NICOTINE ANTIDEPRESSANT EFFECTS AS A PREDICTOR OF RESPONSE TO DESIMIPRAMINE OR FLUOXETINE IN NON-SMOKING MAJOR DEPRESSED PATIENTS

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SUMMARY

It has been reported that there is a link between major depression and nicotine dependence. Also, it has been shown that acute administration from one to four continuous days of transdermal nicotine improved depression in non-smoking major depressed patients. The goals of this study were to observe the antidepressant effect of transdermal nicotine in placebo non-responders non-smoking major depressed patients, after one week of daily nicotine administration, and to see if the antidepressant response to nicotine could predict the clinical outcome after fluoxetine or desimipramine administration.

Forty-two non-smoking major depressed patients were studied. After a complete explanation about the protocol, signed consents were obtained from all the subjects. Patients received placebo during two weeks. Placebo responders were removed from the study. Placebo non-responders patients received one-week transdermal nicotine patches (17.5 mg/24 hr) and placebo capsules for one week. Subsequently the patients were randomly assigned to desimipramine (150 mg/day) or fluoxetine (20 mg/day). Weekly visits were evaluated using both clinical scales, during six follow-up visits.

Twenty-three patients ended the study. Eleven showed an improvement in their depressed moody, after one week with nicotine patches (47.8 %). After this first week with antidepressant administration, nine patients with desimipramine and three with fluoxetine showed improvement (Fisher exact test: $p<0.05$). Wilcoxon Matched-Pairs Signed Rank-Test comparing baseline with each visit evaluation showed statistical differences from the first week after nicotine administration in the desimipramine group ($p<0.01$). Fluoxetine group showed clinical improvement two weeks after nicotine patches use ended.

A synergistic effect of both nicotine and desimipramine was observed with a high predictive value for this antidepressant. This may be related to the enhancement in the availability in catecholamines produced both by desimipramine and nicotine.

Key words: Major depression, desimipramine, fluoxetine, nicotine.

RESUMEN

Existe una relación documentada entre depresión mayor y dependencia a la nicotina. Por otro lado, se ha demostrado que la administración entre uno y cuatro días de nicotina transdérmica mejora la depresión de pacientes con depresión mayor que no sean fumadores. Los objetivos de este estudio fueron: observar el efecto antidepresivo de nicotina transdérmica en pacientes con depresión mayor no fumadores, y que antes no hubieran respondido al placebo y, por otro, observar si la respuesta antidepresiva con nicotina predice respuesta al tratamiento antidepresivo con desimipramina o fluoxetina.

Se estudiaron 42 pacientes deprimidos. A los pacientes se les explicó el estudio y se obtuvo de ellos un consentimiento firmado. Los pacientes recibieron el placebo durante las dos primeras semanas. Los enfermos que respondieron al placebo fueron separados del estudio. Los sujetos que no respondieron al placebo recibieron durante una semana continua parches de nicotina transdérmica (17.5 mg diariamente) y cápsulas de placebo. En la semana siguiente se les asignaron de manera aleatoria dosis de desimipramina (150 mg/día) o fluoxetina (20 mg/día). Se hicieron visitas diarias para evaluar su respuesta clínica durante seis semanas.

Finalizó el estudio un total de 23 pacientes. Once de ellos (47.8%), presentaron una mejoría en su estado de

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ánimo, tras una semana de usar parches de nicotina transdérmica. Después de la primera semana con tratamiento antidepresivo, mejoraron nueve pacientes con desimipramina y tres con fluoxetina (prueba exacta de Fisher, $p<0.05$). La prueba de signos pareados de Wilcoxon, que comparó cada visita con antidepresivos contra la basal de las escalas de Hamilton para depresión, mostró diferencias significativas desde la primer semana de tratamiento después de la nicotina para el grupo de desimipramina ($p<0.01$). El grupo que recibió fluoxetina mostró una mejoría clínica significativa después de dos semanas de tratamiento. Se observó un efecto sinérgico entre la nicotina y la desimipramina. Haber respondido en un principio a la desimipramina predice una mejor y más rápida respuesta a ésta que a la fluoxetina, lo cual puede deberse al efecto que ejercen sobre las catecolaminas las dos moléculas estudiadas.

Palabras clave: Depresión mayor, fluoxetina, desimipramina, nicotina.

INTRODUCTION

The relationship between nicotine and depression has been focused upon recently (Glassman et al., 1990). Smokers having major depression are less successful in quitting smoking cigarettes than non-depressed subjects (Bresalau et al., 1991). It has also been shown that during smoking-cessation treatment, a subgroup of subjects developed major depression disorders after quitting cigarettes, although some of them were on fluoxetine 30 mg/day (Borreli et al., 1996).

Nicotine transdermal patches were studied in normal volunteers and depressed patients (Salín-Pascual et al., 1995). The first group of subjects presented a reduction in both total sleep time as well as REM sleep, while depressed patients showed an increase in total sleep time as well as in REM sleep; they also reported mood improvement. The antidepressant effect of four continuous days of nicotine administration in non-smoking depressed patients has been studied too (Salín-Pascual et al., 1996). After two days of nicotine administration, a significant clinical improvement was observed, and then patients relapsed four days after the last nicotine patch administration.

We studied just one week of daily nicotine administration in a group of major depressed patients that were placebo non-responders. After that, patients were randomly assigned in a single blind protocol to either fluoxetine or desimipramine. The goal of this second part of the study was to observe if the previous response to nicotine could predict clinical improvement in either one of the two antidepressants used.

METHOD

Forty-two non-smoking major depressed outpatients were studied. They were diagnosed for the first time and were drug-free. Before entering the study, a signed consent was obtained from them after the procedure had been fully explained. Patients were submitted to a medical and psychiatric history, where a structured psychiatric examination was obtained (Structured Clinical Interview for DSM-III-R/SCID), (Spitzer et al., 1987). Non-smoking status was defined as no more that three cigarettes a day for no more than a month during their life time, and no exposure to tobacco in the year before the study. Patients should not have other medical conditions that could put them at health risk when nicotine was used. All the subjects were scored with a Hamilton Rating Scale for Depression (HAMD) of 21 items. Inclusion criteria was to have an score equal or above 18 points. In addition, the Beck Inventory Depression Scale (BIDS) was used.

Patients received placebo capsules for two weeks, and were scored one each week. Placebo responders were not allowed to follow the next part of the protocol. A placebo responder was an individual showing a reduction in his/her HAMD scores below 50% from his/her baseline. Placebo non-responders were on the second part of the study, consisting of nicotine patches administration (Nicotinell - Ciba-Geigy, 17.5 mg/day) for the next seven days. All patients were taking placebo capsules at the same time they were using nicotine patches (one week).

During the following week, all patients, disregarding their response to nicotine patches, were randomly assigned to fluoxetine (20 mg/day) or desimipramine (150 mg/day). Identical capsules to the ones with placebo were provided with the active drugs during the entire protocol. Medication was given after breakfast and lunchtime (10 mg fluoxetine and 75 mg desimipramine in each capsule). Patients were evaluated weekly for six weeks and in

each visit they were scored with HAMD and BIDS. Also, a side effect scale was taken. A responder was defined as the patient who reduced their HAMD more than 50% compared to his/her baseline scores. The statistical analysis was performed with non-parametric tests. For the predictive value of each group Fisher exact test was performed.

RESULTS

From the 42 patients that entered the study, 11 were placebo responders (26.2%), and eight were drop-outs (19.04%); three of them dropped out due to nicotine's severe side effects (i.e., anxiety, insomnia, nausea and vomiting). The rest of the patients who did not complete the study were on antidepressants (three on fluoxetine and two on desimipramine). They withdraw due to side effects related to the antidepressants.

Twenty-three patients ended the study. Ten were in the fluoxetine group (mean ± s.d. age = 31.4 ± 8.3 years; eight females and two males); and thirteen were in the desimipramine group (mean ± s.d. age = 31.4 ± 12.6 years, ten females and three males).

Eleven patients showed an improvement in depression after a week using nicotine patches (47.8% from the 23 patients that ended the study). Nine patients in the desimipramine group (n=13) improved during the first week of antidepressant treatment, while in the fluoxetine group (n=10), three patients showed a reduction in their clinical ratings 50% below the baseline during the first week of antidepressant treatment (Fisher exact test: $p<0.05$, from HAMD and BIDS).

Wilcoxon Matched-Pairs Signed-Ranks Test, comparing baseline with each clinical condition (using both HAMD and BIDS) for the desimipramine group, showed statistical differences after the first week in which patients received nicotine and in the following visits ($p<0.01$ each visit vs. baseline). The fluoxetine group statistical differences with the same non-parametric test started two weeks after nicotine administration ended ($p<0.01$ each visit vs. baseline).

Figure 1 shows the HAMD scale average punctuation in the two groups. Although improvement was observed in both groups, at the end of the study the desimipramine group

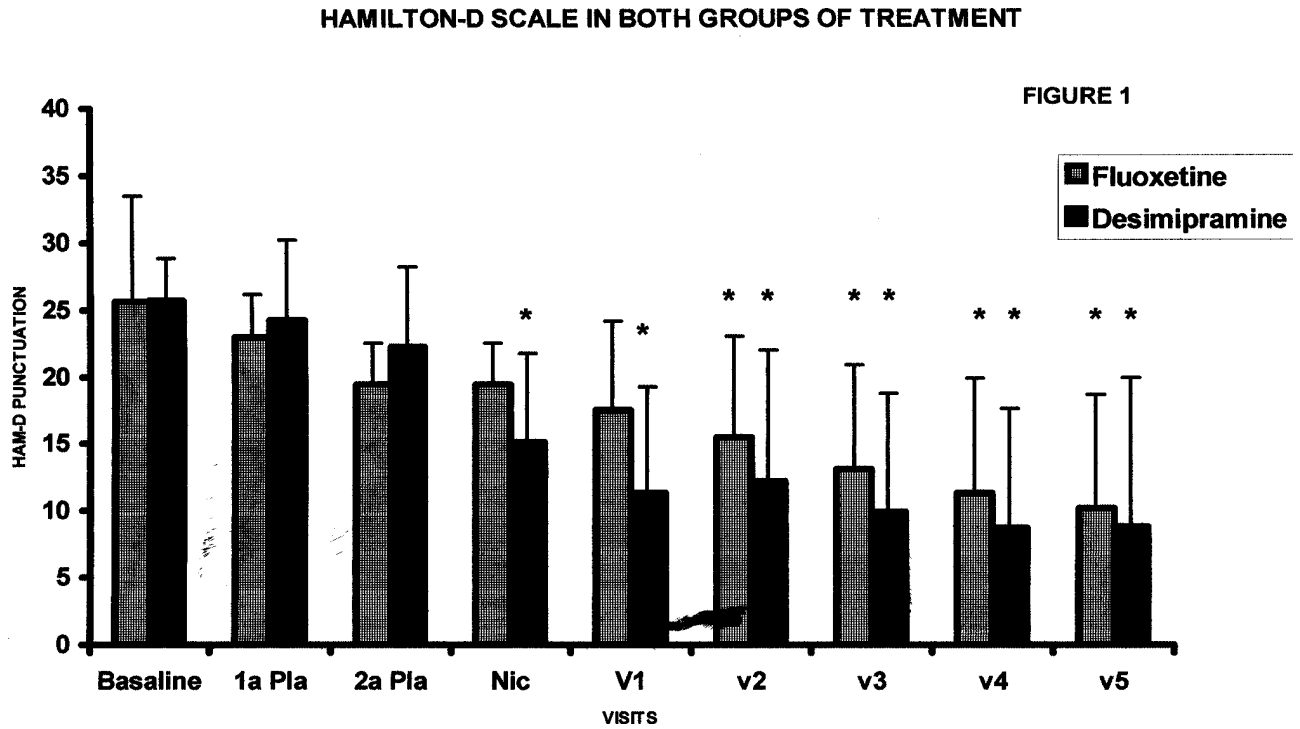

Figure 1. Hamilton Depression Scale in the two groups (i.e., desimipramine and fluoxetine). Both groups of patients improved after antidepressants administration. Wilcoxon Matched-Pairs Signed-Rank Test showed statistical significance from the first week of nicotine administration in the desimipramine group (* $p<0.01$ each visit vs. baseline). The statistical differences in the fluoxetine group were observed two weeks after the antidepressant administration started (* $p<0.01$ each visit vs. baseline).

showed an early response. Likewise, at the end of the study, one fluoxetine group patient (10%) and three from the desimipramine group (23%) did not show any improvement at all.

From the nine patients that improved in the fluoxetine group, six did not improve with nicotine, and from the three patients that improved with nicotine, only two improved at the end of the trial with fluoxetine. Predictive value related to nicotine was 0.66 in this last group. From the ten patients that improved with desimipramine, eight were nicotine responders (61.5% from the total). Predictive value of nicotine in this group was 0.8.

Side effects reported during the week with nicotine were cephalea, nausea, anxiety, dry mouth and anorexia; all these symptoms were scored as mild. Side effects in fluoxetine group were nausea, cephalea and anorexia. Side effects in desimipramine group were dry mouth and anxiety.

DISCUSSION

The main findings of the present study were that, after two weeks of placebo administration, 47.8% of the placebo non-responders patients improved after one week of nicotine administration. Patients that received nicotine, followed by desimipramine, had a rapid onset of antidepressant action, in comparison to the group of patients with nicotine followed by fluoxetine. Mood improvement with nicotine patches predicts good antidepressant treatment with desimipramine. Of course, the main limitation of the present study is the reduced number of subjects that ended up in each cell, which gives this report the ranking of a naturalistic and exploratory study.

In previous studies, acute administration of transdermal nicotine produced a mood improvement in all patients tested (Salín-Pascual et al., 1995; Salín-Pascual et al., 1996). The present study is the first one in which non-placebo responders have been used in order to see the clinical outcome with nicotine patches. Eleven patients from the 23 that ended the study had a clinical improvement. The exclusion of placebo responders in this study was decided because the high response to placebo reported in depressed patients, and also because up to now there is not a double-blind controlled study to assess the probable antidepressant effect of transdermal nicotine patches. Given the administration of nicotine patches was restricted to one week, we believe that the clinical response to nicotine was equivalent to some antidepressants.

Because catecholamines inhibition re-uptake seems to be the main mechanism of action of desimipramine —and also because nicotine administration produces a release of catecholamines, among other neurotransmitters (Imperato et al., 1986; Yu et al., 1994)—, a synergistic type of effect could be observed with this antidepressant plus nicotine, because a short onset of antidepressant effect was noticed. This kind of effect has also been reported with methylphenidate when it has been used as co-therapeutic administration for depression. Adjunctive metylphenidate appears to accelerate the response to tricyclics, which occurs between the first and the second weeks of treatment (Gwirstman et al., 1994).

The fluoxetine group behaved quite differently, although at the end of the study nine patients out of ten demonstrated a clinical improvement. However, the pattern was different than that from the desimipramine group. Clinical improvement was significantly different after two weeks of fluoxetine administration. Even the three patients that already responded to nicotine had a relapse the week after nicotine patches use and started having the antidepressant effect two weeks later (only two of them, for the third one did not improve at the end of the protocol). Fluoxetine mechanisms of action are more selective to the serotonin system (Messiha, 1993), which could explain the lack of the synergistic effect observed with nicotine.

The present study seems to indicate that the nicotine antidepressant effect may predict a good response to desimipramine antidepressants, and also that the combination of this antidepressant with nicotine maybe useful in the treatment of some forms of resistant depression. More clinical research needs to be done in this area in the future in order to learn more about some possible therapeutic effects of nicotine in major depression, focusing in patients with resistant depression as reinforcement strategy.

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