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Relationship of gastric myoelectrical and cardiac parasympathetic activity to chemotherapy-induced nausea

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Abstract

Objectives—We evaluated (a) whether pretreatment levels of gastric tachyarrhythmia, a dysrhythmic pattern of gastric myoelectrical activity, or cardiac parasympathetic activity are associated with the development of chemotherapy-induced nausea and (b) whether chemotherapy-induced nausea is preceded by an increase in gastric tachyarrhythmia and a decrease in cardiac parasympathetic activity, as has been observed during motion sickness.

Methods—Electrogastrograms and estimates of respiratory sinus arrhythmia (RSA) were obtained from cancer chemotherapy patients before treatment and for approximately 24 hours after treatment.

Results—Higher levels of pretreatment gastric tachyarrhythmia were observed on chemotherapy sessions that were followed by posttreatment reports of nausea. Pretreatment levels of RSA, however, did not differ between chemotherapy treatments that were and were not followed by nausea. No statistically significant changes in gastric tachyarrhythmia or RSA were observed prior to first reports of nausea following chemotherapy.

Conclusions—In contrast to motion sickness, chemotherapy-induced nausea may not be related to an increase in dysrhythmic gastric myoelectrical activity; however, higher levels of pretreatment gastric tachyarrhythmia may be related to posttreatment reports of chemotherapy-induced nausea.

Keywords

Cancer chemotherapy; Electrogastrography; Gastric tachyarrhythmia; Nausea; Parasympathetic

Introduction

Nausea and emesis are reported by cancer patients as two of the most adverse side effects of chemotherapy [1]. These side effects can contribute not only to a decreased quality of life, but also to the refusal of further anticancer treatment [2,3]. Chemotherapy-induced nausea and emesis may also limit the dosage of the anticancer drug that can be prescribed for a patient [4]. Further, whereas chemotherapy-induced emesis may be prevented in many cases by the administration of serotonin 5-HT_3 receptor antagonists, these antiemetics are not as effective in reducing chemotherapy-induced nausea [5].

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Although nausea is a common side effect of anticancer therapy, the same cancer patient may experience nausea following some chemotherapy treatments, but not others, despite identical administrations of cytotoxic and antiemetic agents. To date, however, no studies have examined possible predictors of within-patient variations in posttreatment reports of nausea. Prior research indicates that between-patients differences in anticipatory and posttreatment nausea may be associated with variations in pretreatment autonomic activity [6–8]. Similarly, prior motion sickness research has shown that lower baseline levels of respiratory sinus arrhythmia (RSA), a specific estimate of cardiac parasympathetic activity, predict increased reports of nausea during illusory self-motion [9]. Along with lower basal RSA, the experience of motion sickness has also been related to a concurrent decrease in RSA and an increase in a dysrhythmic pattern of gastric myoelectrical activity, termed gastric tachyarrhythmia [10]. In addition, it has recently been shown that higher baseline levels of gastric tachyarrhythmia predict a greater severity of vection-induced nausea and motion sickness [11]. In the present study, we evaluated whether pretreatment levels of cardiac parasympathetic activity, as assessed by RSA, and gastric tachyarrhythmia are also related to the development of posttreatment, chemotherapy-induced nausea within a patient.

We also evaluated posttreatment changes in RSA and gastric tachyarrhythmia prior to the report of nausea. Presently, very little is known about the autonomic or gastric myoelectrical changes that precede chemotherapy-induced nausea. In a sample of five ovarian cancer patients, Morrow et al. [12] reported that skin temperature and pulse volume increased while facial pallor and heart rate decreased just prior to the onset of chemotherapy-induced nausea. More recently, Morrow et al. [13] demonstrated that a gradual increase and then a marked withdrawal of cardiac vagal activity occurs prior to the report of chemotherapy-induced nausea. The only studies that have assessed gastric myoelectrical activity following cancer chemotherapy indicated that gastric myoelectrical dysrhythmias are associated with emesis in both adults [14] and children [15]; however, it is still unclear whether gastric dysrhythmias, such as gastric tachyarrhythmia, are associated with chemotherapy-induced nausea.

Method

Patients

Twenty-five female chemotherapy-naive cancer patients (mean age: 50 years, age range: 34–67 years) from the University of Rochester Cancer Center were studied beginning immediately prior to their first cycle of intravenous chemotherapy. The patients received six treatments on an outpatient basis for a variety of histologically confirmed malignancies (12 breast, 8 ovarian, 2 lung, 1 bladder, 1 non-Hodgkin's lymphoma, 1 Hodgkin's lymphoma), and received a different combination of antiemetics (Ativan, Compazine, Decadron, Kytril, Reglan, Zofran) and chemotherapy agents (Adriamycin, Carboplatin, Cisplatin, Cytoxan, Methotrexate, MTX, Navelbine, Nitrogen mustard, Novantrone, Taxol, Vincristine, VP-16, 5-FU) in standard dosages.

Procedure

All patients provided informed consent prior to participation. Prior to chemotherapy treatment, patients were instrumented with a Biolog Ambulatory Recording System (UFI, Morro Bay, CA). The patients were instructed to wear the ambulatory device prior to treatment and for the first 24 hours following treatment. The patients were also instructed to press one of five event markers on the device, which indicated whenever she ate, drank, received medication, felt nauseated or vomited.

Physiological measures

Electrogastrographic (EGG) activity was recorded using three disposable Ag/AgCl electrodes. One active electrode was positioned approximately 4 cm above the umbilicus and another was positioned approximately 8 cm left of the midline at the level of the lowest rib. A reference electrode was placed approximately 6 cm right of the midline and 2 cm above the umbilicus. The EGG signal was digitized at 4.267 Hz, and was sent to the ambulatory device with low and high frequency cutoffs at 0.01 and 0.26 Hz, respectively.

All EGG data were quantified using running spectral analyses of 10 minutes epochs for which there were no respiratory or movement artifacts in the EGG record [10]. Each EGG time series was linearly detrended and mean-centered prior to spectral analysis. The first and last 5% of the EGG signal were then tapered using a Hamming window, and spectral density estimates were derived from fast Fourier Transforms (FFTs) in 0.25 cpm wide bins from 0.75 to 15 cpm. The percentage of total power in the gastric tachyarrhythmic (4–9.75 cpm) bandwidth was calculated using the following equation: % gastric tachyarrhythmia = (4–9.75 cpm power/0.75–15 cpm power) × 100.

The EKG signal was recorded from two Ag/AgCl electrodes that were placed in a modified Lead II configuration. The EKG signal was sampled at 4 KHz, and interbeat intervals (IBIs) from the same 10-minute epochs described above were derived as the interval in ms between sequential R spikes. Prior to analyses, all IBIs were edited for artifacts using the artifact detection program of Berntson et al. [16]. A time series of 500-ms samples was then created from the IBIs. Using the algorithm developed by Porges and Bohrer [17], RSA was calculated by removing the complex trend in the IBI data with a moving 21-point polynomial filter. After filtering, a residual IBI series was created by subtracting the filtered data from the original time series. Finally, the natural logarithm of the variance in the residual time series at the respiratory frequency (0.12–0.40 Hz) was taken as the estimate of RSA.

Data reduction and analysis

Two sets of statistical analyses were performed. In the first set, pretreatment estimates of gastric tachyarrhythmia and RSA were evaluated in a subset of 11 patients who reported nausea following at least one treatment, but did not report nausea following a different treatment (6 patients reported nausea following Treatment 1, 3 following Treatment 3, and 2 following Treatment 6). For these patients, pretreatment gastric tachyarrhythmia and RSA from a 10-minute epoch approximately 30 minutes prior to the administration of antiemetics and cytotoxic agents were compared between the two types of chemotherapy sessions (nausea and nonnausea inducing) using paired-samples *t* tests.

In the second set of analyses from the entire sample of 25 patients, 10-minute estimates of gastric tachyarrhythmia and RSA 60 minutes prior to the patient's first report of nausea were compared to estimates obtained during the 10-minute, artifact-free period just prior to nausea using paired-sample *t* tests. An alpha level of .05 was adopted.

Results

A greater percentage of gastric tachyarrhythmia was observed prior to the chemotherapy treatment that was followed by nausea (M = 22.86%, S.E. = 3.05) compared to a treatment that was not followed by nausea (M = 12.86%, S.E. = 3.41; $t(10) = 2.55$, P = 029). The 95% confidence interval of the mean difference in the percentage of pretreatment gastric tachyarrhythmia between the two sessions was 1.27–18.71%. In contrast to these findings, RSA did not differ significantly prior to sessions for which nausea was later reported (M = 5.95

ln units, S.E. = 0.33) relative to those after which nausea was not reported (*M* = 5.91 ln units, S.E.=0.37; *P*>.05). No patients reported nausea or vomited during the pretreatment period.

Gastric tachyarrhythmia and RSA were also examined 60 minutes prior to nausea and during the 10-minute period just prior to the patient's first report of nausea following chemotherapy. There was no significant change in the percentage of gastric tachyarrhythmia from the 60-minute period prior to nausea (*M* = 18.72%, S.E. = 2.17) to the 10-minute period just prior to reported nausea (*M* = 16.00%, S.E. = 2.00; *P*> .05). RSA decreased from the 60-minute period prior to nausea (*M* = 4.94 ln units, S.E.=.34) to the period just prior to reported nausea (*M* = 4.50 ln units, S.E. = 0.23), but this difference was not statistically significant, *P*> .05.

Discussion

Higher levels of pretreatment gastric tachyarrhythmia were observed on those chemotherapy sessions that were followed by posttreatment reports of nausea. These findings are comparable to those indicating that the development of motion sickness may also be predicted by baseline levels of gastric tachyarrhythmia [11]. It is possible that these differences in pretreatment gastric tachyarrhythmia were related to increased levels of anticipatory anxiety prior to treatment. Indeed, a growing body of evidence suggests that stress and anxiety affect gastric myoelectrical activity (e.g., Refs. [18,19]). Further, both anxiety and patient expectations have been shown to predict chemotherapy-induced nausea [20]. Future studies are needed, however, to further evaluate the possible relationship between pretreatment anxiety and gastric myoelectrical activity. Nonetheless, it may prove to be clinically beneficial to identify those patients who display increased levels of gastric tachyarrhythmia prior to treatment, as they may be at a greater risk of experiencing nausea following chemotherapy.

In contrast to the findings that higher levels of pretreatment gastric tachyarrhythmia were associated with posttreatment reports of nausea, we found that pretreatment estimates of RSA did not differ between nausea- and no-nausea-inducing chemotherapy treatments. These results appear to contrast with prior motion sickness research indicating that lower levels of basal RSA predict greater susceptibility to motion sickness. This discrepancy may be due to (a) age differences in the samples studied, (b) differences in the underlying autonomic pathways that contribute to motion sickness and chemotherapy-induced nausea or (c) the relatively small sample employed here.

In addition to the findings that pretreatment RSA was not associated with posttreatment reports of nausea, we did not observe statistically significant changes in gastric tachyarrhythmia or RSA prior to first reports of chemotherapy-induced nausea. The failure to find a significant increase in gastric tachyarrhythmia prior to reports of nausea is contrary to the findings of numerous studies of motion sickness, but is in agreement with prior reports [14,15] that have also failed to observe a change in gastric tachyarrhythmia following chemotherapy. Again, one reason for the discrepancy between prior motion sickness research and the results of the present study may be that the nauseogenic stimuli of motion sickness and chemotherapy activate different central and autonomic pathways. Another potential reason for this discrepancy may be that the administered antiemetics served as antidysrhythmics, thereby preventing the development of gastric tachyarrhythmia. This possibility is supported by the results of a recent study [21], which showed that serotonin 5-HT_3 receptor antagonists prevented the development of gastric tachyarrhythmia, but not reports of motion sickness, when participants were exposed to a rotating optokinetic drum.

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References

1. Cull, A. Psychological effects of anti-cancer therapy. In: Andrews, GJ.; Sanger, GJ., editors. Emesis in anti-cancer therapy: mechanisms and treatment. London: Chapmand & Hall; 1993. p. 211-28.
2. Stewart DJ. Cancer therapy, vomiting, and antiemetics. Can J Physiol Pharmacol 1990;68:304–13. [PubMed: 2178754]
3. Andrews, PLR.; Sanger, GJ. The problem of emesis in anti-cancer therapy: an introduction. In: Andrews, PLR.; Sanger, GJ., editors. Emesis in anti-cancer therapy: mechanisms and treatment. London: Chapman & Hall; 1993. p. 1-7.
4. Penta, J.; Poster, D.; Bruno, S. The pharmacologic treatment of nausea and vomiting caused by cancer chemotherapy: a review. In: Laszlo, J., editor. Antiemetics and cancer chemotherapy. Baltimore: Williams and Wilkins; 1983. p. 53-92.
5. Morrow GR, Hickok JT, Rosenthal SN. Progress in reducing nausea and emesis: comparison of Ondansetron (Zofran), Granisitron (Kytril), and Tropisetron (Navoban). Cancer 1995;76:343–57. [PubMed: 8625113]
6. Kvale G, Psychol C, Hugdahl K. Cardiovascular conditioning and anticipatory nausea and vomiting in cancer patients. Behav Med 1994;20:78–83. [PubMed: 7803940]
7. Kvale G, Hugdahl K, Asbjørnsen K, Rosengren B, Lote K, Nordby H. Anticipatory nausea and vomiting in cancer patients. J Consult Clin Psychol 1991;59:894–8. [PubMed: 1774373]
8. Morrow, GR.; Barry, MJ.; Jiang, W.; Angel, C.; DuBeshter, B. Pre-chemotherapy total autonomic activity assessed via heart rate spectral analysis as a predictor of chemotherapy induced self-reported nausea. In: Bianchi, AL.; Grelélot, L.; Miller, AD.; King, GL., editors. Mechanisms and control of emesis. London: Colloque INSERM/John Libbey Euro-text; 1992. p. 169-70.
9. Uijtdehaage SHJ, Stern RM, Koch KL. Effects of eating on vection-induced motion sickness, cardiac vagal tone, and gastric myoelectric activity. Psychophysiology 1992;29:193–201. [PubMed: 1635961]
10. Stern, RM.; Koch, KL.; Muth, ER. The gastrointestinal system. In: Cacioppo, JT.; Tassinary, LG.; Berntson, GG., editors. Handbook of psychophysiology. Cambridge: Cambridge Univ. Press; 2000. p. 294-314.
11. Levine ME, Muth ER, Gianaros PJ, Stern RM. A physiological marker for the experience of nausea. Psychophysiology 2000;37:S63.
12. Morrow GR, Angel C, Dubeshter B. Autonomic changes during cancer chemotherapy induced nausea and emesis. Br J Cancer 1992;66:S42–5.
13. Morrow GR, Andrews PLR, Hickok JT, Stern R. Vagal changes following cancer chemotherapy: implications for the development of nausea. Psychophysiology 2000;37:378–84. [PubMed: 10860415]
14. Samsom, M.; Akkermans, LMA.; Neijt, J. Gastric myoelectrical activity in patients treated with Cisplatin. In: Chen, JZ.; McCallum, RW., editors. Electrogastrography: principles and applications. New York: Raven Press; 1994. p. 345-55.
15. Cheng W, Chan GCF, Tam PKH. Cytotoxic chemotherapy has minimal direct effect on gastric myoelectric activity in children with 5HT3 antagonist prophylaxis. Med Pediatr Oncol 2000;34:421–3. [PubMed: 10842249]
16. Berntson GG, Quigley KS, Jang JF, Boyson ST. An approach to artifact identification: application to heart period data. Psychophysiology 1990;27:586–98. [PubMed: 2274622]
17. Porges, SW.; Bohrer, RE. The analysis of periodic processes in psychophysiological research. In: Cacioppo, JT.; Tassinary, LG., editors. Principles of psychophysiology: physical, social, and inferential elements. Cambridge: Cambridge Univ. Press; 1990. p. 708-53.
18. Muth ER, Koch KL, Stern RM, Thayer JF. Effect of autonomic nervous system manipulations on gastric myoelectrical activity and emotional responses in healthy human subjects. Psychosom Med 1999;61:297–303. [PubMed: 10367609]
19. Gianaros PJ, Quigley KS, Mordkoff JT, Stern RM. Gastric myoelectrical and autonomic cardiac reactivity to laboratory stressors. Psychophysiology. in press.
20. Roscoe JA, Hickok JT, Morrow GR. Patient expectations as predictor of chemotherapy-induced nausea. Ann Behav Med 2000;22:121–6. [PubMed: 10962704]

21. Levine ME, Chillas J, Stern RM, Knox GW. Effects of Serotonin (5-HT3) receptor antagonists on gastric tachyarrhythmia and the symptoms of motion sickness. Aviat, Space Environ Med 2000;71:1111–4. [PubMed: 11086664]