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The effect of electroacupuncture as an adjunct on cyclophosphamide-induced emesis in ferrets

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Abstract

The effect of electroacupuncture (EA) on cyclophosphamide-induced emesis in ferrets was studied at acupuncture point Neiguan (P6) with various electrical stimulation parameters (5–100 Hz, 1.5–3 V, 5–20 min, $n=6$/group). The combination therapy of EA (100 Hz, 1.5 V and 10 min) with the lower doses of ondansetron (0.04 mg/kg), droperidol (0.25 mg/kg) and metoclopramide (2.24 mg/kg) significantly reduced the total number of emetic episodes by 52%, 36% and 73%, respectively, as well as the number of emetic episodes in the first phase as compared to the sham acupuncture control ($P<.01$). These EA/drug combinations also showed a significant effect in preventing emesis as compared to either EA or drug alone ($P<.05$). The present study suggests that acupuncture may be useful as an adjunctive therapy in the treatment of chemotherapy-induced emesis.

Keywords: Electroacupuncture; Antiemetics; Cyclophosphamide; Ferret; Emesis; Adjunct; Ondansetron; Droperidol; Metoclopramide

1. Introduction

Nausea and vomiting (N/V) are common incidents among patients who are treated with cancer chemotherapy regimens that include cyclophosphamide (Bosnjak et al., 2000; Coates et al., 1983; Vermeulen et al., 2000). Cyclophosphamide is a commonly used agent in chemotherapy for breast cancer as well as other cancers, and it produces emesis in a ferret model (Andrews et al., 1988; Hawthorn et al., 1988). Cyclophosphamide may induce emesis through the release of serotonin to stimulate the 5-HT_3 receptor in the gastrointestinal tract and the chemoreceptor trigger zone (Fraschini et al., 1991; Hawthorn et al., 1988). Antiemetic drugs do not completely block N/V and often add to the unpleasant effects of the treatment (Cubeddu et al., 1990b; D'Olimpia et al., 1985; Roscoe et al., 2000). The 5-HT_3 antagonists, such as ondansetron, have been shown to be extremely effective antiemetics for cyclophosphamide-induced emesis in the ferret model (Andrews et al., 1988) and in humans (Clavel et al., 1993; Cubeddu et al., 1990a; Doherty, 1999; Fraschini et al., 1991; Roscoe et al., 2000; Rosso et al., 1991), although they do not lead to total control for all patients. Side effects in humans have included headache, light-headedness, constipation and transient elevations of hepatic transaminases (Clavel et al., 1993; Cubeddu et al., 1990a; Einhorn et al., 1990; Fraschini et al., 1991; Hesketh et al., 1991; Lehoczky, 1999; Roscoe et al., 2000). The combination dopamine/5-HT_3 antagonist metoclopramide has been effective in reducing cyclophosphamide-induced emesis in humans (Clavel et al., 1993). Metoclopramide has been shown to produce adverse extrapyramidal side effects and respiratory failure in humans (MacLaren and Shields, 1998; Sanger, 1990).

Acupuncture has been used to treat a variety of diseases, including nausea and vomiting, in China and other Asian countries for thousands of years. Acupuncture's effects as an alternative and complementary medicine have been evaluated in clinical trials for the treatment of N/V associated with postoperation (Alkaissi et al., 1999; Ho et

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al., 1996; Kotani et al., 2001; Lee and Done, 1999), morning sickness (Bruce et al., 1990; Knight et al., 2001), motion sickness (Lentz, 1982), radiation therapy and chemotherapy (Aglietti et al., 1990; Dundee and McMillan, 1991; Dundee and Yang, 1990; McMillan et al., 1991; Vickers, 1996). In most trials, a single acupuncture point, Neiguan (P6), is used because it is traditionally indicated for N/V, and it provides an excellent parameter for facilitating the design and conduct of such trials (Dundee and McMillan, 1991; Parfitt, 1996; Vickers, 1996). Clinical studies by Dundee's group have demonstrated that acupuncture combined with antiemetic drugs benefits cancer patients who are using a variety of chemotherapy agents including cyclophosphamide (Dundee et al., 1989). Recently, Shen (Shen et al., 2000) reported that adjunct electroacupuncture (EA; lower frequency) was more effective in controlling emesis than sham control or antiemetic pharmacotherapy alone in breast cancer patients receiving high-dose chemotherapy. Other studies showed that acupressure and transcutaneous electrical nerve stimulation (TENS) of P6 also benefited the patient undergoing chemotherapy (Dibble et al., 2000; Dundee and Yang, 1990; Dundee et al., 1991; Lui et al., 1994; McMillan et al., 1991; Pearl et al., 1999; Price et al., 1991).

We have reported a ferret acupuncture model to test the effect of acupuncture in controlling N/V induced by morphine (Lao et al., 1995). The study showed that EA significantly reduced the number of emetic episodes induced by morphine by 39–43% as compared to that of the control (Lao et al., 1995). However, the effect of acupuncture on chemotherapy-induced emesis in an animal model has not been previously reported.

In our previously conducted study (Wong et al., 1997), we reported that cyclophosphamide at 177 mg/kg iv induced a biphasic emetic response in ferrets with a mean ± S.E. of 23.3 ± 4.0 emetic episodes during a 4-h observation period. A high frequency of emetic episodes occurred in the first phase (18.6 ± 3.9, 0–70 min) and a low frequency of emetic episodes occurred in the second phase (4.7 ± 1.4, 140–240 min). The two phases had a 1-h interval between them (Wong et al., 1997). We also reported dose response of three antiemetics, ondansetron, metoclopramide and droperidol, against cyclophosphamide in ferrets (Wong et al., 1997).

The purposes of the present study using this previously established animal emesis model were to determine (a) an optimal EA stimulation parameter and (b) whether an EA-drug combination is more effective than either treatment alone as an antiemetic regimen in reducing cyclophosphamide-induced emesis in the ferret.

The experiments involving the chemo-agent cyclophosphamide-induced emesis profile, the profiles of the antiemetic agents and the profile of EA treatment were carried out concurrently during a 6-month period. The results involving the emesis profile induced by cyclophosphamide at the dose of 177 mg/kg and the profiles of antiemetic agents at their lowest effective doses (ondansetron: 0.04 mg/kg, metoclopramide: 2.24 mg/kg, droperidol: 0.25 mg/kg) have been previously published (Wong et al., 1997). However, the data related to all profiles of EA parameters and the results yielding from combinations of EA and antiemetic agents are unique to this report.

2. Material and methods

2.1. Animal preparation

Detailed methods of animal preparation have been reported (Wong et al., 1997). In brief, castrated male ferrets (Triple F Farm, Sayre, PA), 1.0–2.0 kg in weight, were housed in a cage on a 12-h light cycle. Food (Lab Diet) and water were given ad libitum. Each ferret was used once in the experiment. The ferrets were placed under general anesthesia (isoflurane 5%–O_2 mixture) delivered from a vaporizer (Fortec) calibrated for isoflurane through polyethylene tubing into an anesthesia chamber. Ferrets were removed after loss of righting (2–5 min) and immediately weighed. Each animal was then maintained under general anesthesia (isoflurane 2.5%–O_2) delivered from a second vaporizer through a small nose cone. The animal's forepaws were shaved for intravenous administration and acupuncture needle insertion. To induce emesis, chemotherapy agent cyclophosphamide (177 mg/kg) was injected into the cephalic vein on the dorsal aspect of the front paw with a 25-G needle under general anesthesia. This dose produces the maximal number of emetic episodes without other signs of toxicity, as observed in our previous study (Wong et al., 1997). Ferrets were divided randomly into EA treatment, EA/antiemetic combination treatment groups ($n = 6$/group) and a control group ($n = 8$/group). The animals were euthanized immediately following the experiment to avoid unnecessary suffering.

2.2. Emesis behavioral assessment

After cyclophosphamide injection, each ferret was placed into an individual compartment ($60 \times 60 \times 38$ cm^2) in a cage rack holding six compartments with wire mesh floors elevated to the height of the door threshold and modified with a plexiglass front door for ease of viewing. Complete recovery from anesthesia occurred in all ferrets within 3–10 min. Emetic activity of the animal was observed and the onset time of emesis was recorded. The observer was blind to the treatment assignments.

2.3. Experiment 1: comparison of the antiemetic effectiveness of various EA parameters for cyclophosphamide-induced emesis in ferrets

EA was administered immediately prior to intravenous injection of cyclophosphamide (177 mg/kg). After cleans-

ing the skin with a 70% alcohol swab, disposable acupuncture needles (0.22 mm diameter, 1 in. length) were inserted bilaterally at the point equivalent to the human acupuncture point Neiguan (P6) to a depth of 0.3–0.5 in. (Lao et al., 1995). Neiguan (P6) is located on the forearm, 2 units directly above the midpoint of the transverse crease of the wrist (the distance between cubital and carpal creases is 12 units), between the tendons of the flexor carpi radialis and the palmaris longus muscles. Below this point is the median nerve (O'Connor and Bensky, 1981). A pair of electrodes (Grass SD9 stimulator) were attached to the ends of the needles and electrical stimulation was applied. To identify the optimal EA treatment parameter, various EA parameters such as frequency (5 and 100 Hz), intensity (1.5 and 3 V) and duration (5, 10 and 20 min), and their combinations, were tested ($n=6$/group). The frequency and voltage were monitored by an oscilloscope (Tektronix) linked to the electro-stimulator. For vehicle control, animals received cyclophosphamide only. For placebo control, the needles were taped on the skin of the animal (rather than inserted) at the P6 point; electrodes were placed at the end of the needles but no electrical stimulation was applied. In the sham acupuncture group, a nonacupuncture point (dummy point) was used at the elbow area 1 in. superior and lateral to the tip of the olecranon (Dundee and McMillan, 1991), and no electrical stimulation was applied. In order to assess any adverse effects associated with EA, animals were treated with EA alone ($n=6$) without injection of cyclophosphamide. No unusual behaviors that may be associated with adverse effects of acupuncture were observed in the ferrets treated with EA treatment alone.

2.4. Experiment 2: evaluation of the effectiveness of EA in combination with clinically proven antiemetics on cyclophosphamide-induced emesis

After an optimal set of EA parameters were identified, EA/antiemetics combination studies were conducted using the following procedure: EA treatment was conducted immediately prior to the cyclophosphamide injection, which was immediately followed by antiemetic injection. Low doses of three previously tested antiemetics (60): ondansetron (Glaxo, 2 mg/ml), metoclopramide (A.H. Robbins, 5 mg/ml) and droperidol (American Regent, 2.5 mg/ml) were combined with the EA treatment. Based on the data previously reported (Wong et al., 1997), low doses of the antiemetic drugs were given as follows: ondansetron: 0.04 mg/kg, metoclopramide: 2.24 mg/kg and droperidol: 0.25 mg/kg. For administration of the antiemetic drugs, a second intravenous in addition to the intravenous for cyclophosphamide injection was made into the opposite forepaw. Each ferret was then placed into an individual compartment with a plexiglass front door and observed for 4 h after recovering from anesthesia (3–10 min).

2.5. Data collection and statistical analysis

The number of episodes of vomiting was recorded as previously described (Lao et al., 1995). Total emetic episodes were averaged for each group (±S.E.). For descriptive purposes, the effect of treatment was calculated as the percentage of reduction of emetic episodes: (1 − mean emesis of individual group/vehicle control) × 100% (Wynn et al., 1993). Differences between the mean number of emetic episodes for the treatment groups and the control groups were compared by Student's two-tailed t-test, with $P<.05$ considered significant.

This research protocol was approved by the Institutional Animal Care and Use Committees at the School of Medicine and the Dental School, University of Maryland, Baltimore.

3. Results

3.1. Experiment 1: comparison of the antiemetic effectiveness of various electroacupuncture parameters for cyclophosphamide-induced emesis

The results of the five electrical stimulation parameters compared to vehicle, placebo and sham controls are summarized in Table 1. Among the various combinations of EA parameters, the EA parameter involving 100 Hz, 1.5 V and 0.1 ms pulse width for 10 min led to the least emesis in the first phase of emetic episodes (mean 9.3±1.8 episodes, $n=6$) as well as the lowest total (i.e., Phases I and II combined) number of emetic episodes (mean 19.3±1.3 episodes) (Table 1). These values were not statistically different from those obtained for the sham control group (mean 15.2±2.8 and 6.8±1.2, respectively), however, as were none of the other four electrical stimulation parameters. Because of this numerical advantage favoring the 100 Hz, 1.5 V, 0.1 ms pulse, 10 min duration group (coupled

Table 1
The effect of EA on cyclophosphamide-induced emesis in ferrets

EA (frequency, intensity, duration)	n	Emetic episodes (mean±S.E.)		
		First phase[a]	Second phase[b]	Total[c]
Vehicle	8	18.6±3.9	4.7±1.2	23.3±1.4
Placebo	6	12.2±3.0	10.5±1.7	22.7±1.4
Sham	6	15.2±2.8	6.8±1.2	22.0±3.0
5 Hz, 3 V, 10 min	6	10.3±1.9	10.7±2.5	21.0±1.3
100 Hz, 1.5 V, 5 min	6	11.8±4.3	8.7±0.9	20.5±1.8
100 Hz, 1.5 V, 10 min	6	9.3±1.8	10.0±2.5	19.3±1.3
100 Hz, 1.5 V, 20 min	6	16.5±4.6	8.3±1.1	24.8±1.9
100 Hz, 3 V, 10 min	6	13.2±5.3	7.7±2.0	20.9±2.3

Animals were treated once with EA followed by cyclophosphamid at 177 mg/kg. The ferrets were observed for a total of 240 min for the emetic activity. Vehicle, ferrets injected with cyclophosphamide only. No statistical significance was found between the sham control and any treatment group.

[a] Time: 0–70 min.

[b] Time: 140–240 min.

[c] Time: 0–70 and 140–240 min.

with the fact that this group did differ significantly from the vehicle control group; P=.05), this EA parameter was selected for use in the subsequent experiment.

3.2. Experiment 2: an evaluation of the effectiveness of EA in combination with clinically proven antiemetics on cyclophosphamide-induced emesis

3.2.1. Comparison to the sham control (Fig. 1A)

A statistically significant reduction in the mean number of emetic episodes was found in the ferrets treated with EA (100 Hz, 1.5 V, 0.1 ms and 10 min) in combination with all three low dose antiemetics in comparison with the sham acupuncture control ($P<.01$; Fig. 1A) during Phase I and with respect to the total number of emetic episodes. The EA/ondansetron, EA/droperidol and EA/metoclopramide combinations suppressed total emetic episodes by 52.7% (mean 10.4 ± 0.90, $P<.01$), 36.8% (mean 13.9 ± 0.70, $P<.001$) and 73% (mean 6.0 ± 0.70, $P<.001$), respectively, as compared to sham acupuncture control (mean 22.0 ± 3.0 episodes; Fig. 1A). This antiemetic effect, however, occurred only during the first emetic

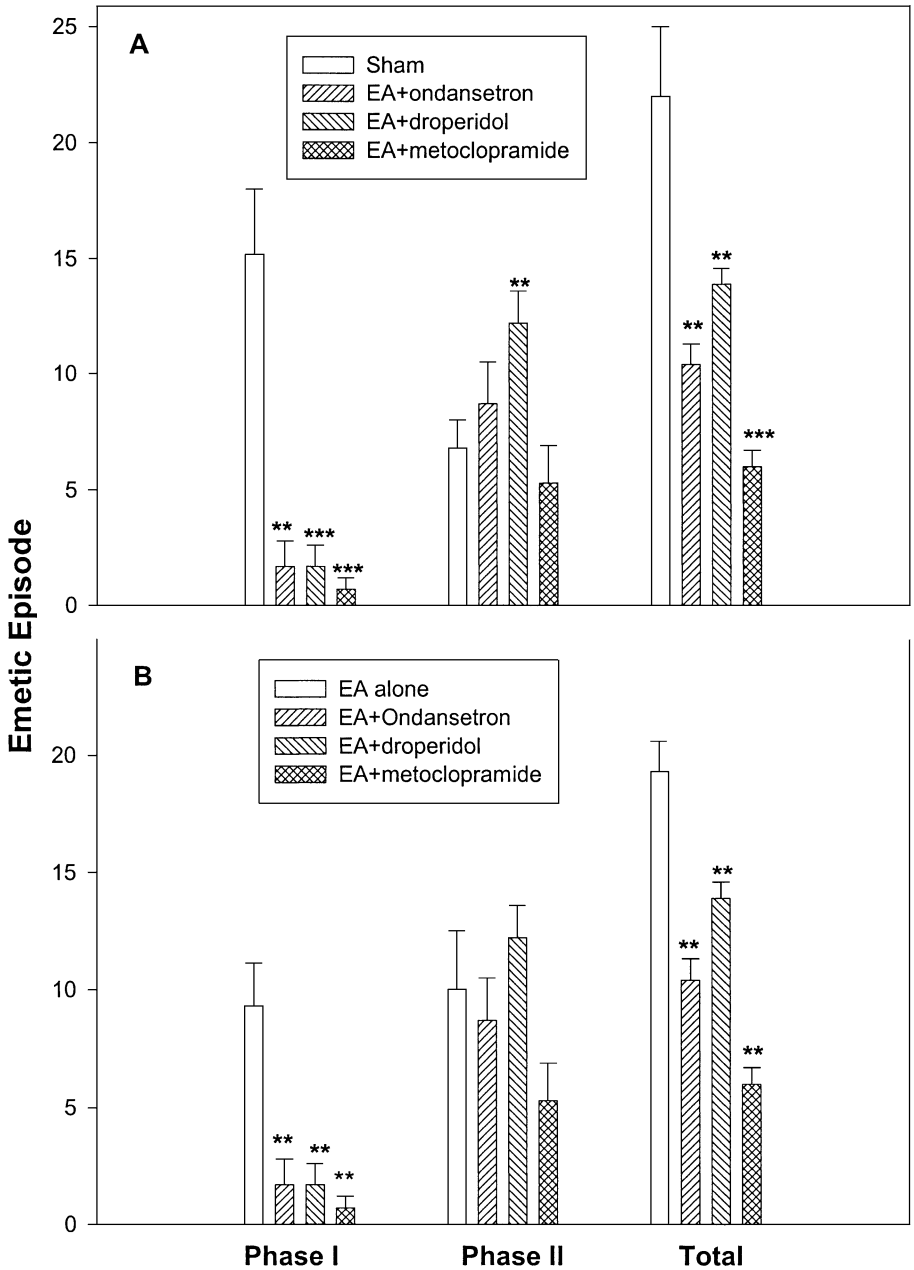

Fig. 1. The comparison of EA–antiemetic combination to sham or EA alone. The ferrets were injected with cyclophosphamide at 177 mg/kg. Two distinct phases of emetic episodes and the combination of the two phases (total) are shown. The data is expressed as mean ± S.E. $**P<.01$, $***P<.001$ as compared with sham in Panel A. $**P<.01$, $***P<.001$ as compared with EA alone in Panel B.

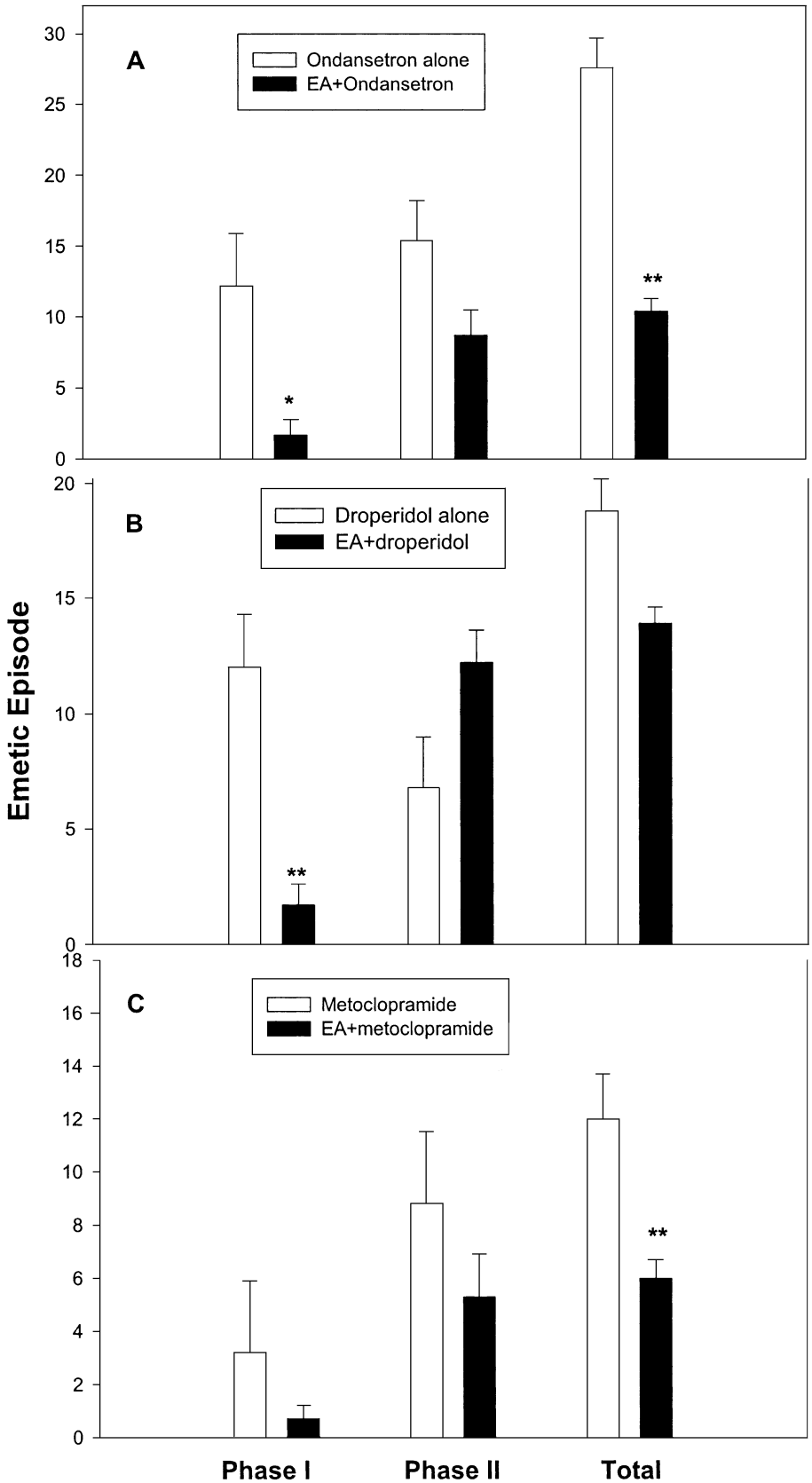

Fig. 2. The comparison of EA–antiemetic combination to antiemetic drug alone. The ferrets were injected with cyclophosphamide at 177 mg/kg. Two distinct phases of emetic episodes and the combination of the two phases (total) are shown. The data is expressed as mean±S.E. *P<.05, **P<.01 as compared with ondansetron alone in Panel A. **P<.01 as compared with droperidol alone in Panel B and **P<.01 as compared with metoclopramide alone in Panel C.

phase (0–70 min following cyclophosphamide administration). In this phase, the EA/ondansetron combination suppressed emetic episodes (mean 1.7 ± 1.1 episodes, $P < .01$) by 88.8%, the EA/droperidol combination (mean 1.7 ± 0.9 episodes, $P < .001$) by 88.8% and the EA/metoclopramide combination (mean 0.7 ± 0.5 episodes, $P < .0001$) by 95.4%, as compared to sham acupuncture control (mean 15.2 ± 2.8 episodes; Fig. 1A).

3.2.2. Comparison to EA alone (Fig. 1B)

All three EA/antiemetic combinations significantly reduced emetic episodes as compared to EA alone, both in the first phase and when the two phases were combined ($P < .05$). In the first phase, the EA/ondansetron combination significantly reduced emetic episodes (mean 1.7 ± 1.1 episodes, $P < .01$) by 81.7%, the EA/droperidol combination (mean 1.7 ± 0.9 episodes, $P < .01$) by 81.7% and the EA/metoclopramide combination (mean 0.70 ± 0.50 episodes, $P < .01$) by 92.5%, as compared to EA alone (mean 9.3 ± 1.8 episodes, $P < .05$; Fig. 1B). Similar adjunctive effects were found in the total number of emetic episodes for the two phases (Fig. 1B), with EA/antiemetic combinations significantly suppressing emetic episodes (EA/ondansetron: mean 10.4 ± 0.9 episodes, 46.1% reduction, $P < .01$; EA/droperidol: mean 13.9 ± 0.7 episodes, 28.0% reduction, $P < .01$; EA/metoclopramide: mean 6 ± 0.7 episodes, 68.9% reduction, $P < .01$) as compared to EA alone (mean 19.3 ± 1.3 episodes, $P < .01$).

3.2.3. Comparison to antiemetic drugs alone (Fig. 2)

Our final analyses consisted of contrasting the effects of each lower dose of antiemetic drug administered alone with the various lower dose of drugs used in combination with EA. In each case, the three EA/antiemetic combinations significantly reduced emetic episodes when compared to the independent effects of the antiemetic drug alone for the two phases combined: EA/ondansetron (mean 10.4 ± 0.9 episodes) vs. ondansetron alone (mean 27.6 ± 2.1 episodes, 62.3% reduction, $P < .01$), EA/droperidol (mean 13.9 ± 0.7 episodes) vs. droperidol alone (mean 18.8 ± 1.4 episodes, 26.1% reduction, $P < .01$) and EA/metoclopramide (mean 6 ± 0.7 episodes) vs. metoclopramide alone (mean 12 ± 1.7 episodes, 50.0% reduction, $P < .01$) (Fig. 2A–C, respectively). In the first emetic phase, however, only the EA/ondansetron (mean 1.7 ± 1.1 episodes) and EA/droperidol (mean 1.7 ± 0.9 episodes) combinations significantly suppressed emetic episodes as compared to ondansetron alone (mean 12.2 ± 3.7 episodes, $P < .05$) or droperidol alone (mean 12 ± 2.3 episodes, $P < .01$). The EA/metoclopramide combination (mean 0.70 ± 0.50 episodes), while numerically more effective than the drug alone (mean 3.2 ± 2.7 episodes; Fig. 2C) was not statistically significant. No significant differences for emetic episode reduction were found during the second emetic phase among these EA/drug combinations.

3.2.4. Assessment of the adverse effects of EA

Assessment of the adverse effects of EA was conducted in the ferrets treated with EA alone without other drug interventions. Close observation was also made in each experiment to determine whether any behavioral changes other than ones induced by emetic and antiemetic drugs presented in the animals. No adverse effects of acupuncture were observed (data not shown).

4. Discussion

Cyclophosphamide is one of the agents commonly used in chemotherapy for breast cancer and other cancers (Andrews et al., 1988; Bosnjak et al., 2000; Hawthorn et al., 1988; Vermeulen et al., 2000). Side effects of chemotherapy agents often add to the difficulties of cancer treatment (Pendergrass, 1998; Tonato et al., 1994). Modern antiemetics have proven to be of use in the prevention of chemotherapy induced N/V. However, these conventional medicines are often accompanied by unpleasant side effects. Furthermore, a subgroup of patients continues to have N/V regardless of administration of antiemetic agents. There have therefore been ongoing efforts to improve antiemetic control, including development of new antiemetic agents, such as 5-HT receptor antagonists (Walton, 2000) and neurokinin (NK-1) antagonists (Diemunsch and Grelot, 2000; Hesketh, 2001; Hesketh et al., 1999; Ladabaum and Hasler, 1999; Tattersall et al., 2000), as well as nonpharmocological approaches such as acupuncture, acupressure or TENS (Pearl et al., 1999; Vickers, 1996).

A number of clinical trials have shown that acupuncture is effective in preventing and reducing N/V caused by chemotherapy (Vickers, 1996). However, there are a number of ethical, clinical and methodological problems associated with evaluating the effects and mechanisms of acupuncture in human clinical trials. (1) It is not appropriate to investigate the effect of acupuncture without combining with antiemetic agents; (2) the patient's anticipated N/V from his/her previous experience may confound the data interpretation; and (3) cancer patients often use different regimens of chemotherapy cocktails, which leads to the difficulty of investigating the effects of acupuncture in a well-controlled homogenous group.

We have employed a well-established ferret emesis model that is commonly used by the pharmaceutical industry and have successfully interpolated human acupuncture points into this model in order to evaluate the efficacy of acupuncture in controlling N/V. This animal model allows for: (1) use of naive animals, (2) identifying optimal EA parameters and (3) a means of controlling the variables of EA and drug combinations. The results of our study suggest that this ferret model is an ideal animal model to evaluate the effect of acupuncture and antiemetics on emesis, and the data may be useful in the clinical situation.

Although there was no statistical difference as compared to the sham control, EA at 100 Hz, 1.5 V, 10 min showed most favored effect on emesis reduction in the first phase (Table 1). It produced an antiemetic pattern similar to that of low doses of antiemetic agents, particularly ondansetron, in which biphasic cyclophosphamide-induced emesis was inhibited in the first phase but increased in the second phase. Our findings are also consistent with reports from clinical trials that acupuncture controls N/V better in the earlier stages of chemotherapy than it does in the later stages (Dundee and Yang, 1990; Shen et al., 2000). It is not clear from this study whether acupuncture is actually less effective on the later phase of emesis or whether the effects of the treatment simply wear off. In future research, it will be important to administer acupuncture at a second time point, prior to Phase II. One clinical trial (Dundee et al., 1988) showed that administering additional acupuncture was beneficial in postchemotherapy N/V; however, two other trials of single-dose chemotherapy using antiemetics plus noninvasive P6 stimulation for a week found that the delayed phase of N/V was still more difficult to control than acute symptoms (Dibble et al., 2000; Pearl et al., 1999). Clearly, the effects of acupuncture on delayed N/V are not yet known.

Another unresolved issue surrounding our methodology involved the question of whether acupuncture can be effective while subjects are under general anesthesia. Some investigators (Christensen et al., 1993; Gupta et al., 1999; Kho et al., 1991) have found no effect for acupuncture on patients under general anesthesia, while others have found acupuncture was effective when weak (e.g., nitrous oxide with oxygen) general anesthesia was used (Christensen et al., 1989; Lee and Beitz, 1992, 1993). In our study, in order to avoid animal stress from the EA procedure, the EA was conducted while the animal was under a shallow general anaesthesia, isoflurane (2.5%). It is not known whether the EA treatment would have had a better antiemetic effect if the animal had been treated while awake.

The most significant finding of this study is the enhanced effect of EA/antiemetic drug combination. While both EA alone and lower doses of antiemetic agents have limited effects upon chemo-induced N/V, EA combined with all three antiemetic drugs significantly enhanced the observed effects. Importantly, the combination treatments not only further suppressed emesis at the first phase, but also suppressed overall emetic episodes when the two phases are combined. In our previous study, we observed that antiemetic agents also have a limited effect on the second phase of the biphasic cyclophosphamide induced emesis, even in higher dosages (except for the high dosage of metoclopramide, which was able to prevent emesis in the second phase), although they were effective in reducing emesis in the first phase in much higher doses (Wong et al., 1997). The combination treatment of EA and antiemetic drugs therefore provides a useful alternative regimen for managing chemotherapy-caused emesis.

This finding has important implications for clinical research. Since the advent of 5-HT_3 antagonists, some have argued that examining the effectiveness of acupuncture for chemotherapy-induced N/V is obsolete (Taub, 1998). However, none of the published acupuncture randomized clinical trials (Dundee, 1988; Dundee et al., 1989; Shen et al., 2000) have examined the benefits of acupuncture as an adjunct to the state-of-the-art antiemetic therapy. The findings in this animal model suggest that clinical research designs combining these modalities are warranted.

Cyclophosphamide may induce emesis through release of serotonin to stimulate the 5-HT_3 receptor in the gastrointestinal tract and the chemoreceptor trigger zone (Fraschini et al., 1991; Hawthorn et al., 1988). Antiemetic agents appear to inhibit chemotherapy induced N/V by different mechanisms: ondansetron is a 5-HT_3 antagonist (Andrews et al., 1988; Clavel et al., 1993; Cubeddu et al., 1990a; Fraschini et al., 1991; Rosso et al., 1991), droperidol is a D_2 receptor antagonist, and metoclopramide is a combination dopamine/5-HT_3 antagonist (Clavel et al., 1993).

Our study determined that EA enhanced the effect of all three antiemetic drugs in the first phase, indicating that the EA-mediated antiemetic effect probably operates through a broad mechanism (Miller, 1999). This is supported by the finding that metoclopramide, which acts on both D_2 and 5-HT_3 receptors, produced the highest synergistic effect of all three antiemetics when combined with EA. EA effectively prevented the recurrence of emesis in the second phase with ondansetron and metoclopramide, but not with droperidol (Figs. 1 and 2). These two findings, then, suggest that EA produces better results with antiemetics that act on the 5-HT_3 receptor. However, it is not known whether the enhanced antiemetic effect of EA/drug combinations is via an additive action or a synergistic action. The mechanism of this action needs further investigation.

In conclusion, previous studies indicate that acupuncture is an effective antiemetic. No acupuncture studies have been conducted on patients who were receiving the newer generation of $5HT_3$ antagonists. Our results showed that at lower drug dose levels, EA is useful as an adjunctive therapy in the treatment of cyclophosphamide-induced emesis in the ferrets, suggesting that acupuncture is probably of benefit for patients inadequately controlled by new generation antiemetics. However, clinical studies are needed to confirm this finding.

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