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Prevention of Emesis by ICS 205-930 in Children Receiving Cytotoxic Chemotherapy

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Nausea and vomiting are among the most frequent and severe acute side-effects of cytotoxic therapy and are not optimally controlled by conventional antiemetics. This situation warrants the evaluation of new classes of antiemetic agents such as the 5-HT_3 receptor antagonists. 19 children with a median age of 9 years (range 2–16 years), treated with cytotoxic drug combinations that had previously caused nausea and vomiting refractory to conventional antiemetics, were given the selective 5-HT_3 receptor antagonist ICS 205-930. The drug was given intravenously (i.v.) at 0.2 mg/kg (maximum 5 mg) during the chemotherapy infusion period and was continued orally for up to 5 days in chemotherapy courses containing cisplatin. The number of emetic episodes was recorded and the response was scored according to following scale: grade 1 = no nausea, no emetic episode; grade 2 = up to four episodes of vomiting and less than 5 h of nausea; grade 3 = five or more than five emetic episodes and/or nausea for at least 5 h. The 19 patients received a total of 169 various courses of chemotherapy combined with ICS 205-930. A score of 3 was observed during one course only, a score of 2 in 37 out of the 169 courses, including the four courses with cisplatin. The drug was very well tolerated. Side-effects possibly related to ICS 205-930 were mild to moderate headache in 4 patients during seven courses overall and obstipation in 3 patients during 11 courses. The results strongly suggest that ICS 205-930 is a highly effective and safe antiemetic agent in non-naive pediatric patients receiving non-cisplatin cytotoxic chemotherapy and who had failed conventional antiemetic treatment.
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INTRODUCTION

NAUSEA AND vomiting are among the most distressing and debilitating side-effects of the chemotherapy regimens used for the treatment of childhood cancers.

The currently available antiemetics do afford benefits but none is completely satisfactory: they may induce side-effects such as sedation and extrapyramidal signs [1] and complex dosing regimens may be required to achieve optimal antiemetic activity [2].

ICS 205-930, (1H)-indol-3-carbonic-acid-tropine ester hydrochloride, is a selective 5-HT_3 receptor antagonist. In adult patients, ICS 205-930 is an effective antiemetic agent in patients receiving cytotoxic chemotherapy even when this includes high doses of cisplatin [3]. The present study was the first evaluation of ICS 205-930 in paediatric patients. It was undertaken to assess the tolerability and efficacy of the agent in children receiving moderately or highly emetogenic chemotherapy for the treatment of malignant disease.

PATIENTS AND METHODS

19 children (13 boys and 6 girls) under chemotherapy for malignant disease were studied. Their ages ranged from 2 to 16 years (median 9). The severity of emesis had been daily graded during previous chemotherapy courses, given with conventional antiemetic treatment, according to the following score system:
Grade 1 = no nausea or vomiting = complete control.
Grade 2 = less than 5 h of nausea and up to four episodes of vomiting/day = partial control.
Grade 3 = nausea of 5 h or longer duration or more than four episodes of vomiting/day = no control.

Children who had experienced grade 3 emesis during one or more previous chemotherapy courses and who were due to receive chemotherapy courses with equal or greater emetogenic potential were eligible for the study with the experimental drug ICS 205-930.

The same scoring system was used during the ICS 205-930 treatment. It was carried out by a parent for in-patients as well as for out-patients on standardised flow-sheets. Any vomiting productive of liquid or repeated retches (dry heaves) within a 5 min period were counted as one episode. Conventional antiemetic treatment consisted either of alizapride ("Litican") 4–6 mg/kg/day or of metoclopramide 5 mg/kg/day.

ICS 205-930 was infused intravenously (i.v.) over 15 min at a dose of 0.2 mg/kg with a maximum dose of 5 mg just before the start of chemotherapy. ICS 205-930 was given i.v. once daily during the period of chemotherapy and continued orally at the same dose until day 5 after the stop of chemotherapy for courses including cisplatin. The chemotherapy combination of cytotoxic drugs is indicated in Table 1.

RESULTS

Of the 169 courses given to 19 children who had experienced grade 3 emesis on previous equally emetogenic chemotherapy courses, only one induced grade 3 emesis (more than five emetic episodes per day during 2 consecutive days) and 37 (22%) induced grade 2 emesis. The single patient with grade 3 emesis was completely controlled in the following courses of chemotherapy, however, the single patient, receiving the cisplatin regimen, remains grade 2 on each cisplatin administration. No severe toxicity attributed to ICS 205-930 was observed. 4 patients, during seven courses overall, complained of mild to

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Table 1. Chemotherapy regimens and emesis response to ICS 205–930

Regimen and daily dose in mg/m²	No. of patients	No. of courses	Duration of chemotherapy in days	Grade of emesis		
				1	2	3
Cisplatin 100 + ifosfamide 3000 + vindesine 4	1	4	3	0	4	0
Cyclophosphamide 200–1000 + doxorubicin 30+ methotrexate 1000–5000 + Ara-C 300–6000 + asparaginase 10.000 U + teniposide 165 + vincristine 1,5 + dexamethasone 10	7	23	5	16	7	0
Cyclophosphamide 1000 + Ara-C 75	4	11	1	11	0	0
Cyclophosphamide 50–1000 + etoposide 150–300	2	5	2–3	3	2	0
Cyclophosphamide 300 + doxorubicin 60 + vincristine 1,5	1	4	5	3	1	0
Ifosfamide 400 + cerubidine 50 + vindesine 3 + methotrexate 1000–5000	3	9	5	9	0	0
Ifosfamide 800 + methotrexate 5000 + etoposide 100 + Ara-C 300 + vincristine 1,5	3	8	5	5	3	0
Ifosfamide 1800 + etoposide 150	1	5	5	4	1	0
Doxorubicin 50–70 + etoposide 100	4	24	1–3	12	12	0
Melphalan 180 + TBI 3800 CGY	1	1	1	0	1	0
Mitoxantrone 10 + Ara-C 200 + etoposide 150	3	3	5	2	1	0
Mitoxantrone 10 + Ara-C 75 mg + vincrinstine 1,5	2	8	4	8	0	0
Mitoxantrone 8 + Ara-C 4000	2	6	5	5	0	1
Actinomycin-D 0,5 + vincristine 1,5	1	4	5	3	1	0
Carboplatin 600 + teniposide 150 + vincristine 1,5	1	10	4	8	2	0
Carboplatin 500–600 + etoposide 150	2	8	3	8	0	0
Ara-C 4000 + etoposide 125	2	5	5	5	0	0
Doxorubicin 30 + asparaginase 10.000 U + vincristine 1,5	1	3	1	3	0	0
Methotrexate 5000–12.000	5	28	1	26	2	0

moderate headache during 2 days and obstipation was reported by the parents after 11 courses in 3 patients who also received vincristine as part of their cytotoxic treatment. Overall results are summarised in Table 2.

DISCUSSION

The mechanisms of chemotherapy-induced emesis have not been fully elucidated [4, 5], but 5-HT has been postulated to mediate emesis. Studies in ferrets have shown that emesis can be evoked through a peripheral mechanism involving the activation of vagal afferents by 5-HT_3 receptors [6, 7] and through a central mechanism involving binding to receptors in the area postrema of the brain [8, 9]. The success of ICS 205-930 in abolishing nausea and vomiting in patients with symptoms refractory to the conventional antiemetic therapy underlines the potential of this new drug as an adjunct to cancer chemotherapy. These results are in accordance with those recently achieved with two other 5-HT_3 antagonists in children under cytotoxic therapy, namely granisetron [10] and ondansetron [11]. It is worthy of note that as for granisetron but in contrast to ondansetron total or partial control of emesis was achieved with only one daily dose of the drug. Most studies of 5-HT_3 antagonists so far have been carried out in patients undergoing single-day chemotherapy. In our study, chemotherapy was given in single-day (54 courses), 2-day (four courses) or more than 2-day (111 courses) and the longer duration of chemotherapy was not associated with a decrease in antiemetic efficiency. Moreover, ICS 205-930 maintained its efficiency during subsequent chemotherapy courses in the same patients.

Table 2. Emesis in patients receiving chemotherapy

Grade of emesis	Under conventional antiemesis No. of courses	With ICS 205-930 No. of courses
1	0	131
2	0	37
3	> 19	1

Negligible adverse events were reported, and these may or may not have been associated with ICS 205-930. In our study, the 3 patients who developed obstipation also received vincristine and 2 of the 4 patients with headache received intrathecal injections of chemotherapy. No sedation or neurological side-effects were seen [12]. It should be stressed that all children studied were older than 2 years. In the study by Lemerle *et al.* the youngest age was 3 years [10] and in Pinkerton's study it

was 2 years [11]. Conclusions with regard to the safety of 5-HT_3 antagonist particularly to the absence of central nervous system disturbance cannot be applied to younger children so far and as for other drugs, which may possibly interact with receptors in the cerebrum, further studies in babies should be undertaken with great caution.

In conclusion, for the age group subjected to this study, ICS 205-930 proved safe, easy to use and more efficient than conventional antiemetic therapy. Presently, its most severe side-effect is inherent to its very high cost. Further evaluation of the drug should include an account of the possible shortening of hospitalisation required for chemotherapy treatment, which could compensate for the increased expenses entailed by the use of ICS 205-930.

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Phase II Study of Elliptinium Acetate Salvage Treatment of Advanced Breast Cancer

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Elliptinium acetate (Celiptium^R) is an intercalating agent belonging to the ellipticine family. This agent has demonstrated clinical activity as salvage treatment in breast cancer using a weekly regimen. However, its clinical use was hampered by important toxicities such as xerostomia and immune-mediated haemolytic reactions due to development of anti-elliptinium IgM antibodies. We have studied 83 patients previously treated for metastatic breast cancer using elliptinium acetate with a different schedule: 80 mg/m^2 daily for 3 consecutive days every 21 days. In 80 evaluable patients, an objective response (complete + partial response) was obtained in 5 of 30 patients with visceral metastases (13%), in 6 of 21 patients with soft tissue metastases (29%), and in 3 of 20 patients with mixed metastases (15%). The overall objective response rate was 14/80 (18%, 95% confidence interval = 10–26%). Moderate to severe xerostomia occurred in 10% of patients, while no anti-elliptinium antibodies or haemolytic reactions were detected using this schedule. No significant haematological toxicity, as usually reported with this drug, was observed. Elliptinium acetate has modest but definite activity as salvage treatment of breast cancer. The 3-week schedule seems as active as and less toxic than the weekly schedule.
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INTRODUCTION

ELLIPTINIUM ACETATE (Celiptium^R) is a fully synthetic derivative of ellipticine, a naturally occurring plant alkaloid with demonstrated cytotoxic activity in preclinical models [1–3]. Intercalation into DNA, demonstrated *in vitro*, has been suggested as part of the mechanism of action of drugs of this family [2]. More recently, other mechanisms of action have been put forward, such as generation of toxic free radicals and alkylating electrophilic intermediates [4], interaction with plasma membranes [5], and introduction of DNA strand breaks through an action upon topoisomerase II [3, 6, 7].

Previous phase II studies with elliptinium acetate demonstrated 19% response rate in pretreated breast cancer using a weekly schedule of 100 mg/m^2 given by 1-h infusion every 7 days [8]. However, the reporting of anti-elliptinium IgM antibody-mediated haemolytic reactions with this weekly schedule [8, 9]