

## ACTION OF ACETYL-L-CARNITINE IN ASSOCIATION WITH MIANSERINE ON DEPRESSED OLD PEOPLE

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### SUMMARY

Recent knowledge on the role of neuromediators on senescence encourages therapeutic intervention aiming at the improvement of cerebral function by manipulating the neurotransmittal system. This would be particularly useful in the therapy of patients showing deteriorating performances with depressed mood.

The known cholinomimetic and serotoninomimetic effects of LAC encouraged us to probe the therapeutic validity of LAC on aged patients with involutive depression.

A simple blind test was performed on 20 patients 10 of which were treated with 1 g/day of LAC and another group of 10 patients was treated with the placebo for 40 days. Both the above groups were treated with 30 mg/day of mianserine in the first 20 days of the experimental period. The psychometric test administered were Hachinski ( $t_0$ ) scale, HDRS, LNNB ( $t_0$ ,  $t_{20}$ ,  $t_{40}$ ) and routine hematochemical tests ( $t_0$ ,  $t_{40}$ ).

The results obtained, indicated a significant improvement in the symptoms for HDRS in the LAC treated group. Also patients' cognitive performances, as per LNNB, significantly improved, whereas that of memory and of the intellectual processes, despite its statistical insignificance, evidenced a slow but gradual improvement.

That cerebral aging is mainly due to a deficiency in the neuronal activity rather than due to vascular deterioration, has been confirmed by the recently demonstrated, age dependent, functional alterations in certain neurotransmittal systems. In the aging brain, the levels of synthesis of

acetylcholine, catecholamine and of serotonin (1) as well as the activity of tyrosine hydrolase and Dopa decarboxylase decreases (2), whereas certain enzymes involved in catecholamine catabolism are more active (3).

Mc Geer et al. 1984 (1) has demonstrated a reduction in acetylcholine transferase enzyme (CAT) directly proportional to the age (from 1.2 to 0.5 micromol/h/100 mg). This study also indicated that when the cholinergic neurons are inferior to 100.000 a demential type symptomatology is produced, due to a low CAT activity. Therapeutic attempts to increase the production of Ach by precursor administration, such as choline and lecithin, were found unsatisfactory.

More encouraging results were obtained with Acetyl-L- Carnitine (ALC), a substance which acts on the metabolism of neuronal membranes and shows specific cholinomimetic and serotonergic effects. The cholinergic action of ALC is secondary to a block of post-synaptic inhibitory potential (5) or to a direct synaptic excitation (6). It has also been suggested (7, 8) to be a "metabolic cofactor" and an "acetyl group reserve" for the Ach synthesis.

These properties indicate that ALC is an active cholinomimetic agent and hence seems appropriate for clinical use to improve cognitive functions such as neuronal and biohumoral characteristics of the aging brain (4, 9). In addition, its serotonergic action might indicate its suitability as an auxiliary drug to cure depression.

Based on the above premises we undertook to study the effects of LAC in association with mianserine, on age associated depression in man. Mianserine is an antidepressive quadricyclic agent which, based on its pharmacokinetic and pharmacodynamic characteristics, seems to be a suitable alleviating agent for the age associated depression (10, 11, 12).

#### METHODOLOGY

Twenty hospitalized patients of both sexes, at the psychiatric clinic of the University of Catania, with involutive depression according to ICD 9 criteria, were included in this study. Patient's age was 55-75 years and their score of Hachinski Ischemia Test was not higher than 4 (to exclude the cerebrovascular forms).

Before starting the experiment, patients were observed a wash-out period of 15 days after which they were evaluated for depressive symptomatology according to the Hamilton Depression Rating Scale (HDRS) and for cognitive function as per the Luria Nebraska Neuropsychological Battery (LNNB). Patients had also hematochemical examinations, EEG and ECG.

The patients were divided into 2 subgroups. Group A was orally treated with 1 g of ALC twice a day (at 12 and 18 hrs) for 40 days. Group B was treated with placebo, the dosage and duration of treatment was the same as in group A. Both of the above groups (A and B) were tested with mianserine 30 mg/day (one dose per evening), for the first 20 days of the treatment period. Rating of the patients were performed on day 0 ( $t_0$ ), day 20 ( $t_{20}$ ) and day 40 ( $t_{40}$ ) post-treatment. Non parametric two way analysis of variance (Friedman test) was

carried out to follow up the neuropsychologic parameters in both the experimental groups and their results were compared by using the Mann-Whitney U- test.

### RESULTS

The general characteristics of the patients observed are summarized below (Table I).

Table I - General characteristics of the patients

	Group A (N = 10)		Group B (N = 10)	
	x	s.d.	x	s.d.
AGE	62.5	5.7	62.5	5.3
SEX	8M - 2F		8M - 2F	
HDRS	44.9	3.1	43.9	2.8
LNNT	64.51	5.2	65.27	6.15

Mann-Whitney analysis revealed statistically significant improvement in HDRS test, both in total score as well as in individual measurements, at t<sub>20</sub> with additional improvement on t<sub>40</sub>, in patients treated with LAC and mianserine (Table II).

Despite the fact that some of the results were found more or less similar both in the treated and untreated groups, other factors such as depressed humor, general somatic symptoms, hypochondria and introspection were found significantly improved in LAC treated group.

In placebo treated patients no significant variations were noticed between t<sub>20</sub> and t<sub>40</sub> except a slight improvement of the symptoms for anxiety of psychological origin (p 0.05). No side effects were observed in any of the above two groups.

In the LNNB test demographic variations, if any, among the patients, such as age of education were rectified employing normalizing indices. The average values thus obtained were found homogeneous among the two groups studied.

Table II - Comparison between groups (Mann-Whitney)

HDRS ITEM	BASAL	$t_{40}$
DEPRESSED MOOD	n.s.	p 0.001
FEELING OF GUILT	n.s.	n.s.
SUICIDE	n.s.	p 0.001
EARLY INSOMNIA	n.s.	p 0.05
MIDDLE INSOMNIA	n.s.	n.s.
LATE INSOMNIA	n.s.	n.s.
WORK AND ACTIVITIES	n.s.	n.s.
RETARDATION	n.s.	p 0.01
AGITATION	n.s.	n.s.
PSYCHIC ANXIETY	n.s.	n.s.
SOMATIC ANXIETY	n.s.	n.s.
SOMATIC GASTROINTEST. SYMPTOMS	n.s.	n.s.
SOMATIC GENERAL SYMPTOMS	n.s.	p 0.001
GENITAL SYMPTOMS	n.s.	n.s.
HYPOCHONDRIASIS	n.s.	p 0.01
LOSS OF WEIGHT	n.s.	n.s.
INSIGHT	n.s.	p 0.001
DIURNAL VARIATION	n.s.	n.s.
DEPERSONALIZATION AND DEREALIZ.	n.s.	n.s.
PARANOID SYMPTOMS	n.s.	p 0.01
OBSessional AND COMPULSIVE SYMP.	n.s.	p 0.01
TOTAL SCORE	n.s.	p 0.001

A marked improvement in Memory (p 0.005), Reading (p 0.05), Intellectual Capacities (p 0.005) are observed on t<sub>40</sub> as compared to t<sub>20</sub> in LAC treated patients.

### CONCLUSIONS

The above results demonstrate the synergism of ALC and an antidepressive quadricyclic agent such as mianserine due to their action on cholinomimetic and serotoninomimetic transmission.

ALC, due to its SNC activating effect, could limit the typical sedative effect of mianserine found at the onset of treatment. Eventhough in older patients with further deterioration, an increased irritability was encountered at the suspension of mianserine treatment. The above conclusion derives from the fact that in the ALC treated patients reduced anxiety of psychological origin were observed as compared to those treated with placebo.

The improvement in LNNB at t<sub>40</sub> confirms specific effects on the cognitive processes with positive improvement in attention and perception, short and median term memory and recoll of vocal and graphic detailes regarding the earlier rating. The gradual variation in the scale of memory as well as that of intellectual process, though insignificant, confirms the activating role of ALC on complex functions involved in the information, elaboration and retention. This justifies a prolonged treatment with ALC and mianserine to achieve significant improvement of the patients' performance.

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