way et al., 1960). Intravenous injection of the narcotics can decrease the time to effective analgesia and, providing the injection is performed slowly, no increase in side effects occurs (Scott and Orr, 1969).

The relief of pain in myocardial infarction remains one of our first priorities. It would be unwise to become preoccupied by the side effects of the analgesics, since impressions are easily created that a drug is too dangerous to use except in extreme situations. Complications can be anticipated and prevented by a detailed appreciation of their non-analgesic properties and avoidance of excessive doses (Lasagna and Beecher, 1954b).

Vomiting imposes undesirable stress on the circulatory system (McKenzie, 1965; Sapru, 1966) and nausea demoralizes the already frightened patient. These discomforts can largely be prevented by the administration of the antihistamine cyclizine in a dose of 50 mg. It has also been shown that intravenous cyclizine prevents a fall in blood pressure in normal subjects even when massive doses of morphine (up to 165 mg) are administered (Christie et al., 1958).

The haemodynamic effect of morphine is of practical significance only when the patient is standing or sitting with legs dependent. Transport to hospital after administration of morphine may mean...
carrying the patient down a difficult stair. Whenever possible this should be performed with the patient supine to prevent dangerous postural hypotension (British Medical Journal, 1966). A significant proportion of patients with pulmonary oedema secondary to left ventricular failure who have no previous history of chronic obstructive pulmonary disease develop hypercapnia (Aberman and Fulop, 1972). Since it is difficult to differentiate this group clinically it seems reasonable when administering narcotics to monitor the blood gas changes in patients with pulmonary oedema (Lancet, 1972).

Despite years of research and effort there is still no drug which holds a clear-cut advantage over morphine as an analgesic in myocardial infarction. There is doubt regarding the hemodynamic safety of pentazocine (Jewitt et al., 1970, 1971; Miller et al., 1972) and in any case it differs little from the other narcotics in its degree of respiratory disturbance (Lal et al., 1969; Nagle and Pilcher, 1972) and incidence of nausea and vomiting (Scott and Orr, 1969). Nitrous oxide is promising and may prove a useful adjunct (Kerr et al., 1972), particularly in the relief of pain during transport of the patient to hospital.

The overall evidence favours the use of morphine in a dose of 10 mg with cyclazine 50 mg to control emetic side effects. Such continued acceptance of one of our oldest remedies should not, however, discourage attempts to find an even better analgesic.

References


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