CHAPTER 2

REVIEW OF RELATED LITERATURE

There were many studies reported various anti-emetic intervention. Most of them focused on PONV after general anesthesia. Droperidol, a dopamine receptor antagonist, is an anti-emetic even when small doses are used(18, 19). In one systemic review, doses as low as 0.3 mg IV showed anti-nausea efficacy (NNT about 5), and higher doses were no more effective(19). The anti-vomiting effect was less pronounced, and showed some evidence of dose responsiveness. There was evidence of unnecessary dose-dependent sedation(19). Metoclopramide, a dopamine and serotonin receptor antagonist, although used in clinical practice for almost 40 years, was reported that it had no clinically relevant anti-emetic effect in the prevention of PONV(20). Ondansetron , a 5- HT_3 receptor antagonist, is effective in treatment of PONV. The anti-vomiting effect was shown to be consistently more pronounced than anti-nausea effect(21, 22). In systematic review, ondansetron did not show benefit in prevention of PONV unless the risk of PONV was high(21). Three percent of treated patients will have elevated liver enzymes, and three will have a headache who would not have had these adverse effects without the drug (21).

The severity of nausea can be categorized into four degrees using the standardized scoring algorithm that has been used in previous trials(23, 24); no nausea, mild nausea, moderate nausea , and severe nausea.

Ginger, *Zingiber offinale* Roscoe (Zingiberaceae), is classified as a perennial plant, and its rhizome is consumed. In1999, the World Health Organization (WHO) reported the characteristics and the medicinal uses of ginger preparations to treat vomiting which is supported by clinical data(25) .

Major chemical constituents

The rhizome contains 1–4% essential oil and an oleoresin. The composition of the essential oil varies as a function of geographical origin, but the chief constituent sesquiterpene hydrocarbons (responsible for the aroma) seem to remain constant. These compounds include (-)-zingiberene, (+)-*ar*-curcumene, (-)-β-sesquiphellandrene, and β-bisabolene. Monoterpene aldehydes and alcohols are also present. The constituents responsible for the pungent taste of the drug and possibly part of its anti-emetic properties have been identified as 1- (3'-methoxy-4'-hydroxyphenyl)-5-hydroxyalkan-3-ones, known as [3–6]-, [8]-,[10]-, and [12]-gingerols (having aside-chain with 7–10, 12, 14, or 16 carbon atoms, respectively) and their corresponding dehydration products, which are known as shogaols (1,4,6,14,19). Representative structures of zingiberene, gingerols and shogaols are presented below.

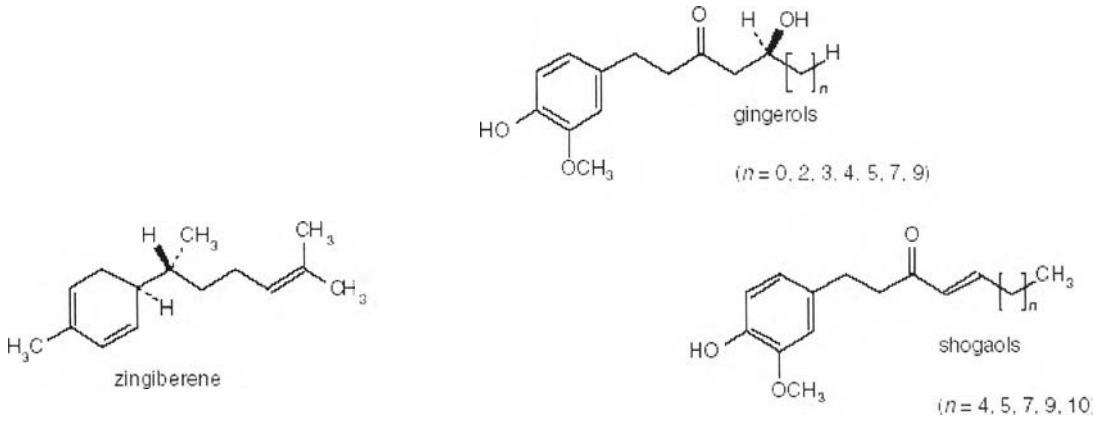

Figure 2 Structures of zingiberene, gingerols and shogaols

Chemical assays

-Contains not less than 2% v/w of volatile oil(26), as determined by the method described in WHO guidelines(27).

-Qualitative analysis by thin-layer chromatography (26)

-Qualitative and quantitative gas chromatography and high performance liquid chromatography analyses of ginger oils for gingerols, shogaols, α-zingiberene, β-bisabolene, β-sesquiphellandrene, and *ar*-curcumene (28).

Dosage forms

The preparations are dried root powder, extract, tablets and tincture (29, 30). Powdered ginger should be stored in well-closed containers (not plastic) which prevent access of moisture. Store protected from light in a cool, dry place (31, 32). There is a dearth of information to determine the onset and duration of any pharmacological action. The dose for PONV prophylaxis in previous study is 0.5-1.0 g daily at one hour before anesthesia(24, 33).

Medicinal uses

Uses supported by clinical data

The prophylaxis of nausea and vomiting associated with motion sickness (7, 13, 34, 35), postoperative nausea (24), pernicious vomiting in pregnancy (11), and seasickness (10, 36).

Uses described in pharmacopoeias and in traditional systems of medicine

The treatment of dyspepsia, flatulence, colic, vomiting, diarrhea, spasms, and other stomach complaints (7, 26, 29, 31). Powdered ginger is further employed in the treatment of colds and flu, to stimulate the appetite, as a narcotic antagonist (7, 26, 29, 31, 37-39), and as an anti-inflammatory agent in the treatment of migraine headache and rheumatic and muscular disorders (38-40).

Uses described in folk medicine, not supported by experimental or clinical data

The ginger is used to treat cataracts, toothache, insomnia, baldness, and hemorrhoids, and to increase longevity (39, 41).

Physiological effects

Experimental pharmacology

The anti-nausea and anti-emetic action of ginger may be on CNS and direct gastrointestinal tract(15). The aromatic, spasmolytic carminative and absorbent properties of ginger suggest that it has direct effects on the gastrointestinal tract(42). The anti-emetic action of ginger has been attributed to the combined action of gingerols, zingerones and shogaols (38). The pharmacological effects of ginger rhizome extracts on the contractile responses to serotonin (5-HT) in isolated guinea pig ileum were examined(16). The acetone extract of ginger was found to possess an anti-serotoninergic effect. The extract was further fractionated by column chromatography and results showed that [6]-, [8]- and [10]-gingerol were the active components exhibiting anti-5-HT_3 action(16). Moreover, [6]-gingerol showed a central effect and led frogs to stop moving and not to vomit(43). The inhibitory action of ginger against motion sickness has been found to be caused by its action on the CNS and/or gastrointestinal system(13, 14).

Clinical pharmacology

Clinical studies have demonstrated that oral administration of powdered ginger root (940 mg) was more effective than dimenhydrinate (100 mg) in preventing the gastrointestinal symptoms of kinetosis (motion sickness)(13). In clinical double-blind randomized studies, the effect of powdered ginger root was tested as a prophylactic treatment for seasickness (10, 36). The results of one study demonstrated that orally administered ginger was statistically better than a placebo in decreasing the incidence of vomiting and cold sweating 4 hours after ingestion(10). The other investigation compared the effects of seven over-the-counter and prescription anti-emetic drugs on prevention of seasickness in 1489 subjects. This study concluded that ginger was as effective as the other anti-emetic drugs tested (36). At least eight clinical studies have assessed the effects of ginger root on the symptoms of motion sickness. Four of these investigations showed that orally administered ginger root was effective for

prophylactic therapy of nausea and vomiting. The other three studies showed that ginger was no more effective than a placebo in treating motion sickness(35, 44, 45). The conflicting results appear to be a function of the focus of these studies. Clinical studies that focused on the gastrointestinal reactions involved in motion sickness recorded better responses than those studies that concentrated primarily on responses involving the central nervous system. The hypothesis that an increase in gastric emptying may be involved in the anti-emetic effects of ginger has recently come under scrutiny. Two clinical studies demonstrated that oral doses of ginger did not affect the gastric emptying rate, as measured by sequential gastric scintigraphy (46) or the paracetamol absorption technique (47). In a double-blind, randomized, cross-over trial, oral administration of powdered ginger effectively treated pernicious vomiting in pregnancy (11). Both the degree of nausea and the number of vomiting attacks were significantly reduced (11).

Ginger has been formally evaluated for the prevention and treatment of PONV in four randomized double-blind trials. Bones and colleagues(24) studies 60 women before major gynecological operations. Patients were allocated randomly to received either ginger 1 g, metoclopramide 10 mg, or placebo as a single dose given with preoperative medication. The severity of PONV was assessed on a four-point scale. Ginger was superior to placebo in preventing PONV and reducing the need for extra anti-emetic. Phillips, Hutchinson and Ruggier(33) randomized 120 woman before laparoscopic surgery to one of three similar treatment groups (40 women each). The incidence of nausea and vomiting was higher in the placebo group than metoclopramide or ginger treated groups. In contrast, in a study of three groups, 108 women (36 women each), randomly allocated to receive ginger 0.5 g, ginger 1.0 g, or placebo before laparoscopic surgery(48). The incidence of nausea and vomiting was monitored 3 hours after operation. There was no significant difference between groups. Yet, the incidence of PONV was assessed only 3 hours after surgery. Most recently, a randomized controlled trial compared 4 groups of ginger alone, placebo,

droperidol alone or droperidol plus ginger in 120 patients (30 patients each) undergoing gynecological laparoscopy-(23). No significant difference was seen between any groups. However, it might be due to the low power (power = 0.647) and too small sample size. There was no report of adverse reaction to ginger compare with placebo in any of the above studies.

Other biological actions

In animal studies, ginger juice has been found to produce antihistamine effect(15). More recently, the action of [6]-shagaol on substance P-containing primary afferents of rats has also been suspected to be responsible for the analgesic effect of ginger. However, this effect in human has not been reported(15).

Effect on platelet function

Effect of ginger on human platelet function has been reported. Dorso in 1980 reported one patient with impaired platelet function after ingestion of large amount of fresh ginger(49). In 1989, Srivastava measured serum Thromboxane B_2 in clotting blood before and after consumption of 5 g of raw fresh ginger. Mean levels of Thromboxane B_2 decreased from 782 to 498 pmol/ml following the ginger, but were not statistically significant due to large scatter of results(50). However, a randomized , double-blind study of the effects of dried ginger (2g daily , orally for 14 days) on platelet function showed no differences in platelet activity, including bleeding time, platelet count, thromboelastography, whole blood platelet aggregometry, in patients received ginger or a placebo(51). It is concluded that the effect of ginger on thromboxane synthetase activity is dose dependent (more than 12-14 g) , or only occurs with fresh ginger ,and that up to 2 g of dried ginger is unlikely to cause platelet dysfunction when used therapeutically(51).

Contraindications

No information available.

Toxicity

Ginger has been recognized by the US Food and Drug Administration (FDA) and is listed as a food additive that is " Generally Recognized as Safe"(GRAS) and a "natural flavor additive" The British Herbal Compendium documents no adverse effect of ginger(52).

In summary, ginger may be an effective and safe anti-emetic for PONV prophylaxis. Therefore, this study aims to evaluate the efficacy of ginger in prevention of PONV after intrathecal morphine .