

## POSTOPERATIVE NAUSEA AND VOMITING

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### Introduction

Postoperative nausea and vomiting (PONV) are among the most common adverse events following surgery, anaesthesia and opioid analgesia. Although usually of minor medical impact, they can cause a lot of distress, lead to delayed hospital discharge and increased use of resources. The aetiology of PONV is multifactorial, involving physiological, pathological and pharmacological factors. It is more common in women than men and in younger patients. Its incidence is difficult to estimate, but may be as high as 60-70%, particularly when the “older” anaesthetic agents are used, compared to around 30% when using anaesthetics such as propofol and isoflurane. Despite the use of such agents, it may remain high in certain high-risk groups of patients.

As there is no “magic bullet” that will prevent PONV in all patients, the clinician should attempt to identify and minimize contributing factors and employ any anti-emetic techniques

available to them in those patients considered to be high-risk.

The aims of this article are to:

- Define nausea and vomiting
- Outline the anatomy and physiology of nausea and vomiting
- Identify who is at greater risk of PONV
- Review the pharmacological and other associated techniques used to manage PONV

### Definitions

- Nausea is the subjective sensation of the need to vomit.
- Vomiting is a forced expulsion of stomach and gastrointestinal contents through the mouth.

### Anatomy and Physiology

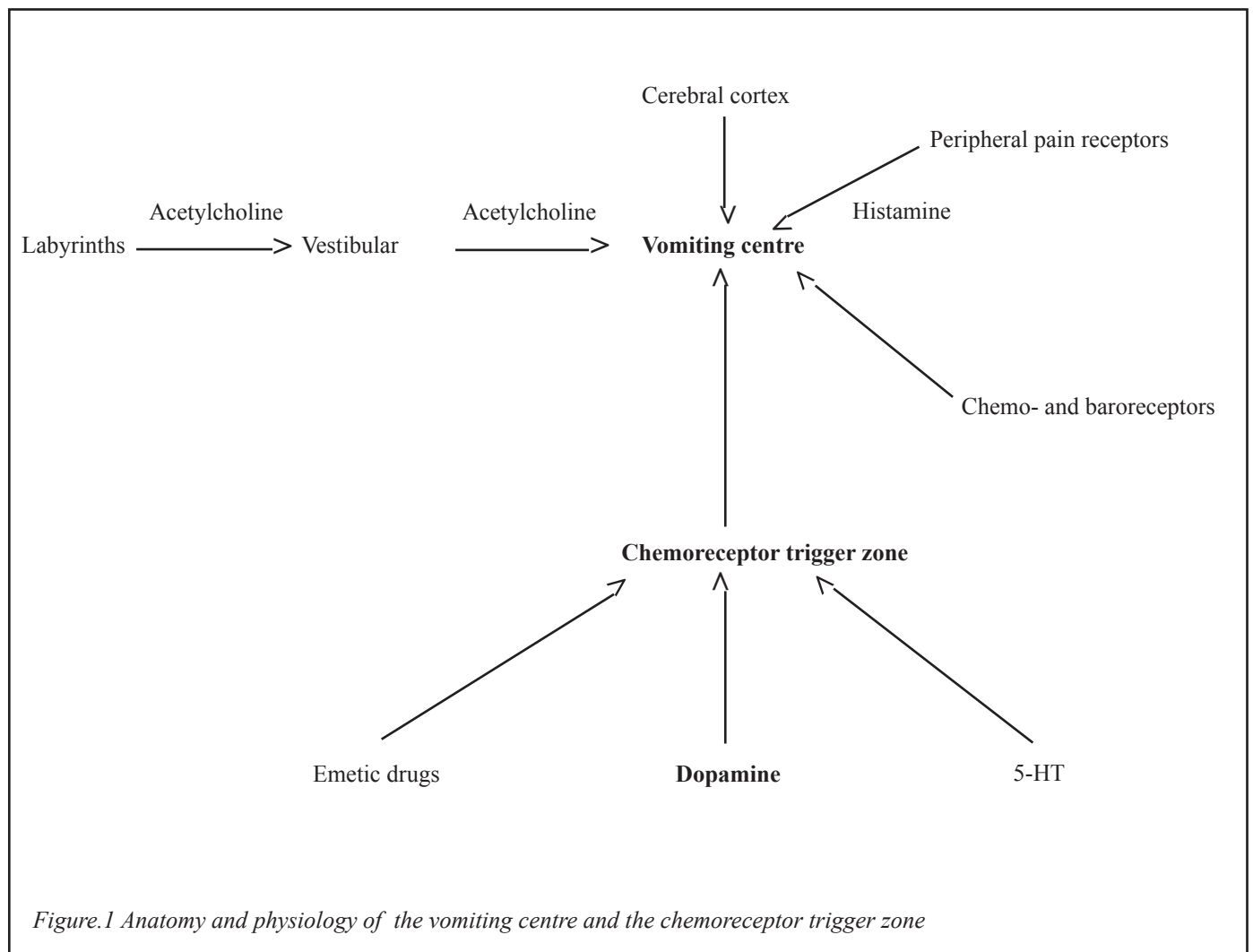


Figure.1 Anatomy and physiology of the vomiting centre and the chemoreceptor trigger zone

It is generally accepted that an indiscrete area located in the lateral reticular formation of the medulla, known as the vomiting centre, is responsible for controlling and coordinating nausea and vomiting. A complex range of interactions occurs here, between the reticular formation, the nucleus tractus solitarius and certain autonomic nuclei, especially of the vagus nerve. The centre also receives a wide range of afferent inputs (figure 1); from receptors in the gastrointestinal tract, peripheral pain receptors (responsible for the nausea that may accompany trauma), the nucleus solitarius (involved in the “gag” reflex), vestibular system (involved in motion sickness), the cerebral cortex and the chemoreceptor trigger zone (CTZ). The neurochemistry of the vomiting center is complicated, with some 40 neurotransmitters being implicated. Two that are believed to be particularly important are acetylcholine and histamine hence drugs that antagonize these substances have a central effect on PONV.

The CTZ is a group of cells situated close to the area postrema on the floor of the fourth ventricle. This area is extremely vascular and is situated outside the blood-brain-barrier making it vulnerable to circulating drugs and toxins. It is thought to have a major impact on the activity of the vomiting centre. The CTZ is also sensitive to systemic stimuli and is linked with the control of blood pressure, food intake and sleep. Two important neurotransmitters located here are dopamine and 5-hydroxytryptamine (5-HT, serotonin) and antagonists of these will have an indirect effect on the vomiting center (Figure 1) to reduce nausea and vomiting.

Thus antagonists of four neurotransmitters, acetylcholine, histamine, dopamine and 5-HT, have acquired much interest in the development of the pharmacological treatment of nausea and vomiting, and most of the currently used anti-emetic drugs are antagonists at one of these receptors.

Vomiting is the result of a complex reflex and the combination of the autonomic and motor nervous systems, with efferents from the vomiting center relaying to the vagus and motor neurons that supply the abdominal muscles. The vomiting process starts with deep inspiration, reversed peristalsis moving contents from the upper small bowel into the stomach and an increase in salivation. The glottis closes to protect the airway, the breath is held and the gastric sphincter and oesophagus relax. The muscles of the abdominal wall and thorax contract, and the diaphragm descends vigorously, increasing the intra-abdominal pressure and the gastric contents are ejected into the oesophagus and out through the mouth.

### Who is at Risk of PONV?

As already indicated, the aetiology of PONV is multi-factorial. Specific factors that are known to increase the risk relate to:

- The patient
- The type of surgery performed
- The anaesthetic technique used

**Patient Factors.** The following groups have been identified as having a greater requirement for postoperative anti-emetic drugs:

- Female patients

- Patients with a history of motion sickness
- Patients with a previous history of PONV
- Patients who are non-smokers

**Surgical Factors.** The following types of surgery are associated with a higher incidence of PONV:

- Gynaecology
- ENT
- Strabismus surgery
- Breast surgery
- Laparoscopy
- Laparotomy
- Craniotomy

**Anaesthetic Factors.** The following anaesthetic techniques are associated with an increase in PONV:

- The administration of opioids intra and postoperatively
- The use of nitrous oxide
- The use of volatile inhalational anaesthetics (e.g. ether)
- Some intravenous anaesthetics (e.g. ketamine and etomidate)

Postoperative factors. Pain, anxiety, hypotension and dehydration all contribute to nausea and vomiting.

Not surprisingly, females undergoing gynaecological procedures where opioids are used as part of the anaesthetic technique, have one of the highest incidences of PONV (up to 70%)! By taking into account the above factors and availability of local resources, a start can be made to try and reduce PONV.

### Pharmacological Treatment of PONV

It is interesting to note that of the drugs generally referred to as anti-emetics and used in the management of PONV, some have more anti-nausea and less anti-vomiting effects, whilst others have less anti-nausea and more anti-vomiting effects.

Pharmacological treatment of PONV is common, using a wide range of drugs, but with variable efficacy. The drugs are generally grouped according to the type of receptor at which they act, usually as an antagonist.

The following text describes the various groups of drugs conventionally used in the treatment of PONV, and their contraindications. Doses and routes of administration can be found in Table 1.

#### Anticholinergic (antimuscarinic) drugs

Anticholinergic drugs that can cross the blood-brain barrier, will act directly on the vomiting center and have anti-emetic properties. This is the oldest group of drugs used to treat nausea and vomiting, although this was not their original intention. Atropine was used to block the vagal effects of chloroform and later used for its drying effect on salivary secretions during ether anaesthesia. It was subsequently replaced by hyoscine (Scopolamine). Both are still used to treat nausea and vomiting, with hyoscine being

Table 1. Anti-emetics; doses and routes of administration

Drug	Group	Dose, Route & Frequency
Atropine	Anticholinergic	0.3 - 0.6mg im or iv, 30 - 60mins pre-op
Hyoscine	Anticholinergic	0.2 - 0.4mg sc or im, 6 hourly 1mg transdermal patch, lasts upto 72hrs
Cyclizine	Antihistamine	50mg orally, im or iv, 8 hourly
Promethazine	Antihistamine	25mg orally, 100mg max in 24hrs
Prochlorperazine	D <sub>2</sub> antagonist	12.5mg orally or im, 6 hourly 25mg rectally as initial dose 3mg buccal preparation is available
Droperidol	D <sub>2</sub> antagonist	0.5 - 1.25mg iv, 8 hourly 2.5 - 5mg orally, 8 hourly
Metoclopramide	D <sub>2</sub> antagonist	10mg im or iv, 6 hourly
Domperidone	D <sub>2</sub> antagonist	10 - 20mg orally, 60mg max in 24hrs 60mg rectally, 4 - 8 hourly
Ondansetron	5-HT <sub>3</sub> antagonist	4 - 8mg orally, im or iv, 24mg max in 24hrs 16mg orally, 1hr pre-op as a one-off dose
Granisetron	5-HT <sub>3</sub> antagonist	1mg iv, 2mg max in 24hrs
Dexamethasone	Corticosteroid	6 - 10mg iv, preferably in combination (see text)

the more potent and effective. They are most effective against motion sickness, labyrinthine disease, vestibular disorders, after surgery in the posterior fossa and to counter the emetic effects of opioids. However, as a result of antimuscarinic actions, side effects include sedation, dry mouth, blurred vision and urinary retention, all more common after hyoscine. Contraindicated in closed angle glaucoma.

### Antihistamines

This group of drugs is similar to the above in that they act on the vomiting center antagonizing the histamine (H<sub>1</sub>) receptors. They are effective in the treatment of motion sickness, the management of labyrinthine disorders and to counter the emetic effects of opioids. In the UK, the most commonly used drug is cyclizine. Alternatives include promethazine. Side effects include mild sedation along with antimuscarinic effects. Cyclizine is contraindicated in acute myocardial infarction as it can aggravate severe heart failure and counteract the beneficial effects of the opioids. The sedative effects of antihistamines are additive with that produced by anaesthetic agents, and hence care must be taken with their use. Promethazine is said to have a slight antanalgesic effect.

### Dopamine antagonists

There is a wide range of drugs that antagonize dopamine (D<sub>2</sub> receptors) at the CTZ and therefore have antiemetic properties. These include the phenothiazines, butyrophenones, metoclopramide and domperidone.

**Phenothiazines.** Prochlorperazine (Stemetil) is more commonly used in the UK as an anti-emetic than chlorpromazine, due to the latter is more marked sedation and drowsiness. Both can produce

extrapyramidal side effects and acute oculogyric crises can occur with high doses and prolonged treatment. The neuroleptic malignant syndrome (catatonia, cardiovascular instability, hyperthermia and myoglobinemia - mortality in excess of 10%) has been reported in association with prochlorperazine.

**Butyrophenones.** This group of drugs was originally developed to treat major psychoses (eg schizophrenia) and includes haloperidol and droperidol. The latter was widely used as a component of "neurolept anaesthesia", but associated with unpleasant side effects including extrapyramidal symptoms, hypotension, hypothermia and unpleasant hallucinations. However, in much smaller doses it has been shown to be a very effective anti-emetic when administered orally or intravenously. Unfortunately, it is no longer manufactured for use in the UK. Droperidol is pharmaceutically incompatible with thiopentone and methohexitone.

**Metoclopramide.** In addition to having an effect on the CTZ, metoclopramide has prokinetic actions on the gut, promoting gastric emptying and increases the barrier pressure of the lower oesophageal sphincter (by about 17mmHg). Although widely used as an anti-emetic evidence for its efficacy in treating PONV is limited. It is perhaps best reserved for use preoperatively in those cases where there is evidence for delayed gastric emptying or patients at risk of gastro-oesophageal reflux. Extrapyramidal side effects can occur. Not recommended following gastrointestinal surgery involving anastomoses.

The neuroleptic malignant syndrome has been reported in association with metoclopramide.

**Domperidone.** Similar to metoclopramide, but does not cross the blood-brain-barrier and therefore not associated with sedation or

extrapyramidal side effects. Not effective against motion sickness. It can cause cardiac arrhythmias in large doses.

### **5-HT<sub>3</sub> receptor antagonists**

This is the most recently introduced (and therefore the most expensive) group of anti-emetics available. Although it is thought that their main action is to antagonize 5-HT<sub>3</sub> receptors that are found in a high concentration in the CTZ, they may also have a peripheral effect. Ondansetron is the most commonly used and appears effective when used orally preoperatively and intravenously for PONV. It is well tolerated with few side effects, headache being the most commonly reported. It appears to produce greater anti-vomiting effects than anti-nausea effects. Recently, more potent 5-HT<sub>3</sub> receptor antagonists have been introduced mainly for use in chemotherapy induced nausea and vomiting, but granisetron has been shown to be effective in treating PONV.

### **Other drugs used for anti-emesis**

Dexamethasone has been shown to be anti-emetic in a dose of 10mg in adults. It appears to be of most use in combination with a 5-HT<sub>3</sub> receptor antagonist, working via an additive or even synergistic effect.

### **Which drug shall I use?**

When using drugs to prevent or treat PONV, find out what is available, then consider what to use, when to use it and how to use it.

The first thing is to know what is available to use. For instance, droperidol is being removed from the formulary in the UK, and 5-HT<sub>3</sub> receptor antagonists are too expensive to be considered in many parts of the World.

Everything else being equal it has been shown that ondansetron is as effective as droperidol, and that both are more effective than metoclopramide. However the administration of one receptor antagonist will reduce the incidence of PONV by only 30%, but a combination anti-emetic therapy (typically a 5-HT<sub>3</sub> receptor antagonist with droperidol or dexamethasone) can achieve a response rate of up to 90%. What to use will also depend upon what are you treating. Ondansetron has more anti-vomiting than anti-nausea properties, dopamine receptor antagonists have more anti-nausea properties than they do anti-vomiting properties.

When should drugs be prescribed? It has been shown that the "number needed to treat" (i.e.; the number of patients you need to treat before the treatment is effective for one of them) with anti-emetics ranges from 5 for ondansetron to more than 10 with metoclopramide. Thus if everyone received anti-emetic prophylaxis, 80% of patients would still be at risk of PONV. The benefit of this has to be weighed up against the exposure to potential side-effects.

It can be seen therefore that the prevention and treatment of PONV using drugs alone is not especially effective. It would appear to make sense to identify those patients at high risk and firstly try to use an anaesthetic technique or anaesthetic agents associated with less nausea and vomiting and supplement this with anti-emetic agents as required.

### **Use of anti-emetics in pregnancy**

The use of anti-emetics in pregnancy is controversial because of the risks of fetal teratogenicity, especially during the first trimester. Unfortunately, the incidence of nausea and vomiting in pregnancy is extremely high (nausea affects between 75 - 85% of women, and vomiting about 50%). In its most severe form, hyperemesis gravidarum, it can lead to dehydration, hyponatraemia, hypokalaemia, metabolic hypochlorhaemic alkalosis, ketonuria and loss of bodyweight. Although initial management consists of intravenous fluid and electrolyte replacement, anti-emetic therapy often has to be added.

Evidence - based reviews suggest that pyridoxine (vitamin B6), antihistamines (H<sub>1</sub> blockers), phenothiazines, ginger root extract and acupuncture are safe for use in pregnancy with variable efficacy. Metoclopramide, droperidol and ondansetron may be effective, but there are insufficient safety data to recommend them as first-line therapy.

Anaesthesia as a cause of nausea and vomiting in labour commonly relates to the hypotension associated with the use of central neural blockade. In these situations nausea and vomiting are often an indication of cerebral hypoperfusion, secondary to hypotension. It can usually be overcome by elevating the blood pressure to normal limits by the judicious use of fluid boluses or vasoconstrictor drugs such as ephedrine or phenylephrine. Surgery may also contribute, particularly exteriorizing the uterus or excessive traction on the bowel or mesentery. Although atropine may help the answer lies in the hands of the surgeon!

### **Non-pharmacological treatments of PONV**

Ginger root has been postulated as an anti-emetic but a systematic review of the available evidence has only shown it to be as effective as metoclopramide, and not significantly different from placebo.

Acupuncture at the Pericardium 6 point (5cm proximal to the palmar aspect of the wrist, between the flexor carpi radialis and palmaris longus tendons) has been shown to be effective in treating early PONV, with a number needed to treat of 5.

Perioperative hypnosis has been demonstrated to reduce PONV following breast surgery.

### **The choice of anaesthetic technique in the prevention of PONV**

It has already been stated that anaesthetic factors contribute to PONV. From the above list, the ideal anaesthetic technique would consist of avoiding opioids, nitrous oxide and volatile anaesthetic agents, and result in no pain, anxiety, hypotension or dehydration!

- **Omitting nitrous oxide.** Fifteen percent of patients receiving nitrous oxide will experience nausea and vomiting and omitting it from a general anaesthetic has been proven in three systematic reviews to reduce the incidence of PONV. This was also most pronounced in high-risk patients, with a number needed to treat of 5. However, there was also an increase in the incidence of awareness.

- **Omitting reversal of neuromuscular blockade.** Neostigmine increases salivation, lower oesophageal and gastric tone, gastric acid output and lower gastrointestinal tract motility, thus nausea

and vomiting may occur. Omitting anticholinesterase drugs at the end of surgery may decrease the incidence of PONV, but only in doses greater than 2.5mg of neostigmine. There is a concomitant risk residual neuromuscular block with all the attendant risks.

- Propofol appears to possess intrinsic antiemetic properties, possibly by the antagonism of dopamine D<sub>2</sub> receptors. It has been used in the treatment of refractory nausea and vomiting in chemotherapy patients. When used for induction and maintenance there is a reduction in the incidence of PONV, with a number needed to treat of 5. Induction alone has no influence. Total intravenous anaesthesia with propofol is an expensive option, both in terms of the cost of the propofol itself, and the equipment required.

- Ether is one of the most emetogenic of all the inhalational anaesthetic agents. It has been reported as being associated with an over-all incidence of PONV in excess of 80% of patients. It seems to be worse when high inspired concentrations are used, or when administered over prolonged periods. Ether is therefore best avoided, but if it has to be used, then the lowest concentrations for the shortest period of time should be used.

- Regional Blockade is a useful technique in the prevention of PONV. When used as the sole technique, opioids can be avoided thereby reducing the risk of PONV. If a technique is used with an in-dwelling catheter (for example an epidural), opioids may also be avoided postoperatively. If a regional technique is used in combination with general anaesthesia, both opioids and nitrous oxide can still be avoided and therefore provides a better bet than general anaesthesia using opioids. However, it is essential when using regional anaesthesia, in particular any form of central

neural block to avoid hypotension and ensure hydration, otherwise perioperative nausea and vomiting will still be an issue.

Therefore an anaesthetic technique that reduces anxiety by using an appropriate premedicant along with reassurance at the preoperative visit, avoids opioids and pain using alternative analgesics for example local or regional anaesthesia and substitutes total intravenous anaesthesia for nitrous oxide and volatile anaesthetic agents, avoids reversal of neuromuscular blockade and results in a warm, well hydrated normotensive patient, would be ideal to minimise the incidence of PONV, especially in the high risk patient.

**Cost-effectiveness of anti-emetics**

The result of cost-effectiveness trials has shown that treatment of PONV with ondansetron is more cost-effective than prophylaxis with ondansetron in all patients. However, the pre-emptive treatment of high risk patients with droperidol is cost-effective and leads to greater patient satisfaction.

**Future development**

Future development in anti-emesis is looking at the neurokinin 1 (NK-1) receptor, where substance P is the natural ligand. This receptor is found in the nucleus tractus solitarius and the area postrema, as well as the peripheral nervous system. Early

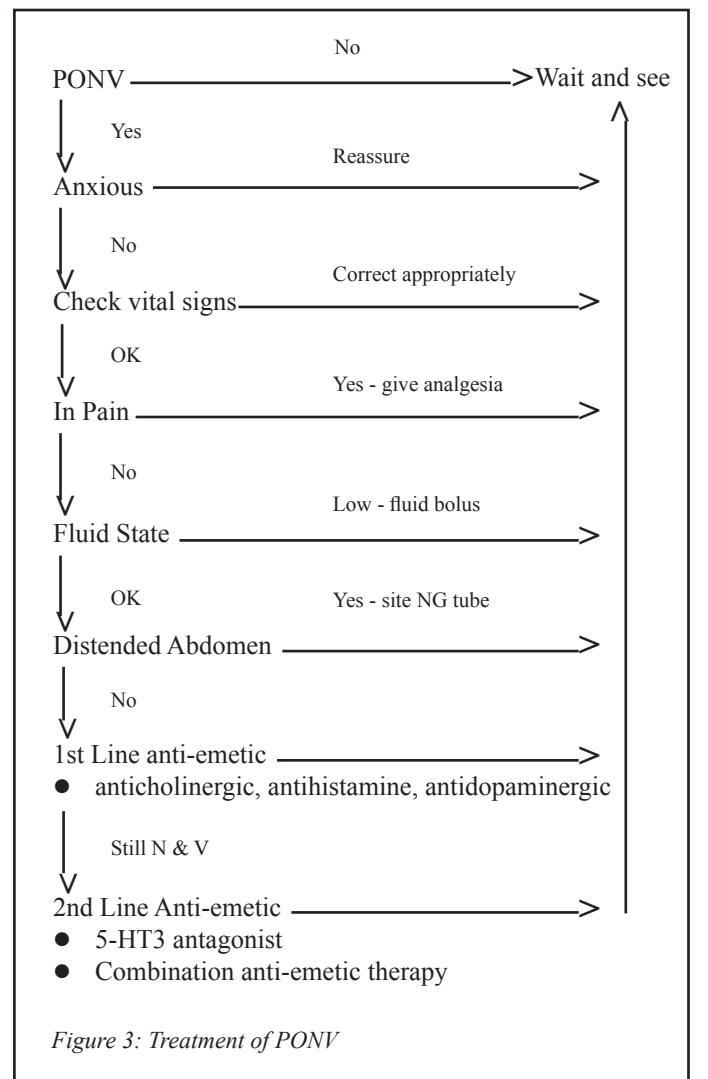
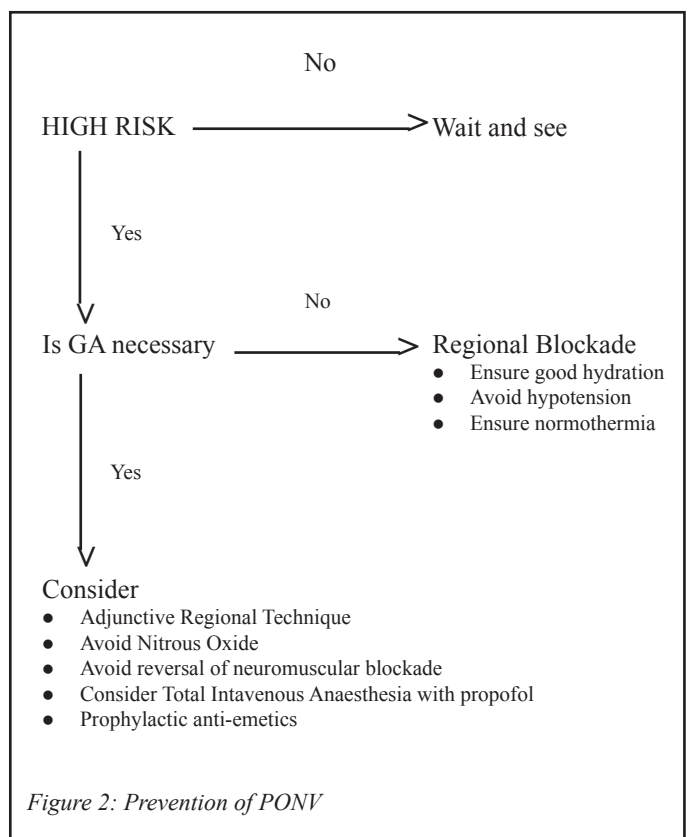


Figure 2: Prevention of PONV

Figure 3: Treatment of PONV

studies of NK-1 antagonists have been promising, especially in combination with ondansetron.

Development of new non-opioid analgesia will help to decrease PONV in the future.

### Conclusion

Despite an improvement in the incidence of PONV with modern pharmacology and techniques, there is still no "Gold Standard". This affects both patients and research, such that a new anti-emetic strategy has no ideal to compare with. Thus we are left with numerous approaches to the problem, with no satisfactory answer. When considering the problem on a World scale where funds are limited, it would appear that the best strategy is first to identify the high risk patients. Once these patients are known an anaesthetic technique should be employed that avoids as many emetogenic factors as possible, combined with combination anti-emetic drug therapy. Thus providing a balanced anti-emetic technique (Figure 2). It would appear that for low risk patients, the most cost effective plan is to "wait and see", and treat as required (Figure 3).

### Further Reading

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