Multimodal analgesia captures the effectiveness of individual agents in optimal dosages that maximize efficacy and attempts to minimize side effects from one analgesic (mainly opioids). This important concept employs the theory that agents with different mechanisms of analgesia that may have synergistic effects in preventing or treating acute pain when used in combination. These regimens must be tailored to individual patients, keeping in mind the procedure being performed, side effects of individual medications, and patients’ pre-existing medical conditions. The concept and theory of multimodal analgesia is not new; however, several novel pharmacological agents have emerged and can be added to the drugs that can be used in this fashion. It is vital to realize that blocking the neuronal pathway during surgery with local anesthetics does not decrease the hemural biochemical responses that occur during surgery which have to be inhibited by administering systemic pharmacological therapy. This abstract will only focus on the recent advances in pharmacological agents for multimodal therapy.

**ACETAMINOPHEN**

Oral acetaminophen has been used for several decades and Paracetamol, an intravenous formulation of acetaminophen, became available in 2002 and has been studied in Europe. Göröcs and colleagues administered a single dose of 1 gram of intravenous paracetamol (Perfalgan®) prior to the termination of surgery and observed high patient satisfaction and good tolerance of the drug in 601 patients undergoing minor outpatient surgical procedures. Nearly half of these patients (42.7 %) received the single dose of paracetamol as monotherapy for post-operative pain. Salihglu, et al. randomized 40 patients undergoing laparoscopic cholecystectomy to 1 gram paracetamol (after intubation and prior to incision) or saline infusion. Significant improvements in outcomes in the paracetamol group included lower VAS, lower morphine consumption, and shorter stay in the recovery room (32 ± 11 versus 48 ± 14 minutes). Approved by the United States FDA in November 2010, intravenous (IV) acetaminophen (Ofirmev®) has been studied and shown to be safe. IV acetaminophen endorses a quick onset due to the pharmacokinetics.

Combinations of acetaminophen and non steroidal anti-inflammatory drugs (NSAIDs) have been investigated and may offer enhanced effects as based on current research. In 55 children undergoing hernia repair, 30 mg ketorolac and 20 mg/kg acetaminophen resulted in significantly lower post-operative fentanyl consumption, less sedation and vomiting. A systematic review of this subject determined that when used as a combination, NSAIDs and paracetamol “offer superior analgesia compared with either drug alone and 18/21 studies included had positive results with regard to lowering visual analogue score (VAS) and/or use of rescue analgesics. The combination was more effective than paracetamol (85 % of studies) or NSAIDs (64 % of studies) as individual agents.

**NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)**

The use of NSAID use in the perioperative period has been well established taking into consideration the adverse effects of bleeding. The utility of COX-2 inhibitors in this scenario has been demonstrated to be a benefit. Randomized, double-blind, placebo-controlled study to examine celecoxib 200mg versus placebo in patients undergoing major plastic surgery demonstrated the ability of celecoxib to reduce VAS and postoperative morphine consumption. More recent formulations of NSAIDs include an intranasal (IN) ketorolac spray, IV ibuprofen, and topical diclofenac. Southworth and colleagues conducted a randomized, double-blind trial of varying dosages of IV ibuprofen (Caldolor®) versus placebo in 406 patients having an elective abdominal or orthopedic surgery. Those receiving ibuprofen 800 mg every 6 hours consumed 22 % less morphine postoperatively. IV ibuprofen 400 mg every 6 hours appeared to attenuate postoperative pain for up to 24 hours, but had no benefit thereafter when compared to placebo. Aside from dizziness, IV ibuprofen was generally well-tolerated.

In a randomized, double-blind, placebo-controlled study comparing intranasal (IN) ketorolac to placebo in 40 patients undergoing third molar extraction, Grant and Mehlisch demonstrated 31.5 mg IN ketorolac resulted in higher pain relief scores and greater patient satisfaction. 60 % of participants in the study group reported good to excellent pain control compared to 13 % in the placebo group. IN ketorolac 31.5mg every
6 hours for 48 hours, then up to four times daily (up to 5 days) in patients undergoing abdominal surgery decreased morphine use over 48 hours and resulted in higher quality of analgesia scores. The authors of this study indicated that pain relief occurred within 20 minutes of administration, which may be due to higher blood brain penetration of ketorolac via the nasal route (cribriform plate). The availability of IN ketorolac can now be used in the ambulatory setting after discharge home taking the same general precautions as IV formulation.

Topical diclofenac exists in several forms, including diclofenac epolamine 1% topical patch (FLECTOR Patch®), diclofenac sodium 1% topical gel (VOLTAIREN Gel®), and diclofenac sodium 1.5% w/w liquid (PENNNSAID®). A review by Massey and colleagues showed that topical NSAIDs are not only safe, but efficacious in the treatment of acute soft tissue injuries and localized regions of pain. They did find a difference between placebo and topical NSAIDs with regard to local skin irritation but the systemic side effects were less with topical. This research has even led to the National Institute for Health and Clinical Excellence (UK) to recommend topical NSAIDs, along with acetaminophen, as first line treatment for osteoarthritis pain.

A review of diclofenac epolamine topical patch by McCarberg and Argoff discussed the benefits of a patch, as opposed to NSAID gels or creams. These included application of a defined dose of diclofenac, drug delivery over an extended period of time (typically 12 hours), and ease of application. Application of diclofenac sodium 1% gel versus placebo vehicle (identical composition to the gel component of the study drug) applied 4 times daily for 3 months was investigated by Barthel, et al for the treatment of osteoarthritis pain. Results of their study indicated superior analgesia from 1 to 12 weeks and improved function for the same duration. With regards to diclofenac 1.5% w/w liquid, it has been shown to be as efficacious to oral diclofenac in treating arthritis pain. Gastrointestinal side effects were significantly less common with local skin reactions being more common. A prospective study by Shainhouse and colleagues established the safety of topical diclofenac 1.5% w/w in a study where 793 subjects was followed for an average of 204 days; 144 subjects were followed for 1 year. Application of the study drug, 40 drops four times daily, resulted in local skin reactions (dry skin, contact dermatitis, or dermatitis with vesicles) in 45.1% of study participants. 24 volunteers indicated a similar overall experience when using diclofenac gel and diclofenac liquid. However, they found the gel to have a less desirable scent, found the consistency to be more greasy and sticky when compared to the diclofenac liquid. When side effects have limited oral NSAID use in a multimodal, it may be that IN, IV, and topical formulations of NSAIDs could prove to be of benefit in the perioperative period and should be considered as tools that are emerging for multimodal analgesia.

**ANTICONVULSANTS**

The use of adjunct agents to treat pain includes the use of anticonvulsants such as gabapentin and pregabalin. Clarke and colleagues studied the effects of varying doses of gabapentin given pre-operatively and post-operatively in addition to femoral/sciatric nerve blocks and celecoxib in 36 patients undergoing total knee arthroplasty. When administered pre- and post-operatively, gabapentin decreased morphine consumption on post-operative days (POD) 2 – 4 and increased the amount of active knee flexion on POD 2 – 3. This occurred without an increase in side effects. A randomized, double-blind, controlled trial of gabapentin in children undergoing spinal fusion determined that pre- and post-operative gabapentin resulted in decreased morphine consumption and improved pain scores through the early stages of recovery up to POD2. However, this attenuation of opioid use and decreased verbal pain scores was temporary. An evaluation of gabapentin’s ability to prevent not only acute, but chronic pain by Sen, et al. revealed that gabapentin 1200 mg administered preoperatively decreased morphine consumption, reduced incisional pain at 1, 3, and 6 months, and improved patient satisfaction compared to placebo. Comparing varying dosages of gabapentin in lumbar laminectomy, Khan et al. concluded the timing of dosing (pre-operative versus post-operative) did not affect analgesic efficacy. Gabapentin administered 900 mg or 1200 mg pre- or post-operatively reduced morphine consumption in the first 24 hours post-op and VAS scores without increase in side effects. The use of similar anticonvulsant, pregabalin, has gained attention because of more favorable pharmacokinetics which includes improved bioavailability and faster achievement of therapeutic levels. 30 patients undergoing laparoscopic cholecystectomy were randomized to receive pregabalin 150 mg 1 hour pre-operatively or placebo by Agarwal, et al. Fentanyl use and VAS scores were measured up to 24 hours postop. Both VAS scores and narcotic use were significantly lower in patients who had received pregabalin. No significant difference in side effects was noted. Mathiesen and colleagues studied a single pre-operative dose of pregabalin 300 mg versus pregabalin 300 mg + dexamethasone 8 mg in 120 patients undergoing total hip arthroplasty. Although pain scores were unaffected, the two groups receiving pregabalin pre-op had significantly less morphine consumption at 24 hours post-op. They did notice that those receiving pregabalin had more sedation. A randomized, placebo-controlled, double-blind trial comparing pregabalin (300mg pre-operatively with a tapering dose post-operatively for 14 days) to placebo in 240 patients undergoing total knee arthroplasty has recently been published. Immediate effects observed were decreased epidural drug consumption and increased sedation and confusion on POD 0 and 1. Long-term outcomes included reduced neuropathic pain at 3 and 6 months. A meta-analysis by Zhang et al. demonstrated that pregabalin administered pre-
operative, post-operative or both decreases 24 hour morphine consumption while having no effect on post-op pain scales. Analysis also revealed that pregabalin administration led to lower rates of postoperative nausea and vomiting. It is important to note that this meta-analysis did not include any studies of prolonged (more than 2) doses of pregabalin.

TRPV1 AGONIST: CAPSAICIN

Capsaicin, the active component of chili peppers, selectively stimulates unmyelinated C fiber afferent neurons and causes the release of substance P. Following initial depolarization, continued release of substance P in the presence of capsaicin leads to the depletion of substance P and subsequent decrease in C fiber activation. It is a non-narcotic that acts at TRPV1 receptor as an agonist peripherally. It does not affect the A-delta and A-alpha fibers. Capsaicin causes calcium dependant desensitization.

An ultra-purified capsaicin (ALGRX 4975, 98% pure) has been investigated in a randomized, double-blind, placebo-controlled study of the analgesic efficacy of a single intra-operative wound instillation of 1000 mcg of capsaicin after open mesh groin hernia repair. The VAS pain scores assessed as area under the curve was significantly lower during the first 3 days postoperatively, but this effect was not observed after 72 hours. The local application of capsaicin during hernia repair does not lead to loss of sensory function in patients and has been demonstrated in animal studies not to cause neurotoxicity. Further clinical trials have been carried out in patients undergoing total knee and hip arthroplasty but the entire data has not been published to date. When capsaicin is used in the perioperative setting, the clinical must administer capsaicin well before the end of anesthesia to allow for resolution of the acute burning sensation that occurs immediately after its application. The prolonged duration of analgesia obtained by capsaicin could be extremely valuable in facilitating earlier rehabilitation after painful orthopedic surgery procedures. In contrast to local anesthetic, capsaicin does not affect the motor or autonomic functions and therefore will not interfere with postoperative rehabilitation. The capsaicin patch (NGX-4010) though used for various neuropathic chronic pain conditions, may be useful in acute pain in a multimodal fashion. This needs further large scale randomized controlled trials.

NMERADECEPTORANTAGONISTS:

NMDA receptor antagonists, including ketamine and memantine, have been studied as adjuncts for acute and chronic pain management. Ketamine has options for routes of administration, including IV or IN. Remérand and colleagues demonstrated that an IV bolus at the beginning of surgery followed by a 24 hour infusion decreased morphine consumption in patients undergoing total hip arthroplasty. More interestingly, patients receiving ketamine decreased the incidence of chronic pain. At 6 months 21% of placebo and 8% of ketamine-receiving patients had persistent pain. Loftus et al. found similar results, albeit in opiate-dependent patients undergoing lumbar spine surgery. A ketamine infusion of 10ug/kg/min was started at the beginning of surgery after a bolus of 0.5 mg/kg was administered and terminated at skin closure. Significant results included decreased post-op morphine requirements and lower pain scores at 6 weeks post-op.

Memantine was first synthesized in the 1960s and found to antagonize the NMDA receptor in the 1980’s. The major site of action is the blockade of current flowing through the NMDA receptor channel. Memantine is completely absorbed from the gastrointestinal tract with maximal plasma concentration occurring between 3-8 hours after oral administration. Food does not influence the bioavailability of memantine. Approximately 80% of the administered dose remains as the parent drug. The mean terminal elimination half-life is 60-100 hrs. The dose should be increased in 5 mg increments to 10 mg/day. The recommended maintenance dose is 10 mg twice daily (20 mg/day). There is not an established dose for the treatment of chronic pain states, but case reports and medication trials have started at 5-10 mg bid with increases at 1 week interval to 30 mg/day have been examined. Ketamine causes memory deficits; reproduces with impressive accuracy the symptoms of schizophrenia; is widely abused; and induces vacuoles in neurons at moderate concentrations and cell death at higher concentrations. Memantine, on the other hand, is well tolerated; although instances of psychotic side effects have been reported, in placebo-controlled clinical studies the incidence of side effects is remarkably low.

Memantine, an orally administered non-competitive NMDA receptor antagonist, may prove to be more useful than ketamine as an analgesia adjunct. In one study, daily doses of memantine 30mg decreased phantom pain by up to 80% at one month following upper extremity amputations (in combination with brachial plexus block.) Unfortunately, in patients who have developed phantom pain the pain relief obtained is temporary. Once chronic pain from surgery is established like phantom limb pain, memantine has not been shown to provide analgesia for these patients.

Magnesium seems to exert its analgesic mechanism via inhibition of calcium influx, antagonism of NMDA receptors and prevention of enhanced ligand-induced NMDA signaling in a state of hypo-magnesemia. In addition magnesium may attenuate central sensitization after peripheral tissue injury or inflammation because of dorsal horn NMDA receptors. Magnesium sulfate is available as a 500 mg/ml preservative-free solution for injection. Magnesium administered intravenously lacks efficacy at 4g, however, 50 mg administered intrathecally has been demonstrated to be effective. Perioperative IV magnesium sulfate at very high doses has been reported to reduce postoperative morphine consumption but not postoperative pain scores. Recently, a dose finding study for IV magnesium determined that administration of magnesium at 40 mg/kg prior to induction, followed by a 10 mg/kg/hour infusion, resulted in a reduction...
in perioperative analgesic requirements without any major hemodynamic consequences. Higher infusion doses did not offer any advantage. However, since the magnesium ion poorly crosses the blood brain barrier in humans, it is not clear whether the therapeutic effect is related to NMDA antagonism in the central nervous system or peripheral. This needs to be investigated further.

**ALPHA – 2 AGONISTS:**

Use of alpha-2 agonists as an analgesia adjunct has gained interest with the clonidine and dexmedetomidine. Central and peripheral stimulation of the alpha-2 receptors is believed to be the basic mechanism behind analgesia. Clonidine’s role in neuraxial blockade has been described by a number of studies. Recently, Lena and colleagues compared a clonidine/morphine spinal plus remifentanil infusion to a sufentanil infusion for analgesia in 83 patients undergoing open heart surgery. The clonidine/morphine spinal group had faster times to extubation, lower pain scores post-op, used less PCA morphine, and had improved patient satisfaction.

An infusion of dexmedetomidine, administered prior to induction through wound closure, decreased post-anesthesia care unit (PACU) opioid use in 80 patients undergoing laparoscopic bariatric surgery. In addition to this, nausea and vomiting was decreased, and PACU stay shortened. As presumed higher doses of dexmedetomidine required significantly more rescue doses of phenylephrine intra-op, otherwise there were no differences in side effects compared to placebo. Ramadhyani and colleagues reviewed dexmedetomidine’s use in IV regional anesthesia. They concluded that when added to IV regional solutions, dexmedetomidine had the ability to prolong analgesia and extend the duration of motor and sensory blockade.

**DUAL ACTING AGENT- TAPENTADOL:**

Tapentadol is a novel central acting analgesic with duel mode of action. It has analgesic action via the mu-opioid receptor and norepinephrine reuptake inhibition. Combining both effects in a single molecule eliminates the potential for drug-drug interactions inherent in multiple drug therapy. The analgesic effects of tapentadol are independent of metabolic activation with minimal metabolites. Having limited protein binding, no active metabolites and no significant microsomal enzyme induction or inhibition, tapentadol has a limited potential for drug-drug interactions. The duel mode of analgesia is synergistic as demonstrated by pre-clinical work. The immediate release formulation of tapentadol is FDA approved and has been used in the USA since 2008 with 50, 75 and 100 mg. The drug is a schedule II and as such all precautions that need to be followed for other drugs in this category needs to be followed. The equipotent analgesics dose of 100 mg of tapentadol to oxycodone is 15 mg and needs to be administered 4-6 hours.

This compound though has opioid activity also has activity at the descending pathway and therefore may prove to be a very useful analgesic as more clinical experience is obtained in the postoperative setting. For equipotent doses of narcotics, tapentadol has decreased incidence of nausea and vomiting compared to oxycodone. The concept of obtaining equipotent analgesia with decreased postoperative nausea and vomiting can be of great benefit in treating postoperative pain and earlier discharge with significant cost savings. However, further clinical trials need to be carried to demonstrate this phenomenon.

**EMERGING TECHNOLOGIES IN PAIN MANAGEMENT**

**Transdermal fentanyl:** The use of patient-controlled delivery has led to the development of other modalities that allow patient control in the delivery of opioid medications. Transdermal delivery systems such as IONSYS®, allow demand dosing of fentanyl at a predetermined interval. The fentanyl HCl iontophoretic transdermal system (ITS) is a patient-controlled approach to analgesic delivery that may avoid some of the problems associated with IV PCA. Fentanyl ITS is a compact, needless, self-contained system that is preprogrammed to deliver fentanyl 40 mcg across the skin by means of an imperceptible low-intensity electrical current, a method known as iontophoresis. This needless system is under further research before being released for human use. Inhaled fentanyl has been trialed in pediatric and adult patients. There are investigations into the encapsulated liposomal inhaled fentanyl for acute pain- the advantage of this being that it can provide rapid onset and sustained release.

**Long acting local Anesthetics:** A new developed liposomal long acting bupivacaine is considered for approval by the FDA. A single injection of the liposomal bupivacaine should last 72 hours and is currently considered for infiltration of the local surgical site. Regional analgesia with this product has yet to be established.

**Cannabinoids:** These compounds have been shown to potent analgesics in animal models. There have been several clinical trials, most of them demonstrating no significant analgesic effect superior to placebo. In fact some of the trials demonstrated increase in VAS with nabnilone (oral synthetic cannabinoid) when used in acute postoperative setting. However, these classes of drugs seem to be promising in chronic pain patients.

**CONCLUSION**

Acute postoperative pain is a predictable response. Recent research has demonstrated that un-treated acute postoperative pain can lead to chronic persistent pain. It is imperative that the health care provider managing acute postoperative pain understand the various options such as the multimodal analgesia so that acute pain can be treated and to prevent the development of chronic pain from surgery.
REFERENCES:

42. Ehrnrods M, Kelly K, Okamoto A, Rauschkolb C: Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. Adv Ther 2011; April. (not yet in print)