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Is Navoban® (tropisetron) as effective as Zofran® (ondansetron) in cisplatin-induced emesis?

M Marty,[1] J-P Kleisbauer,[2] P Fournel,[3] A Vergnenegre,[4] P Carles,[5] Y Loria-Kanza,[6] C Simonetta,[6] KM de Bruijn[7] and the French Navoban® Study Group[8]

[1] Hôpital Saint-Louis, Paris, France; [2] Hôpital Sainte Marguerite, Marseille, France; [3] Hôpital Nord, Saint Priest, France; [4] CHRU Cluzeau, Limoges, France; [5] Hôpital Purpan, Toulouse, France; [6] Laboratoires Sandoz, Rueil Malmaison, France; [7] Sandoz Pharma Ltd., Basel, Switzerland; [8] French Navoban® Study Group: Pujade Lauraine E, Hôpital Hôtel Dieu, Paris, France; A Didier, Hôpital de Rangueil, Toulouse, France; D Cupissol, Institut de Cancer, Montpellier, France; J-P Bergerat, Hospices Civiles, Strasbourg, France; MC Pujazon, Hôpital Purpan, Toulouse, France; J-P Kleisbauer, Hôpital Sainte Marguerite, Marseille, France; J-F Heron, Centre Baclesse, Caen, France; B Dreno, Hôpital Hôtel Dieu, Nantes, France; A Taytard, Hôpital du Haut Leveque, Pessac, France; JC Guerin, Hôpital Croix Rousse, Lyon, France; J Clavier, G Robinet, Hôpital Morvan, Brest, France; F Blanchon, Centre Hospitalier, Meaux, France; P Balmes, Centre Hospitalier, Nîmes, France; J-F Muir, D Paillotin, Centre Hospitalier, Bois Guillaume, France; R Poirier, Centre Hospitalier, Aix-en-Provence, France; J Bonneterre, Centre Oscar Lambert, Lille, France; B Melloni, CHRU Cluzeau, Limoges, France; H Roche, Centre Claudius Regaud, Toulouse, France; A Depierre, Hôpital St Jacques, Besançon, France; R Plagne, Centre Anti-cancereux Jean Perrin, Clermont Ferrand, France; PJ Souquet, Centre Hospitalier de Lyon Sud, Lyon Benite, France; J-P Armand, M Deforni, Institut Gustave Roussy, Villejuif, France.

The purpose of this study was to evaluate and compare the antiemetic effectiveness and tolerability of Navoban® (tropisetron) and Zofran® (ondansetron) following high-dose (≥50 mg/m²) cisplatin chemotherapy. In a randomised, multicentre, double-blind, double-dummy, parallel group study, 117 evaluable chemotherapy-naive patients who received Navoban® were compared with 114 who received Zofran®. Patient diary cards were used to assess both acute (Day 1) and delayed (Days 2–6) nausea and vomiting. Total control of acute vomiting was achieved in 54% of Navoban® and 65% of Zofran® patients ($p = 0.052$), and total control of acute nausea in 66% and 62% respectively ($p = 0.655$). Total control of delayed vomiting was achieved in 44% of Navoban® patients and 46% of Zofran® patients ($p = 0.765$), and of delayed nausea in 56% and 47% respectively ($p = 0.207$). Both reactions combined were totally prevented during the entire 6-day trial period in 22% of Navoban® and 24% of Zofran® patients (NS), while a further 42% of patients in both groups remained largely free from both nausea and emesis. The few adverse reactions (e.g. headache, constipation, diarrhoea) were mainly mild and typical of the 5-HT_3-receptor antagonists. In conclusion, there were no significant differences in efficacy and tolerability between Navoban® 5 mg once daily and the highest recommended dose of Zofran® (32 mg on Day 1, followed by 8 mg three times a day).

Key words: Navoban® (tropisetron), Zofran® (ondansetron), emesis, vomiting, nausea.

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Correspondence to Professor M Marty
Hôpital Saint-Louis, 1 Avenue Claude Vellefaux
75010 Paris, France
Tel: (+33) 1 42 49 4949; Fax: (+33) 1 42 49 9938

Introduction

Nausea and vomiting are, from the patient's viewpoint, by far the most distressing reactions related to treatment with anti-cancer chemotherapy.[1]

Because of this, high doses of cisplatin, whose dose–effect characteristics are well known, are limited by the severity of the emetic reactions that this drug may induce.[2] Since the mid-1980s there have been several major efforts to develop and evaluate antiemetic medication. As an alternative to cisplatin, high doses of metoclopramide [3] have been used; however, while these indeed suppressed cisplatin-induced emesis to a certain degree, extrapyramidal effects occurred in up to 5% of patients,[4,5] and 30%–60% continued to suffer nausea and vomiting with high-dose cisplatin, even when treated with metoclopramide.[6–8] The antiemetic action of this drug can be improved considerably by co-administration with other compounds, although there clearly remains a need for antiemetics that are not only more effective, but also better tolerated. Prompted by this need, research has resulted in the development of 5-HT_3-receptor antagonists, a class of drugs which includes Navoban® (tropisetron), Zofran® (ondansetron) and Kytril® (granisetron).[9]

So far, studies indicate that the first of these is as effective as traditional antiemetic regimens in patients receiving highly emetic anti-cancer chemotherapy, such as cisplatin.[10] One particular study – a large, randomised investigation – compared Navoban® with

an antiemetic combination (metoclopramide, dexamethasone and lorazepam) in the prevention of emesis induced by cisplatin. Not only was Navoban® equally effective and easier to administer; it was also better tolerated.[11]

Even though the advantages of the 5-HT_3-receptor antagonists over traditional antiemetic combination therapy are now generally acknowledged, it is of interest to compare these drugs with each other. In one double-blind study involving 496 patients,[12] Zofran® (8 mg or 32 mg) was compared with Kytril® (3 mg) as antiemetic therapy prior to high-dose cisplatin administration (≥ 50 mg/m²). In respect of nausea, vomiting or other drug-related reactions, no significant difference between any of the treatment groups was noted. In another, open study using non-cisplatin chemotherapy,[13] Navoban® (5 mg once daily) was compared with Zofran® (8 mg three times daily); the efficacy and tolerability of the two 5-HT_3-receptor antagonists were found to be almost identical.

Therefore, the purpose of our study – the first double-blind comparison of two such agents – was to compare the efficacy of Navoban®, with its simple, once-daily dosage regimen, with that of the highest recommended dose of Zofran® for the suppression of nausea and vomiting for 6 days following high-dose cisplatin chemotherapy.

Patients and methods

This comparative study was prospective, randomised, multicentre, double-blind, double-dummy, and made up of parallel groups. Patients were chemotherapy-naive and scheduled to receive one or more courses of cisplatin at doses of at least 50 mg/m². Two hundred and twenty sample subjects (110 in each treatment arm) were planned, in order to give the study 80% power to detect a 20% difference in efficacy between antiemetic treatments at the 5% significance level.

Twenty-four centres took part in the study and, at each, patients were grouped randomly in balanced blocks of four to receive either Navoban® or Zofran®. In order to ensure that the study remained double-blind, a placebo matching the non-allocated treatment was given at the same time as each allocated treatment (the double-dummy technique).

On Day 1, therefore, in the half hour before the infusion of chemotherapy, patients received either Navoban® one 5 mg/5 ml ampoule plus 4 ampoules of Zofran® placebo, or 4 Zofran® 8 mg/4 ml ampoules plus one ampoule of Navoban® placebo, as a slow, intravenous infusion.

On Days 2–6, patients received either one capsule of Navoban® 5 mg plus one tablet of placebo, or one tablet of Zofran® 8 mg plus one capsule of placebo *in the morning*; one tablet of Zofran® 8 mg and one capsule of placebo *at noon*; and one tablet of Zofran® 8 mg and one capsule of placebo *in the evening*. No other drugs which might impact on emesis were permitted and high-dose corticosteroid administration was discouraged. The main criteria of efficacy were control of acute vomiting (Day 1) and acute nausea (Day 1).

Control of nausea and vomiting was the criterion of efficacy, considered either as *acute* (Day 1), *delayed* (Days 2–6) or overall (Days 1–6). We measured nausea as the duration of this reaction in hours, rounded to the nearest quarter. Emesis was measured in single events (one vomit or retch). Patient diary cards provided us with the data on these parameters. Nausea control on a particular day was classified as:

Total control	Nausea ≤ 15 minutes
Major control	> 15 minutes to ≤ 4 hours
Minor control	> 4 hours to ≤ 8 hours
No control	> 8 hours

In the absence of reliable methods of quantifying this reaction, no analysis was made of the *severity* of nausea. Vomiting control on a particular day was classified as:

Total control	No vomiting
Major control	1 or 2 vomiting events
Minor control	3 or 4 vomiting events
No control	5 or more vomiting events

Assessment of the control of *delayed* nausea and/or vomiting, or of overall control, was based on the worst days. For some of the statistical analyses, the resulting major and minor control of the two reactions were combined into 'partial' control.

Our criteria for gauging tolerability included the occurrence of adverse reactions (data concerning which were collected from special report forms, investigators' comments in case-report forms and patient diaries) and the measurement of vital signs and routine laboratory safety parameters. Laboratory values were deemed significant on the basis of predetermined, clinically relevant thresholds.

For the presentation of summary statistics, results from all centres were combined. The literature made it clear that the study with the same chemotherapy and antiemetic regimen reported the best result – a 30% higher antiemetic efficacy than the study with the worst result, both in the case of Kytril® and Zofran®.[14] Sandoz data on file in Switzerland confirm that a similar spread of results has been observed with Navoban®. The null hypothesis in this study was, therefore,

based on detecting at least a 20% difference with 80% power. For comparison of treatment response in the case of categorical data, we employed the Mantel–Haenszel test,[15] and, for continuous variables, the Van Elteren test.[16] The two-sided p-values presented were based on an average response across centres, and statistical procedures were adjusted for each participating centre.

The study was given prior approval by the Ethics Committee and the Hôpital St. Louis in Paris, and conducted in accordance with the Helsinki Declaration. All patients gave written, informed consent before taking part.

Results

Patient population

One hundred and seventeen of the 231 participating patients were allocated Navoban® and 114 Zofran®. A higher proportion of the Navoban® patients had undergone prior abdominal surgery for cancer, but the treatment groups were well matched with respect to demographic status and diagnosis (Table 1).

Twenty seven Navoban® patients (23%) and 22 Zofran® patients (19%) dropped out of the study at an early stage. Lack of antiemetic efficacy (14 and 9 respectively) was the main cause of these drop-outs. In the case of 3 Navoban® and 4 Zofran® patients, adverse events (described below) were the cause of discontinuation. A similar number of protocol violations occurred in the Navoban® and Zofran® arms: use of a high dose of corticosteroids in 4 patients; and carboplatin instead of cisplatin (one patient in each group). Patients with missing data, although included in the denominator, were classified as 'not assessed'.

All but the two patients described above were at high risk of emesis induced by chemotherapy, as they received such treatment based on high-dose cisplatin (≥ 50 mg/m²). Several subjects in each group were given other concomitant chemotherapy, also highly emetogenic (cyclophosphamide and ifosfamide), in a somewhat higher percentage of Navoban® than of Zofran® patients; the difference, however, was not significant (p=0.07, Mantel–Haenszel test). In Table 2, we see a summary of the number of patients on each dose of cisplatin and other concomitant chemotherapy in each group; 100 mg/m² cisplatin was the median dose used in the study.

Acute (Day 1) nausea and vomiting

Fifty-four per cent of Navoban® and 65% of Zofran® patients experienced total control of acute vomiting (p= 0.052, Mantel–Haenszel test). A significant centre-by-treatment interaction (p=0.033) was also recorded in a Breslow–Day test[17] for this parameter. Sixty-six per cent of Navoban® and 62% of Zofran® patients (p = 0.655, Mantel–Haenszel test) experienced total

Table 1. Patient characteristics at entry to the study

Characteristic	Navoban® (tropisetron) n = 117	Zofran® (ondansetron) n = 114
Sex (M,F)	83,34	82,32
Mean age (years)	55.9	57.7
Mean weight (kg)	63.0	66.4
Mean height (cm)	166.8	168.3
Primary diagnosis: cancer type		
Respiratory (lung)	79	84
Gastrointestinal (rectum, abdomen)	12	5
Genito-urinary (pelvis)	16	16
Other (skin, endocrine, heart, sarcoma)	10	9
No. of patients with previous surgery for cancer	40	32
Abdomen *	22	13
Thorax *	12	13
Other **	7	7

* p = 0.028 between groups (18.8% vs. 11.4%), Mantel–Haenszel test. ** One patient had two operations.

Table 2. Number of patients receiving each dose of cisplatin and the number receiving concomitant chemotherapy (the number who received highly emetogenic concomitant chemotherapy is shown in parentheses)

Chemotherapy	Navoban® (tropisetron) n = 117	Zofran® (ondansetron) n = 114
Cisplatin dose on Day 1		
50–100 mg/m²	97	102
> 100 mg/m²	19	11
Concomitant chemotherapy (highly emetogenic) *		
Day 1	103 (39)	104 (29)
Day 2	62 (13)	59 (9)
Day 3	52 (9)	55 (8)
Day 4	22 (1)	26 (4)
Day 5	13 (0)	16 (1)

* Non-cisplatin concomitant chemotherapy considered highly emetogenic was cyclophosphamide and ifosfamide (numbers shown in parentheses).

control of acute nausea. Eighty-nine per cent of Navoban® and 89% of Zofran® patients (p = 0.830, Mantel–Haenszel test) experienced total and partial control of acute vomiting and 90% of Navoban® and 92% of Zofran® patients had total plus partial suppression of acute nausea (p = 0.497, Mantel–Haenszel test).

Delayed (Days 2–6) nausea and vomiting

Forty-four per cent of Navoban® and 46% of Zofran® patients experienced total control of delayed vomiting (p = 0.765, Mantel–Haenszel test) and 56% of Navoban® and 47% of Zofran® patients had total control of delayed nausea based on the worst of Days 2–6 (p = 0.207, Mantel–Haenszel test). Figure 1 shows the details of the distribution of responses. Eighty-nine per cent of Navoban® and 85% of Zofran® patients (p = 0.351, Mantel–Haenszel test) experienced total and partial control of delayed vomiting (p = 0.351, Mantel–Haenszel test); 81% of Navoban® and 83% of Zofran® patients (p = 0.605, Mantel–Haenszel test) had total plus partial control of delayed nausea.

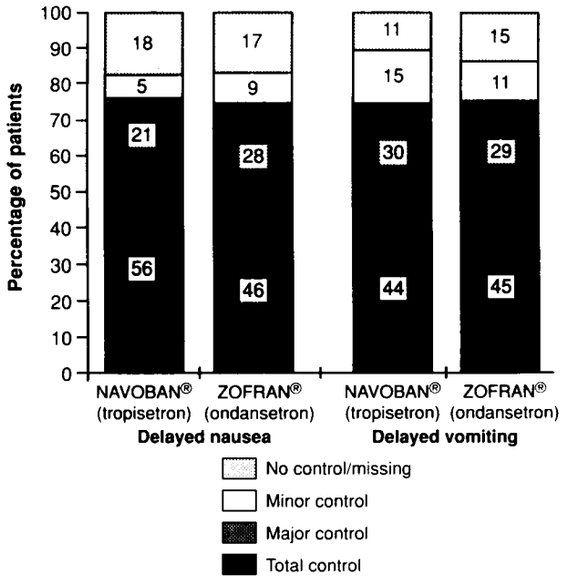

Figure 1. Control of delayed nausea and delayed vomiting (Days 2–6).

Overall control of nausea and vomiting (Days 1–6)

All vomiting was prevented by Navoban® in 33% patients during the study period; 28% had major protection and 22% had minor protection. On the worst of Days 1–6, the mean number of events was 2.8. Forty per cent experienced total freedom from vomiting with Zofran®; 32% had major and 9% minor protection. On the worst day, the mean number of events was 2.4. No statistically significant difference was quoted between the treatment groups in overall control of vomiting.

Forty-eight per cent of patients on Navoban® had total control of all nausea, while 27% had major and 8% minor protection. On the worst of Days 1–6, the median duration of nausea was 30 minutes. Forty-three per cent of Zofran® patients experienced total prevention of all nausea, while 32% had major and 8% minor protection. On the worst day, the median duration of nausea was 45 minutes. No statistically significant difference between the treatment groups was observed in overall control of nausea.

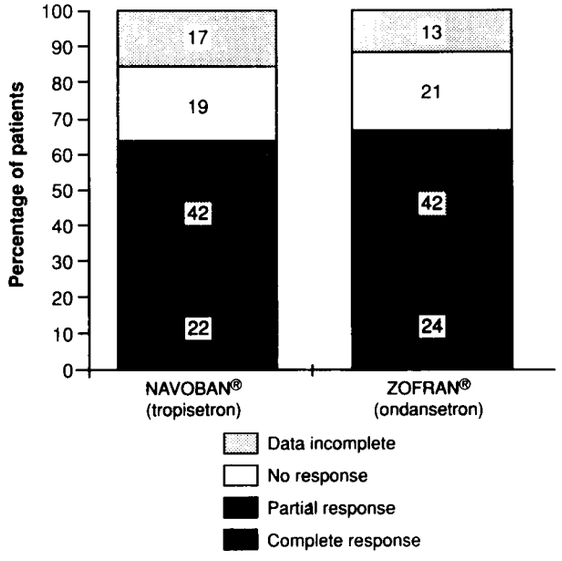

Figure 2. Overall control of nausea and vomiting (combined) during Days 1–6.

Overall control of nausea and vomiting combined (Days 1–6)

Efficacy data based on all 6 days were analysed for complete response (no nausea or vomiting during the study period) or partial response (≤ 8 vomits and a maximum of 16.5 hours of nausea over the 6-day study period). As we see in Figure 2, for Navoban® and Zofran®, respectively, total responses were achieved in 22% and 24% of patients (p = 0.697, Mantel–Haenszel test), partial responses in 42% and 42%, and no response in 19% and 21%. For 17% and

13%, respectively, data were missing for one or more of the 6 study days.

Tolerability

During the study, a total of 459 adverse events were recorded in 175 of the 231 patients (84 on Navoban®, 91 on Zofran®); 47% of these were identified from patient diaries. Most of these reactions were related to the cancer and the results of cancer chemotherapy. Adverse events caused 7 patients to stop study treatment; 3 of these were receiving Navoban® and 4 Zofran®. There was a variety of reasons for premature discontinuation in the Navoban® group: 7 patients stopped study treatment because of an adverse event; 3 were receiving Navoban® and 4 Zofran®. In the Navoban® group, reasons for premature discontinuation included one death due to disease progression on Day 6 or 7 of the study; one case of diarrhoea which was not considered to be related to treatment; one 'vagal' shock with hypotension and loss of consciousness with associated emesis and colitis, for 10 minutes occurring 2.75 hours after Navoban®.

In the Zofran® group, reasons for premature drop-out included one case of erythema, one of gastric stasis, an arterial thrombosis and a respiratory insufficiency. None of these reactions was believed to be related to treatment.

Eighteen per cent of Navoban® and 21% of Zofran® patients reported headache – the most frequent adverse event. In 8 and 3 cases respectively, this reaction was attributed by the investigation team to treatment. The second most frequent reaction was diarrhoea (13% and 16% of patients respectively), followed by constipation (10% and 10%), anorexia (8% and 10%) and abdominal pain (9% and 5%). There was no occurrence of any clinically significant disturbance of vital signs or laboratory parameters attributable to the antiemetic treatments in either treatment group.

Discussion

Recent recommendations for the conduct of clinical trials of antiemetics determined the design and implementation of our study,[18] which therefore had clearly predefined end-points: a prospective parallel-group design; a proven antiemetic for comparison; a homogeneous study population of chemotherapy-naive patients; groups balanced for important variables; and patient participation in efficacy and tolerability evaluation.

The mean value for total control of acute vomiting in previous comparative trials with Navoban® was 53%,[19,20] so the observation of 54% in the trial reported here was wholly consistent. This contrasts with the result of 65% total control and acute vomiting with Zofran® in our study, which exceeds the consolidated efficacy rate of 55% in studies with 32 mg daily.[21–24] Indeed, this is the highest efficacy rate so far reported with the 32 mg dose of Zofran® – apart from the rate in the treatment arm reported by Beck *et al.*,[21] where the dose of cisplatin was 50–70 mg/m² (Table 3), the median cisplatin dose for comparison in the present study.

Table 3. Total control of acute cisplatin-induced vomiting (Day 1) with Zofran® (ondansetron) 32 mg/day

Study	*n*	% with total control
Beck *et al.* (1992)[21]		
50–70 mg/m² cisplatin	93	73%
> 100 mg/m² cisplatin	102	48%
Seynaeve *et al.* (1992)[22]	362 *	53%
Brunet *et al.* (1993)[23]	162	51%
Marty *et al.* (1993)[24]	305 *	57%
Present study	114	65%

* Zofran® given as 32 mg bolus or 8 mg + 1 mg/hour for 24 hours.

Notwithstanding the abnormally high level of complete control of acute vomiting with Zofran® in our study, the difference of 11% between the treatments approached but failed to actually reach statistical significance. Nor did it attain the 20% threshold chosen before the study as the basis for the statistical power statement on growing clinical relevance. Indeed, the dose parameter which accounted for the difference between treatments seems unusually large, and tended towards statistical significance in the total control of acute vomiting; and we explored possible reasons why this was the only parameter.

It is unlikely that lack of efficacy was the cause of early drop-outs from the study treatment. Various other factors may account for the apparently significant interactions between centres for this parameter, such as observed differences between the groups in terms of previous abdominal surgery, cisplatin doses, the population of patients who were given highly emetic doses of non-cisplatin at the same time as cisplatin chemotherapy, or the concomitant use of high-dose steroids, which would have been considered as a deviation from the protocol of the trial. The concomitant administration of steroids on Day 1 of the study was also revealed by additional efficacy subanalyses and, excluding patients with each of these confounding features, was regarded as the

cause of the centre-by-treatment interaction characteristic of this investigation.

Nevertheless, the protocol deviations seemed to be evenly balanced between the various treatment groups. A particular problem is that of delayed emesis, even after acute nausea and vomiting have been adequately suppressed with antiemetics.[25,26] In addition to affecting 90%–100% of patients (if not prevented),[27] the emetogenic action of cisplatin is also recognised as likely to persist for more than 24 hours.[25] Previous studies with 5-HT_3-receptor antagonists have demonstrated that complete control of delayed vomiting following > 49 mg/m^2 cisplatin may be achieved in 30%[28] to 42%[29] of patients with Kytril®, 30%[30] with Zofran®, and 39%[11] with Navoban®. Both drugs, in our study, gave similar protection during the entire 6-day study period – 42% of patients achieving at least a partial response, and 22% of Navoban® and 24% of Zofran® patients not experiencing nausea and/or vomiting. To date, these results are among the best obtained for use of only a 5-HT_3-receptor antagonist following cisplatin chemotherapy.

No statistically significant differences were observed in the control of nausea or vomiting between Navoban® 5 mg once daily for 6 days and Zofran® 32 mg once daily on Day 1 and then 8 mg three times a day for 5 days. Both agents therefore provided good – and comparable – control of the combined clinical syndrome (nausea and emesis) in terms both of total and partial control, and control during the whole of the study. For day-to-day clinical management of patients, this finding may be the most valuable, as overall control of the combined clinical syndrome is regarded as the most clinically relevant measure of the efficacy of an antiemetic.

The types of adverse event in our study, and their frequency, were as might be predicted for the class of 5-HT_3-receptor antagonists in general. By and large, tolerability was excellent, with headaches, constipation and diarrhoea constituting the main adverse events. The most expected adverse event for this class of drugs – headache – has previously been reported as 10%–15% for Kytril®[31] and 15% for Zofran®,[9] as compared with 21% in this study; and as high as 27% with Navoban®,[10] as compared with 18% in this study. The incidence of the 5-HT_3-receptor antagonists has, in the experience of many investigators, frequently been higher in recent reports than in earlier studies. The investigators believed that few events were related to antiemetic therapy, and one case of withdrawal alone was attributable to possible antiemetic (Navoban®) therapy.

The present study shows no significant difference in clinical efficacy on the control of acute nausea and vomiting between Navoban® 5 mg once daily and the highest recommended dose of Zofran® (32 mg on Day 1 followed by 8 mg 3 times daily); nor were there any marked differences between these two agents in the control of other parameters of nausea and vomiting during the 6 days after high-dose anti-cancer chemotherapy.

From the point of view of both the patient and the physician, the simpler, once-daily dose regimen of Navoban® may make this agent easier to use than Zofran®.

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