Episode 164: Keywords part 9: Fentanyl and Breathing Circuits

On this episode: Dr. Jed Wolpaw and Dr. Gillian Isaac

In this 164th episode I welcome back Dr. Gillian Isaac to do another ABA keywords episode. We discuss fentanyl and breathing systems (Mapleson and Circle systems).

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Hyperlinks to section of notes.

Fentanyl Mechanism of Action, Pharmacodynamics, Pharmacokinetics

1:11 – 6:11

- **Mechanism of Action:** activates mu opioid receptors which are distributed throughout CNS including nucleus tractus solitarius in periaqueductal grey area, cerebral cortex, thalamus, substantia gelatinosa of spinal column
    - When binds to mu receptors → voltage sensitive Ca^{2+} channels close → K^{+} efflux → hyperpolarization and reduced cAMP production → reduction in neural cell excitability → reduced transmission
- High lipid solubility → crosses BBB easily and rapidly
- Rapid redistribution phase → effects are short-lived
- Context-sensitive ½ life ↑ with prolonged administration: as infusion increases for longer and longer → building up more fentanyl in rest of body throughout fatty tissues → when turn off infusion, takes longer for plasma concentration to decrease by ½
    - Fentanyl is one of the worst offenders for increasing context-sensitive ½ life
    - Remifentanil is the exception to this in opioids
- Predominantly metabolized by liver to norfentanyl which is NOT active

Related Questions

6:12 – 9:44

- (6:12) Q: The most important reason for the more rapid onset and shorter duration of action of fentanyl with single dose compared with morphine is the difference in:
    - A) volume of distribution
    - B) Hepatic clearance
    - C) Protein binding
    - **D) Lipid solubility → crosses BBB very quickly and washed away**
- (6:48) Q: The short, clinical, duration of action of a single dose of fentanyl is a result of its:
    - A) small volume of distribution
    - B) large volume of distribution
    - C) low lipid solubility
    - **D) rapid redistribution → because of its high lipid solubility**
    - E) short elimination half life
- (7:18) Q: The decreased duration of action of an IV dose of fentanyl compared with an IV dose of morphine is because of its:
    - **A) greater lipid solubility → able to redistribute throughout lipid rich tissues of body**
    - B) increased hepatic metabolism
    - C) less protein binding
    - D) shorter elimination half life
    - E) smaller volume of distribution
- (8:21) Q: A 70kg 20 year old athlete receives nitrous oxide and oxygen, thiopental and 1.25mg (25mL) of fentanyl during a knee reconstruction procedure lasting 3 hours. Post-operatively he does not awaken or resume spontaneous breathing for 3 hours. The most likely explanation for the prolonged effect of fentanyl is:
    - A) dose dependent elimination half-life → the half-life is time it takes plasma concentration to decrease by half; even if you give a large dose, the time it takes to

decrease by half is still the same, but it will take several half-lives to get to a concentration where patient can awaken and breath
    - B) genetically slow biotransformation
    - C) large volume of distribution
    - D) presence of active metabolic at high concentration
    - **E) time required for hepatic elimination → large dose takes time to metabolize**

Neuraxial Fentanyl

9:45 – 10:51

- Neuraxial fentanyl provides analgesia through a spinal site of action
- If just doing fentanyl in epidural, can get moderate analgesia in early labour → what is known as "walking epidural"
- Would need massive amounts for complete analgesia → would get too much side effects
    - Side effects: pruritis, nausea, vomiting, maternal sedation, fetal compromise
- By using opioid epidural, able to use more dilute local anesthetic → prolongs duration of analgesia and improves quality

Related Questions

10:52 – 13:10

- (10:52) Q: Which of the following statements concerning the use of epidural opioids during labour is true?
    - **A) Fentanyl decrease the concentration of epidural bupivacaine required for satisfactory analgesia**
    - B) Fentanyl is an effective analgesic for the second stage of labour
    - C) Sufentanil is an unsatisfactory analgesia for labour
    - D) The addition of epinephrine to morphine prolongs the duration of analgesia → epinephrine is often added to local anesthetic
    - E) The duration of analgesia with fentanyl is 6 to 10 hours
- (12:24) Q: Compared with morphine, a single epidural administration of fentanyl is associated with:
    - A) delayed onset of analgesia
    - B) increased incidence of pruritis
    - C) increased incidence of respiratory depression
    - D) longer duration of action
    - **E) more restrictive segmental spread → fentanyl is lipophilic and cross out of the epidural space so won't get as much spread as morphine; morphine won't cross as likely, so it will get carried by epidural spread more**

Transdermal Fentanyl

13:11 – 13:41

- Mostly used for chronic cancer pain
- Patch takes 24 to 72 hours to work because need to build up reservoir in stratum corneum
- Significant amounts of fentanyl continue to be absorbed from skin for > 24 hours after patch removal

Related Questions

13:42 – 14:36

- (13:42) Q: Which of the following is associated with the application of a transdermal fentanyl patch?
    - A) Achievement of a peak plasma level within 1 hour
    - **B) Continued uptake after patch removal**
    - C) Dose independent plasma clearance
    - D) Tachyphylaxis when used for cancer pain
    - E) Naloxone resistant toxicity

Fentanyl Organ Effects and Side Effects

14:37 – 15:18

- Side effects:
    - Muscle rigidity → more likely with higher doses
    - Bradycardia
    - Respiratory depression
    - Increased common bile duct pressure
    - Nausea and vomiting
    - Pruritis

Related Questions

15:19 – 19:17

- (15:19) Q: Fentanyl induced bradycardia is:
    - A) independent of the speed of injection
    - B) independent of dose
    - C) caused by direct inhibition of adrenal catecholamine release
    - **D) caused by vagal stimulation**
    - E) caused by direct SA node depression
- (15:47) Q: Pancuronium blocks the bradycardic effects of fentanyl by a direct effect on:
    - A) beta adrenergic receptors
    - **B) cardiac muscarinic receptors → doesn't have to do with fentanyl, Pancuronium potentially causes tachycardia**
    - C) carotid baroreceptors
    - D) central vagal nuclei
    - E) sympathetic ganglia
- (16:14) Q: A 66 year old man with COPD who underwent colectomy 12 hours ago has been receiving an epidural infusion of fentanyl at a rate of 100mcg/hour. Which of the following is least likely to develop?
    - **A) Hypotension → less common, especially if only narcotic epidural**
    - B) Nausea
    - C) Pruritis
    - D) Respiratory depression
    - E) Urinary retention
- (17:23) Q: Intra-biliary pressure will be increased the greatest extent by IV administration of:
    - A) atropine
    - B) glucagon
    - C) naloxone

- **D) Fentanyl**
- E) butorphanol

- (17:48) Q: Respiratory depression is least after the induction dose of which of the following drugs?
  - A) etomidate
  - **B) ketamine**
  - C) fentanyl
  - D) propofol
- (18:40) Q: Which of the following drugs increases cerebral blood flow while decreasing cerebral metabolic rate?
  - A) etomidate
  - B) fentanyl → increases ICP and cerebral blood flow, but not significantly
  - **C) isoflurane → inhaled anesthetics have this profile**
  - D) lidocaine
  - E) midazolam

Fentanyl Reversal

19:18 – 19:23

- Naloxone reverses opioids

Related Questions

19:24 – 20:52

- (19:24) Q: 55kg 70 year old women with mild chronic renal failure is unresponsive 20 hours after an uneventful CABG. Anesthetic drugs included fentanyl 3000mcg, diazepam 35mg, and Pancuronium 20mg. Which of the following is the most appropriate next step in management?
  - A) administration of edrophonium
  - **B) administration of flumazenil → reverses benzodiazepines; renal involvement in diazepam metabolism**
  - C) administration of naloxone → reverses opioids; 20 hours later, 3000mcg of fentanyl should be out of the system; liver metabolizes fentanyl
  - D) CT scan of the head
  - E) measurement of core body temperature

Fentanyl Abuse

20:53 – 23:15

- (20:53) Q: According to the ASA taskforce on chemical dependence, which of the following is NOT a characteristic of an addicted anesthesiologist?
  - A) 50% are younger than 35 years old
  - B) Residents are over represented
  - C) 76% to 90% abuse opioids as drug of choice
  - **D) 65% are NOT associated with academic departments → 65% ARE associated with academic departments**
- Other characteristics:
  - Many are members of AOA

  - 30 to 50% are poly drug abusers → usually alcohol on top of narcotics
  - 33% have a family history of addictive disease
- (22:39) Q: Which of the following is the most commonly abused narcotic by anesthesiologists:
  - **A) Fentanyl → drugs listed in order of most common to least common; fentanyl > Sufentanil > meperidine, etc.**
  - B) Sufentanil
  - C) Meperidine
  - D) Morphine
  - E) Oral drugs

Circle Systems and Non-circle Systems

23:16 – 29:26

- Mapleson's circuits:
  - Disadvantages:
    - Don't have CO_2 scrubbers so rely on high gas flow → waste gas
    - Minimal rebreathing so will loss heat and moisture
    - Contaminate OR environment
  - Advantages:
    - Less complex, simpler to use
- Circle system:
  - Advantages:
    - Recycle gas → reduce fresh gas flow requirement and decreases waste of gases
    - Scavenging system → prevent OR contamination, retain heat and moisture
  - Disadvantages:
    - More complex
    - One way valves could get stuck or increase resistance to breathing
    - Lower fresh gas flow rate could take longer for changes to anesthetic mixture to occur → could get around this by increasing fresh gas flow
    - In theory, if have low flow rate and using sevoflurane, could get compound A
- Key points about Mapleson's circuits:
  - Have A through F types → fresh gas flow requirements increases from A to F with A requiring the least fresh gas flow and F requiring the most
  - Mapleson A: used for ALIVE&AWAKE patient → good for spontaneous breathing patient
  - Mapleson B: BORING as it is obsolete and not used anymore
  - Mapleson C: traditionally used for CPR
  - Mapleson D: used for "DEAD" patient → mechanically ventilated patient
    - Also known as the Bain circuit
  - Mapleson E: like ET, is from outer space, as there is no bag on it
  - Mapleson F: babysaFe; also known as the Jackson Rees modification
- Mnemonic for spontaneous ventilation: All Dogs Can Bit
  - A is best, then D, then C, then B
- Mnemonic for mechanical ventilation: Dog Bites Can Ache
  - D is best, then B, then C, then A

Related Questions

29:27 – 36:53

- (29:27) Q: Which Mapleson breathing system permits the least amount fresh gas flow to prevent rebreathing during spontaneous ventilation?
  - A: During spontaneous respiration, the most efficient is A
- (29:51) Q: In a 5kg child, the $EtCO_2$ is 35mmHg during spontaneous ventilation through a Mapleson D circuit. Which single change is most likely to increase this value?
  - **A) Decreasing the fresh gas flow → no CO_2 absorber so decreasing fresh gas flow will increase rebreathing**
  - B) Increasing respiratory minute volume
  - C) Opening pressure release valve
  - D) Removing reservoir bag
  - E) Substituting larger tubing
- (30:34) Q: Which of the following decreases dead space in an anesthetic circle system?
  - A) Larger surface area of the expiratory unit directional valve
  - **B) Placing a septum in the Y piece → the only dead space in circle system is what is beyond the Y piece**
  - C) shorter expiratory limb tubing
  - D) smaller CO_2 absorber
  - E) smaller respiratory bag
- (31:20) Q: During anesthesia using the Bain circuit:
  - A) $PaCO_2$ is independent of minute volume if fresh gas flow is > 17mL/kg
  - B) $PaCO_2$ is independent of fresh gas flow if minute volume is > 100mL/kg
  - **C) $PaCO_2$ may be normal in presence of rebreathing**
  - D) CO_2 removal is more efficient during spontaneous ventilation than during controlled ventilation
  - E) Less body heat is lost than with a circle system
- (32:37) Q: Which of the following statements concerning the use of a Bain circuit is true?
  - A) Fresh gas flow can be as low as the patient's minute ventilation
  - B) Heat conservation is better than with a circle system
  - C) Lower flows can be used with controlled ventilation than spontaneous ventilation
  - D) Lower fresh gas flows can be used than with the Jackson Rees circuit
  - **E) the concentration of inhaled vapors can be changed rapidly → using high flows, so can change concentration faster**
- (33:18) Q: All of the following would result in less trace gas pollution of the OR atmosphere except:
  - **A) Use of a high gas flow in a circular system → will increase gas pollution because if something becomes disconnected, pumping out more gas**
  - B) Tight mask seal during mask induction
  - C) Use of a scavenger system
  - D) Allow patient to breath 100% O_2 for as long as possible before extubation → allowing patient to breathe off as much inhalation agents as possible
- (34:57) Q: During general anesthesia administered through a circle system, the soda lime absorber is exhausted. No fresh soda lime is available for use. Which of the following is the most appropriate next step to prevent hypercapnia in this patient?
  - A) Decreasing the dead space of the circle system

- B) Discontinuing N_2O
- **C) Increasing the fresh gas flow → will wash expired gases away**
- D) Increasing tidal volume
- E) Switching to spontaneous ventilation

- (35:35) Q: During use of the ventilator on an anesthesia machine, positive pressure is noted on the airway pressure gauge during exhalation. Positive end expiratory pressure has not been purposely added to the breathing circuit. Which of the following is the most likely cause?
  - A) Closure of the pop-off valve in the circle system
  - B) Excessive tidal volume settings on the ventilator
  - **C) Obstruction of the pressure relieve valve on the scavenging system → creating back pressure**
  - D) Over inflation of the endotracheal tube balloon
  - E) Tension pneumothorax
- (36:26) Q: Of the Mapleson circuits, which is best for spontaneous ventilation?
  - **A) A → remember "All Dogs Can Bite" mnemonic**
  - B) B
  - C) C
  - D) D
  - E) E
- (36:37) Q: Of the Mapleson circuits, which is best for controlled ventilation?
  - A: D → remember "Dog Bites Can Ache"
- (36:41) Q: Which one is the Jackson Rees system?
  - A: Mapleson F
- (36:44) Q: Which one is the Bain system?
  - A: Mapleson D

References

Information from Aaron Sandock regarding Sevo and Compound A:

- The toxicity was reported in rats and research was published in the early-mid 90's.
    - Gonsowski, C., Laster, M., Eger, E., Ferrell, L. and Kerschmann, R. Toxicity of Compound A in Rats: Effect of a 3-Hour Administration. Anesthesiology. 1994;80(3):566-573. https://anesthesiology.pubs.asahq.org/article.aspx?articleid=1949689
- It is actually the case that follow up studies were done in the US on volunteer patients through University of Arizona and Medical College of Wisconsin in the later 1990's.
    - Ebert, T., Frink, E. and Kharasch, E. Absence of Biochemical Evidence for Renal and Hepatic Dysfunction after 8 Hours of 1.25 Minimum Alveolar Concentration Sevoflurane Anesthesia in Volunteers. Anesthesiology. 1998;88(3):601-610. https://anesthesiology.pubs.asahq.org/article.aspx?articleid=1948570
- The key point of the final article concludes that humans are nearly devoid of renal beta lyase, the key enzyme in directing biodegradation of compound A to the toxic renal thiol. Essentially, this research was done in the late 90's but the original possibility of renal toxicity in humans from just a few years prior has stuck in peoples' minds (and therefore textbooks).
    - Kharasch, E. and Jubert, C. Compound A Uptake and Metabolism to Mercapturic Acids and 3,3,3-Trifluoro-2-fluoromethoxypropanoic Acid during Low-flow Sevoflurane Anesthesia. Anesthesiology. 1999;91(5):1267-1278. https://www.ncbi.nlm.nih.gov/pubmed/10551576
- More recent studies agree:
    - Ong Sio L, Dela Cruz R, and Bautista A. Sevoflurane and renal function: a meta-analysis of randomized trials. Med Gas Res. 2017 Oct 17;7(3):186-193. https://www.ncbi.nlm.nih.gov/pubmed/29152212