

# Advanced paramedical science

Science



Nausea and vomiting is a commonly encountered problem in the emergency department as it accompanies a multitude of conditions ranging from seemingly benign conditions such as migraine and gastroenteritis to potentially lethal conditions such as pancreatitis and the acute abdomen.

Studies from the U. S have shown that each year, almost 8 million individuals present to the emergency department with complain of nausea and vomiting, either as a principal complain or as a part of another disease etiology (Braude, Soliz, Crandall, Hendey, Andrews, & Weichenthal, 2006, p. 77).

Nausea and vomiting are not distinct disease entities. Rather, they are symptoms which can be present in a wide range of disease conditions and are considered to be the ‘ end-points’ of several pathological processes (Klosterhalfen and Enck cited in Kowalski, Rapps, & Enck, 2006 p. 28). The term nausea refers to the subjective feeling or the urge to regurgitate gastric contents (Kuver, Sheffield, & McDonald, n. d.).

From a physiological point of view, this is associated with reduced gastric motility and increased smooth muscle tone of the small intestine. Moreover, there might also be the presence of reverse peristalsis in the small intestine, which can cause the feeling of imminent regurgitation (Bowen, n. d.).

On the other hand, vomiting refers to ‘ the forceful discharge of gastric contents’ (Kuver, Sheffield, & McDonald, n. d.) which is meant to serve the purpose of protecting the gastrointestinal tract from potentially harmful substances by preventing their entry and transit through the gastrointestinal tract (Kuver, Sheffield, & McDonald, n. d.).

Vomiting, if persistent can have several potentially hazardous consequences such as dehydration, electrolyte imbalances, metabolic derangements, manifesting as alkalosis and even bleeding and esophageal perforation (Kuver, Sheffield, & McDonald, n. d.). Moreover, from the patient's perspective, nausea and vomiting can be distressful and thus appropriate and timely management of these two conditions is imperative.

The Physiology of Nausea and Vomiting – an overview of the stimuli and pathway involved

For several decades now, it has been established that the chemoreceptor trigger zone in the brain which is responsible for emesis is the area posterema. This is a region located at the dorsal surface of the medulla oblongata near the caudal end of the fourth ventricle. It is one of the 'circumventricular organs' and by the virtue of possessing a relatively permeable blood-brain barrier, is sensitive to a variety of stimuli (Sanger & Andrews, 2006, p. 5).

Thus, it plays an important role in emesis. Studies have shown that there are five main kinds of stimuli which can trigger nausea and vomiting via different pathways viz. the presence of toxic materials within the gut lumen, presence of toxins in the blood, a pathology within the gut, a central nervous system (CNS) stimulus or disturbances in the vestibular system (Sanger & Andrews, 2006, p. 5). The mechanism whereby each of these stimuli brings about nausea and vomiting is discussed below.

The presence of toxic materials within the gut lumen:

The presence of toxins, such as drugs has been shown to stimulate the enteroendocrine cells, such as the enterochromaffin cells, located in the gut mucosa and result in the release of several mediators such as 5HT<sub>3</sub>, Substance P and CCK.

This results in the stimulation of vagal afferent neurons which are located in the abdomen. These neurons traverse through the nucleus tractus solitarius (NTS) and are projected to the dorsal brainstem, with some projection in to the area posterema (Sanger & Andrews, 2006, p. 5).

#### Presence of toxins in the blood

Toxins which have been absorbed and are circulating in the bloodstream can directly stimulate the area posterema and cause induction of emesis (Sanger & Andrews, 2006, p. 5). This is the most common mechanism whereby ingested or parenterally administered drugs, such as chemotherapeutic agents and other toxins such as drugs of abuse, invoke the emetic response.

#### Gastrointestinal tract pathologies

Certain pathologies of the gastrointestinal tract, such as gastritis or hypertrophic pyloric stenosis can stimulate the vagal afferents or directly activate the pathways leading to emesis (Sanger & Andrews, 2006, p. 6).

#### Central nervous system (CNS) stimuli

Certain stimuli such as intense fear, anticipatory anxiety, injury to the brain or a sudden increase in the intracranial pressure can induce emesis (Sanger & Andrews, 2006, p. 6). The mechanism involved in such a response has not yet been elucidated clearly.

## Disturbances in the vestibular system

Amongst other manifestations of disturbances in the vestibular system, such as dizziness, nausea and vomiting is also an important symptom. The vestibular system has been shown to directly stimulate the pathways involved in the emetic response and hence produce nausea and vomiting (Sanger & Andrews, 2006, p. 6).

All these stimuli have been shown to stimulate various pathways which have one common outcome viz. the stimulation of the emetic center in the area posterema. (Kuver, Sheffield, & McDonald, n. d.). Several receptors, both central and peripheral, have been implicated in bringing about emesis.

Amongst these the most pertinent ones are Dopaminergic receptors (particularly D2), Histaminergic receptors (especially H1), Muscuranic receptors (including M3/M5), 5-hydroxytryptamine receptors, in particular, 5-HT3 and the neurokinnin receptor, NK1 (Sanger & Andrews, 2006, p. 8)

Once any of the above mentioned stimuli are encountered, an afferent response as discussed above is generated. This results in the activation of the chemoreceptor trigger zone in the area posterema. Subsequently, a motor response is generated, whereby efferent pathways involving the cranial nerves V, VII, IX and X are activated. Moreover, autonomic responses are also generated (Kuver, Sheffield, & McDonald, n. d.).

The vagal efferents to various muscle groups such as those located in the esophagus, stomach and the intestine are activated bringing about stimulation of these muscles (Sanger & Andrews, 2006, p. 6). Moreover, abdominal muscles, phrenic muscles and the diaphragm are also stimulated

to bring about the required increase in the intra-abdominal pressure. The combination of both these effects leads to the regurgitation of the gastric contents.

Moreover, this is also accompanied by various other manifestations such as an increase in salivation, brought about by the stimulation of the chorda tympani branch of the facial nerve, autonomic stimulation of the cardiovascular and respiratory systems and vasoconstriction of skin vessels (Sanger & Andrews, 2006, p. 6).

#### Antiemetic drugs used in pre-hospital care

Nausea and vomiting are commonly encountered clinical problems. Over the years, several anti-emetic medications have been discovered to effectively alleviate the symptoms of nausea and vomiting.

These drugs work by blocking the pathways involved in the initiation and production of emesis. Various drugs have been developed which block the different receptors, both central and peripheral, involved in producing emesis.

The anti-emetic medications which are used in common clinical practice can be grouped into seven major categories according to their mode of action. These include anti-cholinergics, antiserotonins, antihistamines, Benzamides, Butyrophenones, Phenothiazines and steroids (Scuderi, 2003, p. 43).

The mechanism of action and the dosages of the four main anti-emetics used in Ambulance Services in Australia are discussed below:

1. Metoclopramide (Maxolon):

Metoclopramide has been used in clinical practice for several decades now as an antiemetic and a prokinetic agent (Walkembach, Bruss, Urban, & Barann, 2005, p. 50). These antiemetic functions are thought to be brought about by the antagonistic actions of Metoclopramide on the dopamine (D2) receptors, both central and peripheral, and also on the 5HT3 receptors (Walkembach, Bruss, Urban, & Barann, 2005, p. 50).

On the other hand, the prokinetic action of Metoclopramide are brought about by the relaxation of the pyloric sphincter, the increase in the strength and frequency of peristalsis and an increase in the tone of the lower esophageal sphincter (Australasia, 2008).

This drug is available in both tablet (white, round, 7mm in diameter) and injection (colorless, aqueous solution) forms (Australasia, 2008). The maximum dose of Metoclopramide commonly used in all age groups is up to 0.5 mg/kg body weight.

The recommended dosage regimen for adults is 10mg three times daily while for children it varies between 2.5mg-5mg three times daily (Australasia, 2008). The metabolism of Metoclopramide takes place in the liver and it is eliminated from the body predominantly via the kidney. (Australasia, 2008)

## 2. Prochlorperazine (Stemetil)

Prochlorperazine is a phenothiazine which has been shown to block the dopamine receptors (D2) in the chemoreceptor trigger zone located near the area postrema. By blockage of these receptors, Prochlorperazine exerts its antiemetic actions. The recommended dosage of Prochlorperazine is 10

mg intravenously (Goodman and Gilman's: The Pharmacologic Basis of Therapeutic cited in Ernst, Weiss, Park, Takakuwa, & Diercks, 2000, p. 92).

In emergency practice, IV administration of 2. 5-10 mg of Prochlorperazine at a rate of up to 5mg/min is recommended for adults. The maximum dose should not exceed 40mg per day. Moreover, IM injections of this drug are also available. They are administered at a dose of 5-10 mg every 3-4 hours (Bartlett, 2009, p. 861).

### 3. Ondansetron (Zofran)

Ondansetron is a carbazole derivative and is a potent antiemetic drug which is widely used in alleviating the symptoms of nausea and vomiting associated with chemo- and radio- therapies and also in the management of post-operative nausea and vomiting (Scuderi, 2003, p. 59). Its proposed mechanism of action is via selective antagonism at the level of the 5 HT<sub>3</sub> receptors (Scuderi, 2003, p. 59).

Chemotherapeutic agents are thought to bring about nausea and vomiting via the stimulation of enterochromaffin cells in the gut mucosa leading to 5HT<sub>3</sub> production and subsequent vagal stimulation. This pathway is blocked by 5HT<sub>3</sub> antagonists such as Ondansetron.

Ondansetron has been shown to have a short half life of approximately 3 to 5 h (Ho & Gan, 2006, p. 607). The recommended dosage of Ondansetron varies between 8-16 mg twice daily (Bartlett, 2009).

### 4. Promethazine (Phenergan)

Promethazine is also a phenothiazine but is shown to have dual modes of action. It not only blocks the dopamine receptors (D<sub>2</sub>) but has also been  
<https://assignbuster.com/advanced-paramedical-science/>



shown to have anti-H1 histamine receptor effects. It is used for a wide range of purposes including in the treatment of motion sickness, vertigo and even allergies (Bartlett, 2009, p. 869).

The recommended oral dose of Promethazine is 25 mg twice daily. It can also be administered intravenously at a dose of 12.5-25 mg every four hours. The maximum dose is 150 mg/day (Bartlett, 2009, p. 869).

## PART II

There are several clinical conditions which can present with the symptoms of nausea and vomiting. Amongst these the most common condition is gastroenteritis, migraines and pancreatic amongst others.

The adequate and timely management of patients with nausea and vomiting has posed a challenge for the clinicians for several decades and although several effective anti-emetics have been discovered, there has been a quest for a single anti-emetic which is efficient, fast acting and relatively safe.

In the practice of ambulance services and emergency situations, different anti-emetics are commonly used including Metoclopramide, Chlorpromazine, Ondansetron and Promethazine. Amongst these, in my opinion, the most suitable drug for use in the ambulance service and emergency departments is Metoclopramide.

This is because on comparing the onset of action, clinical efficacy and side effect profiles of the most common anti-emetic agents, it is apparent that Prochlorperazine is superior to all other agents used. Moreover, its cost, availability and easy administration make it suitable for use in the

emergency practice. Following is a comparison of the four most commonly used anti-emetic drugs.

A common concern with the use of any drug is its safety and side effect profile. Safety becomes more important while dealing with patients in the emergency or ambulance care since limited resources, time and personnel are available in such settings, and the prime concern is the stabilization of the patient and alleviation of his symptoms.

Drugs which have potentially unsafe need to be administered with caution and the patients need to be monitored for the occurrence of adverse effects. This is not feasible in emergency and ambulance practice and thus the ideal drugs for use in such settings are those which have no or minimal side effects.

With Metoclopramide, there is a 10-20% incidence of side effects and these side effects are mild. The most common side effects observed with this drug are CNS effects such as anxiety, restlessness and insomnia which can vary in severity (Australasia, 2008).

Moreover, it has also been shown to cause fatigue and occasionally can cause extrapyramidal side effects. Another relatively common side effect of Metoclopramide is gynecomastia which occurs as a result of enhanced prolactin secretion (Kuver, Sheffield, & McDonald, n. d.).

A rare complication associated with the use of Metoclopramide is Neuroleptic Malignant Syndrome which is a medical emergency and can lead to death. However, it is observed in only less than 1 in 10, 000 cases (Australasia, 2008) .

On the other hand, the phenothiazines including Prochlorperazine and Promethazine have been shown to have a greater number of side effects. Amongst these the ones which arouse the most concern are extrapyramidal symptoms.

Extrapyramidal symptoms can range from tremor to akathisia and the potentially hazardous tardive dyskinesias (Australia, 2009). Moreover, they can also manifest as dystonic reactions are similar to the manifestations of Parkinson's disease. Less commonly, Neuroleptic Malignant Syndrome, which is a medical emergency, can also result from the use of these drugs.

These effects are thought to be caused due to the central antidopaminergic properties of the phenothiazines on the dopamine receptors. The occurrence of these symptoms is noticed most commonly within 36 hours of initiation of treatment. However, these symptoms are reversible and once the drug is discontinued, they disappear within 24 hrs (Australasia, 2008).

It is important to note that with Metoclopramide, the occurrence of extrapyramidal side effects is not very common. On the other hand, the phenothiozones such as Prochlorperazine and Promethazine have a much greater incidence of these side effects.

Drotts and Vinson (1999) in their study showed that with the use of Prochlorperazine, incidence of akathisia was 44% within 1 hour and 5% within 48 hours. (Braude, Soliz, Crandall, Hendey, Andrews, & Weichenthal, 2006, p. 181). Other studies, such as those of Ernst et. al., have supported these findings.

These extrapyramidal symptoms, if severe, have to be treated with intravenous infusions of an anti-cholinergic agent such as diphenhydramine (Ernst, Weiss, Park, Takakuwa, & Diercks, 2000, p. 92).

Other common side effects of phenothiazines include constipation, blurred vision, mild elevation of the hepatic enzymes (if the patient develops cholestatic jaundice), ECG changes, arrhythmias and hypotension (Australia, 2009).

Hypotension in patients who are already dehydrated due to vomiting can lead to significant patient distress and is also important from the point of view of healthcare professionals, as it poses difficulties in patient management in emergency and ambulance settings. Moreover, most phenothiazines, in particular Promethazine are known to cause sedation due to histamine blockade.

Promethazine has also been shown to reduce the seizure threshold. Due to the multitude of serious adverse effects of Promethazine the Food and Drug Administration (FDA) has restricted its use in children under two years of age (DeCamp, Byerley, Doshi, & Steiner, 2008, p. 859).

As compared to Metoclopramide, Ondansetron has relatively lesser side effects. The most commonly encountered adverse effects of this agent include headaches, constipation and mild elevation of serum transaminases (Kuver, Sheffield, & McDonald, n. d.).

But this drug is not preferred over other anti-emetic agents due to its cost and availability issues (Ernst, Weiss, Park, Takakuwa, & Diercks, 2000, p. 92). Moreover, it is used more commonly to prevent post-operative nausea and

vomiting and in patients receiving chemotherapy and its role in acute settings has not been extensively studied.

Pregnancy is one of the most common conditions which present with nausea and vomiting. Amongst the commonly available anti-emetics only a few are safe to use in pregnancy.

Studies have shown Metoclopramide to be safe for use during pregnancy and this drug has not been shown to cause any long term complications in children of mothers using it during pregnancy (Sørensen, Nielsen, Christensen, Tage-jensen, Ekbom, & Baron, 2000). Similarly the safety of Ondansetron has also been proven by several studies conducted recently (Einarson, Maltepe, Navioz, Kennedy, Kennedy, & Koren, 2004, p. 940).

However, both Promethazine and Prochlorperazine belong to Category C and thus have limited use in pregnancy (Australia, 2009).

Another advantage of Metoclopramide is its ability to provide faster relief from the symptoms of nausea and vomiting. Metoclopramide has been shown to have a rapid onset of action. Following IV administration, its effects start manifesting in around 1 to 3 minutes, whereas following intramuscular administration, 10 to 15 minutes is required (Australasia, 2008). This rapid action makes it suitable for use in emergency practice,

Although there is a paucity of studies comparing the cost effectiveness of Metoclopramide with other antiemetics, studies comparing the cost-effectiveness in patients undergoing chemotherapy have shown that Metoclopramide to be more cost effective than Ondansetron (Ballatori, et al., 1994).

Thus, in conclusion, keeping the side effect profiles, the availability and cost effectiveness of all the anti-emetics in view, in my point of view Metoclopramide is best suited for use in ambulatory settings. Metoclopramide has several benefits over other anti-emetics.

It has a fast onset of action which makes its practical for use in emergency settings. Moreover, it has lesser and milder adverse effects as compared to other anti-emetics. In addition, it can be used in all age groups and is safe in pregnancy. Thus, all these properties make Metoclopramide ideal for use in ambulatory care settings.

#### References

Australasia, V. P. (2008, October 22). Metoclopramide hydrochloride-Data sheet. Retrieved May 1, 2009, from Medsafe-INFORMATION FOR HEALTH PROFESSIONALS: <http://www.medsafe.govt.nz/Profs/datasheet/m/Maxolontabsyrinjsupp.htm>

Australia, S.-A. (2009). Sanofi-Aventis Australia. Retrieved May 1, 2009, from Product Information: [http://www.sanofi-aventis.com.au/products/aus\\_pi\\_phenergan.pdf](http://www.sanofi-aventis.com.au/products/aus_pi_phenergan.pdf)

Ballatori, E., Roila, F., Berto, P., De Angelis, V., Neri, C., Olivieri, A., et al. (1994). Cost and cost-effectiveness analysis of ondansetron versus metoclopramide regimens: a hospital perspective from Italy. *Pharmacoeconomics* , 227-37.

Bartlett, J. &. (2009). 2009 Nurse's Drug Handbook . Jones & Bartlett .

Bowen, R. (n. d.). Physiology of Vomiting. Retrieved May 1, 2009, from The Stomach: <http://www.vivo.colostate.edu/hbooks/pathphys/digestion/stomach/vomiting.html>

Braude, D., Soliz, T., Crandall, C., Hendey, G., Andrews, J., & Weichenthal, L. (2006). Antiemetics in the ED: a randomized controlled trial comparing 3 common agents. *American Journal of Emergency Medicine* , 177-182.

DeCamp, L. R., Byerley, J. S., Doshi, N., & Steiner, M. J. (2008). Use of Antiemetic Agents in Acute Gastroenteritis: A Systematic Review and Meta-analysis. *Archives of pediatric and adolescent medicine* , 858-865.

Drotts, D. L., & Vinson, D. R. (1999). Prochlorperazine Induces Akathisia in Emergency Patients. *Annals of Emergency Medicine* .

Einarson, A., Maltepe, C., Navioz, Y., Kennedy, D., Kennedy, D., & Koren, G. (2004). The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. *BJOG: an International Journal of Obstetrics and Gynaecology* , 940-943.

Ernst, A. A., Weiss, S. J., Park, S., Takakuwa, K. M., & Diercks, D. B. (2000). Prochlorperazine Versus Promethazine for Uncomplicated Nausea and Vomiting in the Emergency Department: A Randomized, Double-Blind Clinical Trial. *Annals of Emergency Medicine* , 89-94.

Ho, K.-Y., & Gan, T. J. (2006). Pharmacology, pharmacogenetics, and clinical efficacy of 5-hydroxytryptamine type 3 receptor antagonists for postoperative nausea and vomiting. *Current Opinion in Anaesthesiology* , 606-611.