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GABAPENTIN ADMINISTRATION IN PATIENTS UNDERGOING SURGICAL

PROCEDURES

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Abstract

Title: Gabapentin Administration in the Patient Undergoing Surgical Procedures

Background: A 75-year-old male patient undergoing elective total knee arthroscopy, received 600 mg of oral gabapentin pre-operatively. With multiple co-morbidities, a spinal anesthetic was not an option, and the surgeon preferred a femoral block not be completed. In an effort to avoid significant post-operative narcotic use, gabapentin was administered pre-operatively. Gabapentin is a gamma-aminobutyric acid mimetic medication. It has historically been utilized in the areas of adjunctive seizure treatment and management of post-herpetic and other nerve related pain, but has been found to have analgesic properties. With its low side effect profile, the medication has drawn the attention of anesthesia providers to be utilized in the perioperative setting as part of multimodal pain management care plans.

Purpose: To evaluate current recommendations for anesthesia providers regarding gabapentin use in the perioperative setting.

Process: A systematic search was conducted utilizing online search engines CINAHL and PubMed for research articles, as well as anesthesia textbooks, in an effort to find recently published material pertaining to gabapentin use in the perioperative setting. Information was utilized from the review of literature to cultivate evidence-based recommendations on the inclusion of gabapentin in multimodal anesthesia care plans.

Results: While more research is needed regarding standardized dosing regimens, studies show gabapentin is useful in the perioperative setting as part of a multimodal pain management plan.

Implications: Anesthesia providers should be well-versed in the use of gabapentin in the perioperative setting. Its use should be determined on a case-by-case basis to ensure individualized patient care.

Keywords: gabapentin, pain, perioperative setting, anesthetic management

Background

Pain control is a very important component in the perioperative setting. It is a major factor in patient recovery time and overall patient satisfaction. With more healthcare financing institutions moving towards utilizing patient satisfaction in the funding equation, it becomes imperative that every effort be made to adequately control patients' pain. A multi-modal pain management course should be employed by those providing anesthesia care to help attenuate the discomforts of surgery. Gabapentin, a gamma-aminobutyric acid mimetic medication, has been shown to be useful in this effort.

Gabapentin was first developed to imitate the structure of gamma-aminobutyric acid, a neurotransmitter. In 1994, it was approved by the United States Food and Drug Association (FDA), as an adjunct to anti-seizure medication regimens. While the drug was originally created in an effort to help control seizures, this is actually it's least marketed area of use today (Sirven, 2010). Gabapentin has also been FDA approved for postherpetic neuralgia and other nerve related pain (Sirven, 2010). Because of its unique properties, gabapentin has proven itself useful in multi-modal anesthesia care plans.

Since the practice of utilizing gabapentin in the perioperative setting has been suggested, much research has been completed on this specific area of the drug's use. The development of gabapentin use in the perioperative setting is exciting, as this medication offers pain management, a low side-effect profile, and reduction of post-operative opioid consumption (Tiippana, Hamunen, Kontinen, & Kalso, 2007). It is important for anesthesia providers to be well-versed on gabapentin and consider its use when developing a perioperative plan of care for their patients.

Case Report

A 75-year-old male presented for an elective left total knee arthroplasty, with a diagnosis of degenerative joint disease of the knee. The patient was 180 cm and 107.6 kg, with a body mass index (BMI) of 34. Significant medical history included type 2 diabetes mellitus, lung cancer, peripheral vascular disease, hypertension, coronary artery disease, aortic stenosis, and hyperlipidemia. Surgical history included an abdominal aortic aneurysm repair, a thoracotomy, bilateral carotid endarterectomy, mediastinoscopy, coronary artery bypass grafting, cardiac stent placement, and right total knee arthroplasty. The patient had allergies to lisinopril, flonase, simvastatin, levoquin, levofloxacin, and fluticasone propionate.   Home medications included amlodipine, aspirin, clopidogrel, losartan, metformin, metoprolol succinate, multivitamin, niacin, and pravastatin sodium. Pre-operative vital signs consisted of a blood pressure of 135/80 mmHg, heart rate of 75 beats per minute, respiratory rate of 18 breaths per minutes, temperature of 36.4 degrees Celsius, and oxygen saturations of 97% on room air. Pre-operative laboratory data included blood sugar of 158 mg/dL, sodium of 136 mEq/L, potassium of 4.6 mEq/L, blood urea nitrogen of 21 mg/dL, creatinine of 1.0 mg/dL, chloride of 104 mEq/L, carbon dioxide of 23 mEq/L, anion gab of 9 mEq/L, calcium of 9.8 mg/dL, hemoglobin of 12.7 g/dL, hematocrit of 36.5%, and platelets of 157,000/microliter. The patient's blood type was found to be O positive, and negative for antibodies. Mallampati classification was assessed as a 2 pre-operatively, with an ASA classification of 3.

The plan was to perform general anesthesia with a normal induction sequence, and place an endotracheal tube. This plan was chosen over a spinal anesthetic with sedation because the patient had not withheld his home medication, clopidogrel, for the recommended length of time. Also, per surgeon preference, a femoral nerve block was not performed. Pre-operatively, 600 mg

oral gabapentin was administered 30 minutes before the procedure. There would be no post-operative doses administered. In addition to the gabapentin, the patient received 975 mg oral acetaminophen prior to the start of his procedure.

Once in the operating room, the standard non-invasive monitors were applied, vital signs were found to be stable. Pre-oxygenation and denitrogenation was completed by having the patient breathe 100% oxygen through a mask. The patient was then induced intravenously, through a 20- gauge intravenous catheter, with 100 mcg Fentanyl, 150 mg propofol, and 50 mg Rocuronium. Utilizing a Mac 4 blade, a Cormack-Lehane grade 1 view was visualized, and a size 8.0 endotracheal tube was placed with one attempt. Placement was verified by condensation appearance within the tube, bilateral chest rise and breath sounds, and end-tidal carbon dioxide. The tube was secured and the patient's eyes were lubed and taped. The anesthetic was maintained with sevoflurane 2% with a mixture of 1.0 L/min of oxygen and 1.0 L/min of air. Mechanical ventilation was applied with an auto-flow volume control mode utilizing a tidal volume of 650 mL, rate of 12 breaths/min, and a positive end-expiratory pressure of 5 cm/H2O.

Following induction, the patient was supinely placed with all positioning concerns corrected and verified, and all pressure points padded. The patient received 2 grams of cefazolin prior to incision. During the maintenance phase, the patient received 15 mg of ephedrine, 250 mcg of Fentanyl, and 1200 mL of lactated ringers. The surgeon did utilize a tourniquet which was inflated for 82 minutes. Blood loss was estimated to be less than 50 mL. The non-depolarizing muscle relaxant was reversed, after confirming presence of at least one twitch on train of four monitoring, with 0.8 mg of glycopyrulate and 5 mg of neostigmine. To prevent post-operative nausea and vomiting, 4 mg of ondansetron was administered towards the end of the case. The patient went through emergence without difficulty and was extubated in the

normal fashion after confirmation of command following, regular depth and rate of breathing, and stable vital signs.

The patient was transported to the post-anesthesia care unit, and then transferred to the orthopedic medical floor. Within the first two hours following his operation, the patient received 100 mcg fentanyl in divided doses. He then started taking 1-2 10 mg hydrocodone/325 mg acetaminophen tablets approximately every 4 hours. At 0500 on post-operative day one, the patient received 0.4 mg hydromorphone IV, after he had not received pain medicine for 6 hours while sleeping. At 0830 on post-operative day one, the patient reported minimal surgical pain, with a current rating of 4/10. He mentioned that after a full night of sleep, the pain was a "little worse in the morning," but "was very tolerable." The patient continued receiving 1-2 tablets of 10 mg hydrocodone/325 mg acetaminophen every 4-6 hours throughout his hospital stay. Without post-surgical complications, the patient was discharged home on post-operative day two with prescriptions for subcutaneous enoxaparin sodium and oral 10 mg hydrocodone/325 mg acetaminophen.

Discussion

Adequate post-operative pain control has received much attention in the last decade. There has been a widespread understanding across multiple disciplines, including not only clinicians, but economists and health policy experts as well, that acute pain following surgical procedures is undertreated (Miller et al., 2015). In 1992, this issue drove the United States Department of Health and Human Services Agency for Healthcare Quality and Research to develop a national clinical practice guideline for the management of acute pain. It is a landmark document that includes the acknowledgement of the inadequacies of perioperative pain control, the importance of adequate pain control, and the need for providers to stay accountable for their

patient's pain experience. Because of this, national standards regarding perioperative pain

management were developed by which providers are now measured against (Miller et al., 2015).

It is imperative that anesthesia providers use their expertise in pain management to be at the

forefront of advancements in this area of medicine.

Because pain management is, and will always be, a main concern of anesthesia providers,

it is important to employ multimodal strategies when dealing with patients in the perioperative

setting. One important adjunct to a pain related plan of care is gabapentin. Gabapentin is

becoming more and more attractive for anesthesia use in the perioperative setting because of its

unique mechanism of action. In the following paragraphs, pain physiology, pain management,

and gabapentin's place in pain control will be discussed.

Pain Physiology

Pain is an experience that varies significantly from patient to patient. It is very complex

and often difficult to outline. The International Association for the Study of Pain (IASP) has

defined pain as "an unpleasant sensory and emotional experience associated with actual or

potential tissue damage" (2012). Pain classification is usually based upon longevity (whether the

pain is acute or chronic), and the underlying pathophysiology (whether the pain is nociceptive or

non-nociceptive) (Nagelhout & Plaus, 2014).

Nociceptive pain is often referred to as pain arising from the stimulation of nerve cells in

contrast with non-nociceptive pain, which involves messages of pain regardless of noxious

stimuli. Nociceptive pain can then be further categorized into somatic or visceral pain. Somatic

pain has an identifiable localization, and is a result of actual damage to tissue, leading to the

release of pain-mediating chemicals from the injured cells (Nagelhout & Plaus, 2014). Visceral

pain is more diffuse. It is often described as dull or aching, in contrast to the sharp, localized,

stabbing nature of somatic pain. Visceral pain is associated with the distention of an organ

capsule or some kind of obstruction in normally hollow viscera. At times, visceral pain can be

associated with an autonomic response, invoking feelings of nausea and diarrhea (Nagelhout &

Plaus, 2014).

Non-nociceptive pain is categorized as being either neuropathic or idiopathic.

Neuropathic pain refers to a disorder of the central nervous system caused by damage to neural

structures. This causes painful stimuli to be abnormally processed. "Burning" or "tingling" are

words often used to describe neuropathic pain (Nagelhout & Plaus, 2014). Idiopathic pain is a

term used to describe pain that has no apparent cause. There is no mechanism identifiable for the

pain, and there are often psychological symptoms present as well (Nagelhout & Plaus, 2014).

The anatomy and physiology of pain is quite complex. Surgery produces an obvious

tissue injury, with subsequent release of inflammatory mediators. These go on to activate

peripheral nociceptors (pain receptors), which initiate the transduction and transmission of

nociceptive information to the central nervous system (Miller et al., 2015)

The first of four commonly referred to processes of a pain response is transduction. This

occurs when a noxious stimulus is detected by the free nerve endings of nociceptors, and an

action potential is produced. The peripheral nociceptors are categorized according to diameter,

myelination, and conduction velocity, and transfer the noxious stimuli to the dorsal horn of the

spinal cord (Nagelhout & Plaus, 2014). Also at this time, there is a release of inflammatory

chemical mediators and neurotransmitters, arising from the free nerve endings of the nociceptors.

Some of the more prominent of these include Substance P, Glutamate, Bradykinin, Histamine,

Serotonin, Prostaglandins, and Cytokines. These chemical mediators and neurotransmitters cause

an influx of sodium ions to enter nerve fiber membranes leading to depolarization. There is also

an efflux of potassium ions, subsequently leading to repolarization. This process creates an action potential, thereby generating a pain impulse (Nagelhout & Plaus, 2014).

Transmission is the second process involved in pain. This process describes how an action potential is conducted from the periphery to the central nervous system. Utilizing the spinothalamic system, afferent neurons (which have cell bodies located in the dorsal root ganglia of the spinal cord) enter the dorsal cord. Here the fibers are said to be in the tract of Lissauer, and either ascend or descend several spinal segments (Nagelhout & Plaus, 2014). After the fibers leave the tract of Lissauer, the axons of these afferents enter the gray matter of the dorsal horn. It is here that they synapse with second-order neurons, primarily terminating in Rexed's laminae I, II and V (Nagelhout & Plaus, 2014). Next, second-order neurons cross the midline of the spinal cord, and ascend the spinothalamic tract to the thalamus. It is here that the second-order neurons synapse with third-order neurons, which then send projections to the cerebral cortex (Nagelhout & Plaus, 2014).

The cerebral cortex is where the third process of pain, perception, occurs. Perception occurs when certain areas of the brain, including the amygdala, somatosensory areas of the cortex, the hypothalamus, and the anterior cingulate cortex, recognize the pain signal. This causes the actual realization of pain (Nagelhout & Plaus, 2014).

Finally, modulation of the pain transmission is a process that involves either suppression or enhancement of the pain signals. Suppression occurs through descending efferent pathways, which are often described as the body's own analgesia system (Nagehout & Plaus, 2014). When the efferent pathway is stimulated with a noxious event, descending axons from the cerebral cortex, hypothalamus, thalamus, periaqueductal gray area (PAG), nucleus raphe magnus (NRM), and locus coeruleus synapse with and suppress pain transmission in the brainstem and dorsal

horn of the spinal cord (Nagelhout & Plaus, 2014). In addition, several neurotransmitters and their receptors play roles in the inhibitory modulation of pain. These include endogenous opioids (encephalin/dynorphin), glycine, norephinephrine, serotonin, and gamma-amino-butyric acid (GABA). Many pain related pharmacotherapies are directed at these neurotransmitters and their receptors (Nagelhout & Plaus, 2014).

Pain and Surgery

In general, the pain involved in the perioperative setting is acute pain. The intensity of acute pain should diminish over the course of healing and is self-limited. It is responsive to pharmacotherapy and the treatment of its initiating cause (Nagelhout & Plaus, 2014). More than 80% of patients who undergo surgical procedures experience acute post-operative pain, with 75% of these patients rating their pain as moderate, severe, or extreme (Chou et al., 2016). Unfortunately, less than half of patients who undergo surgical procedures state their pain was adequately controlled post-operatively (Chou et al., 2016).

When pain is not adequately treated in the post-operative setting, it causes multiple, well-documented adverse effects involving multiple organ systems. The increased release of catecholamines and cortisol produce an increase in heart rate, an increase in vascular resistance, an increase in myocardial contractility, and an increase in arterial blood pressure. These responses will ultimately increase myocardial oxygen consumption and demand. With the increased demand in oxygen, the patient may experience dysrhythmias, angina, myocardial ischemia, and myocardial infarction. While these implications have the potential to be detrimental in a healthy patient, they could cause severe repercussions in those individuals with an already compromised cardiovascular system (Nagelhout & Plaus, 2014).

Inadequate pain management can also negatively affect the respiratory system. For some, post-operative respiratory function is markedly decreased, especially in those who have undergone thoracic or upper abdominal surgery (Miller et al., 2015). Patients may experience decreases in tidal volumes, vital capacity, inspiratory capacity, and functional residual capacity. When patients are experiencing pain, it is an innate response to limit movement in an attempt to minimize the unpleasant feeling. However, this is detrimental, as limiting physical activity or coughing post-operatively can lead to atelectasis and pneumonia (Nagelhout & Plaus, 2014).

Nociceptive stimuli to the CNS from the periphery leads to the neuroendocrine stress response. This is when a combination of local inflammatory substances and systemic mediators are released, and there is an increase in catabolic hormone secretion with a decreased secretion of anabolic hormones (Miller et al., 2015). Catabolic hormone release without an antagonizing anabolic hormone release leads to higher levels of cortisol, antidiuretic hormone, glucagon, aldosterone, renin, and others. This response creates sodium and water retention, increased blood glucose levels, and increased lactate levels (Miller et al., 2015). In addition, a hypermetabolic state occurs, increasing oxygen demand and mobilizing metabolic substrates from storage. This stress response is detrimental to healing, and prolongs recovery time (Miller et al., 2015).

If acute post-surgical pain is left untreated, the continuous release of inflammatory mediators actually sensitizes functional nociceptors and triggers dormant ones, leading to an increased rate of discharge from a decreased threshold for activation. While not well understood, this effect can cause functional changes in the dorsal horn of the spinal cord and lead to chronic pain after acute surgical injury (Miller et al., 2015).

Pain can also decrease gastric emptying leading to nausea and vomiting, as well as cause urinary retention and oliguria by increasing urinary sphincter tone. If allowed to persist, gastrointestinal return to function may become delayed, even leading to paralytic ileus (Miller et al., 2015). Additionally, pain can increase platelet aggregation and venous stasis leading to thrombosis and DVT/PE. Furthermore, unresolved pain can impair immune function, leading to increased infection rates (Nagelhout & Plaus, 2014).

In addition to the physical effects, pain can have significant psychological effects for patients such as fear, anxiety, depression, anger, and feelings of helplessness (Nagelhout & Plaus, 2014). The consequences of inadequate post-operative pain management include a delayed recovery, an increase in healthcare costs, a reduction in functional reclamation, and a negative patient perception of his/her healthcare experience. All of which lead to reduced satisfaction with care (Chou et al., 2016; Nagelhout & Plaus, 2014).

Multimodal Pain Management

It is imperative that anesthesia providers be at the forefront of management of acute pain in the perioperative setting. Anesthesia providers have a responsibility to participate in the assessment, management, and treatment of pain, and to utilize strategies to individualize plans of care for their patients. This is where multi-modal pain management is important.

The American Society of Anesthesiologists (ASA) strongly recommends exercising a multimodal approach whenever possible based on individual patient needs. The ASA defines multimodal techniques for pain management as those that, "include the administration of two or more drugs that act by different mechanisms for providing analgesia, the drugs may be administered via the same route or by different routes" (2012, p. 253). In addition, the Journal of Pain featured post-operative pain management recommendations from a panel of prestigious

organizations, which included the utilization of multimodal pain strategies for the best patient satisfaction and outcomes. In this specific article, Chou and his colleagues defined multimodal pain management as, "the use of a variety of analgesic medication and techniques that target different mechanisms of action in the peripheral and/or central nervous system" (2016, p. 136). It goes on to reveal that, based on the research completed by the panel, multimodal pain management may have additive or synergistic effects, rendering it more effective at relieving pain than single-modality interventions (Chou et al., 2016).

Multimodal pain management is important as it can reduce the side-effect profile that may come with utilizing a single-modality approach. This effect is most commonly seen with reducing the respiratory depression and/or the nausea and vomiting that may come with the administration of opiates (Helander et al., 2017). By taking advantage of analgesia production through different cellular pathways, the anesthesia provider is able to offer a more complete plan of care to their patients including optimized pain relief, minimization of side effects, and timely discharge. Multimodal pain management allows early mobilization, early nutrition, and early attenuation of the perioperative stress response (Miller et al., 2015)

When implementing multimodal anesthesia, important additions to the traditional opiate-based analgesia regimens to consider include NSAIDs, acetaminophen, ketamine, alpha-2 agonists, glucocorticoids, and gabapentinoids (Helander et al., 2017). Tiippana, Hamunen, Kontinen, & Kalso point out that local anesthetics/regional anesthesia may be appropriate choices when assembling a multimodal approach to pain management post-operatively (2007). The ASA also suggests combining regional blockades as indicated to provide the best anesthetic experience possible for their patients (2012).

The multimodal approach not only helps alleviate postoperative pain, it may lead to shorter intubation times, earlier return of bowel function, decreased risk of chronic post-operative pain development, and a preservation of total body protein to aid the healing process. It lessens recovery time, helping more patients qualify for early hospital discharge (Miller et al., 2015). Multimodal pain management integrates the most recent data and techniques, aiding institutions in increasing patient satisfaction while remaining economically sound (Miller et al., 2015).

Gabapentin

Chemical make-up

Gabapentin [1-(aminomethyl) cyclohexane acetic acid] is a gamma-aminobutyric acid (GABA)-mimetic compound. GABA, with regard to pain modulation, is an inhibitory neurotransmitter released via the descending pathway. In this way, it is able to suppress ascending pain signals, decreasing pain sensation (Nagelhout & Plaus, 2014). GABA receptors in the body utilize signal transduction, otherwise known as secondary messenger pathways. Secondary messenger pathways are processes in which a cell converts one signal or stimulus, into another. They may also involve specifically ordered sequences or cascades of events. Many of our commonly used anesthetic medications work in this fashion, including gabapentin (Nagelhout & Plaus, 2014).

While gabapentin is technically a synthesized form of GABA, it exerts no GABA agonist effects and it does not inhibit GABA uptake or degradation. Gabapentin is a structural analogue of the neurotransmitter, GABA, with a cyclohexane ring added to its chemical make-up (Rose & Kam, 2002). Gabapentin's molecular weight is 174.34 and it is stable at room temperature. At a

physiologic pH, it is highly charged and exists as a zwitterion. It is bitter tasting and is a white

crystalline substance (Rose & Kam, 2002).

Gabapentin, as a medication, is only available in an oral preparation. It possesses a high

lipid solubility, and does not significantly partake in protein binding, with less than 3% of

circulating drug found bound to plasma proteins (Kim et al., 2016). It has been assigned an FDA

pregnancy risk category of "C," meaning risk of use during pregnancy cannot be ruled out. This

is because adequate human studies in the area are lacking and animal studies have shown risk to

the fetus in rare instances. Although there is a chance the drug may cause fetal harm, potential

benefits of administration during pregnancy may outweigh the potential risk. In addition,

gabapentin is distributed into breast milk with oral administration. (Kim et al., 2016).

Mechanism of Action

Gabapentin's mechanism of action is still not completely clear. Researchers do

understand that the drug blocks voltage-gated calcium channels by binding to the alpha-2-delta

subunits on the pre-synaptic side, reducing calcium influx (Miller et al., 2015).

Calcium channels are important to consider when thinking about analgesic medication

administration. The opening of these channels facilitates the release of neurotransmitters from

presynaptic sites; and when the concentration of intracellular calcium shifts, cell membrane

excitability is modulated, triggering a cascade of intracellular responses (Miller et al., 2015).

These voltage-gated calcium channels regulate a variety of actions in the body, playing a

significant role in both nociceptive and anti-nociceptive processes. After a pain-evoked action

potential is triggered, the influx of calcium through voltage-gated calcium channels causes a

fusion of the synaptic vesicle and the neuronal membrane. This leads to the release of

neurotransmitters in the dorsal horn of the spinal cord (Schmidt, Ruchelli, Mackey, Carroll, &

Epi, 2013). By blocking/reducing calcium influx through modulation of this process, gabapentin

produces a reduction in the release of pain-causing neurotransmitters (e.g. glutamate) from

nociceptive afferents (Miller et al., 2015; Yan, Butler, Kurowski, & Perloff, 2014). In addition,

it is hypothesized that gabapentin may also exert analgesic effects by activating descending,

inhibitory pain pathways (Schmidt et al., 2013).

Pharmacokinetics

Gabapentin is absorbed only in the small intestine. Its absorption is limited to a relatively

small part of the duodenum (Schmidt et al., 2013). The process is a combination of diffusion and

facilitated transport. As mentioned previously, the drug is only available in oral form. Upon

oral administration, the drug binds to a receptor (as yet to be fully identified) which is linked to a

saturable L-amino acid transport mechanism (Rose & Kam, 2002). Because of the saturability of

this carrier-dependent transport system, gabapentin's bioavailability varies inversely with its

administration dose (Khahi, Yaghooti, Marashi, & Nadjafi, 2011). This means that the

bioavailability of a 300 mg dose of gabapentin is higher than that of a 600 mg dose.

Gabapentin's dose-dependent saturable absorption indicates that as the dose is increased, a lesser

percentage of the drug is actually available for absorption. As the active transport mechanism

for gabapentin in the duodenum reaches peak saturation, progressively higher levels of

gabapentin ingestion yield progressively smaller blood concentrations (Schmidt et al., 2013).

Peak plasma levels of the drug are achieved approximately 2-3 hours after ingestion, with peak

cerebrospinal fluid levels occurring at 4-6 hours after ingestion (Rose & Kam, 2002; Schmidt et

al., 2013).

Gabapentin has an extensive volume of distribution, indicating it has an extensive amount

of tissue distribution, as well as minimal protein binding (Schmidt et al., 2013). Its cerebral

spinal fluid concentrations are 20% of plasma concentrations, and brain concentrations are 80%

of plasma concentrations (Rose & Kam, 2002). Gabapentin is actually not metabolized in

humans and is eliminated unchanged in the urine. Renal impairment will decrease gabapentin

elimination, as it follows a first-order kinetic elimination process in a linear fashion. This

correlates well with creatinine clearance levels (Rose & Kam, 2002). Gabapentin has an

elimination half-life that ranges from 4.8 to 8.7 hours (Schmidt et al., 2013). The drug is

eliminated with hemodialysis, so it should be administered after treatments to maintain a steady

state. Also, along with gabapentin's lack of hepatic metabolism comes a lack of induction or

inhibition of hepatic microsomal enzymes. With this attribute, gabapentin does not cause

significant drug interactions (Rose & Kam, 2002).

Side Effects

Over considerable research, gabapentin has been found to boast a low side effect profile.

Because of the duodenal receptor saturation properties of gabapentin, there seems to be a limit

placed on its efficacy in comparison to those medications without transporter saturations

affecting absorption. This same concept can be applied as a favorable attribute to gabapentin's

drug profile, in that there is an upper border placed on adverse effect potential (Schmidt et al.,

2013).

The most common side effects of gabapentin appear to be somnolence/sedation and

dizziness, with some relatively rare reports of ataxia, headache, visual disturbances, convulsions,

and peripheral edema (Rose & Kam, 2002; Schmidt et al., 2013). Should significant side effects

occur with gabapentin administration, often just decreasing the dose will help to attenuate any

adverse results. Data suggests that gabapentin administration may have a positive effect in

actually reducing postoperative delirium, though this may also be attributed to subsequent decreased opioid use (Schmidt et al., 2013).

Speaking to gabapentin's safety profile is the practitioners' ability to manage even massive overdoses with supportive care alone (Schmidt et al., 2013). In extreme over-consumption, the patient could exhibit signs of severe ataxia, labored breathing, ptosis, sedation or excitation, and hypo-activity. Treatment in overdose begins with airway protection and includes any supportive measures needed in conjunction with presenting symptoms. Although an overdose has been shown to be manageable, it is suggested that even asymptomatic patients be observed for at least 4-6 hours (Kim et al., 2016).

While gabapentin has relatively minimal drug to drug interactions, there are some that are noteworthy. One such interaction is gabapentin's relationship to antacids. Antacid administration can significantly impair the absorption of gabapentin by up to 20%, even when the medications are given greater than two hours apart (Kim et al., 2016). This concept should be considered when utilizing gabapentin in perioperative situations requiring the use of antacids, such as bicitra (Schmidt et al., 2013). In addition, morphine and hydrocodone have both been found to increase the AUC value (plasma concentration levels plotted against time) of gabapentin, when given concomitantly. Decreases in either of these and/or gabapentin may be necessary to avoid central nervous system depression. This is especially true for the relationship between gabapentin and morphine (Kim et al., 2016). Also, naproxen may increase the absorption rate of gabapentin by up to 15%. Finally, as with many drugs, patients may experience increased central nervous system depression if gabapentin is taken along with alcohol consumption (or other central nervous system depressing agents) (Kim et al., 2016).

Original use of Gabapentin

Gabapentin was originally synthesized to purposefully imitate the structure of the neurotransmitter, gamma-aminobutyric acid. In 1994, the drug was first approved by the United States FDA for use as an adjunctive anticonvulsant medication, to be added to anti-seizure medication regimens in an effort to help control partial seizures. Ironically, despite the fact that the drug was developed for seizure prevention, the smallest current market for gabapentin use is in cases of epilepsy and seizure disorders (Sirven, 2010).

In 1998, a double blind, randomized, placebo-controlled trial revealed that postherpetic neuralgia pain was decreased up to 33% after a 4-week gabapentin regimen. This study also revealed that after an 8-week regimen of the drug, patients experienced improved sleep, quality of life, and total mood quality (Yan, Butler, Kurowski, & Perloff, 2014). After more studies were completed in the area of nerve pain treatment, the FDA approved gabapentin for the treatment of post-herpetic pain and other nerve related pain in 2002 (Sirven, 2010).

While adjunctive treatment of seizure disorders and management of post-herpetic pain and other nerve related pain are the two indicated uses for gabapentin currently approved by the FDA, the drug has numerous off-label uses. Such uses include management of perioperative pain, cancer pain, attention deficit disorder, restless leg syndrome, migraine headaches, premenstrual syndrome, and anxiety related disorders (Sirven, 2010; Yan, Butler, Kurowski, & Perloff, 2014).

Perioperative Gabapentin Use

Perioperative gabapentin administration can be employed in a variety of surgical situations, ranging from orthopedic procedures to abdominal procedures to head and neck procedures. The Journal of Orthopaedic Surgery and Research recently published a meta-

analysis of randomized controlled trials which found that administration of gabapentin in the perioperative course of a patient receiving a total hip arthroplasty was effective in decreasing postoperative narcotic use and reducing pain scores (Han, Li, Jiang, Ma, & Ma, 2016). Interestingly, the researchers found no difference in side effect profiles between those control groups that received gabapentin and those who received a placebo. In fact, it was discovered that there was less reported postoperative nausea and vomiting in the gabapentin group (Han et al., 2016).

Khahi and colleagues completed a double-blind, randomized controlled clinical trial and found that just 300 mg of pre-emptive gabapentin administration significantly decreased postoperative pain two hours after patients had undergone an internal fixation of the tibia (2011). Montazeri, Kashefi, and Honarmand found similar results in their study of postoperative pain and morphine demand following lower extremity orthopedic surgery (2007). In this randomized, double-blind study, patients either received 300 mg of gabapentin or a placebo two hours prior to surgery. It was found that patients who had received gabapentin reported significantly lower pain scores and exhibited reduced rescue analgesic requirements postoperatively (Montazeri et al., 2007).

A systematic review and meta-analysis was completed to examine the evidence of pre-emptive use of gabapentin in abdominal hysterectomy procedures. A total of fourteen trials, consisting of 448 cases in the gabapentin control group and 443 in the placebo control group, met inclusion criteria. The authors found that preemptive administration of gabapentin was effective in decreasing postoperative pain scores, decreasing postoperative narcotic consumption, and decreasing postoperative nausea and vomiting (Alayed, Alghanaim, Tan, & Tulandi, 2014).

As a final example, a recent systematic search was conducted investigating gabapentin use in otorhinolaryngology, head, and neck surgery. It too, found that gabapentin appears to have a significant beneficial effect on perioperative pain relief, as well as on analgesic consumption. This effect was most prominent for those undergoing rhinologic and thyroid surgery (Sanders & Dawes, 2016).

Gabapentin and Opioids

One of the most cited reasons for utilization of perioperative gabapentin is the ability to utilize decreased quantities of opioids in an effort to treat postoperative pain. Opioids have undesirable side effects, such as nausea, respiratory depression, and sedation. They also have the increased potential for tolerance and addiction (Arumugam, Lau, & Chamberlain, 2016). While multiple studies indicate gabapentin use is beneficial in decreasing perioperative opioid use, Arumugam et al., completed a comprehensive literature search with the sole purpose of studying this effect (2016). Seventeen randomized control trials met inclusion criteria, consisting of 1,793 patients. The researchers concluded that administration of preoperative gabapentin did reduce opioid consumption in the first 24 hours following surgery. They go on to recommend clinicians utilize gabapentin in multimodal treatment plans as an effective analgesic adjunct (Arumugam et al., 2016)

Perioperative Dosing

Because of gabapentin's pharmacokinetic profile, its use in perioperative pain management should be initiated two hours before surgery in a pre-emptive manner. In this way, it can be more effective in reducing postoperative pain, than if it were to be started early in the postoperative period (Khahi et al., 2011). When considering the time gabapentin needs to reach peak cerebrospinal fluid levels (4-6 hours), practitioners may even consider home administration

the night before surgery. This effect may prove beneficial, but with the possibility of dizziness, sedation or confusion, many choose to forego this strategy as it has not yet been formally recommended (Schmidt et al., 2013).

Conversely, Schmidt and colleagues also found that preoperative dosing is not absolutely critical for reducing immediate postoperative pain or opioid use (2013). Although, because most completed studies on gabapentin use to manage acute perioperative pain include preoperative dosing, it is still concluded that preoperative administration is desirable. However, failure to provide a preoperative dose should not dissuade the practitioner from administration through an oral gastric tube directly after incision or from immediate postoperative dosing (Schmidt et al., 2013). Preoperative, intraoperative, or postoperative initial dosing have all shown to reduce early postoperative pain. Difference in timing of gabapentin administration in relation to pain attenuation and decreased opioid use seems to have minimal effect on outcomes, but more research would be required before recommendations can be developed in this area (Schmidt et al., 2013).

There have been relatively few comprehensive studies completed to address optimal dosing instructions for perioperative gabapentin administration. While further research is needed in order to determine the best method, existing studies find that higher preoperative doses, in addition to postoperative doses, seems to be the most advantageous for patients. Schmidt and colleagues suggest 1200 mg gabapentin be administered at least two hours prior to surgery, followed by 600 mg every 8 hours for up to two weeks (2013). However, many studies indicate their research was completed utilizing different dosing than this example. Optimal duration of treatment is also yet unknown (Schmidt et al., 2013).

Conclusion

In conclusion, the majority of recent research suggests perioperative gabapentin is a beneficial medication for anesthesia providers to consider when contemplating a plan of care. The drug has been shown to provide adequate post-operative pain management, while allowing the patient to consume decreased doses of narcotic medication. It also boasts a low side effect profile and minimal drug interactions, speaking to its exemplary safety profile. In the aforementioned case study, gabapentin was pre-operatively administered to a patient undergoing total knee arthroplasty. While there is no way to determine if his individual pain control was aided by gabapentin specifically, based on the research the idea can be adopted as probable. It is also noteworthy to mention that post-operative gabapentin doses may have added to the patient's pain control. The importance of patient satisfaction scores is increasing in all facets of healthcare, including financial considerations for institutions performing surgical procedures. It is apparent that gabapentin is a worthy addition to a multi-modal, operative pain management plan. With adequate pain management, patient satisfaction scores can be expected to improve. It would be prudent for anesthesia providers to become well-versed on gabapentin administration and consider its use in developing patient specific plans of care.

References

Alayed, N., Alghanaim, N., Tan, X., & Tulandi, T. (2014). Preemptive use of gabapentin in

abdominal hysterectomy: A systematic review and meta-analysis. *Obstetrics and*

Gynecology, 123(6), 1221-1229.

American Society of Anesthesiologists. (2012). Practice guidelines for acute pain management in

the perioperative setting: An updated report by the American Society of

Anesthesiologists task force on acute pain management. *Anesthesiology, 116*(2), 248-

273.

Arumugam, S., Lau, C. S. M., & Chamberlain, R. S. (2016). Use of preoperative gabapentin

significantly reduces postoperative opioid consumption: A meta-analysis. *Journal of Pain*

Research, 9, 631-640.

Chou, R., Gordon, D. B, de Leon-Casasola, O. A., Rosenburg, J. M., Bickler, S., Brennan, T., . . .

Wu, C. L. (2016). Management of postoperative pain: A clinical practice guideline

from the American Pain Society, the American Society of Regional Anesthesia and Pain

Medicine, and the American Society of Anesthesiologists' Committee on Regional

Anesthesia, Executive Committee, and Administrative Council. *The Journal of Pain,*

17(2), 131-157.

Han, C., Li, X., Jiang, H., Ma, J., & Ma, X. (2016). The use of gabapentin in the management of

postoperative pain after total hip arthroplasty: A meta-analysis of randomized controlled

trials. *Journal of Orthopaedic Surgery and Research, 11*(79).

Helander, E. M., Menard, B. L., Harmon, C. M., Homra, B. K., Allain, A. V., Bordelon,

G. J., . . . Kaye, A. D. (2017). Multimodal analgesia, current concepts, and acute pain

considerations. *Current Pain and Headache Reports, 21*(3).

International Association for the Study of Pain (IASP). (2012). *IASP taxonomy*. Retrieved from

      http://www.iasp-pain.org/Taxonomy?navItemNumber=576#Pain

Khahi, P., Yaghooti, A. A., Marashi, S. H., & Nadjafi, A. (2011). Effect of pre-emptive

      gabapentin on postoperative pain following lower extremity orthopaedic surgery under

      spinal anesthesia. *Singapore Medical Journal, 52*(12), 879-882.

Kim, S., Thiessen, P. A., Bolton, E. E., Chen, J., Fu, G., Gindulyte, A., . . . Bryant, S. H. (2016).

      PubChem Substance and Compound databases: Gabapentin. Retrieved from

      https://pubchem.ncbi.nlm.nih.gov/compound/gabapentin#section=Information-Sources

Miller, R. D., Cohen, N. H., Eriksson, L. I., Fleisher, L. A., Wiener-Kronish, J. P., & Young, W.

      L. (2015). *Miller's Anesthesia* (8th ed.). Philadelphia, PA: Elsevier Saunders.

Montazeri, K., Kashefi, P., & Honarmand, A. (2007). Pre-emptive gabapentin significantly

      reduces postoperative pain and morphine demand following lower extremity orthopaedic

      surgery. *Singapore Medical Journal, 48*(8), 748-751.

Nagelhout, J. J., & Plaus, K. L. (2014). *Nurse Anesthesia* (5th ed.). St. Louis, MO: Elsevier

      Saunders.

Rose, M. A., & Kam, P. C. A. (2002). Gabapentin: Pharmacology and its use in pain

      management. *Anaesthesia, 57*, 451-462.

Sanders, J. G., & Dawes, P. J. (2016). Gabapentin for perioperative analgesia in

      otorhinolaryngology-head and neck surgery: Systematic review. *Otolaryngology – Head

      and Neck Surgery, 155*(6), 893-903.

Schmidt, P. C., Ruchelli, G., Mackey, S. C., Carroll, I. R., & Epi, M. S. (2013). Perioperative

      gabapentinoids: Choice of agent, dose, timing, and effects on chronic postsurgical pain.

      Anesthesiology, 119(5), 1215-1221.

Sirven, J. I. (2010). New uses for older drugs: The tales of aspirin, thalidomide, and gabapentin.

    Mayo Clinic Proceedings, 85(6), 508-511.

Tippana, E. M., Hamunen, K., Kontinen, V. K., & Kalso, E. (2007). Do surgical patients benefit

    from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety.

    International Anesthesia Research Society, 104(6), 1545-1556.

Yan, Z. Y., Butler, P. M., Kurowski, D., & Perloff, M. D. (2014). Beyond neuropathic pain:

    Gabapentin use in cancer pain and perioperative pain. *The Clinical Journal of Pain,

    30*(7), 613-629.

Gabapentin Administration in Patients Undergoing Surgical Procedures
Kirsten Crawford (Boekelheide), SRNA

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Pain Management and Surgery

* Adequate perioperative pain control has received much attention in the last decades
* Unfortunately, there has been a widespread understanding that acute pain following surgical procedures is undertreated
  – Realized across multiple disciplines including clinicians, economists, and health policy experts
* In 1992, this issue drove the United States Department of Health and Human Services Agency for Healthcare Quality and Research to develop clinical practice guidelines for the management of acute pain
  – Landmark document including the acknowledgement of the inadequacies of perioperative pain control, the importance of adequate pain control, and the need for providers to stay accountable for their patient's pain experience
  – National standards regarding perioperative pain management were developed, by which providers are now measured against

(Miller et al., 2015)

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Multimodal Pain Control

* Multimodal pain control is, "the use of a variety of analgesic medication and techniques that target different mechanisms of action in the peripheral and/or central nervous system" – (Chou et al., 2016)
* By taking advantage of analgesia production through different cellular pathways, the anesthesia provider is able to offer a more complete plan of care including optimized pain relief, minimization of side effects, and timely discharge
* Important additions to traditional opiate-based analgesia regimens include NSAIDs, acetaminophen, ketamine, alpha-1-agonists, glucocorticoids, and gabapentinoids

(Hatsiandi et al., 2017; Miller et al., 2015)

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History of Gabapentin

* Originally developed to imitate the structure of gamma-aminobutyric acid, a neurotransmitter
* In 1994, the drug was first approved by the FDA for use as an adjunctive anticonvulsant medication, to be added to anti-seizure medication regimens in an effort to help control partial seizures
* In 2002, FDA approved gabapentin for the treatment of post-herpetic pain and other nerve related pain
  – Approved after a double blind, randomized, placebo-controlled trial revealed that post-herpetic neuralgia pain was decreased up to 33% after a 4-week gabapentin regimen
  – This study also revealed that after an 8-week regimen of the drug, patients experienced improved sleep, quality of life, and total mood quality
* Now has numerous "off-label" uses, including management of perioperative pain

(Brun, 2010; Yen, Asley, Kornusz, & Parikh, 2016)

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Review of Literature

* A review of literature was conducted, utilizing the Harley E. French Health Sciences Library to determine current recommendations regarding gabapentin use in the perioperative setting.

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Case Information

* **Surgical Procedure:** elective left total knee arthroplasty
* **Age:** 75
* **Weight:** 107.6 kg
* **Height:** 180 cm
* **Gender:** Male
* **Allergies:** Lisinopril, Flonase, simvastatin, levoquin, levofloxacin, fluticasone propionate
* **ASA:** 3

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Pre-operative Evaluation

- **Past Medical History:** type 2 DM, lung cancer, PVD, HTN, CAD, AS, hyperlipidemia
- **Surgical History:** AAA repair, thoracotomy, bilateral carotid endarterectomy, coronary artery bypass grafting, cardiac stent placement, and right total knee arthroplasty
- **Home Medications:** amlodipine, aspirin, clopidogrel, losartan, metformin, metoprolol succinate
- **Pre-op VS:** BP - 135/80, HR - 75, RR - 18, SpO2 - 97%, temp - 36.4 degrees C
- **Airway evaluation:** Mallampati 2, full neck ROM, large mouth opening, TM distance >3 FB, large neck circumference

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Anesthetic Plan

- General anesthetic with endotracheal tube, normal induction
  - Chosen over a spinal with sedation because patient had not withheld his home medication, clopidogrel, for the recommended length of time
  - In addition, no femoral block would be performed per surgeon preference
- Pre-operatively 600 mg gabapentin was administered 30 mins prior to procedure, along with 975 mg oral acetaminophen

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Anesthetic Course

- After adequate pre-oxygenation/de-nitrogenation completed, patient was induced intravenously with 100 mcg Fentanyl, 150 mg Propofol, and 50 mg Rocuronium
- Utilizing a Mac 4 blade, a Cormack-Lehane grade 1 view was established and a size 8.0 mm endotracheal tube placed and confirmed with positive bilateral breath sounds and chest rise, condensation appearance within the tube, and end-tidal carbon dioxide
- Anesthesia maintained with sevoflurane 2%
- Tourniquet utilized for procedure; time = 82 mins
  - Blood loss less than 50 mL

- Maintenance phase unremarkable
- The non-depolarizing muscle relaxant was reversed, with 0.8 mg glycopyrulate and 5 mg neostigmine. The patient went through emergence without difficulty and was extubated in the normal fashion after confirmation of command following, regular depth and rate of breathing, and stable vital signs
- Other medications utilized for case: 2 grams cefazolin, 15 mg ephedrine, 250 mcg more of Fentanyl, & 1200 mL LR

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PACU

- With first 2 hours following operation – 100 mcg Fentanyl in divided doses was administered
- When he was able to tolerate oral intake, the patient began 1-2 10 mg hydrocodone/325 mg acetaminophen (Norco) tablets approx. every 4 hrs
- At 0500 post-op day 1, the patient received 0.4 mg hydromorphone IV after no pain medication while sleeping for 6 hrs
- At 0830 post-op day 1, the patient reported minimal surgical pain with a current rating of 4/10. He mentioned that after a full night of sleep, the pain was a "little worse" but "was very tolerable"
- The patient continued receiving 1-2 Norco tablets every 4-6 hrs throughout his hospital stay
- Discharged home on post-op day 2 with prescriptions for subcu enoxaparin sodium and oral Norco tablets

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Review of Pain Physiology

- International Association for the Study of Pain (IASP) definition of pain – "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (2012)

- Nociceptive – pain arising from stimulation of nerve cells
  - Somatic – identifiable localization, result of actual damage to tissue leading to the release of pain-mediating chemicals from the injured cells, sharp and stabbing nature
  - Visceral – more diffuse, can be associated with autonomic responses, dull or aching nature
- Non-nociceptive – messages of pain regardless of noxious stimuli
  - Neuropathic – results from a disorder of the central nervous system, such as damage to neural structures, burning or tingling in nature
  - Idiopathic – describes pain that has no apparent cause, often psychological symptoms present as well

(Nagelhout & Plaus, 2014)

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Review of Pain Physiology

- **Transduction:**
  - Noxious stimulus is detected by the free nerve endings of nociceptors
  - Peripheral nociceptors transfer the noxious stimuli to the dorsal horn of the spinal cord
  - There is a concurrent release of inflammatory chemical mediators and neurotransmitters, which cause an influx of sodium ions to enter nerve fiber membranes leading to depolarization
  - Then, an efflux of potassium ions leads to repolarization, creating a full action potential, thereby generating a pain impulse

(Nagelhout & Plaus, 2014)

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Review of Pain Physiology

- Transmission: describes how an action potential is conducted from the periphery to the central nervous system
  - Afferent neurons enter the dorsal cord – it is here they are said to be in the tract of Lissauer, and either ascend or descend several spinal segments
  - The axons of these neurons then extend into the grey matter of the dorsal horn, where they synapse with second-order neurons, primarily terminating in Rexed's Laminae I, II, & V
  - Next, the second-order neurons cross the midline of the spinal cord and ascend the spinothalamic tract to the thalamus
  - Here, they synapse with third-order neurons, which then send projections to the cerebral cortex

(Nagelhout & Plaus, 2014)

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Review of Pain Physiology

- Perception: the actual realization of pain
  - Occurs when certain areas of the brain (including the amygdala, somatosensory areas of the cortex, the hypothalamus, and the anterior cingulate cortex) recognize the pain signal
- Modulation: suppression or enhancement of pain signals
  - Suppression occurs through the descending efferent pathways, while enhancement occurs through the ascending pathways
  - Several neurotransmitter and their receptors play roles in the inhibitory modulation of pain – including gamma-amiobutyric acid (GABA)

(Nagelhout & Plaus, 2014)

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Pain and Surgery

- More than 80% of patients who undergo surgical procedures experience acute post-operative pain, with 75% of these patients rating their pain as moderate, severe, or extreme
- Unfortunately, it has also been found that less than half of patients who undergo surgical procedures state their pain was adequately controlled post-operatively
- Inadequate post-operative pain control causes many well-documented adverse effects involving multiple organ systems

(Chou et al., 2016; Mariano, 2015; Nagelhout et al., 2014)

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Multimodal Pain Management

- Utilizing medications and techniques with varying mechanisms of action is more effective at relieving pain than single-modality interventions alone
  - Incorporates additive or synergistic effects of medications
- A multi-modal approach helps to decrease perioperative pain, while simultaneously decreasing medication side effects and shortening recovery times
- It integrates the most recent data and techniques, aiding institutions in increasing patient satisfaction while remaining economically sound

(Chou et al., 2016; Mariano, 2015)

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Gabapentin

- Gabapentin [1-(aminomethyl) cyclohexane acetic acid] is a gamma-aminobutyric acid (GABA) – mimetic compound
  - GABA (with regard to pain modulation) is a neurotransmitter released via the descending pathway
  - While gabapentin is technically a synthesized form of GABA, it exerts no GABA agonist effects, no does it inhibit GABA uptake or degradation

(Rose & Kam, 2002)

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Gabapentin MOA

- Gabapentin exerts its action by blocking voltage-gated calcium channels
  - It does this by binding to the alpha-2-delta subunits on the pre-synaptic side of the channel, reducing calcium influx
  - Voltage-gated calcium channels play a significant role in both nociceptive and anti-nociceptive processes
  - Calcium influx through these channels causes a release of neurotransmitters in the dorsal horn of the spinal cord
  - By blocking this influx, gabapentin produces a reduction in the release of pain-causing neurotransmitters from nociceptive afferents
- It is also hypothesized that gabapentin may exert analgesic effects by activating descending, inhibitory pain pathways

(Mikkelsen, 2015; Schmidt, Bartell, Stanley, Carrel & Epi, 2018; Rose et al., 2018)

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Gabapentin

- The medication is only available in oral preparation
  - It is absorbed only in a relatively small part of the duodenum, through a process of diffusion and facilitated transport
  - The transport system is saturable, therefore gabapentin's bioavailability varies inversely with its administration dose
    - As the dose is increased, a lesser percentage of the drug is actually available for absorption
- Peak plasma levels of the drug are achieved approx. 2-3 hours after ingestion, with peak cerebrospinal fluid levels occurring at 4-6 hrs after ingestion

Gabapentin

- Extensive volume of distribution
  - Extensive amount of tissue distribution
  - Minimal protein binding
- Actually not metabolized in humans, eliminated unchanged in urine
  - Renal impairment will decrease elimination, as it follows a first-order kinetic elimination process in a linear fashion
  - The drug will be eliminated with hemodialysis
- Lack of induction or inhibition of hepatic microsomal enzymes
  - Does not cause significant drug-to-drug interactions

Gabapentin

- Low side effect profile
- Most commonly reported side effects are somnolence/sedation and dizziness
  - Relatively rare reports of ataxia, headache, visual disturbances, convulsions, and peripheral edema
- If side effects occur, often just decreasing the dose will attenuate any adverse results

Perioperative Gabapentin Use

- Can by employed in a large variety of surgical situations
  - In 2016, the Journal of Orthopaedic Surgery and Research found perioperative gabapentin dosing decreasing postoperative narcotic use and reduced pain scores in those who had received a total hip arthroplasty (Han, Li, Jiang, Ma, & Ma, 2016)
  - In 2014, it was found that preemptive administration of gabapentin was effective in decreasing postoperative pain scores, decreasing postoperative narcotic consumption, and decreasing PONV in those who had received an abdominal hysterectomy (Alayed, Alghanaim, Tan, & Tulandi, 2014)
  - In 2016, gabapentin was found to have significant beneficial effects on perioperative pain relief for those who have undergone HEENT surgeries, most prominent positive effects for those who had received rhinologic or thyroid surgeries (Sanders & Dawes, 2016)

Gabapentin and Opioid Use

- Opioids have undesirable side effects such as nausea, respiratory depression, and sedation
  - They also have the increased potential for tolerance and addiction
- In 2016, Arumugam and colleagues completed a comprehensive literature search to study gabapentin and it's effect on postoperative opioid use
  - Included 17 randomized control trials, consisting of 1793 patients
- Concluded preoperative gabapentin administration did reduce opioid consumption in the first 24 hrs following surgery.
- Recommend clinicians to utilize gabapentin in multimodal treatment plans

Perioperative Dosing

- Optimal dosing of gabapentin and duration of its use is yet to be decided upon, as there have been relatively few comprehensive studies to address this specific facet of administration.
- Because most completed studies on gabapentin use for the management of acute perioperative pain do include preoperative doses, it is concluded that administration two hours prior to surgery is desirable
- It also seems that postoperative doses of gabapentin should be utilized for a time period following the procedure.
- Preoperative, intraoperative, and/or postoperative initial dosing have all shown to reduce early postoperative pain

Recommendations

- More research should be completed addressing optimal perioperative gabapentin dosing standards
- There is ample, recent evidence that indicates gabapentin is a useful tool for anesthetists to utilize in a perioperative, multimodal pain management plan

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Conclusion

- Gabapentin administration has been shown to provide adequate post-operative pain management, while providing a low side effect profile and allowing the patient to consume decreased doses of narcotic medication
- In the aforementioned case study, gabapentin was pre-operatively administered to a patient undergoing total knee arthroplasty
  - While there is no way to determine if this patient's individual pain control was aided by gabapentin specifically, research would indicate the idea as probable
  - post-operative gabapentin doses may have added to the patient's pain control

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Conclusion

- Importance of patient satisfaction scores increasing in all facets of healthcare
  - Including financial considerations for institutions performing surgical procedures
  - With adequate pain management, patient satisfaction scores can be expected to improve
- Gabapentin has proven itself a worthy addition to a multimodal, operative pain management plan
- It seems it would be prudent for anesthetists to become well-versed on gabapentin administration, and consider its use when developing patient specific plans of care

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References

- Alayed, N., Alghanaim, N., Tan, X., & Tulandi, T. (2014). Preemptive use of gabapentin in abdominal hysterectomy: A systematic review and meta-analysis. Obstetrics and Gynecology, 123(6), 1221-1229.
- American Society of Anesthesiologists. (2012). Practice guidelines for acute pain management in the perioperative setting: An updated report by the American Society of Anesthesiologists task force on acute pain management. Anesthesiology, 116(2), 248-273.
- Arumugam, S., Lau, C. S. M., & Chamberlain, R. S. (2016). Use of preoperative gabapentin significantly reduces postoperative opioid consumption: A meta-analysis. Journal of Pain Research, 9, 631-640.
- Chou, R., Gordon, D. B., deLeon-Casasola, O. A., Rosenberg, J. M., Bickler, S., Brennan, T., ... Wu, C. L. (2016). Management of postoperative pain: A clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. The Journal of Pain, 17(2), 131-157.
- Han, C., Li, X., Jiang, H., Ma, J., & Ma, X. (2016). The use of gabapentin in the management of postoperative pain after total hip arthroplasty: A meta-analysis of randomised controlled trials. Journal of Orthopaedic Surgery and Research, 11(79).
- Helander, E. M., Menard, B. L., Harmon, C. M., Homra, B. K., Allain, A. V., Bordelon, G. J., ... Kaye, A. D. (2017). Multimodal analgesia, current concepts, and acute pain considerations. Current Pain and Headache Reports, 21(3).

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References

- International Association for the Study of Pain (IASP). (2012). IASP taxonomy. Retrieved from https://www.iasp-pain.org/Taxonomy?navItemNumber=576#Pain
- Khan, F., Yaghoobi, A. A., Menarsi, S. H., & Nadjafi, A. (2011). Effect of pre-emptive gabapentin on postoperative pain following lower extremity orthopaedic surgery under spinal anesthesia. Singapore Medical Journal, 52(12), 879-882.
- Kim, S., Thiessen, P. A., Bolton, E. E., Chen, J., Fu, G., Gindulyte, A., ... Bryant, S. H. (2016). PubChem Substance and Compound databases. Gabapentin. Retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/gabapentin#section=Information-Sources
- Miller, R. D., Cohen, N. H., Eriksson, L. I., Fleisher, L. A., Wiener-Kronish, J. P., & Young, W. L. (2015). Miller's Anesthesia (8th ed.). Philadelphia, PA: Elsevier Saunders.
- Montazeri K., Kashefi P., & Honarmand, A. (2007). Pre-emptive gabapentin significantly reduces postoperative pain and morphine demand following lower extremity orthopaedic surgery. Singapore Medical Journal, 48(8), 748-751.
- Nagelhout, J. J., & Plaus, K. L. (2014). Nurse Anesthesia (5th ed.). St. Louis, MO: Elsevier Saunders.
- Rose, M. A., & Kam, P. C. A. (2002). Gabapentin: Pharmacology and its use in pain management. Anaesthesia, 57, 451-461.
- Sanders, J. G., & Dawes, P. J. (2016). Gabapentin for perioperative analgesia in otorhinolaryngology-head and neck surgery: Systematic review. Otolaryngology—Head and Neck Surgery, 155(1), 893-903.

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References

- Schmidt, P. C., Ruchelli, G., Mackey, S. C., Carroll, I. R., & Xyl, M. S. (2013). Perioperative gabapentinoids: Choice of agent, dose, timing, and effects on chronic postsurgical pain. Anesthesiology, 119(5), 1215-1221.
- Siman, J. J. (2010). New uses for older drugs: The tales of aspirin, thalidomide, and gabapentin. Mayo Clinic Proceedings, 85(8), 900-911.
- Tiippana, E. M., Hamunen, K., Kontinen, V. K., & Kalso, E. (2007). Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. International Anesthesia Research Society, 104(6), 1545-1556.
- Yan, Z. Y., Butler, P. M., Kurowski, D., & Perloff, M. D. (2014). Beyond neuropathic pain: Gabapentin use in cancer pain and perioperative pain. The Clinical Journal of Pain, 30(7), 613-629.

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