NAUSEA AND VOMITING

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Vomiting has long been regarded as one of the most unpleasant aspects of anaesthesia. In addition, it is a feature of many medical and surgical conditions and of travel by land, sea and air. Its effects range from the simply annoying, to life-threatening electrolyte upset. The choice of a cytotoxic drug or the alternative of radiotherapy may be determined by the likelihood of vomiting rather than efficacy against the neoplasm. All these aspects are of importance to the anaesthetist and this review describes the mechanisms and physiology of vomiting, in addition to the pharmacology of its causes and means of prevention.

The events of vomiting

Vomiting may be defined as the forceful expulsion of gastric or intestinal contents through the mouth. The word forceful distinguishes it from the passive regurgitation which occurs in infants or comatose individuals in whom the lower oesophageal sphincter may be partly relaxed. It is preceded in man by a sensation of nausea and retching, but in the infant or in animals under direct stimulation of the vomiting centre, projectile vomiting may occur, unaccompanied by any apparent discomfort or autonomic disturbance. In man also, vomiting caused by increased intracranial pressure is not preceded by nausea. The usual precursors in adult man are copious salivation, swallowing, sweating, pallor and tachycardia, related presumably to the close proximity of the autonomic centres in the medulla. Respiration may also be laboured, with the mouth partly or entirely closed. The experienced observer learns to recognize these signs in a patient and some last-minute action may be taken to prevent vomiting or at least reduce the undesirable consequences.

The mechanism of vomiting has been studied by the use of radiography (Lumsden and Holden, 1969). There is first a deep inspiration as the diaphragm moves downwards with closure of the glottis and elevation of the soft palate to occlude the nasopharynx. At this stage, a sudden contraction of the abdominal muscles causes a sharp increase in intrathoracic and intra-abdominal pressure, which in turn is transmitted to the stomach. If the glottis is not closed completely at this stage, forcing of air through it causes the high-pitched sound associated with retching or vomiting. The oesophagus, lower oesophageal sphincter and body of the stomach now relax and there is a strong contraction of the gastric antrum, shifting contents into the upper stomach. Secretion of hydrochloric acid is inhibited although secretion of mucus is increased. There are rapid segmental contractions and later spasms occur in the duodenum and jejunum (but not anti-peristalsis), resulting in forcing up their contents into the stomach. Even the colon may contract during vomiting, but it is rare for ileal or colonic contents to be expelled. These intestinal movements appear to be mediated by the vagus as they are abolished by vagal section and unaffected by sympathetic denervation.

The effect of all the intra-abdominal contractions against a lowered diaphragm is to force food through the open sphincter and into a relaxed oesophagus. It may not pass further if the inferior constrictor of the pharynx is closed, resulting in abortive retching and return of the material to the stomach. However, after several episodes of this when the pharyngeal sphincter does relax, forceful propulsion of stomach contents through the mouth occurs. The cycle may be repeated several times before the abdominal muscles relax and respiration is resumed.

The control of this complicated group of activities involves co-ordination of both striated and visceral muscle in an essentially involuntary activity. This is managed through the vomiting centre in the lateral reticular formation deep in the medulla. Stimulation of this area in experimental animals results in a sharp inspiration and immediate vomiting, which ceases as stimulation ceases. Such vomiting is projectile in type without concomitant retching (or presumably, nausea). The vomiting centre in turn is influenced by psychic factors, the vestibular nucleus, the Chemoreceptor Trigger Zone (CTZ) and sensory afferents from pharynx, gastrointestinal tract or genitalia. The CTZ (Borison and Wang, 1953),

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which is in the floor of the fourth ventricle, is probably the most important to anaesthetists for drugs do not act on the vomiting centre directly, but rather on this distinct medullary area. Electrical stimulation of this area does not cause vomiting, although stimulation of the vomiting centre itself is effective. Likewise, ablation of the CTZ in the dog prevents the emetic response to apomorphine, opiates and digoxin. All these areas will be considered separately but they often summate, as for instance, in postoperative sickness in gynaecology, where the analgesic, the stimulus of cervical dilatation, the movement of sitting up and the thought of eating even a light meal, may be enough to provoke active vomiting.

**The effects of vomiting**

The most worrying effect to the anaesthetist is the possibility of aspiration of stomach content into the trachea. It is usually believed that true vomiting is unlikely to be aspirated because the laryngeal reflex ensures against soiling of the respiratory tract. However, there is clearly an intermediate zone of hazard if the patient is supine following an injury or a surgical operation, when impaired reflexes are unable to protect the trachea. In these patients, prevention of active vomiting is useful in addition to prevention of regurgitation or aspiration, although impractical in the emergency situation.

Prolonged vomiting is a feature of many patients coming for surgery and its effects depend on the main substances which are lost. Gastric juice has two components—the mucus secretion of the surface epithelial cells and the acid secretion of the parietal or oxyntic cells. The former has a pH of approximately 7.7 and electrolyte components (mmol litre⁻¹) are: \( \text{Na}^+ = 150-160, \text{K}^+ = 10-20, \text{Ca}^+ = 3-4, \text{Cl} = 125, \text{HCO}_3^- = 35 \) (Hunt, 1959). The composition of the acid secretion is less certain because there is nearly always some admixture with mucus. It does seem, however, that at high rates of secretion it approximates to an isotonic solution of pure hydrochloric acid with a small quantity of potassium and sodium chlorides. At high rates of secretion, as when stimulated by histamine, the acidity is high and as the rate diminishes there is an increase in the relative proportion of \( \text{Na}^+ \) to \( \text{H}^+ \).

Gastric juice is isotonic with plasma and when it is secreted \( \text{H}^+ \) and \( \text{Cl}^- \) are removed from plasma, together with enough water for isotonicity. However, the \( \text{H}^+ \) is manufactured by the mucosa and \( \text{HCO}_3^- \) reabsorbed to balance the \( \text{Cl}^- \) secreted so that, overall, water is lost from the plasma in this phase of digestion, with an increase in tonicity. Normally, the whole gastric juice is reabsorbed in the intestine but, if not, as in prolonged vomiting, the loss of water is an important effect as part of an overall extracellular dehydration. However, water is usually the easiest substance to replace and, if replaced, loss of ions becomes the more notable effect of vomiting.

The loss of \( \text{H}^+ \) in continual vomiting leads to a gradual increase of \( \text{HCO}_3^- \) in the plasma (metabolic alkalosis). The excess of \( \text{HCO}_3^- \) is excreted by the kidney, in the initial phase at least. However, the other electrolyte changes conflict with the renal compensation and limit its effectiveness. There is some loss of \( \text{Na}^+ \) in the gastric juice and the proportion to \( \text{H}^+ \) depends on the acidity of the juice. As vomiting continues, the acidity of gastric juice is reduced and the loss of \( \text{Na}^+ \) increases, until the latter becomes a limiting factor. Loss of \( \text{Cl}^- \) is always severe because it is the anion associated with \( \text{H}^+ \) or \( \text{Na}^+ \) and cannot be spared while gastric juice is secreted.

Potassium is present in gastric juice in a concentration at least twice that of plasma, but the main reason for hypokalaemia in prolonged vomiting is the selective excretion of \( \text{K}^+ \) in the renal tubules as \( \text{H}^+ \) is conserved. The result is depletion of extracellular and later intracellular potassium which cannot easily be assessed by blood sampling. It can be assumed, however, in treating any patient with metabolic alkalosis losing gastric juice, even though plasma potassium concentration is within normal limits.

**Causes of nausea and vomiting**

**Motion sickness** (Glaser, 1959) results essentially from actions on the vestibular apparatus of the ear. Patients with congenital inner ear deafness or destruction of the vestibular apparatus do not suffer. The stimulus appears to be a sequence of bursts of linear acceleration which set the endolymph in the semicircular canals in motion, resulting in the stimulation of the otoliths in the utricle. Waves of impulses pass back by the vestibular part of the eighth nerve to the chemoreceptor trigger zone in the medulla, with relays to the cerebral cortex involving nausea and to the cerebellum and vomiting centre for the motor response. Destruction of the CTZ eliminates the response to centrally applied emetics and the vomiting accompanying uraemia, radiation sickness and motion sickness.
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The role of the cerebral cortex in initiating vomiting has been mentioned but, conversely, sufficient mental distraction may also inhibit the reflex. Habituation may eventually terminate motion sickness so that it becomes less likely in those who travel regularly by the same type of vehicle. Certain other measures also reduce the risk of vomiting in susceptible individuals, for example lying down to reduce vestibular stimulation or looking at the sky or vessel wall to avoid rhythmical visual stimulation from a moving horizon.

Other labyrinthine disorders come into the same group, including the vertigo and nausea associated with Menière’s disease and middle ear surgery.

Sensory stimulation, either somatic as from tactile stimulation of the back of the throat or stretch responses from one of the viscera can initiate nausea or vomiting. The visceral group include distension of or injury to the uterine cervix, renal pelvis or bladder, injury to the testes or a blow to the upper abdomen, in addition to many inflammatory conditions within the abdomen.

Metabolic disturbances or intoxications include hyperemesis gravidarum, radiation therapy, uraemia and hypo- or hyper-glycaemia, and it seems that these are mediated through the CTZ, as in the case of motion sickness.

Increased intracranial pressure acts presumably by direct stimulation of the vomiting centre in the medulla.

Spinal anaesthesia is commonly accompanied by nausea and vomiting and it has been suggested that this is a result of the accompanying hypotension. Recently Datta and his colleagues (1982) have confirmed this relationship and shown that, if the arterial pressure was maintained after the spinal anaesthetic by immediate administration of ephedrine i.v., there was no significant hypotension. The frequency of nausea and vomiting was then similar (10%) to that in the control group whose pressure remained unchanged, compared with 66% in the hypotensive group whose treatment was delayed.

Cytotoxic drugs cause severe nausea and vomiting in a high proportion of patients and this has been largely ignored until recent years (Seigel and Longo, 1981). The CTZ has been implicated with some of the drugs, but cisplatin at least appears to act peripherally as it does not readily penetrate the blood–brain barrier.

Anaesthesia and analgesia form the causes of sickness which most concern the anaesthetist and which are still not entirely eliminated. The non-drug-related components have been discussed already, but the various groups of drugs implicated merit separate discussion.

Inhalation anaesthetics. The older volatile anaesthetics, diethyl ether and chloroform, were notorious for their prolonged emetic action, lasting in many for more than 12 h. There are few comparative figures for halothane and the older agents, but Bamforth and his colleagues (1960) in a small series found chloroform to be much more emetic than halothane. Dundee, Kirwan and Clarke (1965) published a comparison in minor gynaecological surgery of different anaesthetic agents and the influence of premedication (fig. 1). Intermittent thiopentone was followed by significantly fewer sequelae than halothane during the first hour after anaesthesia, although the difference was entirely in respect of nausea. Cyclopropane caused much more sickness in the first hour than the other drugs tested. However, it is notable that overall, less than 5% of patients were still vomiting 1 h after operation in the absence of premedication. Gold (1969) also showed that in more than 1000 gynaecological patients cyclopropane was associated with significantly more sickness than were halothane or thiopentone–nitrous oxide–oxygen. It was also seen that thiopentone induction followed by a primary inhalation agent was associated with a smaller frequency of emesis than was induction with the inhalation agent alone. Emphasizing the lack of sickness after halothane anaesthesia, some workers (Novoa, 1960; Haumann and Foster, 1963) have actually demonstrated an anti-emetic effect from it, for instance when it was added to trichloroethylene anaesthesia.

I.v. anaesthetics. The study by Dundee, Kirwan and Clarke (1965) showed that anaesthesia with intermittent thiopentone and nitrous oxide, for minor gynaecological surgery, was followed by nausea or vomiting in approximately 12% of patients. The frequency following propanidid is approximately 38%. Table I analyses the percentage of patients vomiting in the first 6 h after the eight principal i.v. anaesthetics given under standard conditions. It appears that drugs with a moderately slow and smooth recovery, for example diazepam, di-
isopropyl phenol, Althesin and thiopentone, have an acceptably low frequency of sickness. A high frequency of excitatory effects during or after anaesthesia (etomidate and ketamine) and rapid recovery (propanidid and methohexitone) are associated with frequent sickness after operation. However, it was noted that most of the sickness with propanidid and methohexitone was “emergence vomiting”, that is, immediately after waking up. At this stage it could be more hazardous for the patient, but less unpleasant than prolonged vomiting.

Analgesics. As long ago as 1955, anaesthetists in the U.S.A. were recommending the avoidance of narcotic premedication and Riding (1960) stressed the role of morphine as a cause of postoperative sickness. Morphine stimulates the CTZ and, although it depresses the vomiting centre, frequently causes nausea and vomiting by the former mechanism. It also decreases gastric motility and prolongs emptying time. In common with the other side-effects of morphine, sickness is dose-related and its severity continues to increase when the upper analgesic dose is reached. It is therefore desirable to restrict the dose to the minimum necessary.

The majority of other analgesics also cause sickness, but it is notable that when morphine 10 mg and pethidine 100 mg (both with atropine 0.6 mg) are given as premedicants, the emetic effects of

| Table I. Percentage frequency of nausea and vomiting during the first 6 h after minor gynaecological surgery with atropine premedication and intermittent i.v. nitrous oxide-oxygen anaesthesia. (Data taken from partly unpublished figures in the Department of Anaesthetics, The Queen's University of Belfast) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Main analgesotic | Vomiting | Nausea | Nil |
| Thiopentone 4 mg kg⁻¹ | 11 | 6 | 83 |
| Methohexitone 1.6 mg kg⁻¹ | 14 | 12 | 74 |
| Propanidid 4 mg kg⁻¹ | 25 | 18 | 57 |
| Diazepam 0.6–0.8 mg kg⁻¹ | 5 | 3 | 92 |
| Althesin 50 µg kg⁻¹ | 5 | 7 | 88 |
| Ketamine 1.0–3.0 mg kg⁻¹ | 18 | 23 | 59 |
| Etomidate 0.3 mg kg⁻¹ | 27 | 12 | 61 |
| Di-isopropyl phenol 2.0 mg kg⁻¹ | 0 | 5 | 95 |
pethidine occur mainly before operation and in the first hour after operation, whereas those of morphine persist for 6 h or more after operation (fig. 1) (Dundee, Clark and Loan, 1965). Comparative studies (Dundee, Loan and Clarke, 1966; Loan, Dundee and Clarke, 1966) have shown that neither diamorphine nor papaveretum had any less emetic action than morphine, although the duration of action and side-effects of diamorphine were shorter.

Certain synthetic analgesics, however, including dipipanone, dihydrocodeine, dextromoramide, and pentazocine may have a less marked emetic action in the period after operation (Dundee, Loan and Morrison, 1970). In addition these may be given by the oral route and, therefore, have a place as premedicants and in the ambulant patient.

ANTI-EMETIC DRUGS
These are used for the sympatomatic control of nausea and vomiting, but it is essential to make a diagnosis before administration. It is axiomatic that they are not given when there is a cause which can be eliminated, but with motion sickness, vestibular disorders, certain drug treatments or intoxications (for example pregnancy or uraemia,) it is clearly legitimate to give an anti-emetic. As with most drug treatment, the choice is a balance between the most effective drug for the type of sickness, and the one causing the least side-effects.

The exact mode of action of the drugs is not always known and (surprisingly) some appear to have two widely differing modes of action. All have some central action on CTZ or the vomiting centre, but some such as metoclopramide and the anticholinergics, accelerate gastric emptying. Others of diverse chemical groups, including metoclopramide and domperidone, increase the tone of the lower oesophageal sphincter. It is not always possible to predict the efficacy of an anti-emetic from its pharmacological group and only well-controlled studies in a particular type of clinical situation can provide reliable information.

Parasympatholytic drugs—hyoscine and atropine
This is the oldest group of anti-emetics and has been used for many centuries in the form of crude extracts of hyoscyamus or belladonna. Interest was renewed during World War II and many drugs were tried out in experimental situations to simulate the motion of a ship or life-raft at sea. As described above, the vagus has an important role in initiating vomiting and it might be assumed that vagal block-
ten when their use as antisympathetics is diminishing (Mirakhur et al., 1978). Their main role is probably to reduce the emetic action of the opiates, although these drugs are now often replaced by diazepam for sedation and anaesthesia before operation. Hyoscine 0.4 mg i.m. and, to a lesser extent, atropine 0.6 mg i.m., reduce the emetic effects of pethidine 100 mg or morphine 10 mg (Dundee, Moore and Clarke, 1964; Clarke, Dundee and Love, 1965) in the periods before and early after operation. However, the emetic action of morphine may last for at least 6 h and the protective action of hyoscine or atropine is considerably shorter.

The disadvantage of the use of hyoscine or atropine as anticholinergic anti-emetics is that they both decrease the tone of the lower oesophageal sphincter (Brock-Utne et al., 1977) and facilitate the reflux of gastric contents into the oesophagus. While the significance of these findings in the context of clinical vomiting is not clear, it is presumably desirable to use a drug such as metoclopramide which contracts the sphincter, in the preoperative patient.

In summary, therefore, hyoscine is an effective anti-emetic, especially when sedative action is also required. Because it has less central action generally, atropine is a weaker anti-emetic. Both are effective by the oral route and both are more effective against vomiting than against nausea. Hyoscine may be given for prevention or treatment of motion sickness and labyrinthine disorders, but its side-effects limit its usefulness.

**Phenothiazines**

These are broadly anti-histamines, tranquillizers and sedatives and all of this group of drugs have some anti-emetic action (Dundee et al., 1965), chlorpromazine being one of the first to be used in the control of nausea and vomiting. They appear to be particularly effective against drugs acting on the CTZ, while larger doses may also depress the vomiting centre. In general the group is best for the prevention of opiate-induced nausea and vomiting, but less effective against motion sickness and with no direct effect on gastric emptying. This group is of limited benefit in treating sickness from cytotoxic drugs (Seigel and Longo, 1981).

The phenothiazines based on the piperazine ring, are more effective as anti-emetics than the other groups, but they carry a high risk of causing extrapyramidal effects. These are more likely when the drugs are repeated 6–8 hourly as the side-effect liability is cumulative and outlasts the anti-emetic action. These effects, which occur with several different groups of anti-emetics, fall into four groups (Ayd, 1961; Dundee, Clarke and Carruthers, 1975): (1) Akathisia or motor restlessness may be described aptly as “the jitters”; the patient is unable to sit or lie still. While it frequently requires some days of continuous medication to develop, it has been seen following a single dose.

Phenothiazines

(2) Acute dystonia involves painless spasmodic contractions of one or more muscle groups, producing trismus, torticollis and opisthotonos. The best known condition of this group is the ocular gery crisis during which the eyes, after being fixed in a stare, move to one side while the head tilts backward towards the same side. These are common in young males and it is particularly important to be aware of this condition in the differential diagnosis of tetanus. The history of drug administration and lack of pain are the main points in confirming their origin.

(3) Pseudo-parkinsonism is characterized by immobility, muscular weakness and excessive salivation, while tremor is unusual.

(4) Persistent “tardive” dyskinesia, like pseudo-parkinsonism, is mainly a phenomenon of prolonged administration of these drugs for schizophrenia and both problems occur particularly in the elderly.

All these side-effects subside with discontinuation of the drug therapy, but the acute episode can be terminated rapidly with promethazine (12.5 mg i.v. + 12.5 mg i.m.)—another phenothiazine, but lacking the incriminated piperazine ring. Perhaps the most important practical point is that extrapyramidal side-effects are much less common when the drugs are given in combination with opiates, as indeed they usually are.

The anti-emetic efficacy of the phenothiazines is compared in figure 2, showing the greater effectiveness of those with a piperazine ring. Members of this group include perphenazine, prochlorperazine, thiethylperazine and trifluoperazine.

**Perphenazine** (Fentazin) is the most widely used of this group, in a dose of 2.5–5 mg i.m. or 2–4 mg orally. It is effective i.m. as a prophylactic against the emetic effects of morphine 10 and 15 mg or pethidine 100 mg when both opiate and anti-emetic are given together, but its action does not last as long as that of morphine (Dundee et al., 1975). The oral route is more commonly used for prevention of sickness in patients having radiotherapy or
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Post-operative emetic score

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pethidine</td>
<td>100 mg</td>
</tr>
<tr>
<td>Atropine</td>
<td>0.6 mg</td>
</tr>
<tr>
<td>Promazine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Promazine</td>
<td>25 mg</td>
</tr>
<tr>
<td>Trifluromazine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Propiomazine</td>
<td>40 mg</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>20 mg</td>
</tr>
<tr>
<td>Thiethylperazine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Promethazine</td>
<td>50 mg</td>
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<tr>
<td>Promethazine</td>
<td>25 mg</td>
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<tr>
<td>Promethazine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Promethazine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Hyoscine</td>
<td>0.4 mg</td>
</tr>
</tbody>
</table>

FIG. 2. Ridit analysis of the postoperative “emeti scores” following premedicant combinations as listed. (Reproduced by permission of the editor, British Journal of Anaesthesia (from Dundee et al., 1965.).)

chemotherapy, but with repeated dosage in the absence of an opiate the likelihood of toxic side-effects is considerable.

Prochlorperazine (Stemetil; Compazine) is less potent than perphenazine and the effective dose is 5–20 mg i.m. or oral. It is similar in action to perphenazine, although its lesser sedative action may commend it as an alternative.

Thiethylperazine (Torecan) is available as a 10-mg tablet or injection and is indistinguishable clinically from the above. It is used mainly for the relief of dizziness and nausea in middle ear disturbances.

Trifluoperazine (Stelazine) is used in a dose of 1–2 mg, but mainly in psychiatric practice.

Promethazine (Phenergan) is used widely in a dose of 25–50 mg as a premedicant, singly and in combination with pethidine (Pamergan). It is a potent sedative and anti-emetic, but does cause some restlessness and an increase in the excitatory effects of methohexitone anaesthesia (Dundee et al., 1965). It should be used only when the sedative action is required.

Piperazines are closely related chemically to the phenothiazines, and cyclizine is the most effective and least toxic of the group. It is available in tablet form as the hydrochloride (Marzine) and in injectable form as the lactate (Valoid), the usual dose being 50 mg for an adult. It is absorbed rapidly from the gastrointestinal tract, its effect commencing in 15–30 min and lasting 3–6 h. It is used widely in the prevention of motion sickness or postoperative vomiting and Dundee and co-workers (1975) have demonstrated its efficacy when given with morphine or pethidine. Cyclizine 50 mg appears to be as effective as perphenazine 5 mg, but again its duration of action may be exceeded by that of morphine. It frequently causes drowsiness and drying of the mouth, but extrapyramidal effects are rare, apart from some restlessness with high or repeated doses. With high and repeated doses, teratogenic lesions have been found in rats, mice and rabbits, but several extensive studies when it was given in the management of morning sickness (McBride, 1963; Stalsberg, 1965; Midwinter, 1971) have not demonstrated these effects in man.

Other drugs of this family include meclozine (Ancoloxin) buclizine (Equivert) and cinnarizine (Stugeron), but they have no clear advantages over the better known cyclizine.

Ethanolamines constitute a third group of antihistamines which is also anti-emetic. They include diphenhydramine hydrochloride (Benadryl), and dimenhydrinate (Dramamine, Gravol). They are more effective as antihistamines with significant atropine-like and sedative activity in the 50-mg oral dose. Unlike the phenothiazines, they have been used more in the prevention of travel sickness and vertigo and the fact that they are more likely to cause sedation than extrapyramidal effects makes them safer for use outside hospital. Dimenhydrinate is, however, less effective than hyoscine in prevention of motion sickness (Brand and Perry, 1966) while causing greater disturbance in co-ordination.

Butyrophenones include haloperidol and droperidol, both powerful anti-emetics in clinical doses, but the high frequency of motor restlessness and anxiety when they are given alone prevents their use...
for anti-emetism (Morrison, Clarke and Dundee, 1970; Patton, Moon and Dannemiller, 1974). Droperidol also has a sedative action and in conjunction with an opiate it may be used as a premedicant in doses of 2.5–5.0 mg i.m., although there seems little place for a compound with such troublesome effects, outside the operating theatre or in treating the severe vomiting associated with cytotoxic therapy.

**Metoclopramide** (Maxolon) has the specific property of hastening emptying of the stomach and movement along the upper gastrointestinal tract (Jacoby and Brodie, 1967). It has also been shown to inhibit both the vomiting centre and the CTZ and to increase the tone in the lower oesophageal sphincter (Brock-Utne et al., 1978). It has been of particular value in radiology and gastroenterology, but its place in prevention of emesis after operation is less certain. Handley (1967), Clark and Storrs (1969) and Lind and Breivik (1970) have demonstrated the effectiveness of metoclopramide 10 and 20 mg when given at the end of minor gynaecological procedures, but Ellis and Spence (1970) and Dundee and Clarke (1973) found that it did not significantly reduce the frequency of sickness after operation. On the other hand, when given in combination with pethidine 100 mg, it does cause a significant reduction in the frequency of nausea and vomiting. Assaf and his colleagues (1974) accounted for some of the discrepancy by showing that it had a short duration of action and was, therefore, of limited value against morphine-induced nausea or vomiting. It is one of the least toxic of the anti-emetics, although extrapyramidal symptoms, including oculogyric crises, have occurred following prolonged use. I.v. injection of normal doses may cause restlessnes.

Recently a new regimen of “high dose metoclopramide” has been advocated (Strum et al., 1982) for the treatment of cisplatin-induced emesis. The dosage studied has been up to 10 mg kg\(^{-1}\) over 24 h and while there have been sedation and the expected side-effects, these were not clinically important. At present this appears to be the most effective treatment for this particularly intractable problem which might otherwise have necessitated discontinuing therapy.

**Domperidone** (Motilium) is a benzimidazole derivative, chemically unrelated to the phenothiazines or butyrophenones, and experimental work showed that it inhibited the CTZ and increased gastric emptying. Clinical studies (Fragen and Caldwell, 1978) in which domperidone 4 mg or 10 mg i.v. was given for treatment of established vomiting showed that it was significantly more effective than a placebo. Brock-Utne and his colleagues (1980), giving 0.2 mg kg\(^{-1}\) to pregnant and non-pregnant patients, demonstrated an increase in the tone of the lower oesophageal sphincter which could contribute to this. However, the drug has a short duration of action (2–4 h) and Wilson and Dundee (1979) found that it was not effective as a prophylactic against pethidine- or morphine-induced emesis when given in a 10- or 15-mg dose with the opiate.

The cannabinoids (THC) and particularly the synthetic derivative, nabilone, have recently been evaluated (Vincent et al., 1983) as anti-emetics with chemotherapy, but their high efficacy is marred by the expected side-effects.

A useful hypothesis regarding anti-emetism by Peroutka and Snyder (1982) made the point that all these drugs block histamine \(H_1\), muscarinic cholinergic or dopamine \(D_2\) receptors and new advances might be achieved with a drug combining these actions.

**REFERENCES**


