Modelling of the Hamilton Depression Rating Scale in Unipolar Depression Trials

Giles Santen(1), Roberto Gomeni(2), Meinert Danhof(1) and Oscar Della Pasqua(1,3)

(1) Division of Pharmacology, LACDR, Leiden University, The Netherlands
(2) Clinical Pharmacology and Discovery Medicine, GSK, Verona, Italy
(3) Clinical Pharmacology and Discovery Medicine, GSK, UK

INTRODUCTION

Depression trials are known to show a large placebo response, which makes it very difficult to separate placebo effect from drug effect before 8 to 12 weeks of treatment. The main clinical assessment tool in depression studies is the Hamilton Depression Rating Scale (HAMD), which consists of 17 items that are summed up to provide a total score. However, little attention has been paid to the time course of changes in those scores and to the sensitivity of the scale in separating responders from non-responders.

OBJECTIVES

The objective of this investigation was two-fold:

(a) to characterise the time course of the scores of the Hamilton scale over a course of 12 weeks in patients treated either with placebo or therapeutic doses of SSRIs.

(b) to investigate the sensitivity of the various subscores in separating responders from non-responders. In addition we devised a new subscale including only the most sensitive items from the original HAMD. This scale was used as a clinical endpoint in an empirical model.

METHODS

Data

Data from 8-week to 12-week double blind, placebo-controlled studies in unipolar depression were used.

Sensitivity Analysis

The HAMD was analysed to assess the sensitivity of specific sub-scores to treatment effect (clinical response defined as >50% decrease from baseline). Data exploration and sub-score analysis was performed in R using trellis graphs. To obtain these graphs, the population was split in responders and non-responders. These populations are denoted in the graphs as RESP (responders) and NRESP (non-responders).

RESULTS: HAMD SENSITIVITY

Sub-score | Sensitivity to response
---|---
Depressed Mood | +
Feeling of Guilt | ++
Suicide | ++
Insomnia Early | +
Insomnia Middle | +
Insomnia Late | +
Work and Activities | ++
Retardation: Psychomotor | +
Agitation | +/-
Anxiety Psychic | +
Anxiety Somatic | +
Loss of Appetite | +
Anergia | ++
Genital Symptoms | +
Hypochondriasis | -
Loss of Weight | -
Loss of Insight | -

Table 1: Summary of results of the sensitivity analysis of the HAMD

Two types of sub-scores could be identified using statistical and graphical assessments (figure 2). From figure 2 it is clear that the Depressed Mood sub-score is sensitive to drug and placebo effects, whereas the Loss of weight sub-score is insensitive to either treatment. One can argue that the latter only produces noise if a separation between responders and non-responders is sought. The results of the analysis for all sub-scores are summarised in table 1.

The seven most sensitive sub-scores to response were selected and added up to form a new sub-scale. Interestingly, 6 of these items are present in the 6-item Bech-Rafaelsen Melancholia scale and 5 are included in the 6-item Maier and Philipp sub-scale.

RESULTS: MODELLING

The identification of responders and non-responders by NONMEM was in good agreement with external criteria for this distinction. The population fit of both populations is shown in figure 3.

To assess the sensitivity of HAMD and the new sub-scale to detect treatment effect, data was re-analysed using the seven most sensitive items. As expected, differences between endpoints were negligible for studies showing large effect size. However, the new sub-scale was more sensitive to treatment effect than the HAMD (table 2) in these studies showing smaller effect sizes.

Table 2. Mixture parameters for the HAMD 17-item scale and the new 7-item scale. A study with a large effect size and a study with a small effect size are shown.

<table>
<thead>
<tr>
<th>Sub-score</th>
<th>SENSITIVITY ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed Mood</td>
<td>++</td>
</tr>
<tr>
<td>Feeling of Guilt</td>
<td>++</td>
</tr>
<tr>
<td>Suicide</td>
<td>++</td>
</tr>
<tr>
<td>Insomnia Early</td>
<td>+</td>
</tr>
<tr>
<td>Insomnia Middle</td>
<td>+</td>
</tr>
<tr>
<td>Insomnia Late</td>
<td>+</td>
</tr>
<tr>
<td>Work and Activities</td>
<td>++</td>
</tr>
<tr>
<td>Retardation: Psychomotor</td>
<td>++</td>
</tr>
<tr>
<td>Agitation</td>
<td>++</td>
</tr>
<tr>
<td>Anxiety Psychic</td>
<td>++</td>
</tr>
<tr>
<td>Anxiety Somatic</td>
<td>++</td>
</tr>
<tr>
<td>Loss of Appetite</td>
<td>++</td>
</tr>
<tr>
<td>Anergia</td>
<td>++</td>
</tr>
<tr>
<td>Genital Symptoms</td>
<td>++</td>
</tr>
<tr>
<td>Hypochondriasis</td>
<td>++</td>
</tr>
<tr>
<td>Loss of Weight</td>
<td>++</td>
</tr>
<tr>
<td>Loss of Insight</td>
<td>++</td>
</tr>
</tbody>
</table>

CONCLUSIONS

- Characterisation of the time course and evaluation of the sensitivity of the clinical endpoint is essential to adequately model and predict treatment effect in depression.
- Not all items of the HAMD are equally sensitive to drug or placebo response.
- A more sensitive sub-scale consisting of 7 items of the HAMD is proposed to capture drug effect and separate responders from non-responders.
- A mono-exponential model was used to describe the time course of the HAMD and the new 7-item sub-scale. The model successfully characterised the individual time course of the clinical endpoint throughout a 8 to 12-week clinical study.
- The new sub-scale was more sensitive to treatment effect in studies showing small effect sizes.