REVIEW

Nausea and vomiting associated with cancer chemotherapy: drug management in theory and in practice

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Arch Dis Child 2004;**89**:877–880. doi: 10.1136/adc.2003.037341

The function of cytotoxics is to damage cells, and it makes teleological sense for the body to expel them as soon after ingestion as possible. Ideally, from the body's point of view, they should simply be avoided, and it is not surprising that the experience of chemotherapy induced nausea and vomiting (CINV) is powerfully aversive. Nausea and vomiting were once among the most intractable and unpleasant experiences of a child undergoing treatment for cancer.

Over the past decade there have been major additions to the armamentarium of clinicians caring for children with cancer, and CINV is now largely preventable and treatable. This article will review the management of CINV in children, considering its pathophysiology and theoretical principles of therapy, and then how well this translates into practical clinical effectiveness by reviewing some of the published literature.

PATHOPHYSIOLOGY OF CINV

CINV can be acute, delayed, or anticipatory.[1] Acute begins within minutes of chemotherapy administration and resolves within 24 hours. Delayed can persist for several days. Anticipatory emesis occurs before chemotherapy is given, once an association has been established between environment and CINV. Prevention of acute CINV reduces the risk of delayed or anticipatory emesis.

Incidence and severity of CINV are affected by patient specific and treatment specific factors.[2] Characteristics associated with a higher risk include female sex, age greater than 3 years, anxiety, motion sickness, and poor control with previous chemotherapy. Treatment related risk factors include the emetic potential, schedule, dose, route, and rate of drug administration. The risk of CINV is higher with short intravenous infusions than protracted infusions or oral administration.

The single most important of these is the intrinsic emetogenicity of the drug. Hesketh *et al* classify commonly used cytotoxic agents according to their emetic potential[3] (table 1). Although based on the experiences of adult patients, it seems reasonable to apply it to children.

There are at least six receptors[4] involved in initiating, coordinating, and activating CINV (table 2). Three are for 5-hydroxytryptamine (5-HT_2, 5-HT_3, and 5-HT_4). The others are dopamine (D_2), histamine (H_1), and acetylcholine (ACh).

The gut wall and liver are the next lines of defence against toxins if avoidance has failed. Enterochromaffin cells in the intestinal mucosa are rich in 5-HT and D_2 receptors. Damage results in massive release of 5-HT. Chemotherapy is one cause, but others include radiotherapy and bowel distension.

In the systemic circulation, drugs are quickly brought into contact with the ''chemoreceptor trigger zone'' (CTZ). This is part of the area postrema which, although anatomically the floor of the fourth ventricle, is outside the blood-brain barrier and in intimate contact with the blood. D_2 receptors predominate, and are directly stimulated by toxins in the blood. The CTZ also has 5-HT_3 receptors and receives vagus nerve fibres.

The vomiting centre (VC) is close to the area postrema, but is within the blood-brain barrier. Its function is to coordinate the complex process of vomiting[5] and it is also known as the EPG, or emetic pattern generator. It has H_1, muscarinic ACh, and 5-HT_2 receptors.

Cytotoxics, then, can cause nausea and vomiting both by the damage they cause to cells, particularly those in the gastrointestinal tract, and through their interaction with the CTZ. They can also have more indirect effects such as anticipatory CINV. Higher cortical centres input directly into the VC and anxiety is a powerful inducer of nausea. The experience of being treated for cancer has emotional, psychological, and existential implications which can powerfully amplify or even initiate CINV.

DRUGS AVAILABLE TO MANAGE CHEMOTHERAPY INDUCED NAUSEA AND VOMITING

Dopamine blockers

The commonest examples are metoclopramide, domperidone, and haloperidol. In doses above 100 mg/day in adults, metoclopramide blocks 5-HT_3 receptors.[6] Domperidone does not cross the blood-brain barrier and carries a smaller risk of dystonic adverse effects. Haloperidol is rarely used in childhood CINV, although it is finding a place in palliative management of nausea and vomiting.[7]

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Accepted 18 January 2004

Abbreviations: 5-HT, 5-hydroxytryptamine; ACh, acetylcholine; CINV, chemotherapy induced nausea and vomiting; CTZ, chemoreceptor trigger zone; D_2, dopamine; VC, vomiting centre

Table 1 Emetogenic potential of chemotherapy agents (modified from Hesketh *et al*[3])

Emetic level*	Frequency of emesis†	Agent
5	>90%	Carmustine >250 mg/m^2
		Cisplatin ⩾50 mg/m^2
		Cyclophosphamide >1.5 g/m^2
		Dacarbazine ⩾500 mg/m^2
		Lomustine >60 mg/m^2
		Mechlorethamine
		Streptozocin
4	60–90%	Carboplatin
		Carmustine ⩽250 mg/m^2
		Cisplatin <50 mg/m^2
		Cyclophosphamide 0.75–1.5 g/m^2
		Cytarabine ⩾1 g/m^2
		Dacarbazine <500 mg/m^2
		Dactinomycin >1.5 mg/m^2
		Doxorubicin >60 mg/m^2
		Methotrexate >1000 mg/m^2
		Mitoxantrone >15 mg/m^2
		Procarbazine
3	30–60%	Cyclophosphamide <0.75 g/m^2
		Dactinomycin ⩽1.5 mg/m^2
		Daunorubicin
		Doxorubicin 20–60 mg/m^2
		Epirubicin ⩽90 mg/m^2
		Hexamethylmelamine
		Idarubicin
		Ifosfamide
		Methotrexate 250–1000 mg/m^2
		Mitoxantrone ⩽15 mg/m^2
2	10–30%	Asparaginase
		Cytarabine <1 g/m^2
		Doxorubicin <20 mg/m^2
		Docetaxel
		Etoposide
		Fluorouracil <1 g/m^2
		Gemcitabine
		Methotrexate 50–250 mg/m^2
		Mitomycin
		Paclitaxel
1	<10%	Bleomycin
		Busulfan
		Chlorambucil
		Fludarabine
		Hydroxyurea
		Melphalan
		Methotrexate <50 mg/m^2
		Thioguanine
		Vinblastine
		Vincristine

*Emetic levels 3–5 constitute *high* emetogenicity, emetic level 2 constitutes *moderate* emetogenicity, and emetic level 1 constitutes *low* emetogenicity.
†Proportion of patients experiencing emesis in the absence of antiemetic prophylaxis.

5-HT$_3$ blockers

There are a number of 5-HT$_3$ blockers including ondansetron, granisetron, and tropisetron. They are logical first line antiemetics whenever the cause is gut mucosal damage, including CINV and nausea following radiation.

Cyclizine

Cyclizine is antihistamine and anticholinergic and therefore operates at several pathophysiological levels. It is a logical complement to 5-HT$_3$ blockers. Like all anticholinergics, it should not be co-prescribed with prokinetics (for example, metoclopramide or domperidone), since it antagonises effects on the myenteric plexus in the bowel wall. Cyclizine is often poorly tolerated by children, who report dizziness and drowsiness. Its use for breakthrough CINV is limited by its eight hour dosage interval.

Corticosteroids

The mechanism of action of corticosteroids in CINV may be to reduce inflammatory damage to mucosal cells, reducing 5-HT release, or to alter permeability of the blood-brain barrier.[8] Laboratory studies suggest steroids may interfere with response to chemotherapy in osteosarcoma cell lines,[9] but this has not been shown in vivo.

Drugs that moderate anxiety

Benzodiazepines are valuable adjuncts in managing anticipatory CINV. Formulations that are quick acting and have relatively short half lives (for example, midazolam, lorazepam) and are ideal for this. Nabilone, a derivative of marijuana, can similarly help to break the association between context and nausea.

Levomepromazine

Levomepromazine, a phenothiazine, is remarkable for the breadth of its antiemetic spectrum. It covers dopamine, histamine, acetylcholine, and some serotonin receptors (table 2). At antiemetic doses[7] it is not sedating, although drowsiness can occur in higher doses which can limit escalation. Although there is little experience of levomepromazine in managing CINV in children, it would be a logical choice where CINV has not responded to other drugs. It should replace these other antiemetics, to avoid duplication of effect.

EFFECTIVENESS OF ANTIEMETICS IN CINV IN CHILDREN: THE EVIDENCE

Chemotherapy induced acute emesis

Dopamine (D$_2$) antagonists

These were once the most widely prescribed antiemetics in paediatric oncology. Metoclopramide, chlorpromazine, and prochlorperazine are known to be effective in children.[10–12] Chlorpromazine may be more effective than metoclopramide.[13] Unfortunately, the use of D$_2$ blocking drugs is often limited by concern for their extrapyramidal side effects.

Table 2 Commonly used antiemetics and the receptors they block (adapted from Twycross and Back[4])

	D$_2$	H$_1$	ACh	5-HT$_2$	5-HT$_3$	5-HT$_4$
Metoclopramide	++	0	0	0	(+)	++
Domperidone	++	0	0	0	0	0
Ondansetron	0	0	0	0	+++	0
Cyclizine	0	++	++	0	0	0
Hyoscine	0	0	+++	0	0	0
Haloperidol	+++	0	0	0	0	0
Prochlorperazine	++	+	0	0	0	0
Chlorpromazine	++	++	+	0	0	?
Levomepromazine	++	+++	++	+++	0	?

Serotonin (5-HT_3) antagonists

The advent in the early 1990s of 5-HT_3 receptor antagonists was a breakthrough in the management of acute CINV. Ondansetron,[14 15] granisetron,[16] and tropisetron[17 18] are all highly effective at controlling acute emesis in children treated with moderately and highly emetogenic chemotherapy. Side effects include headache, flushing, and constipation. Any of these alone is superior to metoclopramide or chlorpromazine, even if the latter are combined with corticosteroids.[19–22] Their efficacy is further enhanced by combination with steroids.[23 24]

Oral dosing is effective.[25] Dose ranging studies of ondansetron suggest an effective dose of 5 mg/m^2/day.[26] Ondansetron and granisetron are more effective than tropisetron in managing CINV for high and moderate emetogenic schedules.[22 27 28]

Dolasetron is another effective 5-HT_3 blocker.[29 30] It is not available in the UK and has yet to be compared with other antiemetics in children.

Corticosteroids

Corticosteroids are better antiemetics in CINV than chlorpromazine or metoclopramide.[31 32] The combination of a corticosteroid and metoclopramide is more effective than chlorpromazine alone.[33] They are often given as single intravenous doses of 12 mg/m^2 (dexamethasone) and 100 mg/m^2 (methylprednisolone).

Cannabinoids

Although evidence is sparse, the effect of cannabis derivatives in relieving CINV may exceed that of metoclopramide or prochlorperazine.[34 35] Adverse effects, including dizziness, drowsiness and mood alteration limit their routine use, but they can be effective in management of anticipatory CINV.

New agents

A novel class of antiemetic, the substance P/neurokinin (NK1) receptor antagonists, has recently emerged. The oral agent aprepitant has shown promise in the prevention of cisplatin induced emesis in adults.[36 37] There are no studies in children yet.

Delayed and anticipatory CINV

Delayed CINV is less common in children than in adults.[38] Risk factors include high emetogenicity, multi-day regimens, and failure of antiemetic prophylaxis.[39] It is usual in UK centres for children receiving chemotherapy of moderate or high emetogenicity to have prophylactic oral 5-HT_3 antagonists for 48 hours after administration.

Anticipatory CINV may occur in 25% children.[40] It usually starts one to four hours before chemotherapy, but can occur several days prior to chemotherapy. It is influenced by emetogenicity of chemotherapy, severity of symptoms after first dose, anxiety, motion sickness, and taste aversions.[41] Drug management should be combined with psychological and emotional support. Cannabinoids are often used, but evidence for particular effectiveness for this indication is largely anecdotal.

Non-pharmacological interventions

Non-pharmacological methods such as hypnotherapy and counselling can be highly effective adjuvant interventions, particularly for delayed and anticipatory CINV.[42 43] Many other approaches have been used including acupuncture, acustimulation, progressive muscle relaxation, guided visual imagery, music therapy, and dietary modification.[44] Their efficacy in CINV in children remains unproven at present. Most seem unlikely to do harm and there are anecdotal reports of benefit.

UNRESOLVED ISSUES

Some important questions regarding chemotherapy related emesis in children have not yet been addressed by clinical studies. It is not yet clear which 5-HT_3 antagonist or corticosteroid is most appropriate in children, nor which combinations of them are most effective. There are no studies of tropisetron and dolasetron in combination with corticosteroids. Optimal paediatric dosing and scheduling remains uncertain, and large robust trials are needed to determine, for example, whether oral drug administration is as effective as intravenous administration, and whether single doses are as effective as multiple divided dose schedules. It seems likely that children receiving chemotherapy of low emetic potential do not need prophylactic antiemetics, but this is not yet shown; children probably tend to under-report nausea. Finally, optimal management of delayed and anticipatory CINV in children is not yet clear.

SUMMARY

Clearer understanding of the pathophysiological mechanisms that underlie nausea and vomiting, and particularly the receptors involved, mean that clinicians are now in a position both largely to avoid CINV in children, and to treat it effectively when it occurs. Selecting an appropriate antiemetic medication can be seen as analogous to selecting an antibiotic. The first line is chosen on the basis of an empirical understanding of the likely cause, for example a 5-HT_3 antagonist if gut mucosal damage is thought to be a principal factor. If this should fail, second line should be complementary, expanding the range of effectiveness; for example, by adding an anticholinergic or antihistamine to a 5-HT_3 antagonist. If second line fails, or if it is important to get control more quickly, there are ''broad spectrum'' antiemetics available in the form of levomepromazine and some other phenothiazines. A more empirical approach to antiemetic selection antiemetic using an ''emesis ladder'' can also be effective.[45]

The conclusions from available evidence can be summarised as follows.

- In all children receiving cancer treatment, antiemetic prophylaxis should be given on each day that chemotherapy is administered, concomitant with or up to one hour prior to chemotherapy.
- The choice of antiemetic should be dictated primarily by the total emetic potential of the chemotherapy regimen.
- For highly emetogenic regimens, a 5-HT_3 antagonist plus a corticosteroid offers the best protection from nausea and vomiting.
- For moderately emetogenic regimens, a 5-HT_3 antagonist or corticosteroid can offer adequate emetic control.

It is important to consider the most effective route. Oral medications may not be tolerated or effective in the child who is actively vomiting, but 24–48 hours of parenteral administration may be enough to secure good control so that oral dosing can be started.

Lastly, although this review has focused particularly on the pharmacological approaches to CINV, it is important to remember that, like all symptoms, nausea and vomiting do not occur simply as physical phenomena but in a wider psychosocial, emotional, and even existential context. While it is most clearly illustrated by anticipatory CINV, in which psychological support is at least as important as the judicious use of anxiolytics, this multidimensional understanding of symptoms is essential if we are to meet the wider needs of children with potentially life threatening conditions.

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REFERENCES

1 **Bender CM**, McDaniel RW, Murphy-Ende K, *et al.* Chemotherapy-induced nausea and vomiting. *Clin J Oncol Nurs* 2002;**6**:94–102.
2 **LeBaron S**, Zeltzer LK, LeBaron C, *et al.* Chemotherapy side effects in paediatric oncology patients: drugs, age, and sex as risk factors. *Med Pediatr Oncol* 1988;**16**:263–8.
3 **Hesketh PJ**, Kris MG, Grunberg SM, *et al.* Proposal for classifying the acute emetogenicity of cancer chemotherapy. *J Clin Oncol* 1997;**15**:103–9.
4 **Twycross R**, Back I. Nausea and vomiting in advanced cancer. *European Journal of Palliative Care* 1998;**5**(2):39–45.
5 **Naylor R**, Rudd J. Emesis and anti-emesis. In: Hanks G, ed. *Cancer Surveys, vol. 21. Palliative medicine: problem areas in pain and symptom management*. New York: Cold Spring Harbor Laboratory Press, 1994:117–35.
6 **Twycross R**, Wilcock A, Charlesworth S, *et al. Palliative care formulary*, 2nd edn. Oxford: Radcliffe Medical Press, 2002.
7 **Hain R**, Ballantine N, Brook L, *et al.* Palliative care. In: Carson D, ed. *Medicines for children*, 2nd edn. London: RCPCH/NPPG, 2003:G81–5.
8 **Twycross R**, Wilcock A. Alimentary symptoms. In: *Symptom management in advanced cancer*, 3rd edn. Oxford: Radcliffe Medical Press, 2002:111.
9 **Davies JH**, Evans BA, Jenney ME, *et al.* In vitro effects of combination chemotherapy on osteoblasts: implications for osteopenia in childhood malignancy. *Bone* 2002;**31**:319–26.
10 **Allen JC**, Gralla R, Reilly L, *et al.* Metoclopramide: dose-related toxicity and preliminary antiemetic studies in children receiving cancer chemotherapy. *J Clin Oncol* 1985;**3**:1136–41.
11 **Relling MV**, Mulhern RK, Fairclough D, *et al.* Chlorpromazine with and without lorazepam as antiemetic therapy in children receiving uniform chemotherapy. *J Pediatr* 1993;**123**:811–16.
12 **Nahata MC**, Ford C, Ruymann FB. Pharmacokinetics and safety of prochlorperazine in paediatric patients receiving cancer chemotherapy. *J Clin Pharm Ther* 1992;**17**:121–3.
13 **Graham-Pole J**, Weare J, Engel S, *et al.* Antiemetics in children receiving cancer chemotherapy: a double-blind prospective randomized study comparing metoclopramide with chlorpromazine. *J Clin Oncol* 1986;**4**:1110–13.
14 **Jurgens H**, McQuade B. Ondansetron as prophylaxis for chemotherapy and radiotherapy-induced emesis in children. *Oncology* 1992;**49**:279–85.
15 **McQueen KD**, Milton JD. Multicenter postmarketing surveillance of ondansetron therapy in pediatric patients. *Ann Pharmacother* 1994;**28**:85–92.
16 **Craft AW**, Price L, Eden OB, *et al.* Granisetron as antiemetic therapy in children with cancer. *Med Pediatr Oncol* 1995;**25**:28–32.
17 **Otten J**, Hachimi-Idrissi S, Balduck N, *et al.* Prevention of emesis by tropisetron (Navoban) in children receiving cytotoxic therapy for solid malignancies. *Semin Oncol* 1994;**21**(5 suppl 9):17–19.
18 **Benoit Y**, Hulstaert F, Vermylen C, *et al.* Tropisetron in the prevention of nausea and vomiting in 131 children receiving cytotoxic chemotherapy. *Med Pediatr Oncol* 1995;**25**:457–62.
19 **Miyajima Y**, Numata S, Katayama I, *et al.* Prevention of chemotherapy-induced emesis with granisetron in children with malignant diseases. *Am J Pediatr Hematol Oncol* 1994;**16**:236–41.
20 **Hahlen K**, Quintana E, Pinkerton CR, *et al.* A randomized comparison of intravenously administered granisetron versus chlorpromazine plus dexamethasone in the prevention of ifosfamide-induced emesis in children. *J Pediatr* 1995;**126**:309–13.
21 **Dick GS**, Meller ST, Pinkerton CR. Randomised comparison of ondansetron and metoclopramide plus dexamethasone for chemotherapy induced emesis. *Arch Dis Child* 1995;**73**:243–5.
22 **Jimenez M**, Leon P, Gimeno J. Comparison of chlorpromazine plus dexamethasone vs ondansetron vs tropisetron in the treatment of emesis induced by highly and moderately emetogenic chemotherapy in pediatric patients with malignancies. *Med Pediatr Oncol* 1997;**29**:496.
23 **Alvarez O**, Freeman A, Bedros A, *et al.* Randomized double-blind crossover ondansetron-dexamethasone versus ondansetron-placebo study for the treatment of chemotherapy-induced nausea and vomiting in pediatric patients with malignancies. *J Pediatr Hematol Oncol* 1995;**17**:145–50.
24 **Hirota T**, Honjo T, Kuroda R, *et al.* Antiemetic efficacy of granisetron in pediatric cancer treatment. Comparison of granisetron and granisetron plus methylprednisolone as antiemetic prophylaxis. *Jpn J Clin Oncol* 1993;**20**:2369–73.
25 **White L**, Daly SA, McKenna CJ, *et al.* A comparison of oral ondansetron syrup or intravenous ondansetron loading dose regimens given in combination with dexamethasone for the prevention of nausea and emesis in pediatric and adolescent patients receiving moderately/highly emetogenic chemotherapy. *Pediatr Hematol Oncol* 2000;**17**:445–55.
26 **Brock P**, Brichard B, Rechnitzer C, *et al.* An increased loading dose of ondansetron: a north European, double-blind randomised study in children, comparing 5 mg/m^2 with 10 mg/m^2. *Eur J Cancer* 1996;**32A**:1744–8.
27 **Stiakaki E**, Savvas S, Lydaki E, *et al.* Ondansetron and tropisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. *Pediatr Hematol Oncol* 1999;**16**:101–8.
28 **Aksoylar S**, Akman SA, Ozgenc F, *et al.* Comparison of tropisetron and granisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. *Pediatr Hematol Oncol* 2001;**18**:397–406.
29 **Coppes MJ**, Lau R, Ingram LC, *et al.* Open-label comparison of the antiemetic efficacy of single intravenous doses of dolasetron mesylate in pediatric cancer patients receiving moderately to highly emetogenic chemotherapy. *Med Pediatr Oncol* 1999;**33**:99–105.
30 **Coppes MJ**, Yanofsky R, Pritchard S, *et al.* Safety, tolerability, antiemetic efficacy, and pharmacokinetics of oral dolasetron mesylate in pediatric cancer patients receiving moderately to highly emetogenic chemotherapy. *J Pediatr Hematol Oncol* 1999;**21**:274–83.
31 **Mehta P**, Gross S, Graham-Pole J, *et al.* Methylprednisolone for chemotherapy-induced emesis: a double-blind randomized trial in children. *J Pediatr* 1986;**108**(5 pt 1):774–6.
32 **Basade M**, Kulkarni SS, Dhar AK, *et al.* Comparison of dexamethasone and metoclopramide as antiemetics in children receiving cancer chemotherapy. *Indian Pediatr* 1996;**33**:321–3.
33 **Marshall G**, Kerr S, Vowels M, *et al.* Antiemetic therapy for chemotherapy-induced vomiting: metoclopramide, benztropine, dexamethasone, and lorazepam regimen compared with chlorpromazine alone. *J Pediatr* 1989;**115**:156–60.
34 **Ekert H**, Waters KD, Jurk IH, *et al.* Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. *Med J Aust* 1979;**2**:657–9.
35 **Chan HS**, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics* 1987;**79**:946–52.
36 **Hesketh PJ**, Grunberg SM, Gralla RJ, *et al.* The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin—the Aprepitant Protocol 052 Study Group. *J Clin Oncol* 2003;**21**:4112–19.
37 **Chawla SP**, Grunberg SM, Gralla RJ, *et al.* Establishing the dose of the oral NK1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting. *Cancer* 2003;**97**:2290–300.
38 **Kris MG**, Roila F, De Mulder PH, *et al.* Delayed emesis following anticancer chemotherapy. *Supportive Care in Cancer* 1998;**6**:228–32.
39 **Dupuis LL**, Lau R, Greenberg ML. Delayed nausea and vomiting in children receiving antineoplastics. *Med Pediatr Oncol* 2001;**37**:115–21.
40 **Dolgin MJ**, Katz ER, McGinty K, *et al.* Anticipatory nausea and vomiting in pediatric cancer patients. *Pediatrics* 1985;**75**:547–52.
41 **Tyc VL**, Mulhern RK, Barclay DR, *et al.* Variables associated with anticipatory nausea and vomiting in pediatric cancer patients receiving ondansetron antiemetic therapy. *J Pediatr Psychol* 1997;**22**:45–58.
42 **Zeltzer LK**, Dolgin MJ, LeBaron S, *et al.* A randomized controlled study of behavioral intervention for chemotherapy distress in children with cancer. *Pediatrics* 1991;**88**:34–42.
43 **Liossi C**. Clinical hypnosis in paediatric oncology: a critical review of the literature. *Sleep & Hypnosis* 2000;**2**(3):125–31.
44 **Keller VE**. Management of nausea and vomiting in children. *J Pediatr Nurs* 1995;**10**:280–6.
45 **Foot AB**, Hayes C. Audit of guidelines for effective control of chemotherapy and radiotherapy induced emesis. *Arch Dis Child* 1994;**71**:475–80.