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Brief Communication

Cholesterol concentrations and clinical response to sertraline in patients with epilepsy: Preliminary results

René Andrade Machado [a,*], Arlety García Espinosa [b], Ariadna Perez Montoto [a]

[a] Epilepsy Section, National Neurology and Neurosurgery Institute, Havana, Cuba
[b] Psychiatry Hospital Eduardo Bernabé Ordaz, Havana, Cuba

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ABSTRACT

Objective: Low cholesterol levels are associated with depression and suicide in persons with epilepsy. The goal of this study was to determine whether plasma cholesterol concentration is a predictor of response to sertraline.
Methods: We carried out a prospective open-label study on the efficacy of sertraline as therapy in the treatment of depressive disorder in patients with mesial temporal lobe epilepsy. Patients were treated for 24 weeks at dose levels between 50 and 100 mg/day. All patients were evaluated at the beginning of the investigation and 6 months later by two psychiatrists using a structured interview.
Results: The mean total cholesterol concentration of nonresponding patients was lower than the mean (SD) cholesterol level of responders [3.2 (0.9) mmol/L vs 5.2 (1.5) mmol/L]; this difference reached statistical significance ($P = 0.0000$). We found a negative correlation between scores on the Hamilton scale and cholesterol concentrations ($r = -33$).
Conclusion: The response to sertraline may depend on the baseline cholesterol concentration.

1. Introduction

Recent epidemiological investigations have suggested that low cholesterol levels are associated with depression and suicide in persons with epilepsy [1,2]. Selective serotonin-reuptake inhibitors (SSRIs) increase serotonin concentration in central nervous system synapses, improving depressive symptoms and suicidal risk [1,3]. Taking into consideration that low cholesterol concentration may cause decreased serotonergic transmission in this type of synapse, we wondered whether plasma cholesterol concentration could be a predictor of response to SSRIs.

2. Methods

2.1. Design

The study described here was a prospective open-label study on the efficacy of sertraline as therapy in the treatment of depressive disorder in patients with mesial temporal lobe epilepsy. Patients were treated for 24 weeks at dose levels between 50 and 100 mg/day. The protocol was approved by our hospital ethics committee.

2.2. Subjects

After giving informed consent, 42 patients with mesial temporal lobe epilepsy were enrolled in the study. All patients were taking antiepileptic drugs (AEDs): 37 patients were on monotherapy and 5 were on polytherapy. Fifteen of 42 patients were taking lamotrigine (average target dose range: 1–5 mg/kg daily), 3 gabapentin (1130–2050 mg daily), 19 valproic acid (30–60 mg/kg/daily), and 5 polytherapy (valproic acid 30–43 mg/kg daily in association with lamotrigine 0.5–1.2 mg/kg daily and clobazam 1–2 mg/kg daily).

2.3. Procedures

All patients were evaluated at the beginning of the investigation and 6 months later by two psychiatrists employing a structured interview (Mini-International Neuropsychiatric Interview [MINI]) [4], Hamilton's standardized scale for depressive symptoms [5], and Plutchik's Suicidal Risk Scale [6].

Blood samples were collected from all subjects. Patients were divided into two groups on the basis of cholesterol level: low cholesterol (≤3.1 mmol/L) and high cholesterol (>3.1 mmol/L). These cholesterol concentrations were selected from a receiver operator characteristic (ROC) curve.

* Corresponding author. Epilepsy Section, National Neurology and Neurosurgery Institute, 29 and D, Vedado Plaza Cuba, Ciudad de la Havana, Cuba.
E-mail address: rene@inn.sld.cu (R.A. Machado).

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2.4. Statistical analysis

A psychiatrist, blind to cholesterol concentration, classified the patients as responders or nonresponders. Linear regression analysis was carried out to determine the correlation between plasma cholesterol level at baseline and score on Hamilton´s scale at the end of the study. To analyze the number of suicide attempts during the follow-up with respect to cholesterol level at baseline, we compared patients with lower or higher cholesterol concentration by means of Kaplan–Meier survival analysis.

3. Results

3.1. General data

Thirteen patients were male (31%) and 29 female (69%). The mean ± SD age of patients was 38.5 ± 13.5 years; the mean ± SD age at onset of epilepsy was 24.9 ± 16.9 years. Thirteen of 42 patients had high plasma cholesterol concentrations (mean = 5.9 ± 1.2). Twenty-four patients had Major Depressive Disorder, and 18 patients had Bipolar Type II Disorder.

3.2. Cholesterol concentration, suicide attempts, and Suicidal Risk Scale score

Sixteen patients with low cholesterol levels (38.1%) scored >7 on the Suicidal Risk Scale (mean ± SD = 11.8 ± 4.4), whereas only eight patients (19.4%) with high cholesterol concentrations scored >7 on this scale (5.8 ± 4.4). This difference was statistically significant ($P = 0.02$). Twelve of 42 patients had attempted suicide, 8 (21.4%) in the low cholesterol group and 3 (7.1%) in the high cholesterol group ($P = 0.03$).

3.3. Sertraline efficacy and cholesterol concentration

The mean (SD) total cholesterol concentration of nonresponders was significantly lower ($P = 0.0000$) than the mean (SD) cholesterol level of responders [3.2 (0.9) mmol/L vs 5.2 (1.5) mmol/L] (Fig. 1A). There was a negative correlation between Hamilton scale score and cholesterol concentration ($r = -0.33$, $P = 0.002$). Low cholesterol concentration predicted a bad outcome of the depressive disorder despite antidepressant treatment (OR = 3.8, 95% CI = 1.5–6.3, $P = 0.011$) (Fig. 1B). Kaplan–Meier survival analysis (Fig. 1C) supported the predicted relationship between lower cholesterol levels and likelihood of later suicide attempts despite an SSRI regimen. The cumulative survival estimate for those with low cholesterol concentrations was lower than that of the high cholesterol group ($P = 0.008$).

3.4. Suicidality, efficacy of sertraline, and cholesterol concentration with respect to psychiatric disorder (subanalysis because of sample heterogeneity)

Major Depressive Disorder was diagnosed in 24 of 42 patients: the mean (SD) total cholesterol concentration for nonresponders in this subgroup of patients was significantly lower ($P = 0.0000$) than the mean (SD) cholesterol level for responders [2.6 (0.7) mmol/L vs 5.7 (1.6) mmol/L]. In the subgroup of patients with Bipolar Type II Disorder, the mean (SD) total cholesterol concentration of

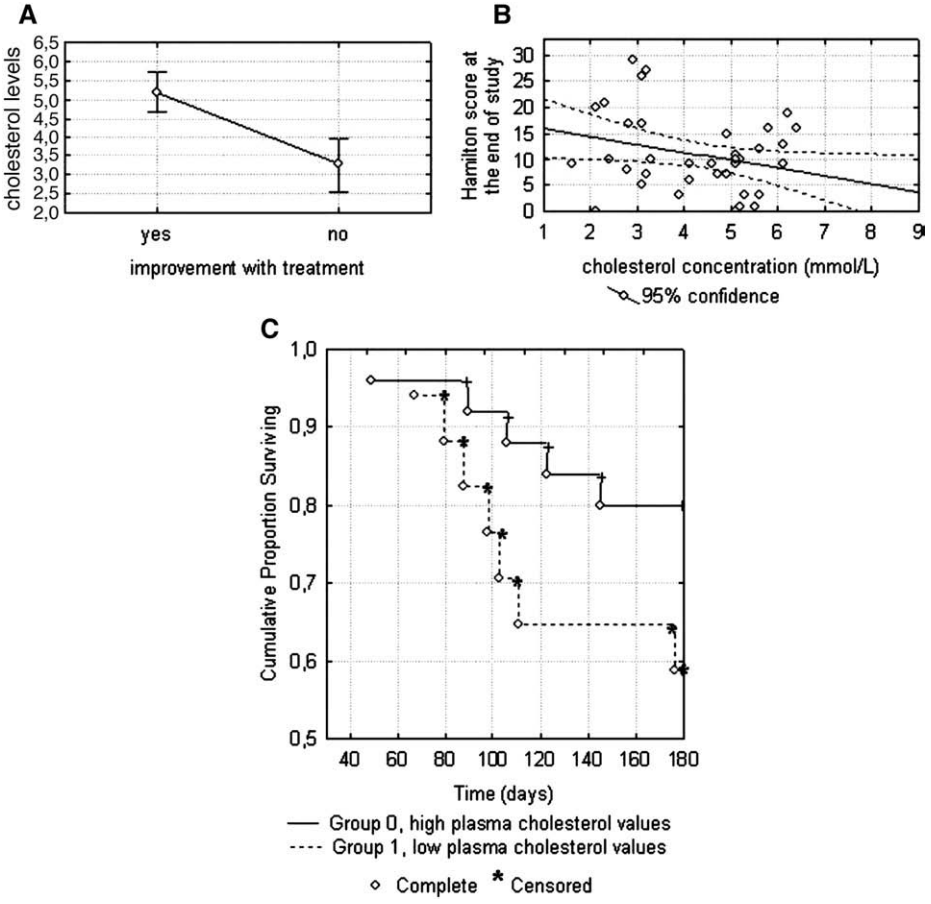

Fig. 1. (A) Response to sertraline treatment with respect to cholesterol concentration. Current effect ANOVA: $F(1, 42) = 18.9$, $P = 0.0000$. Mean (SD) cholesterol concentration in responders = 5.2 (1.5), and that in nonresponders = 3.2 (0.5). (B) Plasma cholesterol level at baseline and severity of depression 6 months after treatment. Linear regression: $r = -0.33$, OR = 3.8, 95% CI = 1.5–6.3. (C) Plasma cholesterol levels and future suicide attempts after sertraline treatment: Gehan test, $P = 0.008$.