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Review

5-HT_3 Receptor Antagonists: Differences and Similarities

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Differences among 5-HT_3 receptor antagonists have been reported in pharmacological studies with regard to selectivity of receptor binding, potency, duration of action and dose–response curves. However, whether these pharmacological differences can affect clinical efficacy and safety remains to be determined. A careful analysis of the literature revealed 22 comparative studies among the 5-HT_3 receptor antagonists available for review. Unfortunately, several of these trials have some important shortcomings especially in the study design, the size of population studied and the type of anti-emetic treatment selected, making their conclusions often difficult to interpret. However, among these studies, seven large, double-blind clinical trials have clearly shown that the antiemetic activity and tolerability of ondansetron, granisetron, tropisetron and dolasetron is almost identical at least in the prevention of cisplatin-induced emesis. Therefore, from the efficacy and safety point of view, there is no reason to prefer one with respect to the other compound. From the economic perspective, instead, differences may exist and they are strictly related to the dose and schedule of administration chosen for each compound. The information available on the use of 5-HT_3 receptor antagonists in the prevention of emesis induced by moderately emetogenic chemotherapy is at best scant. Contrasting results have been reported and only one well-conducted study has been published in full. Therefore, the possible differences among the various compounds are difficult to evaluate. More studies should be carried out in this group of patients. © **1997 Elsevier Science Ltd.**

Key words: anti-emetics, ondansetron, granisetron, tropisetron, dolasetron

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INTRODUCTION

THE INTRODUCTION of 5-HT_3 receptor antagonists has dramatically improved the management of chemotherapy-induced emesis. In fact, the combination of a 5-HT_3 receptor antagonist plus dexamethasone is able to induce complete protection from acute vomiting in approximately 80% of cisplatin-treated patients and in approximately 90% of patients submitted to moderately emetogenic chemotherapy [9, 33]. However, faced with the ever-growing availability of new 5-HT_3 compounds, there is a need to understand if there are real differences in efficacy and safety among these compounds.

Preclinical pharmacological studies have shown differences among ondansetron, granisetron and tropisetron with regard to selectivity of receptor binding, potency, duration of action and dose-response. Therefore, it may be of interest to show whether these pharmacological differences affect therapeutic outcome in terms of efficacy and safety. Several comparative studies among 5-HT_3 receptor antagonists have been carried out and this review will present and discuss the results of these studies, with the aim of giving some guidelines for selecting 5-HT_3 receptor antagonists.

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PHARMACOLOGICAL DIFFERENCES

Preclinical studies have hypothesised possible differences among ondansetron, granisetron and tropisetron.

Receptor selectivity

Ondansetron seems to have weak antagonistic activity on 5-HT_{1b}, 5-HT_{1c}, adrenergic $\alpha 1$ and μ opioid receptors, while tropisetron seems to have weak antagonistic activity on 5-HT_4 receptors. On the basis of these data, some

authors have speculated that granisetron and tropisetron are more selective than ondansetron with respect to 5-HT_3 receptors and this can be relevant for efficacy. However, all three drugs have a selectivity ratio of approximately 1000:1 for the 5-HT_3 receptors with respect to any other type of receptor and, therefore, it is unlikely that these minor differences have clinical relevance [6, 15].

Receptor antagonism

While in the rat, there is an insurmountable antagonism of granisetron and tropisetron to 5-HT_3 receptors, in the case of ondansetron the antagonism is overcome by increasing the concentration of 5-hydroxytryptamine (5-HT) [25].

Potency and duration of action

The potency and duration of action of ondansetron is less that that of the other 5-HT_3 antagonists. This does not necessarily mean that repeated doses of ondansetron are required. In fact, at least three studies have shown that a single intravenous (i.v.) dose works as well as repeated i.v. doses or a continuous infusion [3, 18, 30]. Probably the anti-emetic efficacy of 5-HT_3 antagonists is not correlated to their plasma levels, but to the duration and intensity of inhibition of central and peripheral 5-HT_3 receptors.

Dose response

A linear dose–response correlation has been demonstrated with granisetron and tropisetron, but not with ondansetron. In fact, it seems that in ferrets submitted to cisplatin treatment or total body irradiation and receiving ondansetron as an anti-emetic, an initial decrease in emesis was followed by an increase and then, as the dose was further increased, full control of emesis was achieved [1]. This does not happen with granisetron and tropisetron.

Autoreceptors

The presence of 5-HT autoreceptors on the enterochromaffin cells of the guinea pig has been demonstrated. It appears that activation of a 5-HT_4 receptor on the enterochromaffin cells suppresses the release of 5-HT, whereas activation of an enterochromaffin cell 5-HT_3 receptor enhances the release of 5-HT. While ondansetron, granisetron and tropisetron block vagal afferent 5-HT_3 receptors, the enterochromaffin 5-HT_3 receptor is blocked only by granisetron or tropisetron [7].

COMPARATIVE CLINICAL STUDIES: EFFICACY

A careful review of the literature shows that 22 comparative studies of 5-HT_3 receptor antagonists have been published [2, 4, 5, 8, 10–14, 17, 19–24, 26–29, 31, 32]. Nine studies were performed in patients submitted to cisplatin chemotherapy [2, 10, 14, 17, 19, 23, 24, 26, 29], 12 in patients receiving moderately emetogenic chemotherapy [4, 5, 11–13, 20–22, 27, 28, 31, 32] and one involved both types of patients [8].

Unfortunately, several of these trials have some important shortcomings such as:

—the information is insufficient as they have been published only as abstracts [2, 4, 13, 20–23, 27, 28, 31].

—the patient population studied was not large enough to show small but clinically important differences (i.e. a 10–15% difference in terms of complete protection from vomiting) [5, 8, 11, 12, 14, 19–22, 31].

—eleven of these studies are open to criticism because of unblinded design [4, 5, 8, 11, 12, 14, 17, 20–22, 31].

—in all but four trials [10, 12, 13, 27], 5-HT_3 receptor antagonists were not studied in combination with dexamethasone as is done in daily practice to maximise treatment efficacy.

All these shortcomings make the interpretation of the results of these studies difficult. Despite this, we have reviewed all these trials examining those conducted in cisplatin-treated patients separately from those related to moderately emetogenic chemotherapy.

CISPLATIN-BASED TRIALS

Three open [8, 14, 17] and seven double-blind [2, 10, 19, 23, 24, 26, 29] comparative studies have been performed in patients undergoing cisplatin chemotherapy.

Open trials

Mantovani and associates carried out an open, single-institution, randomised trial on head and neck cancer patients, comparing 24 mg i.v. of ondansetron with 3 mg i.v. of granisetron and 5 mg i.v. of tropisetron [14]. 117 chemotherapy-naive patients submitted to cisplatin 80–100 mg/m^2 were enrolled in the trial. A total of 463 chemotherapy cycles were evaluated. Patients received the same anti-emetic treatment during the subsequent cycles unless failure was experienced; in this case, the patient was randomly assigned to one of the other two drugs (19 patients). Two of these patients again failed to respond to treatment and were subsequently crossed-over to a third group. Complete protection from acute vomiting was achieved by 72.1%, 73.3% and 67.6% of patients receiving granisetron, ondansetron and tropisetron, respectively (difference not statistically significant). When authors considered the major responses (not more than one emetic episode in the 24 h or no vomiting but moderate to severe nausea), tropisetron was significantly inferior to the other two drugs.

This study can be criticised for at least three reasons. First, the authors evaluated the responses to anti-emetic treatments by pooling together the results of 463 chemotherapy cycles. This is incorrect because the response obtained in a cycle subsequent to the first is dependent on the response obtained in the previous cycles, and, therefore, responses cannot be pooled together across cycles and treated as being independent. In other words, the same subject evaluated for multiple cycles cannot be considered as different patients evaluated at the same cycle; in fact, if the subject had vomiting (nausea) at the first cycle his/her probability of vomiting (nausea) is superior at any subsequent cycle. Second, by randomising to an alternative anti-emetic treatment the patients who failed in a previous cycle, the authors assigned to these treatments patients at a particularly high risk of emesis, thus reducing the possibility of detecting any significant difference among anti-emetic treatments. Finally, the calculation of the sample size was incorrectly performed.

Martoni and associates carried out an open trial, at a single institution, randomised, with a crossover design in 124 chemotherapy-naive patients submitted to cisplatin ≥ 50 mg/m^2, that compared granisetron 3 mg i.v. with ondansetron 8 mg $\times$ 3 i.v. on day 1 followed by 8 mg $\times$ 2 orally on day 2 [17]. The incidence of complete protection from vomiting (71% versus 68%, respectively) and nausea

(60% versus 53%) was not significantly different between the two groups of patients. An interim analysis of the study was presented as an abstract after enrolling 62 patients [16]. Unfortunately, in the published paper, the significance level was not modified according to Bonferroni's inequality. Furthermore, no reason was reported to justify the different number of patients at the beginning of the study between the two anti-emetic treatments (at first cycle of chemotherapy 58 patients received ondansetron and 66 granisetron). Finally, a crossover design should not be used because of the risk of selection bias. In fact, a different number of patients were lost from the first to the second cycle of chemotherapy [9 patients (15.5%) that received ondansetron and 14 (21.2%) that received granisetron].

Gebbia's study was an open, single-institution, randomised study in 182 patients submitted to cisplatin ≥ 70 mg/m^2, comparing ondansetron 24 mg i.v. versus granisetron 3 mg i.v. [8]. This study showed no difference between groups in complete protection from vomiting (52% and 49%, respectively) and nausea (74% versus 79%). Unfortunately, the real power of this study is 0.75, instead of 0.80 as stated in the text by authors considering 91 patients per arm. Only 83 patients per arm were really evaluated, thus reducing the power to 0.70. Hypothesising a difference of 20% in complete protection between the two antiemetic treatments which have, *a priori*, the same efficacy, is only a ploy to save great power with a low number of patients. In our opinion, comparing two similar anti-emetic treatments which have at most a difference of 15% could be hypothesised, but in this trial such a difference could reduce the power of the study to a value inferior to 0.5.

Double-blind trials

Seven large double-blind studies have been carried out. These are summarised in Table 1.

Ruff's study compared two different single i.v. doses of ondansetron (32 and 8 mg) with 3 mg i.v. of granisetron in 496 patients submitted to cisplatin at doses ≥ 50 mg/m^2 [29]. As shown in Table 1, similar results were obtained. Noble's study compared ondansetron with granisetron administered for 5 consecutive days in patients submitted to low and repeated doses of cisplatin [26]. Similar results were again obtained. For unknown reasons, in this crossover study, patients expressed their preference for granisetron. Marty's study showed similar efficacy between ondansetron and tropisetron, administered for 5 consecutive days, in 231 patients submitted to single-dose cisplatin ≥ 50 mg/m^2 [19].

Two other large trials have been reported by Navari. In the first, in 987 patients, two different doses of i.v. granisetron (10 and 40 μg/kg) showed similar results compared with i.v. ondansetron 0.15 mg/kg × 3 on day 1 [24]. The second study in 609 patients compared two different doses of i.v. dolasetron (1.8 and 2.4 mg/kg), another 5-HT$_3$ receptor antagonist, with a 32 mg i.v. single dose of ondansetron. Again no significant differences were shown [23]. Similar results were also reported in another study carried

Table 1. Comparative studies in patients submitted to cisplatin

Study (Ref.)	No. Pts	CDDP Dose (mg/m^2)	Anti-emetics	C.P. (%)	Results
DB [29]	496	≥50	OND 32 mg i.v. OND 8 mg i.v. GRAN 3 mg i.v.	51.0 59.0 56.0	OND 32 mg = 8 mg =GRAN 3 mg
DB xo [26]	309	≥15 day for 5 days	OND 8 mg i.v. t.i.d. for 5 days GRAN 3 mg i.v. for 5 days	39.8* 44.0*	GRAN = OND >Preference for GRAN
DB [19]	231	≥50	OND 32 mg i.v.+8 mg orally t.i.d. for 5 days TROP 5 mg i.v.+5 mg orally for 5 days	40.0* 33.0*	OND = TROP
DB [24]	987	≥60	GRAN 10 μg/kg i.v. GRAN 40 μg/kg i.v. OND 0.15 mg/kg t.i.d. i.v.	47.0 48.0 51.0	10 = 40 μg/kg GRAN = OND 0.15 mg/kg × 3
DB [23]	609	≥70	DOL 1.8 mg/kg i.v. DOL 2.4 mg/kg i.v. OND 32 mg i.v.	44.4 40.0 42.7	1.8 = 2.4 mg/kg DOL = OND 32 mg
DB [2]	476	≥80	DOL 1.8 mg/kg i.v. DOL 2.4 mg/kg i.v. GRAN 3 mg i.v.	54.0 47.0 48.0	1.8 = 2.4 mg/kg DOL = GRAN 3 mg
DB [10]	976	≥50	OND 8 mg i.v.+DEX 20 mg i.v. GRAN 3 mg i.v.+DEX 20 mg i.v.	79.3 79.9	OND + DEX= GRAN + DEX

DB, double-blind; xo, crossover; CDDP, cisplatin; OND, ondansetron; GRAN, granisetron; TROP, tropisetron; DOL, dolasetron; DEX, dexamethasone; C.P., complete protection from acute vomiting, t.i.d., three times daily; *during 5–6 days.

out in 476 patients, comparing the two abovementioned doses of dolasetron with 3 mg i.v. of granisetron [2].

Finally, the study of the Italian Group for Antiemetic Research compared 8 mg i.v. of ondansetron with 3 mg i.v. of granisetron, both combined with dexamethasone in 976 patients submitted to cisplatin at doses ≥ 50 mg/m^2 [10]. The anti-emetic efficacy of ondansetron and granisetron was very similar in the prevention of cisplatin-induced acute emesis. Furthermore, complete protection from delayed vomiting and nausea while patients were receiving the same antiemetic prophylaxis was not significantly different.

All these studies were planned with sufficient power to detect a difference among anti-emetic treatments of at least 15% with the exception of Marty's study [19]. In fact, in this study, as stated by the authors, a 20% difference between treatments was hypothesised, but the study had a probability of less than 60% of detecting a 15% difference in efficacy. The most conservative hypotheses were those adopted in the Italian Group for Antiemetic Research study that would allow detection of a difference of at least 10% in complete protection from vomiting with over 90% of power.

Therefore, these seven large, randomised, double-blind studies clearly show that the anti-emetic efficacy of the 5-HT_3 receptor antagonists is almost identical in the prevention of cisplatin-induced acute emesis.

NON-CISPLATIN-BASED TRIALS

Nine open [4, 5, 8, 11, 12, 20–22, 31] and four double-blind [13, 27, 28, 32] studies have been carried out in patients submitted to moderately emetogenic chemotherapy.

Open trials

Jantunen and associates [12] published an open, randomised, crossover study comparing ondansetron 8 mg i.v. followed by two oral 8 mg doses at 8-h intervals with tropisetron 5 mg i.v., both combined with dexamethasone (10 mg i.v. before chemotherapy), in 47 patients. Ondansetron achieved complete protection from vomiting in a significantly greater number of patients compared with tropisetron treated patients (97% versus 82%, $p < 0.026$) [12]. In this study, no assumption was reported to allow calculation of the power of the study and, consequently, the sample size. Moreover, a 17% difference between the number of the enrolled (47) and evaluable patients (39), may suggest the existence of a selection bias, frequent with crossover studies, which could lead to misleading conclusions.

Bonneterre and associates, on behalf of The French Northern Oncology Group carried out an open, randomised, crossover study comparing granisetron 3 mg i.v. single dose before chemotherapy with ondansetron 8 mg i.v. followed by 8 mg orally every 8 h for three days. Nausea and vomiting were assessed for 5 days using a diary card. In 150 evaluable patients, no statistically significant differences were shown in complete protection from vomiting on day 1 (71.5% versus 76.6%) and on days 2–5 [4]. Unfortunately, the paper was published only as an extended abstract, making it difficult to evaluate the reliability of the results.

In another open crossover study, Jantunen compared single i.v. doses of ondansetron (8 mg), tropisetron (5 mg) and granisetron (3 mg) in 130 evaluable patients submitted to moderately emetogenic chemotherapy. Complete protection from acute vomiting was significantly superior with granisetron (80.0%) with respect to ondansetron (68.5%). Significantly less failures were also observed with granisetron. There was no statistically significant difference between granisetron and tropisetron in complete protection from vomiting and number of failures [11]. The study has several shortcomings: 21.7% of patients were excluded from evaluation and 70% were not chemotherapy-naive. This patient selection and possibly an incompletely successful initial randomisation could have biased the final results. This seems likely also in consideration of the small number of enrolled patients. Finally, no indication of the study power and, therefore, of the sample size, was reported.

Campora and associates reported the results of an open, randomised study comparing ondansetron 8 mg orally every 8 h for 4 days (first dose administered intravenously) with tropisetron 5 mg orally for 4 days (first dose administered intravenously) in 40 breast cancer patients submitted to three consecutive cycles of FAC/FEC (fluorouracil, doxorubicin, cyclophosphamide/fluororacil, epirubicin, cyclophosphamide) chemotherapy. Complete protection from acute and delayed vomiting was not significantly different between the two anti-emetic treatments. In particular, 75.5% of tropisetron treated patients and 65.4% of ondansetron treated patients achieved complete protection from acute vomiting [5]. In this study, outcomes were evaluated by pooling together the responses obtained in the three cycles and considering them as responses observed in different patients. The lack of independence of the responses across the cycles, a selection bias due to the lack of evaluation of some patients during subsequent cycles and the small sample size make these results of doubtful significance.

The Massidda and associates trial was on open, randomised, parallel group study carried out in 122 patients comparing granisetron (3 mg i.v.) with tropisetron (5 mg i.v. followed by 5 mg orally on days 2–5) and ondansetron (16 mg i.v. followed by 8 mg $\times$ 2 orally on days 2–5). Similar anti-emetic efficacy was shown with the three drugs; in particular, complete protection from acute vomiting was obtained in 68%, 78% and 69% of patients, respectively [21]. Unfortunately, in this study, no assumption was made to evaluate the study power and the necessary sample size. Considering a 15% difference in complete protection from nausea and vomiting among the three treatments (from 78% to 63%), the probability of detecting a significant difference among the groups, if any, was inferior to 0.3. Therefore, these results are unreliable for the lack of power of the study.

Gebbia and associates evaluated in an open randomised trial the anti-emetic efficacy of 16 mg i.v. of ondansetron and 3 mg i.v. of granisetron in 158 cancer patients submitted to moderately emetogenic chemotherapy. Again, no statistically significant difference was found between granisetron and ondansetron in complete protection from acute vomiting (67% and 69%, respectively) [8]. In this study, only 158 of the 182 planned patients were enrolled, decreasing the study's power. Moreover, the hypothesis, made by the authors, to observe a 20% difference in complete protection between the two arms, when the patients received similar anti-emetic treatment, seems unrealistic. If this difference had been fixed at 15%, the study power, with 158 patients, would have been inferior to 0.5.

Mercier and associates, on behalf of The French Granisetron Study Group, compared granisetron (1 mg $\times$ 2 orally on day 1) followed by metoclopramide (30 mg $\times$ 2

orally on days 2–3) with ondansetron (8 mg i.v. on day 1 followed by 8 mg × 2 orally on days 2–3) in an open randomised trial involving 200 breast cancer patients. Complete protection from acute vomiting was not significantly different (71% versus 66%), but the results obtained during days 1–5 were significantly superior with granisetron (53% versus 37%, $P = 0.022$) [22]. The analysis of the data illustrated in the abstract is incomplete and may be incorrect. In fact, the authors performed independently three significance tests on the same experimental units without considering the Bonferroni inequality. This can lead to misleading results. In any case, considering the Bonferroni adjustment for three tests, a $P < 0.022$ cannot be considered definitively significant. Furthermore, neither the dependence of delayed on acute emesis nor any indication of possible patient withdrawals from the first to subsequent days were reported. Finally, no evaluation of the study power, and, consequently, of the sample size was reported. Considering a 15% difference in complete protection from both nausea and vomiting (i.e. from 55 to 70%), the study power was inferior to 0.6.

In another open trial, Massidda compared ondansetron (8 mg i.v.) with granisetron (3 mg i.v.) and tropisetron (5 mg i.v.) in 60 chemotherapy-naive breast cancer patients. In 180 evaluable cycles of chemotherapy, complete protection from acute vomiting was similar among the three drugs (75, 70 and 70%, respectively) as well as complete protection from delayed vomiting. Complete protection from acute and delayed nausea was significantly superior with ondansetron with respect to granisetron and tropisetron [20]. The shortcomings of this trial are similar to those already described for the other studies. Particularly important is the assumption of independence of the observations, when instead, the observations were carried out on the same patients during three subsequent cycles. Furthermore, the study power was not evaluated.

Finally, Spina and associates compared granisetron (3 mg i.v.) with ondansetron (8 mg × 3 i.v.) in 25 patients with HIV-related non-Hodgkin's lymphoma submitted to moderately emetogenic chemotherapy in an open, randomised, crossover trial. The complete protection from acute vomiting and nausea was not statistically different between the two anti-emetics (76.2% versus 80.9%, respectively) [31]. Also, in this study, the power was not evaluated and 21 evaluable patients are really too few to assure that a clinically significant difference between the anti-emetic treatments can be detected.

Double-blind trials

Contrasting results have been obtained in the comparative studies carried out in patients submitted to moderately emetogenic chemotherapy (Table 2). Unfortunately, only one study [32] has been published in full and, therefore, the reasons for the differing results found in these studies can be difficult to understand. All these studies enrolled an adequate number of patients.

Stewart's study [32] compared two different schedules of ondansetron administered for 5 days with a single i.v. dose of granisetron given on the first day of chemotherapy. It showed similar complete protection from acute vomiting, but, as expected, more nausea was reported by granisetron-treated patients on days 2–5, and, furthermore, these patients required rescue medication more frequently [32].

In Perez's crossover study, ondansetron 32 mg i.v. gave similar complete protection from acute vomiting but inferior complete protection from acute nausea compared with 10 μg/kg i.v. of granisetron [27]. The abstract contains only the results obtained at first cycle of chemotherapy and the results of the analysis of the crossover design have not yet been published. Therefore, these results cannot be considered as definitive.

Table 2. Comparative studies in patients submitted to moderately emetogenic chemotherapy

Study (Ref.)	No. Pts	Anti-emetics	C.P. (%)	Results
DB [32]	514	OND 8 mg i.v. + 8 mg orally t.i.d. for 5 days	78.0	OND = GRAN >nausea, >rescue with GRAN on days 2–5
		OND 8 mg orally t.i.d. for 5 days	78.0	
		GRAN 3 mg i.v.	81.0	
DB xo [27]	623	OND 32 mg i.v. ±DEX iv	62.0	OND = GRAN OND>GRAN for nausea
		GRAN 10 μg/kg i.v. ±DEX i.v.	58.0	
DB xo [28]	188	GRAN 1 mg t.i.d. orally	73.3*	
		OND 8 mg t.i.d. orally	68.5*	GRAN ≥ OND especially at second cycle
DB xo [13]	703	OND 32 mg i.v. ±DEX i.v.	67.0	OND>DOL DEX increases efficacy
		DOL 2.4 mg/kg i.v. ±DEX i.v.	57.0	

DB, double-blind; xo, crossover; C.P., complete protection from acute vomiting; OND, ondansetron; GRAN, granisetron; DOL, dolasetron; DEX, dexamethasone, t.i.d., three times daily; *Results at first cycle of chemotherapy.

In contrast, Pion's study showed that oral granisetron 1 mg twice daily was superior to 8 mg oral ondansetron twice daily especially on the second cycle of chemotherapy [28]. The statistical analysis, as reported in the abstract, is inconclusive, because neither the cycle effect nor the carry-over effect were investigated. Moreover, comparisons at the first cycle do not seem to have sufficient power to detect significant differences. Finally, Lofters' study comparing ondansetron 32 mg i.v. with dolastron 2.4 mg/kg i.v. in 703 patients showed that complete protection from acute vomiting was significantly superior with ondansetron [13].

COMPARATIVE STUDIES: TOLERABILITY

Concerning the tolerability profile, in the double-blind studies, no statistically significant differences were shown in the type or frequency of adverse events among the 5-HT$_3$ receptor antagonists. All the 5-HT$_3$ receptor antagonists were generally well tolerated, the most frequently reported adverse events being headache and constipation. A more precise definition of the safety profile of the 5-HT$_3$ receptor antagonists will come from the spontaneous adverse reactions reporting system.

COMPARATIVE STUDIES: PATIENT PREFERENCE

The only advantage of conducting a crossover study is that preference for one of the two treatments can be expressed by the patient. However, a necessary condition to evaluate preference is that the study must be double-blind and one should be aware that preference can depend on many factors which are never sufficiently investigated.

Only one of three double-blind crossover studies showed a difference in patient preference [26]. In that study, although granisetron was preferred to ondansetron, the majority of patients did not express a preference between the two 5-HT$_3$ receptor antagonists. Sometimes the preference is related to the study design as happened in the open trial of Martoni in which 45% of patients preferred granisetron, 25% ondansetron, and 30% did not express a preference ($P = 0.003$) [17]. This was the obvious consequence of comparing in an unblinded trial a single injection (granisetron) with an injection and tablets (ondansetron).

CONCLUSIONS

The 5-HT$_3$ receptor antagonists are highly effective antiemetic drugs that, when used in combination with dexamethasone, represent the most efficacious regimens for the prevention of acute emesis induced by cisplatin and by moderately emetogenic chemotherapy. Preclinical differences among 5-HT$_3$ receptor antagonists have been shown and this has stimulated many comparative clinical studies. Unfortunately, many of them have several methodological shortcomings (i.e. inadequate sample size, crossover design, unblinded treatment) and do not permit any definitive conclusion.

At present, seven large, randomised, double-blind studies have clearly shown that the anti-emetic efficacy and tolerability of ondansetron, granisetron, tropisetron and dolasetron are almost identical in the prevention of cisplatin-induced emesis. Therefore, in this case, the choice among the 5-HT$_3$ receptor antagonists should be based only on their acquisition cost in each country taking into account their optimal dose and schedule. Unfortunately, not all these data are available. For example, a comparison between 1 mg of granisetron and 8 mg of ondansetron (probably the optimal doses) is lacking.

Contrasting results have been reported when 5-HT$_3$ receptor antagonists are compared in patients submitted to moderately emetogenic chemotherapy. Unfortunately, only one study has been published in full and, therefore, the differences among the results of the studies are difficult to evaluate. More studies should be carried out to investigate further possible differences among 5-HT$_3$ receptor antagonists in this group of patients.

There are, at present, no major differences in the tolerability of the various 5-HT$_3$ receptor antagonists, but more data are needed from the monitoring systems of various countries.

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