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Control of nausea and vomiting by Navoban® (tropisetron) in 131 children receiving cytotoxic chemotherapy

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One hundred and thirty-one children with a median age of 5 years were administered Navoban® (tropisetron), a selective antagonist of the serotonin receptor (5-HT_3), dosed once daily at 0.2 mg/kg (with a maximum of 5 mg daily) in a study aimed at evaluating the prevention of nausea and vomiting induced by anti-cancer chemotherapy. The most common malignancy (in 49% of patients) was acute lymphocytic leukaemia. Patients received Navoban® during one or more courses of emetogenic chemotherapy for a total of 455 courses administered intravenously or intravenously and intrathecally (IV + IT). Most patients (89%) had already received cytotoxic chemotherapy before enrolment for the trial. On Day 1, Navoban® was administered slowly and intravenously as a single dose before the start of chemotherapy, or by mouth as a single daily dose on subsequent days (median treatment duration = 5 days). On the first 5 days of each course of chemotherapy, response to Navoban® per 24-hour period was graded as: *complete* (absence of both nausea and vomiting), *partial* (1–4 vomits and/or less than 5 hours of nausea), or *failure* (more than 4 vomits and/or at least 5 hours of nausea). Ninety-six per cent of the intravenous chemotherapy group and 97% of the IV + IT chemotherapy group had a complete (70% and 55% respectively) or partial (26% and 42% respectively) response during the first 24-hour period of the first course in which Navoban® was used. The second and subsequent courses yielded similar percentages. Delayed emesis was observed mainly during those courses employing the most emetogenic chemotherapy. No side effects of Navoban®, other than one case of diarrhoea, were documented in this study.

Key words: Navoban® (tropisetron), nausea, vomiting, children, malignancy.

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Introduction

It is imperative that the risk of anti-cancer treatment-related toxicity in younger patients be alleviated. Emesis and nausea are potentially more hazardous in children than in adults from the point of view of appetite loss and acute disturbances in nutritional and electrolyte balance. Thus, emesis provoked by chemotherapy is a major problem in the treatment of childhood malignancies, and the discomfort and distress of nausea and vomiting suffered by younger patients is acceptable only within the context of the potential cure by aggressive treatment. The issue is further complicated by the intensification of treatment regimens administered to the younger cancer sufferer. Such treatments, which are often more emetogenic than those administered to adults, are frequently administered over several days – a trend which has increased considerably the risk of emesis being the cause of greater patient morbidity.

More side effects are observed in the younger age group, while none of the traditionally prescribed antiemetics is entirely effective, either alone or in combination. Extrapyramidal reactions induced by metoclopramide occur in a significant number of children, which precludes its use in high doses.[1] Moreover, many children dislike, for obvious reasons, the marked sedation provoked by chlorpromazine, promethazine and clorpheniramine, despite the antiemetic capabilities of these compounds.

Over the past few years, 5-HT_3-receptor-antagonists have proved remarkably effective in the prevention of nausea and vomiting in patients receiving emetogenic chemotherapy; among this 'new generation' of agents, Navoban® (tropisetron) is a selective antagonist of the 5-HT_3-receptor. In adults, a single daily dose of 5 mg Navoban® proved highly effective in the prevention of nausea and vomiting induced by chemotherapy.[2]

Table 1. Criteria for emetic grade of chemotherapy courses (dose in mg/m²)

Grade 1	Grade 2	Grade 3 *	Grade 4 *
Amsacrine	Cisplatin < 20	Cisplatin ≥ 20	Cisplatin ≥ 60
Asparaginase	Carboplatin < 150	Carboplatin ≥ 150	Dactinomycin ≥ 0.45
Bleomycin	Dactinomycin < 0.3	Dactinomycin ≥ 0.3	Cyclophosp. ≥ 1000
Etoposide	Carmustine < 75	Carmustine ≥ 75	Cytarabine ≥ 1000
Fluorouracil	Chlormethine < 6	Chlormethine ≥ 6	Ifosfamide ≥ 3000
Mercaptopurine	Cyclophosp. < 300	Cyclophosp. ≥ 300	
Methylgag	Cytarabine < 150	Cytarabine ≥ 150	
Mitomycin	Dacarbazine < 100	Dacarbazine ≥ 100	
Mitoxantrone	Daunorubicin < 45	Daunorubicin ≥ 45	
Procarbazine	Doxorubicin < 45	Doxorubicin ≥ 45	
Teniposide	Epirubicin < 75	Epirubicin ≥ 75	
Thioguanine	Ifosfamide < 1000	Ifosfamide ≥ 1000	
Vinorelbine	Methotrexate < 3000	Methotrexate ≥ 3000	
Vindesine			
Vinblastine			
Vincristine			

* Chemotherapy regimens containing at least two drugs of grade 2 were considered as grade 3. Chemotherapy of grade 3 was considered as grade 4 when combined with grade 2 or grade 3 chemotherapy.

The pharmacokinetics of this compound are known to be comparable in children, in whom the dose is adjusted to correct for the age-dependent distribution volume. A high safety and efficacy profile for Navoban® in paediatric oncology has been reported in three studies using limited patient populations.[3–5] The present study aims to confirm the reported efficacy and safety of Navoban® in the prevention of nausea and vomiting in a large group of children treated with emetogenic chemotherapy.

Patients and methods

This is a prospective, open, multicentre, compassionate-use study of children receiving emetogenic chemotherapy for the treatment of cancer, enrolled after parental consent. A total of 131 children were enrolled in six paediatric oncology centres in Belgium between November 1992 and January 1994. The study respects the guidelines of the Helsinki Declaration concerning medical research in humans.

A single daily dose of Navoban®, 0.2 mg/kg bodyweight (maximum 5 mg) was administered, slowly and intravenously, over at least one minute (undiluted or diluted in normal saline) before the start of chemotherapy on Day 1, and intravenously or by mouth on the following days of each course. By mouth, it was taken as a single morning dose, one hour before breakfast. The contents of the 5 mg/5 ml ampoule were also taken, undiluted or mixed with orange juice; this allowed for the required dose adjustment.

A grading-scale based on a combined measure of nausea and vomiting was used to assess the efficacy of Navoban®. This was a scale that had been used in a previous study.[3] The response per 24-hour period on the first 5 days of each course of chemotherapy was graded as: *complete* (no nausea or vomiting), *partial* (1–4 vomits and/or less than 5 hours of nausea), or *failure* (more than 4 vomits and/or at least 5 hours of nausea).

The first day of the course is referred to as Day 1. The patients, the parents of the younger children and the nursing staff all contributed to the assessment of the efficacy and safety results.

Adverse events are reported for all patients who received at least one dose of Navoban®.

The statistics are purely descriptive, given the open and uncontrolled nature of this study. The efficacy results are reported separately, for all courses grouped together and for the first and second course of each patient. Patients receiving chemotherapy intrathecally as well as via the intravenous route are considered separately from those who received only intravenous chemotherapy. Moreover, chemotherapy courses are grouped by emetic grade (1–4) of chemotherapy (see Table 1). The grade of a chemotherapy course was determined by the highest emetic grade of each agent at the dose used. Chemotherapy regimens containing at least two days of grade 2 or grade 3 were upgraded.

Table 2. Patients by route of administration and emetic grade of chemotherapy for Course 1 and 2

	Course 1			Course 2		
Emetic grade	IV	IV + IT	All	IV	IV + IT	All
Grade 1–2	25	16	41	22	11	33
Grade 3	48	10	58	30	8	38
Grade 4	25	6	31	21	4	25
Total	98	32 *	130 *	73	23	96

IV, chemotherapy administered intravenously. IV + IT, chemotherapy administered both intrathecally and intravenously.
* A single patient received only IT chemotherapy and this course was not graded.

Results

Patient characteristics

Sixty-nine boys and 62 girls (131 children in all) under chemotherapy for malignant disease were enrolled in the study from November 1992 to January 1994. Ages ranged from 10 weeks to 21 years; the median age was 5 years and 15 of the children were under 2 years old. Forty nine per cent were being treated for acute lymphocytic leukaemia, 9% for lymphoma, 8% for neuroblastoma, 8% for Wilm's tumour, 5% for osteosarcoma, 5% for rhabdomyosarcoma, 5% for sarcoma (unspecified) and 5% for acute myeloblastic leukaemia. The remaining 6% comprised other types of cancer.

Eighty-nine per cent of the patients had received cytotoxic chemotherapy before enrolling in the study; 12 underwent abdominal surgery and 8% had received radiotherapy before the study. Fifty-two of the 131 children had information on their response to antiemetic therapy in a previous course of chemotherapy. In 41 of 52 children (79%) the response was incomplete.

Chemotherapy

Highly emetogenic chemotherapy (grades 3 or 4) was administered to 89 children (68%) in Course 1 and to 63 (65%) in Course 2. Chemotherapy was administered by the intravenous route alone in 98 of the 131 first courses (75%) and in 73 of the 96 second courses (76%). Together, these courses, which are analysed separately, comprise the IV group. Thirty-three patients in the first course and 23 patients in the second course also received intrathecal chemotherapy (referred to as the IV + IT group). The number of first and second courses, according to the administration route and emetic grade of chemotherapy are detailed in Table 2.

In 116 patients (89%), chemotherapy agents were given in combination during the first course of the study, in 83% of Course 2 and in 83% of all courses together. Chemotherapy was administered to 53% of patients on a single day, and the results were similar in Courses 1 (47%) and 2 (51%).

Study drug administration

In a total of 455 chemotherapy courses patients received Navoban® during one (25%) or more courses of emetogenic chemotherapy. The median number of chemotherapy courses was 3, with 15 patients receiving Navoban® over more than 6 courses. The compound was administered for a median duration of 5 days during Course 1; this ranged from a single day in 22 patients (17%) to more than 7 days in 4 patients. The intravenous route was used for at least 2 days in 63 patients, and for 5 days in a further 16 patients. For the second and following courses, the duration and route of administration were very similar.

Daily doses (0.2 mg/kg Navoban®, maximum 5 mg) were administered every 12 hours on the first day of the course to 4 patients on Course 1 and to 3 patients on Course 2. In 4% of the first and second courses, and in 3% of the courses overall, rescue treatment was given. Corticosteroids were part of chemotherapy in 18% and 13% on Courses 1 and 2, or were added as an antiemetic agent in 3% and 5%. Chlorpromazine was added to Navoban® in 3% of all courses and alizapride was added in 1% of all courses.

Efficacy results

In 305 out of 455 chemotherapy courses (67%), overall complete response on Day 1 (absence of both nausea and vomiting) was observed. On Day 1, a 70% complete response rate was observed in the IV chemotherapy group and a 26% partial response rate,

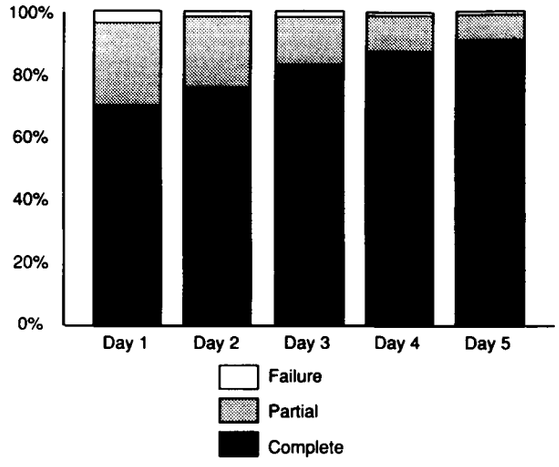

Figure 1. Response rates on the 5 observation days of the first course of chemotherapy (IV group) in which Navoban® was used (n = 98).

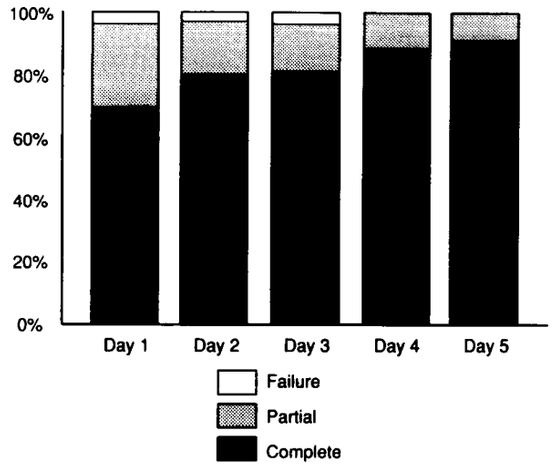

Figure 2. Response rates on the 5 observation days of the second course of chemotherapy (IV group) in which Navoban® was used (n = 73).

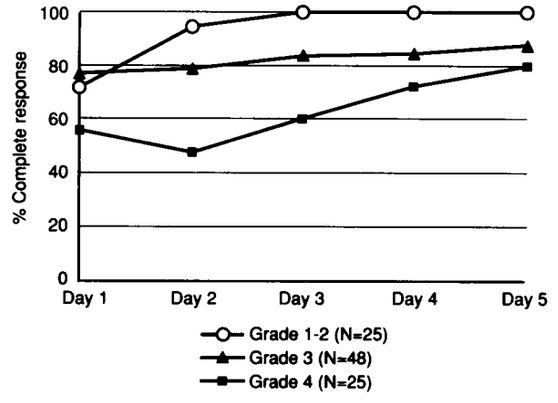

Figure 3. Complete response rates by emetic grade on the 5 observation days of the first course of chemotherapy (IV group).

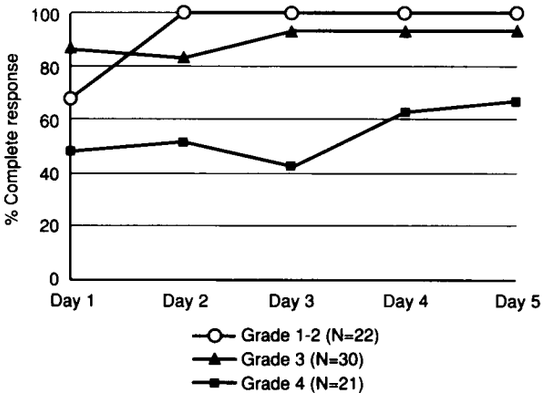

Figure 4. Complete response rates by emetic grade on the 5 observation days of the second course of chemotherapy (IV group).

for both Courses 1 and 2 (Figures 1 and 2). On subsequent days, the percentage of complete responders increased; moreover, 53% of patients in the IV chemotherapy group on Course 1 remained completely free of both nausea and vomiting during the 5 days of observation. This fraction of complete responders over the 5-day period was 56% for Course 2 and 60% for all IV chemotherapy courses as a single group.

The complete response rates for Courses 1 and 2 of the intravenous chemotherapy group by emetic grade are shown in Figures 3 and 4. It will be noted that, while complete response rates of over 80% were seen from Day 2 onwards for grades 1–2 and grade 3 chemotherapy, a significant fraction of incomplete responders on Day 2 for grade 4 chemotherapy remained, and this delayed emesis was also present for grade 4 chemotherapy for Courses 1 and 2. When the same analysis was performed with both the IV and the IV + IT groups, similar tendencies were observed.

Complete response rates for the 33 patients in the first and 23 patients in the second course receiving chemotherapy intrathecally were lower than those for the intravenous group, while nausea and vomiting were controlled completely, on the first day of the course, in 55%, 48% and 45% respectively for Courses 1, 2 and all grouped together.

Fifteen patients were less than 2 years old and 5 were less than one year old. During Course 1, the

children were given chemotherapy IV (N= 14) or IV + IT (N= 1) for acute lymphocytic leukaemia (N= 4), Wilm's tumour (N= 3), neuroblastoma (N= 3), rhabdomyosarcoma (N= 2), medulloblastoma (N= 1), acute myeloblastic leukaemia (N= 1) and germ cell tumour (N= 1).

On Day 1 of Course 1, response was complete in 9 children (60%) and partial in 6. During the 5-day observation period, 7 out of the 15 children (47%) had complete responses for the 5-day observation period.

Safety results

As a result of disease progression, one patient died during the 28 days following drug administration. There was one case of diarrhoea, although whether Navoban® was implicated in this remains unclear. Studies in adults have reported headache and constipation as adverse events, but no such reactions were observed in the young patients involved in the present study.

Discussion

Nausea and vomiting provoked by emetogenic chemotherapy are no less of a problem in children than in adults. What is more, the side effects associated with traditional antiemetics are all too often more pronounced in the young.

The results published here agree substantially with those reported in previous studies of Navoban® in paediatric oncology. Hachimi-Idrissi *et al.*, reporting on 19 children in whom conventional antiemetic treatment had failed, observed complete control of nausea and vomiting in 131 (77%) out of 169 cycles of cytotoxic chemotherapy.[3] Gershanovich reported a complete response of 69% for nausea and vomiting.[4] Cefalo *et al.* reported recently on 15 children refractory to metoclopramide-based cocktails and receiving cisplatin-based chemotherapy (20–30 mg/m^2/day).[5] In all but one patient, a significant improvement over metoclopramide-based cocktails was obtained.

In the present study, side effects to Navoban® were almost totally absent – in striking contrast to the sedative effect of chlorpromazine and the extrapyramidal reactions so often seen in children treated with metoclopramide.[1,6] The once-daily single-agent dose regimen of Navoban® is also a great improvement over the combination schemes of conventional antiemetics.[7]

This study represents, as far as we can ascertain, the first report of the use of Navoban® in infants suffering from malignancy. In such patients, safety and efficacy data appear to be comparable to those noted in older children.

Findings on the use, efficacy and safety of other 5-HT$_3$-antagonists in children treated with chemotherapy have been reported elsewhere.[8–10] However, in the absence of properly designed comparative studies, it is difficult to make direct comparisons.

In conclusion, the effect of once-daily Navoban® at 0.2 mg/kg (maximum 5 mg daily) on chemotherapy-induced nausea and vomiting in children was evaluated. Despite the uncontrolled and open nature of this multicentre study, the data point to a high degree of safety and efficacy for this compound. On the first day of the first chemotherapy course in which Navoban® was used, 70% of all children had a complete response rate and 26% had a partial response rate. The response rate for the courses with the highest emetic grade remained around 50% on Days 1 and 2, and only improved subsequently. In the second course using Navoban® response rates were similar to the first. This finding indicates a consistent response for Navoban® over courses based on multiple chemotherapy.

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