Opioids & Anesthesia

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History of Opioids

- Opium
  - opium poppy fossils date back to 30,000 BC
  - ancient Persia, Greece, Egypt, & Rome
    - nutritional, euphoric, & religious uses
  - 1st medicinal use 4000 BC
  - used for post operative pain relief in 1784
- Morphine
  - isolated in 1805
  - hypodermic needle injections in 1853
- Heroin
  - synthesized by Bayer in 1898

Opioids & Surgery

- Desired clinical effects
  - analgesia, antitussive, & anti-shivering
- Undesirable effects
  - respiratory depression, nausea & vomiting , decrease GI motility

Opioid Receptors

Mu Receptor	υ	MOR
Kappa Receptor	κ	KOR
Delta Receptor	δ	DOR
Sigma Receptor	σ	SOR

- 3 identified υ receptors
- 3 identified κ receptors
- 2 identified δ receptors

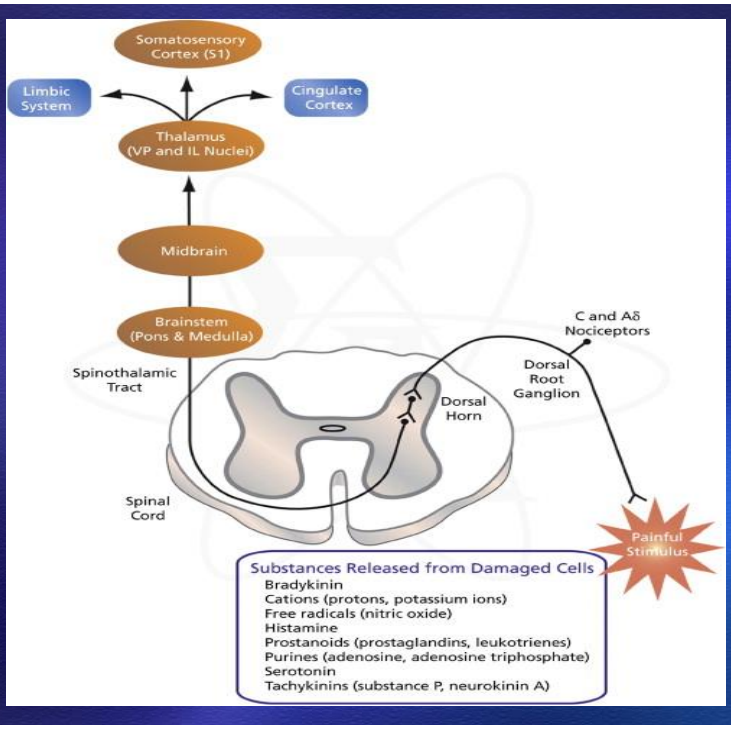
Opioid Receptors

υ 1	analgesia, miosis, urinary retention, nausea & vomiting, pruritis
υ 2	sedation, respiratory depression, decreased GI motility
δ	analgesia, alterations of affective behavior
κ	analgesia, sedation, decrease in GI motility, psychotomimesis, dysphoria, & miosis
σ	dysphoria, psychotomimesis

- opioids act primarily on mu (υ) receptor for surgical pain analgesia

Pain Pathways

- Surgical trauma causes release of mediators
  - bradykinin, serotonin, leukotrienes, prostaglandins, substance P, & histamine
- peripheral nociceptors send signals to dorsal root ganglion and dorsal horn of spinal cord
- secondary transmission then goes to brainstem

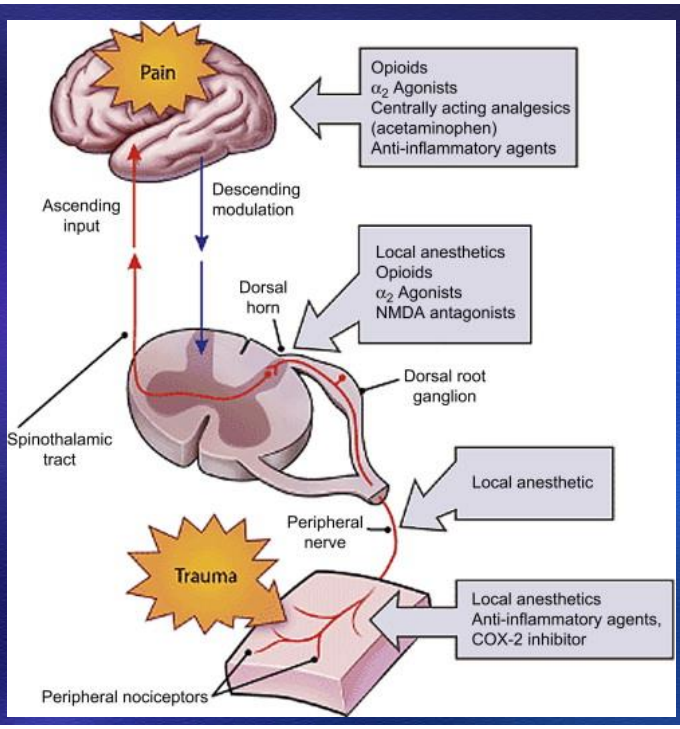


Opioid Mechanism Action

- Analgesic effect
  - directly inhibit → ascending nociceptive transmission from dorsal horn of spinal cord to brain
  - mu receptors in brain → stimulate descending inhibitory pathways to block nerve transmission from nociceptive dorsal horn neuron
- Analgesic effect
  - mostly due to mu receptors activation
  - some from delta & kappa receptors as well

Pain

- modulation of pain can occur
  - at site of injury
  - peripheral nerves
  - spinal cord or brain
- multi modal drug therapy is key to success



Opioid Tolerance

- Patients with prolonged opioid use
  - patients using a minimum of 60 mg morphine PO per day or an equianalgesic dose of another opioid for 1 week
- Pain relief from usual dose is less than before
  - need to increase the opioid dose for relief
- Patients require 2 to 3 times the dose as an opioid naïve patient for same amount of relief
  - increased risks of side effects like respiratory depression

Opioid Tolerance

- Chronic use of opioids by patients
  - immediate release, short acting opioids
    - morphine, oxycodone, hydrocodone, hydromorphone
  - long-acting opioids
    - morphine (MS Contin), oxycodone (OxyContin), & transdermal fentanyl patch
  - patients should maintain these agents the day of surgery & they need additional analgesics for pain

Opioid Induced Hyperalgesia

- paradoxical effect of diminished pain thresholds & increased atypical pain unrelated to original, preexisting pain
- hyperalgesia = increased response to noxious stimuli induced by opiate use
- increased pain when opioid dose is increased

Opioid Induced Hyperalgesia

- multifactorial process in pain pathway
  - neuroplastic changes in central & peripheral pain receptors and nerves
  - NMDA receptors are activated to increase pain excitation
- remifentanil in high dose infusions can precipitate hyperalgesia
  - Doses in excess of what we typically use for office anesthesia

Opioid Respiratory Depression

- central respiratory center is located in medulla & pons
  - generates respiratory drive
  - modulated by inputs from the cortex, brainstem, and peripheral chemoreceptors in the carotid & aortic bodies
  - decreases in cerebrospinal pH & increases in CO_2
    - stimulate the medulla to increase respiration
    - increase respiratory rate and tidal volume (Vt)

Opioid Respiratory Depression

- peripheral chemoreceptors
  - as PaO_2 decreases → especially below 60 → carotid & aortic body inputs by way of glossopharyngeal nerve to respiratory center increase respirations
  - increases in CO_2 from hypoventilation are more of a stimulus to breath than hypoxia
  - hypoxia is neither a good stimulus for respiration nor an early sign of opioid respiratory depression

Opioid Induced Respiratory Depression (OIRD)

- primary receptor for OIRD = mu receptor
  - kappa receptor also reduces respiratory rate
- low opioid doses decrease respiratory rate
- higher doses will also decrease tidal volume
- opioids decrease stimulation by CSF pH
  - need even higher levels of CO_2 + lower pH to overcome the respiratory depression

Opioid Respiratory Depression

- infusion of opioids at low rate
  - opioids cause respiratory depression
  - develop hypercarbia which increases the respiratory rate
- high bolus or rapid infusion
  - opioid binding can result in severe respiratory depression or apnea
  - need to decrease infusion; let CO_2 build up to resume respirations
    - may need to ventilate the patient

Respiratory Depression

- Respiratory Depression magnified
  - use of high dose opioids
  - combination of opioids + other CNS depressants
    - benzodiazepines & propofol
    - patient's maintenance medications
  - very young patient
  - very old patient

CVS Side Effects

- Enhanced vagal & parasympathetic tone
  - causes bradycardia
  - exception is meperidine which causes tachycardia
- Decreased sympathetic tone
  - vasodilation & hypotension
  - will attenuate the response to surgical stress

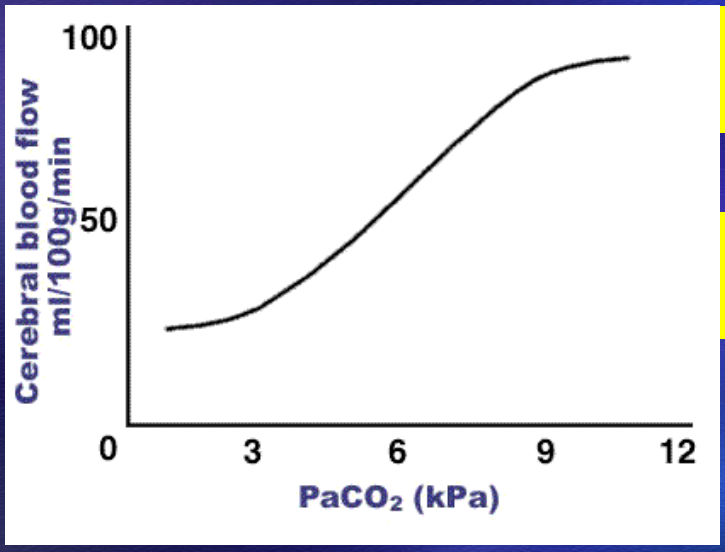
Opioid Side Effects → CNS

- CNS effects
  - sedation, dizziness, lightheadedness, & drowsy
  - euphoria & dysphoria
  - CTZ & vomiting center can be stimulated for N/V
- Pupils
  - miosis
  - mu receptors in Edinger – Westphal nucleus stimulated → parasympathetic effect on oculomotor nerve will cause muscles to iris to constrict

Opioids → ICP

- Intracranial Pressure
  - opioids have minimal effect on ICP
  - closed head injury → ICP is increased
- Are opioids potentially harmful with ↑ ICP?
- Opioids can cause hypoventilation
  - hypoventilation → ↑ CO2
  - ↑ CO2 → dilates cerebral vessels which ↑ blood volume in head
  - get further ↑ ICP
  - avoid opioids in closed head injury

CO2 Effect on Cerebral Blood Flow



Increased CO2 → dilates cerebral vessels → Increases cerebral blood flow

Aggressive hyperventilation will decrease cerebral flow → can create cerebral ischemia

Ventilate patient until normocarbic

Opioids & GI Side Effects

- GI motility & Opioids
  - inhibit intestinal & pancreatic secretions
  - increase bowel tone
  - decrease intestinal propulsive activity
- Overall result on GI from opioids
  - delayed gastric emptying
  - constipation
  - bowel distention
  - paralytic ileus
  - lower esophageal sphincter tone

Opioids & GI Effects

- Opioid receptors in wall of urinary bladder & ureters → cause acute urinary retention
  - urethral sphincter muscle can not relax
  - bladder tone increases
  - unable to void
- Increased biliary duct pressure and sphincter of Oddi spasm
  - get acute upper abdominal pain

Opioid Induced Nausea & Vomiting (OINV)

- Opioids
  - directly stimulate CTZ
  - decrease gastric motility
    - prolongs emptying time
    - fluids remain in stomach for vomiting
- Opioids → sensitize otic & vestibular areas
  - leads to motion sickness, nausea, & vomiting
  - *immobile patients less likely to have OINV*
- OINV typically lasts for ~ 2 days & stops

Andersen & Krohg. Can Anaesth Soc J. 1976; 223: 366

Opioid Side Effects

- Pruritus from opioids
  - itch specific neuronal pathway in spinal cord
    - uses spinothalamic tract to get to thalamus
    - distinct pathway not associated with pain pathways
    - histamine sensitive pathway
  - opioid itch → usually nose area
    - opioid spinal injections → 60 to 90% incidence

Opioid Side Effects

- Morphine, codeine, & meperidine
  - histamine release from mast cells
  - redness & itching along the path of the injected vein
- Phenylpiperidines → fentanyl & analogues
  - no histamine release

Chest Wall Ridgity

- Stiff and rigid increase in muscle tone in
  - chest wall rigidity
  - vocal cord closure is possible
  - abdominal wall stiffness
- Secondary to rapid injection or high doses
  - fentanyl
  - remifentanil
  - sufentanil or any fentanyl analogue

Management of Chest Wall Rigidity

- 3 treatment options
  - opioid reversal with naloxone
  - NMB agent → succinylcholine
  - no treatment & wait for opioid to redistribute to regain spontaneous ventilation
- Naloxone
  - adult → usual dose = 0.4 mg IV
  - children → 10 to 100 mcg/kg IV
  - if patient is not hypoxic → give naloxone in 0.1 mg increments to avoid excessive sympathetic reaction

Chest Wall Treatment

- Succinylcholine will reverse as well
  - intubating dose on adult
  - 0.5 to 1.5 mg/kg
  - support ventilations → mask, LMA, or intubate
- Apneic oxygenation
  - use nasal cannula & turn it to maximum flow
  - pressure differences between lungs and outside environment will allow oxygen to pass into lungs
    - you are oxygenating but not ventilating
    - still may need to use naloxone so can ventilate

Opioids & Shivering

- Opioids reduce thermoregulation thresholds
  - shivering threshold is lowered
  - kappa receptor mediated threshold reduction
  - α2B receptors are also involved in shivering
    - dexmedetomidine covers those
- Meperidine has unique property
  - terminates shivering in 70 to 80% of patients

Opioids in Office Anesthesia

Morphine

- Office anesthesia → rarely used
  - pruritus & long duration
- Dose → 0.1 mg/kg → dose range 2 to 10 mg
- Onset 5-10 minutes
- Duration 2-4 hours
- Analgesia, sedation, & euphoria
  - titrate by euphoria response by patient
- Histamine release & pruritus
- OINV not uncommon

Morphine Dystonia Paralysis of Lower Extremities Cae

Meperidine

- Long history in dental office anesthesia
  - inexpensive & effective
- Phenylpiperidine agent
- Dose → 50 to 100 mg IV
- Duration → 45 min to 1.5 hours
- Analgesia & sedation
- Euphoria, sometimes dysphoria
- OINV not uncommon
- Tachycardia & dry mouth (atropine like)
- Shivering treatment is main purpose

IV Fentanyl

- initial bolus dosing → 1 to 2 mcg/kg
  - adult range of 50 to 100 mcg
- onset → 30 seconds
- duration → 30 minutes
- no euphoria with agent
  - can not titrate agent
- lack of histamine release
- short acting agent
- poor agent to use as an infusion

IV Sufentanil

- Initial bolus dose → 0.25 to 2 mcg/kg
- Onset → 30 seconds
- Maintenance → 0.5 – 1.5 mcg/kg/hr
- Additional boluses → 2.5 – 10 mcg
- Respiratory depression
  - more likely than fentanyl if not used properly

IV Sufentanil

- Ultra-potent agent
- 5 mcg sufentanil = 50 mcg fentanyl

- Drug comes: 50 mcg/ml ampule
  - 1 ml and dilute to 10 ml → now 5 mcg/ml
  - use just like you would fentanyl

- Context Sensitivity Half Time > Alfentanil
  - mcg/kg/hr vs mcg/kg/min

IV Alfentanil

- Dose → 25 mcg
- Onset → 30 seconds
- Maintenance → 0.5 – 2 mcg/kg/min
- Less potent than fentanyl
- 500 mcg alfentanil = 50 mcg fentanyl
- Better agent than fentanyl for infusion

IV Remifentanil

- Ultra short acting agent
- Context sensitivity half time = 3.65 minutes
- Metabolized by plasma esterases
- Fast on & Fast off
- Excellent short acting agent
- More expensive than Fentanyl

IV Remifentanil - Bolus

- Remifentanil bolus dosing to intubate
  - 1st drug is propofol at 100 mcg/kg/min or just use bolus propofol induction (2 mg/kg)
  - 2nd drug is remifentanil as a bolus dose
    - 1.0 to 3.0 mcg/kg over no less than 30 seconds → 1 minute to 2 minutes
    - 2 mcg/kg bolus over 1 minute → very effective
    - too fast = chest wall rigidity

IV Remifentanil

- Remifentanil bolus dosing to intubate
  - onset of action with bolus = 1.3 minutes
  - intubating without NMB agents
  - run maintenance remifentanil
    - 0.25 mcg/kg/min
    - range = 0.05 to 2.0 mcg/kg/min

IV Remifentanil Infusion

- GA intubating dose using infusions
  - 1st drug = propofol at 100 mcg/kg/min
  - 2nd drug = remifentanil at 0.5 – 1.0 mcg/kg/min for 1 to 2 minutes
  - intubate without NMB agents

Glaxo Product 2005

IV Remifentanil

- GA intubating dose using infusions
  - run remifentanil maintenance dose
    - 0.25 mcg/kg/min
    - range of 0.05 to 2.0 mcg/kg/min
    - raise or lower maintenance as needed
    - raise in 25 to 100% increments → Q 2 to 5 minutes
    - lower in 25 to 50% decrements → Q 2 to 5 minutes

Propofol - Remifentanil Open Airway Technique

IV Remifentanil - Propofol

- Open airway deep sedation – GA anesthesia
  - 2 pumps
  - Propofol → start at 100 to 125 mcg/kg/min
  - Remifentanil → start at 0.05 mcg/kg/min
    - adjust up or down depending on airway obstruction, decreased respiratory (< 8 to 9 per minute), hypoventilation, or patient discomfort
    - range is 0.05 to 0.1 mcg/kg/min in most cases

IV Remifentanil - Propofol

- Open airway deep sedation – GA anesthesia
  - single pump technique
  - 20 ml propofol = 200 mg propofol
  - remifentanil vial → 1 mg vial = 1000 mcg
    - dilute 1 mg vial → 2 ml of saline = 500 mcg/ml
    - TB syringe → draw up 0.2 ml of diluted remifentanil
    - 0.2ml X 500 mcg/ml = 100 mcg Remifentanil
    - 100 mcg diluted by 20 ml propofol = 5 mcg Remi per ml

IV Remifentanil - Propofol

- Propofol – Remifentanil Single Pump
  - 1 ml = 10 mg propofol - 5 mcg remi
- Pump settings based on propofol infusion
  - run propofol at 100 mcg/kg/min
  - 100 kg → gets 10,000 mcg propofol in minute
  - 10 mg propofol = 10,000 mcg = 1 ml
  - remifentanil = 5 mcg/ml → means remi was running at 0.05 mcg/kg/min

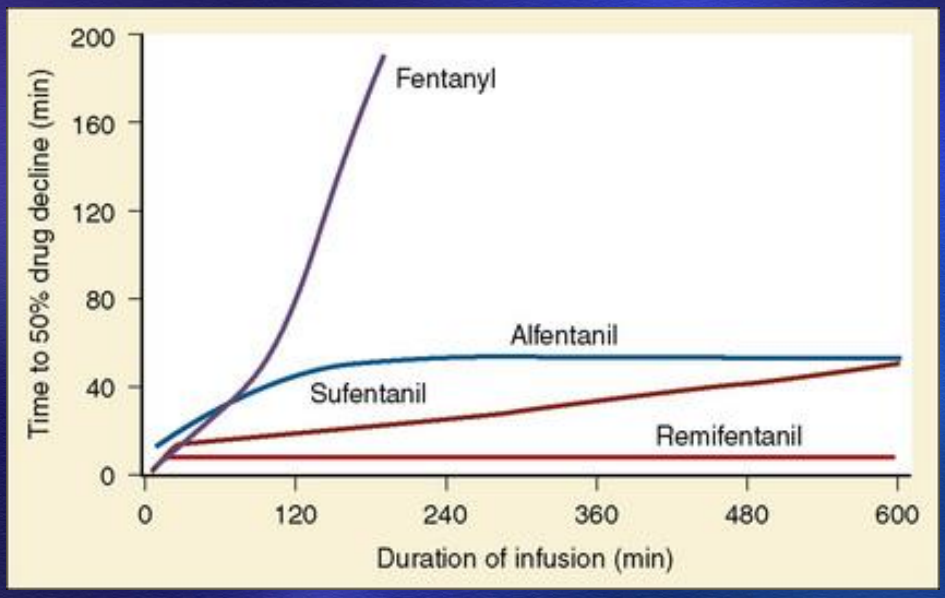
Remifentanil – Propofol Single Pump

- Bolus at start of case
  - 150 mcg/kg → 2 up to 4 bolus to start
    - range → 100 to 200 mcg/ml
    - 100 kg person → 15000 mcg propofol = 1.5 ml
    - remifentanil dose = 7.5 mcg per bolus
- Infusion after bolus
  - start at 70 mcg/kg/min
- Infusions without bolus therapy at start
  - 100 mcg/kg/min

Infusion vs Bolus of Opioids

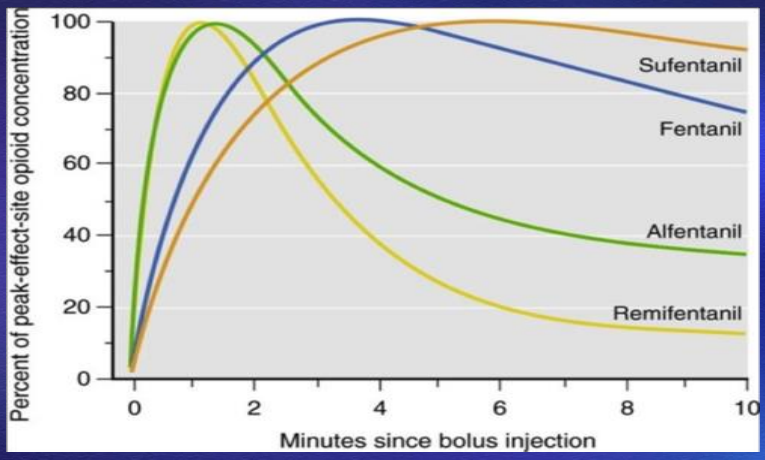
- Do I want to use infusions for all of my agents?
- While we can infuse all agents → we may just prolong our recovery time
- Office anesthesia → want our patients sedated or asleep → but we want a short recovery time

Infusion of Opioids



Intraoperative opioids

- Looking at context sensitivity graph
- Remifentanil will be ideal for an infusion
  - quick on but quick off
  - run infusion for hours & still see context sensitivity half time of 3 to 4 mins
- Fentanyl is not good infusion agent
  - as infusion continues → blood levels continue to rise over time
  - poor context sensitivity half time
  - recovery time will take too long
  - better to use as a bolus



Bolus Dosing of Opioids

- Remifentanil bolus will peak & eliminate the fastest
- Alfentanil bolus tends to act like remi but is slower
- Fentanyl & Sufentanil bolus therapy will take longer to peak and will last longer
  - expect a slower recovery time

Repeat Bolus of Opioids

- Remifentanil bolus will wear off clinically
  - looking at graph → 50% decrease in blood level in less than 4 minutes
  - if vital signs warrant additional opioids → repeat dosing in 5 to 6 minutes for 2nd dose
  - appears that even with multiple repeat bolus doses → recovery from opioid should be in 15 to 20 minutes after all remifentanil is stopped

Fentanyl as Bolus Therapy

- Fentanyl repeat bolus for office surgery
  - start with 1 to 2 mcg/ kg → 50 to 100 mcg IV
  - drug peaks in about → 5 minutes
  - should last at least → 30 minutes

  - looking at graph → blood levels have not dropped significantly by 10 minutes
  - if you repeat even small doses → 25 mcg IV → you can expect blood levels to remain high
  - expect longer recovery times for repeat doses of fentanyl

Opioid Chart

	MS	Fentanyl	Remifent	Alfent	Sufent	Demerol
Compare Potency	1	75 to 125	250	10 to 25	500 to 1000	0.1
Peak Effect (min)	20 to 30	3 to 5	1.5 to 2	1.5 to 2	3 to 5	5 to 7
Duration (hr)	3 to 4	0.5 to 1	0.1 to 0.2	0.2 to 0.3	0.5 to 1	2 to 3
Half-life (hr)	2 to 4	1.5 to 6	0.15 to 0.3	1 to 2	2.5 to 3	3 to 4

MS = morphine

Thank you