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Original Article

Benefits of domperidone in ambulatory acute diarrhea with severe vomiting

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Abstract

Background Recently, most patients with diarrheal disease (DD) cases are hospitalized not due to severe dehydration, but due to severe vomiting which interferes with fluid and food intake. Use of anti-vomiting medicines is not recommended because of its "central" side effects. Domperidone has prokinetic and antiemetic effects with only minimal extrapyramidal side effects.

Objective To evaluate domperidone in preventing hospitalization of DD patients in outpatient setting.

Methods This randomized double blind, placebo-controlled clinical trial, was conducted from February to August 2005 at Mohammad Hoesin Hospital, Palembang. We included patients aged 6 to 59 months old with acute diarrhea who had vomited at least 4 times in the last 24 hours, not in need of hospitalization, and agreed to participate. We excluded patients who had taken anti-vomiting drug, or those who had severe diseases, including severe malnutrition. The dose of domperidone was 1.25 mg per 5 kg body weight.

Results There were 183 subjects randomized, consisted of 91 who took domperidone (treatment group) and 92 who took placebo (control group). The duration and decrease of vomiting frequency were significantly different in favor of domperidone. Domperidone prevented hospitalization significantly (P=0.001, OR=4.1, ARR = 20%, RRR=71%, NNT=5). No overt acute clinical side effects were found.

Conclusion Domperidone significantly shortened the duration and decreased the frequency of vomiting in DD cases. **[Paediatr Indones 2007;47:207-210]**.

Keywords: *domperidone, diarrheal disease, vomiting*

Diarrheal disease (DD) still contribute a significant share to the under-five child mortality rate.[1] However, our recent observation showed that more than half of hospitalized DD cases were not due to severe dehydration, but because of severe vomiting.[2] WHO guidelines do not recommend anti-vomiting medicines due to the "central" side effects.[3,4]

Domperidone is a derivative of benzimidazole, a dopamine antagonist, which has prokinetic and antiemetic effects. It prevents gastric relaxation, improves anthral contraction and increases the tonus of lower gastro-esophageal sphincter. This speeds gastric emptying, and prevent vomiting and gastro-esophageal reflux. The antiemetic effects are based on central mechanism through antagonism of dopamine receptors of the central trigger zone (CTZ). Domperidone is not a lipophilic substance, and can not enter the blood brain barrier, so has minimal extrapyramidal side effects;[5,6] it has been studied and

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widely used as an antiemetic and anti-reflux in children.[7,8] We studied the effect of use of domperidone in children with acute diarrhea accompanied with significant vomiting.

Methods

This randomized double blind clinical trial was performed at the out-patient department (OPD) of the Department of Child Health, Mohammad Hoesin Hospital, Palembang. Blinding was achieved by using a placebo of bottled syrup with similar physical appearance to domperidone syrup. The concentration of domperidone was 5 mg/5 ml and the dose was 1.25 mg per 5 kg BW. The syrup should be taken half an hour before feeding, 3 times a day, up to 12 hours after the last vomiting, for a maximum of 3 days. The bottles were coded by random number by the person who prepared the drugs. The code was unveiled after data collection had finished.

We included OPD patients with acute diarrhea aged 6 to 59 months old who vomited at least 4 times in the last 24 hours, and who had no indication for admittance. Patients whom their parents refused to participate, those who had taken anti-vomiting drug, or suffering from severe diseases or severe malnutrition (grade III, IV or kwashiorkor) were excluded.

The benefits of domperidone were assessed through observing the need for hospitalization as indicated by severe dehydration, weakening general condition which hampered fluid / food intake, or other gastrointestinal complications such as severe meteorism. Participants were managed with hospital standard treatment based on WHO guidelines.[9] If the condition of the patients deteriorated, they were asked to come to the OPD and see the duty physician. Otherwise, they were asked to come back 2 days after the study onset. If they did not come voluntarily, they were visited at their home.

Based on the assumption that the hospitalization rate of 25%, effect size of 0.20, a = 0.05 and power = 0.80, 90 participants in each group were needed. The protocol was approved by Ethical Review Committee on Biomedical Research of The Faculty of Medicine Sriwijaya University and Mohammad Hoesin Hospital.

Results

Data collection began from 25 February 2005 and ended on 30 August 2005. Two hundreds and twenty eligible subjects were enrolled. There were 37 drop outs, 5 changed medication, 32 were lost to follow-up. Of the remaining 183, 91 were on domperidone (treatment group) and 92 on placebo (control group).

Table 1 shows that the general characteristics of the subjects were comparable; the course of the diseases before the assignment to the study were also similar **(Table 2)**.

Table 1. Characteristics of the participants

Characteristics	Groups	
	Treatment (n=91)	Control (n=92)
Sex		
Boy	54	51
Girl	37	41
Age in months		
6–11	20	23
12–59	71	69
Nutritional status		
Good	45	47
Poor	46	45
Still breastfed		
Yes	87	89
No	4	3
Parents' education		
High school or more	54	62
Lower	37	30
Parents' income		
Middle class or higher	59	61
Lower class	32	31

Table 2. The course of DD before the onset of the study

	Groups	
	Treatment (n=91)	Control (n=91)
Duration of diarrhea, hr, mean (SD)	48.2 (27.1)	48.7 (30.10)
Frequency of diarrhea per day, mean (SD)	6.5 (2.93)	5.7 (2.82)
Duration of vomiting, hr, mean (SD)	43.2 (23.20)	43.9 (24.10)
Frequency of vomiting per day, mean (SD)	6.7 (2.12)	6.5 (2.24)
Treatment		
Antibiotics + ORT	11	13
Only antibiotics	12	15
Only ORT	8	3
Degree of dehydration		
Without dehydration	29	41
Mild / moderate dehydration	62	51
Accompanying symptoms		
Fever	16	12
Cough	5	5

Table 3. Effect of domperidone towards vomiting

Vomiting	Treatment group (n=91) Mean (SD)	Control group (n=92) Mean (SD)	P
Duration (hrs)	36.9 (15.82)	44.3 (18.15)	0.003*
Frequency (mean/day)	1.9 (2.19)	3.1 (3.71)	0.009*

* = t-test

Table 4. Comparing levels of dehydration and the need for hospitalization

Dehydration		Hospitalized	Not Hospitalized	P	OR	ARR	RRR	NTT
Mild	Treatment (62)	7	55	0.000	5.96	0.32	0.74	4
	Control (51)	22	29					
None	Treatment (29)	1	28	0.313	3.02	0.06	0.666	17
	Control (41)	4	37					

Table 3 shows the effect of domperidone. Vomiting stopped within 60 hours in 82 out of 91 subjects in the treatment group and in 64 out of 92 subjects in the control group (P=0.001). Multiple regression analysis shows that among the variables analyzed (age, breastfeeding status, nutritional status, duration of diarrhea at home, duration of vomiting at home and degree of dehydration), only the degree of dehydration related to the outcome significantly.

Concerning hospitalization, only 8 (8.8%) out of 91 treated participants needed hospitalization compared to 26 (28.3%) of 92 in the control group. The odds ratio of the control group to be hospitalized after treatment was 4.1 (95%CI 1.7;9.6, P=0.001). Actual and relative risk reduction for hospitalization on the benefit of therapy were 20% and 71%. The number needed to treat (NNT) of domperidone in DD patients who vomited at least 4 times in the last 24 hours was 5.

We performed multiple regression analysis to find out if age, breastfeeding status, nutritional status, duration of diarrhea at home, duration of vomiting at home and degree of dehydration associated with the outcome significantly. Among those variables, only the degree of dehydration was significantly associated with the outcome. After the regression, the benefit of domperidone in preventing hospitalization was still significant. The adjusted odds ratio was 5.4 (P=0.000).

The reasons for hospitalization were severe dehydration or deteriorating general condition accompanied by poor intake. In the treated group, of the 8 patients hospitalized, 3/8 was due to dehydration and 5/8 due to the second cause. While in the control group 18/26 was due to dehydration and 8/26 due to deteriorating conditions.

Table 4 shows the benefit of domperidone to prevent hospitalization evaluated through the levels of dehydration. This stratification shows that the benefit was more striking in dehydrated subjects. The absolute risk reduction (ARR) was 32%, the relative risk reduction (RRR) was 74% and the number needed to treat (NNT) was 4. For all subjects the ARR was 20%, the RRR was 71% and the NNT was 5. There were no overt clinical side effects, i.e., itching, sleepy and headache in 16 subjects who could be asked.

Discussion

This study shows the benefits of domperidone in preventing hospitalization of acute diarrheal disease cases by shortening the duration and decreasing the frequency of vomiting. With an ARR of 20%, RRR 71% and NTT 5 the benefits are clinically significant. Since ORT is the core of DD management, severe dehydration or hospitalization after appropriate ORT are regarded as the failure of ORT and the term ORT failure rate is used as a measure.[10] Domperidone decreased ORT failure rate in our study. Domperidone showed significantly better results in subjects with mild dehydration compared to those without dehydration. It is well known that dehydration could trigger or accentuate vomiting in DD patients. It seems domperidone could alleviate this type of vomiting.[10,11]

In all hospitalized subjects, vomiting stopped more than 48 hours after the onset of the study (**Table 3**). Vomiting stopped after the patients were admitted, which

meant after iv fluids therapy, implying that vomiting has an important role in ORT failure. We found that following domperidone therapy, the ORT failure rate was still 8.8%. There were no clinical side effects reported. Unfortunately we did not record the effects of domperidone on the course of diarrhea, or its effects on the frequency and volume of the diarrhea.

Domperidone has been well studied as a safe and effective antiemetic medicine in children.[7,8] When we planned this study in early 2005, we could not find any report using domperidone to alleviate vomiting in children with DD. There is no definitive explanation on the pathogenesis of vomiting in DD. However it is reasonable to believe that receptors of vomiting reflex should be in the GI tract. Since domperidone is a peripherally acting anti- vomiting drug, we assumed that domperidone might be effective in alleviating vomiting in DD. Further study is needed before applying domperidone as part of DD case management guidelines.

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