Assessment of nausea

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Summary. In a standardized way three different methods of measuring nausea have been assessed in 849 patients enrolled in 4 double blind, randomized, clinical trials, and 2 observational studies. Nausea was measured before and 2, 4, 6, 8 and 24 hours after cancer chemotherapy by using a discrete scale (DS), a visual analogue scale (VAS) and a continuous chromatic analogue scale (ACCS), and it was evaluated according to 4 different dimensions: maximal intensity (MI) entity (E) duration (D) and quantity (Q).

The distributions of nausea measurements in the population, agreement between the scales and their sensitivity, and agreement between dimensions and their sensitivity were analyzed.

A uniform distribution of nausea measurements was found only in patients receiving chemotherapy without any antiemetic treatment. There was substantial equivalence of the different scales, and no advantage was shown an using an analogue (VAS) than a discrete (DS) scale.

A trend toward increasing sensitivity in detecting differences as the dimensions of nausea considered became more inclusive of the various aspects of this symptom (Q more sensible than E more sensible than MI) was observed.

Key words: nausea, chemotherapy, cancer patients; nausea assessment

Emesis caused by cancer chemotherapy is a notable clinical problem and the effects of drugs used to prevent or control it are a priority area of research [1]. Much less attention has been devoted to the methodological problems encountered in conducting clinical trials on antiemetic treatments, in particular to the search for reliable measurements of nausea and vomiting.

Even if a degree of consensus has been reached regarding criteria to be adopted in the assessment of vomiting [2], the measurement of nausea has not been adequately validated. It remains an object of controversy, with individual studies reporting results which claim reliability and advantages for new methods, that cannot really be compared [3].

Over the past few years a standardized assessment has been made of the yield of the most widely used instruments for the measurement of nausea during studies on the efficacy of various antiemetic treatments [4–7].

Aim of this study is to provide new information on the validity of existing methods for the evaluation of nausea and the best way to utilize them in clinical trials on antiemetic drugs.

Subjects and methods

The population studied is represented by 849 patients in 6 studies, four double blind randomized controlled clinical trials and two observational studies. Nausea was evaluated in 275 of the patients, who suffered from this symptom (Table I).

Nausea was measured using three different methods, a discrete scale (DS) and two types of analogue scale. The DS consisted of a questionnaire in which patients were asked to rate their nausea as: 0 = no nausea; 1 = slight nausea; 2 = moderate nausea; 3 = severe nausea. The first visual analogue scale (VAS) was a 100 mm long, vertical line with the extremes marked as “no-nausea” (bottom) and the “worst nausea I’ve ever felt” (top), with no intermediate divisions or discrete terms. A score from 0 to 100 was determined by measuring the distance from the bottom to the mark placed by the patient along the line.

The second analogue scale, an analogue chromatic continuous scale (ACCS); [8], consisted of a coloured horizontal strip, 100 mm long and 25 mm wide, containing no markings except for the anchor points at each end; the extremes were “no nausea” (left) and “worst nausea I’ve ever felt” (right), with the words on a white background at the two extremities of the coloured strip. The colour was graduated from left to right from pale pink to dark red. The coloured strip lay on one face of a double-sided device; the patient evaluates the intensity of the nausea by positioning a transparent slider containing a narrow black line perpendicular to the coloured strip. The opposite side of the ruler contained a 0–100 mm scale, which exactly fitted the ACCS on the other face. It was not visible to the patient. It allowed the observed immediately to record the nausea score. The position of the slider was fixed by a stopper inside the slider.
The VAS and ACCS were presented to patients in randomized order.
Nausea in each patient was measured by these methods before and 2, 4, 6, 8 and 24 h after chemotherapy. These six specific time points were chosen for the assessment both for practicality and because of the need to evaluate the usual time course of nausea after chemotherapy. Nausea was evaluated according to four different dimensions:

1. **Maximal intensity (MI):** defined as the highest value of the score obtained with the DS, VAS or ACCS at any evaluation carried out over the 24th period;
2. **Entity (E):** defined as the sum of all the values of intensity of nausea (I) recorded at each evaluation time (E = \( \sum I \));
3. **Duration (D):** expressed in minutes. Patients were asked at each point of evaluation for how many minutes they had experienced nausea during the previous time period.
4. **Quantity (Q):** defined as the sum of the products of the intensity multiplied by the duration recorded at each evaluation time (Q = \( \sum (I \times D) \)).

Using these different evaluation scales and dimensions of degree of nausea the following parameters were analyzed:

1. distribution of the measurements of nausea in the population studied;
2. agreement between scales and their sensitivity;
3. agreement between dimensions and their sensitivity;
4. correlation between nausea and vomiting.

**Statistical analysis**
To evaluate the variability of the distribution of the measurements of nausea in the population studied a \( \chi^2 \)-test was used to prove the null hypothesis of homogeneity between the observed data and the theoretical uniform distribution. Correlations between the scales for the various dimensions of nausea considered and for the dimensions of the various scales were measured by Spearman’s correlation coefficient. A regression line was fitted between VAS and ACCS values. The mean values of VAS and ACCS were compared by Wilcoxon’s matched-pairs signed-ranks test. Evaluation of results from clinical trials was done by comparison between the means using the Mann-Whitney U test.

### Table 1. Patients studied for assessment of nausea

<table>
<thead>
<tr>
<th>Patients (with nausea)</th>
<th>Type of study</th>
<th>Antiemetic treatment</th>
<th>Chemotherapy</th>
<th>Scales of measurement (DS, VAS, ACCS)</th>
<th>Dimensions studied (MI, E, Q)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 (23)</td>
<td>a) Open</td>
<td>None</td>
<td>DDP</td>
<td>DS, VAS, ACCS</td>
<td>MI, E</td>
<td>b</td>
</tr>
<tr>
<td>297 (114)</td>
<td>b) Db</td>
<td>Mtc 60 mg vs Mtc 120 mg</td>
<td>DDP</td>
<td>DS, VAS</td>
<td>MI, E, Q(^a)</td>
<td>4</td>
</tr>
<tr>
<td>177 (43)</td>
<td>c) Db</td>
<td>Mtc vs Mtc + Mp</td>
<td>CMF</td>
<td>DS, VAS, ACCS</td>
<td>MI, E</td>
<td>6</td>
</tr>
<tr>
<td>(d) Open</td>
<td></td>
<td>Hd-Mtc</td>
<td>DDP</td>
<td>DS, VAS, ACCS</td>
<td>MI, E</td>
<td>b</td>
</tr>
<tr>
<td>343 (95)</td>
<td>f) Db</td>
<td>Mtc + Mp vs Dex + Diph + Mtc</td>
<td>DDP</td>
<td>DS, VAS</td>
<td>MI, E, Q</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total 849 (275)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Measured in a subset of 61 patients with nausea \(^b\) Unpublished data Db = Double-blind Mtc = metoclopramide Hd = High-dose Mp = methylprednisolone Domp. = domperidone DDP = cis-diamminedichloroplatinum CMF = cyclophosphamide, Methotrexate, 5-Fluorouracil Dex = dexamethasone Diph = diphenhydramine