

# Post-operative nausea and vomiting

In the seventh article of a series on peri-operative care, **Mohamed H. Rahman** and **Jane Beattie** give an overview of the causes and risk factors, and the pharmacological management of post-operative nausea and vomiting

**P**ost-operative nausea and vomiting (PONV) is a common complication of surgery and anaesthesia. Although it is rarely fatal, PONV is unpleasant and associated with patient discomfort, and dissatisfaction with their peri-operative care. Patients have reported that avoidance of PONV is of greater concern than avoiding post-operative pain. PONV is also associated with delayed discharge from the recovery room and prolonged hospital care and, therefore, increases health care costs.

Morbidity associated with PONV includes wound dehiscence, dehydration, electrolyte disturbance, interference with nutrition and, more rarely, oesophageal rupture (Boerhaave syndrome) or aspiration pneumonitis.

It is important that staff involved in caring for surgical patients understand PONV. A questionnaire-based study in 2000 demonstrated knowledge gaps, with only 60 per cent of ward nurses questioned giving correct responses.<sup>1</sup>

## Physiology

Nausea is the sensation associated with the awareness of the urge to vomit. Vomiting is the forceful expulsion of upper gastrointestinal contents via the mouth, brought about by powerful sustained contraction of the abdominal muscles. Both are protective reflexes against the absorption of toxins (which trigger chemoreceptors in the gastrointestinal tract) but can also occur in response to olfactory, visual, vestibular and psychogenic stimuli.

Nausea is not well understood. It is associated with gastrointestinal relaxation, retroperistalsis in the duodenum, increased salivation, pallor and tachycardia. Vomiting and retching (repeated attempts to vomit without stomach contents being expelled) are brainstem responses; nausea involves higher brain regions.

Vomiting begins with deep breaths, closure of the glottis and elevation of the soft palate. The diaphragm then contracts strongly and the abdominal muscles contract to raise the intra-gastric pressure. This causes forceful ejection of gastric contents up the oesophagus and out of the mouth.

The exact nature of vomiting pathways are also not fully understood but a number of pathophysiological mechanisms known to cause nausea or vomiting have been identified.

The main coordinator is the vomiting centre, a collection of neurones located in the medulla oblongata. This receives inputs from:

- The chemoreceptor trigger zone (CTZ) in the area postrema
- The vestibular system (which is associated with motion sickness and the nausea of middle ear diseases)
- The higher cortical centres within the central nervous system
- The vagus nerve (which brings signals from the gastrointestinal tract)
- The spinoreticular system (which promotes nausea associated with physical injury)
- The nucleus tractus solitarius (which completes the reflex arc of the gag reflex)

The CTZ is rich in dopamine and 5-hydroxytryptamine receptors, in particular D<sub>2</sub> and 5HT<sub>3</sub>. The CTZ is not protected by the blood brain barrier, so is particularly susceptible to circulating stimuli (eg, drugs and toxins). It can be affected by anaesthetic agents, opioids and humoral factors (eg, 5HT) released during surgery.

The vestibular system can stimulate PONV as a result of surgery involving the middle ear, or post-operative movement. Sudden movement of the patient's head after awakening leads to middle ear vestibular disturbance, and an increased incidence of PONV. Acetylcholine and histamine are involved in the transmission of signals from the vestibular system to the vomiting centre.

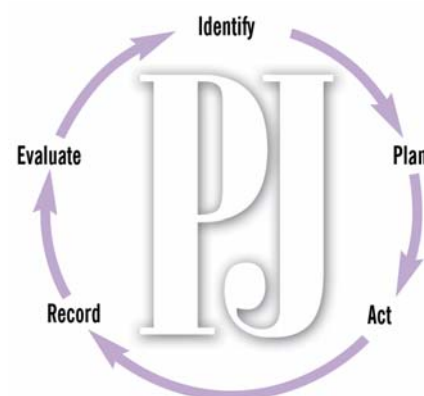
Higher cortical centres (eg, in the limbic system) can also be involved, especially if there is a history of marked PONV. They promote nausea and vomiting associated with unpleasant taste, sight, smell, memory and fear.

The afferent vagus nerve relays information from mechanoreceptors in the muscular wall of the gut (which releases 5HT when distended or damaged during surgery) and from chemoreceptors in the mucosa of the upper gastrointestinal tract (triggered by noxious substances in the luminal environment).

## Predisposing factors

The overall incidence of PONV is reported to be around 30 per cent but this can reach 70 per cent in high-risk patients. Among the many factors that influence PONV risk, four are well recognised:

- Being female
- Being a non-smoker
- Having a history of PONV
- Use of peri-operative opioid analgesia



## Identify knowledge gaps

1. What are the predisposing factors that contribute to PONV?
2. Which drugs can be used to manage PONV? Describe their modes of action.
3. Discuss the pathophysiology of nausea and vomiting.

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to "drug therapy in the context of overall patient and disease management" (see appendix 4 of "Plan and record").

In one study,<sup>2</sup> these factors were shown to be additive. The risk of PONV in the presence of no, one, two, three and all four risk factors was 10, 20, 40, 60 and 80 per cent, respectively.

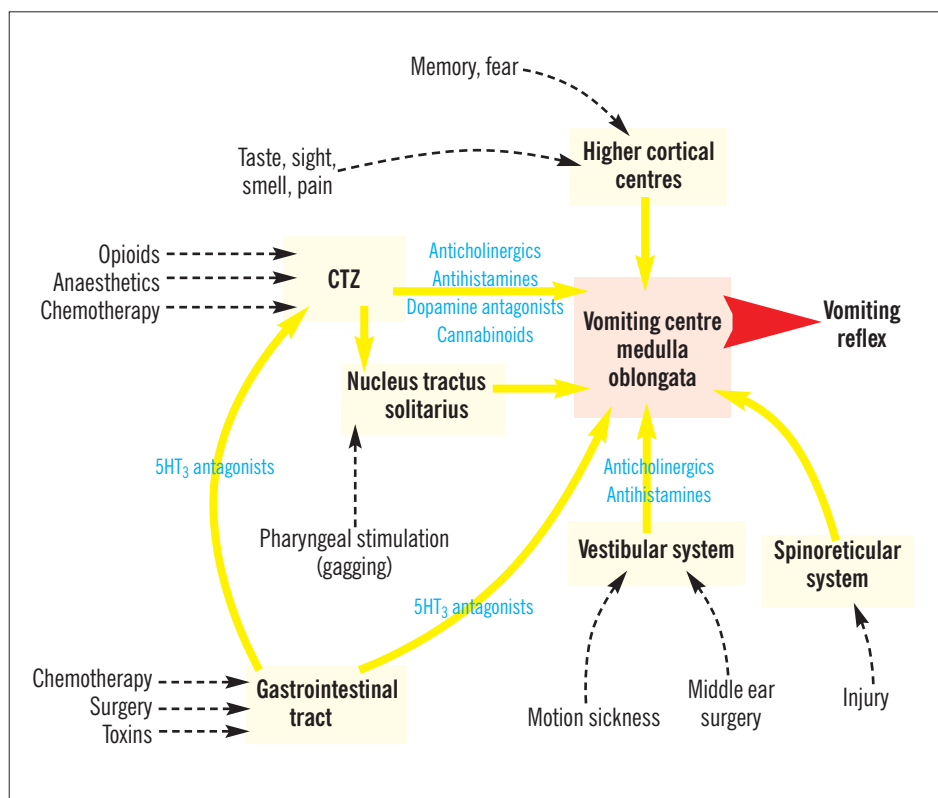
Females have a higher incidence of PONV than males and those of reproductive age suffer up to three times more often with PONV than men. This suggests a hormonal influence. Patients who have a history of motion sickness or previous PONV can have a well developed reflex arc for vomiting so are at an increased risk of PONV.

Opioids contribute to PONV via stimulation of the CTZ.

**Other patient-specific factors** Age is thought to play a role in risk of PONV and emesis occurs less frequently in elderly patients. Post-operative pain and the analgesia given to manage it, movement and ambulation, eating too early after surgery, hypotension and hypoxaemia can all contribute to PONV. Risk factors also include obesity and gastric stasis.

**Obesity** Studies have suggested an increased risk of PONV in obese patients, possibly

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**Figure 1: Vomiting pathways and drugs commonly used for nausea**

because of the longer time required to clear fat-soluble anaesthetic agents. Obese patients also have higher residual gastric volumes and an increased incidence of oesophageal reflux.

**Delayed gastric emptying** Delayed gastric emptying is also associated with increased incidence of vomiting. This delay can be due to pain, anxiety, disease process (eg, gastric outlet obstruction) or the administration of opioids. Pre-operative anxiety raises levels of endogenous catecholamines, which stimulate CTZ receptors. Anxious patients can also swallow air causing gastric distention, which contributes to PONV.

**Surgical factors** The type of surgery influences the incidence of PONV. Intra-abdominal surgery, ophthalmic surgery (particularly for strabismus), gynaecological surgery and middle ear surgery are all associated with higher rates of PONV. The high incidence of PONV following open abdominal or intra-abdominal laparoscopic surgery may be due to gut ischaemia releasing 5HT.

It has been suggested that the longer the surgery the greater the incidence of PONV, possibly due to post-operative ileus (associated with extensive bowel handling during surgery and bowel wall oedema in longer procedures). Adequate but not excessive hydration has been reported to reduce the incidence of PONV.

Orthopaedic surgery has a lower risk of PONV because there is less autonomic stimulation than during abdominal surgery and patients are more likely to receive a regional anaesthetic.

**Anaesthesia** The anaesthetic induction agent etomidate is associated with an increase in PONV compared with thiopental sodium or propofol. Propofol (for induction or maintenance of anaesthesia as part of a total intravenous anaesthetic technique [TIVA]) has been reported to reduce the risk of PONV.

Of the volatile inhaled anaesthetic agents, sevoflurane and desflurane are reported to be associated with lower rates of PONV than enflurane or halothane. Nitrous oxide increases the incidence of PONV. It affects central opioid receptors, causes changes in middle ear pressure and causes bowel distention.

The use of intubation is thought to increase risk of PONV because of pharyngeal mechanoreceptor afferent stimulation. Peripheral nerve blocks, total intravenous anaesthetic techniques and regional anaesthesia are all associated with a lower incidence of PONV than general anaesthesia with intubation and a traditional volatile agent dependent anaesthetic technique (see Resources).

Gastric inflation during mask ventilation can cause PONV because gaseous distention of the stomach and upper small intestine activates mechanoreceptors, sending afferent signals via the vagus nerve. If nitrous oxide is used, subsequent diffusion of the gas into spaces in the intestine worsens this situation. Avoidance of nitrous oxide during any anaesthetic can decrease the incidence of PONV, particularly in patients undergoing abdominal surgery.

It has been suggested that patients cared for by experienced anaesthetists have a lower incidence of PONV than those cared for by

inexperienced anaesthetists. Possible explanations include that inexperienced anaesthetists accidentally insufflate more gas into the stomach or do not give prophylactic antiemetics.

**Drugs** Many drugs given peri-operatively affect the incidence of PONV. For example, premedication with atropine or opioids (eg, morphine for analgesia) delays gastric emptying. Atropine also lowers oesophageal tone. Neostigmine, used to reverse residual muscle relaxation at the end of surgery, also increases the risk of PONV. Other common peri-operative drugs that can contribute to PONV include:

- Those with actions on the CTZ (eg, opioids, digoxin, cytotoxic chemotherapeutic drugs)
- Those causing gastrointestinal irritation (eg, non steroidal anti-inflammatory drugs, iron supplements)
- Those causing gastric stasis (eg, opioids, hyoscine butylbromide)

### Management of PONV

It is often easier to treat nausea and prevent vomiting than to stop vomiting once it has started. Identifying levels of risk helps staff to select appropriate action. Patients identified as low-risk do not usually need prophylaxis, unless there is risk of serious morbidity if vomiting does occur. Those at moderate or high risk of PONV will benefit from prophylaxis with an agent that prevents nausea and an appropriate anaesthetic technique. In some circumstances, such as where a patient has his or her jaws wired (eg, following maxillo-facial surgery) or has raised intracranial pressure, every effort must be made to avoid PONV.

Prophylaxis should include identification of risk factors for PONV, reducing them where possible and administering appropriate anti-emetic drug(s) at appropriate dose intervals. For example, opioids are highly emetogenic — they directly activate the CTZ, slow gastrointestinal motility and stimulate the vestibular nerve. Risk can, therefore, be reduced by substituting a non-opioid analgesic where appropriate. If opioids are necessary, the lowest possible doses should be used. Fentanyl and alfentanil are less likely to cause PONV than morphine and pethidine but have a short duration of action.

The choice of prophylactic agent should be based on level of risk, efficacy of agents available, their side effect profiles and the cost of prophylaxis versus the cost of treating vomiting. Patients at moderate risk should be considered for monotherapy, whereas high-risk patients can require several prophylactic agents with different pharmacological actions.

There are four main classes of drugs used in the management of PONV: anticholinergics, antihistamines,  $D_2$  antagonists and 5HT<sub>3</sub> antagonists. However, because of the many ways in which the vomiting centre can be

triggered, no single drug or class of drug is completely effective in controlling PONV.

**Anticholinergic drugs** Anticholinergic drugs (eg, hyoscine hydrobromide or scopolamine) inhibit stimulation of the vomiting centre by mainly blocking the action of acetylcholine at muscarinic receptors in the vestibular system. These drugs are, therefore, effective against nausea and vomiting arising from vestibular pathways. They also reduce gastric motility and afferent stimulation of the vomiting centre.

Transdermal scopolamine applied the evening before surgery or at least six hours before the end of anaesthesia is an effective antiemetic. Common side effects (anticholinergic) include drowsiness, blurred vision, urinary retention and dry mouth.

**Antihistamines** Antihistamines (eg, promethazine or cyclizine) block H<sub>1</sub> and muscarinic receptors in the vomiting centre. They are particularly effective in managing PONV associated with activation of vestibular pathways (eg, in middle ear surgery) but have less effect on vomiting induced by direct stimulation of the CTZ. Due to antimuscarinic activity antihistamines can display anticholinergic side effects, such as drowsiness and sedation. Cyclizine should be used with caution in patients with glaucoma or heart failure.

**Dopamine antagonists** The CTZ has an abundance of D<sub>2</sub> receptors. If these receptors are stimulated, vomiting is induced. Dopamine antagonists include the benzamides, phenothiazines and butyrophenones. Dopamine inhibition limits emetic input to the vomiting centre. D<sub>2</sub> antagonists work best against the actions of agents that mainly stimulate the CTZ (eg, opioids).

**Benzamides** Benzamides (eg, metoclopramide and domperidone) have a prokinetic effect. They exert a direct anti-emetic effect by blocking D<sub>2</sub> receptors in the CTZ (central action). They also enhance gastric and upper intestinal motility by blocking peripheral dopamine receptors. At high doses, metoclopramide also exhibits a weak 5HT<sub>3</sub> blocking activity. However, metoclopramide has been shown to be relatively ineffective in PONV and should be avoided in cases of intestinal obstruction or where there are new bowel anastomoses. Because it crosses the blood-brain barrier, metoclopramide is associated with extrapyramidal side effects. Domperidone is a central dopamine antagonist but does not exhibit 5HT<sub>3</sub> antagonist effects. It does not cross the blood brain barrier so is the preferred drug in this class for patients who have nausea and Parkinson's disease. It is also less likely to cause central effects such as dystonic reactions and sedation.

**Phenothiazines** Phenothiazines (eg, chlorpromazine and prochlorperazine) mainly block D<sub>2</sub> and 5HT receptors in the CTZ. They also

have weak muscarinic (vomiting centre and vestibular centre) and histamine receptor blocking activity. They act against agents that directly stimulate the CTZ (eg, opioids, cytotoxics and general anaesthetics) and are active against emetic stimuli arising from the gastrointestinal tract.

Antidopaminergic side-effects include akathisia, dystonia and dyskinesia. Prochlorperazine is probably the commonest phenothiazine used for PONV. It is available as oral, buccal, rectal and parenteral preparations.

**Butyrophenones** Butyrophenones (eg, haloperidol) block D<sub>2</sub> receptors in the CTZ. They have similar properties to phenothiazines but are not commonly used for PONV. Droperidol was withdrawn in 2001, following a risk-benefit assessment because of concerns about its potential effect on prolonging the cardiac QT interval.

**5HT<sub>3</sub> antagonists** 5HT<sub>3</sub> receptor antagonists (eg, ondansetron, dolasetron, tropisetron and granisetron) have proven efficacy in nausea and vomiting, and limited side effects. They specifically block 5HT<sub>3</sub> receptors, both peripherally in the gut (5HT<sub>3</sub> receptors of the vagal afferent nerves) and centrally in the CTZ. This action subsequently decreases afferent visceral and CTZ stimulation of the vomiting centre respectively.

**Other agents** Dexamethasone is the steroid most commonly used for PONV. It is almost always used in combination with other agents. Its mechanism of action is unclear, but could be due to inhibition of prostaglandin formation. Adverse effects are not likely following a single bolus dose.

Somatostatin analogues (eg, octreotide) have been used to reduce vomiting as a consequence of surgery. It reduces gastrointestinal secretions and motility.

Synthetic derivatives of cannabis (eg, nabilone) have been found to have antiemetic properties and are useful in preventing vomiting caused by CTZ stimulation. Their effect is antagonised by naloxone. Neurokinin-1 receptor antagonists (eg, aprepitant) selectively antagonise substance P at human neurokinin-1 receptors. Both nabilone and aprepitant are currently only licensed for use in nausea and vomiting caused by cytotoxic chemotherapy.

**Single versus multiple drug use** Generally, the use of a single anti-emetic reduces the incidence of PONV by about 30 per cent. Combinations of anti-emetics acting on different receptors are superior to monotherapy and drugs with different mechanisms of action should be used where a single agent has not been effective. It is beyond the scope of this article to look at the efficacies of different combinations studied.

**Treatment** If patients do vomit treatment should be given. Rescue therapy is usually administered parenterally, rectally or via buc-

cal mucosal absorption. If PONV continues over a long period, anti-emetics can be given by continuous infusion using a syringe driver intravenously or subcutaneously. Physical and chemical stability of drugs needs to be considered if the anti-emetics are to be added to an infusion containing another drug (eg, syringes containing an analgesic).

**Alternative treatments** Acupressure at the Chinese acupuncture point P6 has been shown in many studies to decrease the incidence of nausea, including post-operative nausea. The acupressure is usually applied before the procedure and can be continued for several days post-operatively. There are no side effects with this treatment.

Ginger and peppermint have also been used for many centuries to relieve nausea. Ginger is useful for post-operative nausea, once the patient has started to eat again. Peppermint is more commonly given as an infusion to drink. It is thought to act as a muscle relaxant in the gastrointestinal tract. Note that interactions can occur between large doses of peppermint and statins or felodipine.

## References

1. Jolley S. Post-operative nausea and vomiting: a survey of nurses' knowledge. *Nursing Standard*. 2000;14:32-4.
2. Pierre S, Benais H, Pouymayou J. Apfel's simplified score may favourably predict the risk of post operative nausea and vomiting. *Canadian Journal of Anesthesia* 2002; 49: 237-42.

## Resources

- An article in Hospital Pharmacist explains inhaled and intravenous anaesthesia. Digger T, Viira DJ. Anaesthesia and surgical pain relief — the ideal anaesthetic agent. *Hospital Pharmacist* 2003;10:432-40.
- The Royal College of Anaesthetists provides patient resources, such as "What is anaesthesia?" Available at: [www.rcoa.ac.uk/](http://www.rcoa.ac.uk/) (accessed 22 November 2004).

## Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Make sure your hospital has a policy for PONV.
2. Try to find out the rationale for the different agents used in your hospital for managing PONV.
3. Look at the evidence comparing different anti-emetic agents both singly and in multiple combinations for a range of surgical procedures.

## Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities.

Answer the following questions:

What have you learnt?

How has it added value to your practice? (Have you applied this learning or had any feedback?)

What will you do now and how will this be achieved?