Indonesian Journal of Pharmacy

VOL 36 (3) 2025: 515–522 | RESEARCH ARTICLE

Comparison of Antiemetic Use Ondansetron and Metoclopramide, Evaluation of Effectiveness and Adverse Effects

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Article Info

Submitted: 21-05-2024
Revised: 17-12-2024
Accepted: 31-12-2024

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ABSTRACT

Ondansetron and metoclopramide are the most often used antiemetics in clinics. According to the Indonesian National Formulary, ondansetron is exclusively approved for the prevention of nausea and vomiting caused by chemotherapy and radiation. Furthermore, Extrapyramidal Symptoms (EPS) are a adverse effect of metoclopramide that both patients and professionals less preferred. This research aimed to compare the efficacy and adverse effects of ondansetron with metoclopramide in adult internal medicine patients. This is a prospective cohort observational research with inclusion criteria of internal medicine patients aged ≥ 18 years who received ondansetron or metoclopramide as antiemetics. Sampling was carried out using purposive sampling on internal medicine patients with complants of nausea and/or vomiting who received ondansetron or metoclopramide. A difference test was carried out between the 2 groups on the variable effectiveness (analyzed statistically using Wilcoxon and Mann Whitney-U test) and adverse effects (analyzed statistically using chi-squared and Fischer exact test). From a total of 194 patients, 107 received IV ondansetron and 87 received IV metoclopramide. The result showed a significant reduction in nausea before and 30 minutes after drug administration in both groups ($p < 0.05$). There was no significant difference in effectiveness of anti-nausea and anti-vomiting in the two groups ($p > 0.05$). However, a significant difference was also found in headache adverse effects after 30 minutes between the 2 groups ($p < 0.05$). In conclusion, ondansetron and metoclopramide are effective in treating nausea and vomiting in adult internal medicine patients.

Keywords: Ondansetron, Metoclopramide, effectiveness, adverse effects

INTRODUCTION

Nausea and vomiting are common symptoms that are often encountered in clinical practice. Based on epidemiology research, more than 50% of adults had experienced at least one episode of nausea, and 30% reported vomiting in the previous 12 months (Singh *et al.*, 2016). Approximately 90% of gastroparesis patients experience symptoms of nausea and vomiting (Shakhatreh *et al.*, 2019). Approximately 550,000 children aged <5 years die from acute gastroenteritis each year with vomiting being the leading cause of death due to unsuccessful oral rehydration therapy (Wu & Zhan, 2020). Several classes of antiemetics are used to treat nausea and vomiting, such as 5-HT3 antagonists (5-hydroxytryptamine 3), D2 (Dopamine 2), H1 (Histamine 1), muscarinic, and NK-1 antagonists (Neurokinin-1), as well as cannabinoids, benzodiazepines, corticosteroids, and olanzapine. (Wilhelm & Lipari, 2019; Zhong *et al.*, 2021).

In Indonesia, metoclopramide and ondansetron are widely used for treating the symptoms of nausea and vomiting. Based on the Indonesian National Formulary, ondansetron is known for the prevention of nausea and vomiting during chemotherapy and radiation. Meanwhile, metoclopramide, domperidone, chlorpromazine, and dimenhydrinate could be used for all types of nausea and vomiting (Kemenkes RI, 2021). Ondansetron has quite broad effectiveness in various etiologies of emesis but is limited based on National Formulary policy. Metoclopramide has a similar therapeutic property compared to ondansetron but differs in peripheral mechanisms and limited use in conditions of Gastrointestinal tract obstruction and bleeding (Joint Formulary Committe, 2022; Flake *et al.*, 2015). Moreover, the adverse effects of EPS constitute the reasons for the less preference given to metoclopramide (Heckroth *et al.*, 2021).

The National Health Insurance (JKN) program was implemented in Indonesia since 2014, and administered by the Social Security Administrator for Health (BPJS Kesehatan), which was one of the several national administering bodies. The JKN program policies related to drug management are dynamic, requiring strong efforts from regions in adjusting to developments in drug management policies (Raharni et al., 2021).

Ondansetron is a 5-HT3 antagonist that blocks receptors at the end of the vagal afferent nerve, thereby preventing the flow of impulses to the center. Meanwhile, metoclopramide is a D2 antagonist that blocks receptors in the LES (Lower Esophageal Sphincter) and the gastric part of the fundus and antrum, thereby preventing the vomiting mechanism (Anandabaskar, 2021; Zhong *et al.*, 2021).

In contrast to ondansetron, metoclopramide penetrates the blood-brain barrier, causing EPS adverse effects, such as akathisia, dystonia, tardive dyskinesia, and parkinsonism gastroparesis (Shakhatreh *et al.*, 2019). This antagonist does not have EPS effects but can prolong the QT interval at high doses. Therefore, caution and monitoring are advised when administering metoclopramide to patients with QT prolongation symptoms (Heckroth *et al.*, 2021). Based on the background, this research aimed to compare the efficacy and adverse effects of ondansetron with metoclopramide in adult internal medicine patients at Airlangga University Hospital.

MATERIALS AND METHODS

Study Design and Location

This analytical observational research with a prospective cohort method was conducted in April-June 2023 at Airlangga University Hospital, Surabaya based on the ethical approval Number: 045/KEP/2022.

Population and Sample

The Study Population was on internal medicine patients with complants of nausea and/or vomiting who received ondansetron or metoclopramide. Sampling was carried out using purposive sampling. The Inclusion criteria were internal medicine patients aged ≥ 18 years who received ondansetron or metoclopramide as antiemetics. Exclusion criteria were patients who used antiemetics <8 hours previously, had gastrointestinal obstruction, ileal perforation, were pregnant or breastfeeding, experiencing chemotherapy or radiotherapy, or had a history of mental symptoms.

Assessment

Nausea severity was rated with a visual analog scale (VAS) on enrollment and 30 minutes after drug administration. Vomiting frequency was observed 30 minutes before enrollment, as well as 0, 15, 30, 60, and 120 minutes after drug administration. Adverse effects, such as headache, sedation, diarrhea, constipation, akathisia, dystonia, facial muscle stiffness, and sleep disturbances, were observed at 30 minutes (IV), and every 24 hours after drug administration for 3 days.

Nausea symptom improvement was self-reported 30 minutes after drug administration and described as "a lot less", "a little less", "the same", "a little more", or "a lot more". Patient satisfaction was self-reported 120 minutes after drug administration and described as "satisfied", "not satisfied", or "no opinion". Meanwhile, analysis was carried out for patients whose symptom severity worsened and those who received rescue antiemetic treatment.

A descriptive analysis was carried out for the reduction of nausea VAS score with a cut-off value of 5 mm. A difference test was also conducted for the reduction in the VAS score of nausea, the incidence of vomiting, as well as adverse effects between ondansetron and metoclopramide groups.

Table I. Characteristic and Clinical Symptoms of Patients

Patients Characteristic	**Antiemetic**		***P***
	Ondansetron (n=107) frequency (%)	Metoclopramide (n=87) frequency (%)	
Gender			
Male	34 (32)	31 (36)	0.571 (a)
Female	73 (68)	56 (64)	
Age			
18-40 years	41 (38)	36 (41)	0.426 (b)
41-59 years	33 (31)	30 (35)	
>59 years	33 (31)	21 (24)	
Mean ± SD	46.22±19.1	46.17±18.8	
Min-Max	18 – 81	19 – 86	
Symptoms			
Nausea	89 (84)	71 (82)	0.898 (a)
Vomiting	9 (8)	7 (8)	
Nausea and Vomiting	9 (8)	9 (10)	
Total	107 (100)	87 (100)	
Nausea Severity (VAS0)			
Low (5-49 mm)	27 (28)	25 (31)	0.936 (b)
Moderate (50-79 mm)	50 (51)	35 (44)	
High (80-100 mm)	21 (21)	20 (25)	
Mean ± SD	57.86±20.4	58.78±20.7	
Min-Max	15-100	15 – 100	
Total	98 (100)	80 (100)	
Vomiting frequency (12 hours before drug administration)			
1-5 times	63 (77)	50 (79)	0.528 (a)
6-10 times	11 (13)	5 (8)	
>10 times	8 (10)	8 (13)	
Total	82 (100)	63 (100)	
Vomiting incidence (30 minute before drug administration)			
Once	6 (33)	5 (31)	0.957 (b)
Twice	8 (45)	10 (63)	
3 times	4 (22)	1 (6)	
Total	18 (100)	16 (100)	
Antisecretory agents			
With antisecretory	20 (19)	24 (28)	0.141 (a)
Without antisecretory	87 (81)	63 (72)	0.547 (a)
H2 Blocker	29 (33)	24 (38)	
Proton Pump Inhibitor	58 (67)	39 (62)	

(a): Analyzed statistically using chi-squared test; (b): Analyzed statistically using Mann Whitney-U test

Table II. Antinausea Effectiveness based Nausea VAS Score before and after Drug Administration

Antiemetic	***Mean ± SD***			
	VAS0	**VAS30**	***p (a)***	**ΔVAS**
Ondansetron (n = 98)	57.86±20.4	17.53±22.7	0.001	40.33±19.9
Metoclopramide (n = 80)	58.78±20.7	14.20±18.7	0.001	44.6±20.6
p (b)	0.840	0.526		0.152

VAS0: Nausea VAS score before drug administration; VAS30: Nausea VAS score 30 minutes after drug administration; (a): Analyzed statistically using the Wilcoxon test; (b): Analyzed statistically using Mann Whitney-U test

RESULTS AND DISCUSSION

The total number of patients who met the inclusion criteria was 196 patients but 2 dropped out due to surgery and required intensive care during the observation period. A total of 194 patients were included, where 107 received IV ondansetron therapy and 87 were administered IV metoclopramide therapy.

Effectiveness

Nausea severity was rated with a VAS on enrollment and 30 minutes after drug administration. Vomiting frequency was observed in the 30 minutes before enrollment and 0, 15, 30, 60, and 120 minutes after drug administration. Furthermore, the observation time for the evaluation of antiemetic effectiveness was determined based on the pharmacokinetic profile of the drug. The onset of action of metoclopramide was 1-3 minutes with peak levels reaching 15 minutes after intravenous administration. Ondansetron reached peak levels 10 minutes after intravenous administration (Medscape, 2022; Chow *et al.*, 2010). The half-life of metoclopramide was 5-6 hours with a duration of action of 1-2 hours. In the case of ondansetron, the half-life was 2-6 hours with a duration of action ranging from 2-8 hours with standard doses (Chow *et al.*, 2010).

The characteristics of patients (Table I), such as matching data on age, gender, symptoms of nausea vomiting, severity, vomiting frequency (12 hours before drug administration), vomiting incidence (30 minutes before drug administration), and use of antisecretory agents. The result showed that there was no significant difference between the 2 groups, as evidenced by $p > 0.05$. The number of patients included in the anti-nausea effectiveness test was 98 in ondansetron and 80 in metoclopramide group. Meanwhile, for the anti-emetic effectiveness test, ondansetron and metoclopramide group had 18 and 16 patients, respectively.

The anti-nausea effectiveness of the two drugs based on nausea VAS score (Table II). The average nausea VAS score before and 30 minutes after administration of ondansetron and metoclopramide were 57.86 ± 20.4 mm vs. 17.53 ± 22.7 mm and 58.78 ± 20.7 mm vs. 14.20 ±18.7 mm respectively. The result showed a significant reduction in nausea VAS scores before and 30 minutes after drug administration in each group ($p < 0.05$).

The reduction of nausea VAS score from administrating ondansetron and metoclopramide was 40.33 ± 19.9 mm and 44.6 ± 20.6 mm respectively. This result is consistent with previous research in Iran which included 41 and 44 patients of ondansetron and metoclopramide group. The result showed that there was a significant difference in nausea VAS scores before and after the administration of antiemetics ($p=0.01$) (Feiz Disfani *et al*., 2022).

The result of subgroup analysis in the 3 most diagnostic groups (dyspepsia, Acute Gastroenteritis (AEG), DM and its complications) (Table III), are not different from the analysis in all previous groups, both antiemetics ondansetron and metoclopramide have no significantly different effectiveness based on the decrease in VAS nausea scores.

In this research, an MCSD (Minimum Clinically Significant Difference) of 5 mm was used to assess effectiveness of anti-nausea in patients. Effectiveness of antiemetics based on the reduction of nausea VAS score was achieved when the MSCD value for reducing the nausea VAS score was 5 mm in 30 minutes after drug administration (Meek *et al.*, 2015). A total of 95 of 98 patients experienced nausea VAS score reduction of more than 5 mm in ondansetron group. In metoclopramide group, 79 of 80 patients had the same experience, as shown in Table IV. There was no significant difference in anti-nausea effectiveness between the two drugs ($p > 0.05$)

A total of 3 patients from ondansetron group and 1 in metoclopramide did not reach MCSD. The first patient was a 25-year-old woman with UTI (Urinary Tract Infection) and abdominal colic. The second was an 18-year-old woman with dyspepsia, while the third patient aged 62 years old had typhoid fever and dyspepsia. The fourth patient was a 20-year-old woman with a diagnosis of typhoid fever.

The result of this research showed that there was no significant difference in the comparison of anti-nausea effectiveness between the two drugs ($p > 0,05$). This result is also consistent with previous research in Australia, which included 87 and 88 ondansetron and metoclopramide groups, respectively. The result showed that there was no significant difference in reducing the nausea VAS score between the two antiemetics, with a reduction of 27 mm observed for ondansetron and 28 mm for metoclopramide (Egerton-Warburton *et al.*, 2014). A Cochrane systematic review concluded that there was no significant difference in reducing VAS nausea scores 30 minutes after administration of antiemetics between both groups with $p=0.53$ (Furyk *et al*., 2015).

Table III. Antinausea Effectiveness Based on VAS Nausea Scores in the 3 Largest Diagnostic Groups

Diagnosa	*Mean±SD*			
	VAS0[a]	**VAS30[b]**	***p*[a]**	**VAS0-VAS30**
Dyspepsia				
Ondansetron (n = 40)	54.7±18.9	16.06±24.4	0,001	38.64±18.7
Metoclopramide (n = 28)	54.35±18.6	13.85±21.6	0,001	40.50±16.8
p[b]	0.859	0.787		0.734
Acute Gastroenteritis				
Ondansetron (n = 34)	62.91±21	19.06±22	0.001	43.84±23.1
Metoclopramide (n = 28)	69.48±19.4	18.85±22	0.001	50.63±22.2
p[b]	0.245	0.981		0.169
Diabetes Mellitus type 2 and It's Complication				
Ondansetron (n = 24)	63.78±19.5	17.83±25.2	0.001	45.96±19.6
Metoclopramide (n = 25)	61,74±23.1	15±21,2	0.001	46.74±21.5
p[b]	0.706	0.971		0.876

(a): Analyzed statistically using the Wilcoxon test; (b): Analyzed statistically using Mann Whitney-U test

Table IV. Nausea Vomiting Effectiveness in Each Group

Parameters	**Antiemetic**		***P***
	Ondansetron (n nausea= 98, n vomiting= 18) frequency (%)	**Metoclopramide (n nausea= 80, n vomiting= 16)** frequency (%)	
Reduction of nausea VAS score			
> 5 mm	95 (97)	79 (99)	0.629 (a)
≤ 5 mm	3 (3)	1 (1)	
Total	98 (100)	80 (100)	
Vomiting Frequency			
-30 minutes			
Once	6 (33)	5 (31)	0.646 (b)
Twice	8 (45)	10 (63)	
3 times	4 (18)	1 (6)	
+15 minutes	0 (0.0)	0 (0.0)	
+30 minutes	0 (0.0)	0 (0.0)	
+60 minutes	0 (0.0)	0 (0.0)	
+120 minutes	0 (0.0)	0 (0.0)	
Total	18 (100)	16 (100)	
P Value (c)	0.001	0.001	
Nausea Symptom Improvement			
a lot less	71 (72)	65 (81)	0.168 (b)
a little less	23 (24)	13 (16)	
the same	4 (4)	2 (3)	
a little more	0 (0.0)	0 (0.0)	
a lot more	0 (0.0)	0 (0.0)	
Rescue Medication	0 (0.0)	0 (0.0)	N/A
Patient satisfaction			
Satisfied	87 (81)	76 (87)	0,314
Not satisfied	19 (18)	11 (13)	(d)
No opinion	1 (1) (e)	0 (0)	

(a): Analyzed statistically using Fisher's Exact test; (b): Analyzed statistically using Mann Whitney-U test; (c): Analyzed statistically using the Friedman test; (d): Analyzed statistically using Chi square test; (e): One patient who answered abstain not included in statistical test

Table V. Adverse Effects Post Antiemetic Administration

Adverse Effects	Observation time (Frequency (%))				
	Minute 0	**Minute 30**	**Day 2**	**Day 3**	**Day 4**
Headache					
Ondansetron	40 (37)	44 (41)	41 (38)	24 (22)	10 (9)
Metoclopramide	24 (28)	19 (28)	22 (25)	17 (20)	7 (8)
p-value	0.149	0.004	0.054	0.826	0.629
Sedation					
Ondansetron	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metoclopramide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea					
Ondansetron	33 (31)	30 (28)	19 (18)	4 (4)	0 (0.0)
Metoclopramide	31 (36)	30 (35)	22 (25)	8 (9)	0 (0.0)
p-value	0.480	0.334	0.201	0.285	N/A
Akathisia					
Ondansetron	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metoclopramide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dystonia					
Ondansetron	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metoclopramide	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Facial Muscle Stiffness					
Ondansetron	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metoclopramide	0 (0.0)	0 (0.0)	2(1)	1 (0.5)	1 (1.3)
p-value			0.200		
Sleep disturbance					
Ondansetron	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metoclopramide	0 (0.0)	0 (0.0)	1(1)	1 (1)	1 (1)
p-value	N/A	N/A	0.448	0.448	0.448

P value: Analyzed statistically using chi-squared and Fisher exact test

Table VI. The Number of Patients who do not Defecate

Antiemetic	**Observation time** (Frequency (%))						P
	Day 0	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 7**	
Ondansetron	79 (74)	1 (1)	10 (9)	3 (3)	13 (12)	1 (1)	0.011
Metoclopramide	75 (86)	5 (6)	5 (6)	1 (1)	1 (1)	0 (0)	

P value: Analyzed statistically using chi-squared test

The number of patients who experienced vomiting 30 minutes before and 120 minutes after administration of ondansetron and metoclopramide were 18 vs 0 and 16 vs 0, respectively. This result is consistent with previous research, showing that no patients experienced vomiting at 15 minutes after antiemetic administration. The anti-vomiting effects was visible during the period because the onset of action in ondansetron and metoclopramide was 1-3 and 10 minutes, respectively (Medscape, 2022; Chow *et al.*, 2010).

The number of patients who self-rated nausea symptoms after 30 minutes of drug administration as "a lot less", "a little less", "the same", "a little more", and "a lot more" in ondansetron and metoclopramide group are 72%, 24%, 4%, 0%, 0% and 81%, 16%, 3%, 0%, 0%, respectively. There was no significant difference in nausea symptom improvement between the two groups, as shown by $p > 0.05$.

The number of patients who self-rated as "satisfied", "not satisfied", and "no opinion" in ondansetron and metoclopramide groups are 81%,

18%, 1%, and 87%, 13%, 0% respectively. There was no significant difference in patient satisfaction between the two groups ($p > 0.05$). This result is consistent with the report of previous research that 54% of patients in ondansetron group and 62% in metoclopramide were satisfied with the administered antiemetic medication (Egerton-Warburton *et al.*, 2014). Furthermore, there was no patient who needed to receive rescue antiemetic treatment. This result is different from the report of previous research that there are 35% and 18% of patients in ondansetron and metoclopramide group needed rescue antiemetic medication (Egerton-Warburton *et al.*, 2014). Another research reported that 48% and 22% of patients in ondansetron and metoclopramide group needed rescue antiemetic medication (Barrett *et al.*, 2011).

The results of this research showed that both antiemetics 100% resolved vomiting, but could not address nausea symptoms completely due to different physiology (Quigley et al., 2001). Vomiting was controlled in the brain stem connected to the gastrointestinal tract. Conversely, the sensation of nausea was expected to appear from complex activation in the CNS (Central Neurovascular System) including many areas in the cerebral cortex (Zhong et al., 2021).

Adverse Effects

The adverse effects experienced by patients, with a significant difference in the number of those who experienced headaches 30 minutes after administering ondansetron compared to metoclopramide ($p < 0.05$) (Table V). There was no significant difference in the incidence of other adverse effects ($p > 0.05$). The adverse effect of constipation, with a significant difference in days in which patients did not defecate between the groups ($p < 0.05$) (Table VI). The result showed that ondansetron group had a greater number of patients who had not defecated for more than 2 days, as compared to metoclopramide (27 vs 7 patients).

The result of this research suggested that ondansetron may be associated with adverse effects, such as headache (8%) and constipation. Meanwhile, the adverse effects associated with metoclopramide are facial muscle stiffness (2%) and sleep disturbances (1%). In previous research, adverse effects were observed in 9 patients out of 258, accounting for 3.5%. Six patients in metoclopramide group experienced adverse effects of akathisia, anxiety, muscle twitches, and sweating. In ondansetron group, 2 patients experienced dizziness and pain at the injection site (Egerton-Warburton *et al*, 2014). After intravenous administration of metoclopramide, akathisia had an incidence of 20-25% (Hendren *et al.*, 2015).

This research has 2 limitations, first, other therapies during hospitalization were not analyzed. Therefore, there was a possibility that the adverse effects experienced by patients were caused by the other therapies. Second, when observing the incidence of adverse effects, assessment tools, such as the Naranjo score or WHO-UMC criteria were not used. Consequently, the incidence of adverse effects in this research was still included in the list of suspected cases.

CONCLUSION

In conclusion, ondansetron and metoclopramide were effective in treating nausea and vomiting in adult internal medicine patients. Furthermore, It was necessary to consider the use of metoclopramide in treating nausea and vomiting in non cancer patients to increase compliance with the National Formulary.

ACKNOWLEDGMENTS

The authors are grateful to the management at Airlangga University Hospital for granting the permission to conduct this research.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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