Learning Objectives

Upon complete, participants should be able to:

- Evaluate the safety, effectiveness, and cost of intraoperative IV opioids used in general anesthesia
- Identify patient characteristics that place patients at risk of surgical complications following the administration of opioid-based anesthesia regimens
- Outline pharmacokinetic and pharmacodynamic properties that affect selection of intraoperative opioid analgesics

Anesthesia Practice Today

- General anesthesia continues to be the preferred approach for major surgeries
- Patient outcomes can be affected by choice of anesthetic approach
- In current use: a combination of volatile inhalational agents, IV hypnotics and sedatives, muscle relaxants, and opioids

- Safe
- Comfortable
- Minimal postoperative side effects
- Reduced postoperative recovery
- Reduce overnight hospital stays

Mandel JE. *J Clin Anesthesia*. 2014;26:S1-S7;
American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2012;116:248-73.

Short-Acting Opioids: Benefits Versus Risks

Benefits	Risks
• Analgesia – Blunt neuroendocrine activation • Hemodynamic stability – No direct cardiac depression – Blunt catecholamine response to noxious stimuli – Activate the parasympathetic nervous system • Decreased need for hypnotic anesthetics • Preemptive analgesia	• Respiratory depression • Bradycardia, hypotension • Chest wall/laryngeal muscle rigidity • PONV • Pruritus • Delayed emergence • Dependency/tolerance

Mandel JE. *J Clin Anesthesia*. 2014;26:S1-S7; Fukuda K. In: Miller RD, et al. *Miller's Anesthesia*. 7th ed. 2009;
Shafer SL, et al. In: Miller RD, et al. *Miller's Anesthesia*. 7th ed. 2009.

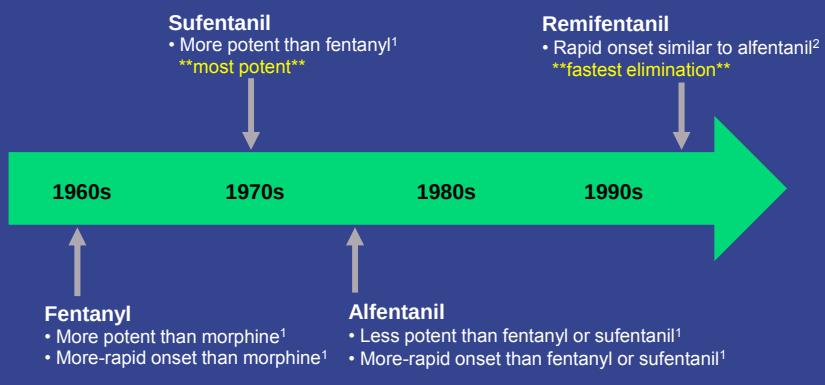
Why Choose a Short-Acting Opioid Intraoperatively?

- Minimize effects of drug accumulation
- Predictable and rapid onset and offset
- Rapid patient response to titration (up or down)
  - Manage intraoperative hemodynamic changes from surgical manipulation or pain
- Generally unaffected by gender, renal/hepatic function, age, or weight
- Decrease MAC and the use of hypnotic agents

Mandel JE. *J Clin Anesthesia*. 2014;26:S1-S7;
Wilhelm W, et al. *Critical Care*. 2008;12:S5.

Evolution of Fentanyl Analogs

Clinical Profile and Attributes of Fentanyl Analogs Have Evolved Over Time



*The fentanyl analogs produce adverse reactions characteristic of μ-opioids, such as respiratory depression, apnea, muscle rigidity, and bradycardia.

[1]Stanley TH. *J Pain Symptom Manage*. 1992;7:S3-7;
[2]Glass PSA. *J Clin Anesth*. 1995;7:558-63.

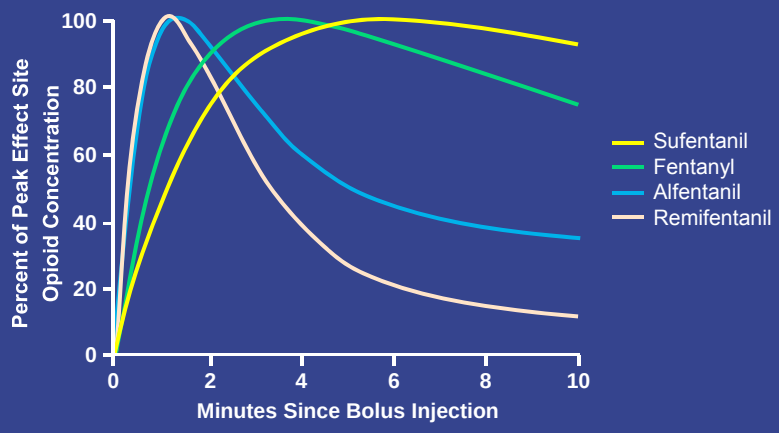
Short-Acting Opioids: Pharmacokinetic Parameters

	Fentanyl	Sufentanil	Alfentanil	Remifentanil
pKa	8.4	8.0	6.5	7.1
% un-ionized at pH 7.4	< 10	20	90	67?
Octanol-H_2O partition coefficient	813	1,778	145	17.9
% bound to plasma protein	84	93	92	80
Diffusible fraction (%)	1.5	1.6	8.0	13.3
Vdc (L/kg)	0.4-1.0	0.2	0.1-0.3	0.06-0.08
VD_{ss} (L/kg)	3-5	2.5-3.0	0.4-1.0	0.2-0.3
Clearance (mL/min/kg)	10-20	10-15	4-9	30-40
Hepatic extraction ratio	0.8-1.0	0.7-0.9	0.3-0.5	N/A

	Fentanyl	Sufentanil	Alfentanil	Remifentanil
$t_{1/2}\beta$ (min)	180-300	150-180	60-120	8-20
$t_{1/2}K_eO$ (min)	4-5	6.2	0.6-1.2	1.0-1.5

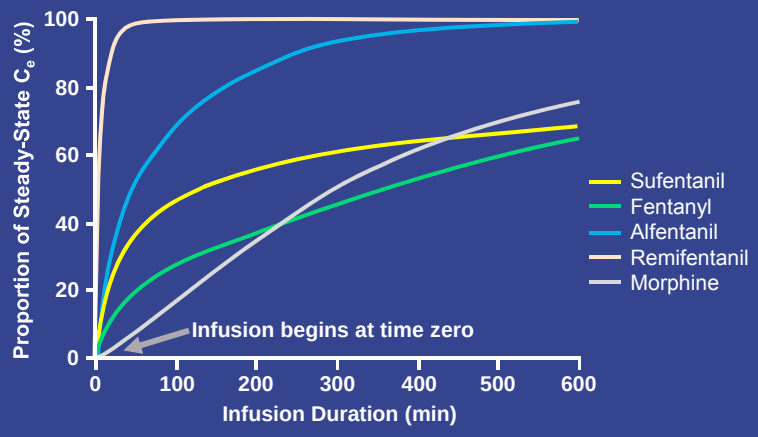
Egan TD. In Miller RD, et al. *Elsevier*. 2011; Egan TD, et al. *Anesthesiology.* 1993;79:881-92; Glass PSA. *J Clin Anesth.* 1995;7:558-63.

Onset of Fentanyl Series of Opioids



Miller RD, et al. *Basic Anesthesia.* 6th ed. 2011;
Bailey P, et al. In: White PF (ed). *Textbook of IV Anesthesia*. 1997;
Minto CF, et al. *Anesthesiology*. 1997;86:10-23.

Infusion Front-End Kinetics



Egan TD. In: Miller RD, et al. *Elsevier*. 2011.

Practical Considerations: Rapid Onset

Advantages

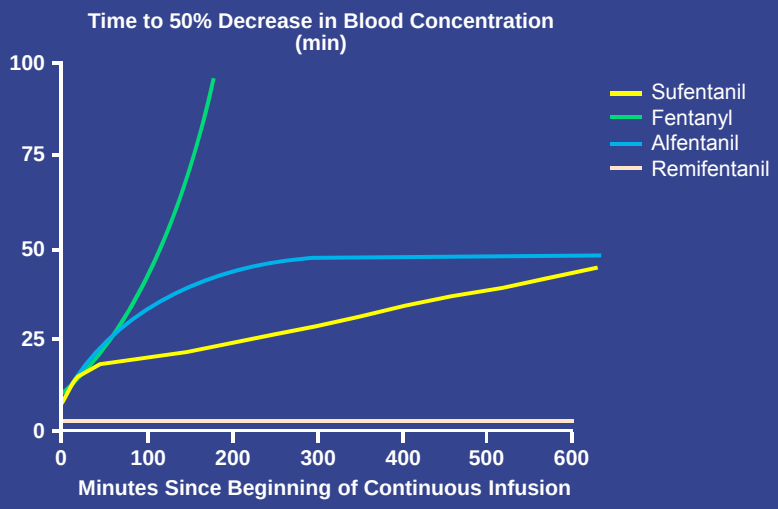
- Rapid response to titration and bolus
- Control of anesthetic depth
- Hemodynamic stability
- Predictable plasma and receptor levels

Disadvantages

- Increased risk of:
  - Bradycardia
  - Hypotension
  - Chest wall rigidity
  - Apnea

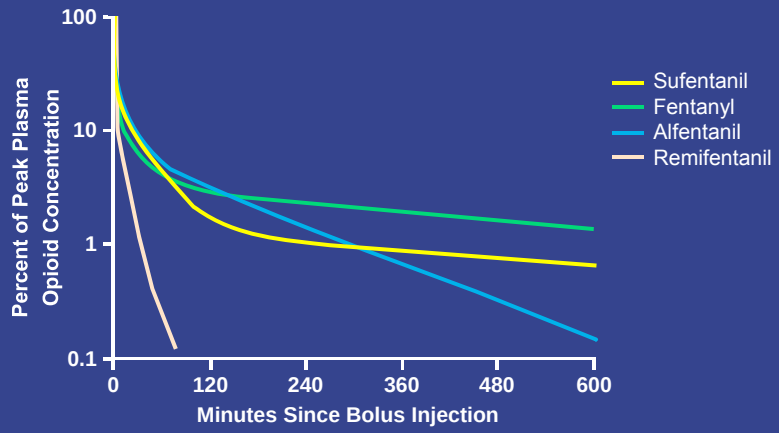
Mandel JE. *J Clin Anesthesia*. 2014;26:S1-S7;
Egan TD, et al. *Anesthesiology*. 1993;79:881-92;
Egan TD, et al. *Anesthesiology*. 1996;84:821-33;
Scott JC, et al. *Anesthesiology*. 1991;74:34-42;
Prescribing information.

Context-Sensitive Half-Time



Egan TD, et al. *Anesthesiology*. 1993;79:881-892.

Pharmacokinetics of Short-Acting Opioids



Miller RD, et al. *Basic Anesthesia*. 6th ed. 2011;
Bailey P, Egan T. In: White PF (ed). *Textbook of IV Anesthesia*. 1997;
Minto CF, et al. *Anesthesiology*. 1997;86:10-23.

Practical Considerations: Rapid Offset

Advantages

- Rapid response to titration
- Predictable emergence
- High-dose opioid technique without need for postoperative ventilation
- Ideal for TIVA

Disadvantages

- No residual analgesia
  - Hemodynamic instability

Mandel JE. *J Clin Anesthesia*. 2014;26:S1-S7; Egan TD, et al. *Anesthesiology.* 1993;79:881-92; Egan TD, et al. *Anesthesiology.* 1996;84:821-33; Scott JC, et al. *Anesthesiology.* 1991;74:34-42; Prescribing information.

Onset and Offset Rates of μ-Opioids

Pharmacokinetics	Alfentanil	Fentanyl	Remifentanil	Sufentanil
Onset: blood-effect site equilibration (mean)	0.96 min	6.6 min	1.6 min	6.2 min
Organ-independent elimination	No	No	Yes	No
Nonspecific esterase metabolism	No	No	Yes	No
Offset: context-sensitive half-time (mean)[a]	50-55 min*	> 100 min*	3-6 min	30 min*

[a] The time required for drug concentrations in blood or at effect site to decrease by 50%. Based on a 3-hour infusion.
* Increases with increasing infusion duration do to accumulation.

Mandel JE. *J Clin Anesthesia*. 2014;26:S1-S7; Egan TD, et al. *Anesthesiology.* 1993;79:881-92; Egan TD, et al. *Anesthesiology.* 1996;84:821-33; Scott JC, et al. *Anesthesiology.* 1991;74:34-42; Prescribing information.

Short-Acting Opioids: Adverse Events

Fentanyl	Sufentanil	Alfentanil	Remifentanil
• Respiratory depression • Apnea • Chest wall and muscle rigidity • Marked bradycardia • Hypertension • Hypotension • Dizziness • Blurred vision • Nausea • Emesis • Laryngospasm • Diaphoresis • Possible seizure activity	• Respiratory depression • Skeletal muscle rigidity including truncal muscle, neck, and extremities • Bradycardia • Hypertension • Hypotension • Somnolence • Pruritus • Nausea • Vomiting	• Respiratory depression • Skeletal muscle rigidity including truncal muscle, neck, and extremities • Bradycardia • Arrhythmia • Hypertension • Hypotension • Tachycardia • Apnea • Blurred vision • Dizziness • Hypoxia • Apnea • Bradypnea • Nausea • Vomiting • Pruritus • Confusion • Somnolence • Agitation	• Respiratory depression • Chest wall and muscle rigidity • Bradycardia • Hypertension • Tachycardia • Hypotension • Nausea • Vomiting • Shivering • Fever • Apnea • Pruritus • Dizziness • Sweating

Please check package inserts for warnings, precautions, and contraindications.

Data derived from prescribing information.

Short-Acting Opioids: Indications and Usage

- Fentanyl citrate injection is indicated:
  - For analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises
  - For use as a narcotic analgesic supplement in general or regional anesthesia
  - For administration with a neuroleptic such as droperidol injection as an anesthetic premedication, for the induction of anesthesia, and as an adjunct in the maintenance of general and regional anesthesia
  - For use as an anesthetic agent with oxygen in select high-risk patients, such as those undergoing open heart surgery or certain complicated neurologic or orthopedic procedures

Data derived from prescribing information.

Short-Acting Opioids: Indications and Usage (cont'd)

- Sufentanil citrate is indicated for IV administration in adults and pediatric patients:
  - As an analgesic adjunct in the maintenance of balanced general anesthesia in patients who are intubated and ventilated
  - As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, in patients who are intubated and ventilated, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated
- Sufentanil citrate is also indicated for epidural administration as an analgesic combined with low-dose bupivacaine, usually 12.5 mg per administration, during labor, and vaginal delivery

Data derived from prescribing information.

Short-Acting Opioids: Indications and Usage (cont'd)

- Alfentanil hydrochloride is indicated:
  - As an analgesic adjunct given in incremental doses in the maintenance of anesthesia with barbiturate/nitrous oxide/oxygen
  - As an analgesic administered by continuous infusion with nitrous oxide/oxygen in the maintenance of general anesthesia
  - As a primary anesthetic agent for the induction of anesthesia in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required
  - As the analgesic component for MAC

Data derived from prescribing information.

Short-Acting Opioids: Indications and Usage (cont'd)

- Remifentanil is indicated for IV administration:
  - As an analgesic agent for use during the induction and maintenance of general anesthesia for inpatient and outpatient procedures
  - For continuation as an analgesic into the immediate postoperative period in adult patients under the direct supervision of an anesthesia clinician in a postoperative anesthesia care unit or intensive-care setting
  - As an analgesic component of monitored anesthesia care in adult patients

Data derived from prescribing information.

What to Consider: Opioid Selection

- Patient characteristics
- Type of procedure, including surgical requirements and idiosyncrasies
- Expected outcome
  - Ambulatory, home/outpatient, admitted to hospital or ICU?
  - Ventilated?
  - Expected level of pain post-op?
- Relationship between dosing regimen and duration of effect
- Pharmacogenetics: variability in drug response as a result of hereditary factors

Mandel JE. *J Clin Anesthesia*. 2014;26:S1-S7; Edan. In: Miller RD, et al. *Basic Anesthesia*. 6th ed. 2011; Shafer SL, et al. In: Miller RD, et al. *Miller's Anesthesia*. 7th ed. 2009.

High-Risk Patient Characteristics

- Sleep apnea or sleep disorder diagnosis
- Morbid obesity with high risk of sleep apnea
- Snoring
- Older age; risk is:
  - 2.8 times higher for individuals aged 61-70
  - 5.4 times higher for those aged 71-80
  - 8.7 times higher for those older than age 80
- No recent opioid use
- Postsurgery, particularly if upper abdominal or thoracic surgery
- Increase opioid dose requirement or opioid habituation
- Receiving other sedating drugs, such as benzodiazepines, antihistamines, diphenhydramine, sedatives, or other CNS depressants
- Preexisting pulmonary or cardiac disease or dysfunction or major organ failure
- Thoracic or other surgical incisions that may impair breathing
- Smoker

American Geriatrics Society Panel. *J Am Geriatr Soc*. 2009;57:1331-46; Dahan A, et al. *Anesthesiology*. 2010;112:226-38; Jarzyna D, et al. *Pain Manag Nurs*. 2011;12:118-45.

Risk Factor: Human Errors

- Lack of knowledge about opioid potency and pharmacokinetic properties
- Insufficient patient history
- Improper prescribing and administration of multiple opioids and modalities of opioid administration
  - Calculation/reconstitutions/infusion programming errors
- IV displacement/infiltration
- Inadequate monitoring of patients on opioids
- Miscommunication when patient transferred between units and facilities

Harris M, et al. *Clin Plastic Surg*. 2013;40:503-13; Sevdalis N, et al. *Br J Anaesth*. 2012;109:i3-i16; Hanna GM, et al. *Anesthesial Clin*. 2011;29:135-44.

What Role Does Cost Play?

- Real cost: direct and indirect cost
  - Direct cost: sufentanil, alfentanil, and remifentanil > fentanyl
  - Indirect cost: fentanyl > sufentanil, alfentanil, and remifentanil
  - Drug-drug interactions
- Risk of incomplete documentation
  - High volume of verbal orders
- Patient satisfaction
  - Comfort
  - PONV
  - Staffing costs/time in PACU (usually fixed cost)
  - Hospital room turnover
  - Shorter length of stay
- Reduced postoperative risk of residual opioid with less need for rescue or ventilatory support

Determine on a case-by-case basis whether the advantages translate to clinical benefits that justify additional acquisition costs

Harris M, et al. *Clin Plastic Surg.* 2013;40:503-13; Uchida K, et al. *J Anesth.* 2011;25:864-71; Reddy P, et al. *J Clin Pharm Ther.* 2002;27:127-32.

Patient Case 1: Vivian

- 34-year-old woman with a history of asthma and OSA presents for sinus endoscopy and septoplasty
- What is the most appropriate short-acting opioid for this patient?
  - Alfentanil
  - Fentanyl
  - Remifentanil
  - Sufentanil

Patient Case 1: Key Points

- Anesthesiologist and CRNA:
  - Avoid exacerbating asthma
  - Provide optimal intraoperative surgical conditions
  - Provide a smooth emergence without reacting to the endotracheal tube
  - Provide an anesthetic that minimizes residual opioid effects postoperatively
- Pharmacist:
  - Are the adverse drug reactions common enough to justify the increased drug cost?
  - How critical is the need for rapid onset/offset of the drug?

Patient Case 2: Theo

- 63-year-old man with a history of CAD, stable angina, type 2 DM, and a BMI of 39 presents for L2-L5 lumbar laminectomy and spinal fusion
- What is the most appropriate short-acting opioid for this patient?
  - Alfentanil
  - Fentanyl
  - Remifentanil
  - Sufentanil

Patient Case 2: Key Points

- Anesthesiologist and CRNA…provide an anesthetic that:
  - Has cardiovascular stability
  - Does not affect SSEP and MEP monitoring
  - Reliably immobilizes the patient without the use of NMB (MEP)
  - Confers a timely emergence for neurologic assessment
- Pharmacist:
  - Are the adverse drug reactions common enough to justify the increased drug cost?
  - How critical is the need for rapid onset/offset of the drug?

Postoperative Analgesia: Management Options

- When using short-acting opioids intraoperatively, consider the following prior to emergence:
  - Continue short-acting opioid
  - Add IV NSAID or acetaminophen
  - Administer long-acting opioids administered 20 to 30 minutes before discontinuation of certain short-acting opioids
  - Infiltrate wound with long-acting local anesthetic
  - Activate epidural (opioid and/or local anesthetic)
  - Perform major nerve block

American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology.* 2012;116:248-73.

Meta-Analysis: Opioid-Induced Hyperalgesia After Surgery

- Meta-analysis of 27 studies (N = 1,494 patients)
- Patients treated with high doses of opioid:
  - Reported higher postoperative pain on a 100-cm visual analogue scale at:
    - 1 hour (MD, 9.4 cm; 95% CI, 4.4-14.5)
    - 4 hours (MD, 7.1 cm; 95% CI, 2.8-11.3)
    - 24 hours (MD, 3 cm; 95% CI, 0.4-5.6)
  - Higher postoperative morphine use after 24 hours (SMD, 0.7; 95% CI, 0.37-1.02)
- Results were mainly associated with the use of high dose remifentanil

Fletcher D, et al. *Br J of Anaesth*. 2014;112:991-1004.

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The Optimal Selection of Short-Acting Intraoperative Opioids: Abbreviations and Acronyms

BMI = body mass index
CAD = coronary artery disease
CI = confidence interval
CNS = central nervous system
CRNA = certified registered nurse anesthetist
DB = diabetes mellitus
ICU = intensive care unit
IV = intravenous
MAC = monitored anesthesia care
MD = mean difference
MEP = motor evoked potential
NMB = neuromuscular blockade
NSAID = nonsteroidal anti-inflammatory drug
OSA = obstructive sleep apnea
PACU = post anesthesia care unit
pKa = negative log of the acid disassociation constant
PONV = postoperative nausea and vomiting
SMD = standardized mean difference
SSEP = somatosensory evoked potential
$t_{1/2}\beta$ = terminal elimination half-time
$t_{1/2}\, k_e0$ = half-time equilibration between plasma and its effect compartment
TIVA = total intravenous anaesthesia
Vdc = volume of distribution of central compartment
VD_{ss}= volume of distribution at steady state