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Intranasal Metoclopramide

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Contents

Abstract

▲ Intranasal metoclopramide is a new formulation of an established and effective antiemetic drug.

▲ Absorption after intranasal administration was lower than after oral or intravenous administration; otherwise the pharmacodynamic and pharmacokinetic profiles of the intranasal and parenteral formulations were similar.

▲ Intranasal and intramuscular metoclopramide showed similar efficacy in the control of acute emesis induced by moderately emetogenic chemotherapy in 12 patients. Intranasal metoclopramide 80mg significantly reduced the frequency of acute vomiting in 43 patients receiving highly emetogenic chemotherapy.

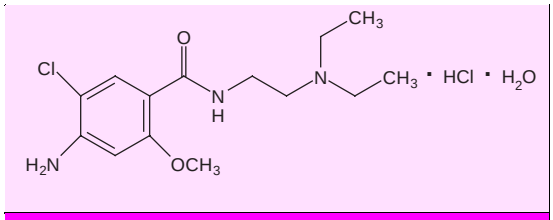
▲ A pilot study suggested that intranasal metoclopramide, with or without dexamethasone, may reduce cisplatin-induced delayed emesis. In a randomised crossover trial in 40 patients, intranasal metoclopramide or oral metoclopramide, both with dexamethasone, were equally effective in the control of delayed emesis induced by moderately-emetogenic chemotherapy.

▲ One 30 patient study suggests that intranasal metoclopramide has similar efficacy to oral metoclopramide in the treatment of functional dyspepsia.

▲ A non-significant trend to reducing postoperative nausea and vomiting has been seen in two trials of intranasal metoclopramide.

▲ Intranasal metoclopramide caused minor irritation of the nasal membrane and unpleasant taste in some patients, but was otherwise well tolerated. None of the more serious extrapyramidal effects sometimes associated with metoclopramide were reported.

Features and properties of intranasal metoclopramide	
Indications	
Chemotherapy-induced emesis, postoperative emesis, functional dyspepsia	
Mechanism of action	
Stimulates upper gastrointestinal motility, inhibits neurological action of emetogenic stimuli	Dopamine and 5-hydroxytryptamine antagonist
Dosage and administration of intranasal metoclopramide	
Dose per puff	10 or 20mg
Chemotherapy-induced emesis: acute	20mg before chemotherapy then 120 to 360mg daily
:delayed	60 to 160mg daily
Postoperative emesis	40 to 80mg in first hours after surgery
Functional dyspepsia	20 to 30mg daily
Pharmacokinetic profile (40mg as single intranasal dose in healthy male volunteers)	
Peak plasma concentration	48.3 μg/L
Time to peak plasma concentration	1.92h
Area under the plasma concentration-time curve	478 μg/L • h
Elimination half-life	7.14h
Adverse events	
Most frequent	Transient nasal membrane irritation, unpleasant taste, sleepiness
Serious events	None reported



Metoclopramide

Control of iatrogenic nausea and vomiting is an important clinical objective following surgery and some cancer chemotherapy regimens. Metoclopramide has been prescribed for these indications for >30 years and is an effective and well tolerated antiemetic. Metoclopramide is primarily a dopamine antagonist, but high doses of the drug block serotonin (5-hydroxytryptamine; 5-HT) agonism of 5-HT_3 receptors, highlighting the role of the serotonin/5-HT_3 receptor interaction in emesis. Although specific 5-HT_3 antagonists are now available, they are expensive and have been shown to be no more effective than parenteral metoclopramide (when both are combined with dexamethasone) for the control of delayed emesis after emetogenic chemotherapy.[1] Similarly, the American Society of Health-System Pharmacists guidelines on the pharmacological management of emesis recommends dexamethasone with either metoclopramide or a 5-HT_3 receptor antagonist for the control of cisplatin-induced delayed emesis.[2] Therefore, on pharmacoeconomic grounds, parenteral metoclopramide still appears to be the first choice for the control of delayed emesis after chemotherapy.[3,4]

However, intramuscular or intravenous administration of antiemetics can meet with patient resistance, particularly following chemotherapy where emesis may need to be controlled for several days. The alternative, oral administration, is often unsuitable because vomiting can prevent absorption of the drug.

The discovery that metoclopramide was readily absorbed through the nasal mucosa[5] led to the development of intranasal metoclopramide spray.[6,7] This formulation aims to provide the advantages of parenteral forms of the drug without the compliance problems.

1. Pharmacodynamic Profile

There are no published data on the pharmacodynamic effects of intranasal metoclopramide. However, oral and injected formulations have been used since the early 1970s and the pharmacodynamic properties of the drug have been clearly established and previously reviewed in *Drugs*.[8,9] Therefore, only a brief descriptive overview of the pharmacodynamic effects of orally or parenterally administered metoclopramide is presented here.

- Several actions of metoclopramide contribute to its antiemetic properties. It stimulates motility of the upper gastrointestinal tract; the mechanism is unclear but may relate to sensitisation of tissue to acetylcholine. The tone and amplitude of gastric contractions are increased and the pyloric sphincter is relaxed, thus promoting gastric emptying.[8]

- At the neurological level metoclopramide is a powerful dopamine antagonist. Dopamine levels increase in response to many emetogenic stimuli and induce nausea and vomiting by stimulating the chemoreceptor trigger zone (CTZ) in the brain. Metoclopramide blocks this action.[8]

- High doses of metoclopramide inhibit the emetogenic effects of serotonin by blocking 5-HT_3 receptors[10] located in both the brain (CTZ and nucleus tractus solitarius) and the intestinal wall.[11] Chemotherapy, especially with platinum-based drugs, induces serotonin release and this may explain why high doses of metoclopramide can limit chemotherapy-induced emesis.[12]

2. Pharmacokinetic Profile

- Absorption of intranasal metoclopramide appeared lower than that of oral and intravenous metoclopramide in a randomised 4-way crossover study.[13] 27 healthy male volunteers received metoclopramide 40mg by the intranasal, oral or intravenous route with a 7-day interval between drug administrations. Blood samples for analysis of metoclopramide concentrations were collected at intervals in the 36 hours after drug administration. The peak plasma concentrations (C_{max}) were 48.3, 105.7 and 367.3 μg/L at times (t_{max}) 1.92, 1.26 and

0.12 hours for intranasal, oral and intravenous administration, respectively. The area under the concentration time curve (AUC) for intranasal, oral and intravenous administrations were 478, 841 and 1082 μg/L · h, respectively, with terminal elimination half life values ($t_{½}$) of 7.14, 6.61 and 5.99 hours.

• Pharmacokinetic studies have also compared intranasal with intravenous metoclopramide administration in patients with cancer. Ten patients with cancer received metoclopramide nasal spray 20mg and 10 blood samples were obtained from each volunteer over the following 8 hours. Seven days later the protocol was repeated with the same 10 patients after intravenous injection of metoclopramide 20mg. To provide comparative data the experiment was duplicated in 10 healthy volunteers.[7]

• After intranasal administration in patients with cancer a C_{max} of 40.05 μg/L was attained at t_{max} 2.5 hours; AUC after intranasal administration was 195 μg/L · h compared with 266 μg/L · h after intravenous injection but this difference was not statistically significant. The elimination half-life ($t_{½z}$) was significantly shorter in the intranasal group than in the intravenous group (1.66 *vs* 2.77 hours, $p < 0.01$). The elimination rate constants after intranasal administration or intravenous administration were 0.698 and 0.255 L/h, respectively and the absolute bioavailabilty for intranasal versus intravenous administration was about 70%.[7]

• When data from patients with cancer and healthy volunteers were compared directly, only the C_{max} for intranasal administration was significantly different: values were 52.77 and 40.05 μg/L, respectively, for healthy volunteers and patients with cancer, ($p < 0.05$).[7] The t_{max} and AUC values for the 2 groups were similar and the authors considered the difference in C_{max} of little clinical significance.

3. Therapeutic Trials

Most of the therapeutic trials of intranasal metoclopramide have focused on chemotherapy-induced emesis. However, trials on the effect of intranasal metoclopramide on postoperative emesis and functional dyspepsia have also been conducted.

Emesis after Emetogenic Chemotherapy

• Emesis associated with emetogenic chemotherapy can be divided into acute (<24 hours) and delayed (24 to 120 hours) phases (fig. 1).[14] The differences in pathophysiology of the 2 phases are poorly understood, but different drug regimens are used to control acute and delayed chemotherapy-induced emesis. Generally, 5-HT_3 antagonists are most effective during the acute phase, whereas metoclopramide, usually with dexamethasone, is the most commonly prescribed antiemetic for the treatment of delayed chemotherapy-induced emesis.[3,16] The effects of metoclopramide on acute and delayed emesis are therefore discussed separately below.

Acute Cisplatin-Induced Emesis

• In a non-blinded pilot study, intranasal metoclopramide and intravenous plus intramuscular metoclopramide demonstrated similar efficacy in controlling acute emesis in patients with cancer given moderately-emetogenic cisplatin chemotherapy (20 mg/m^2).[17] Patients underwent 3 consecutive cycles of chemotherapy 7 days apart. During the first cycle (run-in phase) no antiemetic treatment was prescribed, but patients were allowed to self-administer metoclopramide intramuscularly as required. 12 patients who were nauseated or vomited during the first cycle were entered into the second

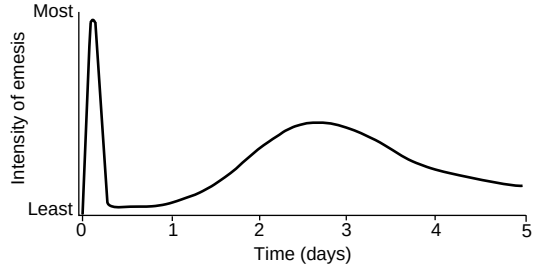


Fig. 1. Pattern of cisplatin-induced emesis. This illustrates the biphasic pattern of emesis after the administration of high-dose cisplatin chemotherapy[15] (reprinted from Tavorath and Hesketh, with permission).

phase of the trial. These individuals received the second dose of cisplatin plus metoclopramide 20mg intravenously, followed 4 and 8 hours later by metoclopramide 20mg intramuscularly. Two hours before the third cycle of chemotherapy, patients received metoclopramide 40mg by nasal spray and self-administered a further 40mg intranasally 4 and 8 hours after chemotherapy.

• Emesis was quantified by recording the number of vomiting episodes and the duration and severity of nausea (0 = absent to 3 = severe). Compared with the run-in phase, both modes of antiemetic treatment were similarly effective (fig. 2). Vomiting was well controlled [complete (0 episodes) or major (1 or 2 episodes) protection] in 9 of 12 and 8 of 12 patients during the intranasal and parenteral phases, respectively. No, or only mild, nausea was experienced by 7 of 12 patients after parenteral metoclopramide and by 9 of 12 who used the intranasal formulation. Because of the small number of patients no statistical analysis was performed.

• During the run-in phase all patients in this study self-administered 1 or 2 vials of metoclopramide intramuscularly as rescue medication to control emesis. During the treatment phases, 1 of the parenteral and 4 of the intranasal metoclopramide recipients used rescue medication. These doses were all self-administered within 8 hours of chemotherapy. Studies comparing intranasal and intramuscular metoclopramide have not been carried out, but the authors suggest that greater use of rescue medication following intranasal antiemetic therapy may reflect slower absorption of intranasal metoclopramide.

• All 12 patients expressed an 'ease of use' preference for the intranasal formulation.

• 163 patients with cancer about to undergo highly emetogenic cisplatin-containing chemotherapy (≤75 mg/m^2) for the first time all received 2 mg/kg metoclopramide intravenously before chemotherapy.[12] Patients were then randomised in a double blind design into groups (n = 38 to 43) and self-administered 8 intranasal doses of either 20, 40 or 80mg metoclopramide or placebo in the 16 hours following chemotherapy. All patients were evaluated on an intent-to-treat basis in this unpublished study.

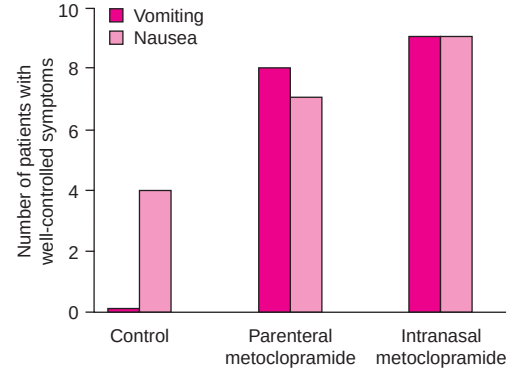


Fig. 2. Intranasal versus parenteral metoclopramide after emetogenic therapy. Comparison of the effect of parenteral metoclopramide 60mg and intranasal metoclopramide 120mg on acute vomiting and nausea after moderately emetogenic chemotherapy (cisplatin 20mg/m^2) in a study of 12 patients with cancer. During consecutive cycles of chemotherapy patients were given no antiemetic treatment, parenteral metoclopramide and intranasal metoclopramide.[17] Emesis was described as well controlled if a patient experienced complete protection (0 episodes) or major protection (1 or 2 episodes) from vomiting during the 24 hours after chemotherapy.

• The mean numbers of vomiting episodes in the 24-hour study period were 2.8, 4.5, 1.7 and 5.2, respectively, for the metoclopramide 20, 40 and 80mg, and placebo groups. The differences between active treatment and placebo reached statistical significance only in patients on the 80mg dose regimen ($p < 0.05$). Nausea was not significantly reduced compared with placebo in any of the active treatment arms.[12]

• A similar protocol to that used in the preceding study produced somewhat different results in another unpublished, double-blind, randomised, multidose trial. 90 patients with cancer received metoclopramide 2 mg/kg intravenously before emetogenic chemotherapy (several regimens were used - most contained cisplatin). Groups of 30 patients then self-administered 8 doses of intranasal metoclopramide 20 or 40mg, or placebo, over 16

hours. All 90 patients were analysed on an intent-to-treat basis.[18]

- Significant control of emesis was seen in the 20mg treatment group ($p < 0.019$ *vs* placebo), but the overall success rate was low: 28% major response (0 to 2 episodes/24 hours), 17% minor response (3 to 4 episodes/24 hours) and 55% treatment failure or equivocal response (> 5 episodes/24 hours). Patients in the 20mg treatment group experienced significantly less nausea during the 6 to 12 hours following chemotherapy ($p < 0.007$ *vs* placebo), but not at other times. Despite a trend toward reduction in vomiting with intranasal metoclopramide 40mg, there was no statistically significant difference in the number of episodes of nausea and vomiting experienced by these patients compared to those on placebo.[18]

- A third unpublished trial using the above protocol evaluated eight 20 or 40mg doses of intranasal metoclopramide or placebo in the 16 hours after cisplatin therapy in groups of 6 or 7 men with cancer.[19] A trend towards an antiemetic treatment effect in the 40mg group was observed, but there were no clinically or statistically significant differences between the 2 intranasal metoclopramide treatment arms and placebo. However, duration of nausea 6 to 12 hours after chemotherapy was reduced from 2 hours in the placebo group to 10 ($p = 0.015$) and 36 ($p = 0.043$) minutes in the 20 and 40mg groups, respectively.

Delayed Chemotherapy-Induced Emesis

Moderately Emetogenic Chemotherapy

- Unpublished results of a randomised, crossover trial reported that intranasal metoclopramide was as effective as oral metoclopramide in controlling delayed emesis induced by moderately emetogenic chemotherapy.[20] 45 patients with cancer were enrolled in this study and 40 were available for analysis. Prior to receiving one of 4 chemotherapy regimens all patients were given ondansetron 8mg intravenously to control acute emesis. On the second and third day of the chemotherapy cycle patients received dexamethasone 8mg intramuscularly every 12 hours and, in crossover fashion, intranasal and oral metoclopramide 40mg every 6 hours. Complete plus major protection from delayed nausea (none or mild) was reported for 31 of 40 (78%) and 34 of 40 (85%) patients after intranasal and oral metoclopramide, respectively. Complete plus major protection from delayed vomiting (0 to 2 episodes) was seen in 37 of 40 patients (93%) after intranasal metoclopramide and 39 of 40 patients (98%) after oral metoclopramide. The level of protection afforded by the 2 regimens was not statistically different.

- This study has been published in part.[21] However, the results of the oral and intranasal phases of the trial were pooled and the data presented did not allow the anti-emetic effects of intranasal and oral metoclopramide to be compared.

Cisplatin Chemotherapy

- A noncomparative phase II trial in 12 patients suggested that intranasal metoclopramide may be effective in the control of delayed emesis following highly emetogenic cisplatin therapy (total dose 50 to 100 mg/m^2).[22,23] To control acute emesis 12 patients received dexamethasone plus a 5-HT receptor antagonist at the time of chemotherapy, and self-administered intranasal metoclopramide 20mg 3 times daily for the following 6 days. Seven of these patients also took decreasing doses of dexamethasone on days 1 to 4 after chemotherapy

- An overall success rate of 50% was reported. This figure was determined by combining the frequency of complete protection from delayed vomiting and nausea (no episodes) and major protection from delayed vomiting and nausea (1 or 2 episodes). There was no difference between the clinical efficacy of intranasal metoclopramide alone or in combination with dexamethasone. No statistical analysis could be performed on the results of this small trial.

Postoperative Vomiting or Nausea

Nausea and vomiting during the postoperative period are common complications of surgery. As well as causing distress to the patient, postoperative emesis can delay recovery time and patient

discharge, and increase hospital cost. Prophylactic metoclopramide is indicated in this situation[24] and 2 studies have investigated the use of intranasal metoclopramide in the control of postoperative emesis.

• A randomised, double-blind, placebo-controlled trial in 109 patients did not reveal significant differences between prophylactic intranasal metoclopramide 20mg and placebo in the prevention of nausea and vomiting during the postoperative period.[25] Female patients scheduled for elective laparoscopic surgery were randomised to receive either intranasal metoclopramide 20mg (n = 59) or placebo (n = 50) 15 minutes before expected emergence from anaesthesia. The incidence and severity of nausea and vomiting was determined by observation, and by questioning the patients every 30 minutes for at least 6 hours after awakening.

• There was a nonsignificant decrease in the incidence of postoperative nausea and vomiting (18%, p = 0.23) for intranasal metoclopramide versus placebo. There were no significant differences between the 2 groups when time to initial episode, severity, or duration of nausea and vomiting were compared, or for the number of patients requiring rescue medication or those experiencing multiple episodes of nausea and vomiting. However, this study had several; limitations: a posthoc power analysis of the data suggested the study was underpowered to detect a difference between groups; 44% of patients randomised to the metoclopramide arm had a history of motion sickness versus 28% of the placebo arm (n = 0.14); inaccuracies in spray volume delivery may have reduced the metoclopramide dosage; the supine position of the patient may have resulted in more of the drug being swallowed and eliminated through first-pass metabolism.

• An unpublished, randomised, double-blind, placebo-controlled, parallel group, multicentre trial was conducted in 129 patients undergoing surgery.[26] Patients (n ≈ 25 per group) received intranasal metoclopramide 5, 10, 20 or 40mg, or placebo, to treat any episodes of nausea or vomiting within 2 hours of surgery. Up to 3 doses of medication were administered by recovery-room staff. Rescue medication could be requested at any time, although this was discouraged until after the second dose of study medication.

• Therapeutic efficacy was assessed by recording time to relief of nausea or vomiting, duration of nausea or vomiting episode and use of rescue medication. Dose-related trends in efficacy were observed for intranasal metoclopramide, but these were not significant. Physicians assessed patients' response to treatment as excellent, good, marginal or poor and found a significant difference in favour of metoclopramide 20 and 40mg versus placebo ($p \leq 0.01$).

Functional Dyspepsia

• In a small randomised, parallel-group trial intranasal metoclopramide had similar efficacy to oral metoclopramide in the treatment of functional dyspepsia.[27] 30 patients with dyspepsia of at least 3 months' duration received intranasal metoclopramide 10mg twice daily or oral metoclopramide 10mg twice daily for 28 days. Symptoms assessed at baseline and after 28 days' therapy included epigastralgia, regurgitation, feeling of postprandial fullness, pyrosis, nausea and vomiting.

• These symptoms were either resolved or improved in 75 to 100% of 29 evaluable patients, and there was no statistical difference between the intranasal and oral metoclopramide arms (fig. 3). 100% of the patients receiving intranasal metoclopramide judged it to be satisfactory.[27]

4. Tolerability

With the exception of effects on the nasal membrane, the adverse events profile of intranasal metoclopramide is essentially the same as that of the oral and injectable formulations. The tolerability of metoclopramide has been previously reviewed in *Drugs*[8] and the following discussion is confined to adverse events reported after intranasal administration.

• No adverse events were reported after a single intranasal dose of metoclopramide 20mg to healthy volunteers.[7]

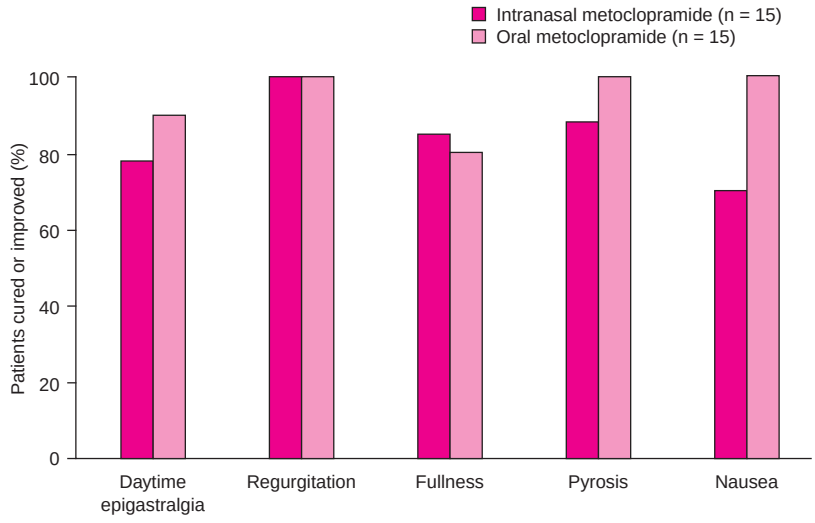


Fig. 3. Comparative therapeutic efficacy of intranasal versus oral metoclopramide in functional dyspepsia. Results of a randomised trial comparing the therapeutic efficacy of oral and intranasal metoclopramide 10mg twice daily for 28 days in functional dyspepsia.[27]

- 12 patients with cancer undergoing chemotherapy received three 40mg doses of intranasal metoclopramide over a 12-hour period. No drug-associated systemic or local adverse events were reported and the nasal mucosa was unaffected.[17]

- Irritation of the nasal membrane and unpleasant taste were reported in a trial of 163 patients with cancer who received intranasal metoclopramide 160, 320 or 640mg over 16 hours to control acute emesis.[12] When intranasal metoclopramide, 5, 10, 20 or 40mg up to 3 doses, was used to treat postoperative emesis, unpleasant taste was the most commonly reported adverse event (36 of 103 patients) and this was graded as severe in 8 of the 36 patients who reported this event.[26]

- Minor adverse events were reported in 12 patients with cancer who took intranasal metoclopramide 60 mg/day for 6 days after chemotherapy.[23] These included sleepiness (n = 3) and epistaxis (n = 1). Restlessness (n = 5) and diarrhoea (n = 3) were also reported, but were not considered to be drug-related. A similar pattern of adverse events was reported after intranasal administration of metoclopramide 160 or 320mg over a 16-hour period to 7 and 6 male patients with cancer, respectively, but no events were considered serious.[19]

- 15 patients with functional dyspepsia received intranasal metoclopramide 10mg twice daily for 4 weeks.[27] No major adverse events were observed, although mild congestion of the nasal mucosa was documented in 3 patients at the end of the study, compared with 1 before treatment. One of 15 patient in the group given oral metoclopramide experienced drowsiness.

- No statistically significant differences between intranasal metoclopramide and placebo were observed when white blood cell parameters, serum chemistry, liver enzymes, and urinary indices were assessed.[12,26]

- Even at very high doses of intranasal metoclopramide (up to 640 mg/day),[12] none of the more serious extrapyramidal adverse events that have been associated with metoclopramide given by other routes[8] have been reported.[19,23,26]

5. Intranasal Metoclopramide: Current Status

Intranasal metoclopramide is a new formulation of a long established and well tolerated antiemetic

drug. With the exception of an extended t_{max}, the pharmacokinetic profile is similar to that of the intravenous formulation. Minor irritation of the nasal membrane and unpleasant taste was reported in some studies, but otherwise the medication was well tolerated. It is approved in Italy for the control of iatrogenic nausea and vomiting and functional dyspepsia. In the USA, phase III trials are underway to support a New Drug Application submission for the use of intranasal metoclopramide in diabetic gastroparesis and chemotherapy-induced delayed emesis.

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