ELSEVIER

Journal of Ethnopharmacology 57 (1997) 93–96

Journal of ETHNO-PHARMACOLOGY

Antiemetic efficacy of ginger (*Zingiber officinale*) against cisplatin-induced emesis in dogs

S.S. Sharma [a], V. Kochupillai [b], S.K. Gupta [a], S.D. Seth [a], Y.K. Gupta [a,*]

[a] *Neuropharmacology Laboratory, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi 110029, India*
[b] *Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India*

Received 28 November 1996; received in revised form 31 March 1997; accepted 20 April 1997

Abstract

Effect of ginger (*Zingiber officinale* Roscoe, Zingiberaceae) extracts (acetone, 50% ethanolic and aqueous) were investigated for antiemetic activity against emesis induced by 3 mg/kg cisplatin (the 100% emetic dose i.v.) in healthy mongrel dogs. The acetone and 50% ethanolic extract at the doses of 25, 50, 100 and 200 mg/kg p.o. exhibited significant protection while aqueous extract at these doses was ineffective against cisplatin emesis. The acetone extract was more effective than ethanolic extract. However, both were less effective when compared to 5-HT_3 receptors antagonist—granisetron. Neither of the ginger extract was effective against apomorphine-induced emesis. The findings suggest that ginger could be an effective and cheap antiemetic adjunct to cancer chemotherapy. © 1997 Elsevier Science Ireland Ltd.

Keywords: Cisplatin; Emesis; Ginger; Antiemetic; Dog

1. Introduction

Nausea and vomiting are frequent and serious side effects of cytotoxic chemotherapy in cancer patients (Lazlo and Lucas, 1981). The traditional antiemetics such as dopamine antagonists, antihistaminics, and anticholinergics have only modest efficacy against cancer chemotherapy-induced emesis, either when administered alone or in combination. The new class of antiemetic 5-HT_3 receptor antagonists, e.g. granisetron and ondansetron, are highly effective and have revolutionized the antiemetic therapy of cancer chemotherapy-induced emesis. However, they are ineffective in 10–30% of the patients (Cubeddu, 1992) and also against delayed emesis that occurs after cancer chemotherapy (Rossel et al., 1992).

Powdered rhizome of ginger has long been used in traditional medicine for alleviating the symptoms of gastrointestinal illnesses (Chopra et al.,

* Corresponding author.

PII S03 8-8741(97)00054-8

1956) and recently, it has been shown to be effective in excessive and uncontrolled vomiting occurring in first trimester of pregnancy (hyperemesis gravidarum) (Fischer-Rasmussen et al., 1990), experimentally-induced motion sickness (Stewart et al., 1991) and cyclophosphamide-induced emesis in *Suncus murinus* (an animal species of insectivore, which is considered to be closer to primates) (Yamahara et al., 1989a). It was therefore, considered worthwhile to investigate the antiemetic potential of different extracts of ginger against cisplatin-induced emesis.

2. Materials and methods

2.1. Extraction of ginger

Ginger rhizomes were procured from a local market in Delhi (winter season, temperature 4–12°C) and confirmed botanically. They were cut into pieces, dried and powdered. The powder of the ginger was extracted with acetone and 50% ethanol for 48 h. The filtered solution was concentrated until dry, under reduced pressure at 40°C. The yield of the extracts were 3.5 and 4.8%, respectively. The aqueous extract of ginger was procured as a gift from Dabur Research Foundation, Delhi, India.

2.2. Antiemetic studies

Antiemetic effects of different ginger extracts were studied in healthy mongrel dogs of either sex (8–12 kg). The animals were given ginger extracts (25–200 mg/kg, p.o.) through intragastric tube, 30 min after the administration of cisplatin emetic challenge at 3 mg/kg, i.v.; this latter dose had previously been established as 100% emetic in studies in our laboratory (Bhandari et al., 1988). The results were compared with granisetron (0.5 mg/kg, i.v., 30 min after cisplatin challenge). Ginger extracts were also studied against apomorphine-induced emesis. In this case, the dogs were treated with ginger ethanolic (200 mg/kg, p.o.) and acetone (200 mg/kg, p.o.) extracts, 60 min before the administration of 100% emetic dose of apomorphine (25 μg/kg, i.v.). The latency to first emetic episode and the number of emetic episodes were observed for 6 h in cisplatin-treated dogs, and for 2 h in apomorphine-treated animals.

2.3. Preparation of reference drugs

Ginger extracts were suspended in 1% gum accacia. Cisplatin was dissolved in normal saline at 50°C and cooled to 37°C before administration. Granisetron was dissolved in saline.

2.4. Statistical analysis

The results were analysed by Kruskall-Wallis test (Kruskall and Wallis, 1952).

3. Results

With cisplatin (3 mg/kg) alone, the mean emetic episodes were 13.7 ± 2.2 and with a mean latency of 103 ± 7 min. Post-treatment of different doses of ginger acetone extract (25, 50, 100 and 200 mg/kg, p.o.) caused significant reduction in mean number of emetic episodes (7.2 ± 0.4, 4.8 ± 1, 4.8 ± 1.4 and 1.3 ± 0.4, respectively), as compared to cisplatin control (Table 1). The emetic latency was also increased. Similar protection was exhibited by different doses of ginger ethanolic extract (Table 1). The maximum protection was observed with ginger acetone and ethanolic extract in doses of 200 mg/kg. However, reduction in emetic episodes with both ginger extracts was less than that of granisetron (Table 1). Ginger acetone extract (100 mg/kg) and granisetron (0.5 mg/kg) produced complete protection in 20% and 40% of the dogs respectively. Aqueous extract of ginger was ineffective against cisplatin challenge. These results suggest that relatively less polar substances are probably responsible for antiemetic activity. The maximum doses of various of ginger used against cisplatin-induced emesis, when tested against apomorphine-emetic challenge, failed to show any protection.

Table 1
Effect of ginger extracts on cisplatin-induced emesis

Drug treatment	Dose and route	No. of dogs tested/ vomited	No. of emetic episodes[a] Mean ± S.E.M.	Emetic latency (min) Mean ± S.E.M.
Cisplatin (control)	3 mg/kg, i.v.	6/6	13.7 ± 2.2	103 ± 7
Ginger-acetone extract	25 mg/kg, p.o.	5/5	7.2 ± 0.4[b]	125 ± 8
	50 mg/kg, p.o.	5/5	4.8 ± 1.0[b]	123 ± 5
	100 mg/kg, p.o.	5/4	4.8 ± 1.4[b]	137 ± 7[b]
	200 mg/kg, p.o.	3/3	1.3 ± 0.4[b]	35 ± 7
Ginger ethanolic extract	25 mg/kg, p.o.	5/5	6.8 ± 0.6[b]	145 ± 12[b]
	50 mg/kg, p.o.	5/5	5.0 ± 1.1[b]	153 ± 19[b]
	100 mg/kg, p.o.	5/5	4.2 ± 0.7[b]	152 ± 10[b]
	200 mg/kg, p.o.	3/3	1.0 ± 1.0[b]	61 ± 26
Granisetron	0.5 mg/kg, i.v.	5/3	0.8 ± 0.4[b]	156 ± 26[b]

[a] Though vomiting has been taken as all-or-none phenomenon, the values shown in fraction is its expression in mean (rounded to 1st place of decimal).
[b] $P < 0.05$.

4. Discussion and conclusions

The acetone and ethanolic extracts of ginger exerted a significant antiemetic effect against cisplatin-induced emesis. The acetone extract was apparently more effective than the alcoholic extract, since it provided complete protection in one out of five animals with a dose of 100 mg/kg. The failure of ginger extracts to prevent apomorphine emesis rules out the mediation at the level of dopaminergic transmission. Gingerol, a pungent constituent of ginger has been shown to inhibit 5-HT-induced contraction in guinea pig ileum (Yamahara et al., 1989b). The anti-serotonergic effect of gingerol was much greater in guinea pig ileum, which has mainly 5-HT_3-receptors unlike the rat fundus strip, where 5-HT_1-receptors predominate and the rabbit aorta strips, which contain mainly 5-HT_2-receptors (Yamahara et al., 1989b). It has been reported that acetone extract of ginger contains a diterpenoid, galanolactone, which possesses 5-HT_3-receptor antagonist activity (Huang et al., 1991). However, it is not known whether antagonism induced by galanolactone is selective or non-selective for the receptor. Recently, we have also reported that free radicals play a role in cancer chemotherapy-induced emesis as antioxidants; e.g. glutathione, tiopronin, vitamin C and vitamin E prevented cisplatin-induced emesis in dogs (Gupta and Sharma, 1996). The free radical scavenging activity of gingerol has also been reported (Krishnakantha and Lokesh, 1993; Aeschbach et al., 1994). Thus, 5-HT_3-receptor blocking action and/or free radical scavenging activity could be suggested as possible mechanisms of the antiemetic action of ginger against cisplatin-induced emesis. As a well accepted traditional medicine, ginger is worth further clinical evaluation as an antiemetic against cisplatin-induced emesis.

Acknowledgements

We acknowledge the financial support of Dabur Research Foundation, Delhi, to Dr Y.K. Gupta.

References

Aeschbach, R., Loriger, J., Scott, B.C., Murcia, A., Butler, J., Halliwell, B., Aruoma, O.I., Antioxidant actions of thymol, carvecrol, 6-gingerol, zingerone and hydroxytyrosol. Food Chemical Toxicology 32, 31–36.

Bhandari, P., Gupta, Y.K., Seth, S.D., 1988. Emetic profile of cisplatin in dogs. Asia Pacific Journal of Pharmacology 3, 131–134.

Chopra, R.N., Nayer, S.L., Chopra, I.C., 1956. Glossary of Indian Medicinal Plants. Council of Scientific and Industrial Research, New Delhi, p. 146.

Cubeddu, L.X., 1992. Mechanism of cancer chemotherapeutic agents. Seminar in Oncology 19, 2.

Fischer-Rasmussen, W., Kjaer, S.K., Dahl, C., Asping, U., 1990. Ginger treatment of hyperemesis gravidarum. European Journal of Obstetrics and Gynaecology and Reproductive Biology 38, 19–24.

Gupta, Y.K., Sharma, S.S., 1996. Antiemetic activity of antioxidants against cisplatin induced emesis in dogs. Environmental Toxicology and Pharmacology 1, 179–184.

Huang, Q., Iwamoto, M., Aoki, S., Tanaka, N., 1991. Anti-5-hydroxytryptamine, effect of Galanolactone, diterpenoid isolated from ginger. Chemical Pharmaceutical Bulletin 39, 397–399.

Krishnakantha, T.P., Lokesh, B.R., 1993. Scavenging of superoxide anions by spice principles. Indian Journal of Biochemistry and Biophysics 30, 133–134.

Kruskall, W.H., Wallis, W.A., 1952. Use of ranks in one certain variance analysis. Journal American Statistical Association 47, 562–583.

Lazlo, J., Lucas, V., 1981. Emesis as a critical problem in chemotherapy. New England Journal of Medicine 305, 948–953.

Rossel, R., Moreno, I., Abed, A., 1992. Delayed emesis after cisplatin treatment: incidence, source and management. In: Diaz Rubio, E., Martin, M. (Eds), Antiemetic Therapy: Current Status and Future Prospects. Creaciones Elba, SA, Madrid, Spain, p. 202.

Stewart, J.J., Wood, M.J., Wood, C.D., Mims, M.E., 1991. Effect of ginger on motion sickness susceptibility and gastric function. Pharmacology 42, 111–120.

Yamahara, J., Rong, H.Q., Naitoh, Y., Kitani, T., Fujimura, H., 1989a. Inhibition of cytotoxic drug induced vomiting in *Suncus murinus* by a ginger constituent. Journal of Ethnopharmacology 27, 353–355.

Yamahara, J., Rong, H.Q., Iwamoto, M., 1989b. Active component ginger exhibiting antiserotonergic action. Phytotherapy Research 3, 70–71.