STATIN AND FIBRATE ASSOCIATED MYOPATHY

Study of eight patients

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ABSTRACT - Lipid-lowering drugs have been occasionally associated with neuromuscular symptoms and muscle biopsy changes. We reported the clinical course and the muscle biopsy in eight patients with hyperlipoproteinemia, treated with lipid-lowering drugs (statins/fibrates). Five patients had myalgias while; in two cases there was proximal muscle weakness. All patients became asymptomatic after the withdrawal of the drug, although creatine kinase remained elevated. We performed muscle biopsy in six cases from three months to two years after suspension of the drug. We found variation in fibers diameters in all cases, with necrosis of fibers in five cases, inflammatory infiltration in one case, the presence of vacuolated fiber in one patient and ragged-red fibers in three subjects. We concluded that although the muscle biopsy findings were not specific, the prolonged use of statins and or fibrates might induce a chronic myopathy even in the absence of symptoms.

KEY WORDS: statins, fibrates, myopathy, muscle biopsy, creatine kinase.

Lipid-lowering drugs are considered as the first choice drugs in the control of dyslipidemias and they are well tolerated by most patients. They have occasionally been associated with myopathy. The most common adverse drug reactions are constipation, flatulence, dyspepsia, nausea and elevated transaminase levels. Adverse reactions affecting the skeletal muscle have been reported, such as myalgia, muscle cramps, rhabdomyolysis, aching, proximal weakness and elevation of creatine kinase (CK). The most severe risk of these drugs is myositis with rhabdomyolysis. Rapid remission of symptoms after discontinuation of therapy has frequently been reported.

We describe the clinical findings in eight patients, along with muscle biopsy in six of these. They all had chronic hyperlipoproteinemia and were treated with lipid-lowering drugs (statins/fibrates).

CASES
We studied eight patients from October, 2001 to August, 2002 (Table 1).

One patient did not present muscular symptomatology. Five reported muscular pains, and there was proximal muscular weakness in two. Electroneuromyography was carried out in five subjects, revealing standard myopathic findings in three. One patient was...
diabetic whereas two had hypothyroidism controlled with specific medication. CK was elevated in all patients (Tables 1 and 2).

Muscle biopsy was performed in 6 of these patients at between 3 months and 2 years after withdrawal of the drug (Table 2). Tissue samples from muscle biopsy (biceps brachial) were fresh frozen in liquid nitrogen and were fixed for pathologic analysis according to standard techniques. The following alterations were observed: 1) disproportion of fibers diameters in all cases and necrosis of fibers in five cases (Fig 1A), 2) vacuolated fibers PAS negative in one case (Fig 1B), 3) inflammatory infiltrates in one patient (Fig 1C), 4) ragged-red fibers - COX positive in two cases and no ragged red fibers - COX negative in one case (Fig 2 and 3).

Those patients with some muscular symptoms become symptom-free on discontinuing the use of the drugs. The CK remained elevated even after the withdrawal of the medications. The patients whose muscle biopsies showed mitochondrial dysfunction were receiving statins only. Three patients had rhabdomyolysis (cases 2, 3, 8) but only the case 3 were using associated therapy (statin and fibrate). Lactate dosage was normal in our cohort. The three patients presenting mitochondrial dysfunction were asymptomatic and presented no signs of compromise to other systems.

**DISCUSSION**

The adverse side effects resulting from the prolonged use of cholesterol-reducing drugs are well known, particularly nausea, dyspepsia, flatulence and intestinal constipation. Recently, both muscular and peripheral nervous system disturbances have been cited. An incidence of 2% - 7% has been

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### Table 1. Analysis of patients.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Race</th>
<th>Age (years)</th>
<th>Drug</th>
<th>Time Of Using</th>
<th>CM</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>W</td>
<td>61</td>
<td>SIMV 20mg/day</td>
<td>3y</td>
<td>NONE</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>W</td>
<td>48</td>
<td>FLUV 20mg/day</td>
<td>15d</td>
<td>HT</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>W</td>
<td>42</td>
<td>CER0.4 mg/d</td>
<td>15d</td>
<td>NONE</td>
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<tr>
<td>4</td>
<td>F</td>
<td>W</td>
<td>69</td>
<td>SIMV 20 mg/day</td>
<td>3m</td>
<td>DM</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>W</td>
<td>38</td>
<td>ETOFI 500 mg/day</td>
<td>28d</td>
<td>NONE</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>W</td>
<td>44</td>
<td>SIMV 20 mg/day</td>
<td>6y</td>
<td>NONE</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>W</td>
<td>56</td>
<td>ATORV 10 mg/day</td>
<td>4y</td>
<td>NONE</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>W</td>
<td>60</td>
<td>FLUV 20 mg/day</td>
<td>15d</td>
<td>HT</td>
</tr>
</tbody>
</table>

M, male; F, female; W, white; CM, comorbidity; HT, hypothyroidism; DM, diabetes mellitus; SIMV, Simvastatin; FLUV, fluvastatin; CER, cerivastatin; GEMF, genfibrosyl; ETOFI, etofibrate; ATORV, atorvastatin; y, years; m, months; d, days.

### Table 2. Analysis of patients.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Symptoms</th>
<th>CK(U/L)</th>
<th>ΔT</th>
<th>Biopsy</th>
<th>ENMG</th>
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<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>303</td>
<td>8m</td>
<td>RRF; VDF</td>
<td>M YOP</td>
</tr>
<tr>
<td>2</td>
<td>myalgia</td>
<td>17000</td>
<td>8m</td>
<td>RRF; VDF</td>
<td>NL</td>
</tr>
<tr>
<td>3</td>
<td>myalgia, hematuria</td>
<td>6060</td>
<td>-</td>
<td>NOT DONE</td>
<td>not done</td>
</tr>
<tr>
<td>4</td>
<td>proximal weakness</td>
<td>515</td>
<td>3m</td>
<td>IM ; VDF</td>
<td>not done</td>
</tr>
<tr>
<td>5</td>
<td>arthralgia</td>
<td>2484</td>
<td>3m</td>
<td>VM ; VDF</td>
<td>M YOP</td>
</tr>
<tr>
<td>6</td>
<td>myalgia, arthralgia</td>
<td>279</td>
<td>2y</td>
<td>RRF; VDF</td>
<td>not done</td>
</tr>
<tr>
<td>7</td>
<td>myalgia</td>
<td>286</td>
<td>3m</td>
<td>I ; VDF</td>
<td>not done</td>
</tr>
<tr>
<td>8</td>
<td>myalgia, proximal weakness</td>
<td>16890</td>
<td>-</td>
<td>NOT DONE</td>
<td>M YOP</td>
</tr>
</tbody>
</table>

CK, creatine kinase; ΔT, interval of time between withdrawal of drug and biopsy; m, months; y, years; ENMG, Electroneuromyography; RRF, ragged red fiber; IM, inflammatory myopathy; VM, vacuolar myopathy; I, inexplic pathologic findings; VDF, variation of diameter fibers; NL, normal.
reported for muscular aches and 0.1% - 0.2% for myopathies. The latter can be acute with grossly elevated CK, myoglobinuria and renal dysfunction characterizing rhabdomyolysis or generalized muscular aching and/or weakness, mainly in proximal muscles. The incidence of these manifestations rises when fibrates and statins are associated\textsuperscript{3,11}. Moreover, microscopic muscular alterations have been reported, such as variations in the diameter of muscle fibers, necrosis, lymphomononuclear infiltration, vacuoles and ragged red fibers\textsuperscript{11,12}.

The cases we report show clinical manifestations in some subjects such as myalgia (cases 2, 3, 6, 7, 8), hematuria (case 3), proximal muscular weakness (cases 4, 8) and arthralgia (cases 5, 6). In addition, we found unspecific myopathic changes in all muscle biopsies performed (6) which, in conjunction with clinical disturbances and persistently elevated CK levels, imply to muscular compromise resulting from the prolonged use of statins, be this alone or associated with fibrates.

The monitoring of CK levels is considered a useful parameter in tracing myotoxicity in patients using anti-lipemics\textsuperscript{3,8}, including those who are asymptomatic\textsuperscript{5,6}, although there are reports of confirmed toxic myopathy cases with normal muscle biopsy and normal CK\textsuperscript{12}. A rise in CK during therapy with statins is well documented, ranging between 0.1% and 10\%\textsuperscript{6}, usually not exceeding 10 times over the upper limit of normal\textsuperscript{3,5}. When the level surpass this value may occur myoglobinuria and renal dysfunction associated with muscular damage\textsuperscript{5,8,11}. The levels of CK in our cases ranged from 2 to 100 times above normal. Cases 2, 3 and 8 presented a clinical and laboratorial picture compatible with rhabdomyolysis.

Fibrates may have a direct toxic action on muscle cells in
patients with an unrecognized predisposition to myopathy. One of the mechanisms by which they cause muscle damage is by increase in lipoprotein lipase activity. They also led to a defect in the cholesterol-like molecules of muscle membrane, resulting in increased ionic permeability especially to calcium and, as a result, the cascade of myofibre necrosis initiates.

The 3-hidroxi-3-methylglutaryl coenzyme A reductase (HMGG-CoA-reductase) catalyzes the formation of mevalonate from HMGG-CoA, an important precursor of cholesterol, ubiquinone and isoprenylated proteins involved in cellular replication. Statins inhibit the HMGG-CoA-reductase resulting in lower intracellular cholesterol levels. This later is an important component of cell membranes modulating their fluidity and intracellular cholesterol can result in reduced levels of the membrane cholesterol leading to physical changes in this and a decrease in cell proliferation. Such changes can result in a compromising of the Na/K pump function with irreversible damage to the cell.

Ubiquinone (Coenzyme Q10) is used by mitochondria in transporting electrons and in the consequent formation of ATP in the respiratory chain. Hence, HMGG-CoA inhibitors would cause a reduction in ubiquinone synthesis with consequent mitochondrial dysfunction, and changes in the duplication of the myocyte. A reduction in plasmatic and intracellular cholesterol can result in reduced levels of the mitochondrial dysfunction and changes in the respiratory chain activity associated with aging, or accelerate the rate of mitochondrial DNA deletions in skeletal muscle.

In conclusion, in spite of the adverse side effects of the statins on the skeletal muscle, they remain the first choice drugs in the treatment of the dyslipidemias. When side effects, which are rare, are presented, a favorable evolution has been seen. Rhabdomyolysis is a significant side effect of statins even when used without fibrate association. Our results indicate that statins, like fibrates, may induce a chronic myopathy even in the absence of symptoms.

In view of our findings, we recommend performing a muscular biopsy on those patients using anti-lipemics and presenting neuromuscular symptoms, and/or elevated CK levels, with the aim of defining the degree of muscular compromise and thereby establishing the best approach for each patient.

REFERENCES

2. Galiana J, Marchán E, Montés I, Pato S. Miopatías tóxicas en relación...


