Peri-operative pain control:

As healthcare providers our goal during the postoperative phase of treatment is for patients to use the least amount of pain medication for the shortest period of time while achieving maximum pain control and comfort. This article summarizes preoperative and postoperative methods to help achieve our goal.

In 1990, WHO devised an “analgesic ladder,” a stepwise approach to treating mild to severe pain. Specifically, nonopioid agents should be used for mild pain, and opioids formulated with non-opioids should be used for mild-to-moderate pain. Severe pain should be addressed with opioids and if needed, non-opioids and adjuvants.¹

Preoperative methods for reducing postoperative pain:

The use of long acting local anesthetics in combination with pre-emptive analgesia and antiinflammatory agents can significantly reduce postoperative pain and therefore minimize our patient’s exposure to opioids.

The first aspect that improves postoperative pain control is the use of long acting local anesthetics by delaying the onset of pain. Peripheral afferent neuronal barrage from tissue injury produces central nervous system hyperexcitability which may contribute to increased postoperative pain. In a study by Gordon et al, patients given .5% bupivacaine preoperatively self-administered fewer codeine tablets for unrelieved pain over 24–48 hours postoperatively. Therefore, blockade of nociceptive input by administration of a long-acting local anesthetic decreases the development of central hyperexcitability, resulting in less pain and analgesic intake.²

The second is pre-emptive analgesia, a therapeutic technique whereby an analgesic is administered before a painful stimulus. The ultimate goal is to prevent or reduce pain following the surgical procedure. Many studies have elucidated the validity of pre-emptive analgesia and the resultant decreased need for opioid analgesics and fewer complications from these
medications are sustained during the perioperative period. Patients have a longer time to first analgesic request and lower consumption of postoperative analgesics. When a procedure is planned with IV sedation, the most effective method of pre-emptive analgesia is to use ketorolac (Toradol®) 30mg or Tramadol 100mg IV in the immediate pre-operative period. When the procedure is planned for a local anesthetic, administer ibuprofen 400-600mg (based on patient ideal body weight) orally one hour prior to the procedure.

The third method is the use of glucocorticoids; they are effective agents for controlling both acute and chronic inflammation by interfering with multiple signaling pathways involved in the inflammatory response. The reduction in postoperative edema can improve patient comfort after surgery. However, studies have shown that glucocorticoids have little or no analgesic effect when used alone. Nevertheless, when used in combination with nonselective (cyclooxygenase 1 and 2 inhibitors) NSAIDS like ketorolac, there is a measurable decrease in prostaglandin E2 (PGE₂) and thromboxane B₂ (TxB₂) immunoassay at the surgical site. Dexamethasone 4-8mg IV or 10mg PO are most commonly used preoperatively for glucocorticoid mediated anti-inflammatory effects.

Arnica Montana has been used medicinally for centuries. Clinical trials conducted suggest benefits of arnica for osteoarthritis, reduction in postoperative swelling and pain. Arnica is most commonly used in topical preparations with few side effects. Side effects are benign and limited to local redness or slight burning sensation. Arnica is also available in oral formulations but the safety profile is not well documented. Recommended instructions to your patients: apply to the skin over the surgical site 3-4x daily. Do not apply intraorally or over broken skin.

These techniques combined are likely to contribute to improvement in patient comfort, pain reduction, decreased postoperative morbidity, and reduction in narcotic rescue analgesic requirement.

**Postoperative pain control recommendation, Analgesic ladder:**

Recommendation for post-operative pain control instructions for 70kg adult patients. Children, patients who are immunocompromised, afflicted with systemic disease must have their doses individualized accordingly:

- Use the prescribed medication as directed for pain. It is recommended your first dose of pain medication be taken before the anesthetic wears off to help control post-operative discomfort more effectively.
- The following is safe and effective pain control method:
  - Alternate between:
    - Acetaminophen/APAP (325 or 500mg)
    - Ibuprofen (200-800mg mg per capsule/tablet) or ASA 325mg
    - Take the medications 3-4 hours apart as needed for pain.
  - If you experience breakthrough pain take the prescribed narcotic medication (Tylenol with codeine, Hydrocodone, Oxycodone) as directed for pain not controlled as above.
Please note that the most narcotic formulations have 500mg of acetaminophen (Norco has 325mg of APAP). Therefore, factor that in when calculating your maximum daily dose of APAP.

- Please note: The maximum daily healthy adult dose of acetaminophen (Tylenol) is 4000mg under direction of health care provider.
- The maximum daily healthy adult dose of Ibuprofen is 3200mg.

By alternating acetaminophen and NSAID you can realize the analgesic benefits of each while keeping well below the maximum daily doses of each. In addition, consider ibuprofen 600mg q6-8mg. If taken at the lower end of the recommended interval (4-6hours) the maximum consumed in a 24 hour period will be 2400mg, well below the 3200mg maximum daily dose. Conversely, by prescribing ibuprofen 800mg, if taken every 6 hours the maximum daily dose will be realized each day. Norco is a formulation of hydrocodone with 325mg of APAP compared with the standard hydrocodone formulation with 500mg APAP. If taken at the lower end of the recommended interval (6-8 hours) the maximum consumed in a 24 hour period will be 1950mg well below the 4000mg maximum daily dose. This approach will also allow patients to take four additional doses of APAP 325-500mg whilst keeping below the 4g maximum daily recommended APAP dose. This methodology will allow for margin for error in the event the patient inadvertently or on their own volition take more than the prescribed doses.

The analgesic ceiling effect of a drug refers to the dose beyond which there is no additional analgesic effect. Higher doses do not provide any additional pain relief but may increase the likelihood of side effects. This concept should be carefully considered when using the common analgesics acetaminophen and ibuprofen. Skoglund and coworkers compared different doses of acetaminophen and they found that analgesic ceiling effect of APAP was reached at 1000 mg. Ibuprofen is commonly used in dosages as high as 800 mg for acute pain, although the analgesic ceiling is only 400mg for a single dose to a ceiling of 1200 mg per day. In addition one must consider the ideal antiinflammatory dose is achieved only after three successive doses every six hours to a maximum 2400 mg per day. The increase antiinflammatory dosage does not provide any additional pain relief. There is no true analgesic ceiling effect for opioids.

### Abbreviated Mechanism of action/pharmacodynamics for commonly used analgesics:

**Acetaminophen (APAP)** is a widely used analgesic and antipyretic drug that is used for the relief of fever, headaches, and other minor aches and pains. Acetaminophen has no anti-inflammatory properties or effects on platelet function, and it is not a member of the class of drugs known as non-steroidal anti-inflammatory drugs or NSAIDs. At therapeutic doses acetaminophen does not irritate the lining of the stomach nor affect blood coagulation, kidney function, or the fetal ductus arteriosus (as NSAIDs can). Unlike opioid analgesics, acetaminophen does not cause euphoria or alter mood in any way. Acetaminophen has the benefit of being completely free of problems with addiction, dependence, tolerance and withdrawal. **Acetaminophen is thought to act primarily in the CNS**, increasing the pain threshold by inhibiting both isoforms of cyclooxygenase, COX-1, COX-2, and COX-3 enzymes involved in prostaglandin synthesis. Unlike NSAIDs, acetaminophen does not inhibit cyclooxygenase in peripheral tissues and, thus, has no peripheral anti-inflammatory affects. The antipyretic properties of acetaminophen are likely due to direct
effects on the heat-regulating centers of the hypothalamus resulting in peripheral vasodilation, sweating and hence heat dissipation. Approximately 90 to 95% of a dose is conjugated in the liver with glucuronic acid and sulfuric acid.\textsuperscript{17}

Ibuprofen is nonsteroidal anti-inflammatory drug (NSAID), with analgesic and antipyretic properties. Ibuprofen is thought to act through inhibition of prostaglandin synthesis. Ibuprofen is a non-selective inhibitor of cyclooxygenase, an enzyme involved in prostaglandin synthesis via the arachidonic acid pathway in peripheral tissues (it has no central CNS effect like ASA). Its pharmacological effects are believed to be due to inhibition cylooxygenase-2 (COX-2) which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever and swelling. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. Inhibition of COX-1 is thought to cause some of the side effects of ibuprofen including GI ulceration. Ibuprofen is rapidly metabolized and eliminated in the urine.\textsuperscript{18}

Hydrocodone is used for relief of moderate to moderately severe pain. Also used for the symptomatic relief of nonproductive cough, alone or in combination with other antitussives or expectorants. Hydrocodone, a semisynthetic opiate agonist and hydrogenated ketone derivative, is similar to other phenanthrene derivatives, such as codeine. Opiate agonists exert their principal pharmacologic effect at specific receptor binding sites in the CNS and other tissues. There are several subtypes of opiate receptors including the \textit{mu} receptor (localized in pain modulating regions of the CNS), the \textit{kappa} receptor (localized in the deep layers of the cerebral cortex), the \textit{delta} receptor (localized in the limbic regions of the CNS), and the \textit{sigma} receptor (thought to mediate the dysphoric and psychotomimetic effects of some opiate partial agonists). Opiate agonists act at several sites within the CNS involving several systems of neurotransmitters to produce analgesia. Opiate agonists do not alter the threshold or responsiveness of \textit{afferent nerve} endings to noxious stimuli nor the conduction of impulses along \textit{peripheral nerves}. Instead, they alter the perception of pain at the spinal cord and higher levels in the CNS and the person's emotional response to pain. Hydrocodone acts as a weak agonist at OP1, OP2, and OP3 opiate receptors within the central nervous system. Hydrocodone primarily affects OP3 receptors, which are coupled with G-protein receptors and function as modulators, both positive and negative, of synaptic transmission via G-proteins that activate effector proteins. Binding of the opiate stimulates the exchange of GTP for GDP on the G-protein complex. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine, and noradrenaline is inhibited. Opioids such as hydrocodone also inhibit the release of vasopressin, somatostatin, insulin, and glucagon. Opioids close N-type voltage-operated calcium channels (OP2-receptor agonist) and open calcium-dependent inwardly rectifying potassium channels (OP3 and OP1 receptor agonist). This results in hyperpolarization and reduced neuronal excitability. It is metabolized in the liver and also in intestinal mucosa.\textsuperscript{19}

Oxycodone is a semisynthetic derivative of codeine that acts as a narcotic analgesic more potent and addicting than codeine. Used for the treatment of diarrhea, pulmonary edema and for the relief of moderate to moderately severe pain. Oxycodone acts as a weak agonist at mu, kappa, and delta opioid receptors within the central nervous system. Mechanism of action similar to hydrocodone as described above. It is metabolized in the liver. Symptoms of overdose include
respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death. Naloxone hydrochloride is a competitive antagonist of opioids. It acts by preventing or reversing the respiratory depression, sedation hypotension and psychotomimetic and dysphoric effects of opioids.

**Pain control alternatives for codeine (and derivatives) allergic patients:**

*Tramadol hydrochloride,* (1RS, 2RS)-2-[(dimethyl amino)-methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, is clinically effective in the treatment of moderate to moderately severe pain with a relative low addiction potential. In acute therapeutic use, tramadol produces analgesia against multiple pain conditions, such as postsurgical pain, obstetric pain, terminal cancer pain, and pain of coronary origin, and it has been used as adjuvant therapy in anesthesia. It acts at opioid receptors and also seems to modify transmission of pain impulses by inhibition of monoamine reuptake. Tramadol is administered as a racemic mixture of 2 enantiomers, (+)-tramadol and (−)-tramadol, that are metabolized by the liver. The (+)-enantiomer has a moderate affinity for the opioid μ receptors, and inhibits serotonin reuptake, and the (−)-enantiomer is a norepinephrine reuptake inhibitor. In addition, biotransformation of tramadol in the liver results in many metabolites. O-desmethyl tramadol (M1) is the only active metabolite with a greater affinity for the μ receptors.

*Ketorolac* is used for the short-term (maximum 5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Ketorolac, an anti-inflammatory agent with analgesic and antipyretic properties, is used to treat osteoarthritis and control acute pain. It is a *peripherally acting analgesic.* Ketorolac tromethamine possesses no sedative or anxiolytic properties. Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) chemically related to indomethacin and tolmetin. Ketorolac tromethamine is a racemic mixture of [-]S- and [+]R-enantiomeric forms, with the S-form having analgesic activity. Its antiinflammatory effects are believed to be due to inhibition of both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) which leads to the inhibition of prostaglandin synthesis leading to decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid. The resultant reduction in prostaglandin synthesis and activity may be at least partially responsible for many of the adverse, as well as the therapeutic, effects of these medications. Analgesia is probably produced via a *peripheral action* in which blockade of pain impulse generation results from decreased prostaglandin activity. However, inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation may also contribute to the analgesic effect.

*Acetylsalicylic acid* (ASA) is the prototypical analgesic used in the treatment of mild to moderate pain. It has anti-inflammatory and antipyretic properties and acts as an inhibitor of cyclooxygenase which results in the inhibition of the biosynthesis of prostaglandins. Acetylsalicylic acid also inhibits platelet aggregation and is used in the prevention of arterial and venous thrombosis. Acetylsalicylic acid is an analgesic, antipyretic, antirheumatic, and anti-inflammatory agent. Acetylsalicylic acid appears to produce analgesia by virtue of both a *peripheral and CNS effect*. Peripherally, acetylsalicylic acid acts by inhibiting the synthesis and release of prostaglandins. Acting centrally, it would appear to produce analgesia at a hypothalamic site in the brain, although the mode of action is not known. Acetylsalicylic acid also acts on the hypothalamus to produce antipyresis; heat dissipation is increased as a result of
vasodilation and increased peripheral blood flow. The analgesic, antipyretic, and anti-inflammatory effects of acetylsalicylic acid are due to actions by both the acetyl and the salicylate portions of the intact molecule as well as by the active salicylate metabolite. Acetylsalicylic acid directly and irreversibly inhibits the activity of both types of cyclooxygenase (COX-1 and COX-2) to decrease the formation of precursors of prostaglandins and thromboxanes from arachidonic acid. This makes acetylsalicylic acid different from other NSAIDS which are reversible inhibitors. The platelet aggregation-inhibiting effect of acetylsalicylic acid specifically involves the compound's ability to act as an acetyl donor to cyclooxygenase. Irreversible acetylation renders cyclooxygenase inactive, thereby preventing the formation of the aggregating agent thromboxane A2 in platelets. Since platelets lack the ability to synthesize new proteins, the effects persist for the life of the exposed platelets (7-10 days). Acetylsalicylic acid may also inhibit production of the platelet aggregation inhibitor, prostacyclin (prostaglandin I2), by blood vessel endothelial cells; however, inhibition prostacyclin production is not permanent as endothelial cells can produce more cyclooxygenase to replace the non-functional enzyme. Acetylsalicylic acid is rapidly hydrolyzed primarily in the liver to salicylic acid, which is conjugated with glycine (forming salicyluric acid) and glucuronic acid and excreted largely in the urine.22

**General precautions:**

Recently, three deaths and one case of severe respiratory depression were reported in children who received codeine after undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome. The children ranged in age from two to five years old. The three deaths occurred in children who had evidence of being “ultra-rapid metabolizers” of substrates of the cytochrome P450 isoenzyme 2D6 (including codeine), and the life-threatening case occurred in a child who was an extensive metabolizer. All children received doses of codeine that were within the typical dose range. In these cases, signs of morphine toxicity developed within one to two days after starting codeine. The post-mortem morphine concentrations in the three children who died were substantially higher than the typical therapeutic range. FDA is conducting a review to determine if there are additional cases of inadvertent overdose or death in children taking codeine, and if these adverse events occurred during treatment of other kinds of pain such as post-operative pain following other types of surgery or procedures. FDA will update the public when more information is available.23

APAP toxicity: Hepatotoxicity with doses greater than 4g/day. Symptoms include but not limited to: Abdominal pain, appetite loss, Coma, Convulsions, Diarrhea, Irritability, Jaundice, Nausea, Sweating, Upset stomach, Vomiting. Acetaminophen toxicity is the most common cause of hepatic failure requiring liver transplantation in US. Rocky Mountain Poison and Drug Center 1-800-525-6115. When a patient is treated with IV N-acetyl cysteine, early in the course of APAP overdose it reduces morbidity and virtually eliminates mortality. The U.S. Food and Drug Administration is asking drug manufacturers to limit the strength of acetaminophen in prescription drug products, which are predominantly combinations of acetaminophen and opioids. This action will limit the amount of acetaminophen in these products to 325 mg per tablet, capsule, or other dosage unit, making these products safer for patients. In addition, to provide a Boxed Warning highlighting the potential for severe liver injury if taken not as prescribed or labeled. These actions will help to reduce the risk of severe
liver injury and allergic reactions associated with acetaminophen. OTC products containing acetaminophen (e.g., Tylenol) are not affected by this action. Information about the potential for liver injury is already required on the label for OTC products containing acetaminophen.

McNeil Consumer Healthcare is voluntarily implementing new measures, including the label changes, that are designed to help lessen the possibility of accidental acetaminophen overdose. The new dosing instructions will lower the maximum daily dose for single-ingredient Extra Strength TYLENOL® (acetaminophen) products sold in the U.S. from 8 pills per day (4,000 mg) to 6 pills per day (3,000 mg). Changes to the dosing instructions for regular strength TYLENOL® (acetaminophen) will take place in the upcoming year. McNeil Consumer Healthcare will be voluntarily lowering the maximum daily dose of Regular Strength TYLENOL® products sold in the U.S. from 12 pills per day (3,900 mg) to 10 pills per day (3,250 mg).

Conclusion:

Use of pre-emptive analgesia and a postoperative regiment will best accomplish our goal of using the least amount of pain medication for the shortest period of time while achieving maximum pain control and comfort for our patients.

References:


17. http://www.drugbank.ca/drugs/DB00316

