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Anticipatory nausea and vomiting

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Abstract Anticipatory nausea and vomiting (ANV) is not only a learned response but can occur without prior exposure to chemotherapy depending on patient emotional distress and expectations. The best method to avoid development or reinforcement of ANV is to avoid both vomiting and nausea from the first exposure to chemotherapy. If ANV develops, benzodiazepines have been documented to help in adult patients, and several psychological techniques are also of help, including systematic desensitization. The evidence on which these conclusions are based is reviewed in this article.

Keywords Anticipatory nausea and vomiting

Introduction: What many believe

Anticipatory nausea and vomiting (ANV) is widely believed to be a learned response to chemotherapy that develops in up to 25% of patients by the fourth treatment cycle [23, 25]. ANV is also variably referred to as conditioned, learned or psychological nausea and vomiting. There are a considerable amount of data from studies in adult patients indicating that classical conditioning contributes to ANV in cancer chemotherapy [33, 38]. ANV related to prior chemotherapy experience has thus been described as reflecting a Pavlovian conditioned reflex, where the conditioned stimulus (CS) is the thought of chemotherapy or of conditioned elements associated with it [5]. When reexposed to the CS, some patients will then experience ANV prior to infusion onset. The risk of ANV tends to increase with the number of cycles received [17], and the symptoms may persist for a long time after the completion of chemotherapy [12].

If postchemotherapy nausea and emesis do not occur, then ANV is supposed not to have occurred. Patient characteristics can predict the occurrence of ANV and prior actual experience is not always needed. Once it develops, ANV is difficult to control by pharmacological means, whereas behavioral therapies involving relaxation, most notably systematic desensitization, can be used to effectively treat ANV. In this paper we review the present understanding of ANV in the setting of cancer chemotherapy with recent references where possible.

Anticipatory emesis and the experimental setting

There is no satisfactory laboratory model for ANV, as there is even no fully satisfactory model for evaluation of acute or delayed nausea and vomiting. Interestingly, a model for ANV has been developed to evaluate tetrahydrocannabinol [28]. Most tests used for the screening of 5-HT3 receptor antagonists are not completely specific but they give satisfactory results when they are used in battery. Potential activities of 5-HT3 receptor antagonists such as neuroleptics, anxiolytics and agents useful against

dependence and cognitive disorders pose some problems in animal psychopharmacology, and remain to be clinically validated [29]. It is of interest that in adult patients, anticipatory immunomodulation (AIM) has also been observed and that some results suggest that ANV and AIM also occur in pediatric cancer patients and show features of a conditioned response [35].

In experimental animal settings certain conditioning techniques can actually be used to alleviate nausea and vomiting [7, 14]. In this context of conditioning as a cause, but also potentially a means of prevention of ANV, researchers have sought to determine in humans whether an overshadowing procedure could prevent ANV. Overshadowing is a technique whereby the subject is conditioned in an adverse experimental setting to respond to a strong stimulus, and then the stimulus is withdrawn at the next exposure to the adverse experience. In one such study, 16 cancer patients were assigned to one of two groups: with overshadowing (OV+) and without overshadowing (OV−). At the start of all infusions of two consecutive chemotherapy cycles A and B (acquisition), OV+ subjects drank a saline bad tasting beverage (the overshadowing CS), whereas group OV- drank water. All patients received water in cycle C (test). As expected, in cycle C (test), no patient of group OV+ showed AN, whereas two patients of group OV- developed AN [34].

Predicting ANV

Patients who have experienced chemotherapy will be at risk of developing ANV and data have been collected prospectively in order to evaluate a risk profile [22, 24]. The risk factors that need to be considered are:

1. Age <50 years
2. Nausea and vomiting after the last chemotherapy
3. Describing nausea after the last treatment as "moderate, severe or intolerable"
4. Reporting the side effect after the last treatment "warm or hot all over"
5. Susceptibility to motion sickness
6. Experiencing "sweating" after the last treatment
7. Experiencing "generalized weakness" after the last treatment

Besides prior experience, other factors can contribute to ANV. As discussed by Montgomery and Bovbjerg [21], expectations are important determinants of experiences of nonvolitional outcomes (e.g., pain, nausea), but little research has explored their source. The dual process model suggests that concurrent experience of emotional distress should be a strong contributor, whereas social learning theory supports the position that expectations of nonvolitional outcomes should be based primarily on prior experience. The authors tested, in a sample of 80 breast cancer patients undergoing outpatient adjuvant chemotherapy, the impact of emotional distress and prior experience on patients' expectations of side effects. Bivariate analyses suggested that emotional distress contributed early in the course of treatment. However, once prior experience of posttreatment nausea (PTN) was accounted for in the statistical model, distress no longer made significant contributions to patients' expectations of PTN, whereas prior experience did (P<0.001).

Hickok et al. [11] evaluated the role of patients' expectations of nausea in the development of ANV in female cancer patients receiving their first course of chemotherapy. Of a total of 63 patients, 20 (32%) expected to experience nausea and 12 (19%) reported ANV before the third cycle. Pretreatment expectations predicted ANV at cycle three (Spearman's r=0.41, P=0.001). Anticipatory nausea developed in 40% of patients who expected nausea, 13% of those who were uncertain whether they would develop it, and none of those who did not expect nausea. Logistic regression indicated that expecting nausea was the strongest predictor (χ^2=13.15, P<0.001)

In another study, the effects of changes in family relationships (cohesion, expression, and conflict) on patients' physical adjustment to chemotherapy were examined. A total of 233 married cancer patients completed questionnaires consisting of measures of family relationships and chemotherapy-related nausea symptoms, at two assessments. An increase in family conflict was associated with an increased duration of PTN and greater severity of anticipatory nausea for younger adult patients but not for older adult patients. An increase in family conflict was also associated with a greater severity of anticipatory nausea for female patients but not for male patients. These findings suggest that intervention programs to help reduce family conflict may be especially beneficial for younger adult and female patients [13].

Notwithstanding the above arguments about the importance of psychological variables as predictors of ANV the most important factor remains the previous experience with symptoms earlier [37].

Appropriate control of acute and delayed emesis reduces ANV

We did a MEDLINE search using the terms "anticipatory emesis" and "randomized clinical trials", and retrieved 32 papers published/indexed up to March 2004. However, none addressed the question of ANV in the chemotherapy setting in an experimental way. One of the largest observational series evaluating ANV comprises data from 574 chemotherapy patients who received granisetron as their antiemetic treatment during repeat cycle chemotherapy. Per treatment cycle, fewer than 10% of patients displayed symptoms of anticipatory nausea and 2% or fewer had symptoms of anticipatory vomiting [1].

This implies that the rate of ANV is much less than observed in older studies, which used less satisfactory antiemetic programs. Two examples of conditions leading to ANV are given to illustrate the issue. One such example is a report by Wilcox et al. in the early 1980s. The authors studied 52 women treated with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) adjuvant chemotherapy for breast carcinoma. Among the 52 patients, ANV occurred in 17 (33%), while acute and delayed emesis was experienced by 46 (88%). Of the 52 patients, 10 (19%) discontinued CMF adjuvant chemotherapy because of nausea and vomiting; seven of the ten (70%) had experienced anticipatory vomiting [39].

Another example of poor acute control leading to a high prevalence of ANV is a report of women receiving CMF or 5-fluorouracil/doxorubicin/cyclophosphamide (FAC). Antiemetic therapy included one corticoid plus ondansetron (in the FAC regimen), or one corticoid plus thiethylperazine (in the CMF regimen). For at least one cycle of chemotherapy, 86.1% and 91.7% patients in the FAC protocol experienced vomiting and nausea, respectively, and 11.1% had anticipatory vomiting and 30.6% had anticipatory nausea. In the CMF protocol, 79.6% had postchemotherapy vomiting and 71.7% had postchemotherapy nausea associated with at least one cycle. In this group, 7.4% had anticipatory vomiting and 16.6% had anticipatory nausea. A high proportion of patients suffered anticipatory anxiety in both groups (75% in FAC, 74.1% in CMF). The stimuli most frequently associated with the appearance of anticipatory emesis were olfactory stimuli and cognitive stimuli [8].

The observation that anticipatory anxiety, a component of the conditioned response to adverse stimuli [2], is more frequent than ANV is also seen in another recent study. Using retrospective ratings derived from the Psychosocial Level System scale in 40 bone marrow transplant patients, anticipatory anxiety was observed in 15% and anticipatory nausea/vomiting in only 5% of patients [19].

Acupuncture and anticipatory emesis

A review of experimental literature on the effects of acupuncture treatment has covered the 14 medical conditions for which the US National Institutes of Health Acupuncture Consensus Development Panel (NIHCDP) concluded that acupuncture either is effective (2 conditions) or may be useful (12 conditions). The author's conclusions partially support those of the NIHCDP, in particular finding evidence that acupuncture is effective for the treatment of postoperative and chemotherapy-induced nausea and vomiting [18]. A more recent review reaches the same conclusion [6]. These reviews do not identify acupuncture as a treatment for ANV, but acupuncture has been suggested for the treatment of a condition quite likely to be similar to ANV: "nervous vomiting at the dentist's office" [40].

Benzodiazepines and ANV

Razavi et al. [30] conducted a double-blind, placebo-controlled study designed to assess the usefulness of adding low-dose alprazolam (0.5 mg to 2 mg per day) to a psychological support program including progressive relaxation training designed to prevent ANV in 57 women undergoing adjuvant chemotherapy for stage II primary breast cancer. At the second evaluation, the results showed a higher rate of anticipatory nausea (18% vs 0%) in the placebo compared with the alprazolam arm (P=0.038). These differences were no more significant at each of the further assessments. Significant differences were found for the intake of hypnotics at each assessment visit, with the rate of hypnotic users being significantly higher in the placebo (19%) compared with the alprazolam (0%) arm at the fourth assessment (P<0.05). The authors concluded that the adjunct of alprazolam to a psychological support program delays the occurrence of anticipatory nausea and controls sleeping problems secondary to adjunct chemotherapy.

Malik et al. [15] conducted a randomized trial to evaluate the efficacy of lorazepam in managing anticipatory, acute, and delayed emesis induced by high doses of cisplatin. A total of 180 events involving cisplatin administration (100 mg/m^2 as a 24-h continuous infusion) were randomized to receive metoclopramide along with dexamethasone and clemastine with and without lorazepam. Lorazepam significantly reduced the incidence of anticipatory nausea and vomiting (P<0.05) as well as acute emesis (P=0.05) induced by cisplatin. Mild sedation and amnesia were significantly more common in patients receiving lorazepam (P<0.001). The authors concluded that lorazepam increases the efficacy of metoclopramide against cisplatin-induced anticipatory, acute, and delayed nausea and vomiting.

Clonidine and ANV

Clonidine is indicated for use as an antihypertensive, acting as an agonist at central alpha-2 adrenergic receptors, and its potential as an agent to decrease postoperative nausea and vomiting has been studied [10, 27]. It has also been suggested for prevention of ANV [9], but its use is limited by its potential side effects.

Psychological intervention and ANV

The efficacy of behavioral intervention methods in controlling aversive side effects of cancer treatments has

recently been reviewed; 67 published studies were identified. The results indicated that behavioral intervention can effectively control ANV in adult and pediatric patients undergoing cancer chemotherapy. However, evidence for the efficacy of behavioral intervention to control post-chemotherapy nausea and vomiting was mixed. The review also identified that behavioral intervention can decrease levels of anxiety and distress and to a lesser extent cancer-related pain [26]. This review is a valuable addition to a previous one in which various techniques (54 studies) of behavioral intervention for cancer treatment side effects were evaluated and which concluded that behavioral intervention can effectively control ANV in adult and pediatric cancer patients undergoing chemotherapy and also indicated that evidence for the efficacy of behavioral intervention to control postchemotherapy nausea and vomiting was less clear [32]. The techniques have varied, including hypnosis [16, 31] and biofeedback [4], and many variations of relaxation methods. It is of interest that even if anxiety levels of the patients are not always influenced, these techniques can control ANV [36].

A randomized controlled trial designed to assess the effectiveness of progressive muscle relaxation training (PMRT) in the clinical management of chemotherapy-related nausea and vomiting has been reported recently. A total of 71 chemotherapy-naive breast cancer patients received metoclopramide and dexamethasone as antiemetics and 38 subjects were randomized to the experimental group including the use of PMRT 1 h before chemotherapy and daily thereafter for another 5 days (for a total of six PMRT sessions). Each session lasted for 25 min and was followed by 5 min of imagery techniques. The use of PMRT considerably decreased the duration of nausea and vomiting in the experimental group compared with the control group ($P<0.05$), whereas there were trends toward a lower frequency of nausea and vomiting ($P=0.07$ and $P=0.08$, respectively). Neither nausea nor vomiting differed in intensity between the two groups [20].

Table 1 Recommendations for the management of ANV

The best approach to the treatment of anticipatory emesis is the best possible control of acute and delayed emesis
Level of evidence: ASCO II/MASCC high
Consensus: high
Recommendation
ANV should be managed by psychological techniques
Level of evidence: ASCO II/MASCC high
Consensus: high
ANV should be managed by psychological techniques and/or benzodiazepines
Level of evidence: ASCO II/MASCC moderate
Consensus: high

Conclusions

The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC) stated in 1998 [3] that the best treatment for anticipatory emesis is the best possible control of acute and delayed emesis. Based on the above review of the literature the 2004 panel has approved the 1998 recommendation and add the adjunctive suggestions shown in Table 1. Unfortunately, the use of behavioral intervention will remain difficult to implement, as most patients are treated in settings where the needed expertise is not available.

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