Br J clin Pharmac 1994; **37**: 525–530

Volunteer models for predicting antiemetic activity of 5-HT_3-receptor antagonists

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1 Selective 5-HT_3-receptor antagonists are highly effective in preventing nausea and vomiting associated with chemotherapy, radiotherapy and surgery. Their pharmacological activity may be determined *in vitro* and in animal models of emesis. However, these methods may not give an accurate indication of the antiemetic dose range of 5-HT_3-receptor antagonists in patients. Two volunteer models have been used to predict more accurately clinically effective antiemetic doses of 5-HT_3-receptor antagonists.

2 The flare response to intradermal 5-HT is thought to be mediated by excitation of 5-HT_3-receptors on cutaneous afferents, with release of substance P and subsequent vasodilation. Antagonism of the flare response appears to provide an indication of the effective antiemetic dose of 5-HT_3-receptor antagonists but data on duration of action are conflicting.

3 Ipecacuanha-induced emesis is thought to be mediated through both peripheral and central 5-HT_3-receptors. Antagonism of this response has demonstrated a close correlation with clinically effective antiemetic doses of the specific 5-HT_3-receptor antagonist, ondansetron, and has the advantage of being more conceptually relevant than the flare model.

4 Further work, with newer 5-HT_3-receptor antagonists, will clarify the role of these models as predictive of the use of these drugs in clinical practice.

Keywords 5-HT_3-receptor antagonists emesis ipecacuanha flare

Introduction

Selective 5-HT_3-receptor antagonists are highly effective in preventing nausea and vomiting associated with chemotherapy [1–14], radiotherapy [15–17] and surgery [18–25]. Their preclinical pharmacological activity may be determined *in vitro* by assessing their inhibitory effects on 5-HT-mediated depolarisation of the rat superior cervical ganglion and vagus nerve [26–28] and *in vivo* on the dose-related fall in heart rate and blood pressure to 5-HT or 2 methyl 5-HT (Bezold-Jarisch reflex, mediated by 5-HT_3-receptors on cardiac vagal afferents) [28–31]. Animal models (ferret and house musk shrew) of chemotherapy and radiotherapy-induced emesis may also be used [32–40]. However, due to species differences in pharmacokinetics and dynamic response, these methods may not give an accurate indication of the antiemetic dose range of 5-HT_3-receptor antagonists in patients.

The selective 5-HT_3-receptor antagonists, granisetron and tropisetron, have been shown to be ineffective in antagonising apomorphine (dopamine D_2-receptor agonist) induced emesis in the ferret [33, 41], unlike the dopamine receptor antagonist, fluphenazine [41], and the μ opioid-receptor agonist, fentanyl [42]. Selective 5-HT_3-receptor antagonists have not been tested in an animal model of motion sickness [36, 43]. However, ondansetron did not prevent emesis in a volunteer model [44].

Two volunteer models have been used in an attempt to predict more accurately clinically effective antiemetic doses of 5-HT_3-receptor antagonists. These models are:

1) The antagonism of the flare response to intradermal 5-HT
2) The antagonism of ipecacuanha-induced emesis.

The relative merits of each will be considered.

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Flare response to intradermal 5-HT

Dose-response

Intradermal injection of 5-HT produces a flare response which is thought to be mediated by excitation of 5-HT_3-receptors on cutaneous afferent neurones [45]. Stimulation of these receptors causes the release of substance P, via an axon reflex, resulting in vasodilatation with subsequent erythema/flare.

A typical study technique [46, 47] involves the intradermal injection, into marked areas of the back, of placebo and three concentrations of 5-HT (2.5, 40 and 640 μM), before and at a specified time (e.g. 30 min) after the test 5-HT_3 antagonist or placebo [47]. The resulting flare areas may be measured at 5 min after the intradermal injections by tracing over the shapes and quantifying by digitisation [47]. Log transformed derived responses are then subjected to analysis of variance.

Using this technique, Fowler *et al.* [47] demonstrated a reduction of flare size compared with placebo at each concentration of 5-HT by a 10 min intravenous infusion of the selective 5-HT_3-receptor antagonist ondansetron (as hydrochloride dihydrate) at a dose of 8 mg (33–75%), a reduction by ondansetron 1 mg (14–54%), but no reduction by ondansetron 0.1 mg.

Another selective 5-HT_3-receptor antagonist, alosetron (0.1–4 mg i.v. over 10 min), has also been shown to reduce the flare response to intradermal 5-HT in a dose-dependent manner [48]. MDL 72222 [1αH, 3α 5αH-tropan-3yl 3,5-dichlorobenzoate] (20 mg i.v. over 4 min), reduced the flare response to intradermal 5-HT, with diminishing effect over the 30 min following post-dose 5-HT injections [49]. This inhibition was overcome at the highest concentration of 5-HT used (160 μM).

Duration of action

The flare model has also been used to assess the duration of action of 5-HT_3-receptor antagonists. 5-HT may be injected at intervals after dosing with the test drug or placebo and flare sizes measured 5 min after each intradermal injection. Using this approach, it was shown that a 10 min intravenous infusion of ondansetron 8 mg and 16 mg (as hydrochloride dihydrate) significantly reduced the flare response to 40 μM 5-HT for at least 9 h [50].

The compound MDL 72422 [1αH, 5αH-tropan-3αyl 3,5 dimethylbenzoate hydrochloride], administered orally (20–80 mg), gave a dose-dependent reduction in 5-HT induced flares with greater inhibition following 5-HT given at 2 h than at 1 h after dosing [51].

Granisetron, 40 μg kg^{-1} over 30 min, gave an inhibition of 5-HT flare response 5 min after infusion. This inhibition remained significant at 24 h after dosing [52, 53]. This is not consistent with clinical data which indicate that the duration of action of a single intravenous dose of granisetron (100 μg kg^{-1}) does not exceed 12 h [54, 55]. Also, one study demonstrated that in 13 patients receiving granisetron (40 or 160 μg kg^{-1}) for chemotherapy-induced emesis, there was no correlation between the observed maximal inhibition of the flare response over 24 h and the individual antiemetic efficacy of the drug [56]. The marketed unit dose of granisetron for chemotherapy-induced emesis, in the UK, is 3 mg (40 μg kg^{-1}) which is considered to be maximally effective [1, 5, 14, 57, 58].

Intradermal injection of 5-HT may be given manually or by autoinjector [59]. The latter is, however, more reproducible and convenient [59]. Adverse events from intradermal 5-HT are generally mild and may include transient local tingling or stinging sensations (Sweetland & Fowler, personal communication).

Ipecacuanha-induced emesis

The antiemetic site of action of 5-HT_3-receptor antagonists may be peripheral [60] at abdominal visceral afferent neurones [61] or central [62] within the area postrema [63] and nucleus tractus solitarius [66] or a combination of these [64–66]. Ipecacuanha, an emetic containing the principal active ingredients emetine and cephaeline [67], is also thought to act through both peripheral and central 5-HT-receptors [41]. In the ferret [41], ipecacuanha-induced emesis is antagonised by the specific 5-HT_3-receptor antagonist, tropisetron, but not by fluphenazine, a dopamine-receptor antagonist.

This model has been used to test the antiemetic activity of ondansetron in healthy volunteers. In a double-blind parallel group, dose-ranging study [68], five groups of 10 subjects received a single dose of intravenous ondansetron (as hydrochloride dihydrate) over 5 min, 30 min before oral syrup of ipecacuanha 30 ml. The time to onset, number of emetic episodes and duration of emesis, in addition to visual analogue scale (0–100 mm) ratings of nausea, were recorded over an 8 h period.

There were no emetic episodes after ondansetron 8 mg or 4 mg. Seven, nine and ten subjects vomited following 1 mg, 0.25 mg and 0.1 mg doses with median times to onset of 62 min, 31 min and 37 min. Median peak nausea scores were 0 mm for both 8 mg and 4 mg doses, and 30 mm, 53 mm and 26 mm for 1 mg, 0.25 mg and 0.1 mg doses. Data relating to the number of subjects experiencing emesis were fitted to a dose-response model using non-linear least squares regression (Figure 1). Mild adverse events, predominately of a gastrointestinal nature, occurred principally in those subjects experiencing emesis; no subject required antiemetic rescue medication.

These emetic episode data correlate well with the current clinical usage of ondansetron. Both 8 mg [18–20, 22, 24] and 4 mg [22] single intravenous doses of ondansetron are effective in the prevention and treatment of post-operative nausea and vomiting, with only partial efficacy with a 1 mg dose for prevention [22] and treatment [21] of this condition. The approved intravenous dose for the prevention and

treatment of post-operative nausea and vomiting in the UK is 4 mg. The lowest recommended single intravenous dose of ondansetron for chemotherapy-induced emesis is 8 mg [3, 69–71], which suggests that some chemotherapy regimens are a more potent emetic stimulus than syrup of ipecacuanha.

The results of this study [68] contrast with those of Goldberg & Cerimele [72] who found that a 30 min intravenous infusion of zatosetron 13 mg delayed but did not prevent ipecacuanha-induced emesis. It is possible that this dosage regimen of zatosetron was insufficient to be maximally effective; there is no published clinical data to explore this. There is no published information on the use of tropisetron in this human model.

Relative merits of the flare and ipecacuanha models

As there are only three currently marketed antiemetics of the 5-HT$_3$-receptor antagonist class (ondansetron, granisetron and tropisetron), validation of the flare and ipecacuanha models is limited (see Table 1) and no studies have combined the two methods. Experience has been mainly with ondansetron but dosing in the flare model [47, 50] did not cover the middle dosage range (4 mg). However the pharmacological activity of ondansetron in this model approximates to clinically effective antiemetic doses. Although there has been no formal dose ranging with granisetron in the flare model, granisetron had pharmacological activity in this model at the clinically effective dose for chemotherapy-induced emesis (40 μg kg^{-1}) [52, 53].

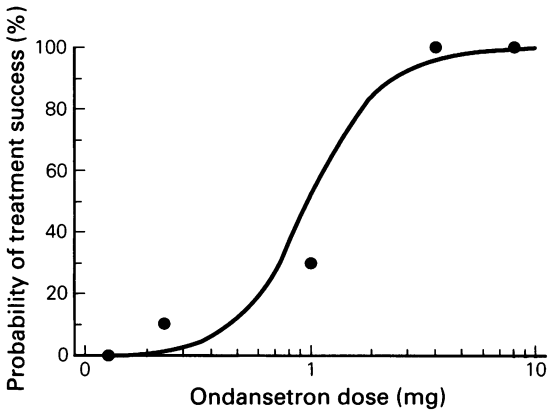

Figure 1 Probability of prevention by ondansetron of ipecacuanha-induced emesis in healthy volunteers. Each data point represents the percentage of each group of ten volunteers not experiencing emesis. Estimated ED_{50} for protection against emesis: 1.27 mg (standard error 0.29 mg, correlation coefficient 0.867). (From Minton *et al.*, 1993 [68]).

The duration of action of a single dose of ondansetron in the flare model (> 9 h) [50] may relate to its clinically effective duration in emesis, unlike granisetron for which the duration of pharmacological activity in the flare model (24 h) [52] exceeds the clinically effective duration of antiemetic activity [54, 55]. However, the relevance of inhibition of the flare response as a predictive model of antiemetic activity is questionable in view of the apparent discrepancy in these two activities in a patient study with granisetron [56]. The flare model does, however, have the advantage of simplicity and excellent tolerability.

The ipecacuanha-induced model of emesis has only been used in man by two authors [68, 72, 73]. Minton *et al.* [68] demonstrated a dose response to ondansetron and an excellent correlation with clinically effective doses in postoperative nausea and vomiting, with a prediction of minimally effective doses in chemotherapy-induced emesis. This model has not yet been used to assess the duration of action of antiemetic activity; this is technically more difficult and may involve administration of ipecacuanha at different time intervals after the antiemetic test drug.

Ipecacuanha can realistically be administered to each volunteer only once such that anticipatory emesis or habituation can be avoided. Thus, many volunteers are required in studies of ipecacuanha-induced emesis. Indeed, in the ferret, tachyphylaxis may occur to the emetic effects of ipecacuanha when administered on more than two occasions (Bountra *et al.*, personal communication).

Ipecacuanha-induced emesis has, however, the advantage of being more clinically relevant than the

Table 1 Comparison of effective doses of ondansetron and granisetron in flare and ipecacuanha models with clinically effective doses

	Maximally effective single dose in flare model	*Duration of action in flare model*	*Maximally effective dose in Ipecacuanha model*	*Clinically effective dose (PONV)*	*Clinically effective single dose (CIE)*
Ondansetron	8 mg [47]*	≥ 9 h [50]*	4 mg [68]*	4 mg [22]*	8 mg [3, 69–71]*
Granisetron	40 μg kg^{-1} (3 mg) [52, 53]*	≥ 24 h [52, 53]*	—	—	40 μg kg^{-1} (3 mg) [1, 5, 14, 57, 58]*

PONV Post-operative nausea and vomiting.
CIE Chemotherapy-induced emesis.
*Reference.

flare model. Its predictive value, coupled with an acceptable safety profile [68, 73] and relative ease of conduct, suggests that it will be of use in defining effective doses of 5-HT_3-receptor antagonists prior to introduction into patients. This may simplify dose ranging in early patient studies and avoid the potential for underdosing many patients with serious illness. Further work, with newer 5-HT_3-receptor antagonists, will clarify the role of these models as predictive of the use of these drugs in clinical practice.

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(Received 9 September 1993, accepted 31 January 1994)