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REVIEW ARTICLE

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Anticipatory nausea and vomiting in the era of 5-HT_3 antiemetics

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Abstract Cancer chemotherapy is known to lead to nausea and vomiting in a large proportion of cases. If emesis is severe it can lead in its turn to anticipatory nausea and vomiting (ANV), which cannot be controlled by antiemetic medication. The etiology of ANV and various methods that have been used to counteract the condition are discussed.

Key words Cancer · Chemotherapy · Antiemetics · Anticipatory nausea and vomiting · Behavioral therapy · Anxiety

Introduction

Patients have reported nausea and vomiting (NV) following the administration of chemotherapy ever since the drugs were first used to treat cancers. Fortunately, since that time, pharmacological control of chemotherapy-induced nausea and emesis has improved. Still, even with the widespread use of the new 5-HT_3 antiemetic agents, such as ondansetron (Zofran), approximately 40% of patients still develop emesis following chemotherapy and over 75% report nausea. If not adequately controlled, these side effects can lead to further complications, such as anorexia and metabolite imbalance, and also contribute to a general deterioration of the cancer patient's psychological and physical condition [4]. The impact of inadequately controlled nausea/vomiting on patient's quality of life is also substantial. One commonly reported consequence, caused by the conditioning effect created by frequent and/or severe posttreatment NV, is the advent of anticipatory NV (ANV). ANV, which develop in approximately 30% of patients by the fourth treatment cycle, appears to link psychological, neurological and physiological systems [5]. Once they develop, ANV cannot be controlled by antiemetics, including the new 5-HT_3 receptor antagonists. Fortunately, behavioral interventions have been effective in mitigating these side effects, and low doses of the anxiolytic agent alprazolam may be potentially useful as a pharmacological preventive intervention [36]. This paper will examine these interventions as well as the prevalence and etiology of ANV.

Etiology of ANV

Several characteristics of ANV suggested that its mechanisms might fit within a learning model. Potential conditioned stimuli (such as the sight of the nurse or other sights, sounds, or smells of the clinic) are present while the chemotherapeutic agents (unconditioned stimulus) that produce the unconditioned response (nausea and emesis) are administered. Over several trials (chemotherapy cycles), the conditioned response stimuli (sights, sounds and even thoughts of the clinic) can be learned; they then pro-

duce what is now the conditioned response of ANV. The frequency of ANV increases almost linearly with the number of chemotherapy cycles given [29] and is related to both the frequency [41] and severity of posttreatment NV. Anticipatory side effects seldom develop unless posttreatment side effects have occurred. Few patients in our series of over 4,000 developed anticipatory nausea without having experienced posttreatment nausea at least once. Other research also supports the conclusion that ANV involves elements of classical conditioning [3–5, 31, 38–40], and no data convincingly contradict the conclusion that ANV is learned.

Several investigators have speculated that anxiety may be involved in the development of anticipatory side effects. Andrykowski [2] and Andrykowski et al. [3] provided evidence that elevated levels of state anxiety may precede the initial occurrence of anticipatory symptoms. These authors caution, however, that the relationship between anxiety and anticipatory side effects may not be a strictly causal one. Their data also support a view that anxiety may be heightened following a particular chemotherapy treatment and that, in turn, the increased anxiety may increase posttreatment nausea/vomiting which, in turn, may increase susceptibility to conditioning on the next chemotherapy cycle. This circular process may facilitate and promote a conditioning process rather than serve as a direct cause itself. It is likely that some degree of anxiety facilitates the conditioning process by alerting or sensitizing the patient in much the same way as somebody who is mildly anxious may be quite prone to suddenly notice and become concerned over a physical sensation, such as irregular heart beats, that had probably been present for a period of time.

A further complication to fully understanding the relationship between anxiety and ANV is that anxiety, which develops initially as a consequence of chemotherapy-related NV, can itself become a conditioned response [10, 15, 19, 35]. This may lead to a situation in which both ANV and anticipatory anxiety develop as a consequence of repeated nausea-producing chemotherapy treatments [18, 38], with each possibly contributing to the magnitude of the other.

It is also known that autonomic, particularly sympathetic, reactivity correlates with the development of conditioned responses. Kvale's group [20, 21] has demonstrated a connection between autonomic reactivity and subsequent development of ANV. Patients in both studies who experienced ANV showed significantly increased sympathetic reactivity compared with patients who did not experience ANV. Similarly, Challis and Stam [8] found that patients who experienced ANV showed significantly higher levels of awareness concerning their autonomic activity than did patients who did not experience ANV. Another group of investigators found increased parasympathetic autonomic conditionability, measured by the development of conditioned heart rate deceleration, in patients with a history of conditioned nausea in response to chemotherapy; patients without conditioned nausea did not develop the conditioned heart rate deceleration [13]. These findings are suggestive of a mediational role for autonomic reactivity in ANV development.

Prevalence of anticipatory nausea and vomiting

The average prevalence of ANV compiled from 35 published studies [33] comprising 4,382 adult and pediatric cancer chemotherapy patients was 29% for anticipatory nausea and 11% for anticipatory vomiting. Reported rates among the studies varied widely. On the lower end of estimates, 18% of 71 patients examined by Nicholas [34] reported anticipatory side effects, while Cella et al. [7] reported that over half of 60 patients previously treated for Hodgkin's disease developed ANV. Factors that contribute to this variance in rates include differences in: (1) the emetic potential of the chemotherapy drugs administered, (2) measurement methodology (e.g., what treatment cycle was investigated, whether reports were compiled retrospectively or as patient logs, and whether or not NV symptoms were recorded independently of each other or combined as one phenomenon), and (3) the definition of NV (i.e., some investigators record any nausea or vomiting that occurs *during* chemotherapy treatment as anticipatory effects, whereas other researchers consider NV symptoms at that time to be a physiological response to the chemotherapy drugs).

Perhaps the best way to avoid some of the methodological and definitional issues associated with this field of research is to look primarily at the University of Rochester Cancer Center study. We collected data on 2,877 patients treated in geographically diverse member sites of the URCC Community Clinical Oncology Program, all of whom were assessed with the same scale (Morrow Assessment of Nausea and Emesis [26]) at a standard point in their treatment (prior to the fourth chemotherapy cycle). It appears that the cross-sectional prevalence rate for anticipatory nausea is around 20%, with approximately one-third of all patients experiencing the symptom at least once by the fourth treatment. Approximately 8% of patients had at least one occurrence of anticipatory vomiting during this time period.

We compared patterns of chemotherapy-related NV in a group of 300 of these patients treated consecutively just prior to the availability of 5-HT_3 antiemetics (September 1987 to January 1991) with those of the 300 most recently treated patients (September 1993 to February 1995). Age and gender were comparable between groups. Eighty-six percent of the patients in the later group received 5-HT_3 antiemetics. A significant reduction over time in the number of patients reporting at least one episode of posttreatment vomiting (51.7% and 41.3%, $P<0.02$), but no difference in posttreatment nausea (78.7% and 76.7%, $P>0.5$) was found. No significant differences were seen in the reported severity of either symptom. A significant increase in the average duration of both posttreatment nausea (from

28.1 h to 37.2 h, $P<0.002$) and posttreatment vomiting (from 10.8 h to 16.5 h, $P<0.02$) occurred.

The numbers of patients experiencing at least one episode of anticipatory nausea (from 31.0% to 32.0%) or anticipatory vomiting (from 8.3% to 6.3%) were not significantly different ($P>0.3$) for all comparisons). Nor were there significant differences between groups in duration or severity of anticipatory symptoms ($P>0.3$ for all comparisons).

Pharmacological treatment of ANV

Antiemetics do not control ANV once it has developed, and indeed have been found by some investigators to paradoxically increase symptoms [6, 23, 25, 28, 30, 32], perhaps by acting as conditioned stimuli themselves [30]. Once developed, ANV does not appear to improve spontaneously [30, 32]. A preliminary study by Razavi et al. [36] does suggest, though, that a potentially useful pharmacological preventive intervention may be low-dose alprazolam (0.5–2 mg) taken daily. Razavi et al.'s double-blind, placebo-controlled study of 57 women with breast cancer patients found a significantly higher occurrence of anticipatory nausea (18% vs 0%) in the placebo arm than in the alprazolam arm of the study. This significant difference between groups was found prior to the third treatment but not at later treatments.

Behavioral treatment of ANV

Systematic desensitization (SD), or counterconditioning, is a well-developed, standardized behavioral technique that is effective against ANV associated with cancer chemotherapy [11, 14, 16, 24, 28]. A key element of SD is the construction of a hierarchy of events related to the original stimulus that elicit the maladaptive response in each patient. This hierarchy might include events related to administration of chemotherapy, such as driving to the clinic, entering the treatment room, and seeing the clinic nurse. Following this, the patient is trained to associate an alternative response (for example, deep muscle relaxation) with these events [27, 28]. SD can be taught to patients in about 20 min, and properly trained nurses and oncologists can clinically use SD with about the same effectiveness as can trained behavioral consultants [32].

Hypnosis has been shown in several studies, most of them involving children and adolescents, to be effective in treating ANV [6, 9, 17, 22, 42, 43]. It is a self-control technique in which patients learn to invoke a physiological state incompatible with NV [37]. In the method usually used to produce the altered state of consciousness, induction of total body relaxation is followed by presentation of restful psychic imagery. Suggestions for specific treatment objectives, such as increasing food intake, can then be made [13, 22] or subjects can be led to visualize a series of events (for example, those associated with ANV), a technique similar to SD [37]. Patients can undergo chemotherapy while hypnotized [37].

Conclusions

Currently available pharmacological agents are still unable to provide complete protection from either anticipatory or posttreatment nausea and emesis associated with chemotherapy. While the introduction of the 5-HT_3 antiemetics has led to a reduction in the frequency of posttreatment vomiting, this comes at the apparent expense of an increase in the duration of posttreatment nausea and emesis when they do occur. Therapeutic effects on anticipatory symptomatology have been limited. A multidisciplinary approach that includes the best possible pharmacological control of postchemotherapy nausea and vomiting, drugs as needed to decrease anxiety, and adjunctive behavioral treatment, ideally given prophylactically [1, 12, 22, 23, 25] remains the best treatment option for ANV.

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