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Special Paper

Efficacy of 5-HT_3 Receptor Antagonists in Radiotherapy-induced Nausea and Vomiting: A Quantitative Systematic Review

M.R. Tramèr,[1]* D.J.M. Reynolds,[2] N.S. Stoner,[3] R.A. Moore[1] and H.J. McQuay[1]

[1]Pain Research and Nuffield Department of Anaesthetics, University of Oxford, Oxford Radcliffe Hospital, The Churchill, Headington, Oxford OX3 7LJ; [2]Department of Clinical Pharmacology, Radcliffe Infirmary; and [3]ICRF Department of Medical Oncology, Oxford Radcliffe Hospital, U.K.

5-HT_3 receptor antagonists are used to treat radiation-induced sickness. The purpose of this study was to define anti-emetic efficacy and potential for harm of these drugs in radiotherapy. A systematic search, critical appraisal and quantitative analysis of relevant data using the number-needed-to-treat or harm (NNT/H) were conducted. Acute (0 to 24 h) and delayed (beyond 24 h) anti-emetic efficacy were analysed separately. Data from 1,404 patients were found in 40 trials published in 36 reports. Data from 197 patients receiving ondansetron or granisetron in five randomised trials were regarded as valid according to preset criteria. One placebo-controlled trial had 10 patients per group and in this ondansetron was not significantly different from placebo. In a larger ($n = 105$) placebo-controlled trial, ondansetron was significantly more efficacious than metoclopramide for complete control of acute vomiting (NNT 2.2, 95% confidence interval (CI) 1.7–3.3) and acute nausea (NNT 3.6, 95% CI 2.2–10.2). Three trials reported delayed outcomes with ondansetron or granisetron: there was no evidence of any difference compared with placebo or other anti-emetics. Two trials reported no acute or delayed but a 'worst day' outcome; in these ondansetron's antivomiting effect was significantly better than placebo (NNT 4.4, 95% CI 2.5–23) or prochlorperazine (NNT 3.8, 95% CI 2.4–10.3), but not its antinausea effect. Constipation and headache were associated significantly with 5-HT_3 receptor antagonists compared with other anti-emetics or placebo (NNH 6.4 and 17.1, respectively). Only 14% of published data enabled valid estimation of the anti-emetic efficacy of 5-HT_3 receptor antagonists in radiotherapy. There was some evidence that these drugs prevent acute vomiting: 40% of treated patients will benefit (NNT approximately 2.5). The evidence for nausea was less clear. There was no evidence that these drugs are of any benefit beyond 24 h. There was evidence that they produce specific adverse effects. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

RADIATION SICKNESS is characterised by a distinct pattern of nausea and vomiting: an asymptomatic latent period of 40–90 min, followed by an acute, 6–8 h period with nausea and vomiting and finally a recovery period [1]. The acute phase may be accompanied by shivering, hyperthermia, headache, xerostomia, parotiditis, and diarrhoea [1, 2].

Data on the incidence of and risk factors for radiation-induced sickness come from uncontrolled series of patients undergoing radiotherapy. Such observational data suggest that the most sensitive part of the body to irradiation is the upper abdomen [1], that fractionated irradiation may have a lower risk of nausea and vomiting [3] and that there is a direct relationship between the cumulative dose of irradiation and the severity of radiation-induced sickness [2, 4].

Correspondence to M.R. Tramèr.
*Present address: Division of Anaesthesiology, Department APSIC, University Hospital, CH-1211 Geneva, Switzerland.
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There is a biological basis for the prevention of radiotherapy-induced nausea and vomiting by 5-HT$_3$ receptor antagonists [5]. In most animal studies, these anti-emetic drugs completely inhibit emesis caused by radiation [6]. Meta-analysis of randomised trials has confirmed the efficacy of 5-HT$_3$ receptor antagonists in prophylaxis of acute chemotherapy-induced vomiting [7]. Meta-analyses have also confirmed the efficacy of ondansetron in both the prevention of postoperative emesis [8] and the treatment of established postoperative emesis [9]. All these data suggest that 5-HT$_3$ receptor antagonists may be beneficial in radiotherapy, and indeed, ondansetron and granisetron have been licensed for this indication.

The purpose of this review was to identify the published literature on both anti-emetic efficacy and likelihood of harm of 5-HT$_3$ receptor antagonists in the prevention of radiotherapy-induced nausea and vomiting.

METHODS

Systematic search

A systematic search was carried out for any published evidence of the anti-emetic efficacy of 5-HT$_3$ receptor antagonists in the prevention of radiation-induced nausea and vomiting. MEDLINE (SilverPlatter® and KnowledgeFinder® 4.0), EMBASE, Biological Abstracts, and Cochrane Library were searched with the generic drug names *ondansetron*, *granisetron*, *tropisetron* and with combinations of different free text terms such as *radiation*, *irradiation* and *radiotherapy*. The last electronic search was carried out on 15 January 1997. Reference lists of published reports and review articles were checked. The search was not restricted to English language and included reports of any study architecture. Abstracts and reviews were not considered. Unpublished data were not sought. Authors of reports and manufacturers of 5-HT$_3$ receptor antagonists were not contacted.

We collated information about patients, radiation (dose per fraction, duration, total dose per treatment, site), dose and route of administration of 5-HT$_3$ receptor antagonists and any control treatments, study design, study endpoints and adverse events from each report.

Endpoints

Acute radiation-induced emesis was arbitrarily defined as emesis within 24 h of the onset of radiotherapy. Delayed emesis was defined as events after 24 h. Dichotomous outcomes which were closest to these times after treatment were extracted. It was assumed that emesis after consecutive radiotherapy doses, given during several days, was 'delayed' emesis. Anti-emetic efficacy was defined as complete control of emesis (absence of any vomiting including retching), or complete control of nausea. Other endpoints, such as number of or delay until the first emetic episode, number of emesis-free days, treatment failure, need for rescue medication, scores of patient satisfaction or quality of life were not taken into account, as trials were inconsistent in reporting such endpoints. *Post hoc* subgroup analyses were not considered.

Trial validity

There was a prior agreement that the only valid study design which could adequately answer the question whether 5-HT$_3$ receptor antagonists were efficacious in preventing radiotherapy-induced nausea and vomiting was a controlled clinical trial in the radiotherapy setting. Other potentially emetogenic treatments should be avoided, and allocation of patients to a 5-HT$_3$ receptor antagonist or control (placebo, no treatment, or another anti-emetic) should be random. This meant that clinical trials without controls (case series), comparative trials without concealment of treatment allocation (historical controls, for instance), and data from patients receiving concomitant chemotherapy (arbitarily defined as within 24 h of radiotherapy) were regarded as invalid for the specific purposes of this study.

Quantitative estimation (efficacy and harm)

Quantitative analyses were performed with data from valid trials only. The relative benefit was calculated as relative risk with 95% confidence intervals (95% CI) [10]. A statistically significant difference between two treatments was assumed when the 95% CI of the relative benefit did not include 1. Point estimates and 95% CIs of the number-needed-to-treat (NNT) were calculated [11, 12]. The NNT was chosen because this number most adequately reflects the clinical relevance of the efficacy of an intervention [13]. A positive NNT indicates how many patients have to be exposed to a 5-HT$_3$ receptor antagonist in order to achieve a particular result in one of them (complete control of acute vomiting, for instance), who would not have achieved this result had they received the control treatment. A negative NNT indicates superiority of the control treatment over the 5-HT$_3$ receptor antagonist.

For an estimation of the frequency of drug-related adverse effects, the numbers-needed-to-harm (NNH) were calculated as for NNT [13]. The NNH indicates how many patients have to be exposed to a 5-HT$_3$ receptor antagonist for one to have an adverse event who would not have had this event with the control treatment.

There was an intention to combine treatment and control arms from different trials to calculate combined estimates of efficacy and harm. CIs of the NNT are reported only when the relative benefit indicated a statistically significant difference between two treatments (because the 95% CI around the NNT point estimate would then not include infinity). Calculations were performed using Excel v 5.0 on a Power Macintosh 7100/66.

RESULTS

Retrieved trials

Forty trials were found in 36 reports, published between 1990 and 1996, with data from adults and children ($n = 1404$). Treatments were with ondansetron (27 trials), granisetron (six), and tropisetron (five) in 13 randomised controlled trials [14–23 (trials I and II) 24, 25], five comparative studies without concealment of treatment allocation (i.e. without an adequate randomisation method) [2, 26–29], 19 uncontrolled series [3–23 (trials III–V) 30, 43], two case reports [44, 45], and one audit [46].

Excluded trials (Table 1)

Thirty-five trials with data from 1,207 patients had to be excluded from analysis. One study did not contain any radiotherapy data [46]. Four reports with data from six trials contained duplicated data [20–23 (trials I to III) 42, 47], and two reported preliminary results [21, 28] of subsequently published full reports. Duplicate and preliminary reports contained data of 256 patients (18% of all published data). The remaining trials contained original data from 1,147

Table 1. *Efficacy of* 5-HT_3 *antagonists in radiotherapy. Excluded reports*

Ref	Drug	Reasons for exclusion	Number*
No relevant data			
[6]	n/a	Audit, no data on 5-HT_3 receptor antagonists	0
Duplicated or preliminary data			
[20]	ond	RCT, duplicate data [21]	38
[23] trial I	ond versus meto	RCT, duplicate data [15]	49
[23] trial II	ond versus prochlor	RCT, duplicate data [22]	70
[23] trial III	ond	Case series, duplicate data [36]	15
[42]	trop	Case series, duplicate data [41]	20
[47]	trop	Case series, duplicate data [41]	20
[21]	ond versus meto	Preliminary data of [15]	38
[28]	ond	Preliminary data of [29]	6
Controlled trials without randomisation, observations			
[27]	ond + dex versus paspertin + dex	Randomisation not stated	70
[29]	ond versus 'anti-emetics' versus no treatment	Not random allocation	13
[2]	ond	Historical controls	10
[26]	ond ± dex versus prochlor ± dex	Historical controls	10
[3]	trop	Case series, ± CT	34
[23] trial IV	ond	Case series, TBI + CT	30
[23] trial V	ond + dex	Case series	11
[30]	trop	Case series	10
[31]	gran	Case series	36
[32]	gran	Case series	20
[33]	ond	Case series	33
[34]	ond	Case series, TBI + CT	15
[35]	gran	Case series	32
[36]	ond	Case series, TBI + CT	429
[37]	ond	Case series	10
[38]	gran	Case series	22
[39]	trop	Case series, CT ± TBI	11
[40]	ond ± levomepromazine	Case series	20
[41]	trop	Case series	20
[43]	ond	Case series, CT ± TBI	15
[44]	ond	Case reports	2
[45]	ond	Case reports	4
RCTs, concomittant use of chemotherapy			
[14]	ond versus prochlor	RCT, TBI + CT, only patient-days reported	40
[18]	gran versus standard	RCT, radiotherapy + CT	20
[19]	ond versus meto	RCT, TBI ± CT	24
[25]	ond + different versus placebo + different	RCT, TBI + CT	10
Total number of excluded patients treated with a 5-HT_3 receptor antagonist			1207

*Total number of excluded patients treated with 5-HT_3 receptor agonist. dex, dexamethasone; gran, granisetron; meto, metoclopramide ond, ondansetron; prochlor, prochlorperazine; trop, tropisetron; CT, chemotherapy; RCT, randomised controlled trial; TBI, total body irradiation; n/a, not applicable.

patients; 16 different regimens of ondansetron, granisetron and tropisetron were tested. The duration of anti-emetic treatment was 1 day to over 5 weeks. The range of total cumulative doses was 10–560 mg for ondansetron, 1.4–27 mg for granisetron and 5–210 mg for tropisetron.

Of the remaining 1,147 patients, data from 857 patients were not considered because the study design was not a randomised controlled trial (Table 1). The other 290 patients were treated with a 5-HT_3 receptor antagonist in nine original randomised controlled trials. In four of these, however, chemotherapy was used concomitantly [14, 18, 19, 25] and, therefore, since the confounding effect of chemotherapy could not be excluded, they were not analysed further (Table 1).

Analysed trials (Tables 2 *and* 3*)*

In the five trials judged to be valid (i.e. randomised comparisons, original data, without confounding factors such as chemotherapy), ondansetron was compared with placebo [16, 24], metoclopramide [15], and prochloperazine [22], and granisetron was compared with a combination of metoclopramide plus dexamethasone plus lorazepam [17]. In these five trials, 474 patients were randomised to either treatment, but, subsequently, 75 were excluded from analysis by the original trialists. From the total of 399 analysed patients, 197 received ondansetron or granisetron. This number accounted for 14% (i.e. 197/1,404) of all published patient data on the anti-emetic efficacy of 5-HT_3 receptor antagonists in the radiotherapy setting.

Quantitative analysis—anti-emetic efficacy (Tables 2 *and* 3*)*

In one valid placebo controlled randomised trial, 20 adults received 4 days of total body irradiation (13.2 Gy delivered in 11 fractions, 1.2 Gy per fraction) as part of their preparative regimen before bone marrow transplantation [24]. The

incidence of acute nausea and vomiting in the 10 placebo patients was 90%. On the first day of irradiation, ondansetron (3×8 mg/day orally for 4 days, total dose 96 mg) was not significantly different from placebo, neither in achieving complete control of vomiting and retching (relative benefit 5.0, 95% CI 0.7–36, NNT 2.5), nor in preventing nausea (relative benefit 4.0, 95% CI 0.54–30, NNT 3.3). 6 patients in each group completed the 4 day trial; the incidence of both delayed nausea and vomiting was very low with either treatment and there was no difference between ondansetron and placebo treated patients on days 2–4. The authors concluded that oral ondansteron was an effective therapy for the prevention of emesis induced by total body irradiation [24].

In a larger placebo-controlled trial (total number of analysed patients = 109), oral ondansetron 8 mg twice a day was given to patients with different malignancies undergoing a 10 day course of abdominal radiotherapy (1.7–2 Gy per fraction) [16]. The study period included at most the first 5 weeks of each patient's radiotherapy treatment course (total dose of

Table 2. 5-HT$_3$ receptor antagonists in radiotherapy. Extracted data on efficacy and drug-related adverse effects from valid randomised controlled trials

Ref	5-HT$_3$ receptor antagonist	Control	Endpoint	EER (%)	CER (%)	Number of patients who achieved endpoint (n/total) with 5-HT$_3$	with control
Anti-emetic efficacy							
Acute efficacy (24h)							
[24]	ond 8 mg p.o.×3	placebo	complete control (retching and vomiting) day 1	50	90	5/10	1/10
[24]	ond 8 mg p.o.×3	placebo	complete control (nausea) day 1	60	90	4/10	1/10
[15]	ond 8 mg p.o.×3 (3–5 days)	meto 10 mg p.o.×3 (3–5 days)	complete control (retching and vomiting) 24h	8	54	45/49	26/56
[15]	ond 8 mg p.o.×3 (3–5 days)	meto 10 mg p.o.×3 (3–5 days)	complete control (nausea) 24 h	33	61	33/49	22/56
[17]	gran 3 mg i.v.×1	meto 20 mg i.v. + dex + lora×1	complete control (vomiting) + only mild (nausea) 24 h	47	87	8/15	2/15
Delayed efficacy (after 24h)							
[15]	ond 8 mg p.o.×3 (3–5 days)	meto 10 mg p.o.×3 (3–5 days)	complete or major (retching + vomiting) day 5	2	4	48/49	54/56
[15]	ond 8 mg p.o.×3 (3–5 days)	meto 10 mg p.o.×3 (3–5 days)	none or mild (nausea) day 5	27	18	36/49	46/56
[17]	gran 3 mg i.v.×1	meto 20 mg i.v. + dex + lora×1	complete control (vomiting) 7 days	87	93	2/15	1/15
'Worst day' outcome							
[16]	ond 8 mg p.o.×2 (< 5 weeks)	placebo	complete control (retching + vomiting)	33	55	35/52	25/56
[16]	ond 8 mg p.o.×2 (< 5 weeks)	placebo	complete control (nausea)	83	91	9/52	5/56
[22]	ond 8 mg p.o.×3 (> 8 days)	prochlor 10 mg p.o.×3 (> 8 days)	complete control (retching + vomiting)	39	65	43/70	23/65
[22]	ond 8 mg p.o.×3 (> 8 days)	prochlor 10 mg p.o.×3 (> 8 days)	none (nausea)	67	78	23/70	14/65

Ref	5-HT$_3$ receptor antagonist	Control	Adverse effect	EER (%)	CER (%)	Adverse effect (*n*/total) with 5-HT$_3$	with control
Drug-related adverse effects							
[16]	ond 8 mg p.o.×2	placebo	Headache: study withdrawal	2	0	1/52	0/56
[17]	gran 3 mg i.v.×1 (3 days)	meto 20 mg i.v. + dex + lora×1	Headache	53	20	8/15	3/15
[21]	ond 8 mg p.o.×3 (3–5 days)	meto 10 mg p.o.×3 (3–5 days)	Headache	3	0	1/37	0/44
[22]	ond 8 mg p.o.×3 (> 8 days)	prochlor 10 mg p.o.×3 (> 8 days)	Headache	4	0	3/70	0/65
[22]	ond 8 mg p.o.×3 (> 8 days)	prochlor 10 mg p.o.×3 (> 8 days)	Constipation	16	0	11/70	0/65

EER, experimental event rate (i.e. incidence in patients given 5-HT$_3$ receptor antagonist); CER, control event rate (incidence in controls); i.v. intravenous; p.o., oral; gran, granisetron; ond, ondansetron; dex, dexamethasone; lora, lorazepam; meto, metoclopramide; prochlor, prochlorperazine.

Table 3. 5-HT_3 *receptor antagonists in the prevention of radiotherapy-induced nausea and vomiting. Number-needed-to-treat (NNT) in valid randomised controlled trials*

Ref	Radiotherapy (setting, dose)	Comparison (number of analysed patients)	Acute efficacy (0–24 h)*		Delayed efficacy (after 24 h)*		'Worst day' outcome*	
			Acute nausea	Acute vomiting	Delayed nausea	Delayed vomiting	Worst day nausea	Worst day vomiting
Ondansetron versus placebo								
[24]	Total body 11 fractions on 4 consequential days (1.2 Gy each), 13.2 Gy total dose	Ondansetron 3×8 mg p.o./day (10) versus placebo×3 p.o./day (10) for 4 days	none NNT 3.3	complete control NNT 2.5	No difference (days 2–4). Data on 6 patients only	No difference (days 2–4). Data on 6 patients only	n/a	n/a
[16]	Abdominal >10 fractions with >1.7–2 Gy/fraction, >10 day course (time between treatments not known)	Ondansetron 2×8 mg p.o./day (53) versus placebo×2 p.o./day (56) for at most 5 weeks	n/a	n/a	n/a	n/a	none NNT 11.9	complete control NNT 4.4 (2.5–23)
Ondansetron versus active								
[22]	Upper abdominal ≥5 fractions/day, >1.8 Gy/fraction, 5 day course (time between treatments not known)	Ondansetron 3×8 mg p.o./day (70) versus prochlorperazine 3×10 mg p.o./day (65) for up to 3 days after completion	n/a	n/a	n/a	n/a	none (5 day course): NNT 8.8	complete control (5 day course) NNT 3.8 (2.4–10.3)
[15]	Upper abdominal 8–10 Gy (single dose)	Ondansetron 3×8 mg p.o./day (49) versus metoclopramide 3×10 mg p.o./day (56) for up to 5 days after completion	none NNT 3.6 (2.2–10.2)	complete control NNT 2.2 (1.7–3.3)	none/mild (day 5) NNT − 11.5	complete/major control (day 5) NNT 65	n/a	n/a
Granisetron versus active								
[17]	Total body 7.5 Gy single fraction fast dose rate (12.2 cGy/min	Granisetron 3 mg i.v. (15) versus metoclopramide 20 mg i.v. (15), + dexamethasone 6 mg/m^2 i.v., + lorazepam 2 mg i.v. All drugs as a single dose	complete control of vomiting and only mild nausea NNT 2.5 (1.4–10.6)		n/a	complete control (day 7) NNT 15	n/a	n/a

*95% confidence intervals of numbers-needed-to-treat (NNT) are shown (in parentheses) only when the relative benefit indicated a statistically significant difference between treatments. p.o., orally; i.v., intravenous; n/a, not applicable.

ondansetron 560 mg). No acute or delayed emesis but a 'worst day' outcome was reported. Ondansetron was significantly more efficacious in achieving complete control of vomiting on the worst day of the study period (relative benefit 1.51, 95% CI 1.06–2.13; NNT 4.4, 95% CI 2.5–23), but there was no significant antinausea effect compared with placebo (relative benefit 1.94, 95% CI 0.69–5.41, NNT 11.9). These authors concluded that ondansetron was effective in preventing nausea and vomiting in patients undergoing fractionated radiotherapy of the abdomen [16].

In an active comparison, oral ondansetron 8 mg was compared with oral prochlorperazine 10 mg (each three times a day), in 135 adults undergoing fractionated upper abdominal irradiation on 5 days (at least five daily fractions with at least 1.8 Gy per fraction) for the treatment of various tumours [22]. Anti-emetic treatments were continued for up to 3 days after completion of radiotherapy (total dose of ondansetron 192 mg). Again, no acute or delayed outcome but a 'worst day' result was reported. Ondansetron was significantly more efficacious than prochlorperazine on the worst day of the 5 day course in preventing vomiting (relative benefit 1.74, 95% CI 1.19–2.53; NNT 3.8, 95% CI 2.4–10.3), but it had no significant effect on nausea (relative benefit 1.53, 95% 0.86–2.7, NNT 8.8). These authors concluded that oral ondansetron was significantly more effective than oral prochlorperazine in preventing vomiting, but not nausea caused by fractionated radiotherapy [22].

In a comparison between ondansetron and metoclopramide, 105 adults underwent irradiation of the upper abdomen with a single fraction of 8–10 Gy for the treatment of a variety of tumours [15]. Data from a preliminary report [21] were used to complete information from the final report. Patients received either oral ondansetron 8 mg or oral metoclopramide 10 mg (each three times a day); anti-emetic treatments were given for as many as 5 days after completion of radiotherapy (total dose of ondansetron 120 mg). Ondansetron was significantly better than metoclopramide in preventing both nausea and vomiting within the first 24 h; for control of acute nausea the relative benefit was 1.71 (95% CI 1.17–2.51), the NNT was 3.6 (95% CI 2.2–10.2). For complete control of acute vomiting the relative benefit was 1.98 (95% CI 1.47–2.65), and the NNT was 2.2 (95% 1.7–3.3). Thereafter, up to 5 days after irradiation, there was no evidence of any difference between the two anti-emetics (relative benefit for delayed antinausea effect 0.89, 95% CI 0.73–1.10, NNT-11.5; relative benefit for delayed antivomiting effect 1.02, 95% CI 0.95–1.08, NNT 65). In the final report, the authors concluded that ondansetron was a highly effective drug in controlling nausea and vomiting following radiotherapy to the abdominal region, but that future studies will have to prove that ondansetron is more effective in controlling delayed emesis than in this trial [15].

The fifth valid trial compared a single dose of intravenous granisetron 3 mg with intravenous metoclopramide 20 mg plus dexamethasone 6 mg/m^2 plus lorazepam 2 mg in 30 patients undergoing single fraction total body irradiation (average dose 7.5 Gy, with an average dose rate of 12.2 cGy/min) before bone marrow transplantation [17]. Granisetron was significantly more efficacious than the combination regimen during the first 24 h after radiotherapy. For complete control of emesis, but including the presence of mild nausea, the relative benefit was 4.0 (95% CI 1.01–15.8), NNT 2.5 (95% CI 1.4–10.6). There was no difference between the two treatments for delayed vomiting (relative benefit 2.0, 95% CI 0.2–19.8, NNT 15). Delayed nausea was not reported. It was concluded that granisetron was superior to the combination therapy [17].

Combining (i.e. pooling) data of treatment and control arms from these five randomised studies for quantitative estimation of combined estimates of efficacy was regarded as inappropriate, because of the variety of treatments, controls, clinical settings and endpoints (Table 3).

Quantitative analysis—adverse effects (Tables 2)

Four trials reported drug-related adverse effects, mainly headache and constipation. It was assumed that there was no difference in the incidence of these adverse effects between different 5-HT$_3$ receptor antagonists (i.e. ondansetron and granisetron), and different controls (i.e. placebo, metoclopramide, or prochlorperazine). Data from 5-HT$_3$ receptor antagonists and control treatments, respectively, were, therefore, combined. During or after radiotherapy headache occurred significantly more often in patients receiving ondansetron or granisetron compared with the controls (combined NNH 17.1 (95% CI 9.6–80) [15 (data from 21) 16, 17, 22]. 1 patient who received ondansetron had to stop treatment because of severe headache [16]. In one trial, patients receiving ondansetron reported constipation significantly more often than patients taking prochlorperazine (NNH 6.4, 95% CI 4.1–13.9) [22]. No dichotomous data on constipation were reported in the other randomised trials. In one uncontrolled series, 4 of 34 patients (12%) had to stop treatment with tropisetron because of constipation [3].

DISCUSSION

How strong is the evidence?

This study examined the evidence for an anti-emetic effect of 5-HT$_3$ receptor antagonists in radiation-induced nausea and vomiting. Trial validity played a crucial role in this evaluation. Three criteria were considered to be important. First, new treatments have to be compared with standard treatments or a placebo (or no treatment) to identify both their relative efficacy and likelihood of harm; an uncontrolled series was, therefore, a priori regarded as inadequate. Second, concealment of treatment allocation (i.e. proper randomisation) minimises selection bias and this reduces the risk of overestimation of treatment effect [48, 49]. It was, therefore, assumed that, the strongest evidence of treatment efficacy would come from randomised controlled trials. Finally, because chemotherapy may be emetogenic to varying degrees, trials where chemotherapy was used within 24 h of radiotherapy were not considered.

The systematic search of the published literature suggested that more than 1,400 patients had received a 5-HT$_3$ receptor antagonist in clinical trials in the radiotherapy setting. Eighteen per cent of these data, however, were duplicated. These data did not add valuable information, but may partly explain why 5-HT$_3$ receptor antagonists are perceived to be highly efficacious [50]. Another 61% of the retrieved data came from reports other than randomised controlled trials. Data from only 14% of all these patients came from trials which were valid according to our criteria and could, therefore, be considered for analysis. A further problem was that of a total of 474 randomised patients in valid trials, 75 (16%) were subsequently excluded from analysis by the original trialists.

A number of issues

This review brought up a number of issues which may have implications for the design of future studies.

Variability in underlying risk. In one valid placebo-controlled trial, 90% of patients who received placebo had both acute nausea and acute vomiting after fractionated total body irradiation [24]. The other placebo-controlled trial reported a lower incidence of vomiting with placebo (55%) on the worst day after radiotherapy to the abdomen, but again a very high incidence of nausea [16]. These event rates without anti-emetic prophylaxis may indeed reflect the true underlying risk in these radiotherapy settings and, hence, justify prophylaxis. But what about other radiation regimens? For instance, in an uncontrolled series of patients undergoing fractionated abdominal radiotherapy (1.5–2 Gy/fraction, 5 days a week) without anti-emetic prophylaxis, vomiting occurred in only 27% [3]. Would anti-emetic prophylaxis be justified in this case? The underlying risk in the other valid trials is unknown, because these trials did not include placebos. Inclusion of placebo arms in such trials would add valuable information on the underlying risk in the respective clinical setting and, therefore, enable proper interpretation of results [51].

Proper use of placebos. In one (invalid) randomised trial, 10 patients receiving ondansetron were compare with 10 receiving a placebo; they underwent single fraction total body irradiation for bone marrow transplantation [25]. They all received melphalan the evening before radiotherapy; 20% of placebo patients and 40% of ondansetron patients also received metoclopramide before total body irradiation; and 20% of the placebo patients, but none of the ondansetron patients vomited or were nauseated before radiotherapy started. For the purpose of this review, this trial had to be regarded as invalid because such data do not allow unbiased evaluation of the anti-emetic efficacy of ondansetron in the radiotherapy setting. Once the decision is taken to include a placebo in a controlled trial despite ethical concerns, the trial design should at least ensure that valuable new information and insight into a treatment can be drawn from the results. This was not the case here.

Limited data with multiple comparators, clinical settings and endpoints. Two 5-HT_3 receptor antagonists were compared with four different comparators in the five valid trials with 197 analysed patients. Multiple radiotherapy regimens were used. Trialists reported numerous different endpoints: acute and delayed nausea and vomiting, pooled nausea and vomiting outcomes, only acute or only delayed outcomes, or combination of complete and major control (one or two emetic episodes). Two trials reported a 'worst day' outcome only, and failed to state whether emesis was related to the first 24 h after radiotherapy (i.e. acute outcome). Clinical relevance of such an endpoint is unknown. Other potentially valuable endpoints, such as quality of life, episodes of emesis or number of emesis-free days, were inconsistently reported and, therefore, were not taken into account.

This extraordinary variety of comparators, clinical settings and endpoints in this limited number of trials most likely reflects uncertainty about optimal study design and lack of established endpoints and, therefore, questions the clinical relevance of any conclusion emerging from any of these data.

What is the evidence?

What is the best current evidence upon which treatment recommendations should be based?

There was evidence, based on data from two trials with 59 patients randomised to ondansetron, that ondansetron is efficacious in preventing acute vomiting after total body or upper abdominal irradiation [15, 24]: of 100 patients treated with ondansetron, 40 will not vomit during the first 24 h who would have vomited with metoclopramide or placebo (NNT approximately 2.5). This estimate of efficacy for the prevention of acute radiation-induced vomiting with a 5-HT_3 receptor antagonist is encouraging, despite being based on limited numbers, and only one trial [15] had sufficient power to show a statistically significant result.

The effect on acute nausea was less convincing. Only one (large) trial reported a significant benefit in the prevention of acute nausea with ondansetron; the 95% CI of the NNT, however, included 10 [15]. The other valid trials were either unable to find a significant effect [24], or they pooled acute nausea and acute vomiting so that extraction of a specific antinausea effect became impossible [17]. Should these results be interpreted as evidence of a lack of an acute antinausea effect or rather as a lack of evidence of such efficacy with 5HT_3 receptor antagonists in radiotherapy? This question is of clinical importance, because nausea may be perceived by these patients as being as distressing as vomiting [52]. Hence, a drug with a good antivomiting effect, but only limited effect on nausea, may be of questionable value.

There was consistent evidence, based on data from 74 patients randomised to either ondansetron or granisetron in three trials [15, 17, 24], that these drugs were of no benefit after 24 h compared with placebo or other anti-emetics. Two trials with 123 patients randomised to ondansetron reported a 'worst day' outcome [16, 22]. There was a significant antivomiting effect compared with placebo or prochlorperazine (NNT approximately 4), but, again, there was no effect on nausea.

Finally, there was evidence that ondansetron and granisetron are associated with an increased incidence of headache and constipation. Of 100 patients treated with these drugs, 6 will have a headache (NNH approximately 17) and 16 will be constipated (NNH approximately 6) who would not have had these adverse effects with another treatment. Headache and constipation may be regarded as a minor harm. A degree of constipation may even be beneficial in the radiotherapy setting [33]. However, withdrawal due to both 5-HT_3-related headache or constipation has been described [3, 16].

Clinical implications and research agenda

The best anti-emetic treatment is still not known. Although 5-HT_3 receptor antagonists have been recommended repeatedly as effective anti-emetic treatments in radiotherapy [53–55], this systematic review of the published literature revealed a lack of relevant data to support strongly their efficacy. Trial design varied, as did clinical setting and outcome reporting. We found no valid information on tropisetron. Neither did we find any relevant data in children. No efficacy data were available for settings with a low to moderate emetogenic risk (such as lower hemibody irradiation). Thus, anti-emetic treatment recommendations in the radiotherapy setting cannot be based on strong evidence.

A number of questions remain unanswered. For instance, valid ondansetron trials used 16 or 24 mg per day prophylactically. In the prevention of postoperative nausea and vomiting a dose-response with ondansetron could be established [8], but not in the treatment of established postoperative

nausea and vomiting [9]. While the most effective prophylactic intravenous dose in the surgical setting is 8 mg [8], established postoperative nausea and vomiting can be successfully treated with only 1 mg intravenously (i.e. eight times less) [9]. We do not know if there is a dose-response with ondansetron or other 5-HT_3 receptor antagonists in radiotherapy. We also do not know if the treatment of established radiotherapy-induced sickness is as effective as prevention, and if so, what doses are needed.

There was no evidence that ondansetron or granisetron were more efficacious than metoclopramide (with or without dexamethasone) after 24 h. However, several reports described administration of 5-HT_3 receptor antagonists over several weeks during irradiation and up to 5 days after completion of radiotherapy; cumulative doses exceeded 550 mg for ondansetron, for instance. There is evidence from randomised trials [24] and uncontrolled series [2] that the emetic response to radiotherapy is highest during irradiation and during the first 24 h after irradiation, but may decline sharply thereafter. The pragmatic questions then are, do we need any regular anti-emetic prophylaxis beyond 24 h after single dose radiotherapy? And if delayed radiation sickness should occur, is it sensitive to 5-HT_3 receptor antagonists?

The final question relates to the difference between single dose and fractionated radiotherapy. There is evidence that the pathophysiology of acute and delayed emesis after single dose irradiation differs [5]. When consecutive radiotherapy doses are given daily it is not known whether emesis on the second or subsequent days represents an acute response to that day's radiotherapy, a delayed response to previous days' radiotherapy, a combination of both, or even a completely new mechanism. The data from Spitzer and colleagues [24] suggest that with fractionated radiotherapy the incidence of emesis on day 2 onwards is very low, even with placebo, and that when emesis did occur it was not controlled by ondansetron.

Clearly, establishing minimum effective doses of these relatively expensive drugs and restricting their use to indications where their efficacy is based on good evidence (for instance the prevention of acute sickness in total body and abdominal irradiation) would have major financial implications. Many millions of pounds are spent each year by radiotherapy departments in the U.K. alone on 5-HT_3 receptor antagonists. It is not unreasonable for purchasers to demand a higher level of evidence to justify this expenditure than is currently available. Valid comparisons are needed between 5-HT_3 receptor antagonists and other anti-emetic drugs in the radiotherapy setting. Validity criteria should include proper randomisation of a reasonable number of patients, clinically useful endpoints (incidence of nausea and vomiting and acute and delayed outcomes separated, for instance) and a placebo group to ensure internal sensitivity of the trial [51]. Clinically relevant questions which remain to be addressed are dose-responsiveness, efficacy in low risk settings and relative efficacy of prevention compared with treatment of radiotherapy-induced sickness including cost-effectiveness of these strategies.

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