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Anticipatory Nausea and Vomiting

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Abstract

A commonly reported consequence of post-treatment nausea or vomiting is the development of anticipatory nausea and vomiting (ANV). In most published work, nausea is reported to occur before chemotherapy drugs are administered by approximately 20% of patients at any one chemotherapy cycle and by 25–30% of patients by their fourth chemotherapy cycle. Most studies in adult patients strongly support the view that the development of ANV involves elements of classical conditioning. The best method to avoid development of ANV is to adequately prevent both vomiting and nausea from the first exposure to chemotherapy. If anticipatory side effects develop, behavioral treatment techniques, such as systematic desensitization, have been shown effective. Benzodiazepines used in combination with behavioral techniques or antiemetics may also be useful. The evidence on which these conclusions are based is reviewed in this article.

Keywords

Anticipatory nausea; vomiting

Introduction

Anticipatory nausea and vomiting (ANV), also referred to as conditioned, learned or psychological nausea and vomiting, is widely believed to be a learned response to chemotherapy that 25% of patients develop by the fourth treatment cycle [34,35]. It appears to link psychological, neurological and physiological systems[8]. The risk of ANV tends to increase with the number of cycles received [30] and the symptoms may persist long after the completion of chemotherapy [20]. ANV is difficult to control by pharmacological means, whereas behavioral therapies, most notably systematic desensitization, can be used to effectively treat it.

The development of ANV best fits a Pavlovian conditioning model [16,30,48] shown below as Figure 1. There are no data about the development, clinical course or treatment of anticipatory side effects that are at variance with this model. In this conditioning model, a conditioned stimulus (CS) (e.g., the sight of a nurse) is paired with an unconditioned stimulus (US) (e.g., chemotherapy), which reliably produces an unconditioned response (UR) (e.g., nausea). Following the conditioning period (repeated chemotherapy treatments),

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the CS is able, over time, to provoke a conditioned response (CR) identical to the UR. In the situation of a patient receiving chemotherapy, he/she finds him/herself at the treatment location surrounded by unfamiliar sights, sounds and smells. In addition, various psychological, cognitive and social factors are present during this experience. These stimuli become associated with the chemotherapy treatment and the subsequent NV that follow the chemotherapy infusion. After repeated chemotherapy cycles in which these stimuli are paired with the experience of subsequent nausea, they acquire the ability to trigger a response of nausea or vomiting even before the receipt of chemotherapy (i.e., ANV).

Predicting ANV

Table 1 shows risk factors shown to be involved in the development of ANV. From a clinical standpoint, younger patients who have experienced severe and frequent nausea/vomiting after their prior treatments are at particularly high risk for the development of ANV. While the conditioning model is well accepted, cognitive factors, such as anxiety, self absorption, and response expectancies, can be involved in ANV development [4,33,35,55,60]. Anxiety may affect the development of NV at least in part through negative expectancies [4,5,22,56], since expectancies have been shown to affect the generation of conditioning effects [24,44,53].

Hickok et al. [19] 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 (AN) 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 ($\chi 2=13.15$, $P<0.001$) of actually developing nausea.

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 AN for younger adult patients but not for older adult patients. An increase in family conflict was also associated with a greater severity of AN for female patients but not for male patients. These findings suggest that intervention programs to help reduce family conflict and anxiety may be beneficial for younger adult and female patients [23].

Anticipatory emesis and the experimental setting

While there is no completely satisfactory laboratory model for ANV, some translational research on ANV has been conducted using a body rotation model as a nausea-inducing stimulus in humans and a conditioned gaping response in rats [18,26] in an attempt to develop better prevention and treatment interventions in addition to preventing post-treatment nausea and vomiting. Studies using the rotation model suggest that an overshadowing procedure could be helpful in reducing the development of ANV [48]. 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. Overshadowing has also been examined in a small study of cancer patients. In that 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 distasteful saline 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[50]. In the experimental animal settings examining the gaping response in rats, certain conditioning techniques, including: overshadowing [18,47,51], systemic treatment with lipopolysaccharide [10], tetrahydrocannabinol [38], manipulation of the endocannabinoid (EC) system [46] have been examined with inconsistent results. Tetrahydrocannabinol and cannabidiol have also been effective in reducing conditioned retching in a Suncus murinus model (musk shrew) [39]. Conditioning procedures in other animal models have been successfully used to alleviate nausea and vomiting [12,25].

Appropriate control of acute and delayed emesis reduces ANV

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 AN and 2% or fewer had symptoms of anticipatory vomiting [2].

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; 7 of the 10 (70%) had experienced anticipatory vomiting[57].

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 AN. In the CMF protocol, 79.6% had post chemotherapy vomiting, and 71.7% had post chemotherapy nausea associated with at least one cycle. In this group, 7.4% had anticipatory vomiting, and 16.6% had AN. 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 [15].

There is some preliminary data that the relationship between ANV and post treatment nausea may be bi-directional as indicated by findings from 40 early stage breast cancer patients who developed AN. A significant correlation between the intensity of AN in the clinic prior to their treatment infusion and subsequent pos-treatment nausea during the 24 hours after the infusion was found in 40 early stage breast cancer patients who had developed AN showing that, once established, conditioned nausea may contribute to the severity of subsequent post-treatment nausea in patients receiving repeated cycles of chemotherapy for cancer [7]. It is also 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 [49].

Treatment of ANV

Psychological intervention and ANV

Behavioral interventions are especially appropriate to address ANV because it is a conditioned response, and they are best implemented prior to the complete/full development of the undesired conditioned response [16]. Evidence suggests that behavioral intervention can reduce ANV, decrease levels of anxiety and distress, and to a lesser extent decrease cancer-related pain and nausea [36]. The techniques have varied, including hypnosis [29,42] and biofeedback [9], yoga [40] and many variations of relaxation methods [16]. It is of interest that even if anxiety levels of the patients are not always influenced, these techniques can control ANV [52]. As a learned phenomenon, ANV is treatable by means of behavioral approaches based on learning principles. Research on the behavioral treatment of conditioned adverse effects of chemotherapy has centered on three principal approaches: progressive muscle relaxation training (PRMT), systematic desensitization (SD), and hypnosis. PMRT appears to exert its greatest effects against adverse events that develop after administration of chemotherapy [32], although when combined with guided imagery, it has shown efficacy in reducing ANV [58].

SD is commonly used to treat learning-based difficulties, such as fears and phobias, and is particularly effective for ANV. One way in which phobias may develop is by means of the classical conditioning mechanism described previously. In many respects, anticipatory side effects display characteristics of phobic behaviors, although the match is far from perfect. SD involves the counter conditioning of a response incompatible with those stimuli that typically elicit a maladaptive reaction. In terms of ANV, the theory predicts that these symptoms would be reduced if patients could be taught an incompatible response (such as progressive muscle relaxation), rather than the conditioned response of NV, in response to the conditioned stimuli (the clinic; the nurse). This treatment has been effective in over half the patients to whom it is administered [13,34].

Hypnosis/suggestion has been used successfully to prevent AN related to chemotherapy[29,42] and to reduce nausea following chemotherapy [21,45,54,61]. Although hypnosis was the first psychological technique used to control ANV, few controlled studies have been done. It has most often been used with children and adolescents, which may be because children are more readily hypnotized than adults [16,27,34,37,45].

Acupuncture/Acupressure

According to the NIH Consensus Development Panel (NIHCDP), acupuncture is effective for the treatment of postoperative and chemotherapy-related nausea and vomiting[1]. Several studies, including a systematic review have shown efficacy of acupuncture and acupressure in reducing chemotherapy-related nausea[11,14,17,31,43]. No studies, however, have found any definitive evidence supporting the use of acupuncture and acupressure in alleviating ANV. One potentially related study reported benefit for the use of acupuncture in treatment of “nervous vomiting” in a dental setting [59].

Benzodiazepines and ANV

Razavi et al. [41] 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 AN (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 AN and controls sleeping problems secondary to adjunct chemotherapy.

Malik et al. [28] 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/m2 as a 24-h continuous infusion) were randomized to receive metoclopramide along with dexamethasone and clemastine with or without lorazepam. Lorazepam significantly reduced the incidence of AN 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.

Conclusions

This review updates work published in 2005.[3] In 1998 and again in 2005, the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC) stated [3,6] that the best treatment for anticipatory emesis is the control of acute and delayed emesis so that ANV does not develop. Based on the above review of the literature, the 2009 panel reaffirms that earlier recommendations add the adjunctive suggestions shown in Table 2. Unfortunately, the use of behavioral interventions will remain difficult to implement, as most patients are treated in settings where the needed expertise is not available.

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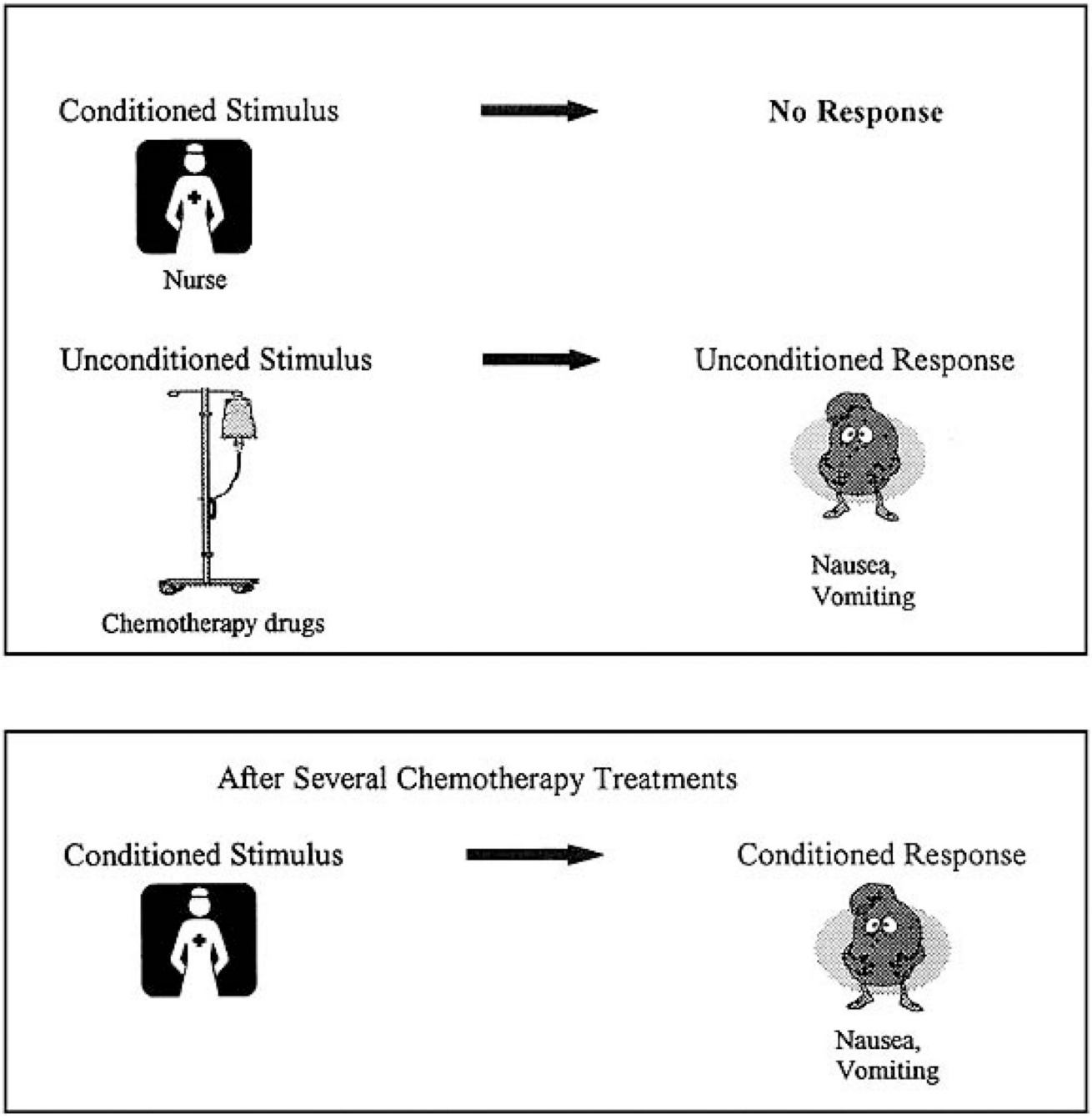

Fig 1.
Classical Conditioning of Nausea and Vomiting

Table 1

Risk factors for ANV

- Age less than 50
- Nausea/vomiting after last chemotherapy session
- Expectations of post treatment nausea
- Anxiety (both state and trait)
- Susceptibility to motion sickness
- Sweating or feeling warm all over after last chemotherapy session

Table 2

Guideline for managing anticipatory nausea and vomiting in patients receiving chemotherapy or radiation therapy

Anticipatory nausea and vomiting should be managed by psychological techniques.
MASCC level of confidence: High
MASCC level of consensus: High
Use of benzodiazepines may be useful in preventing the development of ANV when used in conjunction with antiemetics (no new data since 2003)
MASCC level of confidence: Moderate
MASCC level of consensus: High