Nausea

Nausea is the feeling of unease and discomfort in the stomach with an urge to vomit. For something so common, it is deceptively complicated. Modern treatments for nausea have been some of the pharmaceutical industry's greatest successes and have eased the distress of millions of patients undergoing surgery or cancer therapies.

What is nausea?

Nausea is the sensation of unease and discomfort in the stomach with an urge to vomit. Vomiting is a complex, coordinated reflex orchestrated by the vomiting centre located in the brain. It responds to signals coming from the gastrointestinal tract, i.e. the mouth, the stomach or the intestines, the circulation, the balancing systems in the inner ear, and the brain itself, including upsetting sights, smells, or thoughts. The neurotransmitters histamine, acetylcholine, serotonin, and dopamine frequently are implicated in these pathways and are the targets of most therapeutic approaches.

The word "nausea" derives from the Greek word *"naus"* meaning "ship" and the Latin word *"nauta"* meaning "sailor" and thus originally carried the idea of sickness from sea-travel. Excessive stimulation of the vestibular apparatus in the inner ear by motion is the primary cause of motion sickness. Neuronal pathways from the labyrinth of the inner ear to the vomiting centre in the medulla oblongata of the brain are undefined, but motion sickness occurs only when the neurological system in the inner ear is intact.

Nausea is a symptom of many other conditions, including morning sickness, especially during the first trimester of pregnancy, treatment with certain medicines, food poisoning or food allergies, alcohol intoxication, brain tumors, gastro-intestinal infections by viruses, and other diseases. An amazing variety of stimuli can trigger vomiting, from migraine to kidney stones. Nausea may become a particular problem during some chemotherapy regimens and following general anaesthesia.

In general, short-term nausea and vomiting are harmless, while prolonged symptoms may sometimes indicate a more serious disease. Eventually, prolonged vomiting may cause a dangerous loss of body fluid. Another problem with nausea and vomiting in elderly people is that patients may neglect their usual medications, e.g. to help

control blood pressure or blood glucose, and they may not be able to keep the tablets down. Thus, persistent nausea should receive medical attention.

Who does nausea affect?

The probability that an individual will experience nausea and vomiting during lifetime is 100 per cent. Almost all children will vomit several times during their childhood. In most cases, it is due to a viral gastrointestinal infection. Later on, nausea and vomiting after surgery are common side effects of gas anaesthesia and morphine-related analgesics. It is estimated that post-operative nausea and vomiting (PONV) affects one out of four surgery patients, about 40 million a year in the European Union.

Some 70 per cent of cancer patients experience chemotherapy induced nausea and vomiting (CINV) as a result of their treatment. Some chemotherapy treatments produce CINV in up to 90 per cent of patients. Radiation therapy targeted at the intestine can also cause nausea and vomiting in up to 90 per cent of cases. Anticipatory nausea and vomiting occurs prior to the beginning of a new cycle of chemotherapy, in response to conditioned stimuli such as the smells and sights of the treatment room. It typically occurs after three or four prior chemotherapy treatments, following which the patient has experienced acute or delayed CINV.

Present treatments:

Symptomatic treatment for nausea and vomiting may include short-term avoidance of solid food. This is usually easy, as nausea is often associated with loss of appetite. Dehydration may require replacement of body fluids with oral or intravenous electrolyte solutions.

Prophylactic medications to prevent motion sickness include antihistamines, tranquillisers, or compounds with an anticholinergic effect, e.g. alkaloids. Antihistamines inhibit the action of histamine at the H1-receptor, and anticholinergic agents block acetylcholine at the muscarinic receptor. Both classes decrease stimulation of the vomiting centre from the vestibular system in the ear but have little effect on stimulation from the stomach or the intestines. One innovative treatment is through-the-skin delivery systems. A patch with the active compound is applied behind the ear four hours prior to travel and may be replaced every three days.

Medicines which have been used as a single medication or in combination to treat PONV or CINV belong to the groups of alkaloids, benzodiazepines, cannabinoids, corticosteroids, dopamine-antagonists, and serotonin-antagonists, also known as 5-HT_3 inhibitors. Dopamine-antagonists such as benzamides, phenothiazines and butyrophenones minimize the effect of dopamine at the D2-receptor in the trigger zone, thereby limiting emetic input to the vomiting centre.

5-HT_3 inhibitors are considered to be very effective antiemetics and constitute the single greatest advance in the management of nausea and vomiting in patients undergoing chemotherapy and radiation. Their mode of action is the selective blocking of the serotonin 5-HT_3 receptor. Serotonin is released by cells in the small intestine when patients receive chemotherapy (and possibly in reaction to other events). The serotonin released acts on the vagus nerve to trigger nausea and vomiting. The medicines block receptors on the vagus nerve, thereby reducing and sometimes eliminating nausea and vomiting.

With the early blocking agents of 5-HT_3 receptors, the approach to preventing acute emesis (vomiting) was relatively short-lived. The newer 5-HT_3 inhibitors have a distinct advantage because, in addition to preventing acute nausea and vomiting, they also prevent delayed nausea and vomiting, which occurs during the two to five days after treatment. In postoperative patients who are suffering from nausea or vomiting, 5-HT_3 receptor antagonist have some effect on vomiting and less so on nausea.

Another new mechanism of action to avoid nausea and vomiting is the inhibition of human substance P/neurokinin 1 (NK1) receptors. The molecule is given in addition to medicines which interfere with serotonine (5-HT_3), dopamine, or corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting.

What's in the development pipeline?

Agents approved for other indications are currently under investigation for the treatment and prevention of CINV. For example, a novel antipsychotic used to treat patients with schizophrenia has demonstrated potential as an antiemetic in a Phase 2 clinical study.

Other studies underway are focused on the actual timing of giving anti-nausea medicine, rather than on the medicine itself. Additionally, a number of nutritional and behavioural strategies may improve control of CINV in cancer patients.

Plant from which cannabis is derived. The cannabis receptor is one of several brain receptors targeted by new medicines in development.

The anti-emetic properties of cannabis and cannabinoids are being studied in patients suffering from nausea and vomiting following chemotherapy. A large body of knowledge has now been amassed in this context as a result of several Phase 3 clinical studies in cancer chemotherapy. The biochemical basis of this anti-emetic effect is still being explored, but it is known that cannabinoids inhibit the activity of 5-HT_3 receptors. Recent data also supports the anti-emetic properties of cannabidiol in animal tests. The combination of cannabidiol and tetrahydrocannabinol in cannabis extracts may well have additive or synergistic effects that deserve further investigation in clinical trials.

The longer-term future:

Research on new molecules to treat nausea and vomiting continues to move forward, so new therapies are likely to be available in the future. Despite the many medicines available, there is still no single compound that can claim to be the miracle remedy for this deceptively underestimated condition. Therapy with combinations of medicines having different modes of action could be an answer, since it is reasonable to suggest that administration of two or more compounds of different pharmacological classes should be more effective in inhibiting the complex emetic reflex.

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