GENERAL ANALGESICS USED IN PAIN RELIEF: PHARMACOLOGY

BY

MARK SWERDLOW

Postgraduate Medical Institute, University of Salford, Lancashire, England

The drugs used for the relief of pain in the surgical sphere can conveniently be divided into potent and mild analgesics. The potent analgesics constitute essentially morphine and its semi-synthetic and synthetic derivatives. The mild agents can be subdivided into those which are weak relations of the narcotic analgesics and those which possess antipyretic and anti-inflammatory in addition to analgesic properties.

POTENT ANALGESICS

The pharmacology of the narcotic analgesics will first be detailed as exemplified by morphine and then the special features of the more commonly used morphine-like drugs will be given in comparison and in contrast to those of morphine.

The reader is referred elsewhere for the chemical formulae and molecular relationships of the various narcotic analgesics (Foldes, Swerdlow and Siker, 1964). The addiction liability of narcotics also is beyond the scope of the present paper and the reader is referred to reviews by Seevers and Deneau (1963) and by Halbach and Eddy (1963).

EFFECTS ON C.N.S.

Analgesia.

The basic effect of morphine and its congeners is to produce analgesia. It does this in doses which have relatively little effect on other central nervous system functions. The primary site of action of morphine is probably the sensory cortex of the frontal lobes and diencephalon, but morphine may also depress the after-discharge evoked by nociceptive afferent stimuli in the intermuncial chain between the diencephalic centres and the motor cortex (Wikler, 1950). In addition to raising the pain threshold, morphine alters attitude to pain, so that the hypnotic, psychological and sedative actions of the drug are an inherent part of its analgesic effect. The rate of onset and intensity of analgesia are related to the route of administration, being greatest on intravenous injection and least with oral or rectal administration. The duration of analgesia is shorter after intravenous than after intramuscular or subcutaneous injection.

Several workers have reported that neostigmine has a potentiating effect on morphine analgesia (Slaughter et al., 1940; Slaughter, 1950). It also potentiates analgesia produced by hydromorphone, codeine and papaveretum, although others (De Jongh, 1954) have been unable to confirm this finding. Schneider (1954) demonstrated that reserpine antagonized the analgesic effect of morphine in mice and this has recently been confirmed by Takagi et al. (1964). They suggested that the explanation of this antagonism of morphine-induced analgesia by reserpine might lie in the need for catecholamines and dihydroxytryptamine in the mediation of the action of morphine. The depletion of these amines by reserpine would be expected to result in the failure of morphine to produce analgesia. Rudzik and Mennear (1965), however, consider that the antagonism of analgesia by reserpine is due to some intrinsic property of reserpine other than its effect on brain amines.

Psychic effects

Morphine exerts a depressant action on the hypothalamus and brain stem which contributes to the sedation it causes (Drill, 1958); in large doses it produces profound sleep (accompanied by severe respiratory and circulatory depression). Narcotics have a marked effect on mood and mental performance. The reaction time becomes prolonged but not necessarily accompanied by an increase in errors of psychological test performance (McNally, Neily and Benoit, 1962); memory becomes impaired and ability to concentrate and discriminate are diminished. All these effects, especially if accompanied by pain relief and a low incidence of side effects, produce
a state of euphoria. In some patients, however, excitation rather than sedation (Goodman and Gilman, 1955) occurs with morphine and also with codeine (Goodman and Gilman, 1955) and dihydrocodeine (Eddy and Small, 1934; Swerdlow and Foldes, 1958). It has been suggested that this excitation is due to depression of inhibitory mechanisms rather than to direct cortical stimulation (Sollman, 1957). The excitation may progress to a stage of hallucination and delirium; heroin is especially liable to cause this. Morphine does not raise the threshold of the cortex to electrical or drug-induced stimulation (Tainter et al., 1943) but may enhance the convulsant effects of strychnine (Reynolds and Randall, 1957). Other stimulant effects of narcotics on the central nervous system cause nausea and vomiting, miosis, and bradycardia. Narcotics have a parasympatheticotonic action on the peripheral part of the autonomic nervous system which is partly explained by anticholinesterase activity (Foldes et al., 1959) and partly by their inhibitory effect on the release of noradrenaline (Cairnie, Kosterlitz and Taylor, 1961) and subsequent decrease of sympathetic postganglionic transmission (Dutta, 1949; Cook and Bonnycastle, 1953). The narcotics also have a direct action on some autonomic effector cells (Goodman and Gilman, 1955). Peripheral nerves and sensory end organs are not affected by clinical doses of morphine (Goodman and Gilman, 1965).

Cerebrospinal fluid pressure.
Narcotic analgesics increase the cerebrospinal fluid pressure particularly when administered intravenously (Keats and Mithoefer, 1955; Kepes, 1956). The elevation of c.s.f. pressure results from increased cerebral blood flow caused by a rise in the arterial $PCO_2$, accompanying the respiratory depressant effect of the narcotics. The rise in c.s.f. pressure can be prevented or reversed by hyperventilation (Keats and Mithoefer, 1955) or by administration of narcotic antagonists (Swerdlow, Foldes and Siker, 1955; Swerdlow, 1956). It is unlikely that direct action of narcotics on cerebral vessels is an important factor in producing vasodilatation and resultant increase in c.s.f. pressure (Sokoloff, 1959). Morphine-like drugs do not produce specific changes in the electroencephalogram, but merely changes similar to those of sleep, either natural or when induced by drugs such as barbiturates (Gibbs and Maltby, 1943; Orkin, Bergmann and Nathanson, 1956; Pearcy, Knott and Bjurstrom, 1957).

**Respiratory effects of narcotic analgesics**
The effect of narcotics on the respiration has been reviewed at some length by Krueger, Eddy and Sumwalt (1943) and by Eckenhoff and Oech (1960), to whose monographs the reader is referred. Briefly, narcotics diminish the sensitivity of the respiratory centre to the stimulating effect of carbon dioxide and in addition they may also affect the cortical impulses and the reflexes which influence the activity of the respiratory centre (Slome, 1951). The degree of respiratory depression produced by analgesics varies with the dose and the route of administration. Characteristically, the respiratory rate is slowed in proportion to the dose of analgesic. The effect on rate is somewhat greater than that on tidal volume, depression of which is usually less marked and of shorter duration (Swerdlow, Foldes and Siker, 1955; Foldes, Zeedik and Koukal, 1957). Depression of minute volume results in some accumulation of carbon dioxide (Eckenhoff and Oech, 1960) with the development of a compensatory increase of tidal volume. The respiratory acidosis is usually compensated for by the buffering capacity of the blood and a marked fall in pH occurs only if there is severe respiratory depression. With larger doses of analgesics irregular periodic-type breathing is seen. The respiratory depression caused by narcotics is greater in elderly people and those with pulmonary disease causing diminished respiratory reserve, and is accentuated by the simultaneous administration of barbiturates or inhalational anaesthetic agents, alcohol and phenothiazines. The respiratory depression, on the other hand, is decreased by pain, emotional stress, tolerance, addiction and by narcotic antagonists and non-specific central nervous system stimulants.

Morphine has a definite bronchoconstrictor effect (Higgins and Means, 1915; Adriani and Rovenstine, 1943) which may be due to direct action on the smooth muscle (Reynolds and Randall, 1957) or be mediated by histamine release. Although in healthy subjects clinical doses of narcotics do not cause appreciable bronchocon-
striction, in asthmatics and patients with allergic conditions severe bronchoconstriction may occur (Goodman and Gilman, 1955) and morphine, pethidine and dihydrocodeine have all been implicated (Walton, Penner and Wilt, 1951; Swerdlow, 1957). Morphine-like drugs depress the cough reflex in relatively small doses; thus as little as 2 mg of morphine or 6 mg of codeine will markedly diminish the cough reflex (Drill, 1958). Methyl substituted derivatives of morphine, such as codeine and dihydrocodeine, are more potent depressants of the cough reflex than non-substituted compounds in doses with comparable analgesic potency.

CIRCULATORY EFFECTS

In normal subjects clinical doses of narcotic have little apparent effect on the circulation when administered other than by the intravenous route. The chief effect is hypotension (Eckenhoff and Oech, 1960), which can be most clearly noted on intravenous administration and with patients in head-up position (Drew, Dripps and Comroe, 1946; Dripps, Millar and Kneale, 1957). It is not yet known whether this hypotension is caused primarily by direct action on the vasomotor centre (Huggins et al., 1949; Feldberg and Paton, 1950; Evans, Nasmyth and Stewart, 1952), the autonomic innervation of the heart, the myocardium, or smooth muscles of the vessels, or how much it is due to histamine release. The depressor effect of narcotics may be partially masked by the stimulating effect of accumulated carbon dioxide (Stross, 1928). Experimentally, narcotic analgesics appear to have a direct stimulating effect on the medullary vagal nuclei (Robbins, Fitzhugh and Baxter, 1939), resulting in bradycardia (Reynolds and Randall, 1957). After larger doses of narcotics bradycardia may be complicated by arrhythmias (Sollman, 1957) probably caused by depression of sino-auricular and atrioventricular conduction (Eyster and Meek, 1912); these arrhythmias can be abolished by atropine.

Therapeutic doses of morphine injected other than intravenously do not cause appreciable heart rate changes in subjects in the supine position (Eckenhoff and Oech, 1960). Pethidine and dihydrocodeine, however, frequently produce tachycardia in conscious subjects and this may be excessive in patients with cardiac pathology. There is little clear evidence of the effect of narcotics on the rhythm, conductivity and irritability of the myocardium in man. In supine normal subjects morphine exerts a variable effect on cardiac output (Papper and Bradley, 1942; Drew, Dripps and Comroe, 1946; Beecher, 1955; Malt 1958), but in "cardiac" patients subcutaneous injection of 15 to 30 mg of morphine causes a moderate decrease in cardiac output.

There is some disagreement as to the effect of morphine on the peripheral circulation. The renal blood flow has been found to decrease markedly after 10 mg morphine (Habif et al., 1951) and morphine has been shown to produce vasoconstriction in the placenta (Moya and Thorndike, 1963). Patients with diminished circulatory blood volume may react to narcotics by profound hypotension (Dripps and Comroe, 1946; Lee and Zweifach, 1949). The hypotensive effect of narcotics may be increased by simultaneous administration of atropine or of phenothiazine derivatives (Kalser, Frye and Gordon, 1954; Eckenhoff, Helrich and Rolph, 1957). Narcotic antagonists will partially reverse narcotic-induced circulatory depression but this reversal is less consistent than that of respiratory depression.

EFFECT ON THE GASTRO-INTESTINAL TRACT

Narcotics exert a direct stimulating effect on the smooth muscle of the gastro-intestinal tract and this causes delayed passage of the contents and therefore constipation. There is an increase in the tone of the gastro-intestinal smooth muscle with constriction of the pylorus and increased tone of the ileocaecal and anal valves. The intensity and frequency of propulsive contractions diminish but the amplitude of non-propulsive contractions may be increased (Adler, Atkinson and Ivy, 1942; Chapman, Rowlands and Jones, 1950). Narcotics cause a marked rise in common bile duct pressure. Gastric secretion is initially decreased but later may be markedly increased (Reynolds and Randall, 1957); the flow of bile and pancreatic juice is also decreased by narcotics (Goodman and Gilman, 1965). The tendency of narcotics to cause nausea and vomiting is primarily due to direct stimulation of the vomiting centre in the medulla (Benson, Stefko and
Randall, 1953; Wang and Glaviano, 1954; Goodman and Gilman, 1955); this effect may be enhanced by the increase in gastric secretion and by the spasm of the pylorus. Nausea and vomiting are more likely to occur in ambulatory subjects and in patients who are free from pain.

**EFFECT ON THE URINARY TRACT**

Narcotics exert an antidiuretic effect. Phenazocine stimulates secretion of the antidiuretic hormone but morphine, pethidine and methadone do not; their antidiuretic effect is probably due to interference with the metabolism of the antidiuretic hormone (Ginsburg and Heller, 1953; Crawford and Pinkham, 1955). However, decreased renal plasma flow, excretion of solutes and increased reabsorption may also play a part (Brown, Hodges and Bradbury, 1949). Narcotics also inhibit water and mercurial diuresis, but their effect on excretion of electrolytes is uncertain. Morphine causes an increase in the tone, amplitude and frequency of ureteral contractions by stimulating the smooth muscle of the urinary tract; this effect is antagonized by atropine. Papaverine, on the other hand, diminishes ureteral tone and contractions (Macht, 1917; Reynolds and Randall, 1957).

**EFFECT ON THE GENITAL TRACT**

The effect of narcotics on uterine tone and contractility has not yet been clearly defined but it is agreed that narcotics have little or no effect on the uterus during labour (Goodman and Gilman, 1955; Eskes, 1962). All narcotics readily pass through the placental barrier, and the dose and time of administration relative to delivery are important in avoiding respiratory depression and a decrease in the supply of oxygen to the foetal brain. It has been shown that the concentration of pethidine in the newborn child's blood varies from 45 to 106 per cent of that of the maternal blood (Apgar et al., 1952).

**MISCELLANEOUS EFFECTS**

Morphine produces miosis which may be preceded by a brief period of pupillary dilatation (Klengel, 1950); the miosis depends on intact optic nerves and is antagonized by atropine and increased by neostigmine. Sensitivity of the light reflex (McCrea, 1942) and of the power of accommodation (Leopold and Comroe, 1948) are both increased after narcotics. In clinical doses narcotics reduce the intra-ocular tension in both normal and glaucomatous subjects (Leopold and Comroe, 1948).

Morphine causes moderate leucocytosis often preceded by leucopenia; the effect develops half to one hour after subcutaneous administration. Applied to the skin, morphine causes erythema, itching and urticarial weals (Sollman, 1957), and on intracutaneous injection it can produce the triple response of Lewis (1927); this can be antagonized by administration of an antihistaminic (Nasmyth and Stewart, 1950). Parenteral administration of narcotics causes dilatation of the cutaneous vessels, especially of the face, neck and thorax; the skin becomes flushed, warm and moist, and the mucous membranes are also flushed (Sollman, 1957).

It seems likely that morphine inhibits release of corticotrophin. On prolonged administration morphine produces hypertrophy of the adrenal (MacKay and MacKay, 1926) with hyperplasia of the reticular zone (Reynolds and Randall, 1957). The excretion of ketosteroids is decreased but the glands retain their normal response to corticotrophin (Briggs and Munson, 1955; Eisenman, Fraser and Brooks, 1961). Morphine also causes an increase in adrenaline output which is primarily responsible for the rise in blood sugar frequently observed after its administration.

Clinical doses of morphine and other narcotics cause a fall in the basal metabolic rate of 10–20 per cent (Schoen, 1924; Stark, 1929).

**ABSORPTION AND METABOLISM**

Narcotic analgesics are well absorbed after parenteral administration but absorption from the gastro-intestinal tract and mucous membrane is less reliable. There is considerable variation in the rate of absorption of different narcotics administered by these routes. Codeine and other 3-methyl substituted compounds are better absorbed from the gastro-intestinal tract (Way and Adler, 1962) than morphine (Beecher et al., 1953). After subcutaneous or intramuscular administration, the narcotic effect appears in 15–30 minutes and a peak effect is obtained in
45–90 minutes. On intravenous administration the onset is apparent within 1–2 minutes, and reaches its maximum in 3–6 minutes (Swerdlow, Foldes and Siker, 1955b; Foldes, Zeedick and Koukal, 1957). Free morphine rapidly leaves the blood and tends to accumulate in the kidney, liver, lung, and spleen. The concentration of narcotic in the c.n.s. is relatively low (Way and Adler, 1962). On the other hand, the highest concentration of bound morphine is found in the organs of excretion (kidney, gall bladder). Narcotics are mainly broken down in the liver (Way and Adler, 1962); the processes include conjugation, N-demethylation and oxidation. Pethidine, anileridine and heroin are hydrolyzed in the body and excreted as acids (Way and Adler, 1962). Codeine undergoes demethylation and morphine is detoxified by conjugation, conjugated morphine being much less active than free morphine. It has been suggested that narcotics produce analgesia only when the drug has undergone oxidative N-demethylation after its absorption on to the specific receptors in the c.n.s., the resulting nor-compound (e.g. nor-morphine) being responsible for the analgesia (Beckett, Casy and Harbet, 1956). This theory has much in favour but also much against it (Way and Adler, 1962) and further research will be necessary before it can be accepted.

**SEMI-SYNTHETIC NARCOTIC ANALGESICS**

**Heroin.**

Reichle et al. (1962) showed that 2.3–5.2 mg heroin parenterally gives equal analgesia to 10 mg morphine. Heroin analgesia reaches a peak earlier and is of shorter duration than that of morphine. Respiratory depression is similar with the two drugs in equi-analgesic doses. However, it has been reported that heroin has less effect on the circulation than morphine (Macdonald et al., 1967). Heroin tends to cause less malaise (Ross, 1923) and nausea and vomiting (Goodman and Gilman, 1955) than morphine, and more sedation and euphoria (Saunders, 1967, personal communication). Heroin, like morphine, appears to be much less effective when given by mouth. It is more addictive than morphine and addiction to it develops more rapidly.

**Dihydromorphinone (Dilaudid).**

Dihydromorphinone 2–4 mg provides equivalent analgesia to morphine 10 mg; the former has a quicker onset and a shorter duration of action. Dihydromorphinone is more toxic than morphine, although the incidence of side effects is somewhat less. It has a marked sedative effect but may in some subjects cause excitement and mild euphoria. Its constipating effect is considerably less than that caused by comparable doses of morphine (Reynolds and Randall, 1957). An urticarial reaction has been observed in man with therapeutic doses. It produces effective cough suppression in a dose of 2.5 mg. Dilaudid definitely possesses addiction liability (Reynolds and Randall, 1957).

**Oxymorphone.**

Oxymorphone 1 mg is equi-analgesic with morphine 10 mg (Eddy and Lee, 1959; De Kornfeld 1961); in this dosage it produces more respiratory depression than morphine (Eddy and Lee, 1959; Keats and Telford, 1960; Lasagna, 1964). It causes marked euphoria (Keats and Telford, 1960; De Kornfeld, 1961) and more nausea and vomiting than an equivalent dose of morphine (Keats and Telford, 1960). De Kornfeld (1961) and Swerdlow and Brown (1961) found that oxymorphone produces less sedation than morphine. The time action curves of oxymorphone and morphine are similar (Keats and Telford, 1960). Fraser and Isbell (1955) found that oxymorphone possesses a high physical dependence capacity.

**SYNTHETIC NARCOTIC ANALGESICS**

**MORPHINAN DERIVATIVES**

**Racemorphan and levorphan.**

Racemorphan 5 mg and levorphan 2.5 mg are approximately equi-analgesic with 10 mg morphine; the analgesic potency of the racemate is considered to reside in the laevo rotary isomer. Levorphan produces typical opiate side effects such as nausea, itching, dizziness and drowsiness in healthy volunteers in doses of 2–3 mg by injection or by mouth. However, despite earlier claims to the contrary, it appears that these drugs are less effective by mouth than by injection (Houde and Wallenstein, 1954).
In equipotent dosage the duration of action is similar to that of morphine. The sedative effect of levorphan is less than that of an equi-analgesic dose of morphine (Brown, 1954; Bauer, 1957), but its addiction liability is similar to that of morphine (Isbell and Fraser, 1953).

Phenazocine.
Phenazocine 3 mg is equi-analgesic with morphine 10 mg and in equi-analgesic dosage the two drugs show a similar incidence of side effects (De Kornfeld and Lasagna, 1960a). Phenazocine causes as much if not more respiratory depression than morphine (Papadopoulos and Keats, 1961; Berkowitz, Roderman and Close, 1961; Swerdlow, Starmer and Daw, 1964). Like morphine, phenazocine is much more effective by injection than by mouth. Direct addiction can be induced with phenazocine but the physical dependence liability is less than with morphine though still significant (Fraser and Isbell, 1960).

METHADONE DERIVATIVES

Methadone.
A dose of 7½–10 mg methadone is approximately equi-analgesic with 10 mg of morphine and has a similar duration of action but less sedative effect. On repeated administration sedative effects are seen possibly due to cumulative effect (Isbell et al., 1948). Methadone produces morphine-like side effects; in equi-analgesic doses it causes as much respiratory depression as morphine (Prescott et al., 1949). The drug has significant antitussive effects (Goodman and Gilman, 1965) and, like morphine, produces hyperglycaemia and hypothermia. Methadone has similar effects on the intestine to those of morphine (Gaensler, McGowan and Henderson, 1948) but is less constipating. It causes biliary tract spasm in both man and animals. The ureters are said to become quiescent after methadone, perhaps because of the antidiuretic effect. Methadone-induced miosis is less prominent than that caused by morphine. In contrast to morphine and most other morphine-like analgesics, methadone retains a considerable degree of effectiveness when given orally.

Methadone undergoes extensive biotransformation chiefly in the liver; N-demethylation seems to be the most important metabolic pathway. A major part of the injected methadone appears in the urine and faeces; less than 10 per cent of the drug is excreted unchanged. Tolerance to methadone develops more slowly than to morphine, especially to the depressant effects. Methadone addiction is much less common than that with morphine and this drug has recently been used to wean addicts away from heroin.

Dipipanone.
In analgesic potency 25 mg dipipanone is approximately equivalent to 10 mg morphine (Beecher and Gravenstein, 1957; Houde, Seed and Cochin, 1957) and the duration of action of the two drugs is similar. Cahal (1957) found that dipipanone produced morphine-like side effects in healthy volunteers, the incidence increasing from 4 to 34 mg with a sharp rise after 15 mg. It has little sedative effect and does not greatly depress the cough reflex (Lamoureux, Shooner and Tremblay, 1959). The addiction liability of dipipanone is similar to that of morphine (Fraser and Isbell, 1956).

Dextromoramide.
Dextromoramide 7.5 mg appears to be equi-analgesic with 10 mg morphine. It is somewhat shorter-acting than morphine (Swerdlow, Murray and Daw, 1963) and is effective by mouth. Dextromoramide is a powerful respiratory depressant and apnoea has been reported with clinical analgesic doses (Keats, Telford and Kurosu, 1960; Black, 1966). It has little sedative action (Lear, Suntay and Pallin, 1961). There have been numerous reports of nausea, vomiting, dizziness, drowsiness and other undesirable side effects with dextromoramide (Cahal, 1958). It has an addictive potential at least equivalent to that of morphine (la Barre, 1959).

PETHIDINE DERIVATIVES

Pethidine.
Houde and Wallenstein (1959) showed that 70 mg pethidine gave similar analgesia to 10 mg morphine but was shorter-acting. Masson (1962) found that 100 mg pethidine was significantly better than 10 mg morphine. Pethidine is considerably less potent and reliable by mouth than by injection. In equi-analgesic doses pethidine...
produces as much if not more (Foldes and Torda, 1965) respiratory depression than morphine, but pethidine may have less effect than morphine on the respiratory rate as opposed to the tidal volume. It may also have a less marked effect on the circulatory system than morphine (Foldes and Torda, 1965).

There is some controversy about the effects of pethidine on the gastro-intestinal tract, but it seems likely that it produces a less marked increase of tone than does morphine. Gaensler, McGowan and Henderson (1948) have shown that pethidine produces spasm of the biliary tract but the rise in biliary pressure is somewhat greater and more prolonged after morphine than after equi-analgesic doses of pethidine. However, pethidine, like morphine, can precipitate typical biliary colic. Pethidine exerts an atropine-like effect causing moderate depression of salivary and bronchial secretions. It produces less suppression of the cough reflex (Hori and Gold, 1944) and less sedation (Rovenstine and Batterman, 1942) than morphine.

Pethidine has been shown to possess definite local anaesthetic properties but the drug is irritating (Way, 1946), so that the anaesthetic effect has little practical value. It has been suggested that pethidine has advantages over other opiates in patients with asthma (Batterman, 1943; Herschfus, Salmon and Segal, 1954). Pethidine has a marked addiction liability (Eddy, Halbach and Braenden, 1957).

**Anileridine.**

Anileridine 40–60 mg produces equivalent analgesia to morphine 10 mg but morphine has a somewhat longer duration of action. Anileridine is at least as depressant to the respiration as pethidine when both are given in equi-analgesic doses (Keats, Kurosu and Telford, 1957; Swerdlow, 1960), but the effects of anileridine are shorter-lasting (Chang, Safar and Lasagna, 1958). Side effects are similar with both drugs although sedation is more common with pethidine (Swerdlow, Brown and Tetlow, 1960) and nervousness, restlessness and stimulation more common with anileridine (Keats, Kurosu and Telford, 1957; Chang, Safar and Lasagna, 1958). Anileridine appears to have the advantage that relative to its parenteral potency it is more efficacious by the oral route than most morphine substitutes. Its addictiveness is similar to that of pethidine.

**Piminodine.**

This is an end-substituted derivative of pethidine which is pharmacologically and toxicologically similar to pethidine; it has a high physical dependence capacity. On parenteral injection 7.5 mg piminodine is approximately equi-analgesic to 10 mg morphine (De Kornfeld and Lasagna, 1960b). Respiratory depression (De Ciutiis, 1961) and sedation (Betcher et al., 1962) may be less than with morphine.

**Phenoperidine.**

This drug is a potent analgesic, and in doses of up to 4 mg produces long-lasting respiratory depression in some patients and sometimes loss of consciousness and athetoid movements. Catatonia with lead pipe rigidity may also occur. Nystagmus, nausea and vomiting and respiratory depression are marked (Rollason and Sutherland, 1963). In a dose of 0.05 mg/kg it has little effect on the cardiovascular system (Foldes et al., 1966).

Fifty per cent is excreted unchanged by the kidneys; the remainder is metabolized to pethidine and pethidinic acid, 75 per cent of which is recovered from the urine (Shephard, 1965).

**Fentanyl.**

This is a highly potent short-acting analgesic with an activity some 200 times that of morphine (Janssen, 1962; Gardocki and Yelnoski, 1964). Marked respiratory depression and apnoea occur and also muscular rigidity and laryngospasm (Foldes et al., 1966). An intravenous dose of 0.5–1 mg/70 kg produces dizziness, suppression of cough reflex, bradycardia and other morphine-like effects; the duration of action is about 30 minutes (Shephard, 1965). About 10 per cent of fentanyl is excreted unchanged in the urine and the remainder is probably oxidized in the liver.

**NARCOTIC ANTAGONISTS**

The introduction of nalorphine raised the hope of a drug which would provide analgesia without addiction; unfortunately nalorphine produced
marked unpleasant psychotomimetic effects which ruled it out as a clinical analgesic. Some more recent antagonists appear to show promise as effective non-addictive analgesics.

**Pentazocine.**
This is a weak narcotic antagonist with significant analgesic properties (Keats and Telford, 1964; Stoelting, 1965). The precise dose which is equi-analgesic with 10 mg morphine has not yet been defined but it appears to be about 30 mg. Pentazocine has been found to be effective orally, 50 mg being more potent than 60 mg codeine; pentazocine has a quicker onset but a shorter duration of action (Lasagna and Werner, 1966; Lister, 1966). The incidence of subjective side effects is similar to that produced by morphine, but pentazocine causes less nausea and vomiting than morphine. On the other hand, it produces a high incidence of hypertension and tachycardia (Sadove, Balagot and Pecora, 1964). The incidence of psychotomimetic symptoms appears low and in equi-analgesic dosage it depresses respiration rather less than does morphine (Fraser and Rosenberg, 1964). The addiction liability of pentazocine is low and thus pentazocine is the first clinical potent analgesic with minimal psychotomimetic action and addiction liability.

**Cyclazocine.**
Cyclazocine is a benzo-morphan derivative which has been shown in laboratory and clinical studies to be a potent analgesic agent. It is also a potent narcotic antagonist with powerful anti-convulsive, sedative and muscle relaxant properties (Harris and Pierson, 1964; Weiss and Laties, 1964). Cyclazocine is highly effective when given either by mouth or parenterally in doses as low as 0.25 mg which can produce pain relief equivalent to 10 mg of morphine (Lasagna, De Kornfeld and Pierson, 1964). Circulatory changes following intravenous injection of 0.25 and 0.5 mg of this drug are not significantly different from those seen following 10 mg of morphine (Witherspoon, Montaner and Rusy, 1966). It depresses respiration in volunteers but, as with the other morphine antagonists, the dose response curve seems to flatten out at a lower ceiling than for morphine (Lasagna, 1964). It is said to have little addiction liability but occasionally it produces confusion, depersonalization and dysphoria reminiscent of nalorphine.

**MILD ANALGESICS**
The mild analgesics are usually administered orally and even in large doses are generally less effective against severe pain than are the potent analgesics.

**THE WEAK MORPHINE-LIKE ANALGESICS**

**Codeine.**
Codeine, like aspirin, is widely used as a standard for comparison of analgesia with mild analgesic agents: 60 mg of codeine gives significantly better analgesia than a placebo and similar analgesia to 600 mg aspirin. In equipotent dosage the two drugs appear to have similar durations of action. The addiction liability of codeine is of a very low order despite the very wide use of this drug as an analgesic and antitussive. It does not appear to produce morphine-like psychic effects. Codeine can cause all the side effects characteristic of the narcotics (Boyle, Solomonson and Petersen, 1960) but when administered in clinical doses by mouth the incidence of side effects is low: 60 mg of codeine orally depresses respiration to a measurable degree (Bellville et al., 1958) but this is not of clinical significance. Nausea, vomiting, sedation and dizziness may occur with 30 mg and more commonly with 60 mg of codeine (Gruber, 1957). These side effects are more frequently noted in ambulatory patients than in recumbent ones. Constipation occurs on chronic administration. Codeine may also produce allergic reactions. Acute overdosage produces a picture not unlike that seen in intoxication by potent narcotics. There is evidence that repeated administration of codeine may lead to the development of renal damage (Prescott, 1966).

**Dextropropoxyphene.**
This drug is related to methadone and on oral administration it appears to give less analgesia than codeine mg for mg (Sadove, Schiffrin and Ali, 1961). On parenteral administration dextropropoxyphene produces tissue irritation and on intravenous administration of large or repeated doses thrombophlebitis occurs as well as nervousness, toxic psychoses and sometimes convulsions.
In clinical dosage by mouth this drug produces similar side effects to codeine but perhaps with a lower incidence, though this difference is marginal when equi-analgesic doses are considered. On oral administration it appears to cause little respiratory depression (Burget and Green, 1962). Overdosage with dextropropoxyphene gives a picture similar to acute narcotic intoxication, but with a greater incidence of convulsions. The addiction liability is very low although the narcotic status of dextropropoxyphene is somewhat confused (Lasagna, 1964).

**Dihydrocodeine bitartrate.**

The optimal dose of dihydrocodeine is 60 mg and this is considered to be equi-analgesic with 10 mg of morphine although shorter in action (Keats, Telford and Kurosu, 1957). Keesling and Keats (1958) found that 30 mg dihydrocodeine was more effective than 600 mg aspirin orally in pain relief but produced a higher incidence of side effects. Dihydrocodeine is a powerful antitussive; it has been shown to produce suppression of the cough reflex in a dose of 2 mg/kg against 0.5 mg/kg morphine and 3 mg/kg for codeine (Haas, 1955). Dihydrocodeine produces considerably less and shorter respiratory depression than morphine (Eckenhoff, Helrich and Rolph, 1957a; Keats, Telford and Kurosu, 1957) or pethidine (Swerdlow, 1957).

Dihydrocodeine causes marked hypotension (Swerdlow and Foldes, 1958) especially with the tilt test (Eckenhoff, Helrich and Rolph, 1957b). Sixty mg produced subjective effects similar in type to those of morphine but much less sedation and those much less frequently (Keate, Telford and Kurosu, 1957). Dihydrocodeine 30 mg produces no greater nausea and vomiting than placebo; increasing the dose to 60 or 90 mg results in some nausea but even at these high doses the incidence of gastro-intestinal symptoms is less than with 10 mg morphine (Keats, Telford and Kurosu, 1957).

It is fully effective orally and the tablets contain 30 mg of the drug.

**Analgesics with Antipyretic and Anti-Inflammatory Activity**

This group of drugs appear to be effective mainly in headache, rheumatic and musculo-skeletal pain, in which they have been observed to have a reducing effect on inflammation and swelling. Lim et al. (1963) consider that the antipyretic analgesics block pain transmission at the periphery unlike the narcotics which produce this block in the central nervous system. The ability to raise the pain threshold in the inflamed foot of the rat has been used by Randall and Selitto (1957) as a means of grading the relative potencies of this group of anti-inflammatory analgesics. There is no good evidence that this group of drugs produces psychic effects, nor that tolerance develops to their analgesic action. Long continued use does not appear to induce physical dependence. The antipyretic action is rapid and marked in febrile subjects but rarely demonstrable in those with a normal temperature.

**Aspirin (acetyl salicylic acid).**

A large number of controlled studies have demonstrated the superiority of aspirin over placebo in the relief of pathological pain (Beaver, 1965). However, the dose response curve with aspirin has been inadequately studied; it has been shown that 600 mg produces better analgesia than 300 mg but the work of Modell and Houde (1958) suggests that 900 mg does not produce a rise in peak relief. On the other hand, Kantor and his co-workers (1964) showed a significant increase in peak analgesia with 1200 mg as compared to 600 mg of aspirin. It is interesting to note that many of these analgesia studies were carried out in patients who were not suffering from pain of a rheumatic or inflammatory aetiology.

Aspirin is absorbed as such from the gastrointestinal tract but is then rapidly hydrolyzed to salicylate by blood and tissue esterases. It has long been considered that aspirin exerts its activity as a result of liberation of salicylate in the blood (Goodman and Gilman, 1955). However, the analgesic activity of aspirin has been found by several workers to be superior to that of an equal dose of sodium salicylate despite the fact that sodium salicylate is more rapidly absorbed and produces higher total blood salicylate levels than does aspirin (Lasagna and De Kornfeld, 1959). In clinical dosage salicylates may produce dyspepsia, nausea, vomiting and sometimes occult bleeding or frank intestinal haemorrhage. Nausea is due to a direct stimulant effect.
on the c.n.s. and is often noted in patients with high plasma salicylate levels such as in the treatment of rheumatic fever. Dyspepsia unrelated to blood salicylate levels may also be seen less commonly in patients on small doses of salicylates.

Aspirin may cause mild occult gastro-intestinal blood loss in one-half to three-quarters of subjects receiving it. A smaller percentage of patients will experience a greater degree of blood loss if aspirin is administered for long periods; the primary site of bleeding is the stomach. In clinical dosage as an analgesic, aspirin produces few other side effects. A dose of 3 g per day may prolong bleeding time (Gast, 1964) and somewhat larger dosage may cause a modest increase in prothrombin time (Quick and Clesceri, 1960). Small doses of aspirin may sometimes cause allergic reactions such as urticaria, asthma and rhinorrhoea. Salicylates stimulate respiration and in full therapeutic dosage they increase oxygen consumption and carbon dioxide production (Tenney and Miller, 1955) and changes in the acid base balance. In clinical dosage they have no direct action on the cardiovascular system. Salicylates increase the urinary excretion of urates (Goodman and Gilman, 1965).

Aniline derivatives.

This group of coal-tar antipyretic analgesics includes acetanilid, phenacetin and paracetamol. Brodie and Axelrod (1948) demonstrated that in man acetanilid and phenacetin are rapidly biotransformed to paracetamol which is then conjugated and excreted in the urine, and they suggested that the latter might be the active agent through which both the other drugs exert their analgesic and antipyretic effects; this hypothesis is open to doubt.

Acetanilid is no longer used because of undue toxicity, e.g. methaemoglobinaemia. Phenacetin is commonly used in mixtures with other analgesics. It has analgesic properties of its own but there is a risk of methaemoglobinaemia, haemolytic anaemia, sedation, nausea and possibly kidney damage (Prescott, 1966). Paracetamol is considered to be approximately equipotent with aspirin (Wallenstein and Houde, 1954; Lasagna and Pearson, 1964). In active rheumatoid arthritis paracetamol appears to be inferior to aspirin. Paracetamol is well tolerated as a mild analgesic and antipyretic in both adults and children (Batterman and Grossman, 1955; Newton and Tanner, 1956). It tends to cause dyspepsia but not occult gastric bleeding or irritation of the mucosa. Patients allergic to aspirin do not show cross-sensitivity to paracetamol but some patients develop skin rashes with the latter drug. It is not yet certain whether prolonged administration of paracetamol will produce kidney damage of the type suspected to be caused by phenacetin. Paracetamol does not appear to produce methaemoglobinaemia, or haemolytic anaemia and it appears unlikely that it causes agranulocytosis. The side effects produced by the aniline derivatives have recently been reviewed at length (Shelley, 1967).

The coal-tar analgesics have no appreciable effect on the respiratory and cardiovascular systems in clinical dosage.

The pyrazolon derivatives.

This group of antipyretic analgesics includes antipyrine (Phenazone) and aminopyrine (Pyramidon) which were first introduced towards the end of the last century. Their properties are similar to those of the coal-tar analgesics but they are much more toxic, especially aminopyrine, and they are little used today. A related, more recently introduced drug, phenylbutazone, is much used in the treatment of rheumatoid arthritis and similar conditions.

Other antipyretic analgesics such as indomethacin and mfenamic acid find their chief usage in painful musculoskeletal conditions and their pharmacology is therefore outside the scope of the present paper.

ACKNOWLEDGEMENT

I would like to thank Mrs. Audrey Adams for considerable secretarial assistance.

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