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The Roles of Patient and Observer Assessments in Anti-emetic Trials

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The endpoints assessed by both patients and nurses were compared in three anti-emetic studies. In a parallel subjects study, there was no significant difference between the patients' and nurses' assessment of the number of vomiting episodes, but the duration of vomiting, the severity and duration of nausea, and the side-effects of the anti-emetic were given higher scores by the nurses. In two cross-over studies, the patients recorded more vomiting episodes than the nurses, while the nurses recorded more anxiety and sedation than the patients. This resulted in the patients detecting a difference between the side-effects of the anti-emetics being compared that was not apparent from the nurses' forms. Many of the differences reflect differences in the timing and frequency of data collection. Nurses collected data regularly during the assessment period whereas patients reported their experiences only at the completion of 24 h. Both assessments provide useful perspectives on the study outcomes.

Key words: anti-emetic, nausea, vomiting, assessment, patient, nurse, data collection
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INTRODUCTION

IN THE design of many anti-emetic studies, both the patient and an observer assess and record the efficacy of the drugs being studied [1]. It is important to determine how well these assessments correlate.

Intuitively, one might expect that objective parameters, such as the number of vomits, would be recorded more accurately by observers, particularly if sedation were a side-effect of the anti-emetic. Subjective sensations, such as nausea or anxiety, can only be assessed meaningfully by the patient, and an observer should question the patient directly before recording such parameters.

Kris and colleagues reported that the correlation between directly observed and recalled number of emetic episodes was excellent ($r = +0.98$, $P < 0.001$) in a study of nausea and vomiting after high-dose cisplatinum [2]. Fetting and colleagues reported a significant relationship between patients' self-reporting of nausea and that of observers ($P < 0.025$ by χ^2 test) in studying the emesis after high dose-cyclophosphamide [3]. However, they stated that self-report was an inexact way of monitoring emesis when vomiting episodes could easily be counted by an observer. Parikh and associates agree with this, and reported only vomiting as a measure of anti-emetic efficacy because they felt that the more subjective nausea could not be assessed accurately [4].

However, the endpoint in assessing an anti-emetic is not just control of emesis, but the patients' overall experience of their therapy. This allows the influence of other factors, such as the toxicity of the anti-emetic, to be balanced against any improved control of emesis.

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In cross-over phase III comparisons of anti-emetics, the patients' preference must be one of the most important endpoints. Examples can be cited where patient satisfaction was found to correlate with good control of emesis [5, 6], whereas other factors influenced the patients' choice in other studies [7, 8]. Nurses or other observers can collect the data on efficacy and toxicity endpoints, but the overall assessment of benefit of an anti-emetic will depend on the patients' value systems as they are reporting their personal experience. Patients are, therefore, the only ones who can give a global assessment of benefit, and this may differ from an observer's interpretation of the results.

To investigate the relationship between patient and observer assessments, we compared them in three consecutive anti-emetic studies at the Peter MacCallum Cancer Institute. Two of these were of a cross-over design, while the other was a parallel subjects design.

PATIENTS AND METHODS

Parallel subjects study

The parallel subjects study analysed was a randomised comparison of high-dose prochlorperazine with high-dose metoclopramide [9]. 200 patients were entered, and at the completion of the 24-h trial period, were given a questionnaire to assess nausea, vomiting and side-effects, including sedation, extrapyramidal and autonomic effects. The nurses recorded their observations hourly. They directly observed objective parameters, such as number of vomits, but questioned the patients about the subjective sensations such as nausea.

Crossover studies

The first of the double-blind crossover trials compared prochlorperazine and lorazepam with high-dose metoclopramide and lorazepam, and provided data on 132 courses from the 66 patients who completed the study [10]. The second trial compared prochloperazine plus lorazepam with or without dexamethasone. Data was available on 168 courses from the 84 reported patients [11], who received both courses with equal

chemotherapy doses and a further 34 courses from patients who either completed only one study course or had chemotherapy dosage modifications for the second course. The patients completed a questionnaire 24 h after each course of chemotherapy, where they recorded the number of vomiting episodes and the duration of nausea and vomiting, and graded the severity of vomiting, nausea and the side-effects, sedation and anxiety, on five-point categorical scales. After assessing their second course, they were asked to record their course preference. The nurses assessed the patients over the 24 h following each course, recording the data at the completion of each 8-h shift.

Statistical methods

Patient and observer assessments were compared using Wilcoxon's signed-rank test for paired data and the correlation between the two assessments was measured by the Spearman rank correlation coefficient. For categorical data, the scores assigned to the grades (1 to 5) were used in all analyses. Comparisons of patient and observer assessments of the incidence of individual toxicities were compared using McNemar's test.

Treatment effects in the second cross-over trial comparing dexamethasone with placebo were estimated using standard methods for crossover trials [12]. Wilcoxon's rank sum test was used to test the significance of each treatment effect [12]. Two-tailed tests of significance have been used throughout.

RESULTS

In the parallel subjects study, there was no significant difference in the patients' and nurses' rating of the number of vomiting episodes ($P = 0.83$, Table 1). The duration of vomiting, however, was assessed as longer by the nurses than the patients ($P = 0.002$), despite the significant correlation between the two assessments ($P < 0.0001$). Both the severity and duration of nausea were assessed as longer by the nurses than the patients ($P < 0.0001$ for each parameter), again despite significant correlations.

In assessing the toxicities of the regimen, the nurses reported significantly higher incidence of sedation ($P < 0.0001$), restlessness ($P < 0.0001$) and dry mouth ($P = 0.0002$) than did the patients (Table 2).

In the crossover studies, the patients recorded a higher number of vomiting episodes than the nurses ($P = 0.001$, Table 3). This was more pronounced in the first study. This difference was not observed in the parallel subjects study where the nurses kept more frequent and presumably more accurate records. It might have been expected that there would be good agreement between the nurses' and patients' assessments when the patients either had no vomiting or just one or two episodes, but there was a surprising disagreement even in those cases (Table 4). There was no difference in the crossover studies between the patients' and nurses' assessments of the duration or severity of vomiting.

Table 2. Parallel subjects study: comparisons of nurses' and patients' assessments of toxicity

Toxicity	Toxicity reported by: Neither	Nurse only	Patient only	Both	P
Sedation	6	43	1	149	<0.0001
Restlessness	85	46	8	60	<0.0001
Muscle spasms	160	11	9	19	0.65
Blurred vision	176	9	4	10	0.17
Dry mouth	70	29	7	93	0.0002
Skin rash	193	3	2	0	0.65

There was very poor correlation between the nurses' and patients' assessments of anxiety and sedation. In grading the side-effects, the nurses tended to record higher levels of anxiety ($P < 0.0001$) and sedation ($P = 0.005$) than the patients, frequently recording mild or moderate anxiety or sedation where none was recorded by the patient (Table 5). In the possibly more important assessment of severe or very severe side-effects, there was no agreement at all for anxiety and very poor agreement for sedation between the nurses' and patients' assessments.

The question of whether the assessment differences between patients and nurses affected the ability to detect differences in the effects of the anti-emetic treatments was tested in the dexamethasone crossover study (Table 6). For example, patients had 1.45 fewer vomits on dexamethasone than on placebo according to the nurses' assessments and 2.02 fewer according to the patients' assessments. The biggest differences were seen in the comparisons of anxiety and sedation. Anxiety was assessed as significantly less on dexamethasone than on placebo by the patients ($P = 0.016$) but not by the nurses ($P = 0.09$).

The postulate that anti-emetic regimens which contain sedative drugs may impair the patients' ability to accurately recall their experiences and that this may account for a difference between what the patients recall and record and what the nurses record was tested by correlating the differences between patients' and nurses' assessments with the degree of sedation assessed by the nurses. Absolutely no correlation was found. The correlation coefficients of the differences in the number of vomiting episodes, duration of vomiting, severity of vomiting, degree of anxiety and degree of sedation with the nurses' assessment of

Table 1. Parallel subjects study: nurses' and patients' assessments of vomiting and nausea

Parameter	Nurses' assessment Mean (S.E.)	Patients' assessment Mean (S.E.)	P*	Correlation coefficient	P†
Vomiting number	3.6 (0.3)	3.4 (0.3)	0.83	0.81	<0.0001
Vomiting duration (h)	5.3 (0.5)	4.1 (0.4)	0.002	0.73	<0.0001
Nausea severity grade	1.3 (0.1)	1.0 (0.1)	<0.0001	0.65	<0.0001
Nausea duration (h)	7.7 (0.6)	5.4 (0.6)	<0.0001	0.72	<0.0001

S.E., standard error. *Significance of the difference between the nurses' and patients' assessments. †Significance of correlation between the nurses' and patients' assessments. Severity was graded on a scale of 1–5.

Table 3. Crossover studies: nurses' and patients' assessments of vomiting

Parameter	Nurses' assessment Mean (S.E.)	Patients' assessment Mean (S.E.)	P*	Correlation coefficient	P†
Study 1					
Vomiting number	2.3 (0.2)	3.7 (0.5)	<0.0001	0.81	<0.0001
Vomiting duration (h)	3.9 (0.5)	4.9 (0.6)	0.06	0.81	<0.0001
Vomiting severity grade	2.0 (0.1)	2.2 (0.1)	0.15	0.67	<0.0001
Anxiety grade	1.8 (0.1)	1.5 (0.1)	0.0006	0.11	0.02
Sedation grade	2.7 (0.1)	2.6 (0.1)	0.13	0.30	0.0005
Study 2					
Vomiting number	3.1 (0.2)	3.5 (0.4)	0.99	0.79	<0.0001
Vomiting duration (h)	3.6 (0.4)	3.5 (0.4)	0.55	0.80	<0.0001
Vomiting severity grade	2.4 (0.1)	2.3 (0.1)	0.20	0.64	<0.0001
Anxiety grade	2.0 (0.05)	1.5 (0.06)	<0.0001	0.06	0.37
Sedation grade	2.9 (0.05)	2.7 (0.07)	0.0088	0.21	0.0033
Study 3					
Vomiting number	2.8 (0.2)	3.6 (0.3)	0.0013	0.79	<0.0001
Vomiting duration (h)	3.8 (0.3)	4.1 (0.4)	0.40	0.80	<0.0001
Vomiting severity grade	2.2 (0.2)	2.2. (0.1)	0.86	0.66	0.14
Anxiety grade	1.9 (0.04)	1.5 (0.04)	<0.0001	0.08	0.14
Sedation grade	2.9 (0.04)	2.7 (0.04)	0.0027	0.25	<0.0001

Severity is graded on a scale of 1–5. S.E., standard error. *Significance of the difference between the nurses' and patients' assessments. †Significance of correlation between the nurses' and patients' assessments.

Table 5. Crossover studies: comparing nurses' and patients' assessments of anxiety and sedation

Patients' assessment	Nurses' assessment None	Mild	Moderate	Severe	Very Severe	Total
Anxiety						
None	69	117	40	1	1	228
Mild	18	34	16	1	0	69
Moderate	10	11	5	0	0	26
Severe	1	3	5	0	0	9
Very severe	0	0	2	0	0	2
Total	98	165	68	2	1	334
Sedation						
None	2	20	19	3	0	44
Mild	3	29	45	11	0	88
Moderate	2	26	93	20	1	142
Severe	0	5	33	12	0	50
Very severe	0	3	7	0	0	10
Total	7	83	197	46	1	334

Table 4. Cross-over studies: comparing nurses' and patients' assessments of the number of vomiting episodes

Patients' assessment	Nurses' assessment 0	1–2	3–5	6–10	11+	Total
0	90	8	4	1	0	103
1–2	6	39	12	1	0	58
3–5	4	20	43	14	0	81
6–10	1	5	15	27	2	50
11+	2	3	5	8	4	22
Total	103	75	79	51	6	314*

*The number of vomiting episodes was not recorded by the nurses and/or the patient in 20 courses.

sedation were 0.06, 0.03, −0.01, 0.02 and 0.06, respectively ($P > 0.25$ for all coefficients).

In the crossover studies, 113 patients expressed a preference for one course over another. 20 patients gave no reason and 12 gave non-specific answers suggesting better tolerance. 12 patients gave two reasons, and 60 patients based their preference on anti-emetic efficacy (Table 7). Only 12 patients specifically based their preference on anti-emetic efficacy. The reasons for a course preference were checked for consistency against the patients' assessments recorded at each course. In 65 patients where such comparisons were possible, the data were consistent in 88% and inconsistent in 12%.

DISCUSSION

Although intuitively it would seem that objective parameters, such as number of vomits, would be more easily quantitated by

Table 6. Second crossover study: comparison of estimated treatment effects (placebo–dexamethasone)

Parameter	Based on nurses' assessments Mean (S.E.)	*P*	Based on patients' assessments Mean (S.E.)	*P*
Vomiting number	1.45 (0.39)	0.0006	2.02 (0.86)	0.0003
Vomiting duration (h)	1.88 (0.82)	0.0452	1.85 (0.66)	0.0021
Vomiting severity grade	0.37 (0.11)	0.0015	0.63 (0.13)	<0.0001
Anxiety grade	0.13 (0.10)	0.0905	0.26 (0.09)	0.0160
Sedation grade	−0.06 (0.01)	0.6881	0.30 (0.15)	0.0621

Effects graded on a scale of 1–5.

an observer who is free of the side-effects of therapy, whereas subjective sensations could only be assessed by the patient, the above analyses demonstrate some of the constraints upon this simplistic view.

In the parallel subjects study, the higher scoring for the severity of nausea and the duration of nausea and vomiting by the nurses may just reflect the increased accuracy of detailed, frequent, prospective recording by the nurses as compared to the 24-h retrospective assessment of the patients. Differences in the duration of a parameter may only reflect data collection procedures. For example, the duration of nausea as assessed by an observer has been calculated as the time from the first to the last notation of nausea, and may include periods inbetween with no nausea. In addition, if only the worst grade of nausea is recorded for each hour and not the time of onset within the hour, a patient who starts feeling nauseous 10 min before the end of 1h and stops feeling nauseous 10 min after the beginning of the next would have a duration of 2 h calculated instead of 20 min.

Different methods of recording data may also invalidate comparisons between studies. In the crossover trials, the patients recorded more vomiting than the nurses, but here the nurses were only asked to tabulate results at the end of an 8-h shift. The result may have been different if they had been recording vomiting hourly as in the parallel subjects study.

Poor correlations were found between the nurse and patient reporting of subjective sensations, such as nausea, sedation and anxiety. Unless observers question the patient before recording a grade for these subjective sensations, they may be reflecting their own prejudices on to the patient. For example, this may have occurred when the nurses perceived anxiety as greater than the patients in the crossover studies. To record a subjective sensation meaningfully, the observers must ask the patients what their experiences were. If the data are from the same source, any differences between the patients' and observers' records can only be due to the methods of recording, particularly the frequency. This may suggest that the nurses' records will be more accurate, but not definitive. However, it may not be desirable to increase the frequency of patients' observations since this may alter the experience of therapy by increasing anxiety or interfering with sedative side-effects, which some patients score as an advantage.

In summary, there is often a good correlation between observer and patient assessments of the efficacy of anti-emetic drugs. When differences exist they may reflect no more than differences in the method of data collection. Objective parameters may be more accurately recorded by observers, but subjective sensations often give greater insight into patient experiences so that both are desirable. There is no external standard against which the accuracy of patient and observer data can be compared. The above analyses highlight the hazards of simply comparing data between studies without knowing how the data were derived.

Table 7. Crossover studies: reasons for course preference

Basis of preference	Number	% of 113
No reason given	20	18
Tolerated better	12	11
Nausea/vomiting	60	53
More sedation	4	4
Less sedation	11	10
Better sleep	3	3
Anxiety	3	3
Other side-effects	10	9
Other	2	2
Total	125*	

*12 patients gave two reasons.

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A Phase I/II Study of the Intralesional Injection of Ricin–Monoclonal Antibody Conjugates in Patients with Hepatic Metastases

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A phase I/II study of the intralesional administration of ricin-labelled monoclonal antibodies was conducted in patients with hepatic metastases of gastrointestinal origin. The anti-carcinoembryonic antigen (CEA) antibody I-1 was conjugated to blocked ricin via a disulphide bridge. After a test dose of antibody, patients were injected with ricin–antibody conjugates under computed tomography (CT) guidance on two occasions 1 week apart. Patients with stable or responding disease would receive a third course. The dose of ricin relative to surface area was increased in a predefined manner in cohorts of 3 patients. A total of 27 patients with hepatic metastases were entered into this study. All patients had metastatic colorectal cancer (26 patients) or adenocarcinoma of unknown primary with elevated CEA levels (1 patient). The presence of malignancy was documented cytologically in 9 of 11 patients tested. Minor responses were seen in 7 patients. However, no major objective responses or changes in the growth rate of injected lesions were observed. Toxicity was generally mild, the most common being hepatic capsular pain 24–48 h after each injection. 6 patients experienced rigors. One patient had anaphylaxis. Human anti-mouse and anti-ricin antibody responses were observed. Although substantial amounts of ricin conjugated to monoclonal antibodies were delivered into single lesions, this therapeutic approach was unsuccessful. Future studies of ricin-labelled antibodies should incorporate the systemic administration of immunoconjugates.
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INTRODUCTION

MONOCLONAL ANTIBODIES have had a major impact on many aspects of cancer research and diagnosis. However, therapeutically, there are only a limited number of examples in which this technology has improved the results of conventional therapy. For the last decade, the effective use of monoclonal antibodies as carriers of drugs, [1, 2] isotopes [3] or toxins [4] has been the ultimate goal of numerous studies. This endpoint has been difficult to achieve and the potential difficulties that need to be overcome before this approach to therapy can be effectively exploited have been extensively discussed [5]. In particular, there has been considerable discussion over the relative tumour specificity of antibodies in comparison to normal tissues. However, in view of the fact that conventional drugs have no specific affinity for tumours, other than that afforded by the unique vascular supply of primary and secondary cancers, limited antibody-related tumour specificity may be able to provide some biological advantage.

A more important limitation of the use of monoclonal antibodies as carriers of various toxic agents may be that in most animal experiments and human trials, where antibody conjugates have been administered systemically, less than 0.1% of the injected dose of antibody actually reaches its target [6]. This finding may have important implications for normal tissue toxicity, although it is not clear that this figure differs markedly when compared to the localisation potential of standard cytotoxic drugs.

To overcome the potential limitation of reduced antibody localisation in tumour tissue, we initiated a study in animal models using a ricin-labelled antibody conjugate [7]. In view of

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