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DOPAMINERGIC AGONIST NOMIFENSINE COMPARED WITH AMITRIPTYLINE: A DOUBLE-BLIND CLINICAL TRIAL IN ACUTE PRIMARY DEPRESSIONS

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1 Nomifensine (8-amino-2-methyl-4-phenyl-1,2,3,4,-tetrahydroisoquinoline) is a new antidepressant which displays an interesting pharmacological profile and acts as a potent dopaminergic agonist.

2 In a double-blind clinical trial nomifensine was compared with a standard and widely tested antidepressant amitriptyline. A total of 24 patients with primary acute depressions, defined by research criteria, were treated for 8 weeks and their clinical condition and laboratory values monitored at regular intervals. The dosage schedule was a flexible one, with a daily dose range from 50–200 mg for nomifensine and 50–225 mg for amitriptyline.

3 Nomifensine and amitriptyline were found to be equivalent in their antidepressant efficacy. Nomifensine, however, showed a trend towards more rapid effect and was relatively free of side-effects.

4 As nomifensine combined antidepressant activity with low frequency of adverse effects, it would seem to be suitable for wider use in the treatment of primary depressions. The results of our study have to be generalized with caution because of the limited sample size.

Introduction

A clinician who decides today to give an antidepressant drug to his patient can choose from a large armamentarium. The pharmacological and clinical development during the past 20 years have supplied him with a wide selection of effective agents. Antidepressants vary in their chemical construction, pharmacological profiles and in their usefulness in clinical practice.

Despite the wide range of alternatives, however, an ideal antidepressant has not been found and there is still need for new mood-altering drugs which would bring relief either faster, or have fewer side-effects, or both. Therapy-resistant patients have also remained a challenge for clinical psychopharmacologists. Thus, the search for antidepressants which would deal with some of these needs still continues.

On the basis of pharmacological testings and early clinical evaluations, nomifensine seemed to be a promising contribution to this search and therefore we carried out a controlled clinical study, using amitriptyline as a reference compound. Two crucial decisions one has to make when setting up an antidepressant trial are concerned with the size of the patient sample and with the choice of the standard antidepressant. We decided to use amitriptyline as this has been the reference drug for all our antidepressant trials during the past eight years and therefore such a comparison would permit us the necessary consistency. Furthermore, in our hands amitriptyline has been superior to placebo. As for the size of the sample, our choice went to limited numbers, with accent on careful selection and close personal observation of the patients.

Nomifensine (8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline) (Hoffmann, 1973) was synthesized by Hoechst Pharmaceuticals. Little has been written so far about nomifensine's background in the English language literature and therefore a brief review seems warranted. In its pharmacological profile, the compound is a powerful inhibitor of dopamine (DA) uptake (Costall *et al.*, 1975; Hunt *et al.*, 1974), possibly with some direct stimulating effect on DA receptors. Noradrenaline uptake is also inhibited but the effect on 5-hydroxytrytamine (5-HT) accumulation is only mild (Schacht & Heptner, 1974. Of particular interest are the centrally stimulating component of nomifensine's action and the absence of anticholinergic properties.

The substance is rapidly and completely absorbed, and peak and steady-state plasma levels are achieved

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fairly rapidly. (Vereczkey *et al.*, 1975). Laboratory and physiological parameters were studied extensively during early clinical testings and no alteration of the values was found, except in high doses. In particular, unlike other antidepressants, nomifensine was found to have no cardiotoxic and a mild positive inotropic effect on the heart (Biamino, 1976). During the early testing stage nomifensine was administered to more than 3,000 patients and over 150 volunteers in several European and South American countries, and good antidepressant properties and satisfactory tolerance documented. For out-patient treatment it may be particularly important that nomifensine did not reduce the reaction time, nor impair vigilance, nor interact with alcohol (Taeuber, 1976; Wittenborn, 1976). In view of these promising early findings, we decided to compare nomifensine in a double-blind study with amitriptyline to assess its efficacy and safety.

Methods

The patient sample for the study was selected from a series of consecutive referrals to the Affective Disorders Clinic at McMaster University, Hamilton Psychiatric Hospital in Hamilton. All patients meeting the following criteria were included: (1) acute primary depression, diagnosed according to research criteria (Feighner *et al.*, 1972); (2) moderate to severe intensity of the depression (a total score of at least 15 on the Hamilton Depression Scale); (3) age from 20–65 yr; (4) no major physical ailment, no history of convulsive disorder. Women of child bearing potential and pregnant women were also excluded.

Before entering the trial, patients had to be clear of psychoactive medication for at least 1 week (placebo wash-out period). Patients were then randomly assigned to nomifensine or amitriptyline and the medication and ratings handled in a double-blind fashion. Flexible dosage schedule was used as we are concerned that the use of standardized dosage reduces the chances of demonstrating the difference in situations where two antidepressants of unequal potency are tested. The dosage was therefore gradually increased until the patient showed a considerable improvement, and then continued at a maintenance level until the completion of the investigation. Daily dosages ranged from 50–225 mg for amitriptyline and 50–200 mg for nomifensine. Chloral hydrate was administered on several occasions for insomnia.

The assessments carried out during the study included psychiatric, medical and biochemical measures. The degree of clinical psychopathology was expressed in ratings using the Hamilton Depression Scale and a 15-point Clinical Global Impression Scale. These ratings took place on a weekly basis. Laboratory testing included haematology (CBC and differential), liver function tests (SGOT, SGPT, alkaline phosphatase, total bilirubin) and other routine measures (BUN), checked initially and after 4 and 8 weeks. Blood pressure, pulse and body weight were checked on a weekly basis. Electrocardiograms (ECGs) were checked before and during the study on selected patients. Blood samples were taken for the determination of serum amitriptyline and serum nomifensine at the end of the second and fourth week (results not available at time of writing).

Collected rating scores were assessed statistically by a two-way analysis of variance using IBM statistical package computer programs. Two of the patients, both from the amitriptyline treatment group, did not complete the 8-week study, as one became hypomanic and had to be switched to phenothiazines and the other did not improve and had to be given electroconvulsive therapy (ECT). Missing readings at week 8 for the above mentioned patients were represented by estimated values using the procedure developed by Armitage. For additional analyses data were also converted into values of percentage reduction in scores from baseline. In the analyses where initial values deviated for both groups, the raw data were standardized by dividing each weekly score by its corresponding baseline score, and the material re-analyzed the same way.

Results and discussion

When the study was completed, the sample comprised 24 patients, 12 on each drug. Both treatment groups, nomifensine as well as amitriptyline, seemed to be well matched in characteristics such as sex, duration of the present episode and time elapsed since the onset of the first episode, the only exception being the present age. The amitriptyline group turned out to be significantly older (average age 53.8 $\pm$ 11.6 yr), than the nomifensine group (mean age 38.5 + 10.6 yr) and this has to be considered when interpreting the results.

Efficacy

Nomifensine and amitriptyline both demonstrated antidepressant action, and the administration of both drugs was associated with a significant decrease in the depressive symptomatology, to a similar degree. Using the scores of the Hamilton Depression Scale, the analysis of variance yielded no significant difference between both treatment procedures (Figure 1). The results of the analyses were essentially the same regardless of whether raw data or percentage reduction from the initial values were used. From the analysis of the data the antidepressant action of nomifensine seemed to be faster. Compared with the initial scores, a significant reduction in the values of

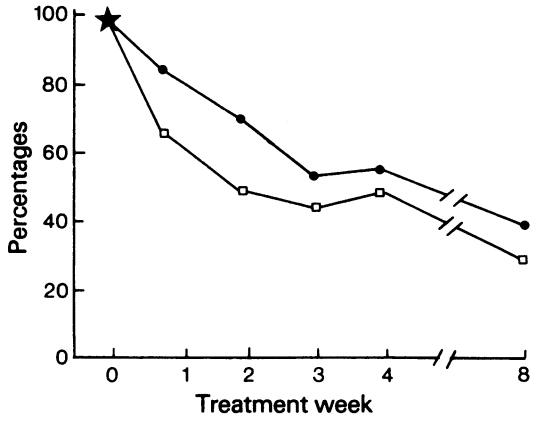

Figure 1 Changes in rating scores during treatment with nomifensine (□), and amitriptyline (●), expressed as percentage reduction in total mean scores of the Hamilton Depression Scale. Using an analysis of variance, there was no significant difference between both treatment procedures.

the Hamilton Depression Scale was achieved by the end of the first week, whereas a significant decrease in symtomatology in the amitriptyline group was not reached until the third week of treatment. This may reflect the pharmacokinetic properties of nomifensine to achieve steady-state levels more rapidly (Vereczkey *et al.*, 1975); or it may be attributed to the activating component of nomifensine which could clinically present as an early change of symptomatology in some patients. The trend favouring nomifensine, however, was more pronounced in the rating scores of the Global Impression Rating Scale; as this scale cannot be standardized, it is, however, not possible to generalize from this observation.

If there is a considerable difference between two drugs, one expects to find not only a difference in the scores of the rating scales, but also a similar difference in the responsiveness as expressed by the proportion of the patients who showed considerable improvement (the reduction of at least two-thirds in initial symptomatology). When we compare responsiveness in our data, nomifensine and amitriptyline seemed to be approximately equal. Regardless of the drug used, the number of patients considerably improved is approximately the same at 4 weeks (5 for nomifensine, 4 for amitriptyline), as well as at 8 weeks (7 for nomifensine, 5 for amitriptyline, respectively). The lower ratings during the nomifensine treatment would therefore be associated rather with a more rapid action of the drug, and not necessarily with a greater therapeutic potency.

Furthermore, when one deals with a small sample such as in our study there is always a risk of not achieving full randomization. Our nomifensine subgroup was significantly younger and the initial scores indicated somewhat more severe depression. These two factors are sometimes associated with faster, spontaneous improvement and in our study may have contributed to the trend favouring nomifensine.

Considering the experimental conditions of our study, we feel the results of the statistical analyses should be interpreted as indicating that both drugs were approximately equivalent in their overall antidepressant activity and that nomifensine showed a trend toward a more rapid effect.

Side-effects

After our study was completed and the data analyzed, the main difference between both drugs seemed to be in the side-effects. Compared with pretreatment values, the scores on the Side-Effect Rating Scale in the amitriptyline group increased and remained elevated during the whole of the first month of treatment, whereas nomifensine treatment was linked with what have already been called "negative side-effects" (Coppen, personal communication). The symptoms rated on the Side-Effect Rating Scale were actually decreasing in their intensity with continuation of treatment. This indicates that the symptoms were primarily related to the depression and improved as the depression was subsiding, whereas the drug administration itself was not contributing much discomfort. Further exploration of this issue is necessary as there is room for distortion in this approach. The existing Side-Effect Rating Scales, including the one we used, were primarily developed for tricyclic antidepressants and therefore may not be that sensitive for pharmacological effects of substances of other chemical structure.

During nomifensine treatment, however, we observed not only a decrease in the total intensity of the side-effects but also a decrease in the proportion of patients who showed any side-effects at all. With amitriptyline, on the other hand, once the treatment was started, the majority of patients did report symptoms recorded on the Side-Effect Rating Scale scores. Unlike nomifensine, the administration of amitriptyline was particularly associated with sedation and side-effects related to parasympatolytic action (dry mouth, accommodation disturbances, and so on). Unfortunately, satisfactory statistical techniques for the analysis of side-effect rating scores don't seem to be available yet.

The difference in side-effects of both drugs may be particularly important for the ambulatory treatment of depressed patients.

In view of the difference in side-effects of both drugs, the question would naturally emerge whether this would enable the rater to recognize the drug that a particular patient was refusing and could in this way

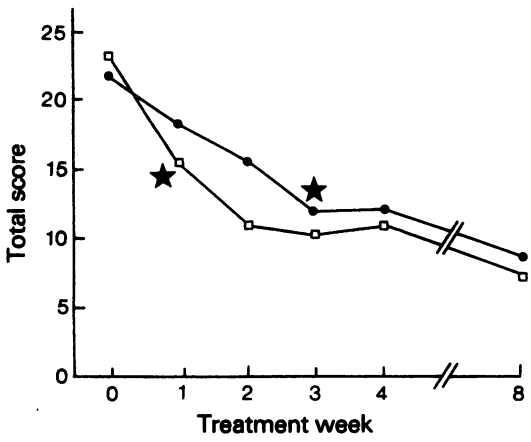

Figure 2 Changes in rating scores during treatment with nomifensine (□) and amitriptyline (●) treatments, expressed as mean total scores on the Hamilton Depression Scale. Analysis of variance showed no significant difference between both treatment procedures. Compared with initial values, a significant reduction in scores during nomifensine treatment was achieved by the end of the first treatment, and during amitriptyline treatment, by the end of third week (both marked with asterisks).

have biased his ratings. On the basis of the different pharmacological profile of both drugs, we anticipated this issue, and as a part of the design of the study asked that the rater, every time he made out his scores, also make a guess as to what medication the patient was receiving. In case of completely unbiased assessment one would expect approximately 50% of guesses to be correct. The subsequent analysis of the guesses showed that the rater was indeed able to guess somewhat better than by chance. The deviation from 50%, however, was not significant. It would seem, therefore, that the difference in the side-effects of both drugs provided the rater with some knowledge of which drug was administered in a particular case, but that this factor was too small to influence in any significant way the results of the study.

Conclusions

To recapitulate, in a double-blind clinical trial carried out with patients suffering from acute primary depression, nomifensine and amitriptyline both exhibited significant antidepressant action. In the overall clinical effect, both drugs showed approximately equivalent therapeutic activity. Nomifensine seemed, however, to induce the improvement in depressive symptomatology more rapidly. Furthermore, in comparison with amitriptyline, the treatment with nomifensine was associated with fewer side-effects.

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