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Original article

Effects of tianeptine on vigilance and memory in young healthy volunteers

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Summary – Tianeptine is a new antidepressant that, in animals, has a faciliting effect on both working and reference memory. To investigate the effects of tianeptine on vigilance and memory in humans, a placebo-controlled cross-over study was performed in 20 healthy volonteers. The duration of each treatment period was 7 days and the dosage of tianeptine 37.5 mg per day. The evaluations consisted of 3 computerized tests assessing alert function, continuous recognition and semantic facilitation. A memory questionnaire and the Rey test (15 words) were added. The analysis of variance (cross-over type) performed on the results did not show any significant difference between the evolution of these tests on tianeptine and on placebo in young healthy subjects, at the height of their intellectual capacities. In this study, tianeptine respected the vigilance as well as the performances of the healthy volunteers and did not impair their memory and cognitive processes, which distinguishes it from many psychotropic drugs. Nevertheless, tianeptine did not produce a faciliting effect on these processes in healthy volunteers. These results allow us to propose new clinical trial with tianeptine in order to investigate its effects on older volunters and patients complaining of memory disorders.

tianeptine / antidepressants / vigilance / memory / young healthy volunteers / data processing

Résumé – Etude des effets de la tianeptine sur la vigilance et la mémoire du volontaire sain jeune. *La tianeptine est un nouvel antidépresseur qui possède chez l'animal un effet faciliteur de l'apprentissage et de la mémoire. Les effets de la tianeptine sur la vigilance et la mémoire ont été recherchés chez l'homme au cours d'une étude réalisée en cross-over contre placebo chez 20 volontaires sains jeunes. La durée de chacune des périodes de traitement était de 7 jours et la posologie de tianeptine de 37,5 mg par jour. Les évaluations consistaient en 3 tests informatisés étudiant respectivement la fonction d'alerte, la mémoire de reconnaissance immédiate et la vitesse de facilitation sémantique. Un questionnaire de mémoire et le test des 15 mots de Rey étaient aussi remplis. L'analyse de variance (de type cross-over) appliquée aux résultats n'a montré aucune différence significative entre les évolutions de ces tests sous tianeptine et sous placebo chez des sujets sains jeunes, au maximum de leurs capacités intellectuelles. Au cours de cette étude, la tianeptine a respecté aussi bien la vigilance que les performances des volontaires sains et n'a entraîné aucune altération de leurs processus mnésiques et cognitifs, ce qui la distingue de nombreux psychotropes. Aucun effet facilitateur de ces processus n'a cependant été mis en évidence chez des sujets sains. Ces résultats permettent d'envisager de nouvelles études cliniques avec la tianeptine afin d'étudier ses effets chez le volontaire sain plus âgé ainsi que chez le patient se plaignant de troubles mnésiques.*

tianeptine / antidépresseurs / vigilance / mémoire / volontaire sain jeune / informatique

Introduction

Tianeptine is a new tricyclic antidepressant that enhances serotonin uptake (Kato *et al*, 1988) and has been shown in double-blind studies to be as effective as standard antidepressants (Defrance *et al*, 1988).

In animal studies, tianeptine does not impair spatial memory and has facilitating effects on both working and reference memory (Kamoun *et al*, 1989).

These effects have been put forward in mice in two discrimination tests of increasing complexity: the T maze test and the automated radial test (Jaffard *et al*, 1988).

The present study has been performed on young healthy volunteers in order to verify in man the hypothesis based on the results observed

in animals. The aim of this study was to determine the effects of tianeptine on vigilance and memory in healthy volunteers and to determine whether tianeptine respects, enhances or impairs these processes.

In a double-blind placebo-controlled cross-over study, the effects of therapeutic doses of tianeptine (37.5 mg per day) on vigilance and memory have been assessed in 20 healthy young subjects after a 7-day treatment period.

Objective computerized memory and vigilance tests have been used and assessment conditions were standardized.

Methods

Healthy volunteers

Twenty healthy volunteers were included in the study. This sample comprised 11 men and 9 women with a mean age of 35.2 years (according to the protocol, minimum age was 30 years and maximum age 45 years). Tests were standardized in the French language.

The volunteers were in good physical and mental health (normal physical examination), within the normal range for weight. They were neither alcohol abusers nor drug addicts and consumed less than 6 cups of tea, coffee or coke per day and less than 20 cigarettes per day. They had not participated in another trial during the previous 2 months. They did not follow any regular treatment and had not taken any psychotropic drug during the 4 weeks preceeding the trial. The women had effective contraception.

This protocol was accepted by the Ethics Commitee of the University of Liège (Belgium). The study was performed according to the Helsinki agreements: all the volunteers were completely aware of the study and signed an informed consent.

Procedures

The study was a double-blind placebo-controlled cross-over trial. In order to study the effects of a chronic treatment with tianeptine, a 7-day treatment period was chosen (approximately 10 times the period necessary to reach the plateau).

The protocol consisted of 2 drug periods of 7-days each, separated by a 7-day wash-out period.

During these periods, the volunteers received either 37.5 mg of tianeptine per day (1 tablet of 12.5 mg at 8 and 12 am and 6 pm) or 3 tablets of placebo according to the conditions of a double-blind trial.

The first drug intake took place on the first treatment day at 12 am and the last one on the eighth day at 8 am.

Before the trial itself, the volunteers were submitted to a training session to minimize the learning effect of the tests.

During the study, these tests were repeated 4 times: twice during each session, on the first and the eighth day (1 hour before the first drug intake and 1 hour after the last drug intake, when tianeptine reaches its maximum plasma level).

At the end of each treatment period, the volunteers were asked if they had noticed any objective or subjective symptoms (side-effects).

To assess the compliance of the healthy volunteers, the remaining tablets were counted at the end of each treatment period (the intake of less than 80% of the prescribed tablets was considered as exclusion criterion).

Evaluation

The evaluations consited of 3 computerized test (Poon *et al*, 1978 and 1980. Cerella *et al*, 1981) The Rey test (Rey, 1982) and a memory questionnaire (Van Der Linden *et al*, 1988).

Five parallel versions of the computerized tests have been used for the learning session and the 4 following sessions of the study.

These psychometric tests can be described as follows:

"Alert function" test

The alert function measures the process of alertness/arousal; that is the ability to concentrate for a short period of time. This process can be investigated by way of a simple reaction time process. The subject observes a square on the screen followed by the message "go" within it. The volunteer must push on a button, as soon as possible, each time the message "go" appears.

When varying the interval (interstimulus interval: ISI) between the pre-stimulus (square) and the target ("go"), one obtains an alertness function. This interstimulus interval is randomly modulated from 25 to 1000 msec in 5 categories (25, 250, 500, 750 and 1000 msec). Each experience is repeated 10 times within each category.

"Continuous recognition" test

This test studies the primary (short term) and secondary (long term) memory and the recognition performance of a subject. The volunteer must identify, in a list of 50 words presented to him twice: the "new" words (seen for the first time) and the "old" ones (already seen on the screen).

In this test, the interval between the first and the second appearance of the same word randomly changes so that some recalls correspond to the primary memory (1 to 7 words separate the two appearances) and other recalls to the secondary memory (8 or more words separate two appearances).

There are 5 sets of 10 words each, each set corresponding to the following intervals: 1, 2, 4, 8, 16 words.

Reaction time and accuracy of the answers are analysed, taking into account the contents of the intervals related to primary or secondary memory.

"Semantic facilitation" test
This test mainly studies the semantic recall system of a subject.
Fifty pairs of words are shown to the volunteer: either real words belonging to the French language, or pseudo-words which are pronounceable but meaningless, or non-words which are unpronounceable.
Five pairs of 10 words exist: 2 pairs of real words (1 semantically associated and 1 semantically non-associated), 1 non-word and 1 word, 1 pseudo-word and 1 word, 1 non-word and 1 pseudo-word. The first word is the initiating stimulus, the second one is the target.
The subject must answer as soon as possible "yes" if he judges that the target word is a real word or "no" if he thinks that it is a pseudo or a non-word.
Reaction time and accuracy score are measured for the target stimuli, according to the 5 different kinds of pairs used.

Rey test
The Rey test consits of parallel list of 15 words with five recalls for each session.

Memory questionnaire
This is a self evaluation containing 10 chapters, each of them investigating a well defined field of memory. They focus on possible lapses of memory in the following fields: discussions, films and books, entertainment, people, directions for use, news, places, actions, personal life, trigger factors. The different items were quantified from 0 (never) to 5 (always).

Statistical analysis

The baseline data before intake of placebo or tianeptine have been compared using analysis of variance with one criterion corresponding to the cross-over sequence.
The evolution of the mean note of all tests, the effect of treatment, the effect of administration order and the corresponding drug interactions have been tested using a univariate analysis of variance with repeated measures. The statistical analysis has been performed on the calculated differences, for each treatment, between the baseline and the terminal data for each of the two weeks of treatment. The analyses were performed with a type one error alpha = 0.05.

Results

Psychometric tests

The basic data (before administration of both treatments) were found to be statistically independant of the administration order for each test.
These results can be illustrated as follows:

"Alerting function" test
Figure 1 shows the mean reaction times (coefficient of variation = ± 15 %) before and after each treatment, according to the different time-intervals between the prestimulus and the target. No statistically significant difference was observed between the two treatments: $F(1,18) = 0.00$, $P = 0.99$.

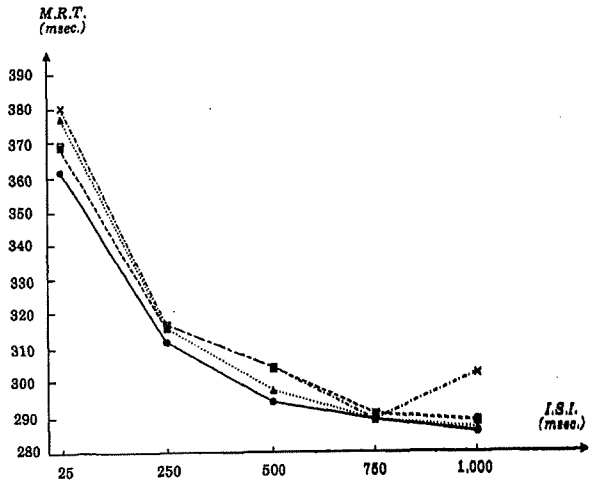

Fig 1. Alerting function. Mean reaction times (MRT), according to the different interstimulus intervals (ISI). Groupe: ▲—·—·▲ before placebo; ×--·-× after placebo; •—• before tianeptine; ■---■ after tianeptine.

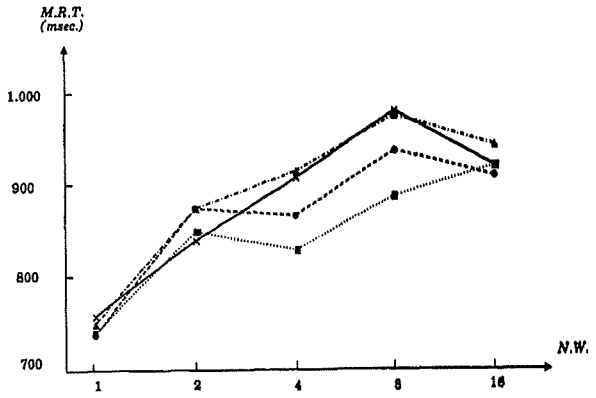

Fig 2. Continuous recognition ("old" words). Mean reaction times (MRT), according to the number of words (NW) between two "old" words. Groups: ▲—·—·▲ before placebo; •--• after placebo; ■----■ before tianeptine; ×— × after tianeptine.

"Continuous recognition" test

Figures 2 and 3 illustrate the evolution of the mean reaction times and the mean number of good answers (coefficient of variation respectively ± 17% and ± 5%) under each treatment for the recognition of "old" words, according to the number of words separating 2 "old" words. No statistically signifiant difference was observed between the two treatments: $F(1,18)=4.16$, $P=0.06$ for the reaction times (assessment of vigilance) and $F(1,18)=2.32$, $P=0.15$ for the number of good answers (assessment of performances).

The same analysis has been performed for the "new" words. No statistically significant difference was observed between the two treatments.

"Semantic facilitation" test

Figures 4 and 5 present the mean reaction times and the mean numbers of good answers (coefficient of variation ± 20% and ± 5% respectively) before and after each treatment, according to the kind of pair of words shown. No statistically significant difference was observed between the two treatments: $F(1,18)= 0.07$, $P=0.79$ for the reac-

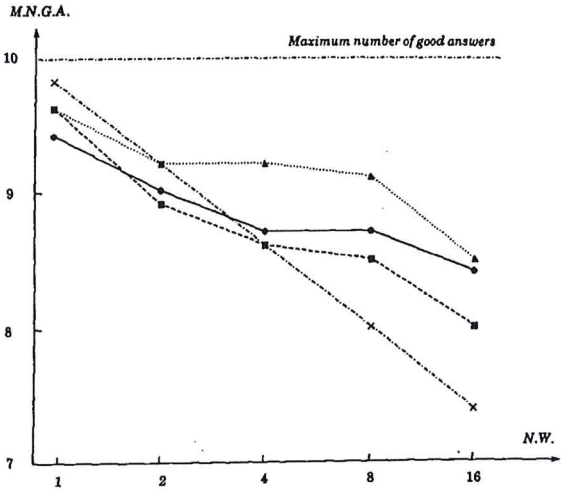

Fig 3. Continuous recognition ("old" words). Mean number of good answers (MNGA), according to the number of words (NW) between two "old" words. Groups: •—• before placebo; ■---■ after placebo; ▲···▲ before tianeptine; ×—·—·× after tianeptine.

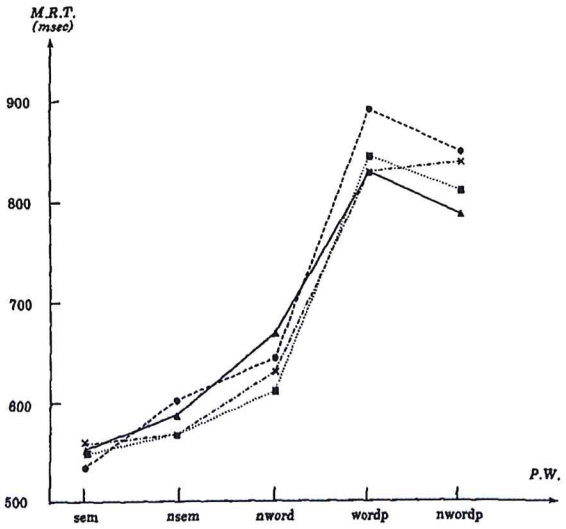

Fig 4. Semantic facilitation. Mean reaction times (MRT), according to the different pairs of words (PW). Groups: •—• before placebo; •---• after placebo; ■···■ before tianeptine; ▲—▲ after tianeptine. sem: semantically associated words. Nsem: non semantically associated words. Nword: nonwordd followed by word. Wordp: word followed by pseudoword. Nwordp: nonword followed by pseudoword.

Table I. Rey Test. Mean (SD) before and after each treatment according to the number of recalls.

No of recalls	*Before placebo*	*After placebo*	*Before tianeptine*	*After tianeptine*
1	7.80 (1.64)	7.05 (1.99)	7.40 (2.23)	7.25 (2.07)
2	10.95 (1.88)	10.60 (2.68)	10.70 (2.54)	9.80 (2.31)
3	12.45 (2.01)	11.80 (2.80)	12.75 (1.94)	12.00 (2.13)
4	13.15 (1.90)	13.30 (1.63)	13.30 (2.13)	12.85 (2.18)
5	13.15 (1.90)	13.25 (1.68)	13.90 (1.45)	13.30 (1.75)

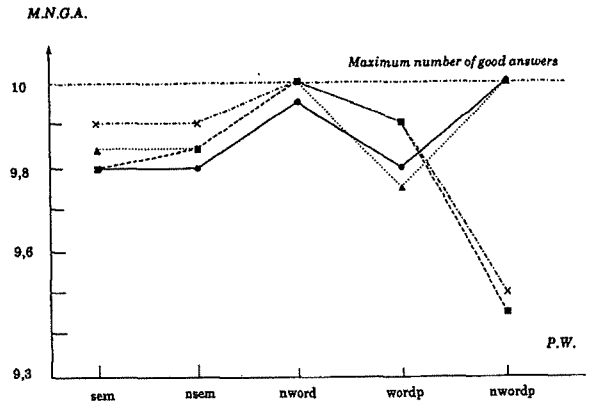

Fig 5. Semantic facilitation. Mean number of good answers (MNGA), according to the different pairs of words (PW). Groups: •—• before placebo; ▲···▲ after placebo; ■---■ before tianeptine. ×—·—·× after tianeptine. Sem: semantically associated words. Nsem: non semantically associated words. Nword: nonworld followed by word. Wordp: word followed by pseudoword. Nwordp: nonword followed by pseudoword.

tion times and $F(1,18)=0.20$, $P=0.66$ for the number of good answers.

Rey test

No statistically significant differences have been observed between the means with each treatment according to the 5 repetitions of the list of 15 words as shown in Table 1: $F(1,18)=0.78$, $P=0.39$.

Memory questionnaire

The evolution of the means of the 10 chapters of the questionnaire did not differ statistically between the two treatments.

No statistically significant difference was put forward between the 2 treatments tianeptine and placebo in any of the tests nor in the computerized tests as well as the Rey test and the memory questionnaire.

Tolerance and compliance

Two side-effects have been mentioned with regard to tianeptine: drowsiness (twice), and 6 side-effects with placebo: drowsiness (twice), tiredness (once), headache (once), lack of attention (once), impulsiveness (once).

Four subjects did not take one tablet: 2 subjects during the placebo session and 2 others during the tianeptine session.

Discussion

At a level of significance of 0.05, none of the parameters (memory questionnaire, Rey test or computerized tests) showed a statistically significant difference between placebo and tianeptine, nor a particular evolution according to the administration order.

Emphasizing the most sensitive tests (computerized tests), it is possible to conclude that tianeptine has no effect on: simple reaction time, vigilance and psychomotor velocity, recognition mechanisms and especially recall, fundamental language and semantic memory facilitation.

These results prove that, in the chronic dose regimens, tianeptine respects these functions. This distinguishes tianeptine from the other antidepressants, notably imipramine and amitriptyline, which produce, in normal subjects at a therapeutic dose schedule, measurable cognitive impairment particularly in performance (increase in the number of mistakes).

Non-tricyclic antidepressants, in contrast, appear to have little or no effect on normal cognition (Judd *et al*, 1987).

The absence of a memory-enhancing effect of tianeptine in this study is not very surprising because of the characteristics of the included population: young healthy volunteers at the height ot their intellectual capacities.

Tolerance was similar and excellent in placebo and tianeptine, no side-effects appeared more frequently in one session than in the other and compliance was good.

With regard to these first encouraging results in young volunteers, it seems of interest to test the effects of tianeptine in older volunteers or patients complaining of memory disorders in which an improvement could more easily be obtained.

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