# Review Article

# Anaesthesia and emesis II: Prevention and management

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Many of the factors which influence the incidence of nausea, retching and vomiting (emesis) were discussed in part one of this review.[1] Some, such as duration of anaesthesia and operative site are predetermined and thus may bias a patient towards a high incidence of emetic symptoms. However, other factors, such as postoperative movements, opiate premedication and gastric inflation, are more easily controlled by the anaesthetist.

This article discusses methods available for prevention and management of postoperative emesis under three main sub-headings: prophylactic measures to help prevent emetic symptoms, specific (antiemetic) agents for prophylaxis and treatment, and general management after emesis has begun.

## Prophylactic measures

Most of the general measures to help prevent postoperative emesis can be taken before or immediately after anaesthesia. Although opiates may be avoided at premedication, it is difficult to suggest that opiates used for maintenance of anaesthesia should be omitted on the strength of their emetic potential, for this in our view is overwhelmingly offset by their other useful properties. However, if opiate premedication is desirable it should be combined with a long acting antiemetic.

Prevention of emesis is paramount in patients with a full stomach presenting for emergency surgery. The problem is one of possible vomiting during induction of anaesthesia, or aspiration of regurgitated stomach contents following muscle relaxation and attenuation of the laryngeal and pharyngeal reflexes. Furthermore, a full stomach preoperatively is likely to remain a full stomach postoperatively and might influence the incidence of emesis during this period. Active vomiting during induction of anaesthesia is uncommon, but regurgitation of stomach contents is more frequent. In an effort to avoid these complications, methods have been devised either to empty the stomach, or prevent its contents from reaching the laryngeal part of the pharynx, thus reducing the risk of aspiration.

Allowing the stomach to empty naturally is normal anaesthetic practice before routine operations and most anaesthetists request that patients be fasting for four to six hours. However, even among non-surgical subjects gastric emptying time is variable and is more likely to be between six to eight hours;[2] unfortunately, in emergency operations this time period is not reliable. Howard's observation, that stomach emptying was delayed for 24 hours after major trauma during the Korean war,[3] suggests that it is prudent to treat all trauma patients as though they have a full stomach, regardless of the period of fasting. Stomach emptying is additionally impaired by pain, anxiety, fear, alcohol, analgesics, pregnancy, labour, hypotension, intra-abdominal conditions that lead to ileus or obstruction, and by large meals. The stomach empties at an

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exponential rate in relation to the size of the meal; thus, within the same time span, large meals will leave a larger residue than smaller ones. Solids and fats similarly will remain in the stomach longer.[4]

Techniques to actively empty the stomach include passage of stomach tubes or administration of apomorphine to induce vomiting, but these methods are both unpleasant and inefficient. Recently, drugs such as metoclopramide have been used to speed gastric emptying; radiologists have been using metoclopramide to accelerate barium meals for a number of years.[5,6] Howarth[7] showed, using barium meals, that after intravenous metoclopramide 20 mg the mean gastric emptying time was 83 minutes, as compared with a group of control patients where the mean gastric emptying time was 142 minutes; in a further group of patients given an intravenous injection of 2 ml physiological saline, the mean gastric emptying time was 195 minutes, the increased duration was attributed to possible inhibition of peristalsis following a vene puncture. On the strength of these findings, Davies and Howells gave 20 mg of metoclopramide intravenously to patients who had sustained a recent injury.[8] These patients had received small barium meals (15 ml) before the administration of metoclopramide and then the barium studies were repeated; although only a small number of patients were studied, the results were encouraging. However, one cannot always rely on metoclopramide to empty the stomach.

The most common method for avoiding vomiting or regurgitation during induction of anaesthesia is a rapid sequence technique following a period of reoxygenation. This combination along with Sellick's manoeuvre (cricoid pressure) has proved popular and efficient. However, it should be noted that, if increasing cricoid pressure is applied before the onset of sleep, a feeling of nausea and a desire to gag is easily elicited. Although we have not seen a patient vomit from this manoeuvre, it would be more pleasant to apply the cricoid pressure as the patient loses consciousness.

In part I of this review it was suggested that gastric inflation, after induction of anaesthesia, by vigorous manual ventilation with a face mask, increases the incidence of emesis in the immediate postoperative period.[1] Preoxygenation before muscle relaxation and avoidance of gastric inflation during the apnoeic phase before tracheal intubation are satisfactory solutions to this problem.

After certain operations, such as rhinoplasty, it is common for the patient to have post-nasal bleeding. Careful and effective oropharyngeal packing with gauze can prevent blood reaching the stomach during surgery. Any blood that does reach the stomach might act as a potent emetic stimulant and vomiting resulting from this can promote further bleeding from the nasal area, which is particularly undesirable postoperatively.

On emergence from anaesthesia there are two potent causes for gagging with possible vomiting, namely pharyngeal suction and the presence of an airway. As patients awaken, the gag reflex returns and pharyngeal stimulation during this period might result in vomiting. Fortunately this period is not often remembered by patients; however, while consciousness is still dulled, vomiting remains hazardous. Pharyngeal suction is best done before reversal of muscle relaxation; any further secretions that might accumulate after reversal are easily dealt with by turning the patient onto one side to encourage free drainage. Similarly, early removal of the airway and positioning should reduce pharyngeal stimulation without jeopardising the patient's airway. Nasogastric tubes may help reduce postoperative vomiting in those cases where an upper gastrointestinal operation is done; however, the continuing presence of a tube in the postoperative period might increase retching.[9]

During the postoperative period, excessive movement of the patient, especially after the administration of opiates might provoke nausea. It is not uncommon to hear that a patient, who had been trouble-free in the recovery room, began to vomit on return to the ward. One answer to this problem is the use of a 24-hour recovery area near the operating rooms; not only does this reduce repeated postoperative movement but might also improve general postoperative care. Attention to other factors, such as adequate pain relief, hydration and maintenance of blood pressure, contributes to the prevention of postoperative emesis.

## Specific methods

*Prophylactic and therapeutic use of antiemetics*

In the early part of this century several agents were used to prevent postoperative vomiting; they in-

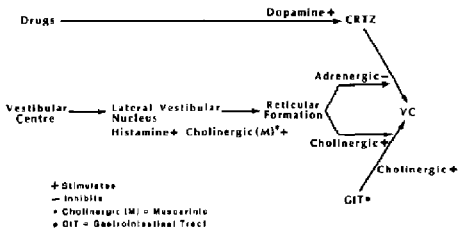


FIGURE Probable neurotransmitter and receptor sites for vomiting.

cluded preoperative administration of chloretone, perfumed gauzes during the later stages of the operation, or rectal administration of potassium bromide, aspirin and glucose.[10] However, the great impetus to the study of antiemetics came during the second World War. Sea sickness was a known handicap to military personnel, and both British and American workers tested a number of agents in a series of unpopular trials (for both the subjects and investigators). Among the agents tested, hyoscine proved to be the most effective against motion sickness. Since then several types of agents have been found to have antiemetic properties, including anticholinergics, antihistamines, phenothiazines, sedatives, cannabinoids and the antidopaminergics metoclopramide and domperidone. Many of these antiemetics have more than one mechanism of action. The Figure and Table show the probable neurotransmitters, their sites of action, and the activity of a number of antiemetic agents at the neuroreceptor sites.

Adriani *et al.* Considered prophylactic administration of antiemetics unjustified[12] and with some exceptions we agree with this view. In their series, only 3.5 per cent of patients had severe persistent vomiting that needed treatment. A large percentage of the postoperative vomiting occurred at emergence from anaesthesia and did not recur; the incident, they suggested, is not usually remembered by the patient, and does not call for treatment by antiemetics. If antiemetics were innocuous, widespread prophylaxis would be acceptable. However, the high incidence of side effects from these drugs should caution anaesthetists against indiscriminate use, reserving antiemetics for specific prophylactic use when indicted, or for therapy when patients are experiencing persistent symptoms.

TABLE Activity of drugs at neurotransmitter receptor sites (adapted from Peroutka and Snyder)[11]

| *Drug* | *Dopamine ($D_2$)* | *Muscarinic cholinergic* | *Histamine ($H_1$)* |
|---|---|---|---|
| *Anticholinergics* | | | |
| Hyoscine | negligible | +++++ | negligible |
| Atropine | negligible | +++++ | negligible |
| Glycopyrrolate | negligible | ++−++ | negligible |
| *$H_1$ Antihistamines* | | | |
| Promethazine | +++− | ++++ | +++++ |
| Diphenhydramine | negligible | ++++ | +++++ |
| Cyclizine | + | +++ | +++++ |
| *Phenothiazines* | | | |
| Fluphenazine | +++++ | +++− | +++++ |
| Prochlorperazine | +++++ | +++− | ++++ |
| Chlorpromazine | +++++ | ++−+ | +++++ |
| *Butyrophenones* | | | |
| Droperidol | ++++− | negligible | + |
| Haloperidol | +++++ | negligible | + |
| *Miscellaneous* | | | |
| Metoclopramide | ++++ | negligible | + |
| Domperidone | ++++ | negligible | negligible |

Some situations might merit prophylactic antiemetics, for instance, oral surgery patients who have their jaws occluded by wires. Such patients are at high risk for aspiration due to an inability to rid the mouth rapidly of vomitus. Patients undergoing ear, eye or plastic operations should also be considered for prophylaxis because of the possible detrimental consequences to delicate surgical work. It is difficult to suggest that all patients with known increased risk of vomiting should be given prophylactic antiemetics, as this would result in all women being so treated. However, if the operating room is a twenty-minute, uneven ride from the ward, and the patient is female, had an opiate premedicant, and is to undergo upper abdominal surgery, prophylaxis would not be unreasonable.

There are now several antiemetic drugs available, but the difficulty is to decide which one to use. Drugs that might be effective prophylactic agents may be ineffective or unsuitable for treatment of active vomiting. Furthermore, the causes of postoperative emesis are multifactorial so that no one single agent is appropriate. Combination antiemetic therapy has not been investigated in relation to anaesthesia. One can speculate that combining

agents active at different sites might have advantages; synergism between drugs might allow smaller individual doses, and might reduce the incidence of side effects.

A review of some of the data on the commonly used antiemetics might help guide our decisions.

*Anticholinergics*

Atropine, hyoscine and glycopyrrolate are familiar drugs in this group; they antagonise the muscarinic effects of acetylcholine. Hyoscine and atropine are tertiary ammonium compounds and differ from glycopyrrolate, a quaternary compound, in their central effects. It is perhaps for this reason that glycopyrrolate appears to have no antiemetic properties.[13] Hyoscine and atropine act on the vomiting centre; however, hyoscine has the greater sedative properties. Hyoscine is a very effective prophylaxis against sea sickness and is also effective once symptoms of motion sickness are present. Sympathomimetics given concurrently with hyoscine improve its effectiveness; dexamphetamine 5 to 10 mg has been suggested but attention was drawn to the abuse potential of this drug.[14]

In a study by Clarke *et al.*,[15] hyoscine proved to be an effective prophylactic agent for pre- and postoperative nausea and vomiting when these were induced by 10 mg of morphine premedication. Unfortunately the antiemetic effect of hyoscine is outlasted by the emetic properties of morphine. Atropine was also an effective prophylactic agent, but only for the postoperative period. Clarke *et al.* concluded that hyoscine was the superior drug for premedication, not only for its antiemetic properties but also for its sedative qualities. However, there are more specific agents than atropine or hyoscine. Furthermore, the side effects of dry mouth, and sedation and occasional disorientation in the elderly after hyoscine, have contributed to the restriction of these drugs as premedicants.

*Phenothiazines*

Although the drug phenothiazine was synthesised in 1883, it was not until the 1940s that the group of phenothiazine drugs was developed in France. Researchers were seeking an antiparasitic agent; however, the antihistaminic and sedative effects of promethazine were discovered and it was used as an adjuvant to anaesthesia.[16] The drugs in this group are qualitatively similar but differ quantitatively in their actions. These differences are predictable from their chemical structure. The phenothiazines share a common tricyclic nucleus; on the ten position in the tricyclic nucleus, the attached radical may be either an aliphatic (dimethylamino) chain or a heterocyclic ring (piperazine and piperidine).[17] The clinical importance of these groups is that the dimethylamino phenothiazines (promethazine and chlorpromazine) are less potent and have significantly more sedative action than the piperazines (prochloperazine and perphenazine); the latter have correspondingly greater antiemetic properties. The phenothiazines are predominantly antidopaminergic agents with moderate antihistaminic and anticholinergic activity. Because of this widespread activity these agents are found to be effective and therefore popular for prophylaxis and treatment of emesis.

Chlorpromazine possesses significant prophylactic antiemetic properties; however, in effective doses, undue sedation and hypotension are frequent side effects.[18] Promethazine has been very popular as a premedicant; other than its antiemetic action it has the advantage of anticholinergic and potent antihistaminic properties which make it a useful premedicant for asthmatic patients. Promethazine is an effective prophylactic antiemetic but tends to cause greater delay in awakening from anaesthesia than the piperazines.[19] When promethazine is administered for treatment of active vomiting, an intravenous dose of 12.5 mg has been shown to be effective with little change in blood pressure, although with varying levels of subsequent sedation.[12] Chlorpromazine has no effect against motion sickness, and promethazine is the most potent of the phenothiazines for this problem. When motion sickness is an important etiological factor in postoperative emesis, this drug would be preferable to hyoscine because of its longer duration of action. Similarly, promethazine is the prophylactic antiemetic of choice for ear sugery. However, chlorpromazine and promethazine administered after anaesthesia have the capacity to induce sleep in patients who are still recovering from other anaesthetic agents. This can be potentially hazardous while vomiting is still not effectively controlled.

Prochlorperazine and perphenazine have justifiably been the most popular of the phenothiazines for both prophylaxis and treatment of vomiting associated with anaesthesia. They both have potent

antidopaminergic activity and are therefore well suited to combat opiate-induced vomiting. Furthermore, prochlorperazine, unlike promethazine, increases lower oesophageal sphincter tone despite its minimal anticholenergic activity.[20] Prochlorperazine and perphenazine are equally effective against vomiting, but perphenazine in clinical situations appears to have more sedative properties. Loeser demonstrated that prochlorperazine was effective treatment for vomiting, but that onset time following an intramuscular injection of 10 mg was between 0.5–1 hour and was only effective for four hours.[21] Perphenazine in a dose of 5 mg intramuscularly has been shown to be effective prophylaxis when administered with either morphine 10 mg or meperidine 100 mg.[22] However, the emetic effect of morphine will outlast the action of perphenazine. In order to reduce the high incidence of restlessness seen with perphenazine, smaller doses of only 2.5 mg have been used; they were less effective against emesis but the incidence of restlessness was reduced.[22] Unfortunately, although perphenazine and prochlorperazine are effective antiemetic agents, they frequently cause extrapyramidal side effects.[23] This can be manifest as simple restlessness, which might be attributed to another cause or, more rarely, as a frank oculogyric crisis. These effects may be seen after a single dose sometimes up to 24 hours after administration. Paradoxically, the most appropriate treatment for extrapyramidal problems is the intravenous administration of another phenothiazine, promethazine 10–25 mg, repeated if necessary. Alternative management with an anti-Parkinsonian drug, such as benzotropine is effective. However, this drug is not an antiemetic, which under these circumstances would be desirable.

*Butyrophenones*

Haloperidol and droperidol are powerful antidopaminergic agents with neuroleptic properties. In a study by Shields *et al.* among volunteer inmates of a state penitentiary, haloperidol was found to be a potent prophylactic antiemetic against apomorphine induced vomiting. Its action lasted for 12 hours after intramuscular injection; also, it caused less restlessness or drowsiness than prochlorperazine and was less painful on injection than perphenazine.[24] In a later study by Tornetta among women undergoing minor gynaecological operations, intramuscular doses of prophylactic haloperidol from 0.5–4 mg were effective antiemetics with no significant effect on the speed of emergence from anaesthesia.[25] Haloperidol for treatment of vomiting was effective in intramuscular doses of 2 mg. It had a rapid onset (within 30 minutes), but its duration appeared to be as short as three hours.[21] Haloperidol is rarely used for emetic control in anaesthesia today; this is difficult to understand for it is very similar to the piperazine phenothiazines in action but seems to have less severe side effects.[26]

Droperidol is similar to haloperidol and has received much attention as an antiemetic. In the comparative study conducted by Loeser the therapeutic effect of droperidol 5 mg intramuscularly had a slower onset (2 hours) than haloperidol; however, its action persisted for 24 hours.[21] This is difficult to explain in view of the shorter half life of droperidol. The prophylactic efficacy of intravenous droperidol in doses of 0.005–0.07 $mg \cdot kg^{-1}$ is well documented, and its action seems to be longer (up to 24 hours) than any other agent in common use.[27–30] This long duration of activity, combined with its efficacy, are significant enough to make droperidol our prophylactic drug of choice. Droperidol in the larger doses might cause disturbing mental effects which are not apparent to the observer and it is best avoided in the awake patient unless given with a long-acting opiate. However, recent work suggests that it may be given alone in small doses of 1.25 mg to awake patients with few side effects.[29] Both droperidol and haloperidol, in repeated doses, might produce extrapyramidal side effects, hypotension, and postoperative sedation but these are less severe than with the phenothiazines. Droperidol 5 mg intravenously, although possessing alpha-adrenergic antagonist properties, does not appear to decrease lower oesophageal sphincter tone.[20] However, in the same study there was a suggestion that gastro-oesophageal reflux was increased.[20]

*Antihistamines*

These drugs were first introduced by Bovet in 1944, and comprise a heterogenous group of agents, among which the most familiar to the anaesthetist are dimenhydrinate, promethazine, cyclizine and diphenhydramine.[31] These preparations are excellent for motion sickness, their main action being at the vomiting centre and on vestibular pathways; however, all these agents can cause sedation. Other

than promethazine, which has been discussed, they have little activity at the chemoreceptor trigger zone (CRTZ). Cyclizine is a widely used antihistamine in anaesthesia. It has proven efficacy equal to perphenazine as a prophylactic antiemetic and is also effective for treatment of established vomiting.[22,32] Cyclizine also increases the lower oesophageal sphincter pressure and reduces gastro-oesophageal reflux.[20] Although cyclizine has a short duration of action (4 hours), it is our first drug of choice for the treatment of postoperative vomiting because of its low incidence of side effects compared to the phenothiazines. It has not been reported to cause oculogyric crisis but repeated doses can lead to restlessness and drowsiness.

*Antidopaminergics*

Metoclopramide and domperidone are specific antidopaminergic drugs which are not phenothiazines and do not possess antihistaminic properties. Metoclopramide has been available for some time, whereas domperidone has been introduced recently. These specific antiemetics have the advantage of causing very little sedation in normal doses. Additionally domperidone, unlike metoclopramide, has difficulty in passing the blood brain barrier, thus its antidopaminergic activity is at peripheral sites only. This allows domperidone to influence the CRTZ which is outside the blood brain barrier without affecting the basal ganglia. Furthermore, both drugs have effects on the gastro-intestinal tract which include increased lower oesophageal sphincter pressure and faster gastric emptying. The extract mechanism for these gastro-intestinal effects is not clear.[33,34] Unlike the groups of drugs that have been discussed so far, metoclopramide and domperidone have not proven to be effective in either prophylaxis or treatment of postoperative vomiting. Prophylaxis with metoclopramide appears to have only been effective when the drug was administered at the end of the operation; it has shown poor antiemetic activity when administered with the premedication.[35–40]

The value of metoclopramide for the treatment of vomiting after anaesthesia has not been extensively studied. In the best controlled of the studies, Korttila *et al.* compared the prophylactic and therapeutic efficacies of droperidol, metoclopramide and domperidone. They observed that metoclopramide and domperidone were no better than placebo for either prophylaxis or treatment of postoperative vomiting.[29] In view of the evidence available, metoclopramide can only be recommended for emetic control if administered at the end of anaesthesia; furthermore, in the event of it being ineffective after a single dose we recommend another agent such as cyclizine. Domperidone was specifically designed as an antiemetic with few central side effects. Studies so far suggest that domperidone appears to be better for treating postoperative vomiting than for prevention.[41–43] Cooke found that 4 mg of intramuscular domperidone given at induction to women undergoing short gynaecological procedures was not statistically better than placebo.[41] Among a similar group of patients, Wilson and Dundee administered either 10 or 15 mg doses of intramuscular domperidone at the time of meperidine or morphine premedication. Their only positive finding was a reduction of preoperative nausea and vomiting associated with meperidine; domperidone had no apparent effect on postoperative emetic sequelae.[42] Thus it would seem that any prophylactic effect of domperidone is short lived.

Domperidone has been more effective in the treatment of postoperative vomiting. Fragen and Caldwell reported a significant reduction in postoperative nausea and vomiting in the first two hours following an intravenous injection of 10 mg of domperidone compared to placebo.[43] Other studies have also confirmed the superiority of intravenous domperidone over placebo for the treatment of nausea and vomiting.[44,45] In the two studies where domperidone 10 mg was given intramuscularly for the treatment of vomiting it has been ineffective; this might be dose related.[29,46] All studies report a low incidence of side effects with both domperidone and metoclopramide. Overall it appears that domperidone is more suited for treatment than for prophylaxis of emesis, whereas metoclopramide should only be considered for immediate prophylaxis.

*Miscellaneous*

Two other groups of agents, benzodiazepines and cannabinoids, are being investigated for their antiemetic effect against cytotoxic agents. The former have been successfully used as an adjunct to conventional antiemetic therapy. Benzodiazepines appear to remove the anxiety associated with the "threat of vomiting," that often leads patients to

refuse chemotherapy. Furthermore, they help reduce the frequency of vomiting.[47,48] Patients who might be anxious about postoperative sickness can benefit from these preparations, but it would be difficult to prove their antiemetic effectiveness under these circumstances.

In 1975, young cancer patients at the Sidney Farber Institute reported that they experienced less emetic side effects from their therapy while smoking marijuana.[49] Much interest was aroused in this substance and its derivatives. The active component delta-9-tetrahydrocannabinol and a synthetic cannabinoid, nabilone, have been shown to have antiemetic properties.[50,51] The mechanism of action of these agents is uncertain, although marijuana is known to possess adrenergic activity.[52] However, it is unlikely that cannabinoids will find a place in routine anaesthetic antiemetic practice, since there is a high incidence of side effects including sedation, hypotension, dysphoria, unsteadiness, dry mouth and feelings of intense panic or fear.

## General therapeutic measures

Once a patient has started vomiting, there is a tendency among anaesthetists to rely heavily on the efficacy of antiemetic drugs. However, there are some simple measures which help reduce the patient's discomfort. The vomiting patient will need increased intravenous fluids. These should be sufficient to offset hypotension caused by both fluid loss and antiemetic drugs; hypotension is thought to make vomiting more likely. If patients have pain, it is better to treat this with opiates than to withhold treatment for fear of further opiate induced vomiting, although local and regional analgesic techniques should not be forgotten. In addition, pain itself can be one of the causes of vomiting, and any patient who is retching can only be expected to suffer more pain from the further stress on incision sites.

Insisting that patients keep their oxygen masks in place while nauseated may only increase the unpleasant feeling of stuffiness that some patients experience. It is common to hear the nursing staff encourage patients to take deep breaths while the latter are feeling nauseated. Although poorly explained, this is a well-recognised and effective way of decreasing nausea, thus "buying" time while antiemetic drugs are being prepared. If patients in the recovery room have vomited a number of times, it would be unkind to send them back to the ward on the strength of their being alert. These patients are best held back, perhaps for a further hour or more. This does not guarantee reduced vomiting, but it does allow the attendants to observe the patients' progress and then perhaps administer a second antiemetic if the first one was ineffective. Finally, we would recommend that patients about to enter the postoperative recovery room not be placed close to a vomiting patient. Any patient, put beside another actively vomiting one, might be sufficiently stimulated by psychic, visual, olfactory and auditory inputs to feel nauseated themselves.

## Conclusion

The causes of emesis associated with anaesthesia are varied and in any one patient are likely to be multifactorial. Our approach has been to emphasise those areas which can be controlled. However, general prophylactic measures, such as reduced gastric inflation, avoidance of opiate premedication and pharyngeal stimulation, might not be sufficient to prevent emesis. Although we do not recommend routine preoperative use of antiemetics because of their relatively high incidence of side effects, we do feel there is a place for prophylaxis under certain circumstances. Our drug of choice for prophylaxis would be droperidol 0.175 $mg \cdot kg^{-1}$ intravenously, given peroperatively, although a smaller dose can be effective. For operations involving the ear we would prefer promethazine given with the premedication or peroperatively. Once nausea and vomiting have begun, cyclizine 25–50 mg intramuscularly, or one of the piperazine phenothiazines (prochlorperazine or perphenazine), would be appropriate. In the event of the first choice drug being ineffective, we would encourage the use of a second agent, preferably one with a different site of action. We feel that familiarity with a few drugs and more attention to the controllable factors mentioned should help reduce postoperative emesis.

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