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A 24-month, double-blind, placebo-controlled multicentre pilot study of the efficacy and safety of nicergoline 60 mg per day in elderly hypertensive patients with leukoaraiosis

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In this pilot study, 72 non-demented and non-depressive elderly hypertensive patients with evidence of leukoaraiosis on cerebral computed tomography scan (Rezek score: $\geqslant 16$) were randomly assigned to receive either nicergoline 30 mg b.i.d. ($n = 36$) or a placebo ($n = 36$) for 24 months. All patients received antihypertensives and their hypertension was controlled under treatment. They were evaluated by nine neuropsychological tests exploring memory, concentration, verbal and motor performances, administered at baseline and at every six-month interval during the study period. At baseline, the two groups were comparable for all demographic and clinical characteristics, including cognitive functions, except for the delayed recall of the Auditory Verbal Learning Test (AVLT), which was better in the placebo group ($P = 0.04$). Changes in scores over time were compared between the two groups. At the last visit, patients on nicergoline ($n = 31$) were found to have deteriorated less or to have improved more on test scores than the patients on placebo ($n = 30$). Significant differences were observed for memory function (AVLT short term recall, $P = 0.026$; AVLT delayed recall, $P = 0.013$; and, Benton Visual Retention Test, $P = 0.002$) and attention and concentration (Letter Cancellation Test, $P = 0.043$; and, WAIS-R Digit Symbol subtest, $P = 0.006$). The Rezek score remained unchanged in the two groups. Tolerance of nicergoline was similar to that of placebo. In conclusion, this study shows that nicergoline 30 mg b.i.d. administered over a 24-month period attenuates the deterioration in cognitive functions in elderly hypertensive patients with leukoaraiosis. Whether these effects were specific for this type of white matter changes could not be determined in the context of this pilot study. Eur J Neurol 6:313–322 © 1999 Lippincott Williams & Wilkins

Keywords: leukoaraiosis, computed tomography, cognitive functions, hypertension, elderly, nicergoline

INTRODUCTION

The term leukoaraiosis (LA) (Hachinski *et al.*, 1987) is now widely accepted to describe patchy or diffuse areas of low-density white matter changes, or lucencies, detected on computed tomography (CT) scan or magnetic resonance imaging (MRI) in demented patients, as well as many elderly subjects with apparently normal intellectual capacities. The frequency of LA has been shown to increase with age and the presence of vascular risk factors, mostly hypertension (Inzitari *et al.*, 1987; Fazekas *et al.*, 1988; Van Swieten *et al.*, 1991) and its prevalence is significant among the elderly (5% in a series studied by Goto *et al.*, 1981).

The clinical significance of LA is still widely debated. Several researchers have reported a negative correlation between the extent of LA and neuropsychological performance (Steingart *et al.*, 1987; Delpla *et al.*, 1990; Junqué *et al.*, 1990; Boone *et al.*, 1992; Schmidt *et al.*, 1993). However, this correlation has not

been confirmed in other studies (Hendrie *et al.*, 1989; Hunt *et al.*, 1989; Rao *et al.*, 1989; Fein *et al.*, 1990; Almkvist *et al.*, 1992). This apparent discrepancy could be attributed to various factors. All these studies involved demented patients who produced very low scores on common neuropsychological testing, thus lowering the likelihood of finding a statistical correlation. Another limitation of these studies was that they did not control for hypertension, the main vascular risk factor associated with LA. For these reasons, the present study was specifically designed to include patients with LA and hypertension, but with no clinical evidence of either cognitive or neurological impairment.

To evaluate further the relationship between LA and cognitive function, we selected a test group of 72 neurologically normal elderly patients with chronic hypertension, and examined each with a CT scan and a battery of standardized neuropsychological tests. Results of this cross-sectional study have been reported elsewhere (Bès *et al.*, 1994). Briefly, significant negative correlations were found between the extent of leukoaraiosis, as determined by the Rezek method, and scores obtained on tests exploring memory (Rey Auditory Verbal Learning Test, $r = -0.27$, $P = 0.025$), attention and concentration (Letter Cancellation Test, $r = -0.26$, $P = 0.027$; WAIS-R Digit Symbol subtest, $r = -0.24$, $P = 0.05$) and psychomotor performances (Finger Tapping Test, $r = -0.34$, $P = 0.005$). These data suggested a relationship between the extent of LA and the decline in cognitive functioning observed in some of the subjects. After completion of the cross-sectional study, our 72 patients were included in a double-blind prospective study reported here and randomly assigned to receive either nicergoline 30 mg b.i.d. or placebo over a 24-month period. Nicergoline (Sermion®; Specia, Montrouge, France), an ergot derivative with -blocking and anti-aggregatory properties (Le Menn *et al.*, 1979; Praga *et al.*, 1979; Rafelson *et al.*, 1979) has been shown to enhance cerebral blood flow (CBF), particularly in ischemic areas (Samso Dies *et al.*, 1979; Philippon and Chazot, 1983; Chapuy *et al.*, 1984; Bès *et al.*, 1986; Oudart and Plotkine, 1988). It has been suggested that LA might be caused by reduced CBF, particularly in the white matter areas where collateral circulation is poor, and could signal the onset of chronic cerebral ischemia (Gerard and Weisberg, 1986; Fazekas *et al.*, 1988). This vascular hypothesis supported by histopathological data (Awad *et al.*, 1986; Kirkpatrick and Hayman, 1987) suggests that enhancing CBF with a drug such as nicergoline might be a relevant therapeutic measure in the context of LA. Therefore, the present study was carried out to evaluate the effect on cognitive functions and tolerance of nicergoline 30 mg b.i.d. administered over 24 months in elderly hypertensive patients with leukoaraiosis.

PATIENTS AND METHODS

Patients

Patients of either sex, aged 60 to 82 years, with diagnosed hypertension for at least one year before inclusion and evidence of LA on CT scan examination but no clinical signs of cognitive or neurological disorders were eligible for the study. Hypertension was defined as the occurrence of at least one medically documented episode of rise in systolic blood pressure (SBP) $\geq$ 160 mmHg and/or diastolic blood pressure (DBP) $\geq$ 95 mmHg. Only those patients who had been under antihypertensive therapy for at least one month before the beginning of the study and whose blood pressure was normalized could be included. LA was defined as the presence of lucency areas involving at least 25% of the white matter and giving a score of $\geq$ 16 using the Rezek method of interpretation of CT scan imaging (Rezek *et al.*, 1987).

Patients were excluded for the following reasons: history of stroke and/or evidence of previous stroke on CT scan; history of severe hypertension (SBP $>$ 210 mmHg and/or DBP $>$ 120 mmHg); dementia as defined by the DSM-III-R criteria; IQ $<$ 90 at the Revised Weschler Intelligence Scale for adults (WAIS-R); MQ $<$ 90 at the Weschler Memory Scale; score $<$ 25 at the Folstein Mini-Mental State (MMS); major depression as defined by the DSM-III-R criteria with a score $>$ 25 at the Montgomery and Asberg Depression Rating Scale (MADRS); neurological abnormality revealed by clinical examination; or a severe concomitant medical condition. Patients with a history of myocardial infarction in the previous three months or with definite cerebral sequelae of myocardial infarction or cardiac arrythmia were also excluded. Previous transient ischemic attacks did not lead to exclusion.

The protocol was approved by the Committee for the Protection of Persons in Biomedical Research of Toulouse (France). All the patients gave their written informed consent before inclusion in the study.

CT scan

Non-contrast CT scans were rated using lucency scores (LS) based on Rezek's semiquantitative method (Rezek *et al.*, 1987). An area was considered hypodense, or 'lucent', if its density was less than that of normal white matter. The size and degree of contrast with the surrounding white matter was quantified as a measure of the severity of each lucency. This scoring method allows a comparison of CT scans but is not intended to

provide a true measure of tissue volume. For the statistical analysis, all computed tomographic images were assessed blindly by an experienced radiologist (D. Gardeur), who was unaware of the subjects' neuropsychologic test results.

Study design

After completion of the initial CT scan, nine validated neuropsychological tests were administered to patients by trained neuropsychologists. These tests were selected to provide accurate measurements of early changes in memory, attention and concentration, verbal function and motor performance (Lezak *et al.*, 1995) (Table 1).

Patients were then randomly assigned to treatment with nicergoline 60 mg per day (two tablets of 30 mg b.i.d.) or placebo over a period of two years. Randomization was performed in each centre by blocks of four patients. Concomitant therapy with drugs interfering with brain metabolism, cerebral vasodilators, centrally acting antihypertensives or neuroleptics was prohibited. All physicians in charge of the patients, including general practitioners, were clearly informed of these restrictions to treatment.

Neuropsychological evaluation was repeated every six months after randomization (months 6, 12, 18 and 24) with the same battery of tests as at baseline. During each visit, treatment compliance was checked by the number of tablets remaining in the boxes returned by the patient. At the month 24 visit, CT scan examination was repeated and the severity of each lucency was scored in the same conditions as at baseline.

Tolerance to treatment was evaluated at each visit by complete neurological examination, determination of standing and supine blood pressure and heart rate, and recording of side-effects spontaneously reported by the patient. Moreover, the following tests were performed at inclusion, at the month 12 visit and during month 24 of the study period: standard 12-lead electrocardiogram (ECG) and determination of biological parameters including ionogram, plasma glucose level, blood urea nitrogen, calcemia, phosphoremia, and liver function tests. Biological tests were performed in the centre at which the patient had been included and normal values were those of the laboratory of that centre.

Statistical analysis

Data from the study were processed using Version 6.08 of SAS on a microcomputer. A significance level of $P < 0.05$ was set for all the tests.

Analyses were performed on the intention-to-treat population, i.e. in patients who had taken at least one tablet of the study drug and had been submitted to at least one neuropsychological evaluation during the treatment period. Characteristics of the groups at baseline were compared with the Student t test.

The analysis of efficacy was carried out using the ANOVA method for repeated measurements to compare the results obtained at the first (J0) and the last observation carried forward (LOCF) visit within each group of treatment, with time, randomization and time × randomization interaction being the factors analysed.

The Fisher exact test was used to compare the incidence of side-effects spontaneously reported by patients of both groups. Patients were included in this analysis if they had taken at least one tablet of the study drug.

RESULTS

Study population

From 9 September, 1990 to 16 January, 1995, 13 neurological centres recruited 72 patients. Their mean age was 72 ± 5.8 years (range, 60–82). Sex ratio was 1:1 (36 men and 36 women). Most of the patients were retired (60 of 72). Of the patients, 10% had not finished elementary school, 40% had completed elementary school, 29% secondary school, and 21% had gone to college. The mean scores were 28 ± 1 on MMS, 101 ± 12 on Intellectual Quotient (IQ), 111 ± 11 on Memory Quotient (MQ), and 3 ± 3 on the MADRS,

TABLE 1. Neuropsychological tests and assessed skills

Memory functions	Rey Auditory Verbal Learning Test (AVLT): verbal memory
	Benton Visual Retention Test (BVRT) Form C: visuospatial memory
Attention and concentration	Paced Auditory Serial Addition Test (PASAT) two rates of speed – 2 and 4 s
	Trail Making Test (TMT) parts A and B
	Letter Cancellation Test
	Stroop test
Verbal functions	Lexical Verbal Fluency Test
	Token Test
Motor performance	Finger Tapping Test (FTT) – manual dexterity

thus confirming the absence of major cognitive impairment.

All the patients had been treated for hypertension, but their blood pressure levels remained within the normal range set by the World Health Organization. The mean duration of hypertension treatment was 11.1 ± 10.4 years and all but one had idiopathic hypertension. Other vascular risk factors were hypercholesterolemia (46% of the subjects), smoking (38%), cardiovascular disease (32%), hyperuricemia (8%), hypertriglyceridemia (19%), obesity (15%), non-insulin-dependent diabetes mellitus (14%) and alcoholism (3%). Twenty-five patients had a history of previous transient ischemic attacks (TIA). The average LS rating was 22 ± 9.

Among the 72 patients, 36 were included in the nicergoline group and 36 in the placebo group. Ten (five in each group) were not evaluable for the intention-to-treat analysis of efficacy. Furthermore, one patient of the nicergoline group was withdrawn from the analysis because of a severe deviation to the protocol: this patient had a severe extrapyramidal syndrome and should have not been included. Thirty patients in the nicergoline group and 31 patients in the placebo group were thus evaluable for efficacy. Baseline characteristics were not different between these two groups (Table 2).

The lucency scores calculated in the two groups of treatment were not statistically different (Table 2). Neuropsychological assessment at baseline revealed no difference between the two study groups, except for the AVLT (delayed recall) which produced significantly better results in the placebo group than in the nicergoline group (Table 3).

Evolution of lucency scores

No change between baseline and two years' follow-up lucency scores was observed. Mean score at baseline was 22 ± 8.4 and at two years follow-up 22 ± 8.1.

Neuropsychological results

Comparisons of changes, between J0 and LOCF, in scores obtained on the nine neuropsychological tests exploring cognitive functions in patients of the two groups are shown in Tables 4 to 7.

Scores on the four tests exploring memory deteriorated in the placebo group but improved in the nicergoline group during the study period (Table 4). The difference was significant for the AVLT short-term recall ($P = 0.026$), the AVLT delayed recall ($P = 0.013$) and the Benton Visual Retention Test ($P = 0.002$), but not for the WAIS-R Digit Span subtest ($P = 0.45$).

Changes in scores obtained on tests exploring attention and concentration showed that this cognitive function improved more, or deteriorated less, in patients of the nicergoline group than in patients of the placebo group (Table 5). The difference was significant for the Letter Cancellation Test ($P = 0.043$) and the WAIS-R Digit Symbol subtest ($P = 0.006$). All other tests showed non-significant tendencies in favour of nicergoline.

TABLE 2. Baseline demographic and medical characteristics of patients evaluable for the intention-to-treat analysis of efficacy

	Placebo group ($n = 31$)	Nicergoline group ($n = 30$)	*P* value
Age	71.8 ± 5.8	71.9 ± 6.3	0.96
Sex ration (H/F)	16/15	14/16	0.80
Weight (kg)	71.5 ± 11.5	68.8 ± 12.3	0.38
Height (cm)	165.9 ± 10.5	164.5 ± 8.1	0.57
Duration of hypertension (years)	10.9 ± 9.3	9.7 ± 8.6	0.61
SBP (mmHg)	150.4 ± 15.4	154.8 ± 17.8	0.30
DBP (mmHg)	88.4 ± 9.8	88.9 ± 8.6	0.83
Previous neurological events			
TIA, no. of patients (%)	11 (35.5)	10 (33.3)	1.00
Others, no. of patients (%)	5 (16.1)	7 (23.3)	0.53
Lucency score	22.0 ± 9.2	20.0 ± 7.7	0.38
Global psychological assessment			
MMS (score ± SD)	28.2 ± 1.3	28.3 ± 1.7	0.85
MADRS (score ± SD)	3.4 ± 3.5	3.0 ± 3.6	0.62
IQ (score ± SD)	102.5 ± 13.9	99.3 ± 9.4	0.29
MQ (score ± SD)	112.4 ± 11.8	110.0 ± 10.3	0.41

SBP = systolic blood pressure, DBP = diastolic blood pressure, TIA = transient ischemic attack, MMS = Mini Mental State, MADRS = Montgomery-Asberg Depression Rating Scale, IQ = intelligence quotient, MQ = memory quotient

TABLE 3. Baseline neuropsychological assessment of patients evaluable for the intention-to-treat analysis of efficacy

	Placebo group ($n = 31$)	Nicergoline group ($n = 30$)	*P* value
Memory			
AVLT (total of five immediate recalls)	44.5 ± 9.6	41.0 ± 9.6	0.15
AVLT (delayed recall)	9.9 ± 3.4	7.9 ± 3.9	0.04
Benton Visual Retention Test	5.7 ± 2.0	5.0 ± 1.8	0.15
WAIS-R Digit Span subtest	11.5 ± 3.9	10.9 ± 3.8	0.54
Attention and Concentration			
PASAT 1	17.4 ± 7.7	13.7 ± 7.8	0.07
PASAT 2	12.5 ± 6.3	9.6 ± 6.2	0.08
STROOP 1	81.7 ± 20.3	76.9 ± 20.1	0.36
STROOP 2	81.5 ± 20.5	73.3 ± 19.8	0.12
STROOP 3	64.3 ± 15.8	60.1 ± 13.6	0.26
STROOP 4	25.6 ± 11	22.7 ± 8.9	0.27
Letter Cancellation Test	139.6 ± 48.7	126.0 ± 37.3	0.23
TMT 1	1.06 ± 0.51	1.19 ± 0.40	0.24
TMT 2	2.49 ± 1.05	2.64 ± 1.28	0.63
WAIS-R Digit Symbol subtest	32.3 ± 11.8	28.3 ± 9.0	0.15
Verbal Functions			
Verbal Fluency	23.5 ± 9.3	20.5 ± 8.0	0.19
Token Test	33.8 ± 1.7	33.6 ± 2.2	0.73
Psychomotor Functions			
Tapping Test	224.4 ± 46.9	207.3 ± 35.5	0.12
WAIS-R Cube subtest			
WAIS-R Cube	19.8 ± 7.4	20.9 ± 7.3	0.59

TABLE 4. Scores obtained on the neuropsychological tests exploring memory at the last visit (LOCF) and comparison of changes between J0 and the last visit observed in the two groups

	Placebo group ($n = 31$)	Nicergoline group ($n = 30$)	*P* value
AVLT (total of five immediate recalls)			
scores at LOCF	41.9 ± 10.3	41.9 ± 10.6	
Δ LOCF – J0	−2.6 ± 4.9	1.0 ± 7.2	0.026
AVLT (delayed recall)			
scores at LOCF	8.3 ± 3.7	8.1 ± 3.5	
Δ LOCF – J0	−1.5 ± 1.9	0.2 ± 3.2	0.013
Benton Visual Retention Test			
scores at LOCF	4.0 ± 2.2	4.9 ± 2.2	
Δ LOCF – J0	−1.7 ± 1.8	0.0 ± 2.1	0.002
WAIS-R Digit Span subtest			
scores at LOCF	11.4 ± 3.0	11.2 ± 3.7	
Δ LOCF – J0	−0.1 ± 2.3	0.2 ± 1.4	0.45

Scores obtained on the tests exploring verbal functions increased slightly in both groups, whereas psychomotor performances increased in the nicergoline group and decreased in the placebo group (Table 6). Differences between the two groups were not significant.

Performances on the WAIS-R Cube subtest increased in the placebo group and decreased slightly in the nicergoline group (Table 7), but the difference observed did not reach the threshold of significance.

Comparison by means of ANOVA of repeated measures carried out in patients who attended all the visits specified by the protocol (22 patients in the nicergoline group and 27 patients in the placebo group) (Table 8) revealed that score progression on the Benton Visual Retention Test was different in the two groups over the two-year period. Comparison of changes from J_0 at each time point showed a significantly better improvement in the nicergoline group at months 18 and 24, but not at months 6 and 12.

TABLE 5. Scores obtained on the neuropsychological tests exploring attention and concentration at the last visit (LOCF) and comparison of changes between J0 and the last visit observed in the two groups

	Placebo group ($n = 31$)	Nicergoline group ($n = 30$)	*P* value
PASAT 1			
scores at LOCF	17.8 ± 7.0	16.7 ± 6.6	
Δ LOCF – J0	0.5 ± 6.2	2.6 ± 5.7	0.17
PASAT 2			
scores at LOCF	11.9 ± 5.7	11 ± 5.8	
Δ LOCF – J0	−0.5 ± 5.8	1.1 ± 5.9	0.29
STROOP 1			
scores at LOCF	89 ± 21.8	87.0 ± 18.4	
Δ LOCF – J0	7.3 ± 16.6	10.1 ± 15.9	0.51
STROOP 2			
scores at LOCF	83.4 ± 21.3	79.3 ± 20.6	
Δ LOCF – J0	1.8 ± 17.7	5.9 ± 15.7	0.34
STROOP 3			
scores at LOCF	63.2 ± 14.7	62.3 ± 14.6	
Δ LOCF – J0	−1.2 ± 12.6	2.2 ± 11.5	0.28
STROOP 4			
scores at LOCF	26.1 ± 12.0	25.8 ± 9.9	
Δ LOCF – J0	0.5 ± 7.6	3.0 ± 6.3	0.17
Letter Cancellatiion Test			
scores at LOCF	141.9 ± 53.5	141.5 ± 39.4	
Δ LOCF – J0	2.3 ± 23.6	15.5 ± 26.2	0.043
TMT 1			
scores at LOCF	1.0 ± 0.4	1.0 ± 0.6	
Δ LOCF – J0	−0.1 ± 0.4	−0.2 ± 0.5	0.33
TMT 2			
scores at LOCF	2.5 ± 1.5	2.5 ± 1.7	
Δ LOCF – J0	0.0 ± 1.1	−0.1 ± 1.7	0.65
WAIS-R Digit Symbol subtest			
scores at LOCF	32.6 ± 13.3	32.5 ± 10.0	
Δ LOCF – J0	0.3 ± 4.9	4.2 ± 5.6	0.006

TABLE 6. Scores obtained on the neuropsychological tests exploring verbal and psychomotor functions at the last visit (LOCF) and comparison of changes between J0 and the last visit observed in the two groups

	Placebo group ($n = 31$)	Nicergoline group ($n = 30$)	*P* value
Verbal Functions			
Verbal Fluency			
scores at LOCF	26.1 ± 10.6	26.8 ± 10.1	
Δ LOCF – J0	2.7 ± 9.7	6.3 ± 8.2	0.12
Token Test			
scores at LOCF	34.1 ± 1.5	33.7 ± 1.9	
Δ LOCF – J0	0.3 ± 1.5	0.1 ± 1.8	0.63
Psychomotor Functions			
Tapping Test			
scores at LOCF	222.7 ± 53	215.3 ± 45	
Δ LOCF – J0	−1.6 ± 27.2	8.0 ± 37.5	0.25

TABLE 7. Scores obtained on the WAIS-R Cube subtest at the last visit (LOCF) and comparison of changes between J0 and the last visit observed in the two groups

	Placebo group ($n = 31$)	Nicergoline group ($n = 30$)	*P* value
WAIS-R Cube subtest			
scores at LOCF	20.5 ± 10.5	20.4 ± 8.7	
Δ LOCF – J0	0.7 ± 7.0	−0.5 ± 6.1	0.49

Clinical and biological safety profile

Events that were regarded as possibly related to the study medication occurred in 12 nicergoline patients and nine placebo patients. The most frequent possibly related events were asthenia (8% of nicergoline pa-

TABLE 8. Comparison by means of ANOVA of scores obtained on the Benton Visual Retention Test in patients attending the five visits specified by the protocol

	Placebo group ($n = 27$)	Nicergoline group ($n = 22$)	*P* value
J_0	6.0 ± 1.8	5.0 ± 1.8	
M_6	4.7 ± 2.0	4.5 ± 1.7	
M_{12}	5.0 ± 1.9	5.0 ± 2.0	0.014
M_{18}	5.7 ± 2.2	5.9 ± 1.7	
M_{24}	4.2 ± 2.2	5.1 ± 1.9	
M_6-J_0	−1.2 ± 1.7	−0.5 ± 1.9	NS
$M_{12}-J_0$	−1.0 ± 1.9	0.0 ± 1.6	NS
$M_{18}-J_0$	−0.3 ± 2.1	0.9 ± 1.7	0.040
$M_{24}-J_0$	−1.7 ± 1.9	0.1 ± 2.0	0.002

tients, 3% of placebo patients), dizziness (6% of nicergoline patients, and 6% of placebo patients), hypotension (8% of nicergoline) and only one subject, in the placebo group, experienced one episode of orthostatic hypotension. Eighteen patients (ten in the nicergoline group, and eight in the placebo group) dropped out of the study. No patients died during the study. Most of the withdrawals occurred between 0 and 6 months, for which the most frequent reason was consent withdrawal. There were no differences between the treatment groups in terms of haematology, biochemistry variables, ECG, blood pressure or pulse.

DISCUSSION

The concept of LA emerged with the introduction of the most recent methods of cerebral imaging. Several studies strongly suggest a link between LA and cerebrovascular risk factors, particularly hypertension (Inzitari *et al.*, 1987; Fazekas *et al.*, 1988; Van Swieten *et al.*, 1991). Different types of lesions underlying the radiological aspect of LA have been described (Awad *et al.*, 1986; Kirkpatrick and Hayman, 1987): rarefaction of myelinated fibres; arteriolar infarction (hypertensive type); atrophic perivascular demyelinization; telangiectasia and/or *état criblé*. Although the precise origin of these lesions – a direct consequence of pathological processes involving the arterioles irrigating the white matter, or an impact of a general vascular disorder on these arterioles – remains speculative, the pattern of these lesions is consistent with a vascular origin. LA might, therefore, be the radiological marker of an early stage of chronic cerebral ischemia, during which appropriate medical intervention could provide substantial long-term benefit to the patients.

On this hypothesis, it seemed particularly interesting to evaluate the effects of nicergoline, a drug with α-blocking properties, which is widely used in several countries for the treatment of intellectual impairment linked to cerebral ischemic disease in the elderly. In humans, nicergoline has been shown to enhance CBF, particularly in ischemic areas (Samso Dies *et al.*, 1979; Philippon and Chazot, 1983; Chapuy *et al.*, 1984; Bès *et al.*, 1986; Oudart and Plotkine, 1988) and its anti-aggregatory properties have been demonstrated by *in vitro* and *ex vivo* experiments (Le Menn *et al.*, 1979; Praga *et al.*, 1979; Rafelson *et al.*, 1979). Several randomized, placebo-controlled clinical studies have demonstrated a significant effect of nicergoline in patients with mild to moderate vascular dementia (Maderna and Marangoni, 1979; Arrigo *et al.*, 1982; Hermann *et al.*, 1992; Saletu *et al.*, 1995).

The aim of this prospective, randomized, placebo-controlled double-blind study was to assess the effect of nicergoline (30 mg b.i.d. taken orally) administered over 24 months on the evolution of cognitive functions in elderly hypertensive patients with evidence of LA on CT scan examination, but without clinical signs of dementia or depression according to DSM III-R criteria, and neurologically normal upon clinical examination.

At the time when this study was designed, there were no available data to establish the prognostic value of LA images visualized in patients without overt neurological or cognitive abnormalies, even though an association between LA and cognitive deterioration had been suggested by several authors (Steingart *et al.*, 1987; Hunt *et al.*, 1989; Rao *et al.*, 1989). Since no individual test had been previously validated as an efficacy outcome in LA, a battery of nine standardized tests was administered between month 0 and month 24 to assess the overall evolution of cognitive functions in our patients. This methodological choice gives our trial the value of a pilot study and the results reported here should be interpreted accordingly.

An important follow-up period (24 months) seemed necessary to detect a progressive deterioration, which was expected to be discrete, of cognitive performances in our population of subjects without massive cognitive deficit at baseline and to evaluate a potential effect of nicergoline on this slight deterioration.

In the 61 patients evaluable for the intention-to-treat analysis of efficacy, the analysis of scores obtained on the three tests exploring memory demonstrated a significant effect of nicergoline on mnesic capacities. This was true for immediate memory (AVLT immediate recall), as well as intermediate memory (AVLT delayed recall) and visuospatial memory (Benton Visual Retention test). It should be underlined that significantly better results on the AVLT delayed recall had been obtained at baseline in the placebo group as compared to the nicergoline group.

In tests of attention and concentration, performances on the Letter Cancellation Test and on the WAIS-R Digit Symbol subtest deteriorated in significantly lower proportions in patients of the nicergoline group than in patients of the placebo group. Changes in performances on PASAT, STROOP and Trail Making Test tended to favour the nicergoline group, although the differences did not reach the threshold of statistical significance.

Changes in tests exploring verbal performances (Verbal Fluency, Token Test) and psychomotor performances (Finger Tapping Test) also showed non-significant tendencies in favour of nicergoline.

The analysis of changes in tests exploring global cognitive performances (MMS, IQ, MQ) did not reveal any significant difference between the groups.

It can be hypothesized that the relatively small number of subjects included in this pilot study may have hindered the demonstration of actual differences in functions explored by tests showing tendencies in favour of nicergoline without reaching statistical significance. For the reasons indicated above, the number of subjects necessary to demonstrate significant differences relative to all the evaluation criteria could not be determined when the study plan was designed. The number of subjects included was determined on an arbitrary basis. Conversely, the utilization of multiple evaluation criteria, inherent to the design of our study, probably increased the chances of revealing a difference between the nicergoline and the placebo groups. However, it should be noted that all differences, whether significant or not, were in favour of the nicergoline group, with the exception of the non-significant difference between changes in performances obtained on the WAIS-R Cube subtest, which was in favour of the placebo.

Comparison of Rezek Scores measured at J0 and the end of our study in the overall population of patients and within each treatment group failed to reveal any difference. This lack of changes in the extent of leukoaraiosis was not unexpected. Several studies have shown an association between hypertension and LA (Inzitari *et al.*, 1987; Fazekas *et al.*, 1988; Van Swieten *et al.*, 1991). In our patients, hypertension was controlled under medical treatment and monitoring during the two-year study period. It can be speculated that LA images observed in this context were sequelae of previously untreated hypertension. Therefore, it was not possible to determine in this study whether the beneficial effects of nicergoline on cognition were related to this type of white matter changes or not. An alternative explanation could be that nicergoline improved cognitive function independently of their etiology.

Studies demonstrating an increase in CBF in patients treated with nicergoline (Samso Dies *et al.*, 1979; Philippon and Chazot, 1983; Chapuy *et al.*, 1984; Bès *et al.*, 1986; Oudart and Plotkine, 1988) would support this hypothesis. The demonstration of this unspecific mode of action in patients such as those included in our study would be compatible with the probable vascular origin of LA. In fact, interpretation of these results depends on the relevance of our tests as early markers of progression towards cerebral ischemic disease and the associated intellectual impairment. Several epidemiological studies have shown that vascular dementia is preceded by a slight cognitive deterioration detected by tests exploring memory and attention, or by exploration of instrumental activities of daily life (Fuld *et al.*, 1990; Barberger *et al.*, 1993; Masur *et al.*, 1994). It would, therefore, appear that nicergoline has the potential to slow this progression.

This 24-month study provides some interesting data on the natural history of LA. In this respect, it should be noted that all the cognitive performances measured tended to deteriorate in the placebo group. These data obtained after a two-year follow-up concur with the conclusions of a recent review of the literature by Pantoni and Garcia, 1995 establishing a correlation between the extent of LA and an impairment in cognitive processes, in particular those involved in rapid psychomotor processing. Moreover, these authors reported that LA in itself appears to be a risk factor for cerebrovascular events.

In conclusion, in elderly hypertensive patients with LA, treatment with nicergoline 30 mg b.i.d. administered over 24 months had no effect on the extent of the white matter lesions, but was associated with a slight improvement, or a less marked deterioration, in cognitive functions observed in our study patients. These effects were statistically significant in terms of changes over time in several cognitive functions including memory, attention and concentration. The impact of nicergoline treatment on verbal and psychomotor functions was not significant in the context of this study, and would require further investigation in a wider population of patients.

APPENDIX

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