Eur J Cancer Clin Oncol, Vol. 25, No. 9, pp. 1333–1335, 1989.
Printed in Great Britain

0277–5379/89$3.00 + 0.00

Clinical Trial Summary

The Effect of Three Dose Levels of ICS 205-930 (a Selective 5HT-3 Antagonist) on Cisplatin-induced Nausea and Vomiting

HARRY SEINEN, BERNARD A. ZONNENBERG, PAOFI TJIA and JEAN P. NEIJT
Department of Oncology, Utrecht University Hospital, Catharijnesingel 101, 3511 *GV Utrecht, The Netherlands*

INTRODUCTION

THE USE of cisplatin in cancer chemotherapy is hampered by the severe nausea and vomiting the drug induces. Current anti-emetic regimens, which are based on high-dose metoclopramide in combination with dexamethasone and a benzodiazepine, achieve control of vomiting in only 40–60% of patients [1]. Metoclopramide in a high dose produces alarming extra-pyramidal side-effects by blocking dopamine receptors. The anti-emetic property of metoclopramide is mediated by serotonin antagonism at the 5HT-3 receptor site in the gut wall [2]. In the ferret the new drug ICS 205-930, a highly selective and potent 5HT-3 receptor blocking agent, has been shown to reverse the retrograde upper gastrointestinal tract motility and to prevent cisplatin-induced vomiting [3]. A tolerability study in healthy volunteers given ICS 205-930 as a single i.v. dose (0.5–90 mg) showed no disabling side-effects such as extra-pyramidal or neuroleptic symptoms.

These findings led us to undertake a study to assess the anti-emetic efficacy and toxicity of ICS 205-930 in cancer patients being treated with cisplatin who had not responded to previous anti-emetic treatment or developed unacceptable extra-pyramidal side-effects.

Accepted 12 May 1989.
Reprint requests and correspondence should be addressed to: J.P. Neijt, M.D., Utrecht University Hospital, Catharijnesingel 101, 3511 GV Utrecht, The Netherlands.

PATIENTS AND METHODS

Twenty-two patients with advanced ovarian or head–neck cancer treated with cisplatin in combination with cyclophosphamide or 5-fluorouracil were entered in the study (Table 1). All patients had previously experienced severe vomiting (more than two vomiting episodes) or unacceptable side-effects (severe extra-pyramidal symptoms requiring specific treatment) of treatment with metoclopramide (6 mg/kg i.v.) in combination with dexamethasone (20 mg i.v.) and diphenhydramine (50 mg i.v.). Other eligibility criteria included: age 75 years or less, WHO performance status ≤ 2, normal renal and hepatic functions, no chronic diarrhoea or severe obstipation and no brain involvement. Patients with a serious concurrent disease or a history of heavy alcohol intake, myocardial infarction within the preceding 6 months, cardiac arrhythmia or intra-abdominal surgery in the preceding month were excluded. All patients gave informed consent. None of the patients developed anticipatory vomiting.

A single dose of 5 mg/m^2 (five patients), 10 mg/m^2 (eight patients), or 20 mg/m^2 (nine patients) of ICS 205-930 diluted in 100 ml saline 0.9% was infused in 15 min just before the administration of cisplatin. Nausea and vomiting were assessed after 8 and 24 h by questionnaires according to Morrow [4]. Grade I was defined as no vomiting at all, grade II as fewer than two episodes, grade III as two to five episodes, and grade IV as five or more episodes of vomiting. After the same intervals, the patients

Table 1. *Patient characteristics*

Characteristics	No. of patients
Total	22
Male	4
Female	18
Median age in years (range)	60 (42–75)
Performance status	
WHO 0	13
1	7
2	2
Site of primary tumour	
Ovary	18
Head–neck	4
Chemotherapeutic agents	
Cisplatin 75 mg/m² plus Cyclophosphamide 750 mg/m²	18
Cisplatin 100 mg/m² plus 5-Fluorouracil 100 mg/m²	4
Median serum bilirubin (μmol/l)(range)	7 (3–13)
Median serum creatinine (μmol/l)(range)	82 (63–115)
Reason for failure of previous treatment	
Severe vomiting	19
Unacceptable side-effects	3

were asked how they felt compared with earlier anti-emetic treatments.

ICS 205-930 (1H-indol-3-carbonic-acid-tropine ester hydrochloride) was supplied by Sandoz Pharmaceuticals Corporations in Basel and delivered by the hospital pharmacy in 10-ml vials each containing 2 mg/ml.

RESULTS

In the first 8 h after cisplatin infusion, 17 out of 22 patients (77%) did not vomit at all. Three patients had one vomiting episode (14%) and two patients vomited two to five times (9%). Complete prevention of nausea was achieved in 13 patients (59%). Eight patients were nauseous for less than 2 h (36%) and one patient for between 2 and 4 h (5%).

Over the first 24 h, complete prevention of vomiting was achieved in only seven patients (31%). One vomiting episode was seen in five patients (23%), five patients vomited two to five times (23%), and five patients had more than five vomiting episodes (23%). Seven patients complained of moderate nausea (32%) and four patients of severe nausea (18%). Nausea lasting less than 2 h occurred in five patients (23%), and complete control was achieved in six (27%).

The contentment concerning treatment with ICS 205-930 was consistent with the degree of control of nausea and vomiting. When asked after 8 h, 16 patients (73%) were much more satisfied with the

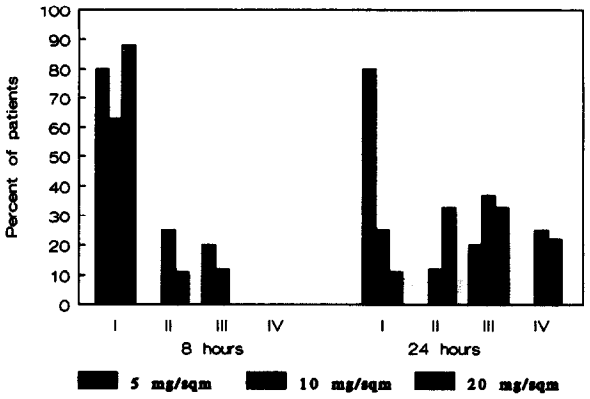

Fig. 1. *Grades of vomiting after* 8 *and* 24 h *of observation in patients receiving ICS* 205-930 *in a dosage of* 5, 10 *or* 20 mg/m².

anti-emetic properties of ICS than they had been with the previous anti-emetic schedule. Only seven (32%) remained satisfied with the treatment throughout the full 24-h observation period. Reasonable satisfaction was reported by five patients (22%) after both 8 and 24 h. One patient (5%) was not very satisfied after 8 h as against seven patients (32%) after 24 h. Three patients (14%) were very dissatisfied with the ICS treatment after 24 h.

Adverse reactions consisted of mild, transient headache and drowsiness, and were not treatment limiting in any of the cases. None of the patients developed an acute dystonic reaction or akathesia. Effects on haematological or laboratory parameters, ECG, pulse or blood pressure were not encountered. No dose–response relation was detected between the patients treated with 5, 10 or 20 mg/m² (see Fig. 1).

DISCUSSION

Our results show ICS 205-930 to be an effective and safe anti-emetic drug in cisplatin-treated cancer patients. In 77% of the patients who had not responded to previous anti-emetic treatment, we observed a complete prevention of vomiting during the first 8 h after cisplatin infusion. Complete control of nausea was achieved in almost 60% of the patients during this interval.

The beneficial effects declined almost entirely between 8 and 24 h after the infusion. This was also reported for BRL 43694, another specific 5HT-3 receptor antagonist [5]. In normal volunteers the overall mean half-life of ICS 205-930 is 11.1 h (range 7.7–14.9 h). Both ICS 205-930 and cisplatin show a high level of plasma protein binding. Under competition between cisplatin and ICS for binding sites at plasma proteins the free plasma ICS level may increase. When hyperhydration is used in cisplatin therapy, the plasma clearance of ICS may increase and cause shortening of the half-life. This may explain why the preventive effect of a

single infusion of ICS on nausea and vomiting only persists for the first 8 h. We found no differences between the different dose groups with respect to efficacy, although the small number of patients treated must be taken into account.

We conclude that ICS 205-930 is effective and safe for the prevention of cisplatin-induced nausea and vomiting in the first 8 h after infusion. Further studies are needed to define the optimum timing and dose schedule for ICS in cisplatin-treated patients who receive hyperhydration.

Acknowledgements—The authors thank Dr. P.K. van Roon and SANDOZ B.V. for providing the ICS 205-930.

REFERENCES

1. Gralla RJ, Tyson LB, Kris MG, Clark RA. The management of chemotherapy-induced vomiting. *Med Clin North Am* 1987, **71**, 289–301.
2. Richardson BP, Engel G, Donatsch P, Stadler PA. Identification of serotonin M-receptor subtypes and their specific blockade by a new class of drugs. *Nature* 1985, **316**, 126–134.
3. Costall B, Domeney AM, Naylor RJ, Tattersall FD. 5-Hydroxytryptamine M-receptor antagonism to prevent cisplatin-induced emesis. *Neuropharmacology* 1986, **25**, 959–961.
4. Morrow GR. Prevalence and correlates of anticipatory nausea and vomiting in chemotherapy patients. *J Natl Cancer Inst* 1982, **68**, 585–588.
5. Cassidy J, Raina V, Lewis C *et al.* Pharmacokinetics and anti-emetic efficacy of BRL 43694, a new selective 5HT-3 antagonist. *Br J Cancer* 1988, **58**, 651–653.