Anesthesia for Post Anesthesia Care Nurses

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Introduction

Welcome to Storm Anesthesia's Anesthesia for Post Anesthesia Care nurses. This is a seven-video series on the basics on pharmacology and anesthesia techniques for the perianesthesia care nurse.

We, a group of five senior students from the University of South Carolina School of Medicine Nurse Anesthesia Program and one CRNA, have created this series in the hopes it will help the transition into the perianesthesia world. The series attempts to shine a bit of light on the techniques anesthesia uses during surgery, as well as explain the basics of the pharmacology behind our drug uses. This is by no means a series that will explain everything that happens during anesthesia, but our hope is that you, the perianesthesia nurse, will find our report a little less intimidating and a little more informative. After all, the better you understand the report, the better you can take care of the patient, and ultimately, this will increase the safety and satisfaction for both your patients and yourself.

The group consists of Alexandra Harman, BSN, RN; Braiden Sightler, BSN, RN; Jordan Coleman, BSN, RN, CCRN; Kelsey Squires, BSN, RN, CCRN; Victoria Koke, BSN, RN; and Michael Storm, DNAP, CRNA, CCRN.

The videos can be watched separately, but there are some references among the videos and the basics of the pharmacology along the way. Therefore, it may be beneficial to watch the series in order. Either way, have fun and don't forget to download the accompanying handouts. These handouts are the complete transcripts of the narrations and include all relevant pictures from the videos.

This video-series is sponsored by Storm Anesthesia and Palmetto Health Richland Anesthesia Department.

Enjoy and let's get started.

Michael Storm, DNAP, CRNA, CCRN
Editor
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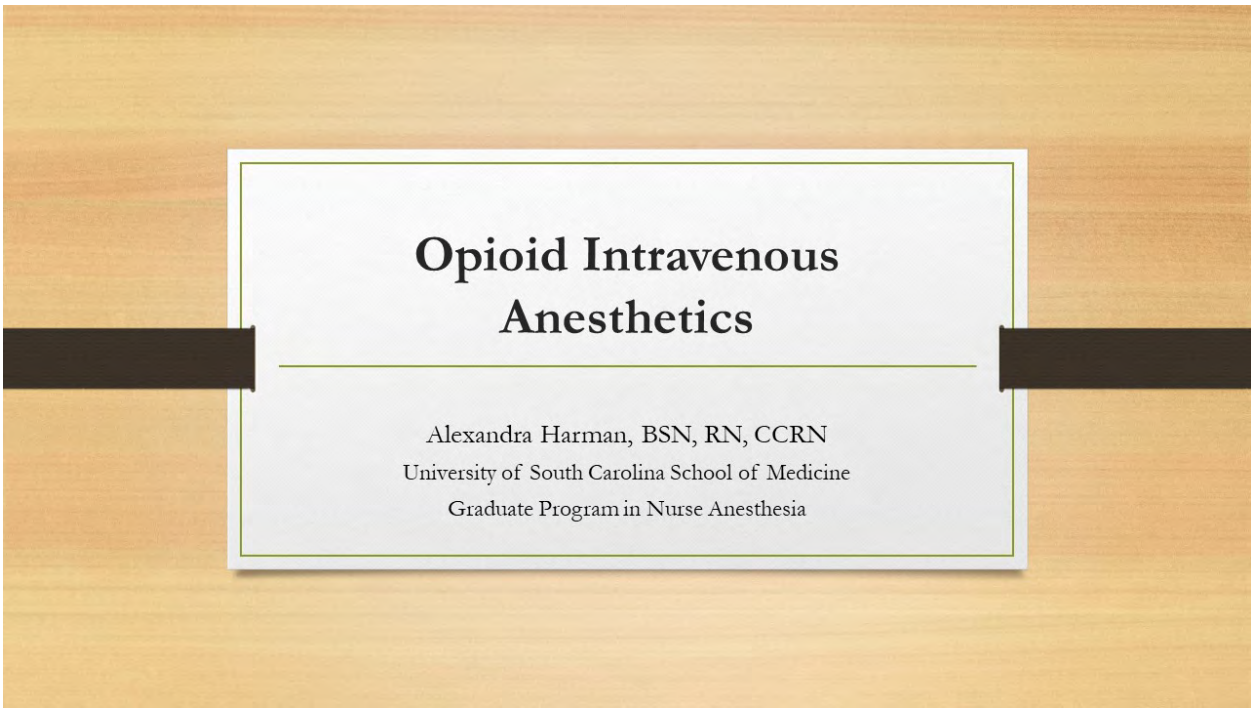

Opioid Intravenous Anesthetics

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Hello, I'm Alexandra Harman and I am senior student of the nurse anesthesia program at the University of South Carolina School of Medicine. This lecture is part of a series of lectures for nurses in the post anesthesia care unit and is specifically directed to teach opioid analgesics.

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Objectives

Opioids are the drug of choice for moderate to severe pain. Almost every patient will receive or has received some form of opioid at some stage in their surgical stay. Thus, it is vital for the PACU nurse to understand how these drugs work to assure safe monitoring of the patient and administration of the drugs.

Objectives for this course will be to:

- Discuss the clinical use of opioid analgesics
- Explain how opioids provide pain relief
- Describe the pharmacokinetic and pharmacodynamics properties of opioids and distinguish commonly used opioids with a focus on key differences
- We will strive to understand signs and symptoms of opioid overdose and plan for appropriate intervention

Basic Keywords and Definitions

We are first going to go over some basic keywords and definitions that will make understanding this lecture a little easier.

Opium: refers to the exudate found from Poppy flowers. Note some of opium's original uses → euphoria, analgesia, sedation, relief from diarrhea, and cough suppression.

Opiate: is a drug that has been extracted from the exudate of the Poppy. Morphine, isolated in the early 1800s, is the prototype opiate.

Unlike an opi**ATE** an opi**OID** can be a natural (like morphine) or synthetic (like fentanyl) drug that binds to opioid receptors in the body to produce an agonist effect. This is the most inclusive of the above terms.

Endorphins: endogenous opioid peptides. This means that they are produced naturally by the body.

There are two places natural opioids occur.

- One is in the juice of the opium plant from which morphine and codeine are derived.
- The second is in endogenous peptides which are our naturally occurring endorphins.

All other opioids are either semisynthetic or synthetic.

- Semisynthetic means that they are prepared from morphine; an example here would be heroin which was originally manufactured for and used in hospital settings.

Synthetic means man made compounds produced to act in a similar manner as the original drug. Meperidine and fentanyl are two examples of synthetic drugs.

Now, how do opioids work?

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Opioid Receptors

Opioids achieve their analgesic effects by first binding to a specific opioid receptor. It is generally accepted that there are three opioid receptor subtypes: Mu; Delta; and Kappa. These subtypes can be further broken down into Mu1 and Mu2, Delta1 and Delta2, and Kappa1 and Kappa3.

Mu1 receptors are responsible for the bradycardia seen with opioids and the euphoric feeling reported by patients.

Mu2 receptors are responsible for physical dependence and respiratory depression.

Spinal analgesia, although mediated by all opioid receptors, is primarily produced via Mu2 whereas supraspinal analgesia is mediated by all opioid receptors except Mu2.

Although subdivided into delta 1 and delta 2 receptor stimulatory effects are not specific to one vs the other.

Kappa1 receptors provide spinal analgesia whereas kappa3 is primarily supraspinal. Kappa receptor stimulation causes dysphoria (hallucinations) and is responsible for sedation.

Opioid Pharmacokinetics

Routes of Administration

Opioids can be given in a variety of ways:

- Orally
- Nasally
- Intramuscular
- Transdermal
- Intrathecal
- Epidural
- Intravenously

When administered orally, opioids are only modestly absorbed and undergo a significant first pass effect in the liver. This means that when the drugs are absorbed in the stomach they pass through the liver before being delivered to their receptors. The liver can breakdown the drugs into inactive forms before the drugs even have a chance to enter the systemic circulation.

Exceptions to this rule are: oral codeine and oxycodone which have reduced first pass effect. This gives these drugs a greater oral efficacy. Efficacy refers to both the maximum response achievable from a dose and to the capacity for therapeutic effect or beneficial change of a given therapeutic intervention in clinical settings.

Anesthesia providers most commonly choose the routes of intrathecal, epidural, and IV for administration of opioids as this allows for rapid and accurate delivery of drugs into the

systemic circulation and is a more exact method of achieving the desired effect from agents delivered. The availability of short, medium, and long-acting opioids, as well as the many routes of administration, give anesthesia providers considerable flexibility in the use of these agents. In this lecture series we will be focusing primarily on intravenous opioids with a few exceptions along the way that are important for consideration in the PACU.

Absorption and Distribution

Opioids exhibit large variations in their physiochemical properties which are what influence their pharmacokinetics and they therefore differ in their absorption and distribution in the body.

To reach their effector sites in the Central Nervous System or CNS, opioids must cross biologic membranes from the blood to their receptors on neural cell membranes.

An opioid's ability to cross such biologic barriers as the blood brain barrier and placental barrier to reach effector sites depends on the drugs:

- Molecular size
- Degree of ionization
- Lipid solubility
- Protein binding

Molecular size: A smaller molecular size lends to easier transport across barriers.

Degree of ionization: affects absorption in that non-ionized forms of drugs are uncharged and thus lipophilic making them better candidates for absorption across lipid barriers. Ionized molecules or drugs are usually unable to penetrate lipid cell membranes easily because of their low lipid solubility. This results from the electric charges exerted by the ionized drug molecules. These charged drugs are repelled by those sections of the cell membranes with similar charges preventing their diffusion across the membrane. So, the higher the degree of ionization, the LESS access the drug has across tissues and barriers. This is important in that ionized drugs then are NOT absorbed well when taken orally and may not be metabolized by the liver to a significant extent.

Lipid solubility: affects absorption across barriers in that those with higher lipophilicity are better absorbed than those drugs that are hydrophilic.

Percent of protein binding: will determine how much of the drug will bind to plasma proteins and with what affinity. Drugs that are bound to proteins in the plasma create a drug-protein molecule that is too large to diffuse through blood vessel membranes and will therefore become trapped within the circulatory system. Protein bound drugs are not free to act on receptors and high protein binding prevents the drug from leaving the blood to enter tissue resulting in high plasma concentrations. Protein binding and lipid solubility are proportional to one another. The more lipid soluble a drug is the more highly protein bound it tends to be. Protein binding plays an important role especially in patients where it is altered. Reduced

proteins such as in patients with severe liver or kidney disease or those patients with poor nutrition and thus experience protein deficiencies. These situations where proteins are not as abundant in the body can cause an increase in absorption due to fewer available proteins for binding. Remember binding drugs with proteins equals inactive drug; less proteins equals more active drug in the circulating system, thus patients may require a reduction in dosing of opioid medications.

Opioids in general have a large volume of distribution which is the volume that the drug disperses into after it is introduced into the system.

The same properties previously discussed: molecular size, lipid solubility, plasma and protein binding, can determine a relative volume of distribution for opioids. Drugs that are "free" or unbound to plasma proteins, and drugs that are lipid soluble, easily cross membranes to tissues; therefore, they have large volumes of distribution with low plasma concentrations.

Fentanyl is an opioid drug that is especially lipophilic and thus has a large volume of distribution.

Physical Characteristics of Opioids that Determine Distribution

Physical Characteristics of Opioids that Determine Distribution			
Agent	Nonionized Fraction	Protein Binding	Lipid Solubility
Morphine	++	++	+
Meperidine	+	+++	++
Fentanyl	+	+	++++
Sufentanil	++	++++	++++
Alfentanil	++++	++++	+++
Remifentanil	+++	+++	++

For all of you visual folks, I really think this is a great chart to look over for additional clarification and reinforcement on what we have been talking about. Here you have a visual representation of the physical characteristics of opioids that determine distribution in the body. You can see that although meperidine and fentanyl both have a low non-ionized fraction, fentanyl's low protein binding and high lipid solubility make it more easily distributed and give it a larger volume of distribution.

Metabolism

Like most drugs, opioids are usually metabolized in the liver to a more polar and less active or inactive compound by both phase 1 and phase 2 processes of biotransformation.

Phase I reactions include oxidative and reductive reactions like those drugs catalyzed by cytochrome P450 and hydrolytic reactions.

Phase II reactions include conjugations. Please refer to your initial lecture on pharmacology basics for additional details regarding these processes.

Opioid metabolites are generally inactive, but two drugs will be exceptions to this rule. Both morphine and meperidine have active metabolites that can prolong the therapeutic effects of their parent compound. These drugs and their metabolites will be discussed in greater detail later in this lecture. Remifentanil will also be an exception to classic metabolism as it is metabolized via ester hydrolysis. Again, this drug and others will be explored in more detail later in this lecture.

Interestingly, when a lower dose of an opioid is used, its effects are usually terminated by redistribution rather than by biotransformation metabolism. But this process is easily saturated when large doses or multiple doses are used thus reverting the opioid to biotransformation for metabolism. For example, if a one-time, low dose of morphine such as 0.1 mg/kg IV is given the drug will be metabolized via redistribution whereas if a larger dose of morphine such as 1 mg/kg IV is given or if multiple smaller doses are administered the redistribution process will become saturated and morphine metabolism will revert to biotransformation.

Elimination

Opioids and their metabolites are excreted primarily by the kidneys and secondarily by the biliary system and gastrointestinal tract.

Opioid	pKa	Percent Nonionized	Protein Binding (%)	Vc (L/kg)	Vd (L/kg)	Clearance (mL/min/kg)	Elimination Half-life (hr)	Partition Coefficient (Octanol/Water)
Morphine	7.9	23	35	0.23	2.8	15.5	1.7-3.3	1
Meperidine	8.5	7	70	0.6	2.6	22.7	3-5	21
Methadone	9.3	n/a	85	0.15	3.4	1.6	23	115
Fentanyl	8.4	8.5	84	0.85	4	13	2-4	820
Sufentanil	8	20	93	0.1	2	12	2-3	1750
Alfentanil	6.5	89	92	0.12	0.6	5	1-2	130
Remifentanil	7.26	58	93	0.1-0.2	0.39	41	0.1-0.3	n/a

This is a nice way to see side by side the many pharmacokinetic differences between common IV opioids used in the PACU. Here you can see that no one property of an opioid will determine its pharmacokinetics but that it is a complex combination.

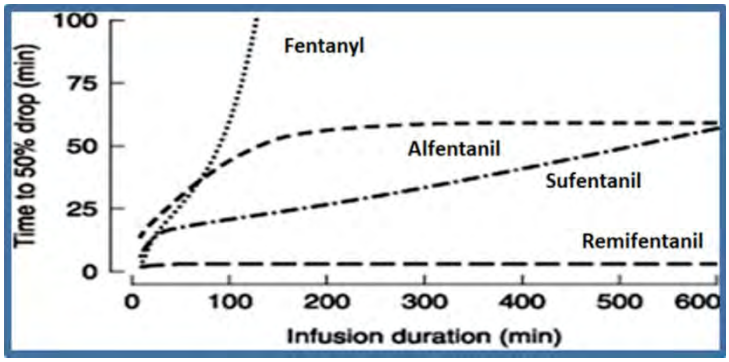
Continuous Infusion and Context Sensitive Half Time

The most common method of administering opioids in the pre, intra, and post-operative periods is intermittent bolus injection, which, although effective, produces wide swings in drug plasma concentration which gives intermittent periods of deep and light sedation and pain relief. Continuous opioid infusion results in plasma concentration that can be maintained more

accurately and consistently. Continuous infusion of opioids is associated with hemodynamic stability, reduces the total necessary dose of opioids, and decreases the need for opioid reversal agents. For these reasons nurses should consider using continuous infusions for patients requiring high doses or multiple doses of opioid medications in the PACU. When choosing opioid infusion medications, it is important to consider the drug's context sensitive half time which is the time required for the drug concentration to decrease by a given percentage, after termination of an infusion of a given duration. Taking context sensitive half time into consideration when selecting continuous infusions of opioids allows for rational drug selection based on anticipated infusion duration.

Here is the graphic representation of context sensitive half time.

In this graph you can see that fentanyl has a much longer context sensitive half time than the other mentioned opioids, alfentanil, sufentanil, and remifentanil. This is due mainly to its high lipophilic status.



Opioid Pharmacodynamics

Now we will move onto the pharmacodynamic effects caused by opioid drugs. We will focus on pharmacodynamics in the:

- Central nervous system
- Cardiovascular system
- Gastrointestinal
- Genitourinary systems
- Miscellaneous pharmacodynamics

Central Nervous System

Opioid pharmacodynamics in the central nervous system include:

- Euphoria
- Dysphoria
- Truncal rigidity
- Antitussive effects
- Miosis
- Analgesia
- Respiratory depression

Euphoria

The feeling of well-being in awake patients. This feeling will vary depending on the agent utilized. Refer to the previous slides in which we discussed different opioid receptors. Those opioids with strong mu receptors such as fentanyl will produce a greater euphoric feeling then those with stronger kappa affinity. Ketamine for example, although not an opioid, has a strong affinity for kappa receptors and dysphoria is a commonly seen side effect with this drug.

Dysphoria

Can also be seen in patients who take opioids in the absence of pain. It is important to remember though that euphoria vs dysphoria is a patient specific interpretation what may be scary to one patient is playful to another.

Truncal rigidity

This is seen primarily with large, IV doses of most opioid agonists although it is most commonly associated with Fentanyl. The problem with truncal rigidity is that it becomes extremely difficult to ventilate patients due to a loss of chest-wall compliance as well as a constriction of the pharyngeal and laryngeal muscles. You may have also heard this called tight chest. Because this effect is most often seen after induction of anesthesia when large doses of opioids are given at one time, its effects are most often dealt with prior to patient arrival in PACU, but do note there are other patients who may be at risk for this side effect including those who were on a Remifentanil drip (such as craniotomy patients), as well as those who may have received nitrous oxide during their procedure.

Antitussive effects

A result of opioids' depressant effect on the cough center in the medulla. This should not be confused with the protective glottal reflex which will remain unaffected. All opioids produce this effect, but codeine is an especially good cough suppressant. Because of their ability to suppress patients' cough, opiates may be beneficial for those patients in PACU requiring assistance in tolerating airway devices and ventilators.

Miosis

Also known as pinpoint pupils is caused when opioids depress GABA causing the oculomotor nerve to constrict the pupil. It is important to note that tolerance does not develop to this side effect. This side effect can be reversed by naloxone, atropine or glycopyrrolate. Note that its reversal by glycopyrrolate can be important in the PACU setting for patients who have had paralytics during surgery as they are most often reversed using a combination of glycopyrrolate and neostigmine.

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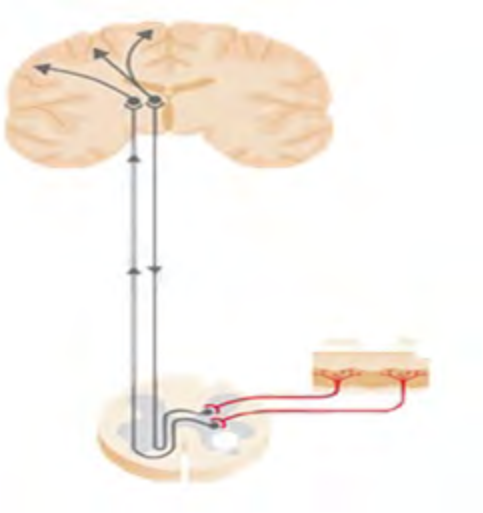
Analgesia



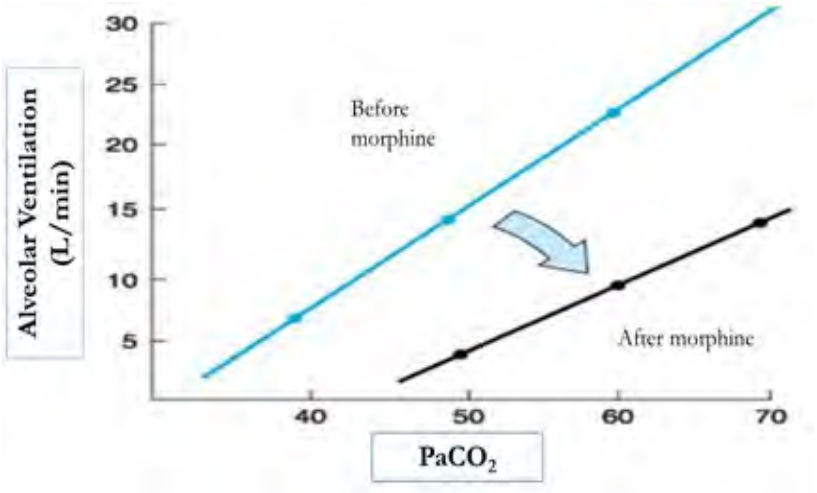
In this picture you can note how the brain receives information about pain via the lateral spinothalamic tract. First, the nerve endings of peripheral nociceptors experience a "trauma." Information about this trauma then travels via nerve fibers which have cell bodies located in the dorsal root ganglia of the spinal cord. From here the nerve fibers enter the dorsal horn of grey matter in the spinal cord. Information then travels up the ascending pathway to the brain where information regarding the initial "trauma" is processed and perceived as pain. Pain control pathways are then activated and descend from the midbrain back to the spinal cord to suppress pain transmission. Providing pain relief is by far the most popular reason to administer opioids.

The analgesic effects of opioids come from their ability to:

- Directly inhibit the ascending transmission of nociception information from the spinal cord dorsal horn
- Activate pain control pathways that descend from the midbrain back to the spinal card.

Respiratory depression

All opiate agonists will produce a dose-dependent depression of respirations via effects on mu and delta receptors in the respiratory centers in the brainstem. The brainstem respiratory centers use hypercarbia and hypoxia as natural stimulants to maintain normal ventilation. Opioids essentially cause the respiratory centers to have a decreased response to hypercarbia and hypoxia. Respiratory rate is going to be affected first and your classic "narcotized" patient will take slow deep breathes. As doses of opiates increase a subsequent apnea is produced. So, monitoring of respiratory rate in the PACU provides a convenient way of detecting early respiratory depression in patients receiving opioid analgesia. It is our goal in anesthesia to leave some residual analgesia without respiratory depression when patients emerge from anesthesia to



This graph represents the relationship between opioid administration, $PaCO_2$, and alveolar ventilation.

address postoperative pain. This can be a true balancing act especially with subsequent dosing of opioids in the PACU because the receptors in the brain that control the analgesic effects of opioid drugs also mediate respiratory depression.

Prior to opioid administration normal ventilation is maintained in a balanced state. This blue line represents normal ventilation prior to opioid administration. You can see that maintenance is balanced between hypoxia and hypercarbia in that 50% of the graph is located above the blue line and 50% below. When an opioid, such as morphine, is delivered it will increase $PaCO_2$ and blunt the response to a CO_2 challenge, which results in a shift of the CO_2 response curve downward and to the right. Basically, the patient's apneic threshold or the greatest $PaCO_2$ at `which the patient remains apneic rises, and hypoxic drive is decreased.

Cardiovascular

Opioid's effects on the cardiovascular system are much less pronounced than many of the other drugs used in the operating room and PACU.

Bradycardia is a usual result of opioid administration in healthy patients. However, there is little effect on blood pressure. The bradycardia associated with opioid analgesics results from medullary vagal stimulation and can be treated, when symptomatic, with atropine or glycopyrrolate.

All opioids induce some degree of dose-dependent peripheral vasodilation, but myocardial contractility, baroreceptor function, and autonomic responsiveness are not affected. For this reason, opiate anesthesia is often utilized in patients with cardiovascular compromise because of the minimal depression seen.

Postural hypotension seen with opioids is noted postoperatively when patients are encouraged to sit upright after having been recumbent for an extended period. This postural hypotension can be accentuated by hypovolemic states.

The opioid medications meperidine, morphine, and codeine can be associated with some degree of HOTN attributed to histamine release. This effect is absent with fentanyl, sufentanil, alfentanil, and remifentanil

Gastrointestinal

Opioids have multiple effects on the gastrointestinal or GI system and its function.

- Decrease gastric motility
- Decrease intestinal propulsive activity
- Prolong gastric emptying time
- Reduce secretory activity

These can lead to the common problem of opioid induced constipation and can ultimately lead to the dreaded postoperative ileus.

Opioid tendency to increase biliary duct pressure and tone of the Sphincter of Oddi can precipitate biliary colic and so their use should be judicious in these patients. Most texts suggest meperidine and/or NSAIDS to be the drug of choice in biliary colic patients as they have the least effect on the biliary duct and Sphincter of Oddi.

Genitourinary

Like those patients with biliary colic, patients with renal colic may have their treatment compromised using opioid analgesics due to their tendency to increase urinary sphincter tone. Again, meperidine and NSAIDS are thought to be the drugs of choice when treating these patients.

Opioids usually produce an antidiuretic effect. Those opioids that are agonists at kappa receptors can cause diuresis, decreasing the bladder detrusor muscle tone while continuing to constrict the urinary sphincter. This results in urinary retention.

Miscellaneous

Pruritus

Also known as itching is a common side effect of opioid analgesia. Along this same line a rash and/or a feeling of warmth or “blush” of the face, upper chest and arms can occur with both histamine and non-histamine-releasing drugs. The mechanism responsible for these effects is thought to be through central mu receptors and not local histamine release. Although this theory is debatable as it is thought that the Histamine release seen with morphine, codeine, and meperidine is a non-immunologic histamine release from mast cells. Facial itching during morphine administration can be seen as a dysesthesia or an interpretation of the pain that the patient is suffering as a facial itch as a true histamine release is more truncal in nature. Pruritus can be treated with antihistamines but remember that these drugs can be additive to the opioids sedative effects and thus nursing interventions should be utilized as a first line treatment.

Emetic effects

Complex and are elicited by stimulating the chemoreceptor trigger zone in the area postrema of the medulla. It is also assumed that there is a vestibular component to the incidence of nausea and vomiting in association with opioid administration as the incidence of nausea and vomiting is much lower pre- and intraoperatively when patients tend to remain supine. It is interesting to note that by a separate action, higher repeat doses of opioids can have an anti-emetic effect by depressing the vomiting center. But clinically speaking, when opiates are used as part of a patient’s anesthetic plan, there is an increased incidence of postoperative nausea and vomiting.

To lesser extent opioids can stimulate the release of ADH, prolactin and somatotropin hormones and inhibition of luteinizing hormone which overtime can lead to a lower testosterone level and can cause a reduced analgesic effect

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Specific Drugs

Opioid Agonists

Now we will begin our discussion of specific drugs that may be given or seen in the PACU. Opioid agonists are by far one of the most highly ordered medications for patients in the post-operative area. They are drugs that bind to opioid receptors and activate them. This can be expressed algebraically as (e=1).

The drugs we will discuss include:

- Morphine
- Codeine
- Hydromorphone
- Meperidine
- Fentanyl
- Sufentanil
- Alfentanil
- Remifentanil
- Methadone

Morphine

Morphine is the prototypical opioid analgesic. It is used for moderate to severe pain and can be administered via the intramuscular, intravenous, subcutaneous, oral intrathecal, and epidural routes. With morphine administration sedation will occur prior to analgesia and thus nurses must not consider morphine-induced sedation as an indication of analgesia. Morphine is one of the least lipophilic of the opioid drugs meaning it is slow to penetrate biological membranes such as the blood brain barrier, it accumulates less in lipid membranes, and it is also slower to provide the onset of pain relief. Morphine does have active metabolites when broken down inside the body. The most important of these metabolites clinically is Morphine-6-glucuronide or M6G which can cause a prolonged effect and excessive sedation in patients with renal failure. Like most metabolites of drugs, M6G is more hydrophilic then its parent drug, morphine, making it harder to cross the BBB into the CNS, but in patients who cannot readily excrete the metabolite, like those in renal failure, high concentrations of the metabolite will build in the blood stream and at high levels M6G can enter the CNS where it is more it is more potent than morphine. Morphine is also associated with a release of histamine from mast cells. This histamine release can cause itching and redness at the injection site or even red-streaking along the IV route. Patients may exhibit a generalized overall flushing. Although considered “cardiac stable” because it has no direct effect on blood pressure, heart rate, or heart rhythm, the histamine release from higher doses of morphine can be associated with a decrease is systemic vascular resistance, hypotension, and tachycardia.

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Codeine

Codeine is a prodrug of morphine meaning that it is an inactive drug that must be metabolized to an active drug and is 1/10th the potency of morphine. When administered orally 5-10% of the codeine drug is converted into the active drug morphine via the CYP2D6 enzyme. Interestingly 10% of the population lacks this CYP2D6 enzyme and thus get no pain relief from codeine. For these patients Tylenol with codeine is just plain Tylenol. Codeine is known to produce great antitussive effects and its combination with acetaminophen for pain relief is often of great benefit in transition from the PACU setting to a lower level of care.

Hydromorphone

Hydromorphone or Dilaudid is a semisynthetic opioid meaning it was derived from morphine. Although its pharmacokinetic profile is similar to morphine, it is 5-10x more potent. Despite this higher potency its duration of action tends to be shorter relative to morphine. Unlike our morphine prototype hydromorphone has no active metabolites and so it is recommended over morphine for patients with renal failure.

Meperidine

Meperidine, also known as Demerol, has been a very common drug used postoperatively for many years. It is one-eighth the potency of morphine making it a good choice for moderate pain relief. It is completely synthetic and structurally resembles atropine which allows for less biliary spasm and constipation than with morphine. Also, meperidine's atropine-like structure means that the common pin-point pupil seen in opioid use will not be present. Don't let this fool you when observing patients for opioid overdose! One of the major down falls to meperidine's use is that it is biotransformed to an active metabolite named Normeperidine. When accumulation of this metabolite occurs as in patients with renal failure and those requiring higher doses such as cancer patients, CNS excitation and a lower seizure threshold are significant risks. Meperidine can also be used for the non-analgesic purpose of postoperative shivering. It is thought that the drug's ability to reduce shivering stems from its activation of Kappa receptors. Its ability to decrease shivering not only provides comfort to patients but also decreases the accompanying increase in oxygen consumption associated with shivering. Meperidine also exhibits significant drug-drug interactions with MAO inhibitors which can lead to hyperthermia, seizures and even death via Serotonin Syndrome. Please refer to the first lesson with Michael Storm: Basic Pharmacology Principles regarding additional details on this topic.

Fentanyl

Fentanyl is the most widely used opioid analgesic in anesthesia and is 80-100x more potent than morphine. One of its great benefits is that its analgesic, respiratory depressant, and sedative effects are dose dependent and thus more predictable. Fentanyl is also highly lipid soluble which makes for rapid tissue uptake in the body. For this reason, a single dose of fentanyl is terminated via redistribution while multiple doses and/or continuous infusions of

fentanyl are eliminated not redistributed. Remember our discussion regarding context sensitive half-life? Well, fentanyl has the highest context sensitive half-life because of its extremely lipophilic nature.

There should be special consideration given to dosing fentanyl in the elderly and neonate as these populations exhibit prolonged elimination of fentanyl.

Fentanyl can also be administered via multiple routes including patches. This is an important concept to remember when taking care of patients postoperatively. When doing thorough skin assessments look for patches which can often be overlooked and remember to pass along in report the administration of fentanyl patches as subsequent dosing can lead to opioid induced respiratory depression.

Sufentanil

Sufentanil is a synthetic opioid derived from fentanyl and is 7-10x more potent than fentanyl. Used most often in surgical situations where profound analgesia is required such as cardiac surgery or in neuro-spine surgeries as part of a balanced anesthesia technique. Analgesia with sufentanil can be induced more rapidly with basically the same technique as that used for fentanyl without an increase in the incidence rate of chest wall rigidity which makes it a great choice in cardiac surgeries requiring sternal incision. In most hospital settings its use is confined to the intraoperative period due to its high potency and risk for respiratory depression without supportive measures.

Alfentanil

Alfentanil is another analog of fentanyl with one-tenth the potency. Although alfentanil has never gained popularity intra-operatively, it appears many of alfentanil's properties may make it a great choice for the relief of immediate, severe pain in the PACU setting. Despite being less lipid soluble than fentanyl, alfentanil has a high non-ionized fraction at physiologic pH and a small volume of distribution which account for its more rapid onset and shorter duration of action than fentanyl. Also, alfentanil has no active metabolites. Besides making alfentanil an extremely predictable drug, this also increase its therapeutic index.

- A therapeutic index is the ratio of the lethal dose to the effective dose; the higher the therapeutic index, the farther the lethal dose is from the dose used for the desired effect.

The therapeutic index of alfentanil is approximately 2.5x more favorable than that of fentanyl. Like most opioid analgesics alfentanil shows minimal hemodynamic changes when administered to patients which prevent dangerous swings in blood pressure and heart rate postoperatively. These properties may make alfentanil an advantageous choice for patients in PACU.

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Remifentanil

Remifentanil is a short-acting opioid with a potency almost equal to fentanyl. It is moderately lipophilic with an ester linkage. It is metabolized by hydrolysis catalyzed by general esterase enzymes to a less active compound and is not dependent on cholinesterase enzymes for metabolism and thus is not influenced by changes in cholinesterase. This means that the administration of succinylcholine and its subsequent metabolism do not influence remifentanil breakdown. Besides its rapid metabolism, remifentanil also has a low volume of distribution and a large clearance with no cumulative effects which result in a short half-life for the drug of approximately 10 minutes. For these reasons remifentanil is easily titratable, and it makes sense that it is only useful in a continuous intravenous fashion and is very popular in TIVA or total intravenous anesthesia techniques especially when assessing neurological status post-operatively is important. Again because of its rapid metabolism, remifentanil is better than most intravenous opioids regarding residual effects and thus there is less postoperative respiratory depression. Also, because of its rapid metabolism additional medications for pain relief will be required in the post-operative period and PACU nurses should work with anesthesia providers to be sure that a plan of care to relieve post-operative pain is in place prior to completing the handoff of a patient who has received remifentanil intraoperatively.

Methadone

As opioid addiction grows, more and more patients will be seen in the operative setting on methadone. Methadone is an opioid agonist that, when administered orally, is 4x more potent than morphine without any active metabolites. It is important to understand that patients on methadone preoperatively will continue this medication and additional opioid administration can have additive effects. This is not to say that these patients should not receive adequate medication to treat their individual pain needs but it should be considered when determining which medication should be administered, dosing of additional opioids, and when considering overdose diagnosis.

Opioid Overdose

Major Signs and Symptoms

Opioid administration although extremely useful for analgesia pre-, intra-, and post- operatively is not without risk. In the intra-operative period a protected airway and mechanical ventilation can often afford anesthesia providers the ability to deliver higher dose opioids to patients while undergoing surgery. Great measures are taken to assure patients can protect their airway with little to no respiratory support prior to transport to PACU. Yet, delayed opioid effects, additive medications, and other factors may cause unforeseen problems for the PACU nurse in the form of opioid overdose. PACU nurses play a critical role in preventing opioid overdoses and in quickly recognizing and treating them.

The major signs and symptoms of opioid overdose include:

- Stuporous state or coma
- Hypoventilation
- Miosis

In addition to routine PACU monitoring, patients receiving opioids in the PACU should have their respiratory status monitored for rate and trend. For example, if a patient's respiratory rate decreases from 18 to 10 in a 45-minute interval, the nurse should have strong suspicion that excessive opioid effect has occurred.

Clinicians should recognize that an overdose from meperidine will not produce the classic overdose sign of miosis. This is because it is structurally similar to atropine. Also, remember that miosis can be masked by atropine or glycopyrrolate administration. These are standard drugs given to reverse muscle relaxation prior to extubation in the operating room.

Skeletal muscles may also become flaccid and airway obstruction is a strong possibility.

A low body temperature is a late sign of opioid overdose and is not considered diagnostic.

Treatment

If an opioid overdose is suspected immediate attention should be paid to respiratory support. Nurses must monitor patients closely and initiate nursing interventions such as the "stir-up regime." The stir-up regimen consists of five major activities as the patient recovers from anesthesia: deep-breathing exercises, coughing, positioning, mobilization, and pain management. Prophylactic, supplemental oxygen should not be delayed, and nurses should place patients on nasal cannula or simple face mask while assessing the need for airway support with oral or nasal airway devices and/or the need for assisted ventilation with bag/mask technique. Assistance from appropriate higher-level providers should not be delayed and invasive airway management performed by skilled providers via intubation should be anticipated especially in the presence of excessive secretions or vomitus.

In addition to respiratory support the treatment for an opioid overdose should include the consideration of administration of naloxone, an opioid antagonist that will be discussed in greater detail in subsequent slides.

Specific Drugs

Opioid Antagonists

Opioid antagonists are drugs that have a competitive affinity for opioid receptors but no efficacy that those receptors. This can be represented algebraically as (e=0).

The two specific opioid antagonists in this lecture will be:

- Naloxone
- Methyl-Naltrexone

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Naloxone

Naloxone is an intravenous drug given for opioid overdose. It is a nonselective, competitive antagonist at all opioid receptors. The non-selectivity of naloxone means that it will reverse not only the respiratory depressant effects of opioids but also the analgesic effects. So, after administration of naloxone patients will be in pain. Please remember that subsequent administration of opioid medication must be done with extreme caution, if at all. This is where the competitive portion of the drug comes into play. Because naloxone is a competitive antagonist, providers delivering opioid analgesics after naloxone administration will have to give higher doses of the opioid to "compete off" the naloxone drug and achieve the desired effects. The reason this is so dangerous is because the half-life of naloxone is much shorter (30-45 minutes) than most opioid analgesics. This means that when the naloxone is no longer active there can be toxic levels of opioid still existing in the body. This is an important concept to be aware of any time naloxone is administered not just with subsequent analgesic administration. Because naloxone can "wear-off" before the opioid that has caused the overdose has been fully eliminated leading to relapse of the respiratory depressive effects requiring a re-dose of naloxone.

When being administered in a controlled environment and under the supervision of advanced practitioners, such as in the PACU, treatment should start with lower doses such as 40 mcg and can then be titrated to effect. This may prevent adverse cardiovascular effects that can occur when an opioid is completely reversed with higher-dose naloxone such as 400 mcg. Traditional administration is in 40 mcg increments every 2-3 minutes until the return of adequate respirations and ventilation. Since naloxone is most commonly supplied in a vial of 0.4 mg in 1 mL (this is 400 mcg in 1 mL) nurses may wish to make incremental dosing easier by aspirating the 1 mL from the vial of naloxone and adding it to 9 mL of crystalloid in a 10-mL syringe. Done this way, the new concentration is 40 mcg/mL.

Care must be taken when giving naloxone as rapid administration can cause severe pulmonary edema, hypertension, arrhythmias, and as previously mentioned, pain.

Methyl-Naltrexone

Methyl- Naltrexone is not a drug that is given in the operating room or the PACU, but it is important to mention in this lecture series as its popularity has increased for patients on chronic opioid medications. It is used to treat the chronic constipation that can be caused by chronic opioid use. Its minimal systemic absorption means that its effects are only produced at its site of action which is the gastrointestinal or GI tract. It does not cross the blood brain barrier, so it cannot block the pain relief pathways in the brain or spinal cord of opioid medications such as morphine.

Side effects of methyl-naltrexone include abdominal pain, flatulence, and diarrhea.

Partial Opioid Agonists

Partial opioid agonists have an affinity for opioid receptors but a low efficacy. This can be represented algebraically as (e=0-1).

The drug we will discuss in this section is:

- Tramadol

Tramadol

Tramadol is a synthetic codeine analog and is a weak mu opioid receptor agonist effective in the treatment of mild to moderate pain. It is a racemic mixture meaning it is a 50:50 mixture of two enantiomers or molecules that are mirror images of each other. In racemic mixtures the two enantiomers can have very different properties. This is the case with tramadol as its positive enantiomer is the one that binds to the mu opioid receptor. The positive enantiomer also inhibits serotonin uptake which aides in the drugs analgesic effects. Tramadol's negative enantiomer inhibits norepinephrine uptake and stimulates alpha 2 adrenergic receptors. Because only one of tramadol's enantiomers binds to an opioid receptor in a weak fashion it is considered a partial opioid agonist. This property also means that tramadol will retain some of its analgesic effects after an administration of naloxone although its respiratory depressant effects (which are caused by the mu opioid receptor activation) can be reversed by naloxone.

Tramadol and Serotonin Syndrome

Serotonin syndrome occurs when there is far too much serotonin in the body and no way to break it down. It can occur with several drug combinations but of particular interest in this lecture is its occurrence with the use of tramadol. Tramadol, as previously discussed, inhibits serotonin uptake as part of its mechanism for analgesia. When combined with other drugs that increase serotonin or prevent its breakdown such as: monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, homeopathic drugs like St. John's Wort, ginseng and nutmeg, and/or over the counter cough and cold medications containing dextromethorphan like Delsym and Mucinex DM the level of serotonin in the body can reach toxic levels leading to Serotonin Syndrome. Please note this is not an inclusive list of drug interactions that can lead to serotonin syndrome. It is important for PACU nurses to recognize home medications taken by their patients to prevent concurrent administration of tramadol to patients at risk for Serotonin Syndrome.

Signs and symptoms of Serotonin Syndrome include:

- High temperature
- Diaphoresis
- Myoclonus
- Hyperreflexia
- Autonomic instability of blood pressure and heart rate
- Coma

These symptoms can resemble Malignant Hyperthermia (MH), a severe and potentially deadly reaction caused by anesthetics. PACU nurses are vital in helping with differential diagnosis as malignant hyperthermia can be treated, when caught quickly, with a medication called Dantrolene whereas Serotonin Syndrome has no cure, and treatment is according to symptoms.

Mixed Opioid Agonist-Antagonist

The partial agonist-antagonist drugs represent a category of drugs that have a primary opioid effect by using the competitive antagonist properties on the mu opioid receptor and an agonist at the kappa receptors. This allows them their analgesic properties. Their benefit is in their low addiction potential and ability to provide mild to moderate pain relief.

Three opioid agonist-antagonists will be presented in this presentation:

- Pentazocine
- Butorphanol
- Buprenorphine

Pentazocine

Pentazocine, commonly known as Talwin, is an opioid agonist-antagonist which is ⅓ the potency of morphine with kappa and delta agonist and weak mu antagonist properties. It is combined with naloxone in the oral form of Talwin NX which has been an important factor in reducing the risk of addiction to pentazocine and aides to its safety profile. Because of naloxone's huge first pass effect it is virtually ineffective orally. So, when pentazocine is taken as prescribed, which is orally, the naloxone has no effect on receptors. But, if the drug is injected intravenously, naloxone will cross the blood brain barrier and "steal" receptors preventing analgesia and the high associated with IV injection of opioids. Pentazocine, like all opioids has the potential for respiratory depression which can be potentiated by general anesthetics. Hallucinations and confusion with pentazocine administration are thought to be due to its kappa receptor activation. Abrupt withdrawal can be precipitated by pentazocine if administered to a patient dependent on opioids.

Butorphanol

Butorphanol is 5x more potent than morphine and is a kappa agonist and weak mu antagonist. It is traditionally given orally or via nasal spray.

Overdose on butorphanol produces respiratory depression but interestingly this side effect has somewhat of a ceiling effect which aide to an increased safety profile for the drug.

- The plateau of the respiratory depression seen with butorphanol can be explained in that 2 mg of butorphanol depresses respirations equal to 10 mg of morphine but the magnitude of respiratory depression with butorphanol IS NOT significantly increased at a dose of 4 mg whereas the magnitude of respiratory depression with morphine IS significantly increased at a dose of 20 mg.

As with pentazocine any respiratory depression produced by butorphanol can be reversed with naloxone. Butorphanol is not normally given IV because unlike most opioids its effect on the cardiovascular system are significant. In IV form butorphanol can increase pulmonary artery pressure, pulmonary wedge pressure, left-ventricular end diastolic pressure, systemic arterial pressure, and pulmonary vascular resistance. Like all other drugs with opioid antagonist properties, butorphanol can induce withdrawal in patients addicted to opioids.

Buprenorphine

Buprenorphine is an agonist-antagonist used for mild to moderate pain relief. It is often used to reduce cravings in people who are trying to recover from addiction to heroine. It is less easily reversed than some other drugs by naloxone because of its high affinity for the mu receptor which makes it harder to "push off" the receptor and allows it to dissociate slowly.

Opioid Withdrawal

Dependence on a drug occurs when the drug is necessary for normal physiological functioning, as demonstrated by a withdrawal reaction or abstinence syndrome upon discontinuation. Withdrawal reactions can usually be said to be the opposite of the physiological effects produced by the drug.

Summary of Opioid Withdrawal Signs	
Drug craving, pain and irritability	Diarrhea, nausea and vomting
Hyperventilation	Mydriasis
Dysphoria and depression	Hyperthermia
Restlessness and insomnia	Lacrimation, runny nose
Fearfulness and hostility	Spontaneous ejaculation
Increased blood pressure	Chilliness and piloerection ("gooseflesh")

As you can see many of the signs and symptoms of opioid withdrawal are also common side effects seen after anesthesia and treated in the PACU such as nausea and vomiting and increased blood pressure. It is important for the PACU nurse to be able to determine when/if a patient is going through an opioid withdrawal in order to provide safe, effective treatment and to prevent withdrawal during the post-surgical time in which the symptoms of withdrawal could be a greater detriment to the patient. As discussed in previous slides some medications such as naloxone and any of the mixed opioid agonist-antagonist drugs can precipitate an acute withdrawal syndrome in patients who are opioid dependent. Remember opioid dependency does not always present in a commercial form and patients with chronic pain, such as those who have received back surgery, may have been on long term opioid medications.

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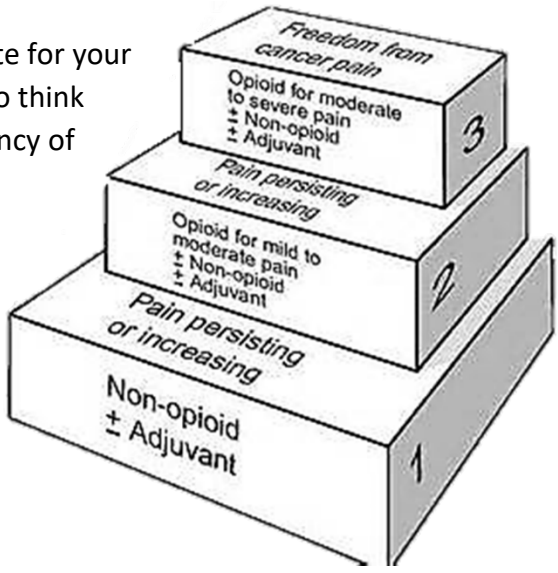
Dosing of Opioid Medications

Here are some of the most commonly used opioid agents used in the PACU area, their route, and suggested dosage ranges. I want to emphasize that these are just suggested dose ranges and reiterate that higher and lower doses may be indicated for specific patient needs.

Agent	Use	Route	Dose
Morphine	Premedication	IM	0.05 - 0.2 mg/kg
	Intraoperative anesthesia	IV	0.1 - 1 mg/kg
	Postoperative analgesia	IM	0.05 - 0.2 mg/kg
		IV	0.03 - 0.15 mg/kg
Meperidine	Premedication	IM	0.5 - 1 mg/kg
	Intraoperative anesthesia	IV	2.5 - 5 mg/kg
	Postoperative anesthesia	IM	0.5 - 1 mg/kg
		IV	0.2 - 0.5 mg/kg
Fentanyl	Intraoperative anesthesia	IV	2 - 150 µg/kg
	Postoperative analgesia	IV	0.5 - 1.5 µg/kg
Sufentanil	Intraoperative anesthesia	IV	0.25 - 30 µg/kg
Alfentanil	Intraoperative anesthesia		
	- Loading dose	IV	8 - 100 µg/kg
	- Maintenance infusion	IV	0.5 - 3 µg/kg/min
Remifentanil	Intraoperative anesthesia		
	- Loading dose	IV	1.0 µg/kg
	- Maintenance does	IV	0.5 - 20 µg/kg/min
	Postoperative analgesia / sedation	IV	0.05- 0.3 µg/kg/min

What Drug, How Much?

When considering what pain medication is appropriate for your patient and/or what dosage is best it can be helpful to think in a step-like fashion. The idea is to increase the potency of the pain medication and dosage in relevance to an increase in pain level and persistence. A good rule of thumb we use in anesthesia when deciding on pain medication is that you can always add more, but you can't take it back. This helps us to treat pain without compromising safety.



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Conclusion

Opioids are one of the most commonly prescribed post-operative medications. For this reason, an excellent working knowledge of the pharmacology of opioids is critical information for the perianesthesia nurse when caring for post-surgical patients. Opioids possess excellent qualities of pain relief but incorrect administration or the absence of appropriate monitoring can lead to dire outcomes. The advent of newer opioids and complex opioid agonist-antagonists will require the PACU and anesthesia team to work cohesively to prevent adverse outcomes.

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