ORAL GRANISETRON IN THE PREVENTION OF POSTOPERATIVE VOMITING IN ADENOTONSILLECTOMIES

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CERTIFICATE

This is to certify that this dissertation entitled

"oral Granisetron in the prevention of post operative vomiting in Adenotonsillectomies"

is the bonafide work done by Dr. G.Shanmugavelu, submitted as a partial fulfillment for the requirements of M.D (Anaesthesia) Degree examination, to be held in February -2006.

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I.INTRODUCTION

Postoperative nausea and vomiting is often referred to as the “big, little problem” within the anesthesia world. Postoperative nausea and vomiting, commonly abbreviated PONV, is defined as nausea and/or vomiting that occurs within 24 hours after surgery and can occur following general, regional, or local anesthesia. PONV has been a potential complication following surgery and anesthesia since the “ether” era. Although the incidence of PONV has decreased significantly from the 75%–80% occurrence rate at that time, it remains one of the most common complications postoperatively despite the numerous advancements in surgery and anesthesia. The incidence of PONV can be as high as 80% following certain procedures like ENT& Laparoscopic surgeries. However, only 10% of post-surgical patients overall will experience PONV during the immediate postoperative period in the PACU (Post-Anesthesia Care Unit), while 30% will experience PONV at some point during the initial 24-hour postoperative period. Additionally, it is important to note that, although PONV may last from minutes to hours and occurs most commonly during the first 24 hours postoperatively, it can actually persist for several days and is, therefore, not isolated to a problem occurring only in the immediate postoperative period.

II. AIM OF STUDY

To study the efficacy of oral Granisetron, a selective 5 HT 3 receptor antagonist, for the prevention of post operative vomiting after Adenotonsillectomy in children

III. PATHOPHYSIOLOGY OF POSTOPERATIVE NAUSEA AND VOMITING

Vomiting Center/ Chemo receptor Trigger Zone

The precise mechanism of PONV is not completely understood, however, the theory behind the occurrence of nausea and vomiting postoperatively is that it is caused by the stimulation of a variety of receptors located in the central nervous system and the gastrointestinal tract which subsequently activate a distinct area of the brain called the vomiting center.

The vomiting center is located in a region of the brain known as the nucleus tractus solitarius, which is situated in the lateral reticular formation of the fourth ventricle in the brainstem and controls vomiting through both direct and indirect stimulation. Impulses are transmitted by afferent fibers of both the sympathetic and parasympathetic nervous system to the vomiting center, whereby an emetic response is initiated. Impulses are sent to the vomiting center from four distinct areas, including

a) the chemo receptor trigger zone (CTZ),
b) higher cortical centers,
c) the vestiblular apparatus of the middle ear, and
d) the gastrointestinal tract.

The nucleus tractus solitarius, or vomiting center, serves as the point of termination in the lower medulla for all visceral afferent nerve fibers and although vagal fibers predominate, fibers from the seventh and ninth cranial nerves and several spinal nerves terminate in this area .

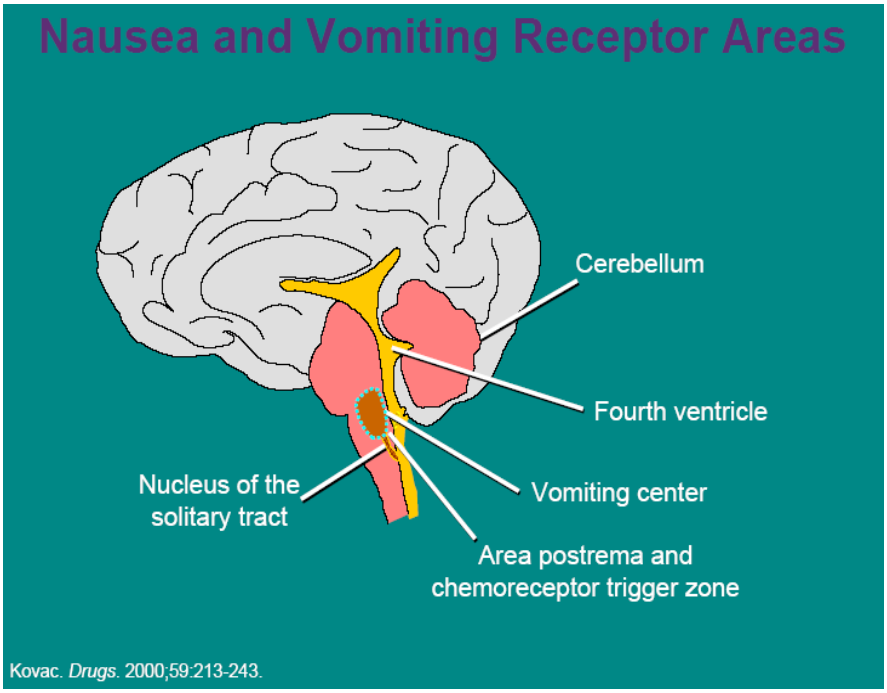


Diagram Showing Location of Vomiting Center

Pharyngeal stimulation, irritation or distension of the gut, distension of the renal pelvis, testicular injury, or cervical dilatation may lead to nausea and vomiting through direct stimulation of the vomiting center in the nucleus tractus solitarius

The vomiting center is indirectly stimulated by another major center known as the chemoreceptor trigger zone (CTZ). The CTZ is located in the brainstem in the area postrema, a spongiform body that protrudes into the fourth ventricle. The area postrema is highly vascularized and the vessels terminate in fenestrated capillaries surrounded by large perivascular spaces. The CTZ contains Adrenergic, cholinergic, histamine, dopamine, Serotonin, and opioid receptors. Because there is no effective blood-brain barrier in the area of the CTZ, it responds directly to chemical stimuli in the blood and cerebrospinal fluid through stimulation of its various receptors. The receptors in the CTZ play an important role in the transmission of impulses to the vomiting center .Another source of indirect stimulation to the vomiting center is movement, which can stimulate equilibrium receptors in the vestiblular apparatus of the middle ear followed by transmission of impulses via afferent fibers carried in cranial nerve VIII to the CTZ with subsequent transmission to the vomiting center. The vestiblular apparatus is unusual, however, in that it may also directly stimulate the vomiting center through these same afferent pathways. The cerebral cortex can directly stimulate the vomiting center through the transmission of psychic stimuli, such as noxious odors or tastes along with unpleasant visual stimuli.

In addition, hypoxia, pain, and increased intracranial pressure directly stimulate the vomiting center by way of various afferent pathways from higher cortical areas.

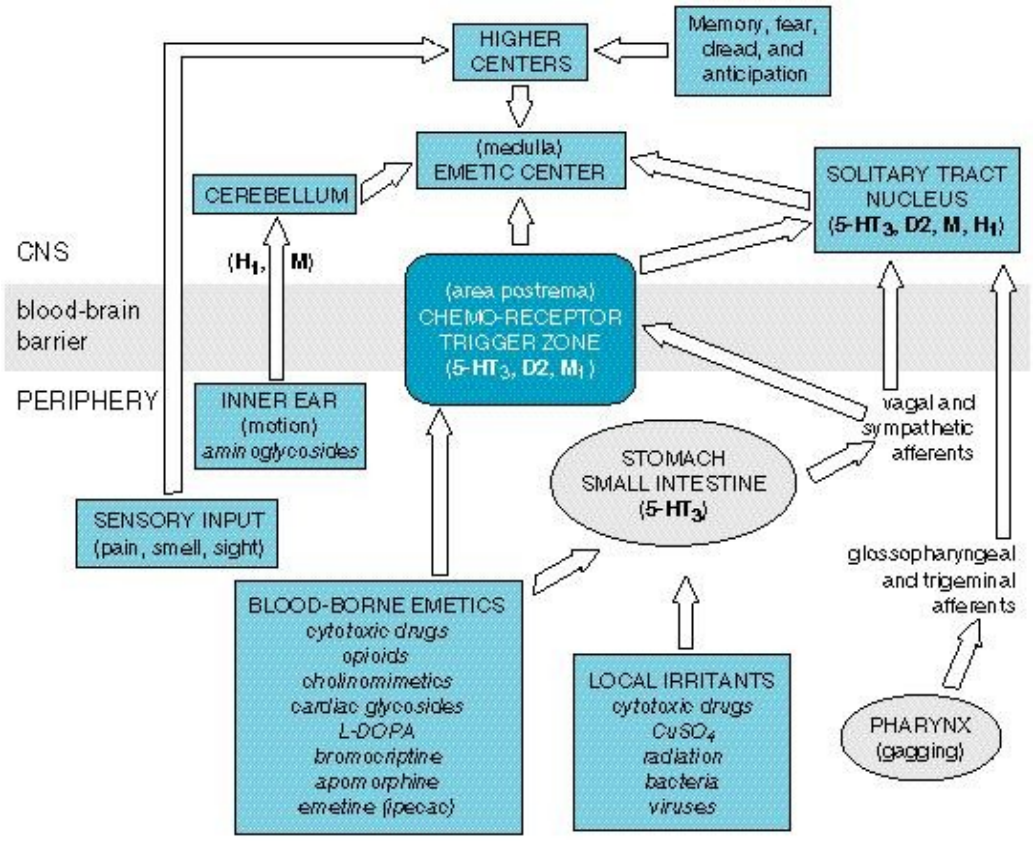
Hormonal influences have an additional impact on the vomiting center, whereby stimulation of α-Adrenergic receptors leads to vomiting due to the release of nor epinephrine, while β-Adrenergic receptor stimulation is associated with inhibition of the vomiting response. Other peptide hormones implicated in the incidence of nausea and vomiting include adreno corticotropic hormone (ACTH), vasopressin, human chorionic gonadotropin, angiotensin II, leu-enkephalin, met-enkepalin, cholecystokinin, insulin, gastrin, Serotonin, oxytocin, bombesin, thyrotopin-releasing hormone (TRH), peptide YY, neurotensin, and vasoactive intestinal peptide (VIP). Co-existing diseases of the heart, gastrointestinal tract, billiary tract, and genitourinary tract or distension of the gastrointestinal tract may stimulate the vomiting center via visceral afferent pathways. Specifically, the gastrointestinal tract, at the level of the small intestine, is a primary location of Serotonin receptors and when stimulated, these receptors send impulses through sympathetic and vagal afferent pathways to the vomiting center

Nausea/Retching/Vomiting

The act of vomiting can be divided into three phases including pre-ejection, ejection, and post-ejection. The pre-ejection phase is marked by the symptoms of nausea including the autonomic signs of salivation, excessive swallowing, pallor, tachycardia, and tachypnea.

Retching and vomiting comprise the ejection phase, while the post-ejection phase consists of the autonomic and visceral responses that return the body to a non-retching and non-vomiting state with or without the presence of nausea.

For purposes of common clarification, nausea is the conscious awareness and unpleasant sensation of urge to vomit. It is often associated with symptoms such as salivation, swallowing, diaphoresis, skin pallor, tachycardia, and decreased GI activity as mentioned above. Retching is the spasmodic, rhythmic contractions of the respiratory muscles including the diaphragm, chest wall, and abdominal muscles without actual expulsion of gastric contents. Emesis, or vomiting, is the forceful expulsion of gastric contents caused by strong and sustained contraction of the abdominal muscles vomiting begins with a deep inspiration, elevation of the soft palate to occlude the nasopharynx, and closure of the glottis. The proximal area of the stomach relaxes and a powerful contraction of the small intestine forces previously ingested contents into the stomach, which then acts to dilute and buffer the gastric acid. Finally, contraction of the esophageal muscles pulls the stomach into the thorax, forming an esophageal funnel, and food is forced out of the stomach by contraction of the abdominal muscles against the lowered diaphragm.



PHARMACOLOGIST"S VIEW OF EMETIC STIMULI

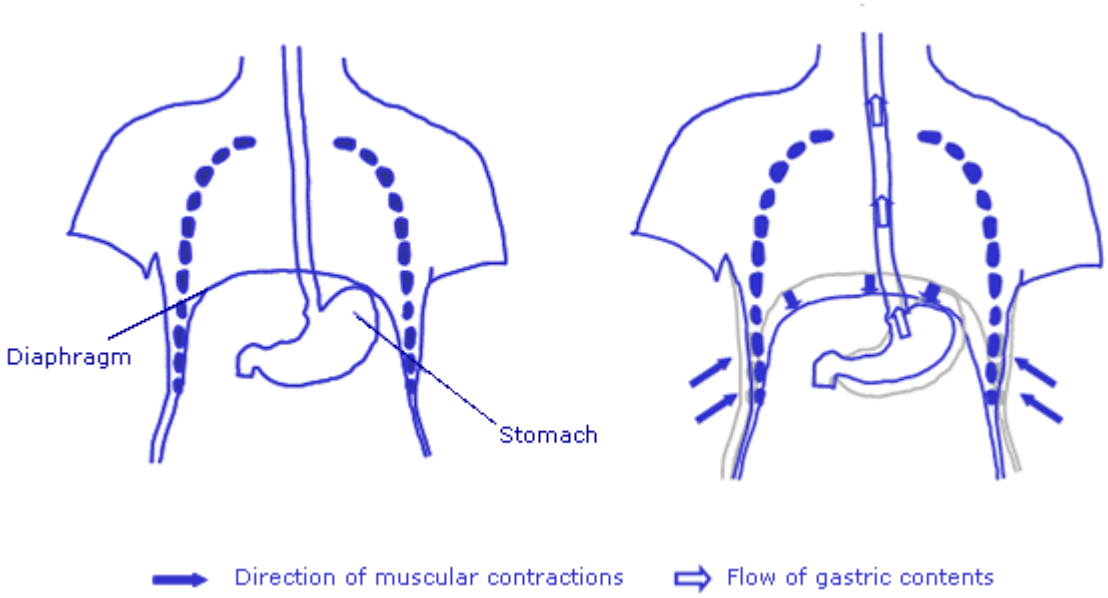


Diagram of the Process of Vomiting

IV. ETIOLOGY OF POSTOPERATIVE NAUSEA AND VOMITING

Factors Contributing to the Incidence of PONV.

- Preexisting Conditions
- Age
- Gender
- History of PONV or Motion Sickness
- Preoperative Anxiety
- Obesity
- Site of Surgery/Type of Surgical Procedure
- Anesthetic Agents and Technique
- Duration of Surgery & Postoperative Conditions
- Pain & Movement
- Hypotension, hypoxemia, or hypoglycemia
- fasting
- Premature intake of fluids and foods.

PONV is most commonly attributed to the administration of anesthesia. This belief stems from the history of nausea and vomiting associated with the use of early inhalation anesthetic agents, such as ether. There was no significant improvement in the incidence of PONV until the introduction of halogenated inhalation agents in the 1960s. With respect to the Pathophysiology of nausea and vomiting and the ongoing research

regarding the incidence of nausea and vomiting specific to anesthesia and surgery, PONV is now known to be the result of many different and interrelated factors. Thus, the etiology of PONV is complex and anesthesia must be considered as only one of many contributing factors. Several pre-existing patient factors, pre- and post-operative factors, and surgical and anesthesia-related factors can contribute significantly to the development of PONV

Preoperative/Patient-related Factors in the Etiology of PONV

Intrinsic patient factors include age, gender, obesity, history of previous PONV or motion sickness, anxiety, and the presence of co-existing disease. Younger patients, particularly 6 to 16 years of age, appear to be more vulnerable to developing PONV, generally with an increased incidence that is twice that of an adult patient regardless of the anesthetic technique or surgical procedure involved. Various studies report an incidence of PONV ranging from 35% to 50% in childhood and early adolescence as compared to the 25%-30% seen in the adult surgical population

There is an increased incidence of PONV noted in female patients after puberty, especially during menstruation or pregnancy, and including postmenopausal women younger than approximately 60 years of age. This is believed to be due to an increase in serum gonadotrophin levels.. The increased incidence of PONV noted when surgery is performed during menstruation is highest on the 4^{th} or 5^{th} day of the menstrual cycle which is four times greater than normal. The increased risk for experiencing PONV associated with obesity is due to the fact that adipose tissue acts as a reservoir for inhaled anesthetic agents, from where continued release of the agent into the circulation occurs after discontinuation the anaesthetics... In addition, obese patients tend to have a larger residual gastric volume along with an increased incidence of esophageal reflux. Obese patients also have more airway difficulties as compared to non-obese patients and often experience increased gastric inflation as a

result of the efforts involved in attempting to maintain an adequate airway during mask ventilation prior to intubation A previous history of PONV is the most significant risk factor and the best indicator of the potential for experiencing nausea and/or vomiting postoperatively. Generally patients with a history of PONV, as well as a history of motion sickness, have a three-fold to six-fold increased risk for experiencing PONV again. The relationship between an increased risk of PONV and a history of PONV or motion sickness is linked to a lower threshold for vomiting due to a well-developed reflex arc for vomiting.

In view of the fact that the process of vomiting is actually a reflex, the vomiting reflex appears to be more highly developed in some individuals. In these situations, it is believed there is also a definite psychological component to the etiology of PONV and that someone with a highly developed vomiting reflex will experience PONV in response to minimal stimuli. In addition, quite often patients with a history of PONV have significant concern and increased anxiety over experiencing nausea and vomiting again which further enhances the potential for developing PONV. The correlation between increased anxiety and an increased risk for PONV is believed to be due to the release of catecholamines. In animal studies, the injection of epinephrine or nor epinephrine into the 3^{rd} or 4^{th} ventricle of the brain results in vomiting whereas the injection of placebo does not. Additionally, anxious patients are known to swallow excessive amounts of air preoperatively, which increases gastric volume and the risk of vomiting postoperatively due to gastric distension.

A history of co-existing diseases that increases the likelihood of PONV include pre-existing metabolic disorders, such as diabetes, uremia, electrolyte disturbance, or renal failure. Obstructions in the gastrointestinal or genitourinary tract, as well as disorders of the central nervous system that involve an increase in intracranial pressure.

Other inherent patient characteristics increasing the susceptibility for PONV include delayed gastric emptying such as with pregnancy, bowel obstruction, or diabetes and increased gastric volume from recent oral intake or full stomach.Obviously, a patient with a full stomach is at a greater risk for vomiting postoperatively. Eating and digestion cause the release of gastrointestinal hormones, such as Serotonin, as well as distension of the stomach, which subsequently activates visceral mechanoreceptors, both of which stimulate the CTZ and induce vomiting.. There is an increased gastric volume in patients who are anxious and swallow large amounts of air preoperatively, increased gastric volume may also occur secondarily from gastric insufflations occurring with mask ventilation, especially with obese patients as mentioned previously. Additionally, inadequate airway-related protective mechanisms that can occur, for example with a hiatus hernia or with an anesthetized upper airway, further increase the risk of aspiration after experiencing PONV.

Anesthesia-related Factors in the Etiology of PONV

Anesthesia-related factors associated with PONV involve primarily the use of preanesthetic and anesthetic medications that are prone to stimulate the CTZ and subsequently the vomiting center. Inhalation agents are associated with a significantly higher incidence of PONV.. Volatile anesthetics alter neurotransmitter release in the area postrema and in other forebrain sites that are known to stimulate vomiting. They also have specific effects on the gastrointestinal tract, leading to reduced motility and relaxation of the gastric pylorus, which facilitates the reflux of bile. In addition, hypo perfusion of the GI tract secondary to the use of volatile agents may directly stimulate a visceral afferent pathway that leads to the release of Serotonin. Numerous peptide hormones can also be

released by volatile anesthetics and surgery, including angiotensin II, ADH, gastrin, insulin, neuropeptide Y, neurotensin, somatostatin, TRH, and VIP. These hormones may indirectly induce vomiting through stimulation of the CTZ. The use of inhalation agents, such as ether and cyclopropane, were associated with a significantly higher incidence of PONV than the currently used agents, presumably due to an increase in the release of endogenous catecholamines caused by the older gases. There are no documented differences in the rate of PONV between halothane, Enflurane, or Isoflurane, however the newer agents, Desflurane and Sevoflurane, are associated with a significantly lower incidence of PONV due to their lower blood: gas solubility .

The addition of nitrous oxide to volatile inhalation agents is also believed to increase the incidence and severity of nausea and vomiting, although this seems to be less likely in combination with the newer inhalation agents. There are three mechanisms attributed to the increased incidence of PONV in association with the use of nitrous oxide. Nitrous oxide causes stimulation of the sympathetic nervous system and subsequent catecholamines release along with changes in middle ear pressure that result in stimulation of the vestiblular system, both of which trigger nausea and vomiting. In addition, nitrous oxide decreases lower esophageal tone.. This subsequently leads to gastric distension that promotes vomiting postoperatively. Nitrous can also cause abdominal distension as a result of the exchange of nitrous and nitrogen in the gas that is introduced into the stomach during mask ventilation.

PONV & IV ANAESTHETICS

PONV is less likely with the use of Propofol. Propofol is a sedative-hypnotic agent and the first of a new class of intravenous anesthetics called the alkyl phenols. It is associated with a significantly lower incidence of PONV, 1%-3%, as compared to the 10%-15% incidence with other IV anesthetic agents. Propofol is actually thought to possess antiemetic properties, however, there is no specific data

describing the effects of Propofol on the CTZ. The mechanism of action of Propofol in reducing PONV is thought to be the result of both anti-dopamine and anti-Serotonin effects and some reports indicate that the incidence of PONV is significantly lower if Propofol is used alone as in a total intravenous anesthetic (TIVA) technique. For this reason, Propofol has become increasingly popular in outpatient anesthesia.

travenous (IV) anesthetic agents associated with an increased incidence of PONV include ketamine, Etomidate and methohexital. Ketamine is linked to an increased incidence of PONV due to the increased release of catecholamines. Etomidate, if given as a continuous infusion, is also associated with a higher incidence of vomiting postoperatively .General anesthesia with oxygen, nitrous oxide-opioid-muscle relaxant, is linked to a higher incidence of PONV and is believed to be due to the direct action of the agents used in this technique upon the CTZ. Neuromuscular blocking drugs are commonly used as a component of balanced anesthesia techniques, but are rarely linked to the occurrence of PONV. The use of high doses of opioid with certain anesthesia techniques for induction and maintenance of anesthesia, and for control of postoperative pain increases the risk of PONV. Increased vomiting is noted with IV, nasal, oral, and/or trans mucosal routes of opioid administration. Although opioids depress the vomiting center in a dose-dependent manner, they also increase the sensitivity of the vomiting center to vestiblular input and stimulate opioid receptors in the CTZ. In addition, opioids delay gastric emptying and increase the release of Serotonin from enterochromaffin cells in the intestine, which may also stimulate the CTZ.

Opioids cause the release of anti diuretic hormone from the pituitary gland that also reduces gastric motility and further enhances the sensitivity of the vomiting center to emetic stimuli. Morphine and its derivatives like Meperidine, Fentanyl, Alfentanil, and Sufentanil, differ in their ability to promote nausea and vomiting. Unlike the opioid-related side effect of respiratory depression, vomiting induced by opioids has not been clearly linked to an interaction between a particular opioid and a specific type of opioid receptor. In fact, it appears that typical analgesic doses of opioids cause little nausea and the nausea and vomiting that does occur with the use of opioids is often related additionally to patient movement, which suggests a vestibular component to opioid-induced vomiting.

General anesthesia, as opposed to regional or local anesthetic techniques, generally contributes to an increased incidence of PONV, although the use of regional anesthesia does not eliminate the potential for nausea and vomiting entirely. Recent statistics comparing the incidence of PONV associated with general versus epidural and spinal anesthesia are noted as 38%, 4% and 7%, respectively. The nausea and vomiting associated with central neuroaxial block is attributed to the sympathetic nervous system blockade leading to postural hypotension or the use of spinal or epidural opioids.

The administration of supplemental oxygen during spinal or epidural anesthesia reduces symptoms of nausea and vomiting associated with a decrease in blood pressure suggesting that hypoxemia acts as a stimulus at the vomiting center. In addition, the incidence of nausea and vomiting during spinal anesthesia can be offset by the administration of atropine, suggesting that vagal stimulation may also trigger nausea and vomiting during this type of anesthesia nausea and vomiting has also been known to occur with the use of peripheral nerve blocks although the incidence is less than that occurring with spinal or epidural anesthesia.

The majority of nausea and vomiting associated with any of the regional anesthetic techniques occurs predominantly during the intra-operative period rather than the recovery stage as with general anesthesia. Although the incidence is significantly lower, nausea and vomiting may also occur during the use of local anesthesia, which is most often combined with intravenous sedation-analgesia techniques. The incidence of nausea and vomiting in this surgical population varies according to the type of surgery performed and the sedative-analgesic medications used.

The use of gastric suctioning intra operatively is controversial in terms of reducing versus inducing PONV. Gastric suction in an attempt to reduce PONV is based upon the advantage gained from emptying gastric contents while suctioning may also lead to unnecessary stimulation that triggers vomiting. There is no clear benefit of gastric suctioning in decreasing the incidence of PONV other than in situations of accumulation blood in the stomach or gastric distension following certain types of surgery or manual mask ventilation.

Additionally, the act of laryngeal suctioning and the presence of oral airways during emergence may cause gagging that induces retching and vomiting postoperatively. It is therefore, recommended that laryngeal and pharyngeal suctioning be performed prior to the reversal of muscle relaxants

Surgical-related Factors in the Etiology of PONV

The physiologic effects of the surgical procedure include metabolic and endocrine changes that may also contribute to the occurrence of PONV. In particular, hypoxia, hypercarbia, and hypotension contribute to an increased likelihood of PONV.

In addition, certain types of surgery are associated with a higher incidence of PONV The impairment in peristalsis and delayed gastric emptying subsequently cause an accumulation of gastric secretions that further stimulates visceral afferent pathways. Manipulation of the gastrointestinal tract also causes a release of Serotonin from enterochromaffin cells, which is then capable of direct stimulation of the CTZ. Surgery involving ocular stimulation or traction on the extra ocular muscles stimulates the afferent pathway and may alter the sensitivity of the vomiting center prior to emergence from general anesthesia. Middle ear surgery interferes with the vestibular apparatus with the potential for subsequent stimulation of the vomiting center. Procedures involving the nose and throat, such as septoplasty and tonsillectomy, that result in blood within the esophagus and stomach increase the incidence for PONV.

Intra operative stimulation of the pharynx, including orotracheal intubation and the use of oral airways, may also increase the frequency of PONV. The increased risk of PONV associated with increased length of surgery & anaesthesia.. One source identifies increased duration as surgery and anesthesia lasting more than 1 hour It is important to note that although the type of anesthesia and surgery is often implicated in PONV, according to one source, nausea and vomiting is a common complication postoperatively and very often, regardless of the type of surgery performed or the anesthetic technique that is utilized

Postoperative Factors in the Etiology of PONV

Finally, postoperative considerations involved in increasing the risk of developing PONV include pain and the use of opioids, movement or early ambulation, hypotension, hypoxemia, hypoglycemia, and premature oral intake. The relationship between pain and vomiting is apparent by

the increased incidence of vomiting after the administration of naloxane for reversal of opioid effects. Additionally, several studies have shown that the relief of pain is frequently associated with the relief of nausea.

As mentioned previously regarding the use of opioids, sudden motion or changes in position, including the transport from the operating room to the post anesthesia care unit, can precipitate nausea and vomiting especially in patients who have received opioids suggesting that opioids sensitize the vestibular system to motion-induced nausea and vomiting.

PONV is also increased in patients experiencing dizziness, most often in association with postural hypotension and/or hypovolemia. Postural hypotension is often an early sign of unrecognized hypovolemia. Patients will experience dizziness when first trying to stand up postoperatively, which may lead to nausea and vomiting. This is believed to be due to decreased medullary blood flow to the CTZ and is most often relieved with adequate hydration and/or sympathomimetics.

The timing of the initial oral intake postoperatively may also influence the incidence of PONV. Multiple studies have shown varied findings with some demonstrating that restriction of oral intake in the early postoperative period does not decrease the overall incidence of PONV but only delays its occurrence, while others have shown a distinct relationship between restriction of oral intake during the first 8 hours postoperatively and a significantly decreased incidence of PONV. Apfel *et al*. point out that although numerous factors have been associated with an increased risk for developing PONV, evidence based on clinical trials is available that correlates with only a few of these risk factors, namely female gender, history of PONV or motion sickness, non-smoking status, volatile anesthetics, nitrous oxide, and opioids. As a result, they conclude that PONV is caused predominantly by opioids and volatile anesthetics when administered to susceptible patients. Emphasis is placed on the

recommendation that the anesthesia provider perform a preoperative patient assessment to include a thorough evaluation of pre-existing patient, surgery and anesthesia-related risk factors for precipitating the incidence of PONV followed by the development of an appropriate anesthesia care plan that takes such risk factors into consideration and the implementation of appropriate therapeutic interventions as necessary.

Interestingly, another factor that may contribute to the incidence of PONV is the skill level of the anesthesia provider in relation to the possible effects on anesthesia administration that may result in gastric distension from improper mask ventilation prior to induction; the incidence of hypoxia, hypercapnia, or hypotension intra operatively or postoperatively; instrumentation of the airway during laryngoscopy, suctioning, or oral airway placement; and vestibular disturbances from rough handling of patients during transfer and transport. It is important to note that due to the multiple and varied factors that may contribute to the incidence of PONV, it is recommended that an optimal study regarding anesthesia or surgical implications in the occurrence of PONV requires careful and precise control of per operative conditions in order to determine that the incidence of PONV can actually be attributed to a specific anesthetic or surgical intervention.

V. COMPLICATIONS OF POSTOPERATIVE NAUSEA AND VOMITING

Medical/Surgical Complications of PONV

PONV has the potential to cause further serious medical and surgical complications. Such complications include aspiration; dehydration and electrolyte imbalances; disruption of oral drug therapy; bleeding at the incision site and disruption of the surgical incision; disruption of vascular

grafts or anastamoses; elevated blood pressure; elevated intracranial, intra ocular, and intra gastric pressure; tachycardia and dysrhythmias; and esophageal tears and injury. The three most significant complications resulting from nausea and vomiting include aspiration of gastric contents, visceral or wound dehiscence, and electrolyte disorders from prolonged vomiting. Laryngeal reflexes that generally accompany the vomiting reflex and prevent aspiration of gastric contents, are blunted in the presence of general anesthesia Vomiting can, therefore, result in gastric contents entering the trachea leading to the risk of aspiration pneumonitis

Vomiting causes a significant increase in both intra-thoracic and intra-abdominal pressure. If the pharyngeal sphincter is incompletely relaxed during vomiting, the accompanying increase in intra-thoracic pressure can cause esophageal rupture or small esophageal tears. The increase in intra-abdominal pressure can cause stress to visceral or vascular anastamoses, as well as wound dehiscence .

Severe and prolonged vomiting may cause significant electrolyte imbalance. The metabolic consequences of vomiting include the loss of gastric acid and water from the stomach; volume contraction alkalosis; elevated aldosterone from the resulting dehydration; and a loss of sodium, potassium, and bicarbonate through the kidneys in response to the alkalosis and dehydration

More importantly, there are several adverse patient consequences that result from PONV including accompanying pain and discomfort along with causing delays in the ability to tolerate food, fluids, and oral medications. Additionally, PONV considerably increases patient anxiety and dissatisfaction along with causing fear and anxiety over PONV in the future

VI. ANTIEMETIC THERAPY

Antiemetic therapy in anesthesia includes both prophylactic and rescue treatment and strategies for per operative and postoperative management of PONV. As with most aspects of healthcare, the primary goal with PONV is for prevention. Certain practices, or physical measures, on the part of the anesthesia provider pre-, intra- and post-operatively, can often assist in reducing the occurrence or severity of PONV without having to rely upon the use of pharmacological measures. The first point to be made is that susceptible paiients for PONV may be identified based upon the type of surgery and the patient's past medical history including the presence of co-existing conditions and/or diseases and previous PONV or motion sickness. Thus, the initial step in the management of PONV is to assess the risks for the probability of experiencing PONV followed by the institution of appropriate strategies for managing PONV as necessary. Certain risk factors for PONV are unavoidable or unable to be manipulated, such as those caused by the type of surgery or certain inherent patient-related characteristics. However, the choice of anesthetic agents, techniques, and adjuncts to anesthesia can be controlled and comprise the components of the anesthesia plan that are individualized for every patient.

Strategies for Perioperative Management of PONV/Intervention Assessment Scale

As mentioned, an essential component of any strategy for the per operative management of PONV is obtaining a thorough history and physical examination to include the determination of preexisting risk factors for PONV including gender and weight, history of previous PONV, co-existing

diseases and current medication regimens for the purpose of identifying patients who are at increased risk for experiencing PONV. Many practitioners utilize an intervention assessment scale for the initial assessment and evaluation of a given patient's risk for experiencing PONV in order to determine the need for prophylactic measures and treatment through the use of such a scale, patients are given a score based upon specific risk factors with each risk factor worth one to three points and a total score of three or more points indicating the need for prophylactic antiemetic therapy

Intervention Assessment Scale

Each worth 3 points

***History of PONV**

***History of motion sickness**

***Gynecologic laparoscopy**

***Breast reconstruction**

Each worth 2 points

***Facelift surgery**

***Strabismus or middle ear surgery**

***Neurosurgery**

***Obesity**

Each worth 1 point:

***Preadolescent**

***Female**

***Anxiety**

***Laparoscopic cholecystectomy**

***Intraop /postoperative opioid**

***Duration of anesthesia > 60 minutes**

3 OR MORE POINTS PROPHYLACTIC ANTIEMETIC IS INDICATED

A similar means for assessing and assigning a risk score for the prediction of PONV was developed by Apfel *et al*. after studying the incidence of PONV and related risk factors and risk scores at different institutions. They identified four primary risk factors that comprised a simple risk factor scoring system, including the characteristics of female gender, prior history of PONV or motion

sickness, nonsmoking status, and the use of intra operative and postoperative opioids, that could be applied broadly from one institution to another with accurate predictability for PONV. As with the method described above, patients are assigned a number value based upon the presence or absence of these four risk factors. According to their study findings, Apfel *et al* determined that if no risk factors or only one risk factor is present, the incidence of PONV varies between 10% and 21%. If two risk factors are present, the probability of PONV increases to between 39% and 78%. In the presence of two or more risk factors, an appropriate modification may be made in the anesthesia plan, including a change in anesthetic technique, such as the avoidance of volatile anesthetics entirely by using a total intravenous anesthetic technique, which is associated with significantly less PONV.A score of two or more indicates the need for prophylactic antiemetic treatment.

In addition to antiemetic drug therapy, other prophylactic measures can be taken to minimize gastric volume and acidity and to avoid regurgitation. This involves the initial determination of appropriate “nothing per os” (NPO) or fasting status, along with the administration of histamine antagonists and gastrokinetic agents as necessary. Fasting prior to receiving general anesthesia is a simple means for decreasing gastric volume and the risk of regurgitation and aspiration of gastric contents. However, because increased anxiety may stimulate gastric acid secretion and delay gastric emptying, the administration of anxiolytics, such as Midazolam, preoperatively may be beneficial and drugs that decrease lower esophageal tone, such as atropine should be avoided. The administration of histamine (H-2) receptor antagonists, such as ranitidine, preoperatively acts to block histamine-mediated gastric acid secretion, which subsequently results in decreased gastric volume and increased pH of gastric contents. Soluble antacids, such as sodium citrate, given preoperatively are also effective in raising the gastric pH for as long as three hours. Metoclopramide, a benzamide, may be given preoperatively to stimulate the release of acetylcholine in the gut which creates a coordinated, peristaltic action in addition to relaxing the pylorus, increasing lower esophageal tone, and causing a

direct depressant effect on the CTZ, all of which assists in decreasing gastric volume and minimizing the risks for vomiting postoperatively. There are several practices and procedures that comprise the strategies for intra operative management of PONV including the use of IV anesthetics such as Propofol; prevention of excessive stomach distension with mask ventilation; gastric suctioning prior to anesthesia; maintenance of adequate fluid status intra operatively;

Prevention of hypoxia, hypercarbia, and hypotension, all of which are associated with an increased incidence of PONV; the use of regional anesthesia when possible, especially for high risk patients; application of cricoid pressure and rapid sequence induction for patients with a full stomach; minimizing the requirement for narcotic analgesics postoperatively through the use of local anesthetics and NSAID; and prophylactic antiemetic administration as necessary However, the timing of prophylactic antiemetic administration is controversial. With shorter surgical procedures, intravenous anti emetics are usually administered at the induction of anesthesia, but for longer procedures anti emetics are often given towards the end of the surgery for maximum benefit. Although it might seem logical to utilize routine prophylaxis, there are numerous anti-emetic agents and the expense of many of them is thought to be too high to be cost-effective and warrant their use on a routine basis. Generally, prophylactic antiemetic therapy is suggested only for those patients with two or more known risk factors for PONV. Postoperative strategies for handling PONV include adequate pain management, prompt removal of oral and nasal tubes that activate the gag reflex, adequate IV hydration, avoidance of hypotension, prevention of early and excessive movement, encouragement of slow, deep breathing, and early treatment with anti emetics as necessary

VI Anti Emetic Therapy

Pharmacological Classification	Receptor Site Affinity	Drugs
5-HT3 Antagonists	5-HT3	Ondansetron, Granisetron, Dolasetron, Tropisetron
Benzamides	Dopamine	Metoclopramide, Cisapride, Alizapride
Butyrophenones	Dopamine	Droperidol, Haloperidol, Domperidone
Phenothiazines	Dopamine	Promethazine, Fluphenazine, Perphenazine, Trifluperazine
Antihistamines	Histamine	Diphenhydramine, Dimenhydrinate, cyclizine, Meclizine hydroxyzine,
Anticholinergic agents	Muscarinic	Hyoscine, scopolamine, Atropine
Others	-	Corticosteroids (Dexamethasone) Benzodiazepines (Lorazepam, alprazolam) Clonidine, Ephedrine,

Classification of Antiemetic Drugs and Receptor at Which Each Works

Many of the concepts of antiemetic therapy in surgical populations have been adopted from successful treatment protocols utilized in oncology in relation to chemotherapy-induced emesis. Based upon the understanding that vomiting is caused by the stimulation of various receptors located within

the central nervous system and GI tract, as previously described, traditional anti emetics consist of a variety of drugs that block the different neurotransmitter receptors involved.

Four major neurotransmitter receptors appear to be involved in a vomiting response, including dopamine, histamine (H_1), cholinergic muscarinic, and Serotonin (5-HT_3) receptors. Subsequently, these four receptors serve as the four corresponding sites of action for the various antiemetic drugs, whereby the blockade of one or more of these receptors by a drug is the mechanism of action involved in the prevention and treatment of both chemotherapy-induced and postoperative nausea and vomiting. Blockade of the receptor site prevents a specific neurotransmitter from working at the receptor after its release from the vesicles within the nerve terminal

It is suggested that the ideal antiemetic drug would be effective at preventing and/or treating nausea and vomiting with minimal side effects and drug interactions. Additionally, it would be convenient to administer and the effects would be sufficiently long acting to last through the per operative period. A single antiemetic drug may work at more than one receptor, but tends to have one receptor at which it exhibits a predominant effect. In this regard, it is believed that no single antiemetic drug is 100% effective due to the multifactorial stimulus for PONV and that a multimodal approach is the best approach in the management of nausea and vomiting postoperatively

The various antiemetic agents utilized for the management of PONV include butyrophenones, benzamides, anti cholinergic, antihistamines, phenothiazines, and Serotonin antagonists .

Conventional anti emetics are associated with clinically undesirable side effects, including sedation, hypotension, dry mouth, dysphoria, restlessness, and extra pyramidal symptoms. Butyrophenones, such as Droperidol, function as a dopamine receptor antagonist whereby antagonism

of dopamine receptors in the CTZ provides an antiemetic effect. However, large doses of Droperidol have been associated with delayed emergence, drowsiness, and extra pyramidal symptoms.

The antiemetic actions of phenothiazines have been attributed to their ability to block the dopamine and histamine-1 receptors in the CTZ. Chlorpromazine and Promethazine are phenothiazines used in the prevention and treatment of PONV however, they can produce significant sedation and lethargy in patients recovering from general anesthesia and therefore delay recovery following outpatient surgery. Prochlorperazine and perphenazine are also phenothiazines noted to have a shorter duration of action that may require repeated dosing and are associated with a higher incidence of extra pyramidal side effects, ranging from restlessness to oculogyric crisis Different cholinergic muscarinic receptors are located in the cerebral cortex and CTZ and drugs with specific antagonistic activity at these receptors may assist with effective antiemetic therapy although the findings are varied. Scopolamine and atropine, two anti cholinergic agents that are capable of crossing the blood-brain barrier, may work effectively as anti emetics. However, scopolamine in particular, can produce undesirable side effects such as dry mouth, sedation, visual disturbances, memory dysfunction, dysphoria, and occasional confusion, disorientation, and hallucinations

Antihistamines, such as dimenhydrinate, hydroxyzine, and diphenhydramine, act on both the vestibular pathways and the vomiting center and are therefore effective in the prevention and treatment of motion sickness, as well as PONV associated with middle ear procedures that interfere with the vestibular apparatus, Metoclopramide is a benzamide that possesses both central and peripheral antiemetic actions. In addition to the ability to block dopamine receptors in the CTZ centrally, Metoclopramide increases lower esophageal tone and enhances gastric and small bowel motility peripherally, thereby preventing delayed gastric emptying produced by opioid analgesics and some of the volatile agents. Other benzamides with potent gastrokinetic action include cisapride, alizapride, and clebopride.

Dexamethasone has also been reported as an effective antiemetic agent, especially when given in combination with another antiemetic drug. The mechanism of antiemetic activity related to the use of Dexamethasone is not fully understood but is believed to be due to either central inhibition of prostaglandin synthesis, a decrease in Serotonin turnover in the central nervous system. It is also pointed out that steroids act to release endorphins and their antiemetic activity may therefore involve a psychological component

The incidence of opiod-related nausea and vomiting may be minimized with the use of potent non-steroidal-anti-inflammatory drugs, such as ketorolac. Because ketorolac is especially effective in the prophylaxis of postoperative pain following ambulatory surgery, thereby reducing the amount of narcotic required for postoperative analgesia, it may be associated with a much lower incidence of PONV in the immediate postoperative period.

The use of local anesthetics has also become increasingly popular as a means of early postoperative management of pain and may significantly reduce the amount of opioid analgesics necessary for pain management postoperatively, therefore minimizing opioid-induced nausea and vomiting.

Combination Antiemetic Therapy

It is important to point out that despite the lack of conclusive research results to date, it is becoming increasingly popular to utilize a multimodal approach, or combination of anti emetics, in the pharmacological management of PONV. As mentioned previously, this practice is based upon the complex and multifactorial etiology of PONV. It is believed that administering a drug that antagonizes

only one of the many receptors that may be involved in the etiology of PONV is often ineffective, whereas using combinations of drugs with different mechanisms of action acts synergistically to provide an overall improved therapeutic effect. This approach is likened to the concepts of balanced anesthesia and balanced analgesia. The multimodal antiemetic approach takes into consideration the fact that each antiemetic agent may selectively block a specific receptors that may or may not be present in multiple anatomic sites. Combining different agents may, therefore, help to make a specific receptor blockade more effective and achieve a blockade in a different anatomic site or block multiple receptor sites. In addition, it may also serve to lessen the incidence of side effects of the anti emetics themselves as a result of being able to use smaller doses of each drug with combination therapy regimens.

Corticosteroids, such as Dexamethasone, are the drug most commonly used in combination with other anti emetics for combination therapy Additionally, it is often recommended that in the event that an initial antiemetic or combination of anti emetics is ineffective, the preferred choice for additional drug therapy should involve an agent that works at a different receptor sites. Multimodal management of PONV, however, refers not only to a combination of pharmacological antiemetic agents, but to the use of multiple anti emetics in combination with numerous non pharmacological techniques that best avoid the incidence of PONV With regard to multimodal management of PONV and patients at high risk for experiencing PONV

Thus, further emphasis is placed on the importance of controlling PONV through minimizing or avoiding the preventable factors that may lead to nausea and vomiting postoperatively and utilizing those measures that assist in lessening PONV in association with appropriate anti emetic drug therapy

Non-Pharmacological Therapy for PONV

In addition, a variety of approaches that do not involve the use of anti emetics have been developed for the management of PONV, including adequate pre-, intra-, and postoperative pain relief, supplemental oxygen, aggressive intravenous rehydration, maintenance of blood pressure, and the use of acupuncture. Recently, the concept of controlled, deep breathing has also been studied for its value in relieving nausea postoperatively and was found to be highly effective.

This is believed to be due to the close proximity of the respiratory and vomiting centers in the brain whereby the focus of the respiratory center on taking deep breaths relieves the vomiting center from being stimulated. A further explanation for the success of this technique is the logical assumption that if hypoxia acts as a stimulus to the vomiting center, increased oxygenation through deep breathing would have the opposite effect

The management of pain postoperatively involves a “fine line” between maintaining patient comfort and triggering PONV through the use of opioids. It is not considered good practice, however, to withhold treatment for pain based upon a fear of opioid-induced nausea and vomiting although the goal should be for using the minimum amount necessary for adequate pain control. The administration of oxygen intra operatively and for the first 2-hour period postoperatively is consistently associated with a decreased incidence of PONV. As for intravenous rehydration, the administration of 20 ml/kg of IV fluid may decrease postoperative drowsiness, dizziness, and nausea and vomiting, although study findings regarding this concept have not been conclusive.[10] Additional study findings have shown a difference in the incidence of PONV between patients receiving adequate hydration preoperatively as compared to those not receiving the fluids and the administration of a fluid bolus preoperatively

associated with a decreased rate of nausea and/or vomiting regardless of antiemetic therapy. The use of acupuncture, that is, manual stimulation of the P-6 acupuncture point with a fine needle may result in a significant reduction of PONV although the findings are varied.

In addition, studies have also been performed using the power of positive suggestion which have demonstrated a decrease in the incidence of PONV in patients who received positive suggestion pre- and intra operatively. Finally, patients recovering from anesthesia should never be near another patient experiencing active vomiting due to the potential for psychological, visual, olfactory, and auditory cerebral input that may lead to PONV in these patients

VII.SEROTONIN ANTAGONISTS

The newest class of antiemetic is the Serotonin receptor antagonists. Serotonin receptor antagonists were developed through alterations of the traditional antiemetic Metoclopramide and were first utilized as part of medical practice in 1991 in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV). However, there are significant differences in the etiology and management of CINV and PONV. CINV is mediated specifically through Serotonin receptors located peripherally on the vagal afferent nerve terminals and centrally in the CTZ. The use of Serotonin receptor antagonists has been considered a major breakthrough in the prevention of CINV and the use of prophylactic antiemetic therapy is a routine part of practice in association with CINV. Success of antiemetic therapy for CINV is generally defined as two or fewer episodes of vomiting. In contrast, the incidence and causes of PONV are highly variable and the use of anti emetics is not considered to be a routine component of anesthesia. In addition, a patient experiencing two episodes of vomiting postoperatively following the use of prophylactic anti emetics would be considered as having severe PONV and a failure of therapy. Although the mechanism of PONV is not completely understood, it is known that PONV often involves stimulation of the enterochromaffin cells of the GI tract by anesthetic agents as well as by the stress of surgery. These cells release Serotonin, which, in turn, activates Serotonin receptors in the CTZ and vomiting center to induce vomiting. Blockade of these receptors through the use of a Serotonin antagonist subsequently prevents this mechanism One source discusses the important role of Serotonin as a major neurotransmitter within the body.

Serotonin, or 5-hydroxytryptamine (5-HT), is a biogenic alkyl amine synthesized from the dietary amino acid tryptophan and accounts for approximately 1% of the metabolism of tryptophan under normal homeostatic conditions. Serotonin has many different physiologic actions related to a wide variety of receptors and effector mechanisms within the central and peripheral nervous systems. Ninety percent of Serotonin is located peripherally in the enterochromaffin cells of the intestinal mucosa and 10% is found in the neurons of the central nervous system. Serotonin receptors are found peripherally in the vagal nerve terminals and centrally within the limbic system (hypothalamus), the cerebral cortex, and the CTZ

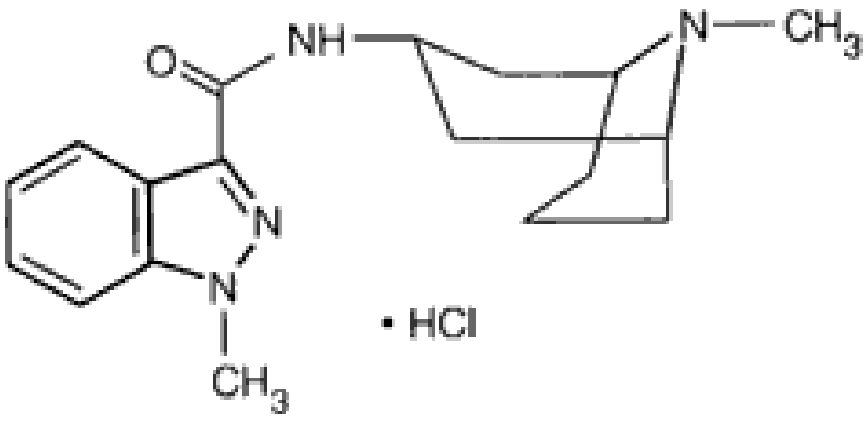
Serotonin receptors have been categorized into five main subclasses of Serotonin, or 5-HT, receptors .The five main groups of 5-HT receptors include 5-HT_1 through 5-HT_5 and the 5-HT_1 receptor is further divided into three different subtypes. The majority of the Serotonin receptors are G-protein-coupled receptors with the exception of the 5-HT_3 receptor subclass, which are ligand gated or fast ion channel type receptors The various 5-HT receptors are each involved in mediating different physiologic functional responses with the 5-HT_3 receptor being the primary receptor involved in the process of reflex-induced vomiting. The 5-HT_1 receptor is believed to be involved in smooth muscle contraction and relaxation, as well as having an effect on anxiety, depression, and appetite. The 5-HT_2 receptors are also involved with smooth muscle contraction and, additionally, with vasoconstriction and platelet aggregation. The 5-HT_3 receptors, as mentioned, are involved in the phenomenon of nausea and vomiting. The 5-HT_4 receptors play a role in gastrointestinal motility and the precise function of the 5-HT_5 receptors is still under investigation.

In addition to the use of 5-HT_3 antagonists in antiemetic therapy, some of the other Serotonin-related drugs are used therapeutically to treat migraines (5-HT_1 receptor antagonist), vascular disorders (5-HT_2 receptor antagonists), gastrointestinal motility disorders (5-HT_4 antagonists) and behavioral psychopathologies (5-HT_1 agonists and 5-HT_{2-4} antagonists). The 5-HT_3 receptor was identified specifically as a target for anti emetics when Fozard[8] observed that Metoclopramide had weak 5-HT_3 antagonistic properties in addition to its ability for blocking dopamine receptors and was, therefore, capable of producing a more complete antiemetic effect. Subsequent research led to the discovery of the complete absence of reflex-induced emesis in ferrets with the use of a selective 5-HT_3 antagonist known as MDL 72222. This led to extensive clinical testing of selective 5-HT_3 antagonists in humans with several selective 5-HT_3 antagonists having since been developed

The 5-HT_3 antagonists are potent and highly selective competitive inhibitors of the 5-HT_3 receptor with a selectivity ratio of 100:1 for the 5-HT_3 receptor as compared to the other 5-HT receptor types. The antiemetic action of the 5-HT_3 antagonists is due to simultaneous effects at both central and peripheral 5-HT_3 receptor sites By selectively working at the 5-HT_3 receptors, 5-HT_3 antagonists avoid the adverse effects of some of the traditional anti emetics and are associated with a significantly lower incidence of side effects. 5-HT_3 antagonists are generally tolerated over a wide dose range and the most common side effects associated with their use are headache and constipation.

Finally, 5-HT_3 receptor antagonists are rapidly absorbed and cross the blood-brain barrier easily. Their elimination half-life varies from 3-4 hours for ondansetron and Granisetron to 7-10 hours for Dolasetron.Overall, the duration of the antiemetic effect of the 5-HT_3 receptor antagonists appears to be longer than what would be expected according to the serum half-life of these drugs which is believed to be due to their increased affinity for the 5-HT_3 receptor site. 5-HT_3 antagonists are metabolized via various subtypes of the cytochrome P-450 system in the liver and the resulting metabolites are excreted mainly in the urine .

GRANISETRON



It is a $5HT_3$ – receptor antagonist, which is 10 –15 times more potent than ondansetron.

Available as injection, tablets & Syrup form. Plasma half life : 5.3 ± 3.5 hrs. But the antiemetic effect persists long after the drug disappears from the circulation, suggesting their continued interaction at the receptor level. So it can be administered effectively just once a day. It is well absorbed from the GI tract. Oral bio availability is 60%. Principally metabolized in the liver, a process that appears to involve CYP3A family of enzymes.

Protein bound : 65 ± 9%

Urinary excretion : 16 ± 14%

Clearance : 11 ± 9 ml / min / kg.

Decreased in aged, Cirrhosis.

No change in Renal disease.

Volume of distribution 3.0 ± 1.5 lit / kg.

Uses

- Post operative nausea & vomiting, Chemotherapy induced vomiting, Radiotherapy induced vomiting, may be useful in pruritis in Uraemic patients.

Side effects

- Generally well tolerated.
- Constipation, diarrhoea, headache, Light headedness.

Induce minor ECG changes, clinically insignificant.

VIII. Review of Literature

Fuji Y and Toyooka et al(1998) studied efficacy of Granisetron in a randomized, double blind, placebo controlled study. A complete response, defined as no emesis and need for another rescue antiemetic during the first 24 hour after Anaesthesia, occurred in 40%,48%,85% and90% of patients who had received placebo and Granisetron 20,40,80 μgm kg-1, respectively($p<0.05$);(overall Fisher's exact probability test).
There were no clinically important adverse events. They have concluded that pre operative oral Granisetron, in doses 40 μgm kg-1, was effective for the prevention of post operative vomiting in children.

Tanaka et al (1999) had undertaken a study to determine the effective dose of Granisetron was effective for the prevention of post operative vomiting in children undergoing general inhalational anaesthesia for surgery. In their study patients were assigned to receive placebo or Granisetron at three different doses(20 mcg kg-1,40mcg kg-1, 100mcg kg –1) immediately after induction of anaesthesia (n=30 each).

A complete response, defined as no emesis and no need for another rescue antiemetic during the first 24 h after anaesthesia, occurred in 57% with placebo,67% with Granisetron 20 mcg kg-1, 90% with granisetron40 mcg kg-1 and 90% with granisetron100 mcg kg-1respectively ($p<0.05$; overall Fisher's exact probability test). There were no clinically important adverse events. Results suggest that Granisetron 40 mcg kg-1 is the minimum effectivefor the prevention of post

operative vomiting after pediatric surgery, and that increasing its dose to 100mcg kg-1 provides no demonstrable benefit.

A.J. Wilson, P. Dieamuscl et al (1996) determined the optimal dose of Granisetron and to evaluate its safety profile. Antiemetic prophylaxis with a single dose of Granisetron 1.0 mg or 3 mg resulted in a significant reduction (P0.001) compared with placebo in the numbers of patients experiencing post of vomiting or who achieved total control during the post of periods 0-6 hrs & 0 – 24 hrs. Two high doses of Granisetron (1.0 mg and 3.0 mg) provided effective prophylaxis against vomiting with 78% and 77% of patients respectively.

Maisano et al (1995) & Ettinger et al (1996) studied antiemetic efficacy of two different doses of Granisetron (1mg & 2 mg) for chemotherapy induced nausea & vomiting. In their study no vomiting has occurred after 24 hrs: Antiemetic efficacy is around 70% & 86.7% in the 1 mg & 2mg groups respectively. All the fore mentioned studies are correlated with our study.

IX. MATERIALS AND METHODS

The institution research committee approved the investigation and informed consent was obtained from all patients on whom the study was conducted.

50 Pediatric patients of ASA Status I aged between 5 – 15 yrs, who were scheduled for Adenotonsillectomy surgery were included in the study. The patients were randomly divided into two groups A & B. Group A consisted of twenty five patients receiving a single dose of oral Granisetron (40 Mcg/Kg) I hour before surgery, group B consisted of 25 patients receiving a placebo. All patients posted for elective Adenotonsillectomy were visited on the day before surgery. A thorough preoperative assessment was done to exclude any systemic illness. Patients with a history of motion sickness, H/o PONV, patients who had vomited or received antiemetics within 24 hour prior to surgery were excluded from the study.

Premedication

All patients were premedicated with Pentazocine 0.5mg/kg with 5mcg/kg Glycopyrrolate 30 minutes before surgery.

Group A – given Granisetron 40 mcg/kg oral

Group B – given a placebo

Technique of Anaesthesia

All patients were given general anaesthesia with endotracheal intubation Anaesthesia induced with Thiopentone sodium $5mgKg^{-1}$. Sympathetic response to laryngoscopy and intubation were attenuated by prior administration of Lidocaine 1 - 1.5 $mgKg^{-1}$. Trachea was intubated with 2 $mgKg^{-1}$ Succinylcholine. Anaesthesia was maintained with oxygen – Nitrous oxide mixture, muscle relaxant Vecuronium 60 – 80 mcg/Kg with small dose opioids.

Monitoring

The following were monitored in all patients

1. Pulse rate
2. Blood pressure
3. E.C.G.

At the end of surgery, the neuromuscular blockade was reversed with Neostigmine 0.05 $mgKg^{-1}$ and Glycopyrrolate 5 mcg/kg.

Postoperative period

Efficacy and safety data were collected for 24 hour postoperatively. For the first 2 hour, patients observed in the post Anaesthesia care unit directly. Vital signs, emetic episodes were noted.

For the next 24 hours, a diary card was kept by the attending staff nurse who recorded the number of emetic episodes and the time at which the incidence took place.

The primary efficacy variable in the two studies was the number of emetic episodes. An emetic episode was defined as a single vomit or retch or combinations of vomits and/or retches occurring within 1 minute of each other.

Complete response defined as no emetic episodes.

Major response – one emetic episode

Treatment failure – two or more emetic episodes or the receipt of a rescue antiemetic.

Rescue antiemetics were allowed at the request of the patient, upon physician determinations, or after two emetic episodes.

The data were recorded according to the Proforma and the results were statistically evaluated.

RESULTS

Table 1

Age distribution of the patients

Age Group (Yrs.)	Granisetron (No: 25)		Placebo (No. 25)	
	No.	%	No	%
5 – 10 Yrs	13	52%	11	44%
10-15 Yrs	12	48%	14	56%
Total	25	100%	25	100%

Group A & B were comparable in age. Mean age of Group A 10.36, Group B was 10.96. So the two group are comparable in patients mean age.

Weight distribution of patients

Weight	Granisetron (No: 25) (Group A)		Placebo (No. 25) (Group B)	
	No.	%	No	%
10 – 20 kg	1	4%	2	8%
20 – 30 kg	20	80%	11	44%
30 – 40 kg	4	16%	6	24%
40 – 50 kg	-	-	6	24%

Mean weight in Group A is 26.88, and in Group B is 30.04. So two group were comparable in patients mean weight.

TABLE 3

Emesis distribution of patients

Study Group	Total No.	Pt. With POV					Pt. Without POV	
		0-2 hrs.	2-12 hrs.	12 – 24 hrs.	Total No. of Emesis	%	No	%
Group A Granisetron	25	-	2	1	3	12%	22	88%
Group B Placebo	25	2	9	3	14	56%	11	44%

Table 3 shows the postoperative emesis in two groups. The table clearly shows that Granisetron is significantly better than placebo in preventing POV. In group A, 3 patients experienced emesis (12%) whereas 22 patients were emesis free (88%). In-group B 14 patients (56%)had emetic episodes whereas 11 patients (44%) were emesis free. The table shows that group A patients who had received Granisetron experienced lesser vomiting than group B who received the placebo.

The following table shows the efficacy of Granisetron in reducing the frequency of emesis in patients who had emesis. 88% in Granisetron had complete response. In placebo group only 44% of patients had a complete response. Major response that is only one episode of emesis was 12% in Granisetron group whereas it was 32% in placebo group. Treatment failure (two or more episodes) is nil in Granisetron received patients, and 24% in placebo group. The observed difference between group A and group B in antiemetic efficacy had compared using Z-test. The calculated value of Z (4.83) is very much above the table value of Z (1.96). So the observed difference is significant $P < 0.05$. This shows that administration of oral Granisetron is more effective than placebo.

Antiemetic efficacy among the study groups in reducing the frequency of occurrence of emesis

Efficacy	Definition	Granisetron (Group A)		Placebo (Group B)	
		No.	%	No	%
Complete	No emetic	22	88%	11	44%

response	episode				
Major response	One episode	3	12%	8	32%
Treatment failure	Two or more episodes	-	-	6	24%

PROFORMA FOR THE STUDY

Sl. No.:	Date:	
Name	Age:	Sex:
IP No.:	Weight	
Pre-operative Diagnosis: Nature of Surgery:		
Surgeon ASA Grade: I II		Anesthesiologist
BP:	PR:	
RESP Rate:	Premedication:	Time:

Technique of Anaesthesia:		
Condition at the end of surgery		
Post-operative nausea and vomiting		
First 2 hour:	Next 10 hour.	Next 12 hour.
Frequency of emesis		Severity of emesis
Patient's general assessment of Post-operative period:		

Diary Card

Time of vomiting	No of episodes

X.CONCLUSION

Anti emetics is the mainstay of therapy for POV. The main pharmacological classes of drugs used in the treatment are muscarinic, dopaminergic, histaminic, or serotonergic.

In the present study, oral Granisetron (40 mcg / kg) was given orally an hour before surgery in patients undergoing Adenotonsillectomies, to evaluate its efficacy in preventing postoperative vomiting. Results showed that oral Granisetron is effective in preventing postoperative vomiting. 88% of patients were emesis free than the placebo received group.

A no. of factors, including age, obesity, history of motion sickness or previous post operative emesis, operative procedure, anaesthetic technique & post operative pain are considered to increase the incidence of post operative vomiting. However in this study there were no difference between the group with regard to patient data, surgical procedure, anesthetics administered & analgesics used after operation, and children with a history of motion sickness or previous emesis were excluded. Therefore, the difference in the incidence of complete response between the groups can be attributed to difference in the antiemetics tested.

In summary, we have found that preoperative oral Granisetron 40 mcg / kg, was effective for the prevention of postoperative vomiting in children undergoing Aden tonsillectomies.

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Master Chart

GRANISETRON GROUP

SL.NO	NAME	IP NO.	AGE	Wt. Kgs.	POV(Hrs)			RESPONSE
					0-2	2-12	12-24	
1	Tamil	974152	07/M	21	-	-	-	CR
2	Naveen	974289	07/M	20	-	-	-	CR
3	Kavi Barathi	974272	08/M	18	-	-	-	CR
4	Anitha	974595	12/F	25	-	-	-	CR
5	Kausalya	977671	08/F	20	-	-	-	CR
6	Veeramani	975870	07/M	25	-	-	-	CR
7	Sivasankar	975861	08/M	25	-	-	-	CR
8	Jones	975867	11/M	26	-	-	-	CR
9	Ajith	976392	10/M	20	-	-	-	CR
10	Baskar	976994	06/M	20	-	-	-	CR
11	Gayathri	977348	10/F	20	-	-	-	CR
12	Joy	977370	10/M	20	-	-	-	CR
13	Venkatesh	977573	08/M	20	-	-	-	CR
14	Akila	977994	11/F	23	-	-	1*	MR
15	Basheer	978160	11/M	25	-	-	-	CR
16	Reshma	978165	05/F	20	-	-	-	CR
17	Vetri	977990	14/M	40	-	-	-	CR
18	Geetha	980307	15/F	40	-	1*	-	MR
19	Deepa	980877	16/F	20	-	-	-	CR
20	Anusuya	981317	12/F	32	-	-	-	CR
21	Thenmozhi	981322	11/F	27	-	-	-	CR
22	Nasreen	982336	11/F	23	-	-	-	CR
23	Suresh	983004	15/M	34	-	-	-	CR
24	Nisha	983150	08/F	24	-	-	-	CR
25	Meenatchi	975152	12/F	20	-	1*	-	MR

PLACEBO GROUP

Sl No	NAME	IPNO	AGE	WT In kgs	POV (HRS)			RESPONSE
					0-2	2-12	12-24	

1	Baranidharan	974395	12/M	25	-	2*	-	TF
2	Kannaki	975865	12/F	26	-	-	1 *	MR
3	Monika	976284	12/F	26	-	6 *	-	TF
4	Manikandan	975712	15/M	45	-	1 *	-	MR
5	Shyam	976817	12/M	25	-	3 *	-	TF
6	Priya	976814	08/F	25	1 *	-	-	MR
7	Praba	977901	13/F	40	-	-	-	CR
8	Roopa	976996	09/F	35	-	1 *	-	MR
9	Nandakumar	977378	09/M	20	-	-	-	CR
10	Shahul ameed	977530	12/M	35		-	-	CR
11	Kausalya	977166	10/F	26	-	2 *	-	TF
12	Keertika	978163	10/F	35	-	-	-	CR
13	Sivaranjini	980453	08/F	17	-	-	-	CR
14	Vembaiyan	980754	10/M	22	-	-	-	CR
15	Prabakaran	981803	11/M	30	-	-	-	CR
16	Apsara	981114	09/F	20	-	-	-	CR
17	Parveen	982258	11/F	32	-	1 *	-	MR
18	Arivazhagan	985519	10/M	26	1 *	-	-	MR
19	Praba	984081	15/M	40	-	1 *	-	MR
20	Kaliammal	984106	15/M	42	-	2 *	-	TF
21	Saravanan	985006	08/M	18	-	-	-	CR
22	Kalistha	984495	12/F	41	-	-	1 *	MR
23	Karthika	984475	13/M	30	-	-	-	CR
24	Mahadevi	985895	10/F	24	-	3 *	-	TF
25	Veeraragavan	973311	10/M	24	-	-	1 *	MR

CR—COMPLETE RESPONSE

MR—MODERATE RESPONSE

TF—TREATMENT FAILURE

* Episode of vomiting