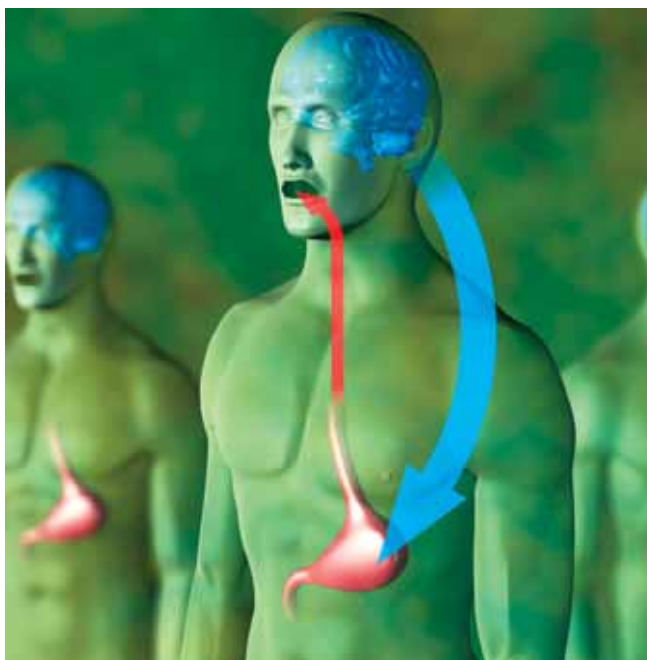


# Nausea and vomiting

## — causes and complications

By Alan Worsley, MRPharmS, PhD, and Andrew Husband, MRPharmS, MSc

Nausea and vomiting are biological defence mechanisms, associated with a variety of stimuli and conditions. This article explains some of the common causes of nausea and vomiting and the complications that can arise



Computer artwork of the vomiting reflex

**N**ausea is the word used to describe the sensation of discomfort and unease in the stomach and is derived from the Greek word for sea-sickness (naus means ship). Nausea itself is not an illness but a symptom associated with a variety of conditions. Nausea and vomiting are produced by the same stimuli and can be viewed as a progressive response to increased stimulus.

The act of vomiting (emesis) is caused by a series of changes within the gastrointestinal tract, in co-ordination with respiratory movements. Generally, salivation precedes the ejection of vomitus and there is a simultaneous increased volume of inspiration into the lungs, which increases abdominal pressure. The epiglottis closes and the soft palate of the mouth rises to prevent vomitus entering the lungs. The pyloric region of the stomach undergoes a strong contraction, while the fundus, cardiac sphincter and oesophagus remain relaxed and the external muscles of the anus and urethra contract. As

a result, the stomach expels the vomitus with great force into the mouth and out of the body.

This sequence may be repeated in co-ordination with respiratory cycles, and retrograde peristalsis from the small intestine to the stomach may refill the stomach several times. Retching is a similar process to vomiting, where the movements involved are less severe and do not result in ejection of vomitus.

**Complications** If vomiting is left untreated, in addition to causing distress, hypokalaemic hypo-chloroemic alkalosis (volume depletion, loss of gastric hydrogen ions and alterations in the renin-angiotensin-aldosterone system) can result.

Vomiting can also cause mucosal damage such as Mallory-Weiss tears, or rupture the oesophagus (eg, Boerhaave syndrome). A fall in haemocrit and subsequent endoscopy should identify any bleed and associated physical damage. Gastrointestinal rupture as a result of vomiting is particularly dangerous in alcoholics who have developed oesophageal varices.

Another complication associated with uncontrolled vomiting is the possible

aspiration of the stomach contents into the lung, potentially leading to aspiration pneumonia and pneumonia.

### — The vomiting process

The act of vomiting is a complex physiologically co-ordinated sequence. It is said to be controlled by the vomiting centre in the brain. Generally, this is no longer considered to be a distinct anatomical structure, but is believed to involve a central pattern generator, similar to that which co-ordinates ventilation. The vomiting process is closely associated with the salivary, vagal and respiratory centres of the brain, and has several excitatory inputs (see Panel 1, p186). Among these is the chemoreceptor trigger zone, as described in Panel 2 (p186).

The remainder of this article explains common causes of nausea and vomiting likely to be encountered in hospital practice.

### — Treatment-induced

**Chemotherapy-induced nausea and vomiting** Chemotherapy-induced nausea and vomiting (CINV) can be classified as acute, delayed or anticipatory. Two further

Alan Worsley and Andrew Husband are senior lecturers in pharmacy practice at the University of Sunderland

## Panel 1: Excitatory inputs controlling the vomiting process

The vomiting centre is associated with several excitatory inputs coming from:

- Receptors in the gastrointestinal tract, responding to either chemical (5-hydroxytryptamine [5-HT] receptors) or intramuscular forces (histamine and acetylcholine receptors)
- The labyrinths of the vestibular centres of the inner ear via cranial nerve VIII (the vestibulocochlear nerve)
- Intracranial pressure receptors
- The cerebral cortex, as a result of conscious stimuli to smells, tastes and conditioned reflexes
- Pain receptors (eg, within the genitourinary tract)
- The chemoreceptor trigger zone
- Cranial nerve X (the vagus nerve) from pharynx irritation, resulting in the gag reflex

categories apply to uncontrolled CINV — breakthrough and refractory nausea and vomiting. CINV is the single most feared adverse effect for patients undergoing chemotherapy and has regularly resulted in patients refusing treatment or physicians having to withhold it. If inadequately controlled, CINV can lead to dehydration, electrolyte imbalance and physical damage (such as Mallory-Weiss tears of the oesophagus). Acute CINV occurs within 12 hours of chemotherapy and late-acute CINV occurs within 12–24 hours. Delayed CINV occurs after 24 hours and may persist for six to seven days.

Depending on its emetic potential, chemotherapy is divided into three classes — highly emetogenic, moderately emetogenic or low emetogenic. Treatment protocols are based on this classification. Examples of highly emetogenic agents include cisplatin, cyclophosphamide, doxorubicin, dacarbazine and carboplatin, all of which have an emetogenic potential of greater than 90 per cent.<sup>2</sup>

Anticipatory nausea and vomiting can occur before, during and after (but before acute symptoms would normally be expected to occur) administration of a chemotherapeutic agent. This is a conditioned response to visual, olfactory, gustatory and environmental stimuli associated with previously administered chemotherapy.

Breakthrough nausea and vomiting refers to cases where prophylactic antiemetic treatment has been given, whereas refractory nausea and vomiting

are those cases where symptoms occur during subsequent cycles when control had been incomplete in previous chemotherapy treatment cycles.<sup>3</sup>

The pathophysiology of CINV is complex. The vomiting centre receives input from the CTZ via 5-HT<sub>3</sub>, dopamine D<sub>2</sub>, neurokinin-1 and muscarinic receptors; from the gastrointestinal tract through vagal and visceral afferent pathways via 5-HT<sub>3</sub> and neurokinin-1 receptors; and from the vestibular apparatus of the inner ear, which controls motion sickness. Increasing evidence has suggested that the gastrointestinal tract may initiate the emetic response, through a bundle of nerve fibres near the vomiting centre called the nucleus tractus solitarius.

The incidence of acute emesis is determined by the emetogenic potential of the chemotherapy used, the dose and efficacy of antiemetic drug therapy, and patient variables. Patient variables include age (there is a lower incidence of CINV in patients under six years and over 50 years of age), sex (females are more prone to CINV), alcohol consumption (there is a greater incidence of CINV in patients consuming more than 10 units of alcohol per week), anxiety levels, and any previous cycles of poorly controlled chemotherapy.

### Radiation-induced nausea and vomiting

The intestinal tract is highly sensitive to ionising radiation, as a result of its rapid cell turnover. Thus, one of the most common side effects of radiation therapy is diarrhoea with associated nausea and vomiting. Whole body doses of radioactivity will affect the gastrointestinal tract. Almost 80 per cent of the total body 5-HT<sub>3</sub> is contained within the gastrointestinal tract, in the enterochromaffin cells, the enteric nerves and mucosal mast cells. Changes in intestinal 5-HT<sub>3</sub> tissue content in animal models with total body irradiation have been demonstrated, which may contribute to enteric neuronal innervation and nausea and vomiting.<sup>4</sup>

## Panel 2: Chemoreceptor trigger zone

The chemoreceptor trigger zone (CTZ) is a small collection of cells based in the medulla. It is located outside the blood-brain barrier and therefore responds to chemical stimuli present in the blood or cerebrospinal fluid. The CTZ responds to a number of drugs (eg, apomorphine) and is also involved in vomiting in conditions such as uraemia and radiation sickness.

The CTZ has a number of receptors, namely dopamine (D<sub>2</sub>) receptors (believed to be the most important in CTZ stimulation), 5-hydroxytryptamine (5-HT) receptors, opioid receptors, acetylcholine receptors and neurokinin-1 receptors. Receptor stimulation occurs via different afferent pathways, all of which stimulate a common substance P pathway.<sup>1</sup>

The CTZ is not separated from the blood by the blood-brain barrier and is therefore susceptible to drugs and metabolites. Communication between circulatory compounds and the CTZ is thought to be via astrocytes (star-shaped glial cells) which release dopamine that connects with neurones in the CTZ.

### Post-operative nausea and vomiting

Post-operative nausea and vomiting (PONV) is a common condition associated with general anaesthetic use and surgery. As with all types of nausea and vomiting, PONV is ultimately associated with dehydration, electrolyte disturbance and, rarely, aspiration pneumonitis, all of which can delay patient recovery. In addition, various post-surgical complications can occur as a result of severe PONV, such as wound dehiscence (where the force of retching causes stitched wounds or anastomoses to burst) and problems for faciomaxillary patients with wired jaws.

The causes of PONV are believed to be multiple, including the use of anaesthetics, drugs such as opiates and surgical factors. In terms of induction anaesthetics, etomidate is associated with an increase in PONV compared with propofol. For inhalation anaesthetics, halothane and enflurane are associated with a higher rate of PONV than sevoflurane and desflurane.

Intubation is also thought to increase the rate of PONV, by stimulating the pharyngeal mechanoreceptor. Gastric distension secondary to mask ventilation is also associated with an increased risk of PONV, as a result of mechanoreceptor stimulation within the stomach and small intestine.<sup>5</sup>

Surgical procedures such as intra-abdominal, middle ear, ophthalmic and gynaecological surgery are associated with the highest rates of PONV. Management of PONV is among the topics covered in the second article in this special feature (p189).

### — Vestibular disorders

The vestibular system is responsible for sensory input to provide information relating to movement and orientation in space. It comprises the semicircular canals which detect rotational movement and the otoliths which detect linear system movement. Disorders of the vestibular system are often accompanied by nausea.

**Vertigo** Vertigo, specifically benign paroxysmal positional vertigo, is thought to be caused by sections of the otoliths having cleaved off and passed into the semicircular canals. Vertigo may potentially have other underlying causes, such as certain tumours, vascular insufficiencies, or the early stages of multiple sclerosis.

**Vestibular neuronitis** Vestibular neuronitis is associated with nausea and vomiting of sudden and rapid onset. It is normally associated with a viral infection of the inner ear. Prolonged dizziness, without deafness, may persist for several weeks.<sup>6</sup>

**Labyrinthitis** Labyrinthitis is a disorder similar to vestibular neuronitis affecting balance, usually resulting from a viral upper respiratory tract infection. Inflammation of the labyrinth results in dizziness, nausea, vomiting, loss of balance, tinnitus, and some deafness. It can also manifest as rapid uncoordinated eye movements (nystagmus) in response to perceived rotational motion. This will often exacerbate the feeling of nausea and vomiting.

Labyrinthitis is normally divided into three phases — the acute period, which can often manifest as periods of nausea and vomiting, the recovery phase and then a final phase of sensory compensation. The condition can last from one to six weeks, with residual dysequilibrium occurring many months after inner ear inflammation has resolved.<sup>7</sup>

Labyrinthitis is often associated with anxiety, which can lead to palpitations, tremor and panic attacks. antiemetics and anxiolytics or selective serotonin re-uptake inhibitors are often prescribed in labyrinthitis although treatment is not always recommended.<sup>8</sup>

**Motion sickness** Motion sickness is a normal response to an abnormal environment. Five per cent of the general population suffer heavily from motion sickness, 5 per cent hardly experience it at all, and the rest experience moderate symptoms.

The condition is often described as a sensory conflict between the vestibular system and other senses, but this does not explain why exposure to certain forms of motion, such as linear oscillation, also causes sickness. Another theory is that motion sickness is caused by the brainstem's mechanism of orientation and motion in response to the body's position being in conflict with sensory information.<sup>9</sup>

The signs and symptoms of motion sickness are nausea and vomiting, pallor, cold sweats and abdominal discomfort. The mildest form of motion sickness, Sopsite syndrome, manifests as some gasping, drowsiness and decreased interest in surroundings. Behaviour modification techniques (as well as medicines — see p189) can be used in the treatment of motion sickness.

**Migraine** Migraine is a neurological condition, with the most common symptom being headache. The headache is characterised by pain on either side of the head, photophobia and nausea. The condition is thought to result from cortical spreading depression, releasing inflammatory mediators which cause irritation of the cranial nerve roots, in particular the trigeminal nerve, causing face and head pain.

Approximately 90 per cent of migraine sufferers experience nausea. It is suggested that nausea and vomiting associated with migraine result from gastric stasis or gastroparesis (delayed stomach content emptying). Consequently the absorption of orally administered anti-migraine medicines may be delayed. Some antiemetics such as metoclopramide also exhibit prokinetic properties, which is especially effective in patients with migraine associated with gastroparesis.

## — Gastrointestinal disorders

The most common causes of nausea and vomiting are duodenal ulcers, dyspepsia, irritable bowel syndrome, often associated with anorexia and pain. Other causes include gastric ulcer, gall-stones, gastro-oesophageal reflux disease, gastric cancer, colon cancer, Crohn's disease and pancreatitis. The probability of organic disease increases with age in comparison to functional disease. Similarly, the incidence of ulceration due to *Helicobacter pylori* infection increases with age.

Chemoreceptors and mechanoreceptors are located in the stomach, jejunum and ileum. These are associated with the detection of emetic stimuli. Mechanoreceptors are fundamentally tension receptors that initiate emesis in response to distension and contraction, as in the case of bowel obstruction. Thus, one possible cause of nausea and vomiting associated with the gastrointestinal tract is intestinal obstruction.

**Intestinal obstruction** Intestinal obstruction is caused by an occlusion of the intestinal lumen. It prevents or delays normal propulsion of the contents of the intestine along the tract. Intestinal obstruction occurs in approximately 3 per cent of patients with advanced cancer, and patients

### Suggestions for future special features

If you would like to suggest a topic for a future special feature in *Hospital Pharmacist*, or if you are a specialist clinical pharmacist interested in writing about your area of practice, please contact Hannah Pike (e-mail hannah.pike@pharmj.org.uk, telephone 020 7572 2425) or Rachel Graham (e-mail rachel.graham@pharmj.org.uk, telephone 020 7572 2419).

with ovarian cancer have a 25–40 per cent risk of obstruction. Other patients who may experience intestinal obstruction are those with metastatic abdominal or pelvic cancer, which may lead to obstruction at multiple sites. Occlusion is generally caused by: extrinsic compression from the primary tumour; malignant adhesions; post-radiotherapy fibrosis and mobility disorder due to tumour infiltration into the musculature of the bowel (specifically the intestinal linitis plastica).

Obstruction usually manifests itself as severe vomiting and is dependent upon the severity and site of the occlusion. Symptoms may worsen and become continuous or may be intermittent with periods of relief. Radiological investigation will often differentiate between malignant obstruction and constipation and will be useful in determining the site of occlusion.

## — Endocrine disorders

### Nausea and vomiting during pregnancy

“Morning sickness”, is believed to affect 70–90 per cent of pregnant women. It is normally a self-limiting condition which begins between weeks 4 and 7 of pregnancy and usually resolves after week 20. However, in approximately 10 per cent of pregnant women, the condition persists and becomes known as hyperemesis gravidarum. The aetiology of hyperemesis gravidarum is unknown. A number of causes have been suggested, including delayed gastric emptying and *H pylori* (found in 60 per cent of women with hyperemesis gravidarum.) Reduced levels of thyrotropin stimulating hormone have been shown in women with the condition and rises in oestrogen, progesterone and prostaglandin E<sub>2</sub> have also been implicated.<sup>10</sup> Vomiting during pregnancy is not teratogenic and babies born to mothers with hyperemesis gravidarum tend to be the same weight as other babies.

Another condition associated with nausea and vomiting during pregnancy is acute fatty liver of pregnancy. In about week 35 of pregnancy some women experience nausea, vomiting, headache and general malaise. Elevated aminotransferases and microvesicular fat (from biopsy) indicate fatty liver of pregnancy.<sup>11</sup> HELLP syndrome, (haemolysis, elevated liver enzymes, low platelet count) is also associated with nausea and vomiting during the latter stages of pregnancy and may complicate delivery.<sup>12</sup>

**Systemic metabolic disorders** Acute exacerbations of chronic diseases, such as diabetes mellitus, endometriosis and renal insufficiency, may cause nausea and vomiting. Severe nausea and vomiting is a clinical symptom of diabetic ketoacidosis.

Acute adrenal insufficiency is also associated with nausea and vomiting, as is uraemia. Other non-specific symptoms include

anorexia and weight loss. Gastric stasis has been demonstrated in a patient with primary adrenal insufficiency.<sup>13</sup>

Hypercalcaemia (serum calcium >3.5 mmol/L) can alter gut motility, which may induce nausea and vomiting. Other gastrointestinal symptoms include anorexia and abdominal pain. Primary hyperparathyroidism and malignancy are the two most common causes of hypercalcaemia.

**Cyclical vomiting syndrome** Cyclical vomiting syndrome is a condition that occurs predominately in children. Vomiting is acute and often requires hospital admission. It is suggested that the syndrome is associated with gastroparesis, gastric stasis and gastric migraine. The symptoms of gastric migraine are severe abdominal pain with nausea, vomiting and headache migraine, which can last for several hours or days, with an abrupt discontinuation of symptoms. There are no proven triggers — however some female sufferers have identified an association with their menstrual cycle.<sup>14</sup>

## Conclusion

Nausea and vomiting are associated with a variety of conditions that are multifactorial in origin. It may be caused by inner ear equilibrium changes, dysmotility of the

gastrointestinal tract, sensory stimuli (eg, bad smells or tastes), pregnancy, chemotherapy, radiation therapy and adverse drug reactions. Complications of vomiting include metabolic disturbances and mucosal damage. Treatment options, which often depend on the cause of the nausea and vomiting, are discussed in the next article in this special feature (p189).

## References

1. Hornby PJ. Central neurocircuitry associated with emesis. *American Journal of Medicine* 2001;111:suppl 8A: 106s–112s.
2. Doherty KM. Closing the gap in prophylactic antiemetic therapy: patient factors in calculating the emetogenic potential of chemotherapy. *Clinical Journal of Oncology Nursing* 1999;3:113–9.
3. Aapro MS, Molassiotis A, Olver I. Anticipatory nausea and vomiting. *Support Care Cancer* 2005;13:117–21.
4. Penttila A, Kormanen M, Ahonen A. Effects of 400 R whole-body X irradiation on 5-hydroxytryptamin content of the rat gastrointestinal tract. *Strahlentherapie* 1975;149:426–37.
5. Benson JM, DiPiro JT, Coleman CL, Hirsch JD, Donnigan LD, Stanfield JA. Nausea and vomiting after abdominal surgery. *Clinical Pharmacy* 1992;11:965–67.
6. Cooper C. Vestibular neuronitis: a review of a common cause of vertigo in general practice. *British Journal of General Practice* 1993;43:164–67.
7. Bronstein A. Visual and psychological aspects of vestibular disease. *Current Opinion in Neurology* 2002;15:1–3.
8. Staab J and Ruckenstein M. Chronic dizziness and anxiety. *Archives of Otolaryngology — Head and Neck Surgery* 2005;131:675–79.
9. Treisman M. Motion sickness: an evolutionary hypothesis. *Science* 1977;197:29.
10. Gadsby R, Barrie-Adshead A, Grammatopoulos D, Gadsby P. Nausea and vomiting in pregnancy: an association between symptoms and maternal prostaglandin E<sub>2</sub>. *Gynecologic and Obstetric Investigation* 2000;50(3):149–52.
11. Usta I, Barton J, Amon E, Gonzalez A, Sibai B. Acute fatty liver of pregnancy: An experience in the diagnosis and management of fourteen cases. *American Journal of Obstetrics and Gynecology* 1994;171:1342–47.
12. Reubinoff B, Schenker J. HELLP Syndrome — a syndrome of hemolysis, elevated liver enzymes and low platelet count: complicating preeclampsia-eclampsia. *International Journal of Gynecology and Obstetrics* 1991;36:95–102.
13. Valenzuela G, Davis T, McGroarty D, Pizzani E, Zfass A. Primary adrenal insufficiency: a new cause of reversible gastric stasis. *American Journal of Gastroenterology* 1990;85:1626–28.
14. Lindley KJ, Andrews PL. Pathogenesis and treatment of cyclical vomiting. *Journal of Pediatric Gastroenterology and Nutrition* 2005;41: S38–40.