COMPARISON OF NOMIFENSINE AND PLACEBO

K. TAEUBER

Medical Department, Hoechst AG, Postfach 80 03 20, D-6230 Frankfurt/Main 80

- 1 Methodological reasons are discussed which make placebo-controlled trials on antidepressant drugs necessary.
- 2 The ethical problem of treating a sick patient with an inactive compound are shown to have an impact on the methodology of such trials.
- 3 Three double-blind placebo-controlled trials with nomifensine are reviewed; one in neurotic depression, one in psychotic depression and one in geriatric patients showing depressive symptoms.
- 4 In all three trials the effect of nomifensine has been shown to be superior to that of placebo.

Introduction

During the course of the clinical investigation of a new drug of potential antidepressant activity, the most embarrassing question usually is: does this drug possess antidepressant efficacy at all?

This question is difficult to answer because of two factors. Depressive states frequently change spontaneously because they are of intrinsically episodic nature. In depressive illness the frequent 'phasic' course of the disease is as well known as the fact that depressive reactions tend to change as the environment changes. Even the elaborate rating scales and psychometric methods now available for the assessment of symptoms and symptom severity, and for the measurement of their changes, are of a reliability which is restricted by both the inaccuracy of the measuring device and the limited competence of the rater. Taking these two factors into account, it is obvious that uncontrolled trials are weak against both spontaneous (that is, not drug-induced) changes in depressive symptoms and unreliability of measuring devices.

Standard drug-controlled trials lead to particular difficulties in the interpretation of their results when—as happens frequently—no differences between the drugs are found. Have both drugs been equally ineffective? Have the methods applied been too insensitive to detect existing differences between the drugs? Or are both drugs in fact not different from each other?

With both concepts it will be difficult to provide a firm answer to our question whether the drug has antidepressant efficacy at all. The most convincing test of a new drug's efficacy, that is, a placebo comparison, therefore remains a necessary step which has to be undertaken in the clinical investigation of an antidepressant substance.

This kind of controlled trial, however, is burdened with a number of problems, the most serious of which relate to the ethical issue involved: treating depressed patients with placebo means to deprive them from available effective treatments. It is obvious that this can only be justified under certain circumstances, most of which depend on the definition of the patients sample. Patients for placebo-controlled trials must not be suicidal, they should be under close and constant control (that is, they should be in-patients), the severity of their illness should not be very high, they should be in a stable state rather than in a phase of rapid change, and so on.

All these exclusion criteria finally make it very difficult to carry out a justifiable placebo-controlled trial in depressed patients and limit the conclusions that may be made from its results. In the course of the clinical investigation of nomifensine, nevertheless, some placebo studies were carried out and will be reviewed here.

Placebo-controlled clinical trials on nomifensine

Placebo-controlled studies in patients with depressive reaction

Eckmann (1974) carried out a double-blind cross-over study in 30 freshly hospitalized patients suffering from depressive reaction. He chose the model of a cross-over trial because he was only willing to admit a limited number of cases to this trial.

After an initial wash-out phase, the patients were randomly assigned to either nomifensine or placebo and treated for 8 days. The nomifensine dosage was constant at 75 mg/day. The crossing over to the

comparative treatment was carried out without an intervening wash-out period. The idea was that, due to the spontaneous changes expected to occur with this type of patient, the whole duration of the investigation should be as short as possible. In fact, it was only 16 d since after the crossing over another 8 d period of treatment followed.

Assessments were made at the beginning and at the end of each treatment period using a symptom checklist (Immich *et al.*, 1971). At the end of a treatment period when those symptoms that had been the main ones at the beginning were rated as 'not present', the patient was rated as 'improved'. When those symptoms were still present or the patients' state had deteriorated, the judgement was 'not improved'.

Results with depressive reaction

Both sequence groups did not differ in their pretreatment characteristics. Table 1 shows the configuration of results found with the above global rating. The expected configuration (improvement on nomifensine and no improvement on placebo) was significantly more frequent than the other combinations.

Since these results were unexpectedly striking, the methodology was re-examined (that is, identical packing and labelling of samples, individual coding, unbroken codes until evaluation was finished), and it was decided to repeat the study with an identical protocol. Table 2 shows that the above findings were confirmed by the repeat trial. In spite of the fact

that a cross-over trial does not seem to be a suitable design for the treatment of the rapidly changing depressive reaction, it has been possible to demonstrate the efficacy of nomifensine against placebo in this study.

Placebo-controlled study in depressive illness

Kröger (1976) selected for this study a group of 24 hospitalized female patients suffering from depressive illness. According to the traditional German classification, 11 of them were diagnosed as having 'endogenous depression' and 13 as having 'involutional melancholia'.

Again, a cross-over design was chosen with an initial wash-out period of 7 days. The first 14-d treatment period (nomifensine 75 mg/d or placebo) was followed by an intervening wash-out period of 1 week and then, after crossing over of the medication, by a second treatment period (placebo or nomifensine 75 mg/d). Assessments on Wechsler's Depression Scale (physician's rating) and the Beck Self-Rating Scale for Depression were carried out at the beginning and at the end of both treatment periods.

Results with depressive illness

Figure 1 shows the Wechsler scores. In the first treatment period improvement under nomifensine is significantly more pronounced than under placebo. During the wash-out period the patients who had been on nomifensine before, relapsed to exactly the level of the placebo-treated patients. In the second treatment

Table 1 Global results of Eckmann's first study

		Placebo		Total
		Improved	Not improved	
Nomifensine	Improved	2	25	27
	Not improved	0	3	
	Total	2	28	30

McNemar's test: $P < 0.0001$.

Table 2 Global results of Eckmann's second study

		Placebo		Total
		Improved	Not improved	
Nomifensine	Improved	2	21	23
	Not improved	5	2	7
	Total	7	23	30

McNemar's test: $P < 0.0002$.

Figure 1 Nomifensine compared with placebo in depressive illness. Wechsler's Depression Scale. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

phase the nomifensine-treated patients improve significantly, whereas those on placebo do not show improvement.

Figure 2 shows consistent findings obtained with the Beck Self-Rating Scale for Depression.

The findings of this trial were difficult to analyze because of the unusual design. Since at the beginning of each treatment period the scores of both sequence groups were not significantly different, it may be concluded that in this trial the efficacy of nomifensine

Figure 2 Nomifensine compared with placebo in depressive illness. Beck Self-Rating Scale. * $P < 0.05$; *** $P < 0.001$.

in depressive illness has successfully been differentiated from placebo.

Placebo-controlled study in geriatric patients

A group of 105 geriatric patients, aged 60–86 yr and suffering from mild to moderate depressive symptoms, were investigated by Jansen & Brückner (1976). Three random groups of 35 patients each were formed and treated with either nomifensine 75 mg/d, placebo, or no psychotropic medication. An initial 10-d wash-out period was followed by a treatment period of 46 d duration.

Assessments using a clinical global impression, the Plutchik Geriatric Rating Scale, the Mosaic Test from the Wechsler Adult Intelligence Scale and the d_2 test for attention, were carried out at days 1, 10, 11, 28 and 56, together with a registration of side-effects. Laboratory tests were carried out at the end of both the wash-out and the treatment period (days 10 and 56). No drug-related drop-outs occurred.

Results with geriatric patients

Analysis showed that the three groups were homogenous with respect to their pretreatment values.

Figure 3 shows the results of global clinical appraisal, demonstrating a significant difference between nomifensine treatment and placebo and/or no treatment.

Figure 4 gives the results obtained with the Mosaic Test, indicating that under nomifensine there occurs an improvement in performance which is significantly different from the two other conditions.

Figure 5 shows significant improvement in the d_2 test of attention and Figure 6 shows improvement in the Plutchik Geriatric Rating Scale, where

Figure 3 Nomifensine compared with placebo in geriatric patients. 6, Extremely severe; 1, border-line. ○, No treatment; ■, placebo; ●, nomifensine.

Figure 4 Mosaic test. Mean values of the three treatment groups. Open columns, Control group; dotted, placebo; hatched, nomifensine.

Figure 5 'd₂' test of attention. Number of errors. Mean values of the three treatment groups. Open columns, Control group; dotted, placebo; hatched, nomifensine.

nomifensine again is superior to placebo and/or no treatment.

In this study, not only in psychiatric ratings but also in psychometric measures of performance an improvement under nomifensine has been shown which is different from placebo. It is felt that the improved mental performance is particularly beneficial in the kind of patient studied here.

Discussion

Proof of efficacy by placebo-controlled trials

In the introduction to this paper, we briefly discussed both the necessity for placebo-controlled clinical trials on antidepressants and the ethical and methodological problems involved.

The first two trials reported here, although methodologically not totally satisfying, played exactly the role a placebo trial is supposed to play: they convinced us in a very early stage of the clinical investigation that nomifensine is active. They were, so to speak, the 'experimentum crucis' and played an important part in our decision processes.

Figure 6 Plutchik Geriatric Scale. Mean values of the total scores. Open columns, Control group; dotted, placebo; hatched, nomifensine.

Patient sample considerations

The definition of the experimental patient sample was a critical point in the planning of these trials. Whereas Eckmann's sample of depressive reactions (mainly of neurotic nature) posed the least ethical problems, as these patients were neither severely ill nor suicidal, it comprised those patients which tend to show most spontaneous improvements. It might well be, therefore, that the success of this study was achieved because the total time a patient was under investigation was only 2 weeks.

Kröger's trial in depressive illness was more critical from the ethical point of view since these patients were severely ill and needed treatment. Looking back at Figures 1 and 2, it can be seen that at the end of the 2 weeks' treatments with nomifensine, the patient's state deteriorated rapidly. These findings confirm both the risk of withholding medication from severely ill patients and the proof of efficacy of nomifensine. Here, the conflict existing between methodological strictness and ethical considerations becomes very evident: it will have to be recognized before the trial is actually started.

Methodological considerations

Let us assume that in a given situation the analysis of the above conflict situation leads to the result that a placebo comparison is scientifically necessary and justifiable. Then this trial should be planned and carried out extremely carefully to reduce the probability that it will have to be repeated due to methodological weaknesses. Since the number of patients which can be admitted to such a trial will always be limited, the often criticized 'cross-over design' should be re-considered.

Finally, alternative methodological concepts must be looked for and be further developed:

dose-response or (in the future) plasma level/response studies might sometimes be a solution. Increased sensitivity and reliability of assessments

together with careful compliance with the protocol might raise the discriminative value of standard drug comparisons.

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