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Prevalence of Anticipatory Nausea and Other Side-effects in Cancer Patients Receiving Chemotherapy

Robert A. Boakes, Nicholas Tarrier, Benjamin W. Barnes and Martin H.N. Tattersall

98 patients receiving chemotherapy for cancer were interviewed to determine the prevalence of anticipatory nausea and vomiting, anxiety and dietary changes. Among those who had received at least four treatments 41% reported at least mild anticipatory nausea (AN). For 24% this was a moderate to severe problem, which was significantly associated with a high level of anxiety about treatment. Prevalence at this level was independent of whether the subject was receiving treatment as an in- or an outpatient. Anticipatory vomiting (AV) was reported by only 12 patients, of whom 11 were women; this was the only effect of gender found in the sample. Independence between moderate AN and AV was also suggested by a difference in type of event triggering the effect: predominantly odours for AN and thoughts of the treatment for AV. Changes in diet after commencing chemotherapy were reported by 50% of patients who had received at least four treatments. These most commonly took the form of aversions to meat and then to coffee, and were attributed most frequently to changes in taste and then to loss of appetite.
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INTRODUCTION

NAUSEA AND vomiting are common side-effects of chemotherapy for cancer patients. They are viewed by patients as the most distressing of all such effects [1], as was confirmed in the present study. Post-treatment nausea and vomiting is produced as a direct effect of chemotherapy and can last for 48 h or more after treatment. Anticipatory nausea and vomiting (ANV) occurs outside this period and has a psychological basis in the sense that it is triggered by events that have no direct physical effect. Both post-treatment and ANV are prevalent in chemotherapy despite the development and careful use of various antiemetic drugs. Consequently a number of psychological procedures, such as relaxation training and systematic desensitisation, have been used to treat ANV [2]. These are based, at least loosely, on the assumption that its psychological basis is some form of conditioning process.

The present study was undertaken as a preliminary to a project designed to compare the efficacy of different forms of treatment for ANV. Before beginning this project data were needed on the prevalence of ANV and other side-effects in the hospital setting where the project was to be undertaken. Several previous studies have measured the prevalence of ANV and have produced widely differing estimates [2, 3]. None of these was based in Australia and it seemed possible that local conditions might produce a different rate from those obtaining in North America where the majority of other studies have been carried out.

While the main point of the study was to establish the prevalence of ANV locally, many questions in the survey were on other side-effects related to psychological approaches to treatment. Thus, one conditioning model of ANV [4] places emphasis on the role of anxiety and on the therapeutic value of acquiring skills to control anxiety. Consequently, patients were asked separately about the degree to which they had experienced ANV and about anxiety concerning chemotherapy, to determine whether responses to these items might be strongly associated. A different conditioning model [5] has emphasised its similarity to nausea-based conditioning in animals where highly selective

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aversions may be established, in particular, towards the taste and smell of ingested food or fluid, but also, less strongly, to places and other events. Related studies have examined the development of food aversions and loss of appetite as a consequence of chemotherapy [5, 6]. Consequently, patients were also asked about dietary changes.

In summary, the primary aim of the study was to estimate prevalence of ANV in an Australian hospital setting, while a secondary aim was to examine possible associations between different side-effects which might have clinical implications.

PATIENTS AND METHODS

Subjects

A sample of 98 subjects was selected from the population of cancer patients attending The Royal Prince Alfred Hospital, Sydney, Australia for chemotherapy during the period May–December, 1990. The only criterion for inclusion was to have received at least one treatment, in the sense of a single exposure to a parenteral chemotherapy regimen. However, as noted below, some analyses were restricted to a subsample of 58 patients who had received at least four chemotherapy treatments. Following the aim to include equal numbers of in- and outpatients receiving chemotherapy, the sample consisted of 47 inpatients and 51 outpatients; the latter included both patients attending outpatient clinics and those treated in the Oncology Department who were not required to remain overnight. There were 31 males and 67 females. Their ages ranged from 17 to 75 years, with approximately equal numbers in the following four subranges: 17–35; 36–45; 46–60; and over 60 years old.

Subjects were being treated for a wide range of cancers. Among inpatients the most common were, in rank order, testicular and lung cancer in males, and breast and ovarian cancer in females; among male outpatients no particular form of cancer was common, while among females, overwhelmingly, the most common was breast cancer. The types of parenteral chemotherapy received were also very diverse. Subjects received antiemetic medication as part of their drug regimen according to standard clinical practice within the hospital, or as participants in a randomised trial [7]. Only in the case of 4 patients was there indication from case records or the subject's own report that additional treatment had been given for ANV; in 3 of these cases this consisted of additional lorazepam.

Questionnaire

This was administered by interview and consisted of four main sections, each containing from three to five questions. Section A asked about anticipatory nausea, B about anticipatory vomiting, C about anxiety and D about dietary changes. A final section concerned possible coping strategies. In the main sections the first question was designed to provide an estimate of the prevalence of a particular effect. Thus, in section A the first item provided four response categories—none, mild, moderate or severe—to the question as to whether the patient had experienced anticipatory nausea (AN). This was defined as "feeling sick before a further course of treatment or as a reaction to things that reminded you of past courses". The first question in section B was identical in form, but concerned anticipatory vomiting. Subsequent questions were designed to gain further information on an effect from those patients reporting it.

The record sheet for each subject also included information gained from case notes such as age, type of cancer, type of chemotherapy, antiemetics and number of treatments.

Procedure

A single interview was carried out either by a member of the regular nursing staff or by a research assistant. This took place during the patient's visit as an outpatient or stay on the ward at a time when he or she was waiting for treatment, for an appointment or for the results of a test. The interview lasted from 10 to 20 min. In asking a patient to participate, it was explained that the interview was part of a survey to establish how common were some side-effects of chemotherapy, that there would not be any pressure to continue if the patient preferred that the interview should end and that all information would be treated in confidence. Once spoken consent had been given, which occurred in every case, the interview commenced immediately.

Statistical analysis

Crosstabs analysis (SPSS) was used to test for relationships between responses. Where significant associations between measures are reported below, these are based on χ^2 tests (Pearson) using an alpha value of 0.05.

RESULTS

Anticipatory nausea

Since patients who have received fewer than four treatments are less likely to have developed AN [2], prevalence was calculated from the remaining subsample. Reports of at least mild AN were obtained from 52% of inpatients in this subsample ($n=23$) and from 34% of outpatients ($n=35$). Using a higher criterion of at least moderate ANV the prevalence rates were 30% for inpatients and 20% for outpatients. These differences between in- and outpatients were not significant and the overall prevalence rate was 24%. There was a suggestion that prevalence was lower (15%) in older, i.e. aged 50 years or more, outpatients, but no significant effect of age was detected.

The records of the 14 patients in the subsample reporting at least moderate AN were examined for possible associations with particular types of cancer or chemotherapy regimen. 6 were being treated for breast cancer, including 5 with cyclophosphamide-methotrexate-5-fluorouracil and 1 with epirubicin plus cyclophosphamide. This reflected the large number of these patients in the sample, since prevalence of AN in breast cancer patients was not found to be higher than in the remainder of the sample. In the remaining 8 patients no disease type was represented more than once.

In the whole sample there were two associations between AN and other items which were significant ($P < 0.05$). Of patients reporting at least moderate levels of AN in section A 60% also reported experiencing anxiety to the extent of involving physical symptoms in relation to their treatment, whereas only 31% of other patients did so. A high proportion, 73%, of the same patients reported developing particular strategies to cope with the effects of chemotherapy, whereas only 32% of other patients did so.

Further questions in section A were asked only when at least mild AN was reported in answer to the first question ($n=40$). One of these was concerned with when AN tended to occur. Where a particular time could be identified, for the majority of patients this was at least 24 h prior to therapy. Another question sought to establish what kinds of events tend to trigger AN. The most common response ($n=14$) was smells, the next 'no particular event' ($n=8$) and the third was places ($n=7$). A third question asked how many times a subject had received chemotherapy before AN first became a problem. Analysis of

these reports was restricted to the subsample that had received at least four treatments. As shown in Fig. 1, almost 40% reported that this occurred after the first treatment.

Anticipatory vomiting (AV)

Only 12 patients reported this effect, and it was the only one for which gender was a significant factor: 11 of these patients were women. This was not associated with a particular form of cancer or treatment. Thus, although 7 of these women were being treated for breast cancer, this is consistent with the fact that half of the women in the overall sample had breast cancer. It was expected that AV would be reported only by those indicating moderate or severe AN; this was not the case in that 5 of these 12 patients reported no or only mild AN. The most common trigger for vomiting was 'thoughts of the treatment', reported by 7 of this group, while no other type of trigger was reported by more than one subject. Thus,'smells' which was the most commonly reported trigger for AN was reported by only one of these patients.

Anxiety and fears

The first question asked whether a subject experienced anxiety or tension in relation to treatment, and required only a yes/no response. Inpatients were significantly more likely (70%) than outpatients (49%) to answer yes to this question. For just over half the patients reporting anxiety, this was accompanied by some form of physical symptom, of which a dry mouth was the most common, followed by sweating and by changes in heart rate.

The next question was concerned with the development of particular fears. These were reported by 28 patients, of whom 57% identified fear of the needles used for intravenous injection. No other specific fears were common. In particular, there was no indication of any tendency for chemotherapy patients to develop agrophobic-like disorders, as would be suggested by reports of fear of travelling or leaving home.

The final question in this section asked patients what side-effect of chemotherapy caused most distress. The most frequent response, given by almost a third of patients, was nausea and vomiting. This was followed by hair loss (23%), tiredness (19%) and then by a wide variety of effects reported by 6% or fewer patients, including soreness of the mouth and diarrhoea.

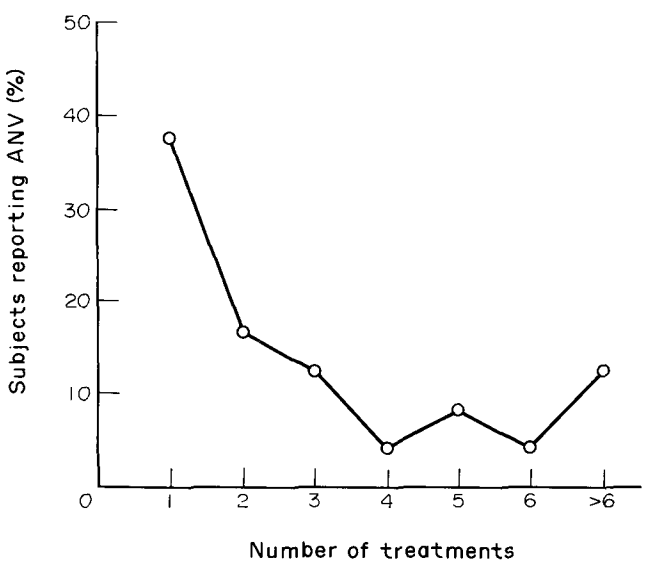

Fig. 1. Number of treatments before anticipatory nausea (AN) reported as becoming a problem. Only those patients who had received at least four chemotherapy treatments are included here.

Dietary changes

In response to the first question in this section moderate to large changes in general liking for foods and drinks were reported by 33% of patients, and by 50% of the subsample who had received four or more treatments. A particularly high frequency (74%) was found for inpatients in this subsample. There was enormous variety in the foods for which patients reported increased liking or the development of a craving in answer to the second question. Examples included: sweet items such as chocolate and fizzy drinks; savoury items such as vegemite and cheese; high protein foods such as milk, eggs and seafood; low protein and low fat foods such a fruit, fruit juices and salads. Perhaps more interesting in the light of the question that followed were items that did not appear on this long, heterogeneous list: no subject reported increased liking for meat or for tea, while only one subject described switching from tea to coffee.

In answer to the next question, about previously liked items that had become unappealing, the most common reply was meat (17% of all patients), followed by coffee (13%) and tea (9%). Of the 58 patients providing a main reason for their dietary change, 41% (24 patients) referred to changes in the tastes of foods—either a loss in taste, a change to a metallic taste or some other change—and 17% (10 patients) to a general loss of appetite. Other reasons were infrequent; they included medical advice (3%), decision to eat healthier foods (7%), attempt to increase weight (9%) and the effect of mouth ulcers (5%).

Other items

The final section of the questionnaire asked patients whether they had developed a particular strategy to cope with the effects of chemotherapy. Positive responses were given by 38% of patients and, as noted above, these were strongly associated with reporting anticipatory nausea. Individual strategies varied widely, but were mainly of four general types: adopting a positive attitude; keeping occupied, maintaining social contacts and other activities which block out thoughts of the illness and treatment; use of relaxation and meditational techniques; and diet and other changes specifically directed towards reducing anticipatory nausea.

DISCUSSION

The main aim of this survey was to establish the prevalence of ANV under the conditions prevailing at the Royal Prince Alfred Hospital. Using a low criterion for AN, whereby the response 'mild' was included, then this side-effect of chemotherapy was found in 41% of patients who had received at least four treatments and tended to be higher in inpatients. Twenty-eight previous surveys, carried out since 1979 and primarily in North America, have been summarised in a recent review by Morrow and Dobkin [2] to produce prevalence estimates for anticipatory nausea ranging from 14 to 63%, with a median of 33%. This wide range reflects considerable variability across studies in terms of size of sample, patient populations, distinguishing between anticipatory and post-treatment nausea, stage of treatment at which data were collected, and measurement criteria. Furthermore, the context in which a questionnaire is given clearly influences how patients interpret terms like 'mild' or 'severe'. The present sample size was no doubt too small to detect many potentially significant associations between the

variables measured in the survey, but nonetheless was larger than most of the surveys referred to above. One unexpected discrepancy between the present results and previous studies was the time at which patients reported AN as first becoming a problem. Whereas this was most frequently reported as occurring after the first treatment (see Fig. 1), previous reports give a later time, namely, until at least after the second or third treatment [2]. These have been obtained by monitoring patients while receiving chemotherapy, while our data relied on patients' memory for events that had often occurred some considerable time before the interview. The possibility that recall is biased towards the start of treatment is currently being investigated in a project involving the same hospital population which monitors AN during treatment.

From a clinical viewpoint AN is likely to be of interest only for patients who report it to be a 'moderate' or 'severe' problem. Using this higher criterion, the prevalence rate in the present survey was 24% for patients who had received at least four treatments. This is almost identical to the previous North American survey employing the largest sample [10], which employed a comparable criterion and was superior methodologically to many of its predecessors. This yielded a prevalence rate of 23%. The present survey found no strong evidence to confirm previous indications [2] that such patients are more likely to be young and to be receiving cisplatin-based treatments. This may be because the sample was too small or that the use of antiemetics in the chemotherapy regimens employed at the Royal Prince Alfred Hospital is well designed to take account of these factors.

The association between AN and anxiety found in the present survey may reflect both cause and effect. Earlier research indicates that patients with high trait anxiety [11] and those reporting anxiety during early injections [12] are more likely to develop AN, while associations between anxiety and AN are more likely after several cycles of chemotherapy have been given. An association between AN and attempts to cope with chemotherapy has been reported previously [13]; in the present case this may simply indicate that those patients who are more distressed by their therapy are more likely to search for ways of reducing this distress.

Previous studies have treated ANV as a unitary effect. In the present survey questions on nausea and on vomiting were placed in different sections, but it was anticipated that the responses and characteristics of those reporting AV would be very similar to those reporting severe AN. Two aspects of the data indicate that this is not the case and suggest that there is a distinctive group of patients reporting AV. First, this was the only association with gender found in the whole analysis. As reported by Morrow and Dobkin [2], of 11 previous studies that have looked for a gender effect on ANV, only two have found this, with both reporting higher prevalence of ANV in females [14, 15]. However, in the single published report of such a gender effect [14] there was a large group of patients receiving treatment for primary breast cancer, in which the prevalence of ANV was far higher than in any other group. Secondly, those reporting AV were most likely to report that it was triggered by thoughts of the treatment rather than by the smells which were most fequently reported as a trigger for AN. Such a distinction does not appear to have been suggested by previous studies, and it is not at all clear how it might be explained.

Responses to the questions on dietary changes are consistent with the suggestion that these largely result from a conditioning process which generates aversions to particular foods [5]. As previously found in the case of cancer patients and in experiments using an animal model of food aversion learning, such conditioning can be highly selective in that aversions are most likely to be acquired to high protein foods such as meat. As such aversions develop and disrupt normal dietary habits, then switches to a variety of alternative foods occur. Responses to the question about liking new foods were notable for their diversity. Why aversions to meat are so common is unclear. In the case of conditioned food aversions in rats it has been found that the distinctive odour of protein-rich foods is important in making these a target for conditioning and that post-ingestional processes are unimportant [16]. However, in the case of cancer patients it seems highly likely that consumption of meat exacerbates any gastrointestinal malaise resulting from chemotherapy, thus increasing the likelihood of an acquired aversion. The same account cannot be easily applied to the two next most common aversions, coffee and tea, which have also occupied this ranking in other studies [17, 18]. In this case what may be important is that, of all foods and drinks, tea and coffee are what patients are most likely to have contact with, if only smelling them, during the period prior to and for many hours after receiving chemotherapy.

With regard to the relevance of the aversive conditioning model to ANV two aspects of the results may be noted. First, that no association between ANV and any form of dietary change was detected. It was anticipated that a weak negative relationship might be found, whereby for patients experiencing considerable post-treatment nausea ANV would be more common in the absence of a conditioned food aversion. This was predicted on the basis that a food might serve as a target for conditioning and thus overshadow other types of potential triggers for ANV. The second point is that, although the most common trigger for ANV was a smell, the most common explanation given for diet changes was a change in taste. The latter explanation is consistent with a conditioned decrease in the hedonic value of particular tastes. It is also consistent with the possibility that chemotherapy acts directly on taste receptors to change their relative sensitivity.

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Correlation Between Changes in the Tumour Markers CA-M26 and CA-M29 and Standard Response Evaluation in Patients with Metastatic Breast Cancer

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In this study we correlated response evaluated by standard WHO criteria to strict defined criteria of tumour marker response in 63 patients with metastatic breast cancer. Pretreatment sensitivity at first evaluation was 71% and 85% for CA-M26 and CA-M29, respectively. Of the 156 evaluations for CA-M26 and 178 for CA-M29 in 26 and 30 patients with evaluable lesions 72% and 67% were concordant with the results of the clinical evaluations. When the discordant evaluations due to lead time were included the concordances were 87% for CA-M26 and 83% for CA-M29. Of the 70 evaluations for CA-M26 and 92 for CA-M29 in 19 and 24 patients with non-evaluable lesions 59% and 72% were concordant with the results of the clinical evaluations. Most importantly, progressive disease according to the changes in the marker level nearly always predicted disease progression. Such knowledge obtained in a simple way may prevent continuation of ineffective treatment in patients with metastatic breast cancer.
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INTRODUCTION

A RELIABLE EVALUATION of response in patients with metastatic disease is important since continuation of a potentially toxic treatment in case of disease progression is not in the benefit of the patient. In patients with metastatic breast cancer the evaluation of response is frequently hampered by the lack of evaluable lesions in more than 50% of the patients. Especially in patients with bone metastases, regression or progression is very hard to ascertain even with nuclear bone scans or X-rays. Decisions to continue treatment or not are often based on subjective considerations.

Although a number of studies have investigated the role of serum tumour markers for disease monitoring, virtually none define criteria for marker response and or correlate these with response assessments according to standard WHO criteria [1–2]. In most longitudinal studies the results are often presented as case reports or as a three point analysis [3–5].

In the present study it was investigated whether two newly developed markers, CA-M26 and CA-M29, could be used for disease monitoring in patients with metastatic breast cancer. The results of response evaluations according to standard WHO criteria [6] were compared with strictly defined criteria of response evaluation by the two markers.

MATERIALS AND METHODS

CA-M26 and CA-M29 serum levels were retrospectively analysed and subsequently compared with the results of the clinical evaluations of response in a group of 63 patients with metastatic breast cancer, who underwent either hormonal treatment or chemotherapy. In these patients blood samples for determination of CA-M26 and CA-M29 serum levels were collected at

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