Methodology of Antiemetic Trials

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Summary

Progress in antiemetic research dictates that clinical trials of antiemetic agents be conducted according to guidelines for Good Clinical Practice, as follows. Studies must be of a prospective, parallel-group design in which the new treatment is compared with the existing best available treatment, after optimal dosage schedules for each have been established. Ethically, placebo-controlled trials can only be justified when chemotherapy with a low emetogenic potential is used. All end-points (nausea, vomiting, adverse events and quality of life parameters) must be specified in detail before the trial is begun. Patient populations must be homogenous with respect to prior chemotherapy and other confounding variables. Finally, patients must actively participate in the evaluation of antiemetic therapy, since only they can provide reliable information regarding the impact of nausea and vomiting on their quality of life.

5-Hydroxytryptamine type 3 (serotonin3) [5-HT3]-receptor antagonists have revolutionised the treatment of emesis induced by cancer chemotherapy. They have also profoundly influenced the methodology of antiemetic trials. As a result, emesis is clearly distinguished from nausea, and the debilitating effect of nausea has become the major target for further improvements in antiemetic care.

The increased efficacy of aggressive chemotherapeutic regimens, particularly those containing cisplatin, has been partly offset by the problems with nausea and vomiting that they provoke. Various antiemetic agents were employed with modest success until Gralla et al. (1981) introduced a successful treatment with somewhat toxic doses of metoclopramide. Metoclopramide became the mainstay of antiemetic treatment and was often combined with other agents to enhance efficacy or to diminish its adverse effects.

A variety of antiemetic regimens were claimed to be efficacious on the basis of small and sometimes uncontrolled clinical trials. General guidelines began to emerge for antiemetic treatment. Firstly, it is easier to prevent chemotherapy-induced nausea and vomiting than to alleviate it; thus, most emetogenic chemotherapy schedules now begin with the prophylactic administration of antiemetic drugs. Secondly, antiemetic treatment must completely inhibit nausea and vomiting so that anticipatory vomiting in later chemotherapy courses is prevented, i.e. activation of a positive feedback mechanism is avoided. Thirdly, the choice of the antiemetic treatment should depend on the emetogenic potential of the chemotherapy. Thus, highly emetogenic chemotherapy may sometimes justify prolonged treatment with dosages or combinations of antiemetic drugs that are known to produce side effects, while less emetogenic chemotherapy regimens need not.

As well as adhering to the general principles of antiemetic treatment mentioned above, the development of the 5-HT3-receptor antagonists con-
formed to the requirements laid down in the guidelines for ‘Good Clinical Practice’. This is a set of standards that encompasses adherence to the human rights declaration (including the obligation to obtain informed consent and not withhold effective treatment from patients) and that governs the design and execution of clinical studies. Requirements include proper randomisation, on-site monitoring, definition of efficacy end-points in advance and comparison with existing treatment or placebo. Although the basic principles of ‘Good Clinical Practice’ apply to all clinical studies, they are most strictly enforced by regulatory authorities in order to ensure the proper conduct of clinical studies that support a registration dossier. Differences in interpretation of some of the guidelines gave rise to discrepancies between the development programmes of the 5-HT3-receptor antagonists.

1. Evaluation of Efficacy

When the clinical development of the 5-HT3-receptor antagonists started, no uniform definitions existed for measuring the efficacy of antiemetic treatment. The term emesis is ambiguous, since it means either vomiting or the combination of vomiting and nausea, and the distinction between acute and delayed emesis was not always made. Consequently, terms like ‘patient response’ and ‘control of emesis’ can be misleading when used without further definition, since they do not unequivocally refer to vomiting alone, but may also include nausea. For example, the WHO scale for measuring nausea and vomiting ranges from 0 to 4, where 0 represents absence of emesis and 4 incapacitating emesis, but it does not distinguish between nausea and vomiting (WHO Handbook, 1979). So, during the development of all the 5-HT3-receptor antagonists, control of vomiting was measured by counting the number of vomits. Control was then classified as total control (no vomits), major (1 or 2 vomits), minor (up to 4 or 5 vomits) and failure (5 or more vomits). These criteria applied to the first 24 hours after the administration of the chemotherapy.

Owing to the subjective nature of nausea, its control cannot be graded as simply as can that of vomiting. Severity and duration are the parameters used to analyse nausea. The grading of intensity as mild, moderate or severe is often based on the degree of interference with normal daily activities. The limitations of this grading system become clear when trying to classify mild nausea that occurs at night and keeps the patient awake. Sometimes, the duration rather than the severity has been chosen as the criterion for classifying nausea. It has not always been specified whether acute or delayed nausea, or the combination of the 2 were considered when defining nausea control.

When grading the severity of nausea, observers rely on reporting by patients. This method may be sufficient for evaluating nausea during a hospital stay, but it fails to represent accurately the patients’ symptoms when they are at home. The retrospective collection of information can result in misrepresentations with regard to delayed nausea after highly emetogenic chemotherapy given on an outpatient or daycare basis. This is especially true when a benzodiazepine with amnestic properties is part of the antiemetic treatment.

In some studies, this problem has been remedied by asking the patients to record their symptoms in a diary or by contacting them daily at home. Such methods have highlighted how delayed nausea and vomiting adversely affect the quality of life of patients when they are no longer under direct observation. The ultimate aim of antiemetic treatment is to prevent all vomiting and all nausea in cancer patients treated with chemotherapy. Therefore, it would be useful to have a single outcome parameter for control of nausea and vomiting combined.

2. Study Design

Randomised trials are important because they reduce the effects of investigator bias. A large sample size allows maximum power, minimum error and subset analysis. The selection of patients receiving highly emetogenic chemotherapy regimens