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REVIEW

Clinical application of 5-HTa-3R antagonist tropisetron in chemotherapy patients

Chang-Tai Xu, Bo-Rong Pan

Chang-Tai Xu, Physician in Charge, Director of the Department of Gastroenterology and Haematology, Chinese PLA 473 Air Force Hospital, 216 Anning donglu, Lanzhou 730070, Gansu Province, China

Bo-Rong Pan, Professor of Internal Medicine, Room 12 Building 621, Fourth Military Medical University, 17 Changlexilu, Xi'an 710033, Shaanxi Province, China.

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Correspondence to: Dr. Chang-Tai Xu, Physician in Charge, Director of the Department of Gastroenterology & Haematology, Chinese PLA 473 Air Force Hospital, 216 Anning donglu, Lanzhou 730070, Gansu Province, China

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INTRODUCTION

The prevention and control of vomiting and nausea is of major clinical importance, particularly in the realm of oncology, where intractable vomiting and nausea may severely limit the use of cytotoxic therapy. For the patient, the most distressing aspect of chemotherapy is its associated nausea and vomiting, and this may cause refusal of further therapy, even when potentially curative[1]. This is particularly true of cisplatin, which is used in the management of solid tumors and is regarded as the most emetogenic of the cytotoxics (Table 1).

PHARMACOLOGICAL PROPERTIES

Chemistry and composition

Navoban, also known as (1H-indol-3 carboxylic acid 8-methy1 - 8-azabicyclo[1-3] oct 3α-Y1-eater), has the molecular formula $C_{17}H_{20}N_2O_2HCl$. Navoban was derived from a modification to 5-HT_3, the indole moiety being used as the nucleus. Like other 5-HT_3 receptor antagonists, navoban has a 6.5 aromatic nucleus connected to a basic nitrogen atom *via* a carbonyl group and a 4-atom unit, and it is thought that the aromatic nucleus may be responsible for the blockade of the 5-HT_3 receptor. Navoban is a white, crystalline powder with good stability, and it has a shelf-life of 3 year. No special packaging or protective condition is required for storage of navoban.

Both navoban capsules and 5 mL ampules, for intravenous administration, contain 5.64 mg of navoban hydrochloride, which is equivalent to 5 mg of the base.

Activity at 5-HT3 receptors

The 5-HT_3 receptors are involved in nausea and vomiting, gastrointestinal motility, anxiety, drug dependency, schizophrenia, the intradermal flare response, the blister-base pain response, and mediation of the von Bezold Jarisch reflex.

In their study comparing zacopride (a metoclopramide analogue) with navoban and ondansetron, Conhen *et al* (1989) used the inhibition of serotonin-induced bradycardia in rats as a measure of duration of action. Oral navoban maintained its inhibition of serotonin-induced bradycardia for 3 h, with heart rate reverting to "normal" (control) levels by 6 h. In contrast, inhibition by oral ondansetron persisted for less than 3 h.

Studies of post-mortem human brain revealed that the nucleus of the solitary tract, the vagus nerve, and the spinal trigeminal nucleus were rich in 5-HT_3 receptors. However, it is the finding that the area postrema possesses the highest density of these receptor sites that is of interest, for this area is known to be important in the vomiting reflex, supporting a central site of action for the 5-HT_3 antagonists.

Antiemetic effects

Gamse (1990) reviewed the early work on acute cisplatin-induced vomiting in humans and concluded that "total inhibition of emesis after a single 5 mg dose…occurred in 80% of [those] receiving 50-100 mg/m^2 cisplatin and in 50% of those treated with > 100 mg/m^2." Two or less than two episodes of vomiting occurred in 92% and 90% of patients, respectively.

The mechanism by which cytotoxic drugs induce vomiting is thought to involve the release of serotonin by damaged intestinal enterochromaffin cells, the subsequent activation of vagal afferents, and the initiation of the vomiting reflex. This theory is supported by studies in which the concentrations of plasma

Table 1 Emetogenic potential of chemotherapeutic agents; 5 = highest, 1 = lowest[1]

Grade 5		Grade 4		Grade 3		Grade 2		Grade 1
Drug	Dose (mg/m^2)	Drug	Dose (mg/m^2)	Drug	Dose (mg/m^2)	Drug	Dose (mg/m^2)	Drug
Cisplatin	> 100	Cisplatin	50-100	Dactinomycin	> 0.3	Dactinomycin	< 0.3	Amsacrine
				Carboplatine	> 150	Altreamine		Asparaginase
				Carmustine	> 75	Carboplatin	≤ 150	Bleomycin
				Chlormethine	> 6	Carmustine	≤ 75	Etoposide
				CyClo		Chlormethine	≤ 6	Fluorouracil
				Phosphamide	> 50	Cisplatin	≤ 50	Mercaptopurine
				Cytarabine	> 1000	Cyclo		Methotrexate
				Dacarbazine	> 100	Phosphamide	≤ 50	Mitomycin
				Daunorubicin	> 45	Cytarabine	≤ 1000	Mitoxantrone
				Doxorubicin	> 45	Dacarbazine	≤ 100	Procarbazine
				Epirubicin	> 75	Daunorubicin	≤ 45	Teniposide
				Ifosfamide	> 1000	Doxorubicin	≤ 45	Thioguanine
						Epirubicin	≤ 75	Vinorelbine
						Fotemustine		Vinblastine
						Ifosfamide	≤ 1000	Vincristine
								Vindesine

Abbreviations: A agents are classified as Grade 1 irrespective of dose.

Table 2 Pharmacokinetic parameters of navoban in poor and extensive metabolizers, normalized for a 10 mg dose

Parameter	Extensive metabolisers		Poor metabolisers	
	IV (n = 18)	Oral (n = 43)	IV (n = 36)	Oral (n = 12)
T_{max} (h)		2		3.6
C_{max} (μg/L)	84	21.7	82	29.9
AUC (μg/L·h)	239	230	1192	1579
$t_{1/2\beta}$ (h)	7.3	8.6	30.3	41.9
V_β (L)	554		463	
F (%)	100	60-100[a]	100	60-100[a]

[a]: Dose dependent; T_{max}: Time to maximum plasma concentration; C_{max}: Maximum plasma concentration; AUC: Area under plasma concentration-time curve; $t_{1/2\beta}$: Terminal phase elimination half life; V_β: Volume of distribution during termination phase; F: Bioavailability.

serotonin and urinary 5 hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, were increased in patients experiencing cisplatin induced vomiting. Selective inhibition of 5-HT$_3$ receptors by navoban could interrupt the vomiting reflex at one or more of the following sites[4]: (1) gastrointestinal receptors; (2) afferent vagal fibers; (3) brain-stem receptors, either in the chemoreceptor trigger zone (CTZ) or the vomiting center; and (4) afferent vagal fibers. Navoban is likely to exert its influence on the peripheral, afferent, and central components of the reflex[4].

PHARMACOKINETIC PROPERTIES

Absorption, plasma concentration and distribution

After oral administration, the absorption of navoban is rapid, with a mean absorption half-life of approximately 20 min. More than 95% of a 100 mg dose is absorbed within 2.2 h[4], and peak plasma concentrations are reached within 3 h. As a result of a saturable metabolic capacity, bioavailability is dose dependent: a dose under 15 mg is 60% bioavailable (under fasting conditions, 75%-80% is bioavailable when taken with food), and doses of ≥ 45 mg are 100% bioavailable. Despite individual variability, the bioavailability is similar for capsules and oral solutions.

Metabolism

Navoban undergoes little hepatic first-pass metabolism. The drug is oxidized mainly at positions 5, 6, or 7 of the indole ring, with hydroxy metabolites being further metabolized to glucuronides and sulfates. N-demethyl and N-oxide navoban are detected in trace amounts only. The metabolism of navoban in humans is linked to the polymorphically expressed cytochrome P-450 IID6 enzyme system, which also determines the metabolism of sparteine, debrisoquine, and other drugs, such as neuroleptics, β blockers, tricyclic antidepressants, and antiarrhythmics. The ratio of "extensive" to "poor" metabolizers in Western populations is approximately 12:1. In extensive metabolizers, between 8% and 9% of a 20 mg dose of navoban is excreted unchanged in the urine, 70% as metabolites, and 15% in the feces, almost entirely as metabolites. The metabolites of navoban are not pharmacologically active[4].

Poor metabolizers excrete a greater proportion of unchanged navoban in the urine than their extensive metabolizer counterparts. While this suggests a potentially greater risk of side effects related to drug accumulation, this risk is negligible when navoban is administered at the recommended dosage (5 mg per day for 6 d)[5], and the side effect profiles of extensive and poor metabolizers are comparable. Therefore, similar doses may be given to both groups and, in the same way that patients need not be screened before initiation of β blocker therapy, screening for poor metabolizers before administration of navoban is not a requirement. The pharmacokinetic parameters for extensive and poor metabolizers are detailed in Table 2[4].

Elimination

The elimination half-life of navoban (oral and intravenous) in extensive metabolizers is about 8 h (range from 7.3-8.6 h). By comparison, the elimination half-life for oral and intravenous ondansetron ranges from 3.2-3.7 h and for intravenous granisetron ranges from 3-4 h (in healthy volunteers) or 10-12 h (in cancer patients)[6]. The relatively long half-life of navoban allows for effective once daily dosing; while the oral forms of granisetron and ondansetron, by comparison, require a bid and tid (or qid) dose, respectively.

Drug interactions

Protein binding is moderate (59%-71%), implying that drug-drug interaction due to displacement of the drug from plasma binding sites is unlikely[4]. Navoban does not induce or inhibit

cytochrome P-450 dependent enzymes that are not induced or linked to the IID6 polymorphism, but P-450 enzyme-inducing drugs, such as rifampicin, phenobarbital, and phenylbutazone, increase the elimination and shorten the half-life of navoban. Extensive metabolizers who are on concomitant therapy with such drugs may, therefore, need a higher dosage of navoban to achieve effective plasma levels[4]. In contrast, liver enzyme inhibitors, *e.g.*, cimetidine, have a negligible effect on navoban plasma concentrations, and the customary 5 mg/d dosage of navoban need not be altered.

The pharmacokinetics of navoban in elderly patients are similar to those of younger patients. Ondansetron, by contrast, has been reported to undergo slower clearance in the elderly[7]. No dosage adjustment is required in patients receiving navoban.

Metabolic clearance of navoban in patients with hepatitis and fatty liver disease is similar to that in healthy extensive metabolizers but is lower (by 50%) in cirrhotic patients[4]. Nonrenal clearance of avoban is reduced, again by half, in those with moderate or severe renal dysfunction. However, when the recommended 6-day course of 5 mg daily is administered, even a 25% loss of hepatic function or risk associated with accumulation of the drug, no dosage adjustment is required in patients with hepatic or renal impairment[4].

Recent studies indicated that navoban (maximum 5 mg/d) is well tolerated by pediatric patients and that the efficacy and tolerability results in children are similar to those in adults[8,9].

Relation between plasma concentration and clinical efficacy

A clear dose response relationship has been demonstrated with the 5-HT_3 antagonists. A navoban dose finding study that compared navoban doses of 5, 10, 20, and 40 mg failed to demonstrate significant differences between the doses for total control of acute nausea and vomiting, with all doses achieving complete control in more than 50% of patients. It has, however, been estimated that a plasma concentration of more than 3 μg/L of navoban is necessary for inhibition of ≥ 90% of 5-HT_3 receptors.

NAVOBAN IN CLINICAL PRACTICE

The development of the 5-HT_3 receptor antagonists has irrevocably changed the treatment of chemotherapy induced nausea and vomiting. Nausea and vomiting are now clearly differentiated, and, with the successful treatment of vomiting, nausea has become the primary therapeutic target in this field of research[10]. Alleviation of nausea and vomiting in patients treated with cytotoxic drugs is of major importance, since this side effect of anticancer therapy may cause the patients considerable distress and may even cause the patient to refuse or delay further courses of such therapy[1].

Some of the general guidelines for effective antiemetic therapy in chemotherapy patients can be summarized as follows: (1) prevention of nausea and vomiting is easier than treatment of established nausea and vomiting; (2) complete abolition of symptoms is required if anticipatory vomiting is to be prevented; and (3) the choice of antiemetic depends on the relative emetogenic potential of the cytotoxic agent used.

Dose finding studies

In multicenter, dose finding studies, navoban (2 and 5 mg and 5, 10, 20, or 40 mg) was administered to patients receiving cisplatin chemotherapy. Total control of nausea and vomiting in the first 24 h was achieved in up to 71% of patients. The 5 mg dose of navoban was more effective than the 10, 20, or 40 mg doses and also more effective than the 2 mg dose, which was apparently subtherapeutic in some patients. Furthermore, on day 1 of chemotherapy course 1, the 5 mg dose was able to achieve total or major control of vomiting and nausea in a greater percentage of patients than the 2 mg dose (86% *vs* 68%, $p = 0.055$ and 92% *vs* 86%, respectively, NS). Comparison of the efficacy of the 5 mg and 2 mg doses in successive courses of this study is questionable, since strict treatment failure criteria caused a reduction (by about 50%) in the efficacy population in courses 2 and 3 (Stamatakis *et al* 1990).

The dosing of navoban is simple. The optimal daily dose for the prevention of nausea and vomiting associated with chemotherapy is 5 mg[4], a single intravenous dose of navoban being sufficient to protect most patients for at least 24 h after chemotherapy.

Navoban in acute nausea and vomiting

Acute nausea and vomiting occur within the first 24 h after the onset of chemotherapy. They usually begin within 1.5 to 3.0 h and last 2-6 h. The effects of navoban on acute nausea and vomiting in cancer patients receiving chemotherapy have been assessed in dose-finding, non-controlled studies.

The antiemetic effects of the optimal dose of navoban (5 mg), as defined in dose finding studies, have already been discussed. Stamatakis *et al* (1990) and ven Belle *et al* (1990) reported that in the first 24 h after chemotherapy (course 1), complete control of cisplatin induced vomiting in 70% and 71% of patients and complete control of nausea in 65% and 71 %, respectively, was achieved with a single intravenous dose of navoban. Stamatakis *et al* (1990) found that with 5 mg navoban, 86% and 92% of patients achieved total or partial control of acute vomiting (≤ two episodes) and nausea (≤ 2 episodes). In a small subgroup of patients on high dose cisplatin (> 90 mg/m^2), navoban (5 mg) achieved 100% total plus partial control of vomiting in the first 24 h.

In their open label study of 476 patients who were refractory to standard antiemetic therapy and who were receiving chemotherapy of varying emetogenic potential, Bleiberg *et al*[1] reported that 62% of patients on day 1 of course 1 had a complete response (no nausea and no vomiting) to pretreatment with navoban (5 mg or 10 mg) by intravenous injection. The number of patients with a complete or partial response (1-4 vomiting episodes and/or episodes of nausea) was as high as 91%. These results are in line with those of a similar study involving patients on cisplatin and non-cisplatin regimens, 67% of whom were completely protected from nausea and vomiting on day 1 of course 1. An additional 27% had a partial response, raising the complete plus partial response result to 94%[11].

When comparing the results of chemotherapy naïve patients with those of patients with prior experience of chemotherapy, Sorbe *et al*[11] found that the former had a higher rate of control (73% *vs* 61%, $p < 0.02$) of acute nausea and vomiting on day 1, and fewer of the naïve group required rescue therapy as a result of treatment failure than did their non-naïve counterparts (3% *vs* 33%, $p < 0.0001$). Bleibery *et al* reported a complete response (no vomiting and no nausea) in 73% and 63% ($p = 0.05$) of chemotherapy-naïve and non-naïve patients, respectively.

Sorbe *et al*[11]demonstrated that navoban was able to achieve complete control of acute nausea and vomiting in 51% of cisplatin-treated patients, compared with 78% of non-cisplatin treated patients ($p < 0.001$). In contrast, however, Bleiberg *et al*[1] found that the emetogenic grade of chemotherapy did not significantly affect the antiemetic response.

Dogliotti and colleagues[12] also administered navoban to patients receiving cisplatin and, although they chose severity of nausea rather than duration, their results for complete control of nausea and vomiting can be compared with those from other studies. They reported that a single intravenous dose of 5 mg navoban afforded

Table 3 Intensity of delayed vomiting on days 1 and 2 after cisplatin therapy with navoban (20 courses) or metoclopramide plus lorazepam (20 courses)

Vomiting	Navoban (% of courses)	Metoclopramide (% of courses)
Day 1	$n = 18$	$n = 19$
No vomiting episodes	75	30
1 to 2 vomiting episodes	10	5
> 2 vomiting episodes	15	65
Day 2	$n = 2$	$n = 5$
No vomiting episodes	90	75
1 to 2 vomiting episodes	10	10
> 2 vomiting episodes	0	15

complete protection from acute nausea and vomiting in 44% and 53%, respectively, of 104 courses.

Comparative efficacy studies have usually compared navoban with metoclopramide monotherapy or metoclopramide-based cocktails. In a study comparing navoban with a metoclopramide-based regimen in chemotherapy naïve patients placed on a non-cisplatin course, 5 mg navoban provided complete protection from acute vomiting for significantly more patients than the comparative regimen (46% *vs* 22%, $p = 0.013$). Complete protection from acute nausea, too, was greater with navoban, although the difference between the two treatments was not statistically significant (25% *vs* 12%). Total or partial control of vomiting occurred in 67% of navoban treated patients compared to only 46% of metoclopramide-treated patients, and this difference was statistically significant ($p = 0.044$). The difference between treatments for complete or partial control of nausea was not significant (63% *vs* 57%).

Dogliotti *et al*[12] studied the acute and delayed antiemetic effects of navoban compared with metoclopramide plus lorazepam in patients receiving cisplatin and reported that for both acute nausea and acute vomiting, navoban was significantly more effective than metoclopramide plus lorazepam ($p < 0.001$). Complete control of vomiting and nausea was achieved in 75% and 40% of navoban patients, respectively, compared with 30% and 30% of metoclopramide patients.

In another study involving 172 patients, McVie *et al*[13] compared navoban with a metoclopramide based antiemetic regimen in the control of vomiting in the first 24 h after cisplatin or cisplatin based chemotherapy. Before chemotherapy, patients treated with the antiemetic cocktail received 2 mg/kg metoclopramide and 20 mg dexamethasone by intravenous infusion plus either oral 50 mg diphenhydramine or 1 mg lorazepam; 4 h later a second, identical dose of metoclopramide with diphenhydramine or lorazepam was administered. Metoclopramide 10 mg tid was given either orally or by suppository on days 2 to 7. Navoban and the control of acute vomiting in 50% and 60% of patients, respectively. Compared with navoban, the metoclopramide-based cocktail achieved significantly superior control of acute nausea (rate of total control 54% *vs* 31%).

In their multicenter, randomized study, Bruntsch *et al*[14] compared the acute antiemetic efficacy of navoban and conventional antiemetic regimens, including dopamine antagonists, antihistamines, tranquillizers, and steroid in 231 patients who had responded poorly to previous antiemetic therapy and who were treated with a variety of chemotherapeutic agents. Navoban was significantly more effective in providing complete protection from acute vomiting (53% *vs* 29%, $p < 0.001$); it was also more effective than the conventional antiemetic therapy for acute nausea, reducing the duration of nausea by 2.5 h ($p < 0.001$) and totally controlling nausea in a significantly greater percentage of patients than the comparative regimens (32% *vs* 19%, $p < 0.05$)[15]. These results confirm those of an earlier interim analysis of the study population[13].

Navoban has also been compared with alizapride for its antiemetic effects in high-dose alkylating agent chemotherapy (cyclophosphamide or melphalan) and was shown to be more effective in providing complete control of acute vomiting (13% *vs* 6%), while the addition of the antidopaminergic haloperidol to navoban further enhanced its antiemetic efficacy[16].

Navoban in delayed nausea and vomiting

Delayed nausea and vomiting are associated with the highly emetogenic chemotherapeutics and occur more than 24 h after the start of chemotherapy. In general, the effects are less severe than the acute form, but they may persist for up to 7 d. For this reason, the use of navoban may be of particular importance in the outpatient setting.

Other studies have shown a somewhat different pattern. McVie *et al*[13]found that control of delayed vomiting was comparable for navoban and a metoclopramide-based cocktail, although metoclopramide was superior in its protection from delayed nausea ($p = 0.003$). Dogliotti *et al*[12] showed that navoban was significantly more effective in controlling nausea and vomiting the day after cisplatin, although by the following day, both nausea and vomiting were less pronounced and the between-treatment difference had diminished (Table 3).

Both patients and investigators rated navoban efficacy highly: 71% of patients and 72% of investigators scored it "very good" or "good", compared with 32% of patients and 31% of investigators in the optimal standard antiemetic group. Thus, even in a population selected for previous treatment failures, navoban was highly effective[15].

A recent study evaluated the antiemetic efficacy of navoban in combination with dexamethasone, both given for 6 d, in patients who achieved only partial control with navoban monotherapy[17]. Chemotherapy-naïve patients who received two identical courses of chemotherapy were assessed according to stringent efficacy criteria. The results of the study showed that patients who were completely controlled by navoban in course 1 were also well controlled in course 2. Those who were incompletely controlled in course 1, however, benefited from the addition of dexamethasone in course 2.

Navoban in multiple courses of chemotherapy

The question of whether or not an antiemetic can maintain its efficacy over several courses of chemotherapy arises, since most patients receive more than one course of chemotherapy. Furthermore, patients inadequately protected from nausea and vomiting in one course are more likely to respond poorly to antiemetic agents in subsequent courses of chemotherapy. A certain reduction in efficacy over multiple courses of chemotherapy may, therefore, be expected. Sorbe *et al*[11]confirmed the ability of navoban to maintain efficacy over multiple courses in patients who received up to 10 courses of chemotherapy, of which only half were chemotherapy naïve. Complete plus partial control of nausea and vomiting was achieved in 90%-100% of patients on day 1 of each

course, with a slightly reduced response on days 2 to 4.

Some factors may be important in predicting patient response to navoban: age, gender, previous chemotherapy, alcohol abuse, and emetogenic potential of the chemotherapeutic agent have all been previously cited[18]. Bleiberg *et al*[1]. analyzed the impact of various factors on antiemetic response in their study of patients who had previously been refractory to standard antiemetic therapy. The emetic grade of chemotherapy had a statistically non-significant effect on the response to navoban, and while non-naïve patients responded well to navoban, their chemotherapy naïve counterparts achieved significantly better response rates.

One thousand seventy two patients who were scheduled to receive at least two identical cycles of emetogenic chemotherapy were treated with 5 mg navoban once daily in their first chemotherapy course. Complete response rates (no nausea and no vomiting) were 72% for day 1 and 48% for days 1 through 6 of course 1. During course 2, more complete responders were observed when dexamethasone was added, both for day 1 (76% *vs* 66%, $p = 0.020$) and for days 1 through 6 (50% *vs* 34%, $p = 0.0004$). A moderate increase in the complete response rate was seen with the addition of conventional dose alizapride (day 1, 75% *vs* 68%, $p = 0.14$; day 1 through 6: 47% *vs* 37%, $p = 0.041$). Doubling the dose of navoban did not change the complete response rate. These data show that the addition of dexamethasone significantly increased the complete response rate of both acute and delayed emesis in patients who have incomplete disease control with navoban alone[19].

Dosage and administration

The recommended dosage of navoban is 5 mg daily for 6 d. The first dose, on day 1, should be administered intravenously shortly before chemotherapy, either as an infusion (1 ampule diluted in 100 mL of a common infusion fluid, such as normal saline, Ringer's solution, 50 g/L glucose, or 50 g/L levulose) or as a slow injection. Thereafter, on days 2 to 6, a single 5 mg oral capsule should be taken with water immediately on rising and at least 1 h before eating. Patients known to be poor metabolizers do not need to alter the recommended 6 d course of 5 mg navoban[5]. Similarly, as indicated in the basic prescribing text, the recommended dose need not be reduced in the elderly or in patients with impaired hepatic or renal function. The dosage regimen for navoban is currently the most simple and convenient of any for the 5-HT_3 antagonists.

SAFETY AND TOLERABILITY

The integrated safety results of two navoban dose finding and five comparative treatment studies have been summarized by de Bruijn *et al*[4]. In total, 417 patients received 5 mg navoban daily, 51 patients received metoclopramide, and 222 received an antiemetic cocktail, in which the dose of metoclopramide was approximately twice that of metoclopramide monotherapy.

Navoban was generally well tolerated at the recommended dose of 5 mg daily for 6 d. As with the other 5-HT_3 antagonists, headache, constipation, diarrhea, and fatigue were the most frequently reported adverse effects, but their relation to antiemetic therapy was not easily assessed, since aggressive chemotherapy or the cancer itself could have accounted for some symptoms. Only headache and constipation with abdominal pain recurred in the same patients with repeated courses of navoban, which suggests that these symptoms were in fact related to the administration of the drug.

Adverse effects (headache, constipation) were mild, seldom requiring symptomatic treatment, and withdrawal of navoban because of adverse effects was rare (0.2%); reports of "extrapyramidal symptoms" (*e.g.*, as ataxia, tremor, and cramps) were not only extremely uncommon (0.3%) but were not clearly attributable to navoban. The side effect profile of navoban did not alter with repeated administration over several courses[11]. There was no evidence of: (1) laboratory of electrocardiogram abnormalities at the recommended dose; (2) induction of liver enzymes; and (3) exacerbation of cisplatin nephrotoxicity, neurotoxicity, or bone marrow suppression.

The concomitant administration of navoban with liver enzyme inducers, such as rifampicin and phenobarbital, may result in a lower plasma concentration of navoban. While extensive metabolizers may require an increase in the dosage of navoban, this is not the case for poor metabolizers. In contrast, liver enzyme inhibitors, such as cimetidine, have a negligible effect on navoban plasma concentrations; the customary 5 mg/d dosage of navoban need not, therefore, be altered.

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