

What's Going on in Anesthesia: Practice Updates

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Conflict of Interest

- Member, Pharmacy Curriculum Development Group, Pacira Pharmaceuticals

Conflicts of interest were resolved through peer review

Pharmacist Learning Objectives

1. Explain the current state of neuromuscular reversal and the role of sugammadex.
2. Discuss multimodal analgesia in the perioperative setting and the role of IV Acetaminophen.
3. Recognize why a comprehensive and interdisciplinary approach to diversion surveillance is necessary in the OR setting.

Pharmacy Technician Learning Objectives

1. Identify medications utilized for reversal of neuromuscular blockade.
2. Identify advantages and disadvantages of IV Acetaminophen.
3. Recognize practices that prevent drug diversion in the OR setting.

Pre-Test 1

Select the FALSE statement about neuromuscular blockade and reversal.

- A. The effects of cisatracurium and atracurium are reversed by neostigmine.
- B. The effects of rocuronium and vecuronium are reversed by sugammadex.
- C. Sugammadex eliminates the need for monitoring the depth of block from rocuronium.
- D. The onset of action of neostigmine is about 15 minutes.

Pre-Test 2

Which statement is FALSE?

- A. Celecoxib does not increase the risk of surgical bleeding.
- B. Local infiltration around the wound is most effective for procedures with a smaller component of visceral pain.
- C. The IV route is preferred to the oral route when providing analgesia for surgical patients.
- D. The addition of gabapentin to a multimodal analgesia regimen may increase the respiratory depressant effect of the opioid.

Pre-Test 3

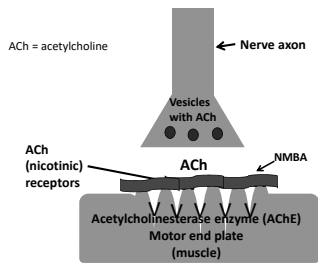
Diversion of anesthesia CS can be prevented by ensuring 100% accountability of all controlled substances and tracking the number of discrepancies by provider.

- A. True
- B. False

Roadmap

- **Section 1: Reversal of neuromuscular blockade**
 - Current state
 - Role of sugammadex
- **Section 2: Multimodal analgesia in the perioperative setting**
 - Early recovery after surgery
 - Role of nonopioids
 - Role of IV acetaminophen
- **Section 3: Preventing drug diversion in the Operating Room (OR)**
 - Draft ASHP Guidelines on Perioperative Pharmacy Services, Anesthesia Controlled Substances

Section 1: Neuromuscular Basics

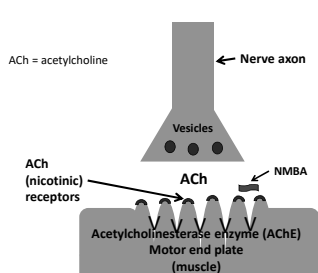


- **Normal neuromuscular transmission**
 - Release of ACh opens ion channel → motor end plate potential → muscle contraction
 - AChE rapidly hydrolyzes ACh → motor end plate repolarizes → muscle relaxes
- **Nondepolarizing neuromuscular blocking agents (NMBAs, a.k.a. muscle relaxants or paralytics)**
 - Competitive ACh receptor *antagonist* → blocks muscle contraction → *paralysis*
 - Types
 - Aminosteroid (rocuronium, vecuronium, pancuronium)
 - Benzylisoquinolinium (cisatracurium, atracurium)
 - Indications
 - Facilitate endotracheal intubation
 - Improve surgical conditions
 - Facilitate mechanical ventilation

Nondepolarizing NMBAs

Drug	Onset	Duration	Primary Route of Elimination	CV Effects
Rocuronium (aminosteroid)	60 - 90 sec	30 - 40 min	Biliary, 30% renal	None
Atracurium (benzylisoquinolinium)	2 - 3 min	30 - 40 min	Hofmann elimination, ester hydrolysis	↓ BP
Cisatracurium (benzylisoquinolinium)	2 - 3 min	30 - 40 min	Hofmann elimination, ester hydrolysis	None
Vecuronium (aminosteroid)	2 - 3 min	30 - 40 min	Hepatic, 15% renal	None
Pancuronium (aminosteroid)	> 3 min	> 60 min	Renal	↑ HR

Neuromuscular Basics – Reversal Agents



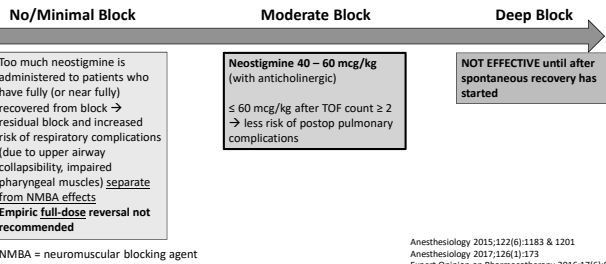
- Neostigmine } **AChE inhibitor** (increased ACh to compete with NMBA → muscle contraction)
- Edrophonium } (increased ACh to compete with NMBA → muscle contraction)
- Pyridostigmine } (increased ACh to compete with NMBA → muscle contraction)
- Sugammadex } **Gamma-cyclodextrin** (encapsulates rocuronium & vecuronium → inactive complex)

Neostigmine

- AChE inhibitor at nicotinic and muscarinic receptors
- Peak effect
 - About 15 minutes
- Adverse effects
 - Muscarinic (cholinergic) effects → N/V, bradycardia, increased secretions, miosis
- Limitations
 - Ceiling effect → cannot reverse a deep/profound/intense block
 - Concurrent administration of anticholinergic (glycopyrrolate, atropine) to minimize muscarinic (cholinergic) side effects

Expert Opinion on Pharmacotherapy 2016;17(6):819

Dose-Dependent Effects of Neostigmine



Sugammadex

- Depending on the dose, reverses moderate, deep and intense block from rocuronium and vecuronium
- Peak effect
 - About 2 minutes when given at appearance of second twitch
- Adverse effects
 - Hypersensitivity reactions, most often occurring within 5 min of administration
 - Transient (< 60 min) effect on coagulation (aPTT, PT/INR)
- Drug Interaction → progesterone may bind to sugammadex
 - From the PI: "If an oral contraceptive is taken on the same day that sugammadex is administered, patient must use an additional, non-hormonal contraceptive method or back-up method of contraception (such as condoms and spermicides) for the next 7 days"

Drugs 2016;76:1041-1052
 Sugammadex package insert (PI)

Factors Influencing Incidence of Postop Residual Neuromuscular Blockade

- Type and dose of NMBA
- Degree of block
- Type (inhalational vs. TIVA) and duration of anesthesia
- Use of monitoring (TOF)
- Dose of anticholinesterase reversal drug
- Time of reversal administration
- Situational awareness of surgical timing
- Patient factors (metabolic derangements, hypothermia)

NMBA = neuromuscular blocking agent
 TIVA = total intravenous anesthesia
 TOF = train of four
 PACU = postanesthesia care unit

Adverse Effects of Residual Neuromuscular Blockade

- Hypoxemia, upper airway obstruction and other critical respiratory events in PACU
- Postoperative pulmonary complications (atelectasis, pneumonia)
- Symptoms and signs of muscle weakness

Anesth Analg 2010;111(1):120
 Anesth Analg 2015;121(2):366

Monitoring

- Why monitor?
 - Rocuronium 0.6 mg/kg, opioid-nitrous oxide general anesthesia ¹
- | | Onset | Duration |
|--------|--------------|-------------|
| Median | 1.8 min | 31 min |
| Range | 0.6 – 13 min | 15 – 85 min |
- Clinical signs of recovery from neuromuscular blockade have poor sensitivity and are unreliable ²
 - Types ^{2,3}
 - Qualitative → conventional peripheral nerve stimulator [train-of-four (TOF) stimulation]
 - Allows rationale drug administration
 - Redosing of NMBA, timing and dose of reversal agent
 - Widely available
 - Less reliable detection of TOF ratio between 0.4 and 0.9
 - Quantitative → e.g. acceleromyography
 - Reliable detection of TOF ratios between 0.4 and 0.9
 - Limited availability, expensive, none are ideal

¹ Rocuronium package insert
² Anesth Analg 2010;111:129
³ Curr Opin Anesthesiol 2014;27:616-622

From the Literature . . .

- Monitoring is important regardless of the reversal agent**
 - "The introduction of sugammadex has produced a hope that residual neuromuscular blockade after rocuronium would be virtually eliminated. Unfortunately, the data indicate otherwise! The use of sugammadex is not an excuse to avoid monitoring the depth of blockade for every case when rocuronium or vecuronium is used." ¹
 - "A quantitative monitor is no substitute for education and skill." ¹
- When is paralysis really necessary?**
 - Decision to administer muscle relaxant should not be taken lightly
- What depth of block for what procedure?**
 - Is deep blockade really necessary in certain laparoscopic procedures?
- POPULAR trial: Post-operative PULmonary complications After use of muscle Relaxants across Europe**
 - Designed to evaluate the effects of management of neuromuscular blockade on post-operative pulmonary complications

¹ Anesthesiology 2017;126(1):13
 Acta Anaesth Scand 2015;59:1 and 2016;60:710

Expert Opinion on Drug Metabolism & Toxicology 2016;12(9):1097
 Anesthesiology 2015;122(6):1183
<http://www.esbg.org/POPULAR>

Our Approach at UI Health

- Drug cost
 - Rocuronium 50 mg = vecuronium 10 mg; cisatracurium ~ 10 x cost
 - Sugammadex 200 mg = 1.4 x (neostigmine + glycopyrrolate)
- Anesthesia record audit, rocuronium shortage and addition of sugammadex led to revisiting NMBA selection, dosing, monitoring and reversal practices
 - Emphasis on appropriate depth of block, dosing and monitoring
 - Vecuronium, not rocuronium, as NMBA of choice
 - Rocuronium for rapid sequence intubation not routine use
 - Cisatracurium in patients with impaired renal/hepatic function
 - Does mivacurium have a role?
 - Restrict sugammadex
 - Criteria for use and attending anesthesiologist approval

Select the FALSE statement about neuromuscular blockade and reversal.

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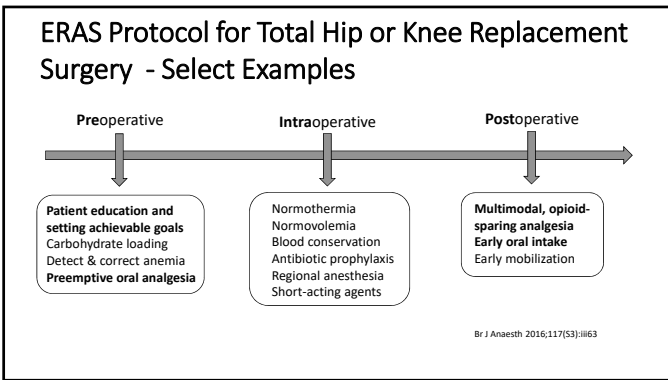
Section 2:
Enhanced Recovery After Surgery (ERAS) Multimodal Care

Multidisciplinary Team
 Education Patient Communication

“No single element by itself will improve outcomes of surgery.”

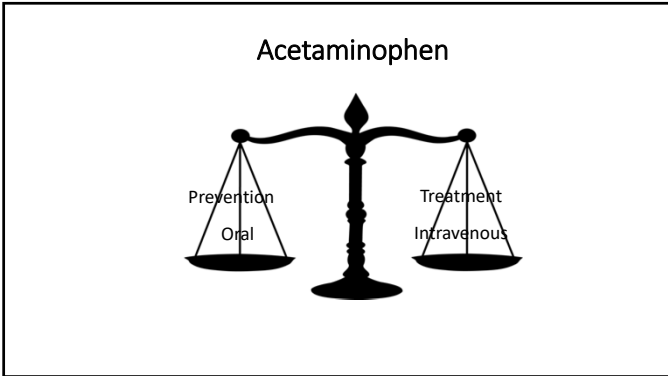
- “The approach to perioperative care must be multimodal, using all available elements of care that improve recovery.”
- “The key is to seek synergy between one process element and the next.”
- “Since elements of ERAS are implemented by different departments, a multidisciplinary approach is necessary.”

JAMA Surgery 2017;152(3):292-298



Multimodal Analgesia

- Combination of therapies that target different mechanisms to provide analgesia
- Types of therapies may include:
 - Non-pharmacological strategies
 - Medications
 - Non-opioids such as acetaminophen, non-steroidal anti-inflammatory drug (NSAID), local anesthetic, gabapentin
 - Opioids
 - Interventions/procedures
 - Psychosocial support



Acetaminophen for Preventing Postop Pain

- Compared with no treatment, oral or IV acetaminophen:
 - Improved early (0-4 hr) pain control in some studies; no difference in others ¹
 - Reduced opioid consumption by about 20% ¹
 - May ² or may not ¹ reduce opioid adverse effects
- Children undergoing outpatient ENT surgery who received a single intra-op dose of IV acetaminophen had a higher rate of requiring an IV opioid in PACU than children who did not receive acetaminophen ³
 - From the authors . . . “When single-dose IV acetaminophen has been studied, the results have been similar to what we found.”

¹ Clin J Pain 2015;31:86082; Br J Anaesth 2005;94:505; Anesthesiology 2005;103:1296
² Pain 2013;154:677
³ ASA Abstract A3021, October 24, 2016

Acetaminophen for *Treating* Postop Pain

Intravenous

- 75 studies (7,200 patients), single dose of IV acetaminophen or placebo ¹
- IV acetaminophen:
 - Provides ~ 4 hrs of analgesia for 36% of patients (NNT = 5)
 - Patients required 26% less opioid over 4 hrs; no reduction of opioid adverse effects

Oral

- High bioavailability
- Rate of gastric emptying determines rate of absorption in small intestine
- When given before abdominal surgery ² . . .
 - Lower peak plasma concentration but overall amount absorbed is unchanged
 - Small intestine begins to function normally about 6 hrs after surgery

¹ Cochrane Database Syst Rev 2016;CD007126 ² Br J Anaesth 2006;97:171

IV vs. Oral Acetaminophen

Systematic Review

Can J Hosp Pharm 2015;68:238

- Results
 - Efficacy (3 studies)
 - Opioid requirements significantly less with IV following CABG; no difference in adverse effects or pain scores
 - No difference in opioid requirements or pain scores following knee arthroscopy
 - Oral noninferior to IV following molar extraction
 - Pharmacokinetic outcomes (4 studies)
 - Higher plasma concentration with IV
 - Adverse events (4 studies)
 - No adverse events associated with use
- Conclusion
 - No strong evidence of superiority of IV over oral
 - No clear indication for IV over oral in patients with a functioning GI tract who can take oral meds

NSAIDs

- Treating* postop pain ¹
 - Effective; NNT generally between 2 and 4.3
- Preventing* postop pain ²
 - Improved analgesia
 - Reduced opioid requirements after surgery, often with reduced postop nausea/vomiting and sedation

NSAIDs = Nonsteroidal Anti-inflammatory Drugs

¹ Cochrane Database Syst Rev 2015;9:CD008659

² Anesthesiology 2005;103:1296;Anesth Analg 2012;114:424

Acetaminophen vs. NSAIDs

Single Dose for Acute Postoperative Pain

Cochrane Database Syst Rev 2015;CD008659

Drug and Dose	NNT (95% CI) for at least 50% Pain Relief over 4 – 6 hrs Compared to Placebo
Acetaminophen 500 mg	3.5 (2.7 – 4.8)
650 mg	4.6 (3.9 – 5.5)
1000 mg	3.6 (3.2 – 4.1)
Celecoxib 200 mg	4.2 (3.4 – 5.6)
400 mg	2.6 (2.3 – 3.0)
Ibuprofen 200 mg	2.9 (2.7 – 3.2)
400 mg	2.5 (2.4 – 2.6)
600 mg	2.7 (2.0 – 4.2)
Naproxen 500/550 mg	2.7 (2.3 – 3.3)

And, from a recent meta-analysis (Br J Anaesth 2017;118:22)

"A combination of acetaminophen with either an NSAID or nefopam was superior to most analgesics other than morphine used alone."

NSAIDs – Adverse Effects

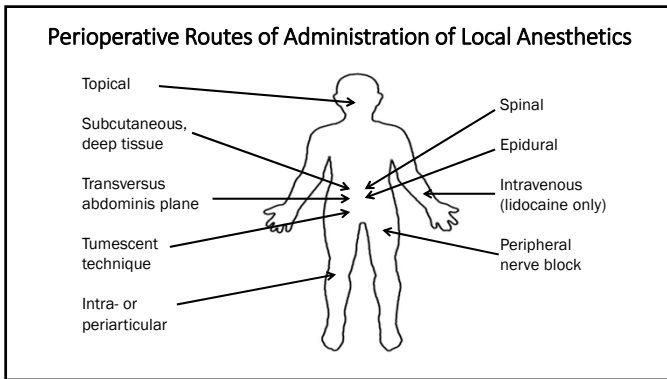
- Cardiovascular** (myocardial infarction, stroke)
 - Risk varies depending upon patient's baseline CV event risk, NSAID chosen and dose
 - Celecoxib may be preferred to nonselective NSAIDs for patients with established heart disease
- Renal**
 - Avoid in patients with chronic kidney disease (stage 3 or worse), volume depletion or high risk for acute kidney injury
- Surgical bleeding** (not celecoxib)
 - No association between ketorolac use and periop blood loss except following tonsillectomy
- Bone healing**
 - Short-term use does not affect fracture union
 - Studies demonstrating negative effect were following prolonged (several weeks) use

ASA abstracts A3015, October 23, 2016
NSAIDs: Acute kidney injury (acute renal failure) (UpToDate, Accessed April 18, 2017)
NSAIDs: Adverse cardiovascular effects. UpToDate Accessed April 18, 2017

Gabapentin and Pregabalin

- Improved analgesia
- Opioid-sparing with reduced opioid adverse effects (nausea, vomiting, urinary retention)
- Adverse effects
 - Dizziness, sedation
 - Although analgesic effect is additive with opioid, addition of gabapentin or pregabalin may:
 - Potentiate respiratory depressant effect of the opioid
 - Adversely affect cognition

Acta Anaesthesiol Scand 2014;58:1165
Anesthesiology 2016;124(1):141-149



Local Infiltration Around Wound

- Local anesthetic provides analgesia by:
 - Blocking transmission of pain from operative site/wound
 - Inhibiting local inflammatory response to injury
 - Decreases sensitization and hyperalgesia
- Most effective for procedures with a smaller component of visceral pain
 - Hernia repair, breast surgery, total joint replacement, Cesarean delivery
- Considerations
 - Agents
 - Timing
 - Pre-incision vs. intra-op vs. wound closure
 - Single injection vs. continuous infusion
 - Injection site and technique
 - Anatomy, physiology and innervation of the wound

Anesthesia 2010;65(Suppl 1):67-75
 Indian Journal of Anaesthesia 2015;59(1):1-4
 BMC Musculoskeletal Disorders 2014;15:200
 ISRN Anesthesiology 2011, Article ID 742927
 CE in Anesthesia, Critical Care & Pain 2011;1(5):167

SUMMARY: POSTOPERATIVE PAIN MANAGEMENT

The Journal of Pain 2016;17(2):131

Agent	Suggested Use
Acetaminophen and NSAIDs	Use as a component of multimodal analgesia (<i>foundation</i>) No clear difference between IV and oral
Oral opioids	Use as a component of multimodal analgesia (<i>rescue</i>) Preferred route for those who can take orals
IV opioids	Use when parenteral route is needed PCA preferred when IV route is needed for analgesia for more than a few hours
Gabapentin, pregabalin	Consider as a component of multimodal analgesia in patients who underwent major surgery
Local infiltration Intra- or peri-articular	Use in surgical procedures for which there is evidence of benefit
Peripheral nerve block	Use in surgical procedures for which there is evidence of benefit
Epidural analgesia	Use for major thoracic, abdominal, cesarean delivery and lower extremity surgery

Which statement is FALSE?

- Celecoxib does not increase the risk of surgical bleeding.
- Local infiltration around the wound is most effective for procedures with a smaller component of visceral pain.
- The IV route is preferred to the oral route when providing analgesia for surgical patients.
- The addition of gabapentin to a multimodal analgesia regimen may increase the respiratory depressant effect of the opioid.

Section 3: Preventing Drug Diversion in the OR

From the DRAFT ASHP Guidelines on Perioperative Pharmacy Services, Section 3. Controlled Substances

What's Unique About Anesthesia Care Providers (ACPs)?

- ACPs obtain and administer addictive substances on a daily basis to:
 - Provide analgesia (*opioids, ketamine*)
 - Blunt stress response to intubation and surgical stimulation (*opioids*)
 - Induce general anesthesia (*propofol, methohexital*) or sedation (*propofol*)
 - Provide sedation, amnesia and anxiolysis (*benzodiazepines*)
- ACPs
 - Have exposure, access and familiarity with the drug's pharmacology
 - Work in a high stress environment, often alone, where it can be relatively easy to divert small quantities for personal use

Psychiatry Clin North Am. 2004;27:45-53 AANA Journal. 2012; 80(2):130-128
 American Society of Anesthesiologists SUD Curriculum, Committee On Occupational Health. November 12, 2015

As with all Controlled Substances (CS), Anesthesia CS:

- Must be 100% accountable from the time CS is dispensed to (received by) ACP to the drug's final disposition (administered, wasted, returned)
 - If a hand-off occurs, documentation should be retrievable
- Must be under the direct physical control of ACP or stored in a locked and secure location such that CS are not accessible to unauthorized individuals
- Must be wasted in a manner that renders waste non-retrievable

From the **DRAFT** ASHP Guidelines on Perioperative Pharmacy Services, Section 3. Controlled Substances
Am J Health-Syst Pharm 2017;74:325-348

Anesthesia CS – Dispensing

- Per case, not per day
- From automated dispensing machines or OR pharmacy, preferably with electronic tracking rather than manual dispensing/paper record
- As close to point of care (OR room) as possible. Great distance between machine and OR room promotes ACP obtaining:
 - More CS than may be needed (ACP can't leave patient to get more)
 - CS for more than one patient (rapid turnover cases)
 - CS well before start of the case without the ability to securely store it

From the **DRAFT** ASHP Guidelines on Perioperative Pharmacy Services, Section 3. Controlled Substances

Anesthesia CS - Discrepancies

- Will occur despite use of automated dispensing machines or automated anesthesia carts. Why?
 - Manual documentation in anesthesia record
 - Manual double documentation (anesthesia record and dispensing machine)
 - Notification of a discrepancy is not real-time (e.g. before anesthesia record is finalized)

For anesthesia meds, it is common to have:

- No barcode scanning of drug and dose administered
- No real-time automatic documentation in anesthesia record once barcode is scanned or inline technology device identifies drug and dose
- No real-time alert of a mismatch between amount of drug dispensed vs. amount administered + wasted + returned

Anesth Analg. 2007; 105(4):1061-1065 Anesth Analg. 2016; 122(6):1841-1855 Am J Health-System Pharm. 2015; 72:1365-1372

An Addicted ACP . . .

- Behaviors at work may include:
 - Removing contents of syringes, vials or amp and replacing with saline
 - Diverting waste
 - Documenting anesthetic was opioid-based but an inhaled anesthetic and a beta-blocker were administered
- Can be extraordinarily attentive at work and rarely puts patients at risk
 - Important to maintain job with its source of CS
- As physicians, anesthesiologists:
 - Know the telltale signs and can hide them
 - Are capable of developing sophisticated denial strategies

Wearing Masks and Wearing Masks 10 years Later videos
<https://monitorpubs.asahq.org/article.aspx?articleid=2446586>
<http://www.aana.com/resources2/health-wellness/Pages/Wearing-Masks,-The-Series.aspx>

Can J Anesth. 2017; 64:211-218

Comprehensive Approach to Anesthesia CS Diversion Surveillance

- Provide CS in ready-to-use concentrations
- Pharmacy reconciliation of all anesthesia CS
 - Investigation of discrepancies until resolved
- Regular review of atypical usage reports
 - Escalating activity, excessive waste
 - Close partnership with anesthesiology; expert knowledge is needed to determine reasonable ranges for various types of procedures
- Waste is returned to pharmacy
 - Verification of amount
 - Analysis on a random basis or when suspect
- Staff education

From the **DRAFT** ASHP Guidelines on Perioperative Pharmacy Services, Section 3. Controlled Substances
Anesth Analg. 2007; 105:1053-1060 Anesth Analg. 2011; 113(1):160-164 Am J Health-Syst Pharm. 2012; 69:552-6

Impact of a Comprehensive Approach at Mayo Clinic

- In response to several episodes of diversion in early 1990's, the Dept of Anesthesiology at Mayo Clinic created a comprehensive system that consisted of:
 - Automated dispensing cabinets in OR
 - Secure return bins to collect waste for analysis
 - Random analysis of waste
 - Reconciliation of all anesthesia CS
 - Investigation of discrepancies until resolved
 - Frequent educational sessions
- Dramatic reduction in frequency of anesthesia CS diversion (unpublished data, Keith Berge MD, Mayo Clinic, Rochester MN)

Mayo Clin Proc. 2012; 87(7):674-682

Diversion of anesthesia CS can be prevented by ensuring 100% accountability of all controlled substances and tracking the number of discrepancies by provider.

- A. True
- B. False

Key Takeaways

- Consider the current state when evaluating the role of sugammadex
 - Choice of NMBAs and dosing
 - Depth of block and monitoring
 - Dosing and timing of reversal
 - Respiratory complications in PACU
- Multimodal, opioid-sparing analgesia is an important element of enhanced recovery after surgery (ERAS)
 - Oral route unless GI tract is not functioning or patient unable to take orals
- A comprehensive and collaborative approach is necessary for drug diversion surveillance of anesthesia CS
 - Controls, investigation, reporting, monitoring, surveillance

What's Going on in Anesthesia: Practice Updates

0121-0000-17-075-LO1-P & T

Speaker: Julie Golembiewski, PharmD

Self-Assessment Questions

1. Sugammadex reverses the effects of:
 - a. Rocuronium alone
 - b. Vecuronium alone
 - c. Rocuronium and vecuronium
 - d. Cisatracurium
 - e. All of the above

2. Neostigmine reverses the effects of:
 - a. Rocuronium alone
 - b. Vecuronium alone
 - c. Rocuronium and vecuronium
 - d. Cisatracurium
 - e. All of the above

3. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are effective for:
 - a. Preventing postoperative pain
 - b. Treating postoperative pain
 - c. A and B

4. Gabapentin may be considered as a component of multimodal analgesia in patients who underwent major surgery.
 - a. True
 - b. False

5. Pharmacy reconciliation of all anesthesia controlled substances, with prompt investigation of discrepancies, is a best practice recommendation.
 - a. True
 - b. False

References for “What’s Going on in Anesthesia: Practice Updates”

Julie Golembiewski PharmD

ICHP Annual Meeting, September 14, 2017

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