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Research Article

Oral olanzapine versus oral ondansetron for prevention of post-operative nausea and vomiting. A randomized, controlled study

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KEYWORDS

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Abstract *Background:* This study was designed to mainly evaluate the efficacy and safety of olanzapine compared with placebo and ondansetron for prevention of postoperative nausea and vomiting in patients undergoing breast surgeries.

Methods: Eighty two female patients scheduled for breast surgeries were randomly assigned to four test groups received placebo or single oral dose of olanzapine 5 mg (OL5) or 10 mg (OL10) or ondansetron 16 mg (ON16) before induction of anesthesia by 4 h for olanzapine and 1 h for ondansetron. All patients were monitored for 24 h. Emetic episodes and nausea occurrence were the primary outcome in this study. Secondary endpoint was the complete response (CR) (without nausea and vomiting, no rescue therapy) for the acute (0–2 h) and late (2–24 h) periods.

Results: Need for rescue antiemetics showed significant reduction ($P < 0.05$) for all groups in comparison with placebo. Number needed to be treated (NNT) improved on increasing dose of olanzapine from 5 mg to 10 mg for prevention of both nausea (48%) and vomiting (36%) in comparison to placebo.

In the 0–2 h postoperative time interval, complete response (CR) rates were insignificant ($P = 0.48$,

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$P = 0.11$) for olanzapine 5 mg and 10 mg when compared to placebo; and significant for ondansetron 16 mg ($P = 0.04$). For the 2–24 h interval after surgery, CR rates were significant for OL5, OL10, and ON16 ($P = 0.02$, $P = 0.005$, $P = 0.007$) when compared to placebo. On comparing both olanzapine doses with ondansetron 16 mg during 0–2 h and 2–24 h study periods, there were no significant differences.

Conclusion: Olanzapine can be used safely and effectively for prophylaxis against PONV especially for late postoperative periods.

1. Introduction

Postoperative nausea and vomiting (PONV) is the most frequent side effect after anesthesia, occurring in 30% of unselected inpatients and up to 70% of ''high-risk'' inpatients during the 24 h after emergence [1]. Postoperative nausea and vomiting can result in morbidity like wound dehiscence, bleeding, pulmonary aspiration of gastric contents, fluid and electrolyte disturbances, delayed hospital discharge, unexpected hospital admission, and decreased patient satisfaction [2]. Nausea, retching and vomiting are among the most common postoperative complications and can occur after general, regional or local anesthesia [3]. PONV is thought to be multifactorial in origin, involving anesthetic, surgical, and individual risk factors [4]. Some of these factors which affect the incidence of PONV include age, sex, history of previous PONV or motion sickness, smoking, surgical procedure, duration of surgery and anesthesia, and anxiety [2]. General anesthesia using volatile anesthetics is associated with an average incidence of postoperative nausea and vomiting (PONV) ranging between 20% and 30% [2].

Some operations are reported to be associated with a higher incidence of PONV than others. These include plastic (breast augmentation), ophthalmologic (strabismus repair), ENT-dental, gynaecologic, laparascopic (sterilisation), genitourinary, orthopaedic surgery (shoulder procedures), mastectomies and lumpectomies [5]. Traditional antiemetics (droperidol and metoclopramide) are frequently used for the prevention of PONV during the first 24 h after anesthesia [6].

Olanzapine, an atypical antipsychotic agent of the thiobenzodiazepine class, blocks multiple neurotransmitter receptors, including dopaminergic (D1, D2, D3, D4), serotonergic (5-HT2A, 5-HT2C, 5-HT3, 5-HT6), adrenergic (alpha1), histaminic (H1), and muscarinic (m1, m2, m3, m4) receptors [7]. By virtue of acting on a number of key receptor sites, olanzapine as a single agent has a distinct advantage over combinations of various antiemetics by improving compliance and reducing drug interactions [8].

The main objective of this study was to evaluate, in a randomized manner, the comparative efficacy of single oral dose of atypical antipsychotic olanzapine (5 mg and 10 mg) and oral ondansetron hydrochloride (16 mg) for the prophylaxis of PONV in patients undergoing elective breast surgery under general anesthesia. Patients were observed for 24 h postoperatively. More specifically, we determined whether there were statistically significant differences in the incidence and severity of nausea and vomiting (including retching), proportion of patients with complete response (no nausea, vomiting and no need for rescue antiemetic) and the number of rescue antiemetic doses needed to treat emetic episodes. Also, undesirable side effects (including sedation, anxiety, restlessness, and abnormal muscle movements, and headache) were recorded.

1.1. Patient and method

After approval of our facility clinical research Ethics Committee, a written informed consent was obtained from all participants. Eighty two female patients scheduled for breast surgeries (mastectomy, tumor biopsy, reductive mastoplasty and other plastic surgery) were studied (mean age 39 ± 9 years). All patients were ASA physical status I or II. Patients were excluded from study if they had preexisting nausea, vomiting or motion sickness, receiving opioids or drugs with known antiemetic properties in the 24 h before surgery, history of esophageal reflux or opioid or alcohol abuse; had a serum creatinine greater than 2.0 mg/dl; had a serum alanine aminotransferase (ALT) or aspartate transaminase (AST) greater than two times the upper limits of normal and patients with body weight twice their ideal body weight. Patients were allowed to eat solids until midnight on the day prior to surgery and to drink clear liquids until 3 h before the scheduled start of surgery. Patients were randomly allocated to one of four groups received placebo or single oral dose of olanzapine 5 mg (OL5) or 10 mg (OL10) or ondansetron 16 mg (ON16). All patients received 1–2 mg midazolam as premedication. Olanzepine groups (OL5 and OL10) received olanzapine 5 mg and 10 mg respectively 4 h before induction of anesthesia while ondansetron group (ON16) received ondansetron 16 mg 1 h before induction of anesthesia orally with sip water. To ensure blindness placebo drug was given in OL5 and OL10 groups 1 h before induction and 4 h before induction in ON16. Placebo group of patients received sugar pills 4 and 1 h before induction. After a patient was assigned to a treatment group, the assignment was recorded and placed in a sealed envelope by a person not involved in the study. A pharmacist, who was also not involved in the study, prepared the study medications and sealed it in an envelope. The appropriate patient envelope according to previous random assignment was sent to a nurse who was responsible for administering the drugs to patients. A nurse or a physician, who were blinded to the patient treatment groups gave the study drugs and recorded preoperative and postoperative data.

Induction of anesthesia was the same for all groups using propofol 2-3 mg kg^{-1}, rocuronium 1 mg kg^{-1} for intubation and maintenance of muscle relaxation. After preoxygenation for 3 min and endotracheal intubation was done. Orogastric tube was introduced and suction was applied to empty the stomach from air and other contents. Maintenance with an opioid fentanyl 2–5 ug kg^{-1}, nitrous oxide and oxygen, and sevoflurane volatile anesthetic as needed. Reversal of

neuromuscular blockade was allowed with standard agents of 50 μg kg^{-1} neostigmine and 8 μg kg^{-1} glycopyrrolate. The nasogastric tube was suctioned and then removed before tracheal extubation.

During anesthesia standard monitoring (electrocardiogram, noninvasive blood pressure, ETco2, and pulse oximetry) was used.

Pre-emptive analgesia was done before patient recovery by Lornoxicam ($ZEFO^R$) 8 mg intravenous and Paracetamol (Perfalgan^R) one gram by intravenous infusion.

Postoperative pain relief was provided by IV $ZEFO^R$ was given for postoperative analgesia *q* 8 h and IV Paracetamol 1 g at 8 h intervals. All patients were kept for monitoring in the PACU for 2 h. After that 2 h the patients moved to the surgical ward to be monitored and watched at 6th, 12th, 18th, and 24th h by a nurse or a physician, who were blinded to the patient treatment groups.

Emetic episodes and nausea occurrence were the primary outcome in this study. An emetic episode was defined as vomiting or retching or any combination that occurred in rapid sequence of less than 1 min between episodes. Nausea was defined using a categorical 11-point linear whole number scale for which 0 represented ''no nausea'' and 10 represented ''nausea as bad as it can possibly be''. Secondary endpoint was the complete response (CR) (without nausea and vomiting, no rescue therapy) for the acute (0–2 h) and late (2–24 h) periods.

Need for rescue antiemetic, the intensity of postoperative pain, opioid pain therapy, and any adverse events (including sedation, anxiety, restlessness, and abnormal muscle movements, and headache) were recorded. 11-point scale in which 0 was no pain at all and 10 represented the worst pain imaginable was used to assess postoperative pain during the study period.

Rescue antiemetic was allowed at any time on patient request, after three emetic episodes, for nausea lasting at least 15 min, or according to physician assessment. The patient was considered a treatment failure if rescue antiemetic was required.

Patient's safety was evaluated including vital signs taken just prior to ingestion of study drug, immediately before induction of anesthesia, every 15 min intraoperatively, upon entry to and every 15 min in the post-anesthesia care unit (PACU) for 2 h, and 24 h postoperatively. Laboratory tests (complete blood count, chemistry, renal and liver function tests) were done preoperatively and again at 24 h postoperatively.

1.2. Statistical analysis

The study was designed to enroll 80 patients to achieve a power of 80% to detect for a 40% difference in the incidence of nausea or vomiting with alpha level of 0.05. The Cochran–Mantel–Haenszel test was used to compare each olanzepine groups and ondansetron group with the placebo group with regard to (1) the proportion of patients with no emetic episodes and no nausea over the 24-h study (2) interdose comparisons between olanzapine 5 mg, 10 mg doses and ondansetron 16 mg dose with respect to the proportion of patients reporting no emesis and the proportion reporting no nausea, (3) analysis of efficacy (complete response rates) among strata. Number needed to be treated (NNT) was calculated as the reciprocal of the absolute risk reduction. The percentage of patients with complete response for acute period and delayed period was calculated separately in test groups and control group. The X^2 test was utilized to analyze complete response and to compare the relative frequency of post treatment abnormal laboratory values. Fisher's exact test was used to make pair-wise comparisons of the ondansetron and olanzapine groups with the placebo group with regard to adverse events.

2. Results

Eighty two patients were included in the study. There were no significant differences in patients' characteristics between treatment groups, including relation of surgery time with stage of menstrual cycle. The mean duration of anesthesia and duration of operation were not different. Also, no significant differences were noted among groups with respect to surgery type (Table 1).

Olanzapine and ondansetron doses were significantly better than placebo in preventing both emesis and nausea (Table 2) during the 24-h observation period. Also olanzapine and ondansetron doses were also more effective than placebo in preventing the need for rescue antiemetics. Fifty-seven percent of the patients in the placebo group required rescue during the 24 h following surgery compared with 48%, 37%, and 38% of those receiving olanzapine 5 mg, 10 mg, and ondansetron 16 mg ($P = 0.04$, $P = 0.002$, and $P = 0.001$), respectively. When comparisons were made for all patients, the olanzapine 10 mg and ondansetron 16-mg dose were better than the 5 mg dose of olanzapine at preventing nausea and emesis but lack significance ($P > 0.05$). NNT improved on increasing dose of olanzapine from 5 mg to 10 mg by 48% and 36% regarding to prevention of nausea and vomiting respectively (Table 2).

2.1. Complete response

Compared with placebo, a trend in the proportion of patients with a complete response (CR) was observed with increasing dose of olanzapine from 5 mg to 10 mg across the 24-h study interval. In the 0–2 h postoperative time interval, CR rates were placebo, 58%; olanzapine 5 mg, 73% ($P = 0.48$); olanzapine 10 mg, 80% ($P = 0.11$); and ondansetron 16 mg, 90% ($P = 0.04$) (Fig. 1). For the 2–24 h interval after surgery, CR rates were significant for OL5, OL10, and ON16 ($P = 0.02$, $P = 0.005$, $P = 0.007$) when compared to placebo. On comparing both olanzapine doses with ondansetron during study period 0–2 h, ondansetron 16 mg was better but lack significance ($P > 0.05$). Olanzapine 5 mg and 10 mg were better than ondansteron 16 mg but lack significance ($P = 0.68$, $P = 0.59$) throughout 2–24 h study period.

Both treatments were well tolerated. There were no significant differences between treatment groups regarding mean vital signs recorded intraoperatively or postoperatively. Also no significant differences were recorded in treatment groups' laboratory values when compared with those obtained preoperatively. The overall incidence of adverse events was similar across all treatment groups. The frequency of adverse affects, including sedation, anxiety, restlessness, and abnormal muscle movements, and headache were evaluated. The most common potentially drug-related adverse event was headache, which occurred insignificantly more in (6%) ondansetron-treated patients compared with olanzapine treated patients (3%). None of the headaches required specific interventions. Arrhythmia was not reported in all treatment groups.

Table 1 Patient characteristics.

	Placebo (n = 21)	OL5 (n = 21)	OL10 (n = 20)	ON16 (n = 20)
Age (year)	42 ± 13	41 ± 14	43 ± 12	42 ± 12
BMI (kg/m^2)	25 ± 5	26 ± 4	27 ± 4	26 ± 5
ASA physical status				
I	12	10	12	11
II	9	11	8	9
Number of days since last menstrual cycle				
0–8 (menstrual)	5	5	4	5
9–16 (follicular)	7	8	7	6
< 16 (luteal)	7	7	7	7
No menses	2	1	2	2
Smokers	4	5	5	3
Type of surgery				
Mastectomy	5	4	6	4
Tumor biopsy	6	5	6	6
Reductive mastoplasty	6	6	4	6
Other plastic surgery	4	6	4	4
Duration of anesthesia (min)	107 ± 53	103 ± 49	110 ± 48	105 ± 51
Duration of operation (min)	81 ± 50	78 ± 52	82 ± 55	87 ± 49
Intraoperative fentanyl (μg/kg)	1.8 ± 03	2.0 ± 0.1	2.1 ± 0.1	1.9 ± 2

Table 2 Efficacy analysis during the whole 24-h.

	Placebo (n = 21)	OL5 (n = 21)		OL10 (n = 20)		ON16 (n = 20)	
		%	NNT	%	NNT	%	NNT
Early outcome 0–2 h							
No emesis	12/21	16/21	5.2	17/20	3.1	18/20	3.0
	57	76		85*		90*	
No nausea	10/21	14/21	5.2	16/20	3.0	17/20	2.4
	47	66		80		85*	
Late outcome 2–24 h							
No emesis	8/21	13/21	4.2	16/20	2.4	15/20	2.7
	(38)	(62)		(80)*		(75)*	
No nausea	5/21	9/21	5.2	13/20	2.6	12/20	2.7
	(23.8)	(42.8)		(65)*		(60)*	

NNT = number needed to treat.
* $P < .05$ compared with placebo.

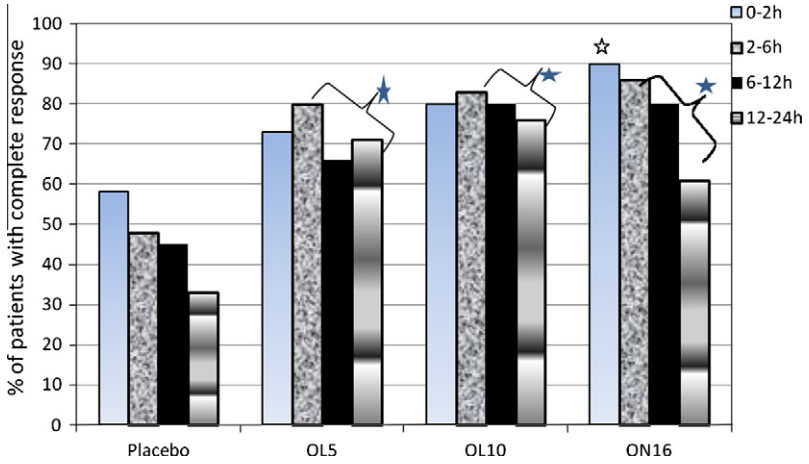

Figure 1 Percent of patients experiencing complete response (no nausea and emesis) during the 2-h, 2–6 h, 6–12 h and 12–24 h study periods for all treatment groups. *$P < 0.05$ in comparison to placebo.

Both the olanzapine 5 mg and 10 mg were well tolerated. No serious adverse events were reported. In all the volunteers drowsiness was reported as an adverse event, which was attributed to the pharmacological action of olanzapine. In one volunteer, elevation in their liver function tests (LFTs) was reported at the end of the study safety evaluation.

Approximately 45% of the patients in this study received postoperative opioids (meperidine), and there were no significant differences with a better tolerance in olanzapine patients (placebo_43%, olanzapine 5 mg_39%, olanzapine 10 mg_ 36%, and ondansetron 16 mg_46%).

3. Discussion

In this study we evaluated the antiemetic efficacy, safety, and use of prophylactic olanzapine and compared it with placebo and ondansetron, a "gold standard" antiemetic, in high risk of postoperative vomiting breast surgery [9] in high risk female patients [10]. Olanzapine and ondansetron doses were significantly better than placebo in preventing both emesis and nausea. NNT and percentage of CR improved on increasing dose of olanzapine from 5 mg to 10 mg regarding to prevention of nausea and vomiting. Also we found that both the olanzapine 5 mg and 10 mg were well tolerated and no serious adverse events were reported.

Olanzapine's activity at multiple receptors—particularly at the D2, 5-HT2c, and 5-HT3 receptors, which appear to be involved in nausea and emesis—suggests that it may have significant antiemetic properties [11]. Phase I study made sure the maximum tolerated dose of olanzapine which is 5 mg per day for the 2 days prior to chemotherapy and 10 mg per day for 7 days post-chemotherapy and revealed effectiveness in prevention of late nausea and vomiting [12]. In phase II trial of olanzapine [13] in combination with granisetron and dexamethasone for prevention of chemotherapy induced nausea and vomiting (CINV), the combination therapy proved to be highly effective in controlling acute and delayed CINV in patients receiving highly and moderately emetogenic chemotherapy.

Ondansetron is a potent, highly selective 5HT3 receptor-antagonist. The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxic induced nausea and vomiting. Following oral dosing with ondansetron, peak plasma concentrations are achieved in approximately 1.5 h [14].

Tramer et al. [15] assessed the efficacy of ondansetron, compared with placebo or no treatment, for the prevention of post-operative nausea and vomiting (PONV); to test dose-response evidence; to identify the optimal dose for oral and intravenous routes; and to investigate the potential of ondansetron for toxic effects in the surgical setting, and they found that ondansetron 16 mg was regarded as the optimal fixed oral dose tested in these trials. Our study results indicate that all doses of olanzapine (5 mg and 10 mg) and ondansetron 16 mg were effective when compared with placebo at preventing both emesis and nausea for the 24 h observation postoperatively. Interdose comparisons showed that 10 mg of olanzapine was significantly better than 5 mg for the complete control of emesis.

In the 24-h prevention of nausea and vomiting, olanzapine 10 mg and ondansetron 16 mg was significantly superior to olanzapine 5 mg. However, in order to assess the clinical significance of a statistically significant finding, some method or measure must be identified. One method is the NNT [16] which is defined as the reciprocal of the absolute risk reduction. The NNT thus identifies the number of patients who must be treated in order to prevent one adverse event. Thus the number-needed-to-treat is a useful estimate of clinical relevance of treatment effect. For the entire study population, the NNT for no emesis are 4.2, 2.4, and 2.7, and for no nausea they are 5.2, 2.6, and 2.7 for 5 mg, 10 mg of olanzapine, and 16 mg of ondansetron, respectively. These figures are better than those documented by Rust and Cohen [17] where the NNT to prevent nausea and vomiting with 16 mg oral ondansetron up to the 48 h compared with placebo were 5.9 and 4.4, respectively. Also, our results regarding the percentage of no emesis and no nausea were 75% and 60% whereas European study results of Rust and Cohen [17] showed 54% and 42% respectively. This difference between our study and Rust and Cohen may be due to differences in study population (Arab and European) and observation period (24 h in our study 48 h in Rust and Cohen study) as efficacy of ondansetron lasts up to 24 h only [25].

In the present study we found that olanzapine 10 mg was comparable to ondansetron 16 mg regarding absence of events (no nausea and vomiting) and NNT. CR rates in our study showed better but insignificant differences between olanzapine 5 mg and 10 mg and placebo during 0–2 h study period ($p = 0.48$ and 0.11 respectively), but ondansetron 16 mg showed significance ($p = 0.04$) in comparison with placebo in the same period. The rest of study period (2–24 h) showed significant differences between the all study drugs and placebo. In the other hand, olanzapine 5 mg and 10 mg did not show significance when compared with ondansetron 16 mg with superiority of olanzapine 10 mg dose. In our study increasing the dose of olanzapine from 5 to 10 mg led to a decrease of more than 20% in the NNT (i.e. an improvement) for the prevention of both nausea (48%) and vomiting (36%) in comparison to placebo.

Based on the preset definition of clinical relevance of antiemetic efficacy (number-needed-to-treat < 5) [18], Tramer et al. [15] considered an increase in efficacy of at least 20% as clinically relevant. Thus a decrease of number-needed-to-treat from 5 to 4 (i.e. treating 4 patients instead of five for one to benefit) was regarded as clinically relevant improvement.

Previous studies [11–13] on olanzapine efficacy and safety in controlling nausea and vomiting were performed in patients receiving highly and moderately emetogenic chemotherapy. Tan et al. [7] concluded that olanzapine can improve the complete response of delayed nausea and vomiting in patients receiving the highly or moderately emetogenic chemotherapy comparing with the standard therapy of antiemesis.

In two phase II studies, olanzapine demonstrated effective prevention of both acute and delayed chemotherapy induced nausea and vomiting (CINV) in patients receiving highly or moderately emetogenic chemotherapy [12,19].

In one small phase III study [20], compared olanzapine with aprepitant both combined with dexamethasone and palonosetron in the prevention of CINV in highly emetogenic chemotherapy and concluded that olanzapine regimen (O) showed comparable results to the aprepitant regimen (A) in regard to acute [100% (O) versus 90% (A)], delayed [77% (O) versus 73% (A)] and overall [77% (O) versus 73% (A)] CR.

In the latest phase III trials [11], olanzapine combined with a single dose of dexamethasone and a single dose of palonesterone was very effective at controlling acute and delayed CINV in patients receiving highly emetogenic chemotherapy.

Our results in this study is consistent with the previous trials on olanzapine use to control CINV taking in consideration that (1) Acute periods in those trials were considered up to 24 h from the start of chemotherapy due to longer course of chemotherapy while acute period of PONV settings was considered 0–2 h. (2) Combination therapy used in these trials aided in better control of N&V during acute period.

In our study, we found better pain tolerance in olanzapine receiving patients without significance that coincide with small study on cancer patients and they concluded that olanzapine may reduce opioid requirements and be ''opioid sparing'' in cancer patients with uncontrolled pain who also have cognitive impairment or anxiety [21].

In this study, for the doses given of olanzapine 5 mg and 10 mg were not associated with significant sedation, weight gain, or induction of significant hyperglycemia that is consistent with Rudolph et al. [11] who used 10 mg daily for 4 days, and concluded that these effects have been associated with olanzapine given for longer periods of time. Previous studies have shown that extrapyramidal side effects of olanzapine are significantly reduced compared to other antipsychotics [22,23].

The trial arms in the study were blinded in spite of different olanzapine and ondansetron pharmacokinetics that affect time of drug administration. Oral Administration, monotherapy of olanzapine is well absorbed and reaches peak concentrations in approximately 5 h following an oral dose. Its half-life ranges from 21 to 54 h (mean of 30 h) [24].

The single dose ondansetron bioavailability is approximately 56% when administered orally with time to peak plasma concentrations occurring at approximately 1.7 h. Despite the plasma half-life of approximately 3–4 h, efficacy is for 24 h, indicating that the therapeutic action of ondansetron exceeds the half-life of the drug [25].

Our study design has several limitations, including studying olanzapine efficacy in patients with prior history of PONV or motion sickness, a lack of cost effectiveness analysis and to extend the observation period to 48 h or 72 h postoperative.

Our study strength was in the comparison of olanzapine with placebo and the gold standard antiemetic, ondansetron, in its best studied dose.

Future investigations may explore the efficacy of olanzapine with adding combination of rapid onset and short acting antiemetic, e.g. propofol may give more satisfactory results in acute postoperative period.

We concluded that olanzapine can be used safely and effectively for prophylaxis against PONV especially high risk surgical procedure under general anesthesia. It was more effective in late postoperative period and olanzapine 10 mg dose was comparable to the ondansetron 16 mg that was described as ''optimal single oral dose'' [15].

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