Influence of cilazapril on memory functions and sleep behaviour in comparison with metoprolol and placebo in healthy subjects

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1 In a controlled, randomized, double-blind study the influence of cilazapril and metoprolol on learning and memory functions and on sleep behaviour was investigated in healthy young volunteers under steady-state conditions. Twenty-three subjects were given either 2.5 mg cilazapril, 200 mg metoprolol, or placebo for 14 days in a latin square design separated by washout periods of 7 days.

2 To test memory functions different modalities—verbal, visual, numerical associative and two dimensional spatial memory were tested for recent anterograde recall, both short-term (less than 10 s) and middle-term (up to 15 min) were selected. The test had a content similar to that used in daily life situations. The sleep behaviour was tested both by objective (all night sleep EEG) and subjective measures.

3 Neither antihypertensive drug had an observable influence on memory performance at the dosages used under steady-state conditions. However, sleep was disturbed during metoprolol, while cilazapril could not be differentiated from placebo. The effects of metoprolol on sleep behaviour were observed in the objective and subjective measures. There was more frequent awakening during the night with the subjective complaint of difficulties in sleeping through.

4 From this study it is concluded that cilazapril has no major effect on memory functions and sleep behaviour. This is only true for the dosages given and under steady-state conditions.

Keywords cilazapril metoprolol memory sleep EEG

Introduction

Lichter *et al.* (1986) recently reported an investigation with the ACE inhibitor enalapril and the β -adrenoceptor blocker atenolol in 25 hypertensive patients. After a 2-week placebo washout phase 13 patients were treated for 16 weeks with atenolol and 12 with enalapril. Four memory tests were performed at the end of the washout phase (week 2) and at the end of the treatment period. In nine out of 28 comparisons the patients treated with atenolol attained significantly poorer scores after active treatment than during the placebo period, while no change was found in the enalapril-treated patients. There have

been repeated reports in the literature of impairment of central nervous function, including memory (Solomon *et al.*, 1983) and sleep (Betts & Alford 1985), following treatment with β -adrenoceptor blockers, but there have been few studies with ACE inhibitors to assess their CNS activity. Olajide & Lader (1985) have, however, reported increased attention and alertness with enalapril. The aim of this study was to investigate under controlled conditions, some central nervous effects of the newly developed ACE inhibitor cilazapril as compared with the β -adrenoceptor blocker metoprolol and placebo.

Table 1 Decision strategy for the clinical-pharmacological model used

1) particular CNS-functions (memory, sleep)	vs	CNS-screening
2) cross over	vs	parallel groups
3) steady state (subacute)	vs	acute (single dosage)
4) volunteers	vs	patients

Particular attention was drawn to memory functions and sleep behaviour in healthy subjects.

Clinical pharmacological models are not always valid indicators of therapeutic effect. However, if the substances tested have constant and measurable effects on memory function and sleep behaviour this should be apparent with the methods used in this trial.

Table 1 demonstrates the decision strategy for such models. It was decided not to perform a general CNS screening, involving several different functions, since information was available in the literature relating to memory and sleep. To test parallel groups would require a large number of subjects (probably more than 50 per group). Such a large number of subjects usually cannot be handled in one laboratory. It was therefore decided to select a cross-over design. Since it is likely that the effects under steady-state conditions are greater than after acute administration it was decided to make the assessments at steady-state.

For sleep behaviour all night sleep EEG and subjective ratings were used, while the following memory tests were considered appropriate since they related well to every day activities.

- 1) **anterograde** memory,
- 2) **recent** (up to 3 months) memory,
- 3) **global** (not separate for acquisition, storage and retrieval) and not particular functions,
- 4) **different** (verbal, visual, numeric, associative etc.) and not only one modality.

Methods

Subjects

Thirty healthy male volunteers aged 20–30 years were recruited into the study. Subjects with hypertension (systolic above 140 mm Hg, diastolic above 90 mm Hg) on three different occasions on 3 different days were excluded. Their physical condition was assessed by a medical examination, in which patients with abnormalities in the ECG,

EEG, or clinical laboratory parameters were excluded. To guarantee as homogeneous a sample as possible for the psychological trial, only subjects who had a standard score of 100–120 in the IST-70 intelligence structure test were included (Amthauer, 1970). Those who showed signs of increased emotional lability or an increased tendency to express physical complaints in a personality test were excluded (Freiburg Personality Inventory FPI-R, Fahrenbert *et al.*, 1984), as were those with a history of sleep disturbance. All subjects were given extensive written information about the study. The study met the guidelines for biomedical research in human subjects in the revised version of Tokyo 1975 and was approved by AFB's Institutional Review Board. The subjects were paid for their participation.

Design and drugs

The investigation was performed as a randomized, controlled double-blind study with a latin square design. Three groups of 10 subjects were treated during three treatment periods of 14 days each. The subjects were randomly assigned to one of the three treatments: 2.5 mg cilazapril, 2 × 100 mg metoprolol, or placebo daily (Figure 1). The treatment periods were separated by a 7-day washout phase. The subjects took the medication at home in the morning and evening (those receiving cilazapril took placebo in the evening). They came to the laboratory every 2 days, where blood samples were taken to determine plasma concentrations to assess compliance. Blood pressure was also checked, and subjects completed two questionnaires (mood-rating scale and catalogue of side effects).

On the 8th treatment day the psychological learning and memory trial was performed. After the 14th treatment day an all-night sleep EEG was recorded in the sleep laboratory (see Figure 1). Subjects spent 2 nights in the laboratory before the start of the study to familiarize themselves with the unusual surroundings.

Memory tests

The learning and memory tests were selected to assess aspects of verbal, visual, numerical, associative and two dimensional spatial memory. They were partly based on the LGT-3 learning and memory test (Bäumler, 1974) and were complemented by a third parallel form for this investigation.

1. Shopping list (SL):

The shopping list consists of 15 goods articles and quantities. It has validity for **verbal**

Figure 1 Design of the study: The subjects were randomly assigned to one of the three treatment groups. In each treatment period there were memory tests after 7 days and an all night sleep EEG recording after 14 days of drug therapy. MET metoprolol, CIL cilazapril, PLA placebo.

memory. Subjects had to read out each item as they were presented one by one on a card for 6 s. After each trial, subjects were tested to establish what they had learned.

2. Telephone numbers (PN):

A telephone list was compiled with 13 names of institutions or persons and the corresponding 2-digit phone number. Subjects had to read out each item as they were presented one by one on a card for 6 s. The phone number test is valid for **numeric** and **associative** memory.

3. Objects (OB):

This test comprised 20 drawings of objects which were presented together on a sheet to be learned by the subjects for 1 min/trial. This is valid for **visual** memory.

4. Pair associations (PA):

The **associative** memory for meaningless material was tested with a list of 10 pairs of meaningless syllables, which the subjects had 1 min/trial to learn.

5. Town map (TM):

This test assessed 'maplike, **two-dimensional spatial** memory' or 'memory for structure plans' (Bäumler, 1974). Subjects had to learn the way to work on an abstract town map and then later draw in the route on a similar map. Subjects had 1 min in each trial to learn the route.

6. Triplets (TR):

This test was taken to examine the **verbal** memory of **work associations**. Subjects had to learn ten groups of three semantically related words and then on hearing one word recall the two associated words. They had 1 min to learn the material in each trial.

7. Digit span (DS):

Short-term memory was tested with the digit span test (Wechsler, 1944). Subjects had to repeat increasing numbers of digits first in the same order and then in a second trial in reverse order.

Learning and recall procedure

The learning and recall procedure was designed to test both short-term memory (the memory up to 10 s) and the middle-term memory (more than 60 s). The middle-term memory was tested as immediate recall (between 60 s and 3 min) and as delayed recall (after 15 min).

Short-term and **recent** memory have been tested in order to cover both the functional and the structural memory aspects.

Subjects were given four trials to learn the material. In order to compare our results with those made with the same tests by Lichter *et al.* (1986), the shopping list and the phone numbers were tested immediately after each trial. The

first test of immediate recall was performed after the fourth trial, with the following subtest separating trial 4 from the first test so that the learned material could be consolidated (Figure 2).

After the test of immediate recall, short-term memory was checked with the digit span test. This was followed by a distraction task to prevent subjects rehearsing material in the 15 min before the tests of delayed recall. The ZVT-G trail-making test was performed in all four parallel forms (Oswald & Roth, 1978), but the results were not assessed.

Sleep EEG

An all-night sleep EEG was recorded after the 14th day of each treatment period. The recording was made according to the specifications of Höller & Irrgang (1985). The EEG activity was plotted on paper. Each page contained a 20 s

sleep EEG corresponding to one sleep epoch. The EEG was evaluated by an expert experienced in the rating of sleep EEG, who determined the predominant sleep stage during each epoch according to the rules of Rechtschaffen & Kales (1978). The visually evaluated data formed the basis for the computerized compilation of sleep profiles and the determination of percentages of each sleep stage.

The following sleep parameters were determined:

- number of arousals (= mini- or pre-arousal reactions)
- sleep stage 0
 - sleep stage 0
 - sleep stage REM
 - sleep stage REM
 - sleep stage 1
 - sleep stage 1
 - sleep stage 2
 - sleep stage 2
- number of epochs
- percentage (of total sleep)
 - number of epochs
 - percentage
 - number of epochs
 - percentage
 - number of epochs
 - percentage

Figure 2 Course of memory tests: The functional short-term memory (up to 10 s) tested for numerical and associative aspects. The structural middle-term memory was tested for several aspects both after immediate (60 s-3 min) and delayed (15 min) recall. ▨ learning phase, □ recall phase.

- sleep stage 3 + 4 - number of epochs
- sleep stage 3 + 4 - percentage
- time in bed - number of epochs
- effective sleep time - number of epochs
- sleep onset latency - number of epochs
- REM latency - number of epochs
- SWS latency - number of epochs
- sleep efficacy - percentage

Definition of EEG variables: One characteristic of well-balanced sleep is the number of so-called mini- or pre-arousal reactions. These are defined as outbreaks of frontally accentuated alpha activity lasting 2–20 s often preceded by a K-complex. The interindividual deviations of such short stimulus reactions are considerable, while the intraindividual numbers are subject to less deviation.

Sleep stage 0 (less than 5%): Included in this stage are all epochs that are scored as 'awake phases during the night'. Mini- or pre-arousal reactions lasting up to 40 s were not included.

Sleep stages 1–4 and REM were defined in strict adherence to the guidelines of Rechtschaffen & Kales (1968).

Stage 1 (5%): Stage 1 is an extremely shallow sleep stage, in which the sleeper still reacts perceptively when addressed. It is expected that hypnotics will attenuate an increased percentage of stage 1 sleep.

Stage 2 (50%): Sleep stage 2 is the most frequent sleep pattern, normally making up about 50% of the total sleep time. The percentage is markedly higher in patients with reduced slow-wave sleep.

Stages 3 + 4 (slow-wave sleep phases; 20%): A marked reduction of slow-wave sleep (SWS) phases is regarded as an expression of a disturbed regulation of sleep quality. With hypnotics, and in particular benzodiazepines, a normal percentage of SWS sleep tends to be reduced—this does not necessarily mean that the objective sleep quality is reduced.

Stage REM (dream sleep, stage of rapid eye movements; 20%): Hypnotics ought to normalize any reduction in the percentage of REM sleep. The REM production of normal sleepers is, however, reduced temporarily by hypnotics. It is known that higher doses of barbiturates and benzodiazepines reduce the REM proportion for a more or less temporary period.

Effective sleep time (EST): The effective sleep time is defined as the number of epochs between

the sleep onset time and the waking time minus the wake epochs during the night (sleep 0).

Sleep onset latency: The sleep onset latency is the time from lights out to the first epoch of sleep stage 2. Sleep onset times of up to 30 min are regarded as normal; a period longer than 30 min indicates a sleep latency disturbance.

SWS latency (slow-wave sleep latency): The SWS latency is the time between the first epoch of stage 2 and the first epoch of stage 3 or 4. It is essentially an expression of how steeply sleep deepens in the first sleep cycle.

REM latency: The REM latency is defined as the time between the first epoch of stage 2 and the first epoch of stage REM. If no rapid eye movements (REMs) are recorded in the first sleep cycle, then the REM latency continues until the first REM phase in the second cycle. In case of prolonged REM latency, one should thus make sure that there has not already been a paradoxical sleep phase without REMs (*REM sine REM*).

Total sleep period (TSP): Time between sleep onset (stage 2) and final awakening.

Time in bed (TIB): Time between 'lights out' and final awakening.

Efficiency: $(TSP/TIB) \times 100$.

Subjective sleep reporting

Within a side effect rating list subjects were asked about frequency and severity of sleep onset disturbance, sleeping through disturbance and nightmares.

Statistics

For the psychological assessment a separate descriptive analysis was made for each medication period, since not enough was known about the test validity of the third parallel form of the different tests. For the sleep EEG analysis and evaluations of the questionnaires, the data from the three treatment periods were summarized for each treatment group and compared.

All data were analyzed nonparametrically with the Wilcoxon signed-rank test and the paired comparison method. The exact distribution was determined using an algorithm by Streitberg & Röhm (1984). The data underwent a descriptive data analysis (Abt, 1987). Such non-parametric tests are in cases of normal distribution almost as

powerful as parametric tests. In cases of non-normal distribution they are more appropriate.

Results

Out of 30 intended cases, 23 were considered valid before the code was broken. There were four dropouts. One subject developed severe bradycardia. When the code was broken, this subject was receiving metoprolol treatment. One subject gave no reason why he dropped out (during the placebo phase). Two subjects dropped out because they became ill (influenza + diarrhoea and severe migraine attack). Three other subjects were withdrawn because of a positive drug screening during the trial.

The remaining 23 subjects entered the analysis for the memory tests and the side effect rating.

Subjects with sleep disturbances were excluded *a priori*. However, during the screening procedure it was not possible to determine whether the 'normal sleepers' would be good laboratory sleepers.

In order to avoid a large variance, we decided to exclude those subjects from the sleep analysis who were bad laboratory sleepers. As criteria for the exclusion, the placebo adaptation night and the randomized placebo night were taken. Those who had poor sleep during *both* nights, were excluded from the sleep analysis (eight out of 23).

Learning and memory

Group II (see Figure 1) fared better than the other two groups during all three treatment periods. In these tests of middle-term memory 'immediate recall' this group had the test performance in all six tests in the first period after cilazapril, in five out of six tests in the second period and in four out of six tests in the third period (Figure 3). A similar result was found in the test of the middle-term memory 'delayed recall' (Figure 4) and in the short-term memory (Figure 5).

A drug-related influence on memory performance could not be identified. Instead, group II was dominant, irrespective of the medication. Attempts to explain the superiority of this group produced only moderate success. There were no differences between the groups, including the subscales of the IST-70. Little additional information was gained by taking the subscales that correlated best with memory performance as convariables in an analysis of covariance. The superiority of the factor 'group' remained. We can therefore offer no satisfactory explanation for the different performance of the groups. The

fact remains that there was no identifiable drug-associated effect on memory performance.

Sleep EEG

As can be seen from Figure 6, there were no significant differences between cilazapril and placebo. However, metoprolol produced two different effects.

One effect was an SWS-increasing drug effect. This effect is probably due to a delta-/theta-wave increasing drug effect. In context with the Rechtschaffen & Kales (1968) rules for sleep analysis this is then misinterpreted as an increase in SWS.

The more important effect of metoprolol is a sleeping through disturbance, expressed as increase in stage 0 (time awake during the night). The percentage of normal sleep (stage 2) is then reduced, while the absolute amount of stage 2 is not. The healthy volunteer tries to compensate for the sleep disturbance by sleeping longer. Thus, the time in bed is increased.

In order to demonstrate the metoprolol effects, the sleep profiles of one subject (No. 17) who best illustrates the results are shown in Figure 7a, b and c.

Under placebo (Figure 7c) the subject had a normal profile of four sleep cycles. The absolute and relative values are normal as well as the sleep architecture. The 13 min (3%) of stage 0 (time awake during the night) as well as a number of 62 mini-arousals are still normal under laboratory conditions. When taking cilazapril (Figure 7b) the subject has the same sleep architecture and comparable values to placebo. That night however the subject slept 30 min longer and had a very long REM phase at the end of the night. This was within normal limits.

During metoprolol treatment (Figure 7a) the subject had a normal sleep onset time of 14 min. The subject fell into deep sleep but then woke up again. There was no REM phase in the first cycle. REM sleep was long in the third sleep cycle and thus compensated, while SWS sleep was compensated in the fourth sleep cycle. Thus, the normal sleep architecture was severely disturbed in the first sleep cycle and the volunteer tried to compensate in the third and fourth cycle.

Subjective sleep reporting

The subjective sleep reporting corresponded very well with the sleep EEG findings. There were no complaints about sleep onset nor was there an increased number of nightmares after metoprolol as had been expected.

Figure 3 Results of the tests of middle-term memory 'immediate recall' (60 s–3 min): Shown are the means and s.d. of the three groups in the three treatment phases for the different memory tests (SL = shopping list, PN = phone numbers, OB = objects, PA = pair associations, TM = town map, TR = triplets, MET = metoprolol, CIL = cilazapril, PLA = placebo).

Figure 4 Results of the tests of middle-term memory 'delayed recall' (15 min): (See legend to Figure 3 for symbols).

Figure 5 Results of the tests of the short-term memory with the digit span. (See legend to Figure 3 for symbols).

	<i>MET</i>	<i>MET</i>	<i>CIL</i>
	vs	vs	vs
	<i>CIL</i>	<i>PLA</i>	<i>PLA</i>
Effective sleeptime (min)			
Sleep onset latency (min)			
SWS latency (min)			
REM latency (min)			
Awake (min)			
Stage 0 (min) time awake during the night		0.030	
Stage REM (min)			
Stage 1 (min)			
Stage 2 (min)			
Stage 3+4 (min) deep sleep (SWS)	0.005		
Stage 0 (%) time awake during the night		0.021	
Stage REM (%)			
Stage 1 (%)			
Stage 2 (%) normal sleep	0.044	0.004	
Stage 3+4 (%) deep sleep (SWS)	0.023		
Arousals (number)			
Arousals (%)			
Sleep efficiency (%)			
Time in bed (min)		0.042	

Figure 6 Overview of the sleep EEG analysis. Significant *P* values of one-sided exact Wilcoxon statistic (descriptive *P* values): % percentage related to the total time (relative values). MET metoprolol, CIL cilazapril, PLA placebo.

Figure 7a, b and c Sleep profiles of one subject (No. 17).

Table 2 Side effect score of 'difficulties in sleeping through': The side effect score is formed by the number of recordings $\times$ severity, for: 1 = mild; 2 = moderate; 3 = severe

Metoprolol	Cilazapril	Placebo	Drug
4.48	1.73	1.79	mean value
2.33	1.81	1.61	95% confidence interval

However, there was a substantial increase in complaints of sleeping through disturbances after metoprolol (Table 2). The 95% confidence interval indicates a significant difference between metoprolol and placebo as well as between metoprolol and cilazapril.

This side effect reporting was not done after the sleep EEG nights in the laboratory but after the nights when the subjects slept in their normal surroundings.

Discussion

It can be concluded from the results of the investigation that both antihypertensive agents, cilazapril and metoprolol, have no influence on memory performance. Our results are thus partly in agreement with those of Lichter *et al.* (1986), who likewise found no difference for the ACE inhibitor enalapril compared with placebo. Yet the study of Lichter *et al.* (1986) requires critical assessment. Their study design was single-blind, and uncontrolled, in which two groups of 12 and 13 patients were tested intraindividually in a pre-post comparison, i.e., after a 2-week placebo washout and after a 16-week treatment with the β -adrenoceptor blocker atenolol and the ACE inhibitor enalapril. Moreover, the dosage was increased during the study and concomitant treatment with hydrochlorothiazide was allowed when necessary. The problems associated with restricting analyses to an intraindividual comparison with only a small sample became evident in our study. If we had evaluated only one drug period, we would have arrived at almost identical results.

Previous investigations into the influence of β -adrenoceptor blockers on memory functions have failed to present a consistent picture. It has been suggested that lipophilic β -adrenoceptor blockers have greater negative effects, yet a survey of the literature does not permit such a

generalization. Moreover, it has to be considered that some studies were performed in patients and others in healthy volunteers. For instance, Ghoneim *et al.* (1984) found a deterioration in the free recall of a 24-word list after administration of propranolol (in doses from 80 to 320 mg) to patients with panic attacks and agoraphobia. The effect was greater with diazepam, however. Hartley *et al.* (1983) found different effects of propranolol in subjects with low and high levels of anxiety. Subjects with low anxiety experienced a decline in performance compared with placebo, while those with high anxiety improved with the β -adrenoceptor blocker. Different effects evidently interfere with peripheral and possible central nervous parameters.

Solomon *et al.* (1983) reported an impairment of verbal but not visual memory when propranolol was given to hypertensive and normotensive subjects. Since a similar effect was found with methyldopa, which is also centrally active, the authors interpreted the result as a specific pharmacological effect and not due to a fall in blood pressure. On the other hand, this study had a number of weaknesses that reduce the validity of the findings: there was, for example, no true control group, since the normotensive subjects had other disorders such as migraine, angina pectoris, arrhythmias, or tremor. The study was also open, and both patient groups received a diuretic.

A completely opposite effect of propranolol on learning was found by Eisdorfer *et al.* (1970). After administration of 10 mg propranolol i.v. to men over the age of 60 years an improvement could be ascertained in the learning of a series of eight words. In contrast, Solkowski *et al.* (1977) found no influence on learning and memory after oral administration of 120 mg propranolol. This study was performed in six healthy marijuana smokers however. Besides propranolol only three other β -adrenoceptor blockers have been investigated, which are less lipophilic. Oxprenolol (80 mg) was found not to influence short-term memory (Desai *et al.*, 1983). This study was similar to that of Hartley *et al.* (1983), since the authors once again distinguished between subjects with a high and low level of anxiety. Bender *et al.* (1980) found that sotalol had different effects on memory functions depending on the dosage. While memory performance improved after 320 mg, it deteriorated after 960 mg. The authors themselves were cautious when interpreting the results, since the statistical analysis of the results involved several comparisons.

There are several explanations for these differing results: the possible impairment of cognitive

performance by the primary disease, hypertension (Wilkie & Eisdorfer, 1980), uncontrollable influences of damage secondary to hypertension, a possible influence of the drug, and consequences of the fall in blood pressure. We believe that drug-specific effects of antihypertensive drugs should only be investigated in normotensive and otherwise healthy subjects. For this reason we consider the results of our study to be valid.

One of the frequently reported side effects of β -adrenoceptor blockers is sleep disorder in the form of insomnia, interrupted sleep, and nightmares (Weiner, 1986; Greenblatt & Shader 1972). It is assumed that the more lipophilic a β -adrenoceptor blocker, the greater its central nervous effects (Borchard, 1983), yet this concept is not without its critics (Turner, 1978). In a comparison of metoprolol and atenolol greater sleep disturbances were found with the more lipophilic metoprolol, i.e., restless nights and interrupted sleep (Cove-Smith & Kirk, 1983). The moderately lipophilic drug pindolol showed a significantly higher number of sleep disorders (36%) than the hydrophilic drug atenolol (14%) in a placebo-controlled study (Greminger *et al.*, 1982). In contrast, the very lipophilic drug propranolol led to sleep disorders in only 19% of 2000 patients (Flemming & Drachman, 1982). All these findings are based on ratings by the patients themselves. Objective measurements of sleep quality with modern neurophysiological methods (sleep EEG) have been rarely used. Bender *et al.* (1980) found no changes in the sleep polygraphy and in subjective sleep quality with sotalol. Betts & Alford (1985) observed an increase of awake phases with pindolol, but not with metoprolol. Both β -adrenoceptor blockers have weak

lipophilic properties. No impairment of REM sleep was determined.

In our investigation, with metoprolol there were frequent awake phases during the night. This is evident in the sleep EEG from the increased number of stage 0 episodes. The subjects also complained of difficulties in sleeping, while at the same time there was an increase of slow waves, which according to Rechtschaffen & Kales (1964) are typical of sleep stages 3 + 4. This probably is a drug-specific EEG effect, as described by Mock & Künkel (1982) for the pharmac-EEG in the awake stages. Rüther *et al.* (1976) reported an increased proportion of deep sleep stages with the combination of L-tryptophan and oxprenolol. They attributed this to the combined effect of both drugs, since there was no control group receiving the β -adrenoceptor blocker alone.

When interpreting the effects of metoprolol observed in our study, it has to be considered that the statistically significant results can only be interpreted as descriptive *P*-values (Abt, 1987).

Our own findings did not confirm reports about nightmares and insomnia in general. However, we did find interrupted sleep in the sleep EEG and the subjective reporting, and based on this, disturbance of the sleep architecture.

It can be concluded from this study in healthy volunteers that neither metoprolol nor cilazapril influenced short-term and middle-term memory functions after 7 days of treatment at the dosages given. However, sleep function was disturbed with metoprolol. There were difficulties in sleeping with frequent awakenings during the night with metoprolol, but not with cilazapril.

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