Indian Journal of Pharmacology 2003; 35: 32-36 **SHORT COMMUNICATION**

GINGER AS AN ANTIEMETIC IN NAUSEA AND VOMITING INDUCED BY CHEMOTHERAPY: A RANDOMIZED, CROSS-OVER, DOUBLE BLIND STUDY

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ABSTRACT

***Objective*:** To study the antiemetic effect of ginger root on nausea and vomiting induced by cyclophosphamide.

***Methods*:** A randomized, prospective, cross-over, double-blind study was carried out in patients receiving cyclophosphamide in combination with other chemotherapeutic agents. Patients with atleast two episodes of vomiting in the previous cycle were included. The patients were randomly assigned to receive one of the three antiemetics: ginger, metoclopramide or ondansetron in the first cycle. They were admitted in the ward for 24 h and observed for the incidence of nausea and vomiting and adverse effects if any, were recorded. Patients were crossed over to receive the other antiemetic treatments during the two successive cycles of chemotherapy.

***Results*:** Complete control of nausea was achieved in 62% of patients on ginger, 58% with metoclopramide and 86% with ondansetron. Complete control of vomiting was achieved in 68% of patients on ginger, 64% with metoclopramide and 86% with ondansetron. No adverse effects attributable to ginger were recorded.

***Conclusion*:** Powdered ginger root in the dose used was found to be effective in reducing nausea and vomiting induced by low dose cyclophosphamide in combination with drugs causing mild emesis. The antiemetic efficacy of ginger was found to be equal to that of metoclopramide but ondansetron was found to be superior than the other two.

KEYWORDS Antiemetic cancer chemotherapy ginger ondansetron metoclopramide

INTRODUCTION

The success of cancer chemotherapy has been marred by criticism due to accompanying adverse drug effects. Nausea and vomiting being commoner side effects of cytotoxic drugs, many antiemetic drugs have been employed for their prevention and treatment. The 5-HT_3 receptor antagonists like ondansetron are highly effective in limiting vomiting associated with many cytotoxics including cisplatin[1].

Ginger, rhizome of *Zingiber officinale*, has been used for antiemetic effect. Several components of ginger such as 6-gingerol, 6-shogaol and galanolactone have been shown to have anti-5HT activity in isolated guinea pig ileum[2,3]. Galanolactone is a competitive antagonist predominantly at ileal 5-HT_3 receptors. The main objective of this study was to find out the effectiveness of ginger in cancer-chemotherapy induced emesis, as a ginger component is reported to have anti-HT_3 activity.

MATERIALS AND METHODS

This study was carried out at government medical college and hospital, Nagpur. It was a randomized, cross-over, double blind study. Study subjects were selected from patients attending the chemotherapy section of radiotherapy department.

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The inclusion criteria were malignancy confirmed by histopathology, combination chemotherapy including cyclophosphamide, occurrence of atleast two episodes of vomiting in previous chemotherapy cycle and age above 18 years. The patients with malignancies of GIT, nausea and vomiting due to reasons other than chemotherapy, hypertension and renal or liver insufficiency were not included. Those who were on concomitant radiotherapy and additional medication apart from chemotherapeutic drugs were also excluded from the study.

Routine hematologic, biochemical assessment was done before each chemotherapy cycle. Study protocol was approved by the ethics committee of the institution. Informed consent of all patients was taken before inclusion in the study. A total of 60 patients were included out of which 50 could complete all three cycles. Rest 10 patients could not complete the study cycles because four died (two after first cycle-metoclopramide treatment, two after second cycle-ginger and ondansetron), two patients refused to continue chemotherapy due to inadequate control of nausea and vomiting (metoclopramide and ginger treatment), two patients dropped out during second cycle (ondansetron treatment) despite adequate control and two patients did not report back for second cycle (ginger and ondansetron treatment in the first cycle).

All patients received cyclophosphamide 500-1000 mg I.V. in combination with other chemotherapeutic agents. Interval between two successive cycles was 21 days. The patients randomly received one of the following antiemetic regimen:

1. Two capsules, each containing 500 mg of ginger powder, orally, 2 ml of normal saline IV, 20 min prior to chemotherapy. Two capsules of ginger were repeated after 6 h of cancer chemotherapy.
2. Two capsules of lactulose orally and injection metoclopramide 20 mg IV, 20 min prior to chemotherapy. Two capsules of 5 mg metoclopramide each, orally after 6 h
3. Two capsules of lactulose orally and injection ondansetron 4 mg IV, 20 min prior to chemotherapy and two capsules of ondansetron, 2 mg each, orally after 6 h.

Dried ginger purchased from the market was identified as *Zingiber officinale* from the department of Botany, Nagpur University. This was supplied to a local pharmaceutical firm which powdered it and prepared the capsules. All the capsules were identical in size, shape, colour and odour. Coded syringes for IV injection were prepared freshly by an investigator who did not participate in the study or in assessment. The patients were randomly assigned to receive one of the three antiemetic treatments during the first study cycle. They were crossed over to the other antiemetic treatments during the next two successive cycles. The sequence of cross-over was as follows: A→B→C, B→C→A, C→A→B where A-ginger, B- metoclopramide, C-ondansetron.

After receiving the anti-cancer drugs and first dose of antiemetic, patients were transferred to the ward where they were monitored for 24 h. Time and number of episodes of vomiting were recorded. If the patient vomited within 2 h of oral administration of the drug, the drug was readministered. If the patient again vomited within 2 h of receiving the antiemetic for the second time, he/she was withdrawn (2 patients-metoclopramide, ginger) from the study and put on regular antiemetic schedule which is same as the regimen 3 described above.

Subjective evaluation of severity of adverse events was carried out. Nausea was graded as none (complete control), mild to moderate (partial control) or severe (no control). Vomiting was graded as no vomiting (Complete control), one or two episodes (partial control), three or more episodes (no control).

The difference in the incidence of nausea and vomiting between the three treatment groups was analysed using Chi-square test. $P < 0.05$ was considered statistically significant.

Calculation of sample size: Sample size was calculated with the assumption that ginger is as effective as metoclopramide as an antiemetic[4] and ondansetron is superior to metoclopramide[1] and ginger, with a minimum significant difference of 30%.

Incidence of emesis in ondansetron group[1]
(100 - 46)= 54% (q1)

Incidence of emesis in metoclopramide group[1]
(100 - 16) = 84% (q2)

alpha = 0.05 (level of significance)

beta = 0.02 (*i.e.* power of study = 80%)

effect size, d = 30

p1 = 46% p2 = 16%

q1 = 54% q2 = 84%

According to the formula given by Charles du V Florey in 1993[5],

Sample size, $n = (1.96 + 0.842)^2 (p1\ q1 + p2\ q2) / d^2$

The sample size that was calculated was, 33.39 *i.e.* 35 (approximately). Though the calculated sample size was 35, it was possible to observe 50 patients who could satisfactorily complete all the three study cycles.

RESULTS

Characteristics of the patients who completed antiemetic evaluation were as follows: Number of patients, n = 50, Gender (men:women) 11:39, Median age- 47 yr (range 24-70). (see table 2 for combination of chemotherapeutic agents)

The study shows that complete control of nausea was achieved in 62% patients with ginger, 58% with metoclopramide and 86% with ondansetron. Complete control of nausea was significantly more with ondansetron than with ginger or metoclopramide ($p < 0.01$). Complete control of vomiting was achieved in 68% patients with ginger, 64% with metoclo-pramide and 86% with ondansetron. The difference between the antiemetic effect of metoclopramide and ginger was not statistically significant but ondansetron was significantly better than both ($p < 0.01$) (Table 1).

Table 2 shows that complete control of vomiting was maximum in patients receiving low dose of cyclophosphamide in combination with cytotoxics causing mild emesis (80% with ginger, 82% with metoclopramide and 95% with ondansetron). Difference in emetic control between the three treatment groups was not statistically significant. Complete control of emesis was lowest in patients who received cyclophosphamide in combination with cytotoxics causing severe emesis (14.3% with ginger, 15% with metoclopramide and 29.5% with ondansetron). Difference in emetic control between ginger and metoclopramide was not statistically significant but ondansetron showed a significantly better emetic control than both ($p < 0.01$).

Table 1. Clinical response to antiemetics.

Response	Number of patients (%)		
	Ginger	Metoclopramide	Ondansetron
Control of Nausea			
Complete (no nausea)	31(62)	29(58)	43(86)*
Partial (mild to moderate nausea)	10(20)	10(20)	04(08)
No control (severe nausea)	09(18)	11(22)	03(06)
Control of Vomiting			
Complete (no vomiting)	34(68)	32(64)	43(86)*
Partial (1 to 2 episodes)	13(26)	17(34)	07(14)
No control (3 or more episodes)	03(06)	01(02)	00

*P<0.01 when compared with ginger and metoclopramide.

The number of episodes of vomiting in the first 12 h following chemotherapy were 10 with ginger, 9 with metoclopramide and 3 with ondansetron while the number of episodes between 12-24 h after chemotherapy were 20 with ginger, 19 with metoclopramide and 6 with ondansetron. The number of episodes of vomiting after 12 h were significantly more than those before 12 h, in all the three treatment groups ($p < 0.05$).

Three patients complained of oral ulcers during the second and third study cycles. Two patients during second and third study cycle and three patients during third study cycle complained of alopecia, while two patients complained of diarrhoea (one during first and the other during second study cycle).

DISCUSSION

The high efficacy of 5-HT_3 receptor antagonists in chemotherapy-induced nausea and vomiting

Table 2. Relationship between dose of cyclophosphamide + cytotoxic agent combination and response to antiemetics.

Combination chemotherapeutic agents	Number of patients	Percentage control of vomiting		
		Ginger	Metoclopramide	Ondansetron
Low dose* with cytotoxics** causing mild emesis	20	80	82	95
Low dose* with cytotoxics** causing severe emesis	07	14.3#	15	29.5
High dose* with cytotoxics	23	58.3#	54.1	87.5

*Dose of cyclophosphamide:
High dose (900-1000 mg) n = 23
Low dose (500-600 mg) n = 27
**Cytotoxics causing mild emesis- vincristine, methotrexate, 5-fluorouracil, Cytotoxics causing severe emesis- actinomycin D.
# $P < 0.01$ when compared to ondansetron.

suggests that 5-hydroxytryptamine is the mediator of chemotherapy induced nausea and vomiting. The present study was based on the fact that galanolactone, a component of ginger, is a competitive antagonist at 5-HT_3 receptors[2].

The antiemetic effect of ginger in chemotherapy-induced emesis was found to be comparable to that of metoclopramide but ondansetron was found to be better than both. Studies in postanaesthetic nausea and vomiting[4,6] have reported that encapsulated ginger in the dose of 1 gm and metoclopramide are equally efficacious as antiemetics. Marty *et al* compared ondansetron with high dose metoclopramide in the control of cisplatin-induced emesis and concluded that ondansetron is significantly better than metoclopramide[1]. Sharma *et al* reported that the acetone and 50% ethanolic extracts of ginger in the doses of 25, 50, 100 and 200 mg/kg orally, exhibited significant protection against cisplatin (3 mg/kg) induced emesis in dogs[7]. But both were less effective when compared to 5-HT_3 receptor antagonist, granisetron.

In this study, the number of episodes of vomiting were significantly more after 12 h of receiving chemotherapy. The higher incidence of vomiting after 12 h may be because of decrease in the effect of the antiemetics after 12 h. As regards ginger, its action is expected to last for atleast 4 h after the last dose[8].

Dose of the ginger (1 gm) was determined based on the same used in the pervious studies[4,6,8]. Second dose was given 6 h after the first dose as the action of ginger was expected to last for at least 4-6 h[8].

Although the chemical structures of some of the ingredients present in ginger have been identified, the active principle and its precise mechanism of action are not exactly known. In rats, four separate compounds isolated from ginger, including (6)- gingerol were shown to enhance gastrointestinal transport of a charcoal meal[9]. Sharma *et al* found that the acetone and 50% ethanolic extract of ginger in the doses of 100, 200 and 500 mg/kg significantly reversed cisplatin-induced delay in gastric emptying[10]. So it is likely that ginger may act by increasing gastrointestinal motility thereby reducing the feedback from the gastrointestinal tract to the central chemoreceptors. Some of the constituents of ginger, could have a possible central antiemetic effect *via* 5-HT_3 antagonism[11].

In the present study, untoward effects like alocepia, oral ulcers and diarrhoea were recorded which are known adverse effects of cytotoxic drugs. Diarrhoea was specifically reported by patients when they were given metoclopramide and it was limited to 3 or 4 episodes. Such diarrhoea is known to occur with metoclopramide. Though ginger can cause gastric distress when given in excess, none of the patients in this study complained of any such ADR.

To conclude, ginger in the dose used was found to be effective in reducing nausea and vomiting induced by low dose cyclophosphamide in combination with cytotoxics causing mild emesis. The antiemetic efficacy of ginger was found to be equal to that of

metoclopramide but ondansetron was found to be better than both. These findings justify further biochemical and pharmacological investigations to establish the efficacy of ginger as an antiemetic in chemotherapy induced emesis, as a cheaper alternative.

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POOR DIABETES CONTROL LINKED TO PREGNANCY COMPLICATIONS

Women with poorly controlled diabetes during early pregnancy run an increased risk of their baby being malformed, finds a study in BMJ. Researchers in Norwich identified 158 first pregnancies in women with type 1 diabetes. They defined adverse pregnancy outcome as spontaneous abortion, major congenital malformation (potentially life threatening or associated with serious long term disability), stillbirth, or infant death. The women were divided into two groups according to their level of blood glucose control - a group with fair control and a group with poor control.

Adverse outcome was over fourfold higher in the poor control group than the fair control group. Compared with the fair control group, the poor control group had a fourfold increase in spontaneous abortion, and a nine fold increase in major congenital malformation. Stillbirth or infant death was also higher in the poor control group, but the difference was not significant. This study confirms earlier reports of increased risk of spontaneous abortion and malformation with poor glycemic control in early pregnancy in women with type 1 diabetes, say the authors. "Our findings suggest that good glycaemic control around the time of conception is necessary to optimise outcome of pregnancy in diabetic women. Diabetic women and their carers need to be advised of the risks and encouraged to optimise glycaemic control before and during pregnancy," they conclude.

(Association between outcome of pregnancy and glycemic control in early pregnancy in type 1 diabetes: population based study-http://bmj.com/cgi/content/full/325/7375/1275)