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The essential oil of ginger, *Zingiber officinale*, and anaesthesia

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KEYWORDS

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Summary It is proposed that a 5% solution of essential oil of ginger, *Zingiber officinale*, is an effective post-operative nausea and vomiting (PONV) prevention when administered preoperatively, naso-cutaneously concurrently with conventional therapies to general anaesthesia patients at high risk for PONV. This is a summary of six months clinical experience and impressions of a single anaesthesia practitioner using best practice multimodal management plus 5% oil of ginger, *Zingiber officinale*, in the prevention of PONV in high risk group adult patients.

The results of the clinical experience show improvement gained in patient response as measured by lower incidence of nausea and vomiting in the post-anaesthesia recovery unit (PACU). The group treated with the essential oil of ginger experienced approximately less than 20% nausea in the PACU. This low percentage of high risk PONV patients that experienced nausea in the ginger group mostly required only one single intravenous supplemental medication to control nausea. Approximately, 80% of high risk patients had no complaint of PONV and therefore did not require any further intravenous therapy during recovery from anaesthesia through discharge from PACU. The non-ginger oil treated patients in this clinical experience had a roughly 50/50 chance of PONV.

A 5% solution of the essential oil of *Zingiber officinale* in grape seed carrier oil, when applied naso-cutaneously, can be administered safely for the effective prevention and therapeutic management of nausea in general anaesthesia patients at high risk for post-operative nausea and vomiting, with increased patient satisfaction and less expense to patients and hospital. Guidelines and regulations established for the safe use of integrative therapy with an essential oil are critical to observe.

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Introduction

Smell is a learned process shaped by language and experience (Stevenson and Boakes, 2003) and genetics (Buck, 1992). The medical science of

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nausea is complexly interwoven with coexisting disease states. Safe practical choices in essential oil therapy can be extrapolated from evidenced based clinical references, which may be integrated into the medical management of various conditions. Specifically, the naso-cutaneous application of essential oil of ginger, *Zingiber officinale*, can be a safe and effective addition to the medical management for the prevention and treatment of the complications of nausea and vomiting associated with general anaesthesia.

The 2004 Nobel Prize in physiology or medicine has been awarded to Richard Axel and Linda Buck for their discoveries of odorant receptors and the genetic organization of the olfactory system (Nobelprize.org, 2004). Previously numerous similar theories for odorant detection systems and mechanisms of actions of anaesthesia have been proposed. These similar theories are the spectral recognition of vibrational molecules (Turin, 1996), metallo-protein "shuttlecock" mechanism (Wang et al., 2003), mnemonic perception (Stevenson and Boakes, 2003), agonist-antagonist receptor binding (Firestein, 2004), cell membrane molecular configuration stress (Cantor, 2001), and cyclic nucleotide ligand-gated ion channels (Yamakura et al., 2001). Our understanding of the odorant detection system is evolving. The mechanism of action of the chemical constituents of ginger oil at the level of cellular biosynthesis shows that ginger extracts block activation of proinflammatory mediators and its transcriptional regulator in human synoviocyte cultures (Fronzoza et al., 2004). The mechanism of action of the chemical constituents of scents at the cellular level may involve intranuclear protein synthesis from DNA.

The uptake and distribution mechanism of anaesthetics is known (Eger, 1998). A predominantly accepted theory ascribed to the action of anaesthetics, namely "molecular membrane stress" applied to the bilipid layer of cell membranes (Ueda, 2001), might conceivably be applied to explain some of the actions of essential oils at the cellular level. Many essential oils and many anaesthetic molecules are aliphatic hydrocarbon chains. The natural plasticity of the bilipid layers of cell walls and organelles of various body tissues is due in part to the orientation of the hydrophilic and hydrophobic lipid layers. The cell membranes have abundant embedded protein receptors and ionic channels, which are thought to be acted upon by the various volatile chemicals of the anaesthetic gas agents. Perhaps the chemical constituents of the vapours from essential oils as well as the absorbed chemical constituents act directly as chemical messengers on the cell membranes and other cellular compo-

nents. The second messenger neurotransmitter, cyclic adenosine monophosphate (c-AMP), working with olfactory G protein and ionic calcium modulate an excitatory synapse at the olfactory bulb mediating γ -aminobutyric acid (GABA) and *N*-methyl-D-aspartate (NMDA) receptors (Chen et al., 2000). GABA is a receptor system for sedation. NMDA is a receptor system for pain.

After an essential oil is applied to the skin a blood level is achieved. The following example is given for *Lavandula angustifolia*. A 2.0% dilution of *L. angustifolia* oil applied to the abdomen of a volunteer showed that approximately 10% of the Lavender oil was absorbed into the general blood circulation. Then plasma levels peaked 20 min after application as circulation via capillaries to tissue continued. After 90 min, both linalool and linalyl acetate had dropped almost to zero, illustrating almost complete metabolism (Jäger, 1992). Renal and hepatic mechanisms probably metabolize the majority of an average essential oil treatment dose.

Similar kinetics could apply to transnasal inhalational absorption. There is potentially more rapid absorption across the highly vascular cribriform plate in the nose, which is a direct transdural pathway to the brain. This complex cellular vasculo-lymphatic plexus, associated with abundant glomerulo-mitral apparatus in the olfactory bulb, cross the blood-brain barrier to perfuse brain tissue. The kinetics of an anaesthetic agent is similar in that the volatilized gas is absorbed across the basement membranes of the lungs. The anaesthetic chemicals cross into the bloodstream and rapidly circulate to vascular rich organs first, such as brain, liver, lungs, heart, kidney and muscles. Then, by mass action, as concentration effect increases over time, less vascular rich organs such as bowels, epidermis, bones and fat gain in tissue anaesthetic content.

Therapy with essential oils is somewhat like general anaesthesia in that volatile anaesthetic vapour is delivered diluted in the carrier gases oxygen and or nitrous oxide via a breathing circuit. In the field of essential oil therapy, 100% pure volatile essential oils from select plant parts are diluted with various carrier oils for delivery by numerous methods in concentrations, usually ranging from 1% to 5%. The concentration chosen depends on the clinical circumstances, which is similar to administration of anaesthesia vapour. The uptake and distribution of the chemical constituents of essential oils are transmitted via chemical messengers directly into the brain and brain stem via complex neuronal and circulatory pathways when inhaled.

The science of nausea

The first cranial nerves, CN I (the olfactory nerves), are embedded into the base of the frontal lobes of the brain. Early human clinical treatment series using surgically implanted glial support cell cultures of olfactory ensheathing cells, OEC, of the olfactory nerves are shown to aid regeneration spinal nerve function (Huang et al., 2003). There appears to be right nasal to right hemisphere dominance of unfamiliar odour recognition. Familiar odours are recognized symmetrically, when language is involved (Savic and Berglund, 2000). The sensory cells for odours have receptor binding sites which have unique properties for odorant chemical recognition and information mediation. In the olfactory bulb, olfactory receptor cells recognize, convert and transmit chemical odorant generated information into chemical messengers across glomerulo-mitral pathways by G-protein activation. These chemical messages are transmitted as chemical data along aroma mediated pathways to various areas of the brain, such as the amygdala, hippocampus and thalamus. The stress of surgery activates the amygdala and learning occurs during general anaesthesia (Gidron et al., 2002; Andrade, 1995).

The cranial nerves of the oropharynx, Facial, CN VII, Glossopharyngeal, CN IX and Vagus, CN X, located at the base of the tongue and back of the throat have taste receptors that transmit chemically translated data to the medulla in the brainstem. Located next to the medulla is the chemotactic trigger zone, CTZ, which mediate nausea and vomiting. These receptors are located bilaterally and lateral to the fourth ventricle in the area postrema. These receptors for nausea and vomiting respond to vagal and sympathetic afferents, as well as blood-borne toxins. The most commonly used volatile anaesthetic, Sevoflurane, is ether-based. Ether is known as a highly emetic anaesthetic vapour agent.

Intravenous medications work on specific pathways and receptors for nausea prevention and treatment. These various classes of medications administered in combination therapy are established as the foundation of effective multimodal therapy for prevention and treatment of nausea and vomiting of various origins (Scuderi et al., 2000). Some causes of nausea and vomiting respond better to different drug choices to manage specific nausea receptors (Bone et al., 1990). The routine prophylactic use of antiemetics decreases the incidence of PONV (Gupta et al., 2003). Escalating multimodal therapy for PONV is generally accepted

as effective, evidence based, best practice with known PONV failure rates (Habib and Gan, 2004; Apfel et al., 2004).

The powdered root of ginger is as effective as metaclopramide in the prevention of PONV in certain settings (Ernst and Pittler, 2000). Ginger juice produces anti-motion sickness action possibly by central and peripheral anticholinergic and has antihistaminic effects (Qian and Liu, 1992). Ginger syrup decreased duration and severity of nausea in pregnancy (Keating and Chez, 2002). Powdered ginger root was shown to be as effective as Vitamin B6 in reducing the symptoms of nausea vomiting and dry retching of pregnancy. No untoward tetraoxygenic effects were shown (Portnoi et al., 2003; Smith et al., 2004). Powdered ginger root has shown negative results for effective prevention of PONV post-laparoscopy (Eberhart et al., 2003). There appears to be a difference between the potency of ginger preparations and the degree of the effects they mediate when comparing the various preparations administered orally, such as ginger juice, ginger powdered root and syrup of ginger. To date no studies have examined the efficacy of ginger essential oil, *Zingiber officinale*, administered naso-cutaneously for prevention of nausea and vomiting in conjunction with surgery and general anaesthesia.

Chemistry receptor applications

Receptor chemistry is a challenging field of study because every system has system specific receptor sites serving as information conversion stations. There are two commonly known receptors of the vomiting centre in the brainstem located in the reticular formation of the medulla. The well-known muscarinic receptors are mediated by acetylcholine. Histamine receptors are blocked by H1 antagonists and H2 antagonists. The chemoreceptor trigger zone (CTZ) has receptor sites for benzodiazepines, histamine and dopamine. D3 dopaminergic receptors are blocked by dopamine antagonists. The therapeutic successes of the expensive intravenous medications, the 5-HT₃ serotonin receptor antagonists, work slowly but degrade quickly, having half-lives on the order of 2–3 h. This peripherally acting class works indirectly via the vagus nerve to block receptor sites to circulating serotonin at end-organs.

Ginger exhibits 5HT₃ receptor antagonism which effectively antagonizes serotonin at 5-HT₃ receptors. This effect is mediated by galanolactone,

a diterpenoid isolated from ginger (Huang et al., 1991). Ginger essential oil appears to mediate its warming effects by decreasing body serotonin (Huang et al., 1990). The shogaols and 6-, 8-, and 10-gingerols, isolated from the methanolic extract of *Zingiber officinale* rhizome, exhibit anti-emetic principles (Kawai et al., 1994). The capsaicin-like effect of 6-shogaol is possibly the analgesic substance found in ginger that inhibits the release of the neuropeptide, substance P (Onogi et al., 1992). Ginger essential oil is thought to be analgesic as well as anxiolytic (Vishwakarma et al., 2002), whilst ginger powder taken orally decreased osteoarthritis symptomatology (Altman and Marcussen, 2001).

Side effect profiles of antiemetics

There are numerous potentially serious adverse drug reactions attributed to the various classes of antiemetic medications. These adverse drug reactions range from mild confusion, dysphoria, headache, phlebitis, tics, torticollis, serotonin syndrome, neuroleptic malignant syndrome, and α -blockade alterations in blood pressure to potential life threatening cardiac rhythm disturbances. Droperidol has recently been subjected to a "Black Box" warning by the FDA (Habib and Gan, 2003). This controversial warning describes the rationale for patients to have a normal QT interval documented by ECG prior to intravenous administration of droperidol. The risk of the malignant ventricular dysrhythmia called Torsades de Pointes associated with droperidol is also known to occur with several of the new selective blocking agents of the serotonin 5-HT₃ receptor antagonists. The chemical restraint, haloperidol is a useful antiemetic, without significant side effects when given intravenously at very low dose (Buttner et al., 2004). Perhaps ginger essential oil could be considered an alternative for droperidol, even though one investigation failed to show benefit when compared with powdered ginger root (Visalyaputra et al., 1998).

Ginger is a food product which is both safe and non-toxic, although sensitization could pose a potential problem. IgE allergy and food spice allergy had negative prick-test results for sensitization to ginger (Moneret-Vautrin et al., 2002). Mild gastrointestinal burning and sedation appears to be the only side effect of several grams orally ingested per day (Sripramote and Lekhyananda, 2003). The essential oil of ginger can be safely and directly administered to the emetic centres of the brain in the chemoreceptor trigger zone via the olfactory pathways and skin absorption, naso-cutaneously.

The nasal route of administration is utilized successfully for many FDA approved medications, especially those related to the treatment of allergic and vasomotor rhinitis.

Ginger had been thought to adversely affect platelet aggregation. Ginger had been thought to adversely affect platelet aggregation. Ginger's platelet inhibition is like that of aspirin and the anticoagulation effect of warfarin is potentiated by acetaminophen (Lesho et al., 2004). It is notable that only two reported cases of bleeding in humans have been associated with the combined anticoagulation effect of warfarin with acetaminophen while dieting on ginger herbal powder tea and eating pieces of ginger root (Lesho et al., 2004; Kruth et al., 2004). Previous studies show that eating large oral doses of ginger powder or raw ginger root do change thromboxane concentration, which is reversible (Guh et al., 1995) but do not adversely affect the clotting ability of platelets as measured with clinical laboratory data (Lamb, 1994; Janssen et al., 1996). Preanaesthesia check lists name "ginger" for possibly associated bleeding problems (Hodges and Kam, 2002). This consideration possibly should be modified to include safe applications for the use of ginger.

Materials

The essential oil of ginger, *Zingiber officinale*, was obtained from lot number 4702 dated August 3, 2002 by The Fragrant Earth. A 5% solution of the essential oil was mixed in grape seed oil and placed in a rollerball applicator. The essential oil used in this clinical application costs a few cents per patient.

Medical management of PONV: procedure and method

Informed consent was obtained prior to surgery for general anaesthesia. As specific consent for the use of ginger essential oil was also obtained, it was positively suggested that smelling ginger essential oil could possibly assist in the prevention of PONV (Laurion and Fetzer, 2003). Patients resulted from daily case work of one clinical practitioner at one facility, adding ginger essential oil to the MD anaesthesia management of PONV. The essential oil of ginger solution was applied to both wrists during preoperative anaesthesia evaluation immediately prior to surgery.

The rollerball applicator method was utilized for application of 5% ginger essential oil to the volar aspects of both wrists at the P6 NEI-KUAN acupressure points (Wang and Kain, 2002). The volume of oil applied covered approximately a 4×4 cm² area, using slight pressure at the P6 sites bilaterally, with the suggestion for the patient to smell those sites ad lib prior to induction of general anaesthesia.

The clinical experience presented here is with patients at high risk for PONV, during a six month period using similar combinations of intravenous multimodal therapy to prevent PONV. The initial three month period consisted of similar combinations of intravenous multimodal therapy alone. During the following three months, similar combinations of intravenous multimodal therapy plus 5% essential oil of ginger were given in combination. All cases were high risk for PONV; defined as either having significant history of prior PONV and/or they were subject to a surgical intervention that predisposed them to PONV. The surgeries chosen were open gynaecological surgeries, upper and lower abdominal laparoscopic procedures and operations requiring high dose intravenous narcotic management of major post-surgical pain, as seen in spine fusion or total joint replacement. Patients were excluded if there was lack of time, interest, known ginger sensitivity, surgical or personnel considerations. Possible congenital, acquired, or iatrogenic coagulation disorders, including preoperative thrombo-embolic prophylaxis were also excluded.

Patients were prescribed multimodal antiemetic intravenous medication regimens including similar intravenous drug combinations of the selective blocking agent of the serotonin 5-HT₃ receptor class, H₁ and H₂ blockers, metaclopamide and dexamethazone. Oxygen was provided for all patients in PACU continuously for SpO₂ less than 94%. Upon awakening in PACU, the patient responded to questioning by a PACU nurse pertaining to nausea and pain and medicated as needed. Response to questioning determined any patient that received an antiemetic in the PACU, as a 'ginger failure'.

Clinical impressions

Prevention of post-op nausea using prophylactic multimodal intravenous medication therapy plus essential oil of ginger was effective over 80% of the time, as measured by no complaint of nausea during the PACU recovery period. The nausea failure rate in the ginger treated group was less than 20%. In a similar group of patients prophylactically treated with multimodal intravenous therapy with-

out ginger essential oil there was almost no difference in the nausea/no nausea in PACU outcome, which was approximately 50/50.

There have been no ill-effects such as gastric burning or sensitization reported in any patients utilizing these methods when administered prior to the induction of general anaesthesia. In this situation, in which sometimes as many as 5–15 different medicines are given intravenously during the course of the anaesthetic and surgery, no known adverse reactions or bleeding due to essential oil of ginger occurred.

Limitations and considerations for future investigations

The following enumerates the problems with the realization of this clinical treatment series. Risk factors mentioned in studies that influence a meaningful clinical investigation included control for multiple variables such as age, gender and non-smoking history (Apfel and Roewer, 2003). More challenging control group considerations possibly could include; nasal dominance, blood pressure, dependent or non-dependent learned states, alternations in sense of smell due to medications and coexisting diseases states, as well as prior ginger experience.

The specific NSAID cyclooxygenase (Cox-2) receptor of anti-inflammatory pain management strategy has been called in question as shown by the FDA issued public health advisory recommending limited use of Cox-2 inhibitors and the voluntary recall of rofecoxib, Vioxx (www.FDA.GOV). These problems arise from the unbalanced critical relationship of the dual actions of Cox and 5-lipoxygenase (5-Lox) receptor inhibition on the arachidonic acid and leukotriene enzymatic pathways combined with the altered induction of receptors for certain broad spectrum protective mechanisms (Fiorucci et al., 2001). Initially known Cox/5-Lox benefits were cardiovascular (stroke/heart attack) gastrointestinal (bleeding/PONV), pulmonary (bronchoconstrictive), and prevention of neurodegeneration (Bertolini et al., 2002). Specifically, the chemical constituent, [8]-paradol, in ginger oil is fibrinolytically active, increasing the Cox-1 inhibitory anti-platelet aggregation activity as strongly as aspirin (Tjendraputra, 2003). The anti-inflammatory action of [8]-shogaol of ginger oil at Cox-2 blocks pro-inflammatory enzymatic biosynthetic pathways of the undesirable prostaglandin-2 (Tjendraputra et al., 2001). The curcuminoid oils of the Zingiberaceae family

chemically mediate the dual action of Cox/5-Lox inhibitors (Chainani-Wu, 2003) while providing anticarcinogenic actions as well as anti-inflammatory mediated pain control (Hong et al., 2004).

These more challenging variables are potentially significant and relatively difficult and are perhaps unquantifiable control variables for most investigational purposes. This review of clinical practice is presented with respect for the investigational review board protocols and thus patient privacy and safety. These considerations should be a primary concern in the care provided by aromatherapy practitioners (Myles and Tan, 2003). Standardized extracts of phytopharmaceutical preparations are available and have been utilized for specific investigations of the various effects of the chemical constituents of ginger (Bonati, 1991).

Increasing numbers of adults are using complementary and alternative medicine (CAM) to improve their health. Some patients and surgeries may not be suited to receive essential oils. Ginger is considered a CAM therapy for migraine headaches (Mustafa and Srivastava, 1990). Perhaps the serotonin mediated vasodilating properties of ginger are propagated via nasal inhalation. Cutaneous application of ginger oil, perioperatively, might contribute in the maintenance of critical body temperature during surgery. Other properties of the various chemical constituents of ginger are recognized such as the anti-tumour promoting effects of 6-gingerol and 6-paradol and the antimicrobial effects of the monoterpenes 1,8-cineole, β -pinene and α -terpineol found in ginger essential oil (Surh et al., 1999; Martins et al., 2001).

Closed circuit anaesthesia utilizes injection of the unit dose of the liquid volatile anaesthetic agent, according to patient weight and square root of time interval, directly into the anaesthesia circuit to induce and maintain general anaesthesia (da Silva et al., 1997). Pulmonary vascular vasodilatation can be accomplished for the management of pulmonary hypertension with inhaled nebulized nitroglycerin, directly into the anaesthesia circuit via the endotracheal tube (Yurtseven et al., 2003). One referenced letter portrays a general anaesthesia study approved by the Ethics Research Committee utilizing sweet orange essential oil. Children assessed themselves as more relaxed and cooperative at induction of anaesthesia for dental surgery. Four drops of sweet orange essential oil were applied into a filter of the anaesthesia circuit. This application was utilized to promote acceptance of the Sevoflurane vapour gas mask induction of anaesthesia and then removed for surgery to proceed in 60 children (Mehta, 1998). Several advantages were noted and it was concluded that it was safe and recommended

to use it more. There is a lack of study data examining the differences between oropharyngeal uptake and distribution of vapour agents versus direct pulmonary uptake and distribution. Exogenous lipoid pneumonia should be prevented by safe inhalational applications of essential oil therapies that have yet to be established (Spickard and Hirschmann, 1994). Other methods of application of oil products could be considered, such as continuous naso-inhalation from a medicated nasal adhesive strip.

Different essential oils might have been used to evaluate the prevention and treatment of PONV, such as essential oil of peppermint (Anderson and Gross, 2004). There is evidence of medical literature pertaining to the effective use of essential oil of peppermint therapy in this field of PONV (Tate, 1997). Peppermint has possible toxicity issues regarding G6PD deficiency (Olowe and Ransome-Kuti, 1980). No other phytopharmaceutical preparations have data as pertains to safety and efficacy in association with general anaesthesia in the medical literature to the same extent to compare to as the studies with the various preparations of ginger.

Conclusions

Integrating prophylactic intravenous multimodal therapy with the essential oil of *Zingiber officinale* therapy in acute care and ambulatory settings to prevent the general anaesthesia complication of post-operative nausea and vomiting significantly increases successful outcomes, resulting in increased patient satisfaction. This clinical experience with various limitations is presented as having generated meaningful information, indicating that a 5% solution oil of ginger essential oil to be a safe and effective choice for the prevention of PONV. A previous multimodal antiemetic study indicated that choice of intravenous medication prophylaxis offered little impact on clinical outcome or in patient satisfaction (Darkow et al., 2001). The resulting clinical impression in this setting implies increased patient satisfaction and outcomes warrants further evaluation as well as consideration for change in the anaesthetic perioperative assessment and management of PONV. These findings are similar to a previous study demonstrating the need for less intravenous anti-nausea medications during the recovery period in those patients that received ginger powder (Phillips et al., 1993). Reducing the incidence of PONV by approximately 30%, if reproducible, is noteworthy. Perhaps other patients having less risk factors for PONV would benefit from application of ginger essential oil alone. Ginger

essential oil might effectively treat the three major components of PONV surrounding surgical interventions related to general anaesthetic agents, narcotics and motion sickness.

These improved results over previous clinical investigations using powered ginger root taken as an oral premedication (Eberhart et al., 2003; Morin et al., 2004) are possibly due to the following combined effects. This therapeutic success may be attributed to the learned smell associated with ginger aromatherapy utilizing suggestion imagery perioperatively, the increased potency of the essential oil of ginger as compared to other preparations, as well as the method of application, the combined naso-cutaneous administration of the essential oil of ginger.

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