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Centro Nacional de Investigaciones Científicas
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Effects of policosanol on patients with ischemic stroke with previous transient ischemic attack: a long-term follow-up

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ABSTRACT. Stroke is one of the three leading causes of disability and death worldwide. Transient ischemic attacks (TIA) pose an increased risk of subsequent ischemic stroke. Platelet antiplatelet therapy, mainly aspirin, remains as first-line therapy to prevent recurrent TIA and/or ischemic strokes, and antiplatelet agents play also a key role in this strategy. Policosanol, with cholesterol-lowering drug and concomitant antiplatelet effects, has shown protective effects on stroke models. Policosanol 20 mg/d added to aspirin during the acute phase of ischemic stroke and thereafter provided good results on neurological outcomes and recurrent events. This study assessed the benefits of policosanol 20 mg/d administered from hospital discharge up to 60 months thereafter in 55 patients of both sexes with ischemic stroke who had previously suffered TIA. At each visit, clinical and neurological examination with the modified Canadian Neurological Scale, request on adverse experiences and laboratory tests were done. All new events were recorded. In addition to the previous TIA, the most frequent personal risk factors at baseline were hypertension (98.2 %), hypercholesterolemia (81.8 %), smoking (32.7 %) and coronary disease (29.1 %). All patients completed the study. Neurological score improved significantly and progressively during the first year, and such improvement persisted to study completion. Only five patients (9.1 %) suffered a new event: one new stroke, four new TIA. After three months, serum cholesterol significantly lowered (21.3 %) compared with baseline, and this effect did not wear off, but improved after long-term therapy. The improvement of the neurological outcome correlated with TC reduction (r = 0.987). Treatment unchanged safety indicators. Then, treatment with policosanol 20 mg/d + aspirin (125 mg/d) after hospital discharge produced good results in the neurological recovery; recurrence of events and cholesterol control in patients with ischemic stroke and a previous TIA, but these benefits should be confirmed in randomized, double-blind, controlled studies.
INTRODUCTION

Stroke remains among the three most common causes of death, the first of disability and the second of dementia among middle-aged and elderly population on developed Western and Asian countries. Stroke affects not only the person who may be disabled, but the entire family as well. Although a decrease in the mortality of stroke and a rise in stroke-free life expectancy has been observed over the last 20 years as a consequence of improved prevention, diagnosis and acute treatment of stroke, stroke prevalence has raised because of the increase in case-fatality rates. Stroke, cardiac events, dementia and depression rates increase with the aging of the population, and as more individuals survive a first stroke. The probability of the stroke recurrence within the first and five years post-stroke is about 12 and 30%, respectively. Then, stroke is a major health problem of adult population worldwide.

Stroke results from the sudden interruption of blood flow to a brain region that impairs the energy supply to the central nervous system, which becomes hypoxic. Strokes can be ischemic (atherothrombotic, embolic, lacunar, hemodynamic (75% to 80%), or hemorrhagic (about a 20% of all strokes). Thrombotic stroke arises from the formation of a clot or thrombus in a cerebral artery that blocks blood flow at the site of formation, embolic stroke results from the block of a cerebral artery with a clot formed elsewhere and carried to the brain through the blood.

Despite the improvement in the treatment of acute ischemic stroke, prevention strategies, aimed to minimize the influence of modifiable stroke risk factors, remains the best treatment for reducing the burden of stroke. Subjects who are at highest risk of stroke, like the elderly, may benefit from rigorous control of modifiable risk factors, and should be followed, since age is a relevant non-modifiable stroke risk factor, since its risk doubles for each decade beyond 55 years. Hypertension, smoking, diabetes, dyslipidemia, obesity and physical inactivity are modifiable risk factors that can be reduced with lifestyle and pharmacological interventions.

Not only previous strokes, but transient ischemic attacks (TIA) are strong stroke risk factors, since they carry a substantial short-term risk (up to a 10%) for a subsequent ischemic stroke within 7 d and a 25% risk of death at 1 year, but unfortunately, TIA remain under-diagnosed. Also, coronary heart disease, atrial fibrillation and other cardiac conditions, carotid stenosis and platelet hyperreactivity are factors that increase the risk of stroke.

Antiplatelet therapy remains as a gold standard for preventing stroke recurrence, lowering the risk of secondary non-cardioembolic ischemic stroke over anticoagulant drugs. First-line therapy for secondary stroke prevention involves the use of antiplatelet drugs (aspirin, aspirin plus extended-release dipyridamole, or clopidogrel for cases refractory or intolerant to aspirin), whereas aspirin plus clopidogrel offers no additive benefits and is linked with safety issues. Among patients with ischemic stroke treated with aspirin 20 mg/d added to conventional therapy with aspirin during the acute phase of stroke and for long-term thereafter was very good.

In light of these issues this study was undertaken to assess the usefulness of policosanol (20 mg/d) routinely administered after hospital discharge on neurological evolution and outcomes of patients who suffered an ischemic stroke with prior history of TIA.

PATIENTS AND METHODS

Study design and conduction

This observational study was conducted in patients with ischemic stroke and previous history of TIA who were admitted in the Institute of Neurology and Neurosurgery (Havana City, Cuba) from June 1997 to November 2005. Subjects were informed that their decision to participate in the follow-up was voluntary. No special risk

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was introduced to study patients, since all received conventional therapy for stroke recovery, as recommended in routine clinical practice.

All patients had been admitted previously in the Intensive Care Unit, wherein the occurrence of ischemic stroke was confirmed through clinical assessment and computerized axial tomography performed within the following 48 h after stroke onset. Self-reported or family-reported risk factors for stroke were obtained on admission (baseline). Subtypes of ischemic stroke were confirmed at the time of discharge (Table 1).

### Table 1. Characteristics of study patients at hospital admission.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (X ± SD)</td>
<td>65.5 ± 11.0</td>
</tr>
<tr>
<td>BMI (kg/m²) (X ± SD)</td>
<td>26.61 ± 2.50</td>
</tr>
<tr>
<td>Gender</td>
<td>n %</td>
</tr>
<tr>
<td>Women</td>
<td>29 52.7</td>
</tr>
<tr>
<td>Men</td>
<td>26 47.3</td>
</tr>
<tr>
<td>Type of the including stroke</td>
<td></td>
</tr>
<tr>
<td>Lacunar</td>
<td>29 52.7</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>25 45.5</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>1 1.8</td>
</tr>
<tr>
<td>Previous history of:</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attacks (TIA)</td>
<td>55 100.0</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>54 98.2</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>45 81.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>18 32.7</td>
</tr>
<tr>
<td>Coronary heart disease (CHD)</td>
<td>16 29.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 10.0</td>
</tr>
</tbody>
</table>

Follow-up controls were done at 3, 6, and 12 months during the first year, and annually thereafter. The final control was conducted at month 60 after hospital discharge. Patients underwent general examination, neurological assessment, laboratory analyses and interviews about adverse experiences (AE). Neurological status was assessed with the modified Canadian Neurological Scale (CNS).63

### SAFETY AND TOLERABILITY

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### Study patients

Women and men diagnosed of suffering ischemic stroke older than 20 years old were included in this study. Patients with suspected or confirmed hemorrhagic stroke were excluded.

Premature withdrawals were predefined as patients suffering AE justifying such decision, unwillingness to follow-up or study violation (stopping the treatment for more than 15 d). Nevertheless, patients who experienced serious AE unlikely due to treatment, but related with its inclusion criteria, continued in the study, whether both doctor and the patient agreed.

### Study outcomes

The primary efficacy variable was to obtain a significant increase of the modified CNS score.45

The occurrence of new cerebrovascular (fatal or non fatal stroke, TIA) was recorded, and the evolution was considered as good if recurrence of stroke occurred in ≤ 10 % of study patients. The frequency of other major vascular event (fatal or non fatal MI, unstable angina, sudden death, peripheral thrombosis) was also evaluated. A reduction of serum total cholesterol (TC) ≥ 15 % was considered as a collateral efficacy variable.

### Blood indicators

Non-fasting total serum TC, triglycerides (TG), glucose and creatinine were assessed by routine methods at the laboratory of the Institute of Neurology.

### Adverse experiences

An AE was any undesirable experience, absent at hospital discharge or worsened thereafter, happening in a patient, independently if it could be or not related with the therapy. AE were classified as mild, moderate and serious according to their intensity. Mild AE should not require discontinuation of policosanol or treatment of the specific AE, moderate AE should require the withdrawal of medication and/or specific treatment, while serious AE should lead to patient hospitalization or to death, and could be fatal and non-fatal (those that did not cause the patient death up to the final cut off (June 2004).

The possible causal relationship of any AE with the treatment should be evaluated with the Naranjo ADR algorithm, using the following score: doubtful < 1; possible 1 to 4; probable 5 to 8; definite ≥ 9.44

### Data analysis

Statistical analysis was performed by Intention to-treat. Continuous data are presented as means with standard deviations (SD), categorical data as frequencies and percentages. Wilcoxon test for paired samples was used to compare data on neurological, physical and blood indicators. Bonferroni adjustment for multiple comparisons in a single test was applied.46 Correlation between CNS score and serum TC was analysed with a lineal regression analysis. All statistical tests were two-tailed, with significance at α = 0.05. Statistical analyses were performed using Statistics for Windows (Release 4.2i).
Most of debuting strokes were lacunar (52.7 %), followed by stroke of thrombotic aetiology (45.5 %). In addition to the previous TIA, the most frequent personal risk factors at baseline were hypertension (98.2 %) and hypercholesterolemia (81.8 %), followed by smoking (32.7 %) and coronary heart disease (CHD) (29.1 %).

**Concomitant therapy**

In addition to policosanol, all patients consumed aspirin (125 mg/d) during the study, 53 (98.1 %) hypertensive subjects consumed some angiotensin converting enzyme inhibitor (ACEI) (49 enalapril, four captopril), one was treated with atenolol and five (9.1 %) diabetics received oral hypoglycaemic drugs, while the other was controlled with diet only.

**Effects on study outcomes**

The neurological score improved significantly and progressively up to the first year after the stroke, and persisted thereafter up to the last visit (5 years post-stroke) (Fig. 1). No patient died during the trial. Fifty patients (90.9 %) did not experience a new vascular event, 1/55 (1.8 %) suffered a new stroke and four (7.3 %) experienced a new TIA. No other serious AE occurred during the trial (Table 2).

**DISCUSSION**

This study demonstrates that patients with ischaemic stroke and previous history of TIA treated with policosanol 20 mg/d and aspirin 125 mg/d had a significant improvement of the CNS score up to reach normal values, a low frequency (< 10 %) of recurrent stroke and TIA, a null occurrence of other vascular events among and an adequate control of serum TC, one of the postulated risk factors for ischaemic stroke. These results confirm the data of a previous study of policosanol in patients with ischemic stroke.

**Fig. 2. Effects of policosanol on serum total cholesterol (TC) and triglycerides (TG). Baseline (B) values obtained during the first assessment (within 24 h after stroke). *p < 0.001 Compared with baseline (Wilcoxon test for matched pairs, Bonferroni adjustment).**

**Table 2. Vascular events during the 5 years follow-up.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>No new event</td>
<td>50</td>
<td>90.1</td>
</tr>
<tr>
<td>At least one recurrent stroke</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>At least one TIA</td>
<td>4</td>
<td>7.2</td>
</tr>
<tr>
<td>At least one of such events</td>
<td>5</td>
<td>9.1</td>
</tr>
<tr>
<td>Other vascular events</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

n Number of patients (55). TIA Transient ischemic attacks.

Mean serum TC values at baseline and after 3 months on therapy were 7.67 and 6.04 mmol/L, respectively (TC reduction of 21.3 %) (Table 3). This effect did not wear off, but improved after longer therapy, since it subsequently decreased to 5.43 and 5.07 mmol/L after 6 and 12 weeks of therapy, respectively. The mean serum TC value at study completion was 4.76 mmol/L. The increase of the disease was significant compared with baseline (Fig. 2).
between men and women across studies. The preponderance of women in the present follow-up, therefore, does not seem to be responsible of an overestimated efficacy of the treatment with policosanol plus aspirin in patients with ischemic stroke.

In addition to the use of aspirin (100% of study subjects), the frequency of cases treated with antihypertensive drugs was high (54/55; 98.2%), consistent with the high frequency (98.2%) of hypertensive subjects, most patients received ACEI inhibitors, mainly enalapril (49/55; 89.1%).

Stroke scales, developed for objectively assessing the degree of patient recovery and the need of standardization for comparing the results across stroke studies, have been used as the primary or secondary efficacy variables for evaluating the neurological improvement in several stroke studies. In the present study, the neurological evolution was assessed with the modified CNS score, one of the properly validated stroke scales.

Table 3. Long-term effects of policosanol on safety indicators.

<table>
<thead>
<tr>
<th>Months on therapy</th>
<th>3</th>
<th>6</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodyweight (kg)</td>
<td>74.05 ± 9.45</td>
<td>71.69 ± 8.43</td>
<td>70.82 ± 8.17</td>
<td>70.02 ± 7.77</td>
<td>69.84 ± 7.86</td>
<td>69.55 ± 7.83*</td>
<td>69.18 ± 7.51*</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>80.40 ± 5.82</td>
<td>79.47 ± 4.70</td>
<td>78.29 ± 4.15</td>
<td>77.91 ± 4.88</td>
<td>77.18 ± 4.77*</td>
<td>77.93 ± 3.76</td>
<td>78.24 ± 4.39</td>
</tr>
<tr>
<td>Blood diastolic pressure (mmHg)</td>
<td>93.36 ± 6.67</td>
<td>84.55 ± 4.84*</td>
<td>81.55 ± 3.62*</td>
<td>79.36 ± 3.34*</td>
<td>77.91 ± 4.58*</td>
<td>78.15 ± 3.54*</td>
<td>77.50 ± 4.72*</td>
</tr>
<tr>
<td>Blood systolic pressure (mmHg)</td>
<td>151.45 ± 11.41</td>
<td>133.82 ± 6.80*</td>
<td>128.55 ± 5.67*</td>
<td>125.35 ± 4.80*</td>
<td>122.82 ± 4.68*</td>
<td>122.41 ± 7.19*</td>
<td>122.02 ± 4.14*</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.81 ± 1.17</td>
<td>4.76 ± 0.86</td>
<td>4.81 ± 0.70</td>
<td>4.71 ± 0.75</td>
<td>4.73 ± 0.69</td>
<td>4.78 ± 0.62</td>
<td>4.72 ± 0.61</td>
</tr>
</tbody>
</table>

X Mean, SD Standard deviation. *p < 0.006; **p < 0.001 Comparison with baseline (Wilcoxon test for matched pairs, Bonferroni adjustment).

The recurrence of stroke (1.8%) and of cerebrovascular events (five events: stroke + TIA) (9.1%) was very low considered the long-term (5 years) of the follow-up. These facts, together with the lack of other vascular events during the study, were particularly good compared with data of mortality and vascular events following ischemic stroke among adults aged ≥ 65 years followed by 3.2 years, in which recurrent strokes were 105.4/1000 during the first year after initial stroke, and 52.0/1000 after the first year. Nevertheless, the distribution of the debuting strokes should have contribute to the present results, since most strokes were lacunar and only one patient had suffered a cardioembolic stroke, which are responsible of the highest mortality (185.4/1000) and recurrence strokes rates (86.6/1000), and lacunar strokes have the lowest mortality (119.3/1000) and recurrence rates (43.0/1000).

Consistent with previous data of long-term effects of policosanol, after three months on therapy policosanol reduced serum TC levels (7.67 mmol/L after 1 and 5 years on treatment, respectively. Although LDL-C is the main target of hypercholesterolemia management in coronary secondary prevention, the authors did not assess the effects on this surrogate because of the use the indicators most routinely used in the clinical practice of Cuba to manage post-stroke patients, but such approach is a limitation of this study because the authors don’t know whether the treatment achieved the LDL-C targets of current guidelines.

The fact that the TC reduction correlated with the improvement on the CNS score suggests that such effect of policosanol could be responsible, at least partially, of the effects on stroke outcomes here shown, since aspirin or antihypertensive drugs, the concomitant therapy most frequently consumed by study subjects, have not documented cholesterol-lowering effect.

In this study, however, the authors found a significant reduction of serum TG after 12 months on therapy, which agrees with data of some studies but not with most of them, including the previous trial in patients with stroke. Although we cannot discard that policosanol had contributed to the decrease of TG, the emphasis on following a healthy low-fat diet after stroke could be responsible of this result, which matches with the reduction of bodyweight over the study.

The authors cannot conclude, however, that the neurological improvement and the low frequency of recurrent stroke and/or TIA during the study were attributable to policosanol since the study did not include a control group treated with placebo plus aspirin. Nevertheless, a comparison of the present data with the recurrence of cerebrovascular events in patients treated with aspirin shows that our results are over these estimates, which suggests that the addition of policosanol could be responsible, at least partially, of these results. The fact that policosanol does not only display cholesterol-lowering, but also exhibits antiplatelet, antioxidant and antiatherosclerotic effects supports the rationale of such speculation.

Policosanol was very well tolerated, as expected. No
previous studies demonstrating that the treatment is safe and well tolerated.\textsuperscript{35-50} A moderate, but significant reduction on arterial blood pressure was found, consistent with data of previous long-term studies of policosanol.\textsuperscript{17,50} Nevertheless, since no patient had hypotension values and the frequency of hypertension among study patients was very high, this effect could be potentially beneficial for stroke recovery, rather than a treatment-related adverse event.\textsuperscript{1,16} On the other hand, although differently from most previous studies,\textsuperscript{3,18,40,50} a significant reduction of bodyweight was observed, this effect could result from the joint action of constant dietary re-education to patients together with a good treatment compliance. In light that weight control is a part of the strategy for reducing the risk of stroke and other vascular events, this result does not imply a safety concern.

These results confirm previous data of policosanol in patients with ischemic stroke, but this study has limitations for stronger conclusions, since it was open, uncontrolled, and all patients consumed conventional aspirin therapy. Then, the benefits of policosanol in patients with ischaemic stroke should be confirmed in randomized, double-blind, controlled studies.

CONCLUSIONS

Treatment with policosanol 20 mg/d plus aspirin 125 mg/d for 5 years after hospital discharge produced good results in the neurological recovery, recurrence of events and cholesterol control in patients who suffered ischemic stroke and had previous history of TIA, which remarks their high stroke risk.

BIBLIOGRAPHIC REFERENCES


