Chapter 34 Opioid Analgesics and Antagonists

Algesia (pain) is an unpleasant bodily sensation perceived as suffering, usually evoked by an external or internal noxious stimulus.

Analgesic A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.

Pain is a warning signal, primarily protective in nature, but causes discomfort and suffering; may even be unbearable and incapacitating. It is the most important symptom that brings the patient to the physician. Excessive pain may produce other effects—sinking sensation, apprehension, sweating, nausea, palpitation, rise or fall in BP, tachypnoea. Analgesics relieve pain as a symptom, without affecting its cause. They are used when the noxious stimulus (evoking the pain) cannot be removed or as adjuvants to more etiological approach to pain. Analgesics can be divided into three groups, *viz.*

A. Opioid/narcotic/morphine-like analgesics.

B. Nonopioid/non-narcotic/aspirin-like/antipyretic or antiinflammatory analgesics (described in Ch. 14).

C. Adjuvant analgesics: Anticonvulsants, *viz.* gabapentin/pregabalin, carbamazepine, lamotrigine; antidepressants, *viz.* amitryptyline, duloxetine.

OPIOID ANALGESICS

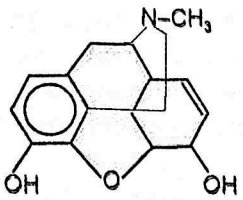
Opium A dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule. It contains two types of alkaloids.

Phenanthrene derivatives

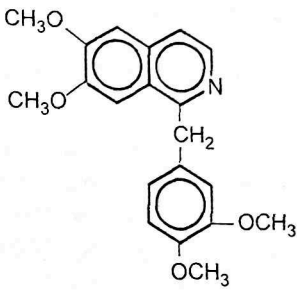
Morphine (10% in opium)
Codeine (0.5% in opium)
Thebaine (0.2% in opium), (Nonanalgesic)

Benzoisoquinoline derivatives

Papaverine (1%)
Noscapine (6%) } Nonanalgesic



MORPHINE



PAPAVERINE

Opium has been known from the earliest times. It is mentioned in the Eber's papyrus (1500 BC), in the writings of Theophrastus (300 BC) and Galen (2nd century AD). Opium eating became a social custom in China in the 18th century. Serturner, a pharmacist, isolated the active principle of opium in 1806 and named it 'morphine' after the Greek god of dreams Morpheus. In the last century a large number of semisynthetic and synthetic compounds have been developed with morphine-like, antagonistic and mixed agonistic-antagonistic properties.

Compounds that are derived from opium or are chemically related to morphine are called '*opiates*', while all those having morphine-like action, irrespective of chemical nature, are called '*opioids*'. Accordingly, pethidine, endorphins, etc. are opioids, but not opiates.

MORPHINE

Morphine is the principal alkaloid in opium and is widely used till today. Therefore, it is described as prototype.

PHARMACOLOGICAL ACTIONS

1. CNS actions Morphine has site specific depressant and stimulant actions in the CNS by interacting primarily with the μ opioid receptor (for which it has the highest affinity), as a full agonist. The depressant actions are:

(a) Analgesia Morphine is a strong analgesic. Though dull, poorly localized visceral pain is relieved better than sharply defined somatic pain; higher doses can mitigate even severe pain; degree of analgesia increasing with the dose. Nociceptive pain arising from stimulation of peripheral pain receptors is relieved better than neuretic pain (such as trigeminal neuralgia) produced by inflammation of or damage to neural structures. The associated reactions to intense pain (apprehension, fear, autonomic effects) are also dampened. Suppression of pain perception is selective, without affecting other sensations or producing proportionate generalized CNS depression (contrast general anaesthetics).

In contrast to nonopioid analgesics which only relieve pain as a sensation, morphine and other opioids suppress both perception of pain and its emotional component (suffering, distress, anxiety, fear) so that pain is no longer as unpleasant or distressing, i.e. the patient tolerates pain better. The analgesic action of morphine has both spinal and supraspinal components. Intrathecal injection of morphine has been shown to cause segmental analgesia without affecting other modalities. It acts in the substantia gelatinosa of dorsal horn to inhibit release of excitatory transmitters (e.g. glutamate, substance P) from primary afferents carrying pain impulses. The action appears to be exerted through interneurones which are involved in the 'gating' of pain impulses. Release of glutamate from primary pain afferents in the spinal cord and its postsynaptic action on dorsal horn neurones is inhibited by morphine. Action at supraspinal sites in medulla, periaqueductal gray matter, limbic and cortical areas may alter processing and interpretation of pain impulses. In addition, supraspinal action of morphine augments the inhibitory impulses through descending pathways to the spinal cord. Several aminergic (5-HT, NA), GABAergic and other neuronal systems appear to be involved in the action of morphine. Simultaneous action at spinal and supraspinal sites greatly amplifies the analgesia.

A *peripheral action* of opioids on small primary afferent terminals in skin or deeper structures, attenuating their sensitization following tissue injury has also been demonstrated. This may play a role in the analgesic action of morphine in conditions like burns and trauma.

(b) Sedation which is different from that produced by hypnotics is seen. Drowsiness, mental dullness and indifference to surroundings as well as to own body occurs without motor incoordination or ataxia. Higher doses progressively induce sleep and then coma. Morphine has no anticonvulsant action, rather, fits may be precipitated.

(c) Subjective effects and euphoria Morphine has prominent calming effect; there is loss of apprehension, feeling of detachment, lack of initiative, limbs feel heavy and body warm, mental clouding and inability to concentrate occurs. In the absence of pain or apprehension, these effects are generally appreciated as unpleasant by normal people. However, patients in pain or anxiety, and especially addicts, perceive it as pleasurable floating sensation: refer it as 'high'. Rapid i.v. injection by addicts gives them a 'kick' or 'rush' which is intensely pleasurable—akin to orgasm. Thus, one has to learn to perceive the *euphoric* effect of morphine.

The pleasurable and reinforcing effects of μ opioid agonists (morphine-like) appear to involve a separate set of neuronal mechanisms than those involved in analgesia and sedation. The euphoric effects are most likely mediated by DA release in nucleus accumbens, whereas κ agonists (nalorphine like) inhibit DA release and produce aversion. The μ opioid receptors appear to inhibit the inhibitory GABAergic neurones, thereby facilitating DA release in nucleus accumbens. Inhibition of NA release in locus ceruleus by opioids is implicated in their action to allay apprehension and fear.

(d) Respiratory depression Morphine depresses respiratory centre in a dose dependent manner; rate and tidal volume are both decreased. However, analgesic dose in an otherwise healthy individual produces no cognizable respiratory depression, but it may be marked in the presence of other sedatives, as well as in patients of asthma, COPD, corpulmonale, liver and kidney disease. Death in morphine poisoning is due to respiratory failure. Neurogenic, hypercapnoeic and later hypoxic drives to the respiratory centre are suppressed in succession. In addition, there is indifference to breathing: apnoeic patient may breath if commanded.

(e) Cough suppression Cough centre is depressed by morphine, and is more sensitive than respiratory centre.

(f) Temperature regulation Hypothalamic thermostatic centre is depressed; hypothermia occurs in cold surroundings.

(g) Vasomotor centre It is depressed at higher doses and contributes to the fall in BP.

The stimulant central actions of morphine are:

- It sensitises the medullary CTZ to vestibular and other impulses, causing nausea and vomiting as side effect, especially if stomach is full or the patient ambulates. Larger doses depress vomiting centre directly. As such, emetics should not be tried in morphine poisoning.
- It stimulates the Edinger-Westphal nucleus of the IIIrd nerve by inhibiting the GABAergic interneurone which keeps this nucleus tonically inhibited, producing miosis. No miosis occurs on topical application of morphine to the eye. No tolerance develops to this action; addicts have constricted pupils. However, morphine causes mydriasis in some species like cats. Another ocular effect is a decrease in intraocular tension.
- Morphine stimulates the medullary vagal centre producing bradycardia as the usual response.
- Certain cortical areas and hippocampal cells are stimulated. Truncal rigidity and immobility is consistently manifested at high doses (especially on i.v. injection). This may hamper respiratory excursions and cause respiratory complications. This response resembles catalepsy seen in rats and mice. Morphine lowers seizure threshold. Convulsions may occur in morphine poisoning. The proconvulsant action has been ascribed to inhibition of GABA release by hippocampal interneurones. Morphine causes excitation instead of sedation in an occasional individual. Species like cat, lion, horse, sheep and cow are uniformly excited and show hyperthermia.

2. Neuro-endocrine actions Hypothalamic activation by afferent collaterals is dampened. Hypothalamic influence on pituitary is reduced. As a result FSH, LH, ACTH levels are lowered, while prolactin and GH levels are raised (these are under predominant inhibitory control). The sex hormone and cortisol levels are lowered. Heavy opioid abusers often suffer loss of libido, impotence, menstrual irregularities and infertility, but clinical hypocorticism is unusual. Morphine can release ADH and reduce urine volume.

3. Peripheral actions

(a) CVS Morphine causes vasodilatation due to:

- histamine release.
- depression of vasomotor centre.
- direct action decreasing tone of blood vessels.

There is a shift of blood from pulmonary to systemic circuit due to greater vasodilatation in the latter. Therapeutic doses cause little change in the BP of recumbent normovolaemic patient. Postural hypotension and fainting do occur due to venodilatation and impairment of vascular reflexes. Morphine has little direct effect on heart; rate generally decreases due to stimulation of vagal centre, but may increase reflexly if the BP falls. Cardiac work is consistently reduced due to decrease in peripheral resistance, imparting anti-ischaemic property to morphine. Intracranial tension tends to rise as a consequence of CO_2 retention leading to cerebral vasodilatation.

(b) GIT The enteric plexus neurones and g.i. mucosa are rich in opioid receptors. Morphine exerts marked effect on g.i. motility as well as on fluid dynamics across g.i. mucosa. Constipation is a prominent feature of morphine action. Several factors contribute:

- Action on enteric plexus and in the CNS increases tone and segmentation but decreases propulsive movements. Tone of duodenum and colon may be increased to the level of spasm.
- Spasm of pyloric, ileocaecal and anal sphincters.
- Decrease in all gastrointestinal secretions due to reduction in movement of water and electrolytes from mucosa to the lumen. This is mainly a peripheral action through opioid receptors on enteric plexus neurones, but also a central action. Absorption of fluid is increased due to stasis.
- Central action causing inattention to defecation reflex.

  No tolerance develops to this action: addicts remain chronically constipated.

(c) Other smooth muscles

- Morphine causes spasm of sphincter of Oddi → intrabiliary pressure is increased several fold → may cause biliary colic. This action is counteracted by opioid antagonist naloxone and direct smooth muscle relaxants like nitrates.
- Tone of both detrusor and bladder sphincter is increased causing urinary urgency and difficulty in micturition. Contractions of ureter are also enhanced.
- Action on uterine muscle is generally insignificant, but morphine/pethidine may occasionally prolong labour.
- Morphine causes bronchoconstriction by releasing histamine (due to its bulky basic molecule; the mechanism is nonimmunological). This is of no consequence in normal individuals, but can be dangerous in asthmatics.

PHARMACOKINETICS

The oral absorption of morphine is unreliable because of high and variable first pass metabolism; oral bioavailability is nearly 1/4th of parenterally administered drug. About 30% is bound to plasma proteins. Distribution is wide; concentration in liver, spleen and kidney is higher than that in plasma. Only a small fraction enters brain rather slowly. Morphine freely crosses placenta and can affect the foetus more than the mother. It is primarily metabolized in liver by glucuronide conjugation. Morphine-6-glucuronide is an active metabolite (more potent than morphine on μ opioid receptors), which accumulates during chronic dosing and contributes to analgesia, despite its restricted passage across blood-brain barrier. Another metabolite morphine-3-glucuronide has neuroexcitatory property. Glucuronides of morphine are readily excreted by the kidney and to some extent in bile. Plasma t½ of morphine averages 2–3 hours. Effect of a parenteral dose lasts 4–6 hours. Elimination is almost complete in 24 hours and morphine is noncumulative. However, small amounts persist in the body due to enterohepatic circulation.

ADVERSE EFFECTS

1. Side effects Sedation, mental clouding, lethargy and other subjective effects which may even be dysphoric in some subjects; vomiting is occasional in recumbent patient; constipation is common and distressing. Respiratory depression, blurring of vision, urinary retention (especially in elderly male) are other side effects. BP may fall, especially in hypovolaemic patient and if he/she walks about.

2. Idiosyncrasy and allergy Allergic reactions manifesting as urticaria, swelling of lips occur infrequently. Anaphylactoid reaction is rare. A local reaction at injection site and generalized itching may occur due to histamine release. However, itching may also be due to activation of pruritoceptive neurons in the spinal cord, because intrathecal morphine also induces itching.

3. Apnoea of the newborn This may occur when morphine is given to the mother during labour. The blood-brain barrier of the foetus is undeveloped, morphine attains higher concentration in foetal brain than in that of mother. Naloxone 10 μg/kg injected in the umbilical cord is the treatment of choice.

4. Acute morphine poisoning It may be accidental, suicidal or seen in drug abusers. In the nontolerant adult, 50 mg of morphine i.m. produces serious toxicity. The human lethal dose is estimated to be about 250 mg. Manifestations are extensions of the pharmacological action.

Stupor or coma, flaccidity, shallow and occasional breathing, cyanosis, pinpoint pupil, fall in BP and shock; convulsions may be seen in few, pulmonary edema occurs at terminal stages, death is due to respiratory failure.

Treatment: Consists of respiratory support (positive pressure respiration also opposes pulmonary edema formation) and maintenance of BP (i.v. fluids, vasoconstrictors). Gastric lavage should be done with pot. permanganate to remove unabsorbed drug. Lavage is indicated even when morphine has been injected. Being a basic drug it is partitioned to the acid gastric juice, ionizes there and does not diffuse back into blood.

Specific antidote: Naloxone 0.4–0.8 mg i.v. repeated every 2–3 min till respiration picks up, is the specific antagonist of choice because it acts rapidly, does not have any agonistic action and does not *per se* depress respiration (*see* p. 512). Due to short duration of action, naloxone should be repeated every 1–4 hours, according to the response.

5. Tolerance and dependence High degree of tolerance can be developed to morphine and related opioids if the drug is taken repeatedly. It is partly pharmacokinetic (enhanced rate of metabolism), but mainly pharmacodynamic (cellular tolerance). Tolerance is exhibited to most actions, but not to constipating, miotic and proconvulsant actions. Rate of development of tolerance depends on the dose and the interval between doses. Larger doses repeated more quickly induce tolerance more rapidly. Addicts tolerate morphine in grams: lethal dose is markedly increased. Patients in intense pain are relatively tolerant to depressant effects. Cross tolerance among opioids is of high degree. Morphine tolerant subjects are partially cross tolerant to other CNS depressants as well.

Morphine produces pronounced addiction and dependence, its abuse liability is rated high. Recently the NMDA antagonists and nitric oxide synthase inhibitors have been found to block morphine tolerance and dependence in animals. Thus, the analgesic action of morphine can be dissociated from tolerance and dependence which contribute to its abuse. Concern about abuse has been a major limitation in the use of morphine, but appropriate medical use of morphine seldom progresses to dependence and abuse. Morphine abuse is higher among medical and paramedical personnel because they have easier access to the drug. Earlier, morphine addicts tended to be from the middle age group, but now younger individuals are also opting for it. Opium eating has been prevalent among natives in the orient.

Withdrawal of morphine is associated with marked drug-seeking behaviour. Physical manifestations of abstinence are—lacrimation, sweating, yawning, anxiety, fear, restlessness, aggression, gooseflesh, mydriasis, tremor, insomnia, abdominal colic, diarrhoea, dehydration, rise in BP, palpitation and rapid weight loss. Delirium and convulsions are not a characteristic feature (contrast barbiturates) and are seen only occasionally. Cardiovascular collapse and fatality are rare if supportive measures are instituted. Administration of an opioid at this time immediately terminates the withdrawal syndrome.

Opioid antagonists (naloxone, nalorphine) precipitate acute withdrawal syndrome in the dependent subject. In the more severely dependent, even 0.2 mg of naloxone can precipitate marked withdrawal.

Treatment: Consists of withdrawal of morphine and substitution with oral methadone (long-acting, orally effective) followed by gradual withdrawal of methadone (*see* p. 504). However, craving for the opioid may persist for long time, and relapse rate among postaddicts is high. Long-term methadone maintenance and other techniques using agonist-antagonistic drugs are also employed.

PRECAUTIONS AND CONTRAINDICATIONS

Morphine is a drug of emergency, but due care has to be taken in its use.

1. Infants and the elderly are more susceptible to the respiratory depressant action of morphine.
2. It is dangerous in patients with respiratory insufficiency (emphysema, pulmonary fibrosis, cor pulmonale); sudden deaths have occurred. Morphine accentuates sleep apnoea; hypoxic brain damage can occur.
3. Bronchial asthma: Morphine can precipitate an attack by its histamine releasing action. A high potency opioid with lower histamie releasing potential (e.g. fentanyl) should be used, if unavoidable, in an asthmatic.
4. Head injury: Morphine is contraindicated in patients with head injury. Reasons are—
   - By retaining CO_2, it increases intracranial tension which will add to that caused by head injury itself.
   - Even therapeutic doses can cause marked respiratory depression in these patients.
   - Vomiting, miosis and altered mentation produced by morphine interfere with assessment of progress in head injury cases.
5. Hypotensive states and hypovolaemia exaggerate fall in BP due to morphine.
6. Undiagnosed acute abdominal pain: Morphine can aggravate certain conditions, e.g. diverticulitis, biliary colic, pancreatitis. Inflamed appendix may rupture. Morphine can be given after the diagnosis is established. Pentazocine, buprenorphine are less likely to aggravate biliary spasm.
7. Elderly male: Chances of urinary retention are high.
8. Hypothyroidism, liver and kidney disease patients are more sensitive to morphine.
9. Unstable personalities: Are able to continue with its use and become addicted.

Interactions

Phenothiazines, tricyclic antidepressants, MAO inhibitors, amphetamine and neostigmine potentiate morphine and other opioids, either by retarding its metabolism or by a pharmacodynamic interaction at the level of central neurotransmitters. Exaggerated CNS depression can occur if morphine is given with a sedative-hypnotic.

Morphine retards absorption of many orally administered drugs by delaying gastric emptying.

Dose: 10–50 mg oral, 10–15 mg i.m. or s.c. or 2–6 mg i.v.; 2–3 mg epidural/intrathecal; children 0.1–0.2 mg/kg. i.m. or s.c.

MORPHINE SULPHATE 10 mg/ml inj; MORCONTIN 10, 30, 60, 100 mg continuous release tabs; 30–100 mg BD; RILIMORF 10, 20 mg tabs, 60 mg SR tab.

OTHER OPIOIDS

1. Codeine It is methyl-morphine, occurs naturally in opium, and is partly converted in the body to morphine. It is less potent than morphine (1/10th as analgesic), also less efficacious; is a partial agonist at μ opioid receptor with a low ceiling effect. The degree of analgesia is comparable to aspirin (60 mg codeine ~ 600 mg aspirin). Codeine can relieve mild to moderate pain only.

However, codeine is more selective cough suppressant (1/3rd as potent as morphine);

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subanalgesic doses (10–30 mg) suppress cough (*see* p. 239). Codeine has very low affinity for opioid receptors. The analgesic action has been ascribed to morphine generated by its demethylation by CYP2D6. Codeine fails to produce analgesia in subjects with polymorphic CYP2D6 who cannot demethylate codeine. However, receptors involved in the antitussive action appear to be distinct, because they bind codeine as well as morphine.

Codeine has good activity by the oral route (oral: parenteral ratio 1:2). A single oral dose acts for 4–6 hours. Constipation is a prominent side effect when it is used as analgesic. Codeine has been used to control diarrhoea (*see* Ch. 48). Other side effects are milder. The abuse liability is low. No parenteral preparation is available.

2. Pholcodine, Ethylmorphine They have codeine like properties and have been used mainly as antitussive (*see* p. 239); claimed to be less constipating.

3. Heroin (Diamorphine, Diacetylmorphine) It is about 3 times more potent than morphine; more lipid soluble, therefore enters the brain more rapidly, acts faster but duration of action is similar. It is considered to be more euphorient (especially on i.v. injection) and highly addicting. Because of its high potency, it has been favoured in illicit drug trafficking. The sedative, emetic and hypotensive actions are said to be less prominent. However, it has no outstanding therapeutic advantage over morphine and has been banned in most countries except U.K.

4. Pethidine (Meperidine)

Pethidine was synthesized as an atropine substitute in 1939, and has some actions like it. Though chemically unrelated to morphine, it interacts with μ opioid receptors and its actions are blocked by naloxone. Important differences in comparison to morphine are:

1. Dose to dose 1/10th in analgesic potency; however, analgesic efficacy approaches near to morphine and is higher than codeine.
2. After i.m. injection, the onset of action is more rapid but duration is shorter (2–4 hours).
3. It does not effectively suppress cough.
4. Spasmogenic action on smooth muscles is less marked—miosis, constipation and urinary retention are less prominent.
5. Tachycardia (due to antimuscarinic action) occurs instead of bradycardia, and cardiac contractility may decrease.

Pethidine is better absorbed than morphine; oral: parenteral activity ratio is higher (1/3 to 1/2). It is nearly completely metabolized in liver. A major part is hydrolysed to *meperidinic acid,* but a small fraction is demethylated to form *norpethidine,* which has excitant effects. The plasma t½ is 2–3 hours.

Apart from usual opioid side effects, pethidine produces some atropinic effects like dry mouth, blurred vision, tachycardia, but constipation, urinary retention and miosis are less prominent.

Overdose of pethidine produces many excitatory effects, *viz.* tremors, mydriasis, hyperreflexia, delirium, myoclonus and convulsions due to accumulation of *norpethidine.* Renal failure patients given repeated doses of pethidine are prone to experience similar effects.

Nonselective MAO inhibitors interfere with hydrolysis but not with demethylation of pethidine—norpethidine is produced in excess and excitement occurs. Pethidine injected in patients receiving a selective serotonin reuptake inhibitor (SSRI) may produce the 'serotonin syndrome' (*see* p. 488) by enhancing 5-HT release.

Clinical use of pethidine as a morphine substitute has very much declined because of these problems. It is occasionally used to control shivering during recovery from anaesthesia and that attending i.v. infusions. Pethidine is not useful in cough and diarrhoea.

Dose: 50–100 mg i.m., s.c. (may cause irritation, local fibrosis on repeated injection). It is occasionally given orally or i.v.

PETHIDINE HCL 50, 100 mg tab. 100 mg/2 ml inj; VERPAT 50 mg/ml inj.

5. Fentanyl A pethidine congener, 80–100 times more potent than morphine, both in analgesia and respiratory depression. In analgesic doses it produces few cardiovascular effects. Cardiac contractility and heart rate are only marginally reduced, and it has lower propensity to release histamine. Because of high lipid solubility, it enters brain rapidly and produces peak analgesia in 5 min after i.v. injection. The duration of action is short: starts wearing off after 30–40 min due to redistribution, while elimination t½ is ~4 hr. In the injectable form it is almost exclusively used in anaesthesia (*see* p. 411-12). Transdermal

fentanyl has become a very frequently used opioid analgesic for cancer/terminal illness pain or other types of chronic pain. Buccal use is possible, but not oral due to high first pass metabolism.

DUROGESIC transdermal patch delivering 12 μg/hr, 25 μg/hr, 50 μg/hr, 75 μg/hr or 100 μg per hour; the patch is changed every 3 days.

6. Remifentanil This faster acting congener of fentanyl has a very brief (10–15 min) duration of action after i.v. injection; Remifentanil is used exclusively in anaesthesia (*see* p. 412).

7. Methadone A synthetic opioid, chemically dissimilar but pharmacologically very similar to morphine. It is a full μ receptor agonist, and has analgesic, respiratory depressant, emetic, antitussive, constipating and biliary actions similar to morphine.

The most important feature of methadone is high oral: parenteral activity ratio (1 : 2) and its firm binding to tissue proteins. In single doses it is only slightly more potent than morphine and has comparable duration of action (4–6 hours on i.m. injection), but it cumulates in tissues on repeated administration—duration of action is progressively lengthened due to gradual release from these sites; plasma t½ on chronic use is 24–48 hours. Plasma protein binding is 90% and it is metabolized in liver, primarily by demethylation and cyclization involving CYP3A4 and CYP2B6. Metabolites are excreted in urine. Rifampin and phenytoin can cause withdrawal symptoms to appear in methadone dependent subjects by inducing its metabolism.

Because of slow and persistent nature of action, sedative and subjective effects are less intense. It is probably incapable of giving a 'kick'. The abuse potential is rated lower than morphine. Tolerance develops more slowly, probably due to progressive filling of tissue stores. Withdrawal syndrome is of gradual onset, taking 1–2 days after discontinuation, is prolonged and less severe.

Methadone has been used primarily as substitution therapy for opioid dependence: 1 mg of oral methadone can be substituted for 4 mg of morphine, 2 mg of heroin and 20 mg of pethidine. After 2–3 days of methadone substitution, it is gradually withdrawn. The resulting withdrawal syndrome is prolonged, but bearable. Another technique is *methadone maintenance* therapy in opioid addicts—sufficient dose of methadone (40–80 mg/day) is given orally over long term to produce high degree of tolerance so that pleasurable effects of i.v. doses of morphine or heroin are not perceived and the subject gives up the habit.

Methadone can also be used as an analgesic for the same conditions as morphine; dose 2.5–10 mg oral or i.m. It is occasionally employed as antitussive.

METHADONE 5 mg/ml and 10 mg/ml syr; 5, 10, 20, 40 mg tabs (for maintenance therapy of opioid dependence).

8. Dextropropoxyphene It is a weak synthetic opioid chemically related to methadone, half as potent analgesic as codeine, which lacks antitussive activity. Perceived to have low/no addicting potential, it was included in many popular over-the-counter analgesic combinations containing paracetamol and other drugs. However, overdose of dextropropoxyphene was found to cause delirium and seizures. Its demethylated metabolite which accumulated on repeated dosing, exhibited cardiotoxicity, and reports of fatalities appeared. Many countries, including UK, Europe, USA withdraw it, and it was banned in India in 2013.

9. Tramadol This centrally acting analgesic is an atypical opioid which relieves pain by opioid as well as additional mechanisms. Its affinity for μ opioid receptor is low, while that for κ and δ is very low. Unlike other opioids, it inhibits reuptake of NA and 5-HT, increases 5-HT release, and thus activates monoaminergic spinal inhibition of pain. Its analgesic action is only partially reversed by the opioid antagonist naloxone.

Injected i.v. 100 mg tramadol is equianalgesic to 10 mg i.m. morphine. Oral bioavailability of tramadol is good (oral: parenteral dose ratio is 1.4). The t½ is 5–6 hours and effects last for 4–6 hrs. Tramadol causes insignificant respiratory depression, sedation, constipation or urinary retention. It is generally well tolerated, but nausea and dizziness may be prominent. Other side effects are sleepiness, dry mouth, sweating and lowering of seizure threshold, therefore contraindicated in epileptics. Haemodynamic effects are minimal. Tramadol should not be

given to patients taking SSRI therapy because of risk of 'serotonin syndrome' (*see* p. 488).

Tramadol is indicated for mild-to-moderate short-lasting pain due to diagnostic procedures, injury, surgery, etc, as well as for chronic pain including cancer pain, but is not effective in severe pain. Little tendency to dose escalation by chronic users is seen and abuse potential is low.

Dose: 50–100 mg oral/i.m./slow i.v. infusion (children 1–2 mg/kg) 4–6 hourly.

CONTRAMAL, DOMADOL, TRAMAZAC 50 mg cap, 100 mg SR tab; 50 mg/ml inj in 1 and 2 ml amps.

ULTRACET, URGENDOL: tramadol 75 mg + paracetamol 325 mg tab.

10. Tapentadol This newer atypical opioid is similar to tramadol in structure and mechanism of action: binding to μ opioid receptor is weak, and it acts mainly *via* monoaminergic pain mechanisms. Compared to tramadol, inhibition of NET is more marked than that of SERT; thus, it primarily activates central noradrenergic pathways to elicit analgesia.

Tapentadol is well absorbed orally, largely glucuronide conjugated, and the metabolite is excreted in urine. It is useful in the treatment of moderately severe pain conditions, and appears to be at least as effective as tramadol, but head-to-head comparative data is inadequate to establish relative efficacy.

Side effects are similar to tramadol, but nausea and vomiting appears to be less troublesome. However, it can trigger 'serotonin syndrome' in patients treated with SSRIs, and carries risk of precipitating seizures in predisposed patients. Thus, tapentadol is a useful alternative to tramadol for acute as well as chronic pain of moderate severity.

Dose: 50–100 mg 2–4 times/day.

TAPOSER, DUOVOLT, TAPCYNTA 50, 75, 100 mg tab; TAPOSER-P: Tapentadol 50 mg + paracetamol 325 mg tab.

USES (Of morphine and its congeners)

1. *As analgesic* Opioid analgesics are indicated in severe pain of any type. However, they only provide symptomatic relief without affecting the cause. Pain may be valuable for diagnosis; should not be relieved by a potent analgesic unless proper assessment of the patient has been done. Indiscriminate use of opioids can be hazardous. On the other hand, inadequate dose or reluctance to use an opioid for a patient in distress is equally deplorable.

Important features of opioid analgesics with agonist, partial agonist and agonist-antagonist action on opioid receptors are compared in Table 34.1.

Morphine (or one of its parenteral congeners) is indicated especially in traumatic, visceral, ischaemic (myocardial infarction), postoperative, burn, cancer pain, renal colic and the like. It should be given promptly in myocardial infarction to allay apprehension and reflex sympathetic stimulation. Opioids, especially pethidine, have been extensively used for obstetric analgesia, but one must be prepared to deal with the foetal and maternal complications.

Adequate use of morphine (even i.v.) is indicated in an emergency. It may prevent neurogenic shock and other autonomic effects of excruciating pain such as that of crush injuries. Patients in severe pain require higher doses of opioids and tolerate them without manifesting toxicity. There is considerable individual variability in the response to opioids. Opioids should not be restricted in case of pain of terminal illness (e.g. cancer pain), but for other chronic conditions, due consideration must be given to their addicting liabilities. Neuropathic pain responds less predictably to opioid analgesics, while pregabalin, amitriptyline, duloxetine are the major drugs for such pain.

Epidural (2–3 mg) or intrathecal (0.2 mg) injection of morphine produces segmental analgesia lasting ~12 hour without affecting other sensory, motor or autonomic modalities. It is being used for surgical analgesia in abdominal, lower limb and pelvic operations as well as for labour, postoperative, cancer and other intractable pain. Respiratory depression occurs after a delay due to ascent of the opioid through the subarachnoid space to the respiratory centre. Use of fentanyl in place of morphine produces faster analgesia and reduces the risk of respiratory depression because of greater uptake of fentanyl by nerves at the site of injection.

Patient controlled analgesia (PCA) is an attractive technique of postoperative pain control in which the patient himself regulates the rate of i.v. fentanyl infusion according to intensity of pain felt.

Table 34.1: Comparative features of opioid analgesics, partial agonist analgesics and agonist-antagonist analgesics

Drug	Nature of analgesia	Ceiling efficacy	Oral: parenteral ratio	Equivalent analgesic dose	Duration of analgesia
1. Morphine	μ agonist	++++	Low	10 mg	4–6 hr
2. Codeine	Partial μ agonist	+	High	60 mg	4–6 hr
3. Pethidine	μ agonist	++++	Medium	60–100 mg	2–4 hr
4. Methadone	μ agonist	++++	High	6–10 mg	4–6 hr $
5. Fentanyl	μ agonist	++++	Low	0.1 mg	1–1.5 hr
6. Tramadol	μ agonist (low affinity)	++	High	50–100 mg	4–6 hr
7. Pentazocine	κ agonist	++	Medium	30–60 mg	3–5 hr
8. Butorphanol	κ agonist	+++	— #	2.0 mg	4–6 hr
9. Nalbuphine	κ agonist	+++	— #	10 mg	3–6 hr
10. Buprenorphine	Partial μ agonist	+++	Low	0.3 mg	6–8 hr

+ to ++++ Low to high (full) analgesic efficacy.
# Parenteral use only; no oral preparation.
$ Duration of action increases after repeated dosing.

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Chronic terminal illness pain, including cancer pain, needs to be treated aggressively without regard to the risk of dependence. Oral morphine in continuous release formulation is often used, but increasing doses are required as tolerance develops. Substituting oral methadon for morphine or rotating the two opioids may some times help. Transdermal fentanyl is a suitable option that is now frequently used. The patch produces analgesia after ~12 hr, but then blood levels of fentanyl and intensity of analgesia remain fairly uniform if the patch is changed every 3 days. For severe chronic pain continuous opioid analgesia with a long-acting preparation works better than a short-acting opioid given intermittently. Rescue short-acting opioid is to be added to the continuous analgesia for 'breakthrough pain'. Buprenorphine (a strong agonist-antagonist) as sublingual tablet or transdermal patch is another opioid used for chronic cancer pain.

For milder pain, e.g. toothache, headache, arthralgia, etc. aspirin-like analgesics are preferred. When they are not effective—codeine/ tramadol/ tapentadol may be used orally, either alone or in combination with paracetamol. The combination enhances the ceiling analgesia. For majority of painful conditions, especially more severe and longerlasting pain, a NSAID may be combined with the opioid. This serves to enhance analgesia while keeping the opioid dose low.

2. *Preanaesthetic medication* Morphine and pethidine are used in few selected patients (*see* p. 413).

3. *Balanced anaesthesia and surgical analgesia* Fentanyl, remifentanil or morphine are an important component of intraoperative anaesthetic techniques (*see* p. 411-12).

4. *Relief of anxiety and apprehension* Especially in myocardial infarction, internal bleeding (haematemesis, threatened abortion, etc.) morphine has been employed. It may prevent worsening of the condition by suppressing reflex overactivity. However, opioids should not be used as anxiolytics or to induce sleep.

5. *Acute left ventricular failure/acute pulmonary edema* Morphine injected i.v. affords dramatic relief by—

(a) Reducing preload on heart due to vasodilatation and peripheral pooling of blood.
(b) Tending to shift blood from pulmonary to systemic circuit; relieves pulmonary congestion and edema.

(c) Allaying air hunger and dyspnoea by depressing respiratory centre.

(d) Cutting down sympathetic stimulation by calming the patient, thereby reduces cardiac work.

Morphine is also indicated to relieve pulmonary edema due to infarction of lung, but not due to irritant gases. It is contraindicated in bronchial asthma.

6. *Cough* Codeine or more commonly its substitutes are widely used for suppressing dry, irritating cough (*see* Ch. 16).

7. *Diarrhoea* The constipating action of codeine has been used to check diarrhoea and to improve the consistency of stools in colostomy. Loperamide and diphenoxylate are synthetic opioids used exclusively as antidiarrhoeals. The risk and benefits of their use are detailed in Ch. 49.

OPIOID RECEPTORS

Morphine and other opioids exert their actions by interacting with specific receptors present on neurones in the CNS and in peripheral tissues. Chemical modification of morphine structure has yielded a number of compounds which have a complex pattern of morphine-like and other agonistic and antagonistic actions that cannot be explained on the basis of a single opioid receptor. Radioligand binding studies divided the opioid receptors into three types (μ, κ, δ); which have been cloned, mapped and studied with modern techniques. Each has a specific pharmacological profile and pattern of anatomical distribution in the brain, spinal cord and peripheral tissues (mainly gut, blood vessels, heart, lungs and immune cells). Subtypes of μ and κ receptor have been identified. Actions mediated by the 3 types of opioid receptors are listed in Table 34.2.

Opioid ligands can interact with different opioid receptors as agonists, partial agonists or competitive antagonists. The overall pattern of effect of a particular agent depends not only on the nature of its interaction with different opioid receptors, but also on its relative affinity for these, e.g. morphine is an agonist on μ, κ and δ receptors, but its affinity for μ receptors is much higher than that for the other two. The effects, therefore, are primarily the result of μ receptor activation.

The nature and intensity of action of complex action opioids and antagonists are summarized in Table 34.3.

μ receptor The μ receptor is characterized by its high affinity for morphine. It is the major receptor mediating actions of morphine and its congeners. Endogenous ligands for μ receptor are peptides called *Endomorphins 1 and 2*, which have been found in mammalian brain. These pepticles produce biological effects ascribed to μ receptor. Other opioid peptides *viz.* β-endorphin, enkephalins and dynorphins bind to μ receptor with lower affinity. High density of μ receptors has been detected in periaqueductal gray, thalamus, nucleus tractus solitarious, nucleus ambiguus and area postrema

Table 34.2: Actions ascribed to the three types of opioid receptors

μ *(mu)*	κ *(kappa)*	δ *(delta)*
Analgesia (supraspinal μ_1 + spinal μ_2)	Analgesia (spinal κ_1) (supraspinal-κ_3)	Analgesia (spinal + affective component of supraspinal)
Respiratory depression (μ_2)	Respiratory depression (lower ceiling)	Respiratory depression
Sedation	Dysphoria, psychotomimetic	Affective behaviour
Euphoria	Miosis (lower ceiling)	Reinforcing actions
Miosis	Sedation	Reduced g.i. motility
Muscular rigidity	Dependence (nalorphine type)	Proconvulsant
Reduced g.i. motility (μ_2)	Reduced g.i. motility	
Dependence (morphine type)		

Table 34.3: Nature of interaction of opioid ligands with the three major types of opioid receptors

Ligand	*μ (mu)*	*κ (kappa)*	*δ (delta)*
1. Morphine	Ago. (Strong)	Ago. (Weak)	Ago. (Weak)
2. Nalorphine	Anta. (Strong)	Ago. (Medium)	—
3. Pentazocine	P.Ago, Anta. (Weak)	Ago. (Medium)	—
4. Butorphanol	P.Ago (Weak)	Ago. (Strong)	—
5. Nalbuphine	Anta. (Weak)	Ago. (Strong)	—
6. Buprenorphine	P.Ago	Anta. (Medium)	—
7. Naloxone	Anta. (Strong)	Anta. (Medium)	Anta. (Weak)
8. Naltrexone	Anta. (Strong)	Anta. (Strong)	Anta. (Weak)
9. Met/Leu enkephalin	Ago. (Medium)	—	Ago. (Strong)
10. β-Endorphin	Ago. (Strong)	—	Ago. (Strong)
11. Dynorphin A, B	Ago. (Weak)	Ago. (Strong)	Ago. (Weak)

Ago.—Agonist; Anta.—Antagonist
P. Ago—Partial agonist: have lower efficacy, though affinity (potency) may be high.

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Two subtypes of μ receptor have been proposed:

μ_1: Has higher affinity for morphine, mediates supraspinal analgesia and is selectively blocked by naloxonazine.

μ_2: Has lower affinity for morphine, mediates spinal analgesia, respiratory depression and constipating action.

κ receptor This receptor is defined by its high affinity for ketocyclazocine and dynorphin A; the latter is considered to be its endogenous ligand. *Norbinaltorphimine* is a selective κ antagonist. Two subtypes of κ receptor κ_1 and κ_3 are functionally important. Analgesia caused by κ agonists is primarily spinal (through κ_1 receptor). However, κ_3 receptors mediate lower ceiling supraspinal analgesia. Other κ actions are listed in Table 34.2.

δ receptor This receptor has high affinity for leu/met enkephalins which are its endogenous ligands. The δ mediated analgesia is again mainly spinal (δ receptors are present in dorsal horn of spinal cord). The limbic areas are rich in δ receptors, suggesting role of these receptors in the affective component of supraspinal analgesia, reinforcing actions and dependence. The proconvulsant action is more prominent in δ agonists. Myenteric plexus neurones express high density of δ receptors, which mediate reduced g.i. motility. *Naltrindole* is a selective δ antagonist.

It thus appears that μ and δ receptor responses are quite similar, but those exerted through κ receptor are distinct. In certain areas κ actions are antagonistic to μ actions.

The σ (sigma) receptor is no longer considered an opioid receptor, because it is neither activated by morphine nor blocked by naloxone. However, certain opioids, e.g. pentazocine, butorphanol and many unrelated compounds (including the hallucinogens phencyclidine) bind to σ receptors. Certain naloxone insensitive effects of pentazocine like drugs, e.g. dysphoria, psychotomimetic action, tachycardia, mydriasis are believed to be mediated by σ receptors.

Opioid receptor transducer mechanisms

All 3 types of opioid receptors (μ, κ, δ) have been cloned; all are GPCRs located mostly on prejunctional neurones. They generally exercise inhibitory modulation by decreasing release of the junctional transmitter (Fig. 34.1). As such, various monoaminergic (NA, DA, 5-HT), GABA, glutamate (NMDA/AMPA) pathways are intricately involved in opioid actions.

Opioid receptor activation reduces intracellular cAMP formation and opens K^+ channels (mainly through μ and δ receptors) or closes voltage gated N type Ca^{2+} channels (mainly κ receptor). These actions result in neuronal hyperpolarization and reduced availability of

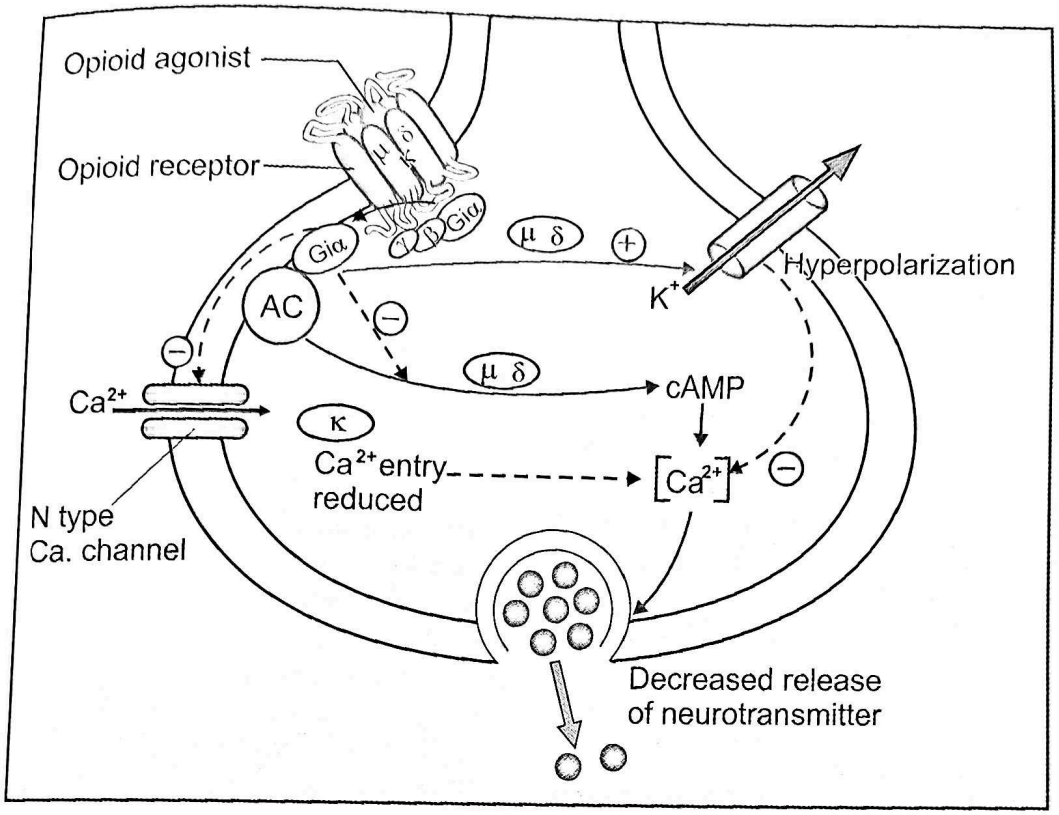

Fig. 34.1: Opioid receptor transducer mechanisms
AC-Adenylyl cyclase; Gi-coupling protein; cAMP-Cyclic AMP

intracellular Ca^{2+} → decreased neurotransmitter release by cerebral, spinal, and myenteric neurones (e.g. glutamate and neuropeptides from primary nociceptive afferents). Opioid receptors are also expressed on postjunctional neurones. Activation of these receptors results in K^+ channel opening, hyperpolarization and neuronal inhibition. However, other mechanisms and second messengers may also be involved, particularly in the long-term.

COMPLEX ACTION OPIOIDS

Clinically, the agonist-antagonist (agonist at one opioid receptor, antagonist at another) and partial/weak agonist (low intrinsic activity) opioids are analgesics of limited efficacy equivalent to lower doses of morphine. They cause submaximal (low ceiling) respiratory depression and are less addicting. However, in only few situations they have proven to be advantageous over the full μ receptor agonists. None of these drugs should be administered to a subject who has received μ opioid agonist, or who is likely to be dependent on such a drug, because analgesia may be reduced or a severe withdrawal reaction may be precipitated.

COMPLEX ACTION OPIOIDS

Agonist-antagonists (κ analgesics)	Partial μ agonist + κ antagonist
Nalorphine	Buprenorphine
Pentazocine	
Butorphanol	
Nalbuphine	

1. Nalorphine It is N-allyl-normorphine, and was the first opioid antagonist introduced in 1951 which could reverse morphine action. Later it was found to have agonistic action on κ receptor as well, producing lower ceiling analgesia. It is not used clinically because of dysphoric and psychotomimetic effects.

2. Pentazocine It is the first agonist-antagonist to be used as an analgesic. Along with being a weak μ antagonist, it has more marked κ agonistic actions. Distinctive features of pentazocine are:

(a) Analgesia caused by pentazocine has a lower ceiling and is primarily spinal (κ_1). It has a different character than that caused by morphine.

(b) Sedation and respiratory depression is 1/3 to 1/2 of morphine at lower doses, and has a lower ceiling, does not increase much beyond 60 mg dose.

(c) Tachycardia and rise in BP are produced at higher doses due to sympathetic stimulation. This may increase cardiac work. Pentazocine is better avoided in coronary ischaemia and myocardial infarction.

(d) Biliary spasm and constipation are less marked.

(e) Vomiting is less frequent. Other side effects are sweating and lightheadedness.

(f) Subjective effects are pleasurable (morphine-like) at lower doses. These are recognised by post-addicts to be opiate. However, as dose is increased, effects become unpleasant (nalorphine-like at > 60 mg i.m.) and psychotomimetic effects (κ, σ mediated) appear.

Tolerance and dependence to pentazocine develops on repeated use. Withdrawal syndrome has features of both morphine and nalorphine abstinence, but is milder in intensity. 'Drug seeking' is less intense.

Injected in morphine dependent subjects, it precipitates withdrawal. In pentazocine dependent subjects, naloxone precipitates withdrawal, but at higher doses.

Pentazocine is effective orally. Though considerable first pass metabolism occurs; oral: parenteral ratio is 1 : 3. It is oxidized and glucuronide conjugated in liver and excreted in urine. Plasma t½ is 3–4 hours, duration of action of a single dose is 3–5 hours.

Oral dose: 50–100 mg.

Parenteral dose: 30–60 mg i.m., s.c., may cause local fibrosis on repeated injection due to irritant property.

FORTWIN 25 mg tab., 30 mg/ml inj., FORTSTAR, SUSEVIN 30 mg/ml inj; FORTAGESIC pentazocine 15 mg+paracetamol 500 mg tab.

Pentazocine is not a favoured analgesic now, but may be used for postoperative and moderately severe pain in burns, trauma, fracture, cancer, etc. Frequent side effects and potential for dysphoric/psychotomimetic effect limits its utility in chronic (cancer) pain.

3. Butorphanol It is a κ analgesic, similar to but stronger and more potent than pentazocine (butorphanol 2 mg = pentazocine 30 mg). Likewise, analgesia and respiratory depression have a lower ceiling than morphine. Sedation is more prominent, but nausea, cardiac stimulation and other side effects are similar to pentazocine. Subjective effects are less dysphoric. Psychotomimetic effects are occasional (it is a weaker σ agonist at higher doses). BP is not raised.

Postaddicts recognize butorphanol as a barbiturate rather than an opiate and mostly dislike it. However, it produces dependence, and withdrawal can be precipitated by high dose of naloxone, but the syndrome is mild. The abuse potential of butorphanol is low. The most outstanding feature is that butorphanol can neither substitute for, nor antagonize morphine. This shows its very weak interaction with μ receptors.

Butorphanol has been used in a dose of 1–4 mg i.m. or i.v. for postoperative and other short-lasting (e.g. renal colic) painful conditions, but should be avoided in patients with cardiac ischaemia. The t½ and duration of action is similar to morphine.

BUTRUM 1 mg/ml, 2 mg/ml inj.

4. Nalbuphine A structural analogue of naloxone, this is another strong κ agonist with weak μ receptor antagonistic property. Nalbuphine is a more potent analgesic than pentazocine, and produces few dysphoric or psychotominetic effects at recommended doses (10–20 mg). Much higher doses, however, do produce weird thoughts, hallucinations and dysphoria. Ceiling effect is exhibited; no further

analgesia or respiratory depression is produced above 30 mg i.m. dose. Unlike pentazocine it dose not cause sympathetic stimulation. There are no cardiovascular effects, and it is considered safe for use in M.I.

Nalbuphine is extensively metabolized with a plasma t½ of 2–3 hours. Dependence, withdrawal symptoms and abuse potential is low and similar to pentazocine. Drug seeking is minimal. Nalbuphine can precipitate morphine withdrawal in dependent subjects, reflecting its weak μ antagonistic property. It is indicated in postoperative and other moderately severe pain requiring a parenteral opioid. Cardiac ischaemia is no restriction to its use.

Dose: 10 mg i.m., s.c. or i.v. every 4–6 hours; increase dose to 20 mg, if needed.

NALFY, RUFFY 10 mg in 1 ml and 20 mg in 1 ml inj.

5. Buprenorphine It is a synthetic thebaine congener, highly lipid-soluble μ analgesic that is 25 times more potent than morphine but with lower intrinsic activity and ceiling effect. The onset of action is slower and duration longer. After a single dose, analgesia lasts for 6–8 hours; but with repeated dosing, duration of action increases to ~24 hours due to accumulation in tissues. Certain other effects last still longer.

Sedation, vomiting, miosis, subjective and cardiovascular effects are similar to morphine, but constipation is less marked. Postural hypotension is prominent. Respiratory depression (and analgesia) exhibit ceiling effect. Buprenorphine substitutes for morphine at low levels of morphine dependence, but precipitates withdrawal in highly morphine dependent subjects, reflecting its partial agonistic action at μ receptors. Antagonistic action on κ receptor has also been detected.

Lower degree of tolerance, dependence and addiction develops with buprenorphine. Its withdrawal syndrome resembles that of morphine, but is delayed for several days, is milder and longer lasting. 'Drug seeking' is present. Abuse liability is rated lower than morphine.

Naloxone (high dose) can prevent buprenorphine effect, but only partially reverses it when given afterwards. Naloxone does not precipitate buprenorphine withdrawal; probably because of more tight binding of buprenorphine to opioid receptors.

Buprenorphine has good efficacy by sublingual route, is highly plasma protein bound and remains in tissues for several days; terminal t½ is 40 hours. It is mostly excreted unchanged in bile and finds its way out of the body in faeces.

Dose: 0.3–0.6 mg i.m., s.c. or slow i.v., also sublingual 0.2–0.4 mg 6–8 hourly.

NORPHIN, TIDIGESIC 0.3 mg/ml inj. 1 and 2 ml amps. 0.2 mg sublingual tab; BUPRIGESIC, PENTOREL, BUPRINOR 0.3 mg/ml inj in 1, 2 ml amp.

Use: Buprenorphine is indicated for long-lasting painful conditions requiring an opioid analgesic, e.g. cancer pain. It has also been recommended for premedication, postoperative pain, in myocardial infarction and in the treatment of morphine dependence as an alternative to methadone.

Buprenorphine is not suitable for use during labour, because if respiratory depression occurs in the neonate, it cannot be effectively reversed by naloxone.

Meptazinol and *Dezocine* are other agonist-antagonist opioids introduced in some countries.

PURE OPIOID ANTAGONISTS

Three opioid antagonists are in use:

Naloxone
Naltrexone
Nalmefene

1. Naloxone It is N-alylnor-oxymorphone and a competitive antagonist on all types of opioid receptors. However, it blocks μ receptors at much lower doses than those needed to block κ or δ receptors. It is devoid of any kind of agonistic activity even at high doses (20 times μ blocking dose). No subjective or autonomic effects are produced in individuals who have not received an opioid. No addiction, dependence or abstinence syndrome has been observed.

Injected intravenously (0.4–0.8 mg) it promptly antagonizes all actions of morphine: analgesia

is gone, respiration is not only normalized but stimulated—probably due to sudden sensitization of respiratory centre to the retained CO_2, or it may be a manifestation of acute withdrawal; pupils dilate. However, sedation is less completely reversed.

At 4–10 mg dose it also antagonizes the agonistic actions of nalorphine, pentazocine, etc., but the dysphoric and psychotomimetic effects of some of them are incompletely suppressed. The naloxone insensitive component is believed to be mediated through σ receptors.

Actions of buprenorphine are prevented but not effectively reversed by naloxone, because it fails to displace buprenorphine that has already bound to the opioid receptors.

Naloxone 0.4 mg i.v. precipitates morphine withdrawal in dependent subjects: the syndrome lasts for 2–3 hours; 5 mg or more is required to precipitate nalorphine and pentazocine withdrawal.

Naloxone also blocks the actions of endogenous opioid peptides (*see* below). These peptides have been implicated in a variety of physiological functions; it is surprising that naloxone does not produce hyperalgesia or other effects in normal individuals. However, it has been found to render those individuals more susceptible to pain who normally have high tolerance. It blocks *placebo, acupuncture* and *stress-induced analgesia,* showing involvement of endogenous opioid peptides in these responses. Naloxone partly antagonizes respiratory depression produced by certain nonopioids, e.g. N_2O, diazepam as well.

Naloxone is inactive orally because of high first pass metabolism in liver. Injected i.v. it acts in 2–3 min. The primary pathway of metabolism is glucuronidation. Plasma t½ is 1 hour in adults and 3 hours in newborns. Duration of action is 1–3 hr.

Adverse effects of naloxone are uncommon; may include rise in BP and pulmonary edema.

NARCOTAN 0.4 mg in 1 ml (adult) and 0.04 mg in 2 ml (infant) amps; NALOX, NEX 0.4 mg inj.

Use Naloxone is the drug of choice for morphine poisoning (0.4–0.8 mg i.v. every 2–3 min; max 10 mg) and for reversing neonatal asphyxia due to opioid use during labour (10 μg/kg in the cord). It is also used to treat overdose with other opioids and agonist-antagonists (except buprenorphine). Repeated doses of naloxone are needed because of its short duration of action.

Other possible clinical applications of naloxone are:

- To reverse respiratory depression due to intraoperative use of opioids: 0.1–0.2 mg i.v. (this dose usually preserves analgesia in the postoperative period).
- It has also been tried as an adjunct to intraspinal opioid analgesia: reverses respiratory depression without abolishing pain relief.
- Diagnosis of opioid dependence—precipitates withdrawal in dependent subjects.
- It also partially reverses alcohol intoxication.
- Naloxone has been found to elevate BP in endotoxic or hypovolaemic shock, stroke and spinal injury. In these conditions injection of morphine worsens cardiovascular status. Opioid peptides are believed to be involved in the pathogenesis. However, the value of naloxone compared to conventional therapy is uncertain.

2. Naltrexone It is chemically related to naloxone and is another pure opioid antagonist, that is devoid of subjective and other agonistic effects, but very high doses have caused unpleasant feelings in some individuals. It is more potent than naloxone. Naltrexone differs from naloxone in being orally active and having a long duration of action (1–2 days) which makes it suitable for 'opioid blockade' therapy of postaddicts: 50 mg/day is given orally so that if the subject takes his/her usual shot of the opioid, no subjective effects are produced and the craving subsides. Alcohol craving is also reduced by naltrexone, and it is approved for prevention of relapse of heavy drinking (*see* p. 421). Nausea is a common side effect; another is headache. High doses can cause hepatotoxicity.

NALTIMA 50 mg tab.

3. Nalmefene This pure opioid antagonist lacks hepatotoxicity of naltrexone, has higher oral bioavailability and is longer acting.

Methyl naltrexone This derivative of naltrexone does not penetrate the blood-brain barrier, but effectively blocks peripheral action of μ opioids. It is being used to reverse constipation

in cancer patients receiving chronic opioid analgesia and in those taking methadone maintenance therapy.

Alvimopan is another peripheral μ receptor antagonist which has limited absorption from the gut and penetration into the brain. It is approved for the treatment of postoperative ileus following gut resection surgery.

ENDOGENOUS OPIOID PEPTIDES

In the mid 1970s, with herculean efforts, a number of peptides having morphine-like actions were isolated from mammalian brain, pituitary, spinal cord and g.i.t. These peptides are active in very small amounts, their actions are blocked by naloxone, and they bind with high affinity to the opioid receptors. There are 3 major families of opioid peptides. Each is derived from a specific large precursor polypeptide.

1. Endorphins β-endorphin (β-END), having 31 amino acids, is the most important of the endorphins. It is derived from Pro-opiomelanocortin (POMC) which also gives rise to γ-MSH, ACTH and two lipotropins. β-END is primarily μ agonist, but also has δ action.

2. Enkephalins Methionine-enkephalin (met-ENK) and leucine-enkephalin (leu-ENK) are the most important. Both are pentapeptides. The large precursor peptide *proenkephalin* has 4 met-ENK and 1 leu-ENK residues. The two ENKs have a slightly different spectrum of activity; while met-ENK has equal affinity for μ and δ sites, leu-ENK prefers δ receptors.

3. Dynorphins Dynorphin A and B (DYN-A, DYN-B) are 8–17 amino acid peptides derived from *prodynorphin* which contains 3 leu-ENK residues also. DYNs are more potent on κ receptors, but also activate μ and δ receptors.

Distribution of the 3 families of peptides is summarized below:

1. *POMC* (limited distribution)
   - Arcuate nucleus which sends projections to limbic areas and medulla.
   - Anterior pituitary (modulates hormone release).
   - Pancreatic islets (modulates insulin, glucagon release).
2. *Proenkephalin* (wide distribution)
   - Pain areas in spinal cord, trigeminal nucleus, periaqueductal grey matter.
   - Affective areas in limbic system, locus coeruleus and cortex.
   - Medulla (autonomic functions).
   - Median eminence of hypothalamus (neuro-endocrine control).
   - Adrenal medulla, gastric and intestinal glands.
3. *Prodynorphin* – Wide distribution roughly parallel to proenkephalin, but in distinct neurones of the same area.

Receptor selectivity of the 3 major opioid peptide families may be graded as:

Opioid peptide	*Relative receptor selectivity*
β-Endorphin	$\mu > \delta >> \kappa$
Enkephalin (Met/Leu)	$\delta \geq \mu >> \kappa$
Dynorphin A,B	$\kappa >> \mu = \delta$

The opioid peptides constitute an endogenous opioid system which normally modulates pain perception, mood, hedonic (pertaining to pleasure) and motor behaviour, emesis, pituitary hormone release and g.i.t. motility, etc.

β-END injected directly into the brain is 20–40 times more potent analgesic than morphine. Its primary localization in hypothalamus and pituitary and its long t½ prompts that it has a *neurohormone* function which modulates the release of other hormones. β-END decreases LH, FSH release and increases GH, prolactin release. Naloxone has opposite effects on the levels of these hormones—suggesting that the system is constitutively active.

The wide distribution of ENKs and DYNs along with their short t½ suggests that they function as *neuromodulator* or *neurotransmitter*. They appear to regulate pain responsiveness at spinal and supraspinal levels. Naloxone blocks placebo, acupuncture and stress-induced analgesia, suggesting the involvement of opioid peptides in these responses. Opioid peptides also appear to participate in regulation of affective behaviour and autonomic function.

A novel opioid peptide Nociceptin/orphanin FQ (N/OFQ) has been isolated from mammalian brain. It is localized in cortex, hippocampus, spinal cord and certain sensory

sites. N/OFQ is believed to play a role in stress response, reward and reinforcing actions, learning and memory. The N/OFQ receptor, is now called *Nociceptin opioid peptide (NOP)* receptor. At certain sites, N/OFQ can act as an 'antiopioid' through the NOP receptor. In the pain control mechanisms, N/OFQ appears to play both opioid-like as well as antagonistic roles, depending on the site and the basal state of pain.

Morphine and other opioids act as exogenous agonists on some of the receptors for these peptides. This has given an explanation for the existence of specific receptors in the body for exogenous substances like morphine. Morphine itself has now been detected in mammalian brain.

PROBLEM DIRECTED STUDY

34.1 A boy aged 14 years is brought to the hospital emergency with crush injury of both lower legs. An eye witness who brought the boy told that a bus had run over his legs about 20 min. ago. The legs were crushed but he had not bled much. He also told that initially the boy was shrieking in pain, but had fainted on way to the hospital. Preliminary examination reveals that the patient is in a semiconscious state, looks pale, the pulse is fast, low volume and collapsing. Both legs have sustained multiple fractures, the skin and soft tissues have lacerated from which blood is oozing, but there is no active bleeding. There is no apparent head injury.

(a) Should any medicine be administered immediately, before even completing a thorough physical examination? If so, which drug, by what route, and why?

(see Appendix-1 for solution)