Opioid Analgesics

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Points to be covered

- Classification of opioid analgesics
- Pain pathways & sites of action of opioids
- Opioid receptors
- Endogenous opioid peptides
- Pharmacological actions of morphine
- Tolerance and dependence
- Some individual opioid drugs
- MCQs

- **Opioid**
  - Compound with morphine-like activity
- Opiate
  - Substance extracted from opium
  - Exudate of unripe seed capsule of Papaver somniferum
  - Contain 2 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%)

    } Nonanalgeslic

Opioids

- Modern definition of opioid
  - Molecule that interact with opioid receptor
- Opioid compound
  - Opioid receptor agonists, antagonists, agonists-antagonists
  - Natural products, synthetic and semisynthetic compounds
  - Peptides synthesized by neuron and other cell

CLASSIFICATION OF OPIOIDS

Natural opium alkaloids:

- Morphine
- Codeine

Semisynthetic opiates:

- Diacetylmorphine (Heroin)
- Pholcodine

Synthetic opioids:

- Pethidine (Meperidine)
- Fentanyl, Alfentanil, Sufentanil, Remifentanil
- Methadone
- Dextropropoxyphene
- Tramadol
- Tapentadol

COMPLEX ACTION OPIOIDS AND OPIOID ANTAGONISTS

Agonist-antagonists (κ analgesics)

- Nalorphine
- Pentazocine
- Butorphanol
- Nalbuphine

Partial/weak μ agonist + κ antagonist

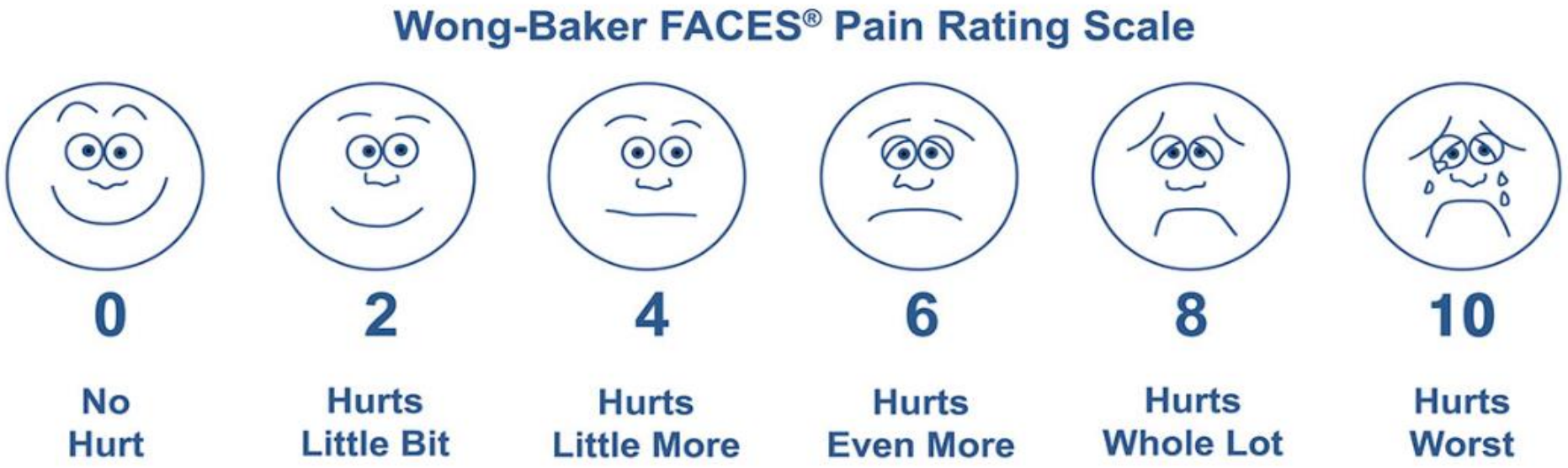
- Buprenorphine

Pure antagonists

- Naloxone
- Naltrexone
- Nalmefene

Pain Pathophysiology

- Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage
- Pain perception has 2 components
  - Nociceptive component
  - Affective component
- Analgesic relieves pain without significantly altering consciousness



Pain Intensity– 0 to 10

Word scale – no pain to excruciating pain

Non-verbal behaviors– stressed, guarded movement, grimacing, moaning, crying

Pain pathway & Sites of action of opioids

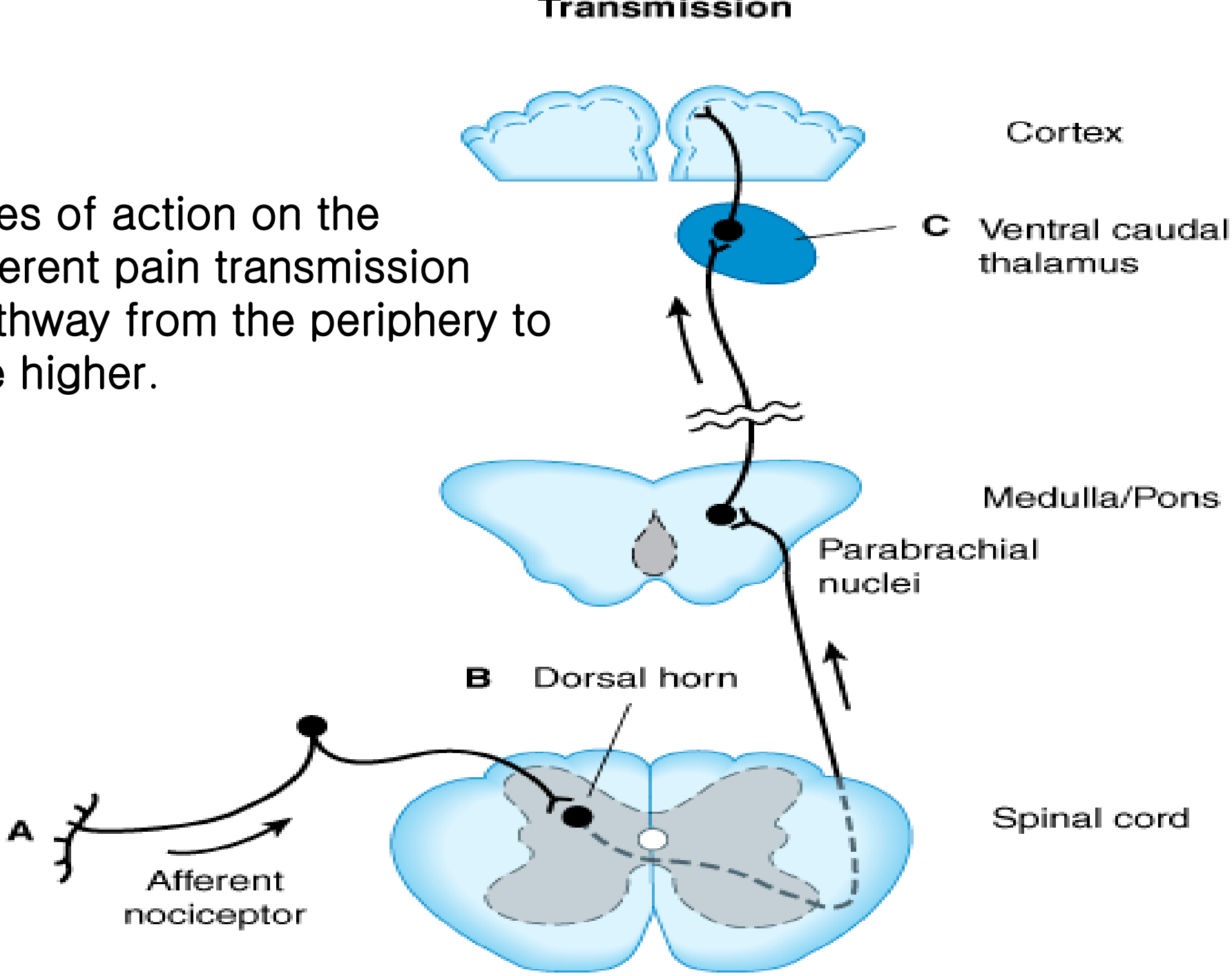
- Pain pathways (ascending & descending)

- Ascending pain pathway-

  Starts from terminals of primary afferent neurons fibres eg.

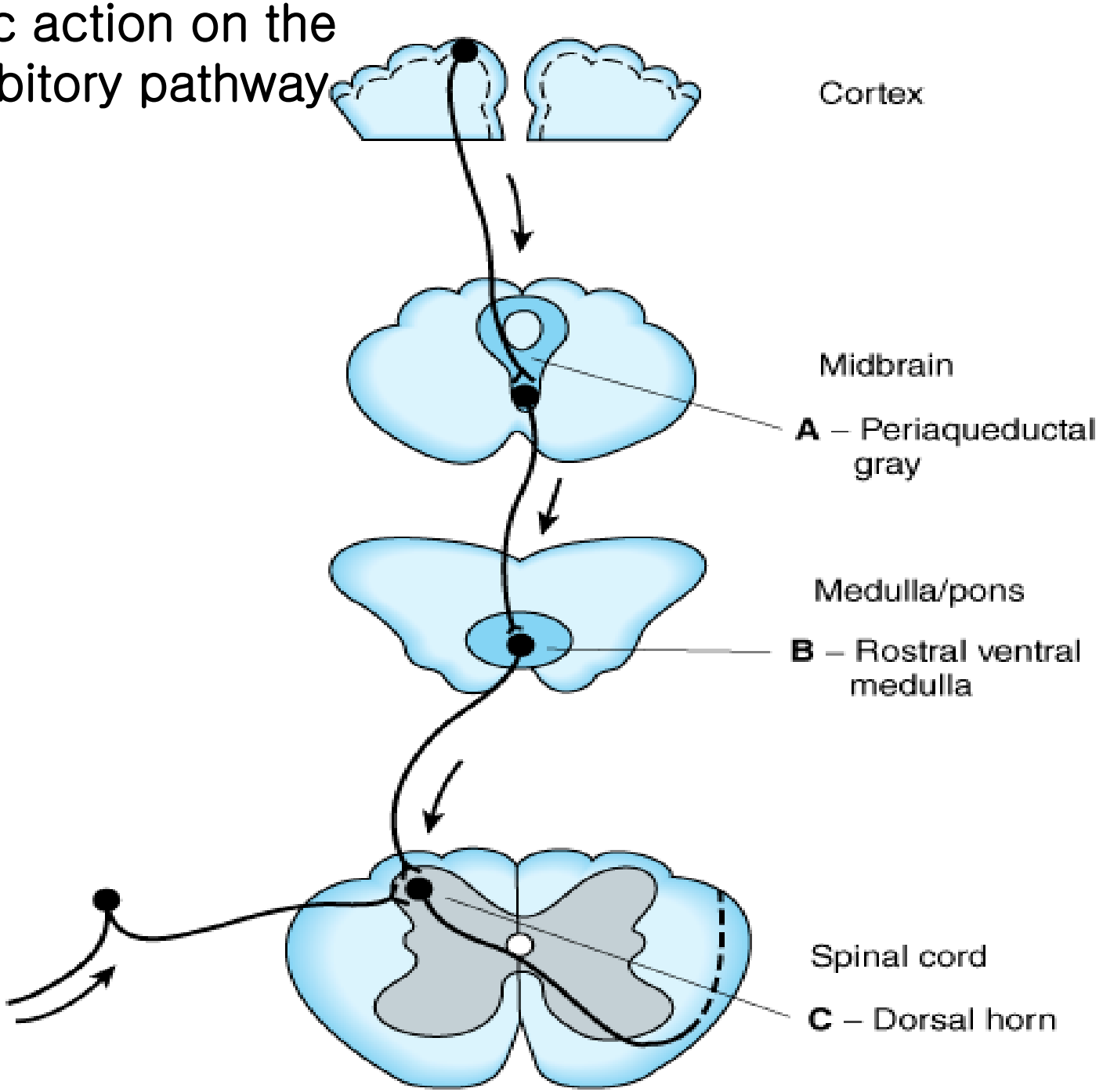
  - Aδ - fast conducting
  - C - slow conducting

Sites of action on the afferent pain transmission pathway from the periphery to the higher.



- Descending pathway exert inhibitory effect on pain transmission through Substantia Gelatinosa (SG)
- Sensory **Aβ fibres** (arising from peripheral tissues) stimulate release of **met-enkephlin** from interneurons of SG and block pain transmission
- So massaging, rubbing, acupunture, counter-irritants provide pain relief
- Morphine inhibit release of glutamate from primary afferent fibres in the spinal cord
- Gate control mechanism

Opioid analgesic action on the descending inhibitory pathway



- Brainstem local circuitry underlying the modulating effect of μ-opioid receptor (MOR)–mediated analgesia on descending pathways.
- The pain-inhibitory neuron is indirectly activated by opioids (exogenous or endogenous), which inhibit an inhibitory (GABAergic) interneuron.
- This results in *enhanced* inhibition of nociceptive processing in the dorsal horn of the spinal cord

Opioid Receptor Transducer Mechanism

- Agonist binding

  ↓

  -conformational changes in the GPCR

  -Inhibition of adenylyl cyclase activity (μ,δ)
  -Stimulation of K^+ current (μ,δ)
  -Inhibition of voltage-gated Ca^{2+} channels (κ)

  ↓

  -decreased release of neurotransmitter
  (substance-P, neurokinin A, neurokinin B, glutamate)

- Most of available opioid analgesics
  - Act at μ-opioid receptor

- Activation of μ-opioid receptor

  → analgesia, sedation, euphoria, respiratory depression, nausea, vomiting, decreased gastrointestinal motility, tolerance, dependence

- δ-, κ-opioid receptor
  - analgesia
  - dysphoria, Psychotomimetic (κ)
  - Affective behaviour, proconvulsant (δ)

Endogenous Opioid Peptides

- A number of endogenous opioid peptides having morphine like activity are found in brain, pituitary, spinal cord, GIT

β-Endorphins - μ	**Dynorphins- κ**
Enkephalins - μ & δ	Endomorphins- μ
Nociceptin- NOP receptor (nociceptin opioid peptide receptor)	

They modulate pain and mood

Effects of Morphine

Central Nervous System Effects

Analgesia

- Opioids reduce both aspects of the pain experience, especially the affective aspect.

Euphoria

- intravenous drug users experience a pleasant floating sensation with lessened anxiety and distress (DA release in nucleus accumbance).

Sedation

- Drowsiness
- clouding of mentation
- little or no amnesia
- No motor incoordination
- Sleep is induced in the elderly (can be easily aroused from this sleep)

Respiratory Depression

- by inhibiting brainstem respiratory mechanisms
- depressed response to carbon dioxide challenge
- In individuals with increased intracranial pressure, asthma, chronic obstructive pulmonary disease, this decrease in respiratory function may not be tolerated.

Cough Suppression

- Codeine in particular
- However, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis.

Temperature regulating center depression

- chances of hypothermia

Vasomotor centre depression

- Fall in BP

Morphine stimulates:

- CTZ (nausea, vomiting)

- Edinger Westphal nucleus of III nerve is stimulated (miosis), no tolerance develops

- Vagal centre (bradycardia)

Truncal Rigidity-

- Truncal rigidity reduces thoracic compliance and thus interferes with ventilation

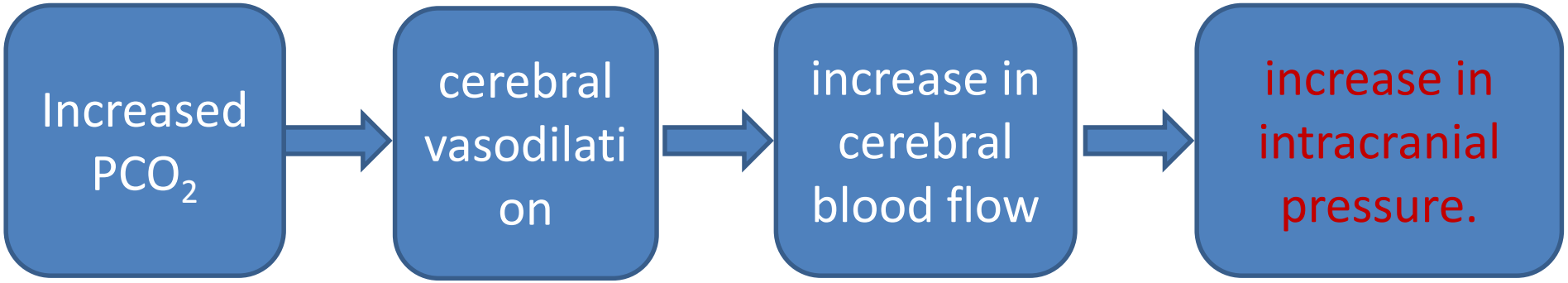
- Truncal rigidity may be overcome by opioid antagonist, which will also antagonize the analgesic action of the opioid

- Preventing truncal rigidity while preserving analgesia requires the concomitant use of neuromuscular blocking agents.

Peripheral Effects

Cardiovascular System

- Bradycardia
  Meperidine is an exception (can result in tachycardia)
- Hypotension - due to
  -peripheral arterial and venous dilation
  -depression of vasomotor centre
  -release of histamine
- increase in intracranial pressure –



Gastrointestinal Tract

Constipation

- no tolerance
- Opioid receptors exist in high density in the GIT
- mediated through both local as well as the CNS effect
- gastric secretion of HCl is decreased
- propulsive peristaltic waves are diminished
- tone is increased
- delays passage and allows increased absorption of water, which leads to constipation
- so used in the management of diarrhea

Biliary Tract

- sphincter of Oddi may constrict
- contract biliary smooth muscle
- result in biliary colic

Renal

- Renal function is depressed by opioids
- decreased renal plasma flow
- Ureteral and bladder tone are increased
- Increased sphincter tone may precipitate urinary retention
- ureteral colic caused by a renal calculus is made worse by opioid-induced increase in ureteral tone

Uterus-

- may prolong labor
- both peripheral and central actions of the opioids can reduce uterine tone

Neuroendocrine-

- stimulate the release of ADH, prolactin, and somatotropin
- inhibit the release of luteinizing hormone

Pruritus-

- histamine release - responsible for pruritus and occasionally urticaria

Clinical Use of Opioid Analgesics

- **Analgesia**
- **Cough**
- **Diarrhea**
- **Acute Pulmonary Edema**
- **Balanced anaesthesia**
- **Preanaesthetic medication**
- **Relief of anxiety and apprehension**

Toxicity & Undesired Effects

Behavioral restlessness, tremulousness, hyperactivity (in dysphoric reactions)
Respiratory depression
Nausea and vomiting
Increased intracranial pressure
Postural hypotension accentuated by hypovolemia
Constipation
Urinary retention
Itching around nose, urticaria (more frequent with parenteral and spinal administration)

Acute morphine poisoning

- >50 mg of morphine
- Lethal dose is 250mg
- Stupor, coma, shallow breathing, cyanosis, pinpoint pupil, fall in BP, convulsions
- Death due to respiratory failure

Treatment

- Positive pressure respiration
- Iv fluids
- Gastric lavage with potassium permagnate
- Naloxone

Tolerance -With frequently repeated therapeutic doses of morphine, there is a gradual loss in effectiveness

- To reproduce the original response, a larger dose must be administered
- NMDA receptor ion channel complex play a critical role in tolerance development and maintenance

Physical dependence is defined as a characteristic **withdrawal** or **abstinence syndrome** when a drug is stopped or an antagonist is administered

Tolerance

- Maintenance of normal sensitivity of receptors requires **reactivation by endocytosis and recycling**.
- endogenous ligands binding- results in receptor endocytosis followed by resensitization and recycling of the receptor to the plasma membrane.

- But morphine fails to induce receptor endocytosis
- In contrast, methadone does induce receptor endocytosis, so used for treatment of opioid tolerance and dependence

Withdrawal

Withdrawal is manifested by significant somatomotor and autonomic outflow-

- agitation
- hyperalgesia
- hyperthermia
- hypertension
- diarrhea
- pupillary dilation

- release of all pituitary and adrenomedullary hormones

- affective symptoms

  -dysphoria

  -anxiety

  -depression

These phenomena are highly aversive and motivate the drug recipient to make robust efforts to avoid the withdrawal state

Contraindications

In Patients with Head Injuries

- Marked respi. depression by therapeutic doses
- Opioids cause respiratory depression, carbon dioxide retention, cerebral vasodilation, elevated intracranial pressure
- Trauma patients may already have elevated intracranial pressure
- Vomiting, miosis, altered mentation by morphine interferes with assessment of pt condition

Use during Pregnancy

- In pregnant women using opioids, **fetus may become physically dependent in utero** and manifest withdrawal symptoms in the early postpartum period.

- Withdrawal syndrome including irritability, shrill crying, diarrhea, or even seizures.

- When withdrawal symptoms are mild - diazepam
- with more severe withdrawal - methadone

Related drugs

Pethidine

- 1/10th in analgesic potency
- Spasmodic action on smooth muscles is less
- Tachycardia (**antimuscarinic** action)- it is related to atropine, even acts on opioid receptors
- Safer in asthmatics (less histamine release)
- Uses- analgesia, preanaesthetic medication
- Analgesia during labour (less neonatal respi depression)

Fentanyl

- 80-100 times more potent than morphine
- little propensity to release histamine
- Not used orally due to high first pass metabolism
- Quick onset of action- **peak analgesia in 5 min** after i. v. injection
- Duration of action- half hour
- **Transdermal** fentanyl has become available for use in cancer (patch changed every 3days)

Methadone

- Slow & persistant action
- Sedative & subjective effects are less intense
- No kick
- Less abuse potential
- Use- as substitute therapy for opioid dependence
- 1mg methadone for 4 mg morphine.

Tramadol

- Analgesic action also by additional mechanism
  - norepinephrine & 5-HT reuptake Inhibition
- Advantage
  - Less respiratory depression, constipation, sedation, urinary retention
  - Less abuse potential
- Disadvantages
  - nausea , vomiting
  - Seizures precipitation (C/I in epilepsy)
  - Serotonin syndrome with SSRI
- Labour pain, injury, surgery (other short lasting pain)
- Moderate pain treatment : as effective as morphine
- Severe pain treatment : less effective than morphine

Tapentadol

- Analgesic action by activating central NA pathway
- Advantage
  - Less nausea, vomiting (vs tramadol)
- Disadvantages
  - Seizures precipitation (C/I in epilepsy)
  - Serotonin syndrome with SSRI

Pentazocine (κ analgesic)

- It has agonistic actions and weak opioid antagonistic activity
- elicit dysphoric and psychotomimetic effects
- increase in blood pressure and heart rate (avoid in MI)

Uses-

- moderate to severe pain
- as a preoperative medication and
- as a supplement to anesthesia

Buprenorphine (weak μ agonist & κ antagonist)

- 25-50 times more potent than morphine
- Sublingual route
- Slower onset & longer duration of action
- Postural hypotension is marked
- Cannot be used during labour (respi dep not reversed by naloxone)

Uses-

- Long lasting pain- cancer
- Post-operative pain, MI
- Tt of morphine dependence

Naloxone (μ, κ, δ antagonist)

- Antagonizes all morphine actions
- Sedation is less completely reversed
- Blocks placebo, acupuncture, stress induced analgesia

Use

- Morphine poisoning
- Diagnostic test for opioid addiction
- Revert neonatal respi depression due to opioid use during labour

Peripherally Acting Opioid

- Loperamide, Diphenoxylate
  - peri μ-opioid receptor agonist
  - Not cross blood-brain barrier
  - Treatment : inflammation-induced hyperalgesia (analgesia without CNS side effect)
  - Relieve diarrhea

- Alvimopan
  - peri μ-opioid receptor antagonist
  - Relieves constipation in opium addicts
  - Without precipitating opioid withdrawal
  - Treat postoperative paralytic ileus

Opioid with Other Analgesics

- Goal of using analgesics in combination
  - Achieve superior analgesia
  - Reduce dose of each drug
  - Minimizing side effect
- NSAIDs
  - Synergistical action with systemic opioid to produce analgesia
- Local anesthetics and opioid
  - Synergistical pain relief when intrathecal or epidural administration

Thank you