Oncology 1992;49:273–278

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The Effectiveness of a Single Intravenous Dose of Ondansetron

Key Words
Single dose
Ondansetron
Emesis

Abstract
This paper reviews data from 3 randomised, double-blind, parallel-group studies carried out in patients receiving high-dose cisplatin chemotherapy (50–120 mg/m^2). These comparative trials show that a single intravenous dose of ondansetron (8–32 mg) is as effective as the continuous infusion and intermittent dose regimens used in previous clinical trials (8 mg i.v. followed by a 1 mg/h infusion for 24 h and 0.15 mg/kg i.v. $\times$ 3). One of the studies, carried out in Europe, demonstrated that a single 8 mg i.v. dose was as effective as 32 mg given either as an 8 mg loading dose followed by an infusion or as a single intravenous dose of 32 mg before chemotherapy. A similar study conducted in the United States showed that a 32 mg i.v. single dose was significantly more effective than both the 8 mg i.v. dose and the intermittent dose schedule. This study used a prospective stratification based on the dose of cisplatin (50–70 mg/m^2 and $\geq$ 100 mg/m^2). In both strata the 32 mg dose was superior. These results emphasise the importance of selecting the dose of ondansetron (8–32 mg) based on factors that predispose patients to emesis, e.g., female gender, patients with a history of chemotherapy or motion sickness and the dose of cisplatin. The ondansetron dosing regimen for patients receiving a highly-emetogenic chemotherapy (8–32 mg i.v. followed by 8 mg orally twice daily) is both simple and flexible.

Introduction

Ondansetron is superior to high-dose metoclopramide in the control of acute emesis following high-dose cisplatin [1–3]. Early studies used either an intermittent ondansetron dosing regimen (0.15 mg/kg i.v. $\times$ 3 [1]) or a constant infusion (8 mg i.v. followed by a 1 mg/h infusion for 24 h [2, 3]). The infusion regimen was designed as a result of pre-clinical findings that suggested a plasma level of 30 ng/ml would be necessary to block 5-HT$_3$ receptors in man. This dosing regimen was therefore designed to maintain this plasma level for 24 h [4]. The early studies demonstrated that the maximum emetic challenge occurred during the first 12 h following cisplatin (fig. 1) [2] indicating that simpler treatment schedules may be just as effective as repeated doses or infusions. In support of this

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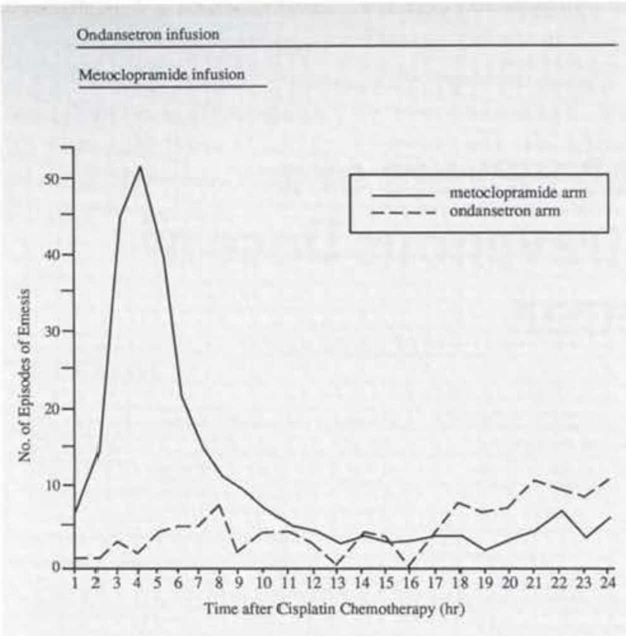

Fig. 1. Episodes of emesis during the 24 h after cisplatin administration [from 2].

observation, a similar degree of emetic control was achieved when ondansetron was administered in doses of 0.15–0.18 mg/kg every 2, 4, 6 or 8 h for 3 doses [1, 8, 9]. The urinary excretion of 5-hydroxyindolacetic acid (5-HIAA), the main metabolite of 5-hydroxytryptamine (5-HT or serotonin), has also been shown to increase in the 4- to 6-hour period following cisplatin, indicating the likely depletion of 5-HT from the enterochromaffin cells within a few hours after cisplatin administration, in parallel with the development of emesis [5]. Kinetic studies have also suggested a correlation between the plasma level of ondansetron 3–6 h following cisplatin and acute emesis control [6,7]. These data suggested that if the initiation of the vomiting reflex is blocked, acute cisplatin-induced emesis may be prevented. A single dose of ondansetron given before cisplatin chemotherapy could therefore be as effective as the regimens used previously in clinical trials. This review summarises 3 studies undertaken to determine whether the recommended total daily dose of ondansetron (32 mg), when given as a single intravenous dose prior to cisplatin, is as effective and as well tolerated as the established continuous infusion and intermittent dose regimens. Two of the studies also included an 8 mg single-dose arm, equivalent to giving only the loading dose of the 'standard' regimens.

Patients and Methods

Three multicentre, randomised, double-blind, parallel-group studies were carried out in hospitalized patients. Study 1 was conducted in France, Study 2 in Europe and Study 3 in the United States. The dose regimens used in these studies are summarised in table 1.

Patients

Male or female patients, aged at least 18 years, and who were scheduled to receive their first course of chemotherapy with cisplatin (50–120 mg/m^2) over a period of up to 4 h, either alone or in combination with other cytotoxic drugs, were recruited into these studies. Patients were excluded from the studies if they experienced nausea or vomiting in the 24-hour period prior to the start of treatment or had received anti-emetic therapy over this time. In addition, patients were excluded if they had a severe concurrent illness other than neoplasia, or metastases to the central nervous system.

Study Designs and Ondansetron Treatment Schedules

Patients randomised to the continuous infusion schedules in Studies 1 and 2 received 8 mg ondansetron (as ondansetron hydrochloride dihydrate) as a 15-min infusion in 100 ml of normal saline, followed by a continuous infusion of 1 mg/h for 24 h. Patients randomised to the intermittent dosing schedule in Study 3 received 3 doses of 0.15 mg/kg in 50 ml of normal saline given over 15 min. The second and third doses were given 4 and 8 h after the initial dose. Patients randomised to the 32 or 8 mg single dose treatments received these doses as 15-min infusions in normal saline. This was followed by a placebo infusion for 24 h in Studies 1 and 2 and by 2 placebo injections of 50 ml normal saline after 4 and 8 h in Study 3. Cisplatin was administered 30 min after the initial dose of ondansetron. Study 3 used a prospective stratification according to the dose of cisplatin; 50–70 and ≥ 100 mg/m^2.

Assessment Criteria

The timing and number of emetic episodes were recorded in hospital for 24 h following cisplatin administration. An emetic episode was defined as any episode of vomiting or retching. Emetic episodes were counted as separate if no vomiting or retching occurred for at least 1 min between episodes. Responses were categorised as follows: complete (0 emetic episodes in 24 h), major (1–2 emetic episodes), minor (3–5 emetic episodes) and failure (> 5 emetic episodes or administration of rescue anti-emetic treatment). In Studies 1 and 2, nausea was assessed by the patient before treatment and at 8 and 24 h after cisplatin using a 4-point graded scale (none, mild, moderate or severe). In Study 3, nausea was assessed using a visual analogue scale (0–100 mm) before treatment and after 24 h (0 = no nausea, 100 mm = nausea as bad as it could be). For Studies 1 and 2, the primary responses for emesis and nausea were based on the percentages of patients in each treatment group with complete or major control of emesis (0–2 emetic episodes) and none or mild nausea. For Study 3, the primary response variable was based on the number of emetic episodes.

Routine haematological and biochemical assessments were carried out before the study, at the end of the 24-hour observation period and 1–4 weeks later. Adverse events were reported or observed during treatment, with a further assessment at 1 week post-treatment for any delayed effects. The protocols were reviewed by the medical ethics committees of the investigational centres. Patients

Table 1. Ondansetron dose schedules

Study No.	Arm	Dose prior to chemotherapy mg i.v.	Subsequent doses	Total dose mg (24 h)
1	A	8	1 mg/h (24 h)	32
	B	32	placebo (24 h)	32
2	A	8	1 mg/h (24 h)	32
	B	8	placebo (24 h)	8
	C	32	placebo (24 h)	32
3	A	0.15[1]	0.15 mg/kg × 2, 4 hourly	32
	B	8	placebo × 2, 4 hourly	8
	C	32	placebo × 2, 4 hourly	32

[1] mg/kg i.v.

gave either written informed consent, or oral informed consent in the presence of a witness.

Statistical Analysis

All analyses were performed on the total population (intention-to-treat analysis) and the evaluable population (patients satisfactorily complying with the study protocol). The results reviewed here are those for the evaluable populations only, as there were no differences in the conclusions from the 2 sets of analyses. Statistical comparisons of the percentage of patients with a complete or major response (Studies 1 and 2) and a complete response (Study 3) are described below. All patients were included in the evaluations of safety.

Results

Study 1: Continuous Infusion versus 32 mg Single Dose

Of the 324 patients randomised in Study 1 (median cisplatin dose of 85 mg/m^2, range 50–100 mg/m^2), 305 (165 men and 140 women) satisfactorily complied with the protocol. The control of emesis and nausea is shown in figures 2 and 3, respectively. There were no statistically significant differences between the 2 treatment schedules in the control of emesis ($p = 0.51$) or nausea ($p = 0.48$). Complete or major control of emesis (0–2 emetic episodes) was achieved in 72% and 76% of patients receiving the infusion and 32 mg single dose regimens, respectively. Nausea was graded none or mild by 74% of patients in both groups.

Study 2: Continuous Infusion versus 32 mg Single Dose versus 8 mg Single Dose

Study 2 enrolled 535 patients, 263 men and 272 women (median cisplatin dose 72 mg/m^2, range 50–120 mg/m^2); 493 were evaluable for efficacy. The results are shown in figures 2 (emesis) and 3 (nausea). As for Study 1, there were no statistically significant differences in anti-emetic efficacy between the different dose regimens. Complete or major control of emesis (0–2 emetic episodes) was achieved in approximately 75% of patients and nausea was equally well controlled in each group. A retrospective stratification of the efficacy data based on patient age, gender, chronic alcohol use, doses of cisplatin and the emetogenic potential of concurrent cytotoxic drugs administered, indicated that there were no significant differences between the treatments when these relevant prognostic factors were considered separately.

Study 3: 0.15 mg/kg × 3 versus 32 mg Single Dose versus 8 mg Single Dose

Study 3 used a prospective stratification based on the dose of cisplatin; 50–70 and ≥ 100 mg/m^2. A total of 359 patients were entered in the high-dose stratum (255 men and 104 women); 317 patients were evaluable for efficacy. 340 patients were enrolled in the medium-dose stratum (210 men and 130 women); 301 patients successfully complied with the study protocol and were evaluable for efficacy. In both strata, the 8 mg single dose was as effective as the 0.15 mg/kg × 3 dose schedule for the control of emesis (fig. 4) and nausea (fig. 5). The 32 mg single dose was superior to the 8 mg single dose and the 0.15 mg/kg × 3 dose regimens in the control of emesis in both the

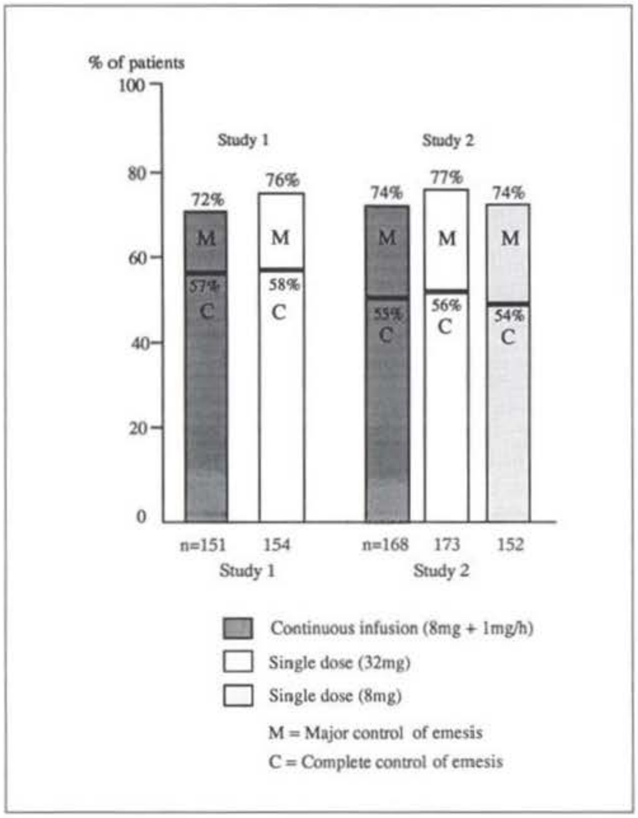

Fig. 2. Control of acute cisplatin-induced emesis with ondansetron as a continuous infusion, 32 mg single dose or 8 mg single dose.

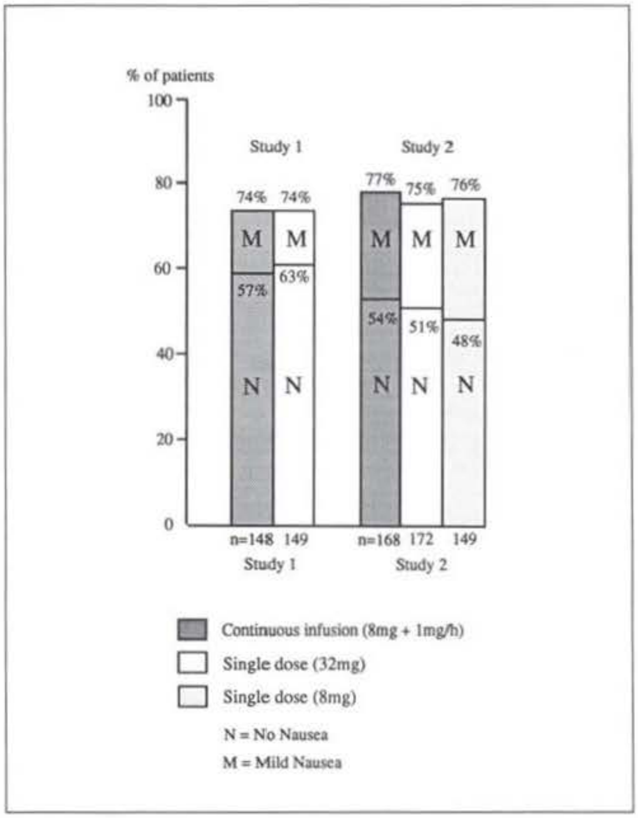

Fig. 3. Control of acute cisplatin-induced nausea with ondansetron as a continuous infusion, 32 mg single dose or 8 mg single dose.

high and medium-dose cisplatin groups (fig. 4). For complete control of emesis (0 emetic episodes), this reached statistical significance when compared with the 8 mg single dose ($p = 0.048$ and $p < 0.001$ for the high and medium-dose cisplatin groups, respectively). In addition, there were significantly fewer treatment failures in the 32 mg single-dose groups of both strata compared with the 8 mg single dose and 0.15 mg/kg × 3 dose groups ($p < 0.02$). The 32 mg single dose was also superior to the other dose regimens in the control of nausea (fig. 5). This reached statistical significance when compared with the 0.15 mg/kg × 3 dose in the high-dose cisplatin stratum ($p = 0.036$) and the 8 mg single dose in the medium-dose cisplatin group ($p = 0.008$). The superiority of the 32 mg single dose was maintained when a retrospective stratification based on age, gender and prior alcohol consumption was carried out and the groups compared.

Adverse Events

Ondansetron was well tolerated in these studies. In particular, there was no increase in the incidence of adverse events in patients given a 32 mg single intravenous dose of ondansetron. Headache was the most commonly reported adverse event, in approximately 12% of patients.

Discussion

The 3 studies reviewed here clearly demonstrate that a single intravenous dose of ondansetron is as effective as the continuous infusion (8 mg i.v. followed by 1 mg/h for 24 h) and intermittent (0.15 mg/kg × 3) dose schedules for the control of acute cisplatin-induced emesis. The efficacy rates in the French (Study 1) and European (Study 2) studies (72–77% of patients with a complete or major response) are similar to those previously reported using

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