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REVIEW ARTICLE

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Consensus proposal for $5HT_3$ antagonists in the prevention of acute emesis related to highly emetogenic chemotherapy

Dose, schedule, and route of administration

Presented in part at the MASCC Consensus Conference on Antiemetic Therapy, Perugia, 28–29 April 1997

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Abstract Selective antagonists to the Type 3 serotonin receptor ($5HT_3$) in combination with corticosteroids are now considered the standard of care for the prevention of emesis from moderately to highly emetogenic chemotherapy. Here we address issues of optimal dose, schedule and route of administration of four currently available selectable $5HT_3$ antagonists. This paper utilizes an evidence based medicine approach to the literature regarding this class of drugs, emphasizing the results large, randomized, controlled trials to make formal recommendations concerning optimal use of this important new class of anti-emetic agents. We conclude that for each drug there is a plateau in therapeutic efficacy at a definable dose level above which further dose escalation does not improve outcome. Furthermore, a single dose is as effective as multiple doses or continuous infusion, and finally, emerging data demonstrate that the oral route is equally efficacious as the intravenous route of administration, even with highly emetogenic chemotherapy.

Key words Chemotherapy induced emesis · Serotonin receptors · Ondansetron · Granisetron · Dolesetron · Tropisetron

Introduction

The development of selective antagonists to the 5-hydroxytryptaphamine ($5HT_3$) receptor has revolutionized the therapeutic approach to chemotherapy-induced emesis (CIE) [22, 29, 50]. These agents, in combination with corticosteroids, have become a new standard of care for moderately to highly emetogenic chemotherapy. The four selective $5HT_3$ antagonists that have completed clinical testing (ondansetron, granisetron, tropisetron, and dolasetron) differ considerably in biological properties such as receptor specificity, potency, and plasma half-life [2, 51]. Nevertheless, each has demonstrated relatively equivalent efficacy in the prevention of CIE in a wide variety of clinical settings. As a class, these agents are characterized by an excellent side e
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Introduction

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number of controversies and uncertainties regarding the optimal use of these agents in day-to-day clinical practice persist.

This discussion will address issues of dose, schedule, and route of administration of the four selective $5HT_3$ antagonists in the prevention of acute emesis induction by moderately to highly emetogenic chemotherapy, based on an assessment of the best available literature. Rigorously designed double-blind randomized trials (phase III) of sufficient sample size were considered to offer the most valid evidence, whereas uncontrolled clinical trials, observation, and retrospective analysis each provided weaker evidence in support of a proposed recommendation. This approach is consistent with recent recommendations regarding evidence-based medicine [17]. Selected studies forming the basis for recommendations for each agent are summarized in selected references. The "No Emesis" rate during the initial 24-h observation period (acute emesis) was selected as an appropriate therapeutic end-point universally reported in the trials under consideration.

In this presentation we have formulated a hypothesis regarding each of the three issues to be addressed (dose, schedule, and route), summarized data in support of and contradictory to the stated hypothesis, reached conclusions based on the balance of evidence, and made recommendations for use of these agents in clinical practice.

Dose

Hypothesis

Despite preclinical differences, the $5HT_3$ antagonists are characterized clinically by: (1) a threshold effect for response, (2) a modest dose-response curve, and (3) a plateau in therapeutic efficacy extending over a several-fold range in dose.

If valid, the therapeutic implications are considerable; they can be summarized as follows: (1) more is not necessarily better, and (2) breakthrough emesis may be due to other mediators and/or receptors and not due to inadequate $5HT_3$ receptor blockade [28, 62].

If this hypothesis regarding dose is valid, how then do we justify the existing uncertainties regarding optimal dose of the available $5HT_3$ antagonists? For two agents in particular (ondansetron and granisetron) there is wide variability in the "approved" single dose level for prevention of acute emesis from highly emetogenic chemotherapy. If approved single dose levels are contrasted between the United States and Europe, there is an apparent paradox: in the United States the approved dose of ondansetron (32 mg or approximately .45 mg/kg) is four-fold that in Europe (8 mg), while for granisetron, exactly the opposite is true (10 mcg/kg vs 3 mg or 40 mcg/kg). Is it possible that the lower dose level for each agent is already on the therapeutic plateau, or do these lower doses fall somewhere along the dose response curve?

In view of the above considerations, analysis of best available literature regarding dose was performed for each of the four $5HT_3$ antagonists which have completed clinical testing. Both dose-response studies of individual agents and comparative trials between agents were considered. Study designs incorporating overlapping issues of schedule are addressed in the next section on this topic.

Highly emetogenic chemotherapy

Cisplatin-based chemotherapy at doses over 50 mg/m^2 serves as a model for highly emetogenic chemotherapy. Randomized studies have generally demonstrated superiority of $5HT_3$ antagonists over high-dose intravenous metoclopramide, the previous standard, for prevention of acute CIE from cisplatin [10, 13, 26, 44, 60]. Furthermore, the addition of dexamethasone has consistently improved efficacy compared to a $5HT_3$ antagonist alone, establishing this combination as a standard for patients receiving cisplatin-based therapy [30, 54]. Dose ranging studies of these agents generally demonstrate evidence of a dose response curve consistent with the hypothesis stated above [23, 24, 38, 40, 46, 54, 61, 63, 64]. There are conflicting data regarding the optimal single dose of ondansetron for prevention of acute CIE from cisplatin. While a study published by Beck et al. led to the conclusion that a 32-mg dose was superior to 8 mg, particularly in patients receiving high dose cisplatin (> 100 mg/m^2), a similarly designed study by Seynaeve showed that the 8 mg dose was equally effective [3, 58]. In both studies, single dose administration was equivalent to other approved dose schedules (see below). Further evidence in support of a single 8 mg ondansetron dose comes from the studies of the Italian Group for Antiemetic Research (IGAR) and from Ruff, an 8 mg dose showing equal efficacy to either a 32 mg dose level, or 3 mg of granisetron, respectively [33, 57].

For granisetron, the balance of evidence from both dose-response studies of this agent and comparative trials against ondansetron supports a recommended dosing level of 10 mcg/kg [46, 47, 54, 60]. The dose-ranging studies of Navari and Riviere suggest that dose levels of 2 or 5 mcg/kg are suboptimal, while there is a relative plateau above 10 mcg/kg, with slightly higher, but probably clinically insignificant, no emesis rates at 40 mcg/kg [46, 54]. The comparative trial by Navari adds further support in favour of the 10-mcg/kg dose, with identical no emesis rates for 10 vs 40 mcg/kg in comparison to an approved and effective multiple dose schedule of ondansetron (0.15 mg/kg × 3) [47].

The dose ranging study of Van Belle and the comparative trial by Marty both support a 5 mg single dose administration of tropisetron as effective in highly emetogenic cisplatin-based chemotherapy, with the study of Van Belle suggesting no further improvement in efficacy at dose levels up to 40 mg [45, 64].

Table 1 Recommendations: $5HT_3$ antagonists in cisplatin chemotherapy-induced emesis

Agent	Daily dose	Schedule	Route	Consensus	Confidence
Ondansetron	8 mg	Single dose	i.v.	High	High
Granisetron	10 mcg/kg	Single dose	i.v.	High	High
	2 mg	Single dose	p.o.	High	Moderate
Tropisetron	5 mg	Single dose	i.v.	High	Moderate
Dolasetron	1.8 mg/kg	Single dose	i.v.	High	High

Initial dose-ranging studies of dolasetron did not clearly define the lowest effective dose, while the subsequent comparative trial of Hesketh supports a dose level of 1.8 mg/kg as effective, with no evidence of clinically significant improvement in efficacy at 2.4 mg/kg [32, 40, 63].

Since the emetogenic potential of cisplatin is dose related, the emesis from regimens in which cisplatin is given at low daily doses differs in severity and pattern from that induced by high-dose cisplatin. Several comparative studies have evaluated the antiemetic efficacy of the $5HT_3$ receptor antagonists in this setting, and have demonstrated equal or superior activity to high-dose metoclopramide or alizapride [7, 21, 59]. These trials have also shown that antiemetic efficacy of $5HT_3$ antagonists is improved by the addition of a corticosteroid, similar to results with high-dose cisplatin [19, 48, 53].

Moderately emetogenic chemotherapy

Intravenous cyclophosphamide, doxorubicin, epirubicin, and carboplatin, alone or in combination, have been used as the emetogenic challenge in studies evaluating the efficacy of $5HT_3$ antagonists in moderately emetogenic chemotherapy. Corticosteroids, with or without other agents, have been the principal antiemetics used in patients receiving this type of therapy. Comparative studies of 5-HT_3 receptor antagonists have shown them to be superior in antiemetic activity to metoclopramide [1, 6, 9, 18, 36, 42, 61] alizapride [11, 14], and phenothiazines [43, 49, 65]. When compared with dexamethasone alone, the 5-HT_3 receptor antagonists show equivalent, but not superior, antiemetic efficacy [34, 35]. Furthermore, a trial by the IGAR demonstrated that the combination of granisetron plus dexamethasone was superior to dexamethasone alone or granisetron alone (complete protection from acute vomiting in 93%, 71% and 72%, respectively) [34]. Thus, the combination of a corticosteroid and a $5HT_3$ antagonist appears to provide optimal antiemetic therapy in patients receiving this type of chemotherapy. Oral $5HT_3$ antagonists are appropriate in this setting, and there is a large body of literature to support this route of administration, as discussed later.

Appropriate dose selection of oral $5HT_3$ antagonists for moderately emetogenic chemotherapy has been problematic, in part due to interactive issues of schedule. Early trials of oral ondansetron utilized a multiple-dose schedule, and these regimens have since become standard practice. Informative trials regarding oral ondansetron dosing in this clinical setting include those of Beck and Cubbedu, demonstrating a plateau in efficacy at a total daily dose of 12 mg (4 mg TID), and a large trial by Dicato et al., in which 8 mg of ondansetron twice daily was equivalent to 8 mg three times daily [4, 12, 15]. Thus, a daily dose of 12–16 mg represents a fully effective dose level of oral ondansetron in moderately emetogenic chemotherapy.

Table 2 Recommendations: oral 5HT3 antagonists in moderately emetogenic chemotherapy

Agent	Daily dose	Schedule	Consensus	Confidence
Ondansetron	12–16 mg	t.i.d. or b.i.d.	High	High
Granisetron	2 mg	Each day (or b.i.d.)	High	High
Tropisetron	–[a]	–[a]	–[a]	–[a]
Dolasetron	100–200 mg	Each day	High	Moderate

[a] Insufficient data available

An oral dose-ranging trial of granisetron reported by Bleiberg et al. [17] compared 0.25 mg b.i.d., 0.5 mg b.i.d., 1.0 mg b.i.d., and 2 mg b.i.d.. All dose levels were superior to 0.25 mg, and there was no increase in efficacy above the 1.0 mg b.i.d. level. Similar results for 7-day efficacy were obtained by Hacking et al [24]. As discussed below in the section on Schedule, a subsequent trial demonstrated equivalence of 1.0 mg b.i.d. and 2.0 mg as a single dose. Therefore, the most appropriate total daily oral dose of granisetron appears to be 2 mg. Studies by Rubenstein and Fauser have defined effective oral dose levels of dolasetron as 100–200 mg administered as a single dose [18, 56]. There is insufficient information at present to allow us to make recommendations on the oral dosing of tropisetron.

In general, these dosing recommendations for oral administration of $5HT_3$ antagonists result in dosing ratios of 1.5–2:1 relative to the recommended single dose levels when they are given i.v. (Tables 1, 2). These dosing recommendations appear reasonable in view of the reported oral bioavailability of approximately 60% for $5HT_3$ antagonists as a drug class [22, 50].

Conclusions

Effective dose levels have been established for each of the four $5HT_3$ antagonists in both moderately and highly emetogenic chemotherapy. The lowest fully effective dose of each agent should be used in clinical practice.

Schedule

Hypothesis

If given at an effective dose level, a single dose provides adequate $5HT_3$ blockade for prevention of acute emesis. If valid, the implications regarding schedule of administration (for acute CIE) are as follows: (1) administration of multiple doses is unnecessary, and (2) breakthrough emesis during the acute phase may be related to other mediators/receptors. If a model for schedule is developed based on this hypothesis, then multiple doses will only provide a better therapeutic outcome if the initial dose were suboptimal, or if optimal therapeutic efficacy were dependent on the either plasma half-life or duration of receptor blockade during the acute phase.

Highly emetogenic chemotherapy

As discussed below, there is substantial evidence in support of the proposed hypothesis regarding schedule. Schedule-effects are best assessed in studies of ondansetron, the first $5HT_3$ antagonist developed. Early clinical trials of i.v. ondansetron in cisplatin chemotherapy explored a variety of schedule-related issues, including variable dosing intervals, number of doses, and schedules incorporating continuous infusion [30, 39]. In general, these studies demonstrated that shortening the dosing interval or increasing the number of doses did not improve efficacy. A continuous infusion schedule following an 8 mg i.v. bolus was also found to be effective [44]. However, as demonstrated in the subsequent studies of Beck and Seynaeve, multiple dose administration or continuous infusion schedules of ondansetron proved no more effective than single dose administration [3, 58]. Based on these observations, development of the three other $5HT_3$ antagonists quickly evolved into determining optimal levels for i.v. single-dose administration.

Moderately emetogenic chemotherapy

Oral administration of $5HT_3$ antagonists by multiple-dose schedules has been extensively studied and is highly effective in the prevention of acute emesis from moderately emetogenic chemotherapy regimens. However, it remains unclear that multiple doses are superior to a fully effective single dose, since few studies have addressed this issue in moderately emetogenic chemotherapy. In a randomized double-blind trial, however, oral granisetron at a single dose of 2 mg was equally effective a standard divided-dose schedule (1 mg twice daily), with no emesis rates of 82% and 77%, respectively [16]. In a similar fashion, a trial by Kaizer et al. showed no difference in efficacy of ondansetron 16 mg i.v. as a single dose, versus 8 mg i.v. plus 8 mg p.o. 12 h later [37]. These findings are compatible with the hypothesis that a fully effective dose of a $5HT_3$ antagonist need be administered only once in the prevention of acute CIE, regardless of the emetogenic challenge.

Conclusions

Single dose intravenous administration is equally efficacious to multiple dose or continuous infusion schedules and is the preferred schedule of administration for prevention of acute emesis from highly emetogenic chemotherapy. For moderately emetogenic chemotherapy, few studies have compared single versus multiple oral doses. However, when direct comparisons have been performed, oral single-dose administration at the appropriate dose level has been equivalent to multiple doses, and is an acceptable alternative.

Route

Hypothesis

Oral administration of the $5HT_3$ antagonists is equally efficacious as intravenous (i.v.) administration.

Obviously, the most important implication of this hypothesis, if valid, is that since oral administration is generally less expensive and less resource intensive, this route may be preferable. There are three qualifiers to be considered in regard to this hypothesis: (1) there should be good oral drug bioavailability, (2) there must be an intact gastrointestinal track to ensure absorption, and (3) compliance must be assured.

Moderately to highly emetogenic chemotherapy

As a class, $5HT_3$ antagonists exhibit good drug bioavailability when administered by the oral route. While oral use is of proven efficacy for moderately emetogenic chemotherapy, to date there has been very little information regarding oral dosing for CIE from cisplatin. However, there is now emerging support for the administration of selective $5HT_3$ antagonists by the oral route even in the prevention of cisplatin-induced emesis. In a study by Heron [27], a standard combination of high-dose i.v. metoclopramide plus dexamethasone was compared with oral granisetron 1 mg alone (b.i.d.) or oral granisetron plus dexamethasone in cisplatin-treated patients. The no emesis rates were: oral granisetron (56%), metoclopramide/dexamethasone (52%), and granisetron/dexamethasone (66%). In a recently completed phase III trial, oral granisetron (2 mg) was compared with i.v. ondansetron (32 mg) in patients receiving cisplatin-based (> 60 mg/m^2) chemotherapy [20]. Concomitant dexamethasone (10–20 mg) was administered in 80% of patients. Rates of total control (no

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