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ORIGINAL ARTICLE

Amisulpride prevents nausea and vomiting associated with highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled, dose-ranging trial

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Abstract

Purpose Chemotherapy-induced nausea and vomiting (CINV) remain significant clinical problems, especially in the delayed phase (24–120 h after chemotherapy). Amisulpride is a dopamine D_2/D_3-receptor antagonist previously shown to be an effective intravenous antiemetic. We conducted a randomised, double-blind study to characterise the dose response of oral amisulpride in delayed phase CINV.

Methods Chemotherapy-naïve patients receiving cisplatin ≥ 70 mg/m^2 or an anthracycline-cyclophosphamide regimen for breast cancer received, on day 1, 20 mg amisulpride and 8–16 mg ondansetron intravenously followed, once daily on days 2–4, by 10, 20 or 40 mg oral amisulpride or placebo. A control group receiving standard three-drug prophylaxis was enrolled for assay sensitivity purposes. The primary endpoint was complete response (CR), defined as no emesis or rescue medication use, in the delayed phase.

Results Three hundred eighteen subjects were evaluable per protocol. CR rate (24–120 h) was 20% with placebo and 46% with 10 mg amisulpride ($p = 0.006$ after multiplicity adjustment); in the three-drug control group, it was 59%. Emesis, nausea and 0–120-h CR rate were significantly improved with 10 mg amisulpride compared to placebo. Higher doses of amisulpride were not more effective than 10 mg. In patients with acute phase CR, delayed phase CR rate was 44% for placebo, 75% for 10 mg amisulpride ($p = 0.022$) and 70% for the 3-drug control. No significant differences were seen between groups in safety parameters.

Conclusions Amisulpride 10 mg orally is safe and superior to placebo at preventing delayed CINV caused by highly emetogenic chemotherapy.

Relevance
This randomised, double-blind trial shows that oral amisulpride, a dopamine D_2/D_3-receptor antagonist, is safe and superior to placebo at preventing delayed nausea and vomiting associated with highly emetogenic chemotherapy. Amisulpride may therefore have a role in improving management of CINV. Future trials should investigate amisulpride as part of multi-drug CINV prophylaxis.

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Introduction

Chemotherapy agents such as cisplatin and the combination of an anthracycline plus cyclophosphamide in women with breast cancer are considered highly emetogenic chemotherapy (HEC), inducing nausea and vomiting (CINV) in more than 90% of patients if prophylactic antiemetics are not provided [1]. Both acute (≤ 24 h after chemotherapy) and delayed (24–120 h) nausea and vomiting can occur, and appropriate prophylaxis is required to reduce these adverse effects [2]. CINV is a complex pathophysiological process involving a number of neurotransmitters, including serotonin acting at 5-HT_3 receptors, dopamine at D_2/D_3 receptors and substance P at NK_1 receptors. These are all targets for antiemetic therapies [3], with 5-HT_3- and NK_1-receptor antagonists currently comprising, along with dexamethasone, the gold standard for prophylaxis of CINV associated with HEC. Dopamine receptor antagonists have been used in CINV prophylaxis but their utility has been limited primarily by the low therapeutic index of most of the available agents, with adverse effects such as QT interval prolongation and extrapyramidal toxicity of particular concern [3], or by lack of worldwide availability [4].

Amisulpride is an antagonist of dopamine D_2 and D_3 receptors, approved since the 1980s as treatment for psychosis, with a favourable safety profile, even when used at doses of 400–800 mg/day [5]. In a pilot study, a combination of ondansetron and a single 20 mg intravenous (i.v.) dose of amisulpride protected 83% of patients from vomiting and use of rescue medication in the acute phase following cisplatin chemotherapy [6]. Amisulpride has also been shown to be effective at preventing post-operative nausea and vomiting [7, 8].

This study was designed to investigate the efficacy and safety in the delayed phase of CINV of different doses of oral amisulpride given on days 2–4, compared to placebo, following a combination of intravenous ondansetron and amisulpride given on day 1. The study also enrolled a positive control group given a standard three-drug antiemetic regimen—ondansetron, fosaprepitant and dexamethasone—for assay sensitivity purposes.

Methods

Study design and patients

Multi-centre, randomised, double-blind, parallel-group, dose-ranging trial conducted at 12 sites in the UK, 10 sites in Germany and 3 sites in Denmark.

Patients entered in the study were at least 18 years of age, naïve to chemotherapy and due to receive treatment with either cisplatin ≥ 70 mg/m^2, or an anthracycline-cyclophosphamide (AC) regimen for breast cancer (female patients only), comprising cyclophosphamide (500–1500 mg/m^2) with either epirubicin (60–100 mg/m^2) or doxorubicin (40–60 mg/m^2). Patients had to have a Karnovsky performance status ≥ 60%, and adequate organ function, specifically cardiac (QT_c < 470 ms), renal (creatinine < 3 times upper limit of normal [ULN] and meeting site specific glomerular filtration rate (GFR) criteria for receiving cisplatin, typically a GFR ≥ 50–60 mL/min), hepatic (aminotransferases and bilirubin < 3 times ULN) and haematological (haemoglobin ≥ 8 g/dL, white blood count ≥ 3.0 × 10^9/L, platelets ≥ 100 × 10^9/L). Patients were excluded if they were due to receive any other moderately or highly emetogenic agents, a taxane or abdominal/pelvic irradiation, had a known prolactin-dependent tumour or phaeochromocytoma, had received amisulpride within the previous 2 weeks or had nausea or vomiting within 24 h of study start. Concomitant treatment with any regular antiemetic therapy, including corticosteroids (unless by inhalation and started more than 1 month prior to study entry), medications that could induce torsade de pointes, levodopa or benzodiazepines (unless at a stable dose for at least 1 month prior to entry), was not permitted.

Study treatments

Patients were randomly assigned to one of 5 treatment groups. Immediately prior to starting chemotherapy (day 1), patients received the following: fosaprepitant 150 mg (group 5) or a saline placebo (groups 1–4) by i.v. infusion over 20 min from obscured infusion bags; then a matching 10-min infusion of either amisulpride 20 mg (groups 1–4) or dexamethasone 12 mg (group 5); and finally, in all groups, a 15-min infusion of ondansetron 8 mg (or 16 mg in patients with high BMI, according to local practice). Chemotherapy was then administered according to usual site practice.

On days 2–4, patients received oral medications each morning. Groups 1–4 received a dexamethasone-matched placebo and a capsule of amisulpride-matched placebo (group 1) or 10, 20 or 40 mg amisulpride (groups 2, 3 and 4, respectively). Group 5 received dexamethasone 8 mg and an amisulpride-matched placebo capsule.

Intravenous drugs were prepared by unblinded staff in each site pharmacy according to the randomisation schedule and provided in blinded form to the investigators. Oral

medications were provided to the site fully blinded. Randomisation was stratified by country and by chemotherapy regimen and sex.

Study assessments

For 120 h following chemotherapy, any episodes of emesis (retching or vomiting), nausea and rescue medication use were recorded, by site staff when the patient was still at the site or by the patient in a diary card after discharge. Severity of nausea was evaluated on a 100-mm visual analogue scale, any score > 5 mm taken to be nausea and any score > 25 mm taken to be significant nausea. Rescue medication, with investigator's choice of agent, was given if a patient requested it due to emetic episodes or nausea, or was judged by the investigator to require an antiemetic.

Adverse events were recorded from enrolment to a 7-day follow-up visit. ECGs were done at screening, immediately after the infusion of amisulpride or dexamethasone on day 1 and at the day 7 follow-up. Safety was also assessed from vital signs and clinical laboratory evaluations.

Ethics

The protocol was approved by independent ethics committees at each site/country (25 sites and 3 countries) and the study was conducted in accordance with Good Clinical Practice and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all individual participants included in the study.

Statistics

The intention-to-treat (ITT) analysis population was defined as all subjects who received at least one dose of intravenous amisulpride or dexamethasone. The per protocol (PP) population (the primary efficacy analysis population) was defined as those subjects in the ITT population who received the correct doses of day 1 study medications and at least the day 2 oral study medications, with no major protocol violations. Any exclusions were decided and documented prior to unblinding.

The primary endpoint was delayed phase complete response (CR), defined as an absence of emetic episodes and no use of rescue antiemetics in the period 24–120 h after initiation of chemotherapy. A sample size of 63 patients per group, though relatively small, was sufficient to provide 80% power to detect a difference of 20 percentage points in delayed phase CR between the placebo group (assumed to be 40%) and one or more efficacious doses of oral amisulpride (assumed to be ≥ 60%), at a 10% one-sided significance level. Secondary efficacy protocol–defined endpoints included the incidence of CR in the acute (0–24 h) and overall (0–120 h) phases; delayed phase CR in the sub-groups of patients who did and did not achieve CR in the first 24 h; and incidences of emesis, nausea and rescue medication use separately.

Differences in incidence efficacy variables (which include emesis, nausea and rescue medication use) were analysed by Pearson's χ^2 test with continuity correction. The Hochberg method was used on the primary endpoint to adjust for multiple pairwise comparison against a single placebo group. Differences in time-to-event variables were analysed by log-rank test and continuous secondary efficacy variables (severity of nausea) were analysed using a Mann-Whitney test.

Results

Disposition and demographics

In total, 342 patients were randomised, of whom 14 did not receive i.v. amisulpride or dexamethasone on day 1 and a further 10 did not receive any oral study medication or the correct dose of i.v. medication or had a major protocol deviation (Fig. 1). The ITT population therefore comprised 328 patients, with 318 evaluable per protocol. Baseline characteristics and chemotherapy regimens were well balanced across groups (Table 1).

Efficacy

Delayed phase CR occurred in 27/59 patients (46%) in the 10 mg amisulpride group, significantly more than the placebo group (13/65, 20%; $p = 0.002$; $p = 0.006$ after adjustment for multiplicity) (Table 2). The relative risk reduction was 32%. The overall phase (0–120 h) CR rate was also significantly higher in the 10 mg amisulpride group (21/59, 36%) than placebo (11/65, 17%; $p = 0.015$). The difference between placebo and either 20 mg or 40 mg amisulpride was not statistically significant. In the three-drug combination group, CR occurred in the delayed phase in 37/63 (59%) and in the overall phase in 33/63 (52%). Appreciably lower CR rates were seen in female patients receiving cisplatin.

In the acute phase, the average complete response rate across the four groups that received IV ondansetron plus amisulpride was 47%; in the group that received IV ondansetron, dexamethasone and fosaprepitant it was 75%.

In patients who had acute phase CR, the delayed phase CR rate was 75% (21/28) in the 10 mg amisulpride group, compared with 44% (11/25) with placebo ($p = 0.022$) and 70% (33/47) in the three-drug group. In those with acute phase failure, the delayed phase CR rate was only 17% (6/35) in the 10 mg amisulpride group, 5% (2/41) in the placebo group and 21% (4/19) in the three-drug group.

The incidences of emesis, nausea and use of rescue medication as individual parameters all mirrored the pattern of complete response rates in the delayed phase (Table 2).

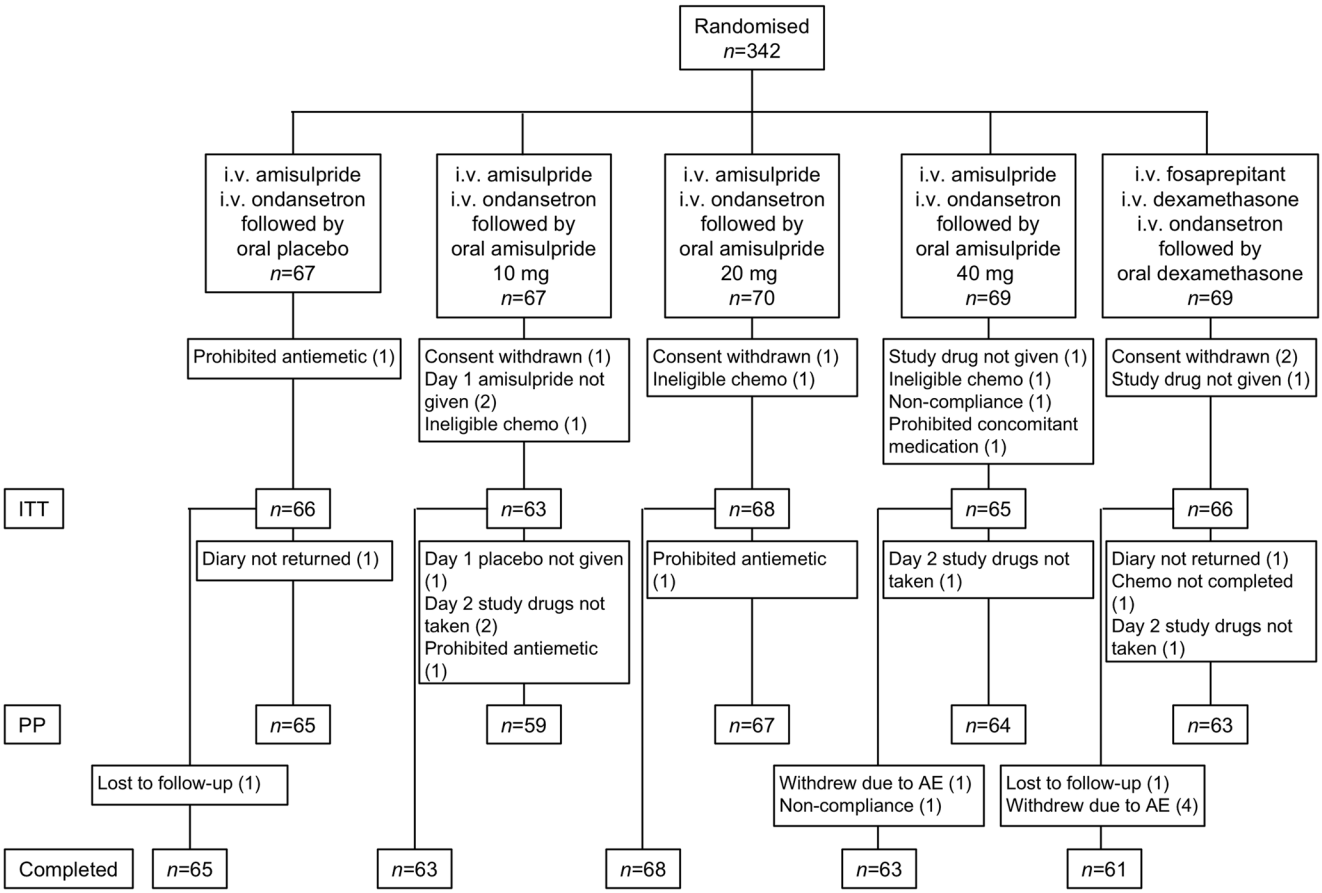

Fig. 1 CONSORT diagram of the trial

Safety

The adverse event profile was similar between the treatment groups (Table 3), showing no evidence of any worsening with increasing dose of oral amisulpride. The most frequently reported adverse event was fatigue, reported by 17% of patients. The only other treatment-emergent adverse events reported by ≥ 5% of patients overall were headache, constipation and diarrhoea, with no significant differences between treatment arms. Almost all adverse events were mild or moderate. There were no anticholinergic adverse events, nor any evidence of sedation. There were 35 serious adverse events, 26

Table 1 Demographics of patients, grouped by oral treatment during days 2 to 4 after chemotherapy

		Placebo ($n = 66$)	Amisulpride 10 mg ($n = 63$)	Amisulpride 20 mg ($n = 68$)	Amisulpride 40 mg ($n = 65$)	OND-DEX-FOS ($n = 66$)
Age (years)	median (range)	57 (27–78)	58 (32–79)	59 (30–75)	57 (32–79)	58 (37–79)
Sex, Female/male	*n* (%)	51 (77.3)/15 (22.7)	52 (82.5)/11 (17.5)	52 (76.5)/16 (23.5)	51 (78.5)/14 (21.5)	51 (77.3)/15 (22.7)
BMI (kg/m^2)	mean (range)	26.7 (15.0–45.7)	26.5 (16.2–49.9)	27.0 (17.9–40.0)	25.7 (17.5–45.5)	26.0 (17.3–37.0)
KPS (%)	mean (range)	96.4 (60–100)	96.5 (70–100)	96.3 (60–100)	96.0 (90–100)	96.6 (70–100)
Country						
Denmark	*n* (%)	12 (18.2)	13 (20.6)	17 (25.0)	15 (23.1)	16 (24.2)
Germany	*n* (%)	23 (34.8)	19 (30.2)	21 (30.9)	22 (33.8)	23 (34.8)
UK	*n* (%)	31 (47.0)	31 (49.2)	30 (44.1)	28 (43.1)	27 (40.9)
AC chemotherapy	*n* (%)	40 (60.6)	42 (66.7)	44 (64.7)	41 (63.1)	41 (62.1)
Cisplatin/male	*n* (%)	15 (22.7)	11 (17.5)	16 (23.5)	14 (21.5)	15 (22.7)
Cisplatin/female	*n* (%)	11 (16.7)	10 (15.9)	8 (11.8)	10 (15.4)	10 (15.2)

BMI body mass index, *KPS* Karnofsky Performance Score, *AC* anthracycline plus cyclophosphamide chemotherapy, *OND-DEX-FOS* ondansetron + dexamethasone + fosaprepitant prophylaxis regimen

Table 2 Efficacy results

	Placebo ($n = 65$)	Amisulpride 10 mg ($n = 59$)		Amisulpride 20 mg ($n = 67$)		Amisulpride 40 mg ($n = 64$)		OND-DEX-FOS ($n = 63$)
			p value[a]		p value[a]		p value[a]	
CR (24–120 h)	13 (20.0%)	27 (45.8%)	0.002	21 (31.3%)	0.098	20 (31.3%)	0.103	37 (58.7%)
CR (0–120 h)	11 (16.9%)	21 (35.6%)	0.015	17 (25.4%)	0.165	17 (26.6%)	0.133	33 (52.4%)
CR (0–24 h)	25 (38.5%)	28 (47.5%)	N/A	30 (44.8%)	N/A	36 (56.3%)	N/A	47 (74.6%)
No vomiting/retching (24–120 h)	24 (36.9%)	32 (54.2%)	0.040	30 (44.8%)	0.230	27 (42.2%)	0.333	48 (76.2%)
No nausea[b] (24–120 h)	12 (18.5%)	22 (37.3%)	0.016	20 (29.9%)	0.093	17 (26.6%)	0.186	30 (47.6%)
No significant nausea[c] (24–120 h)	26 (40.0%)	31 (52.5%)	0.111	27 (40.3%)	0.557	30 (46.9%)	0.271	41 (65.1%)
No rescue medication (24–120 h)	27 (41.5%)	33 (55.9%)	0.078	31 (46.3%)	0.355	28 (43.7%)	0.470	41 (65.1%)

CR complete response, *OND-DEX-FOS* ondansetron + dexamethasone + fosaprepitant prophylaxis regimen

[a] All p values are for comparison with placebo (Yates' continuity-corrected χ^2 test)

[b] VAS score $\leq$ 5 mm

[c] VAS score $\leq$ 25 mm

of which were in the three-drug and placebo groups. Two deaths and one life-threatening event occurred, all in the three-drug group. No patients discontinued the study due to intolerance of amisulpride.

There was a median increase in blood prolactin levels between baseline and post-treatment of around 30 mIU/L in the three-drug group, 10 and 20 mg in the amisulpride groups and 64 mIU/L in the 40 mg group. The post-treatment median level was well below the upper limit of normal in all groups and no clinical events relating to hyperprolactinaemia were reported. The QT_c interval was virtually unchanged after the i.v. dexamethasone infusion but prolonged by around 15 ms in patients who received i.v. amisulpride. At follow-up, QT_c was not significantly different from baseline in any group.

Discussion

The methodology of this study was specifically designed to investigate the efficacy of amisulpride, compared to placebo, in delayed nausea and vomiting induced by HEC: all patients in the investigational groups received the same antiemetics immediately before chemotherapy, were randomised before starting chemotherapy and started antiemetics for delayed emesis the day after chemotherapy [9].

The results showed that oral amisulpride at 10 mg per day on days 2–4 significantly reduced the incidence of nausea and vomiting in the delayed and overall phases after HEC, compared to placebo. In patients with no emesis or rescue antiemetic needed during the acute phase, the improvement in control of delayed phase CINV was not only significantly greater than placebo, but was comparable to that seen with the current gold standard, three-drug prophylactic regimen. The occurrence of nausea during the delayed phase and overall phase was also significantly reduced by 10 mg amisulpride.

Although it is difficult to compare across trials, the relative risk reduction of 32% delivered by amisulpride 10 mg is broadly in line with that seen for effective antiemetics across a large number of placebo-controlled trials, where the range is generally 15–40%. The three-drug control arm in this study provided a useful demonstration of assay sensitivity, confirming broad comparability of this study with other recent studies in the literature, subject to the usual caution around cross-trial comparisons.

Current therapies for CINV are based on a combination of a 5-HT_3-receptor antagonist, corticosteroid and an NK_1-receptor antagonist [1]. Most of the drugs in development or recently launched are 5-HT_3- or NK_1-receptor antagonists, whereas amisulpride has a different mechanism, blocking D_2 and D_3 receptors [10]. It has been hypothesised that dopamine pathways are particularly important in the pathogenesis of nausea [11] and there is evidence in this study of a particular benefit in respect of nausea, especially in the delayed phase (Table 2). This suggests a possible complementary role for amisulpride in combination with 5-HT_3- and NK_1-receptor antagonists, which have tended to have a smaller effect on nausea than emesis [1, 12–14].

Dopamine receptor antagonists have been used historically in the management of CINV but with mixed results. Metoclopramide, which has both D_2 and, in high doses, 5-HT_3 antagonist activity, was previously commonly used in CINV prophylaxis, but proved ineffective at conventional doses and caused neurological problems at high doses [15]. Evidence of efficacy in CINV prophylaxis has been published on several other dopamine antagonists, including metopimazine [4, 16, 17] and olanzapine [18], but its use has been limited by lack of worldwide availability and regulatory approval as well as safety

Table 3 Summary of treatment-emergent adverse events

	Placebo ($n = 66$)		Amisulpride 10 mg ($n = 63$)		Amisulpride 20 mg ($n = 68$)		Amisulpride 40 mg ($n = 65$)		OND-DEX-FOS ($n = 66$)	
	Events	Patients	Events	Patients	Events	Patients	Events	Patients	Events	Patients
TEAEs	106	47 (71.2%)	84	36 (57.1%)	77	29 (42.6%)	87	38 (58.5%)	115	38 (57.6%)
Serious TEAEs	14	12 (18.2%)	1	1 (1.6%)	4	3 (4.4%)	4	4 (6.2%)	12	8 (12.1%)
Withdrawals due to TEAEs		0		0		0		0		2 (3.0%)
Deaths due to TEAEs		0		0		0		0		2 (3.0%)
Severity										
Mild	81	29 (43.9%)	68	25 (39.7%)	55	20 (29.4%)	69	25 (38.5%)	73	12 (18.2%)
Moderate	21	16 (24.2%)	14	9 (14.3%)	19	7 (10.3%)	16	11 (16.9%)	34	21 (31.8%)
Severe	3	2 (3.0%)	2	2 (3.2%)	2	2 (2.9%)	2	2 (3.1%)	7	4 (6.1%)
Life-threatening	0	0	0	0	0	0	0	0	1	1 (1.5%)
TEAEs occurring in ≥ 5% of patients overall										
Constipation	5	5 (7.6%)	7	7 (11.1%)	2	2 (2.9%)	2	2 (3.1%)	4	4 (6.1%)
Diarrhoea	7	6 (9.1%)	3	3 (4.8%)	3	2 (2.9%)	2	2 (3.1%)	4	4 (6.1%)
Fatigue	13	13 (19.7%)	13	13 (20.6%)	5	5 (7.4%)	11	11 (16.9%)	13	13 (19.7%)
Headache	9	9 (13.6%)	7	7 (11.1%)	3	3 (4.4%)	8	8 (12.3%)	4	4 (6.1%)

TEAE treatment-emergent adverse event

concerns. Olanzapine acts at several receptors including D_2 and recently, a randomised, double-blind study showed that adding olanzapine to a three-drug regimen improved CR rates and decreased the severity of nausea in patients receiving cisplatin-based or AC chemotherapy [18]. Sedation has been described with olanzapine, an adverse effect not reported with amisulpride.

The clinical response with oral amisulpride in the delayed phase was highest at 10 mg, and appeared to decline at higher dose, which is consistent with the bell-shaped dose-response curve reported for amisulpride in PONV prophylaxis [7] and for a number of dopamine-receptor antagonists in the control of prolactin secretion [19]. However, the dose-response was not tested statistically and it cannot be excluded that the variation is down to random chance. Of note, a previous study suggested that a higher dose of i.v. amisulpride in the acute phase was associated with improved efficacy [6]. Furthermore, although it cannot be excluded that doses below 10 mg could be even more efficacious, it is unlikely, based on published pharmacokinetic and pharmacodynamic data [20].

A limitation of the study was that patients in the experimental groups received only ondansetron and amisulpride for the acute phase, resulting in lower acute and delayed phase response rates than for the three-drug control group. Furthermore, the day 1 i.v. amisulpride dose, based on that used successfully in a pilot study [6], may not be the optimal dose. It will be important to ascertain in future trials whether a lower i.v. dose of amisulpride could be more effective and whether amisulpride gives a similar benefit when added to a gold standard three-drug regimen.

It is well established that delayed phase control is heavily influenced by success in the acute phase [9], corroborated by this study. The fact that amisulpride 10 mg was effective in the delayed phase in patients who had acute phase CR suggests that amisulpride given after an optimal acute phase regimen may deliver a significant improvement in delayed phase CINV management.

Amisulpride was well tolerated at all dose levels, consistent with extensive experience of amisulpride in psychiatric practice [5, 21]. In particular, there was no extrapyramidal or cardiac toxicity, although the QT interval immediately after infusion of amisulpride was somewhat prolonged, which is consistent with data from a formal evaluation of the effect of i.v. amisulpride on cardiac conduction [22].

In conclusion, this study showed that oral amisulpride 10 mg is safe and superior to placebo at preventing delayed phase CINV associated with cisplatin or AC chemotherapy. Future studies should focus on the optimal acute phase dose of amisulpride and the value of adding amisulpride to a gold standard three-drug regimen.

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Authors' contributions The protocol was drafted by Gabriel Fox and Jørn Herrstedt and all authors contributed to the final version. All other authors included patients in the study. A draft manuscript was prepared by Jørn Herrstedt and Gabriel Fox and finally reviewed and approved by all authors.

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Compliance with ethical standards

The protocol was approved by independent ethics committees at each site/country (25 sites and 3 countries) and the study was conducted in accordance with Good Clinical Practice and with the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all individual participants included in the study.

Conflict of interest Gabriel Fox is an employee and stockholder of Acacia Pharma Ltd.

Karin Jordan has received honoraria for advisory board meetings and/or presentations for Merck, MSD, Helsinn, Tesaro, Amgen, Hexal and Pfizer.

No other potential conflicts are disclosed.

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