CITICOLINE IN CCVD PATIENTS; PRELIMINARY RESULTS OF A MULTICENTER STUDY

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The efficacy of citicoline (Nicholin)® in the treatment of hospitalized patients with chronic cerebral vascular diseases (CCVD) was evaluated in a multicenter, randomized, double-blind (drug versus placebo) study. Patient evaluation employed neuropsychological tests, interviews and observational procedures.

Descriptions of patients were obtained from patients themselves, members of their families, and from their attending clinicians in order to obtain a more precise, reliable, and comprehensive evaluation of the patient before, during and after treatment. This technique of description which combines diverse sources of information, provides a more valid picture of the patient's level of functioning (Martucci N., Fioravanti M. et al., 1980).

METHODS AND MATERIALS

Inclusion Requirements. Patients of both sexes between the age of 50 and 70 years with CCVD were considered for inclusion when they presented the following characteristics: a) one or more acute focal cerebro-vascular episodes including TIA's with at least 2 elapsed months since the last focal episode; b) presence of neurological signs both focal or diffused and/or psychic ones (e.g. depression); c) presence of cerebrovascular risk factors (mainly hypertension); d) positive results of complementary tests (e.g., transmission tomography); e) modest impairment of superior function of the CNS ("ad hoc committee" Paris International Symposium, March 1980).

Participants were also required to have completed at least 3 years of elementary school, to be physically and psychologically capable of completing the various tests and examinations in the protocol and to have obtained Hachinski Scale Ischemic scores between 7 and maximum and

TABLE 1 – Experimental Schedule

	Baseline t_0	Week 2 t_1	Week 4 t_2
Hachinski Scale	Bender Gestalt Test		Bender Gestalt Test
	Attention Test		Attention Test
	Picture Completion		Picture Completion
	Digit Span		Digit Span
	Arithmetics		Arithmetics
	Picture Arrangement		Picture Arrangement
	HRSD		HRSD
	PBRSM		PBRSM
	Neurological Scale		Neurological Scale
	ACL	ACL	ACL
	Trait Ranking	Trait Ranking	Trait Ranking
	Patient Interview		Patient's Judgement
	Relative Interview		Relative's Judgement
			Clinician's Judgement

Hachinski Dementia Scale scores of not more than 31 (below 50%).

Patients with brain tumors or other neoplastic diseases, parkinsonism, psychoses, dementia (except mild vascular type), epilepsy, toxic or metabolic cerebral diseases, peripheral vascular diseases requiring continuous treatment with vaso-active drugs, and patients under treatment with drugs that could in any way interfere with the evaluation of the parameters explored in this study were excluded from participation as well as those who had been administered the Wechsler or any of its subtests within the last 12 months.

Procedure. A multicenter, randomized, controlled, double-blind design was employed for this study. All participants were hospitalized during the trials and received IV infusions for 28 days of either citicoline (1.000 mg, p.d.) or saline solution. Table 1 summarizes the experimental schedule of wash-out, experimental trial, and patient evaluation.

Assessment. Performance and intellectual functioning were evaluated before treatment (for baseline levels) and after treatment by the following measures: the Attention Test (modified version of Toulouse-Pieron Test); Picture Completion, Digit Span, Arithmetics and Picture Arrangement from the WAIS (modified and rearranged in 2 different but parallel forms for test-retest); and the Bender Gestalt Test.

Observational Procedures. Three clinicians independently described each patient using the Adjective Check List (ACL) and a trait ranking procedure developed for this research. Patients were interviewed following a standardized protocol. Their closest relatives underwent the same interview except that they described their participant relatives. The Hamilton Rating Scale for Depression (HRS), the Parkside Rating Scale

Modified (PBRSM), and a Neurological Rating Scale were completed as indicated in Table 1.

Analysis. Performance tests were scored by standard procedures. Chronbach's for interrater reliability was calculated for all observational descriptions and a composite description was derived for each patient. Differences between t_0 and t_2 were tested for each measure.

RESULTS

Subject Description. Thirty-three patients who met the inclusion criteria were selected to participate in this preliminary study. The placebo group (Group P) included 17 males and 1 female with mean age of 62.1 (S.D. = 9.02) and a mean of 5.2 years of schooling. The citicoline group (Group C) was composed of 13 males and 2 females with a mean age of 58.6 (S.D. = 7.39) and a mean of 6.6 years of schooling.

Clinical descriptions of the patients from each group were similar even though Group C had a higher incidence of diffuse damage (Group C = 40%; Group P = 22%) and Group P a higher incidence of focal right hemisphere damage (Group P = 39%); Group C = 20%). Focal signs were present in both groups. An average of 10 months had elapsed since the patients' last acute episode. Fewer than 20% of these patients from each group demonstrated a reduction of higher intellectual functioning.

We can conclude from this overall clinical description that these 2 groups of patients are comparable and do not present any gross differences in their pathologies and clinical descriptions.

Interviews. The patients' spouse was the most frequently interviewed relative (Group C = 100%; Group P = 72%). Although patient self-description generally agreed with the relative's description of the patient, some discrepancies did emerge. Relatives tended to describe the patients' physical and psychological condition as more severe than the patients' self-evaluation.

A majority of the participants were retired (Group C = 67%; Group P = 72%) but still played a prominent role in their family and maintained good relationships with their spouses and had contact with their friends even though they reported no cultural, social or political interests.

There were few distinguishing differences between patients from the 2 experimental groups. Relatives of those in Group C, however, tended to be more pessimistic about the patients' future with respect to their counterparts in Group P. The relative lack of differences between groups again confirms that these groups were comparable, and the overall description of these subjects suggests that they are not untypical of their healthy counterparts of the same age and socio-economic status.

Bender Gestalt Test. The Bender was scored by both the Pascal-Suttel method and the Hutt-Briskin method since these ratings do not overlap but focus on different aspects of the test. The former gives a score

for each individual figure of the test and the latter scores each reproductive distortion.

A. Pascal-Suttel. There were no significant differences between groups for the basal administration of the Bender. After treatment, Group C showed a significant improvement with respect to both basal performance ($p < .01$) and Group P post-treatment performance ($p < .05$). These differences were found for figures 3,7 and the total score. Group P demonstrated a significant improvement pre- versus post-treatment for only figure 2 ($p < .05$). An examination of the scores profile revealed a systematic improvement on all items for the citicoline group but only a random variation of scores for the placebo group.

B. Hutt Briskin. One significant difference ($p < .05$), change in angulation, was identified between the groups during basal testing with Group P demonstrating a lower peformance. Post-treatment results favored the citicoline group when compared with the placebo group on position of first drawing, closure difficulty and overlapping difficulty ($p < .05$). When basal and post-treatment test scores were compared, significant improvement on 4 items was found for Group C (position of first drawing ($p < .05$), closure difficulty $p < .05$), overlapping difficulty ($p < .01$), and perseveration ($p < .05$) while significant improvement on fragmentation ($p < .05$) was the only pre- and post-treatment difference in test scores within the placebo group.

Hamilton Psychiatric Rating Scale for Depression. Basal testing revealed one significant difference between groups with patients from Group C rated as more depressed (depressed feeling states spontaneously reported verbally) than those from group P ($p < .05$). When pre- and post-treatment scores were compared within groups, only citicoline patients demonstrated improvement in mood, disappearance of sleep disturbances, heightened interest in work, increase in activities, and felt more at ease. It should be noted, however, that even though the citicoline group was initially more depressed and demonstrated positive mood changes after treatment, their basal scores were not in the pathological range and their improvement seems to be related to n increase sense of well-being.

Parkside Behavior Rating Scale. Scores on the Parkside Behavior Rating Scale paralleled those from the Hamilton Psychiatric Rating Scale. After treatment, only group C demonstrated mood improvement. Again initial basal differences did not indicate strong psychiatric pathology in either group.

Neurological Evaluation Scale. Pre-treatment scores showed no significant differences between groups but Group C significantly improved on total score ($p < .05$) from pre- and post-treatment rating and obtained a significantly better score on sensation evaluation ($p < .05$) with respect to Group P after treatment. These results indicate that a general improvement in neurological condition can be related to the treatment under study.

Intellectual Performance. Group C took significantly longer to complete the Attention Test ($p < .01$) when compared with Group P during basal testing. No other pre-treatment differences were found. After treatment, patients from Group C significantly improved their Attention Test completion time ($p < .05$). Group P demonstrated a significant improvement on the Picture Arrangement Subtest ($p < .01$).

Trait Rankings. Rank scores were compared for the pre-treatment evaluation of both groups and no differences were found. The scores of all patients were then factor analyzed (Principal Components) and two major factors were identified. The factors were identified as controlled behavior and constructive behavior respectively. After treatment, only Group C showed reduction of factors that can be interpreted as related to an increase in rank for self-control and a decrease for responsiveness (augmented control behavior), as well as increase in rank for flexibility (more effective constructive behavior). Eighty percent of patients in Group C and 50% of patients in Group P showed an increase in alpha coefficient from pre- and post-treatments. Furthermore, Group C demonstrated a significant increment of mean alpha when pre and post-treatment trials were controlled ($p < .01$). This strong increment in description concordance among raters after treatment in Group C can be interpreted as due to changes in psychological and behavioral characteristics of patients who show a better defined and more controlled pattern and behavior.

Adjective Check List. A frequency analysis was performed to identify those adjectives more characteristic of each group of patients and to determine how these frequencies within each group changed after treatment. Patients from Group C were described more favorably after treatment with fewer uses of adjectives such as "slow", "simple", "fearful", "apathetic" and more patients were described as "patient", "quiet", "friendly", "responsible", "generous", and "industrious".

On the other hand, patients from Group P received a different description after treatment with respect to Group C. Patients were more frequently rated as cooperative and adaptative but also as complicated and with narrow interests. Fewer placebo patients were described as patient and friendly. Rater reliability across time was improved for 66% of Group C patients and 55% of Group P. This confirms our previous conclusions from analysis of trait rankings.

Judgements of Therapy, Clinicians judged as improved after treatment 60% of the patients from Group C and 39% of Group P. This difference, however, was not significant. Eighty percent of the patients from Group C and 41% of those from Group P considered themselves improved ($p < .05$).

Patients' relatives rated 80% of patients from Group C and 44% of those from Group P as improved ($p < .05$).

No difference between groups concerning drug tolerability was found.

CONCLUSIONS

The preliminary results reported here on the effect of citicoline in CCVD patients show a consistent improvement in the behavioral and psychological variables measured in this study when the experimental patients (citicoline) were compared with the placebo patients.

The assessment procedure specific to this study was devised to give validity to the usual psychometric methods of performance evaluation which lack empirical validity when used in clinical trials. Observational procedures were related to psychometric performance in order to provide a more global picture of these patients' behavioral changes related to treatment. For instance, citicoline demonstrated an effect on both Attention Test performance and motor perceptual performance as well as enhancing the patients' sense of well-being, improving their practical attitudes toward everyday problems, and fostering self-control. Thus, changes were identified not only under experimental trials but also in the patients' everyday behavior. Citicoline seems to be a well tolerated, effective drug when used with mild CCVD patients.

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International Multidisciplinary Seminar

CEREBRAL PATHOLOGY IN OLD AGE

Neuroradiological and neurophysiological correlations

PAVIA, September 27 - 28th, 1982

EDITORS

A. CECCHINI
G. NAPPI
A. ARRIGO

IInd EDITION

EMI RAS SNC
Pavia, 1983