Improvement of statin-associated myotoxicity by L-carnitine

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Although statins represent the mainstay therapy for the treatment of hypercholesterolemia and have a positive tolerability and safety profile, the occurrence of statin-associated myopathy, an accepted class effect of these drugs, may be more common than originally thought. In this regard, a recent paper by Phillips and colleagues on the myotoxic effect of statin has been followed by a number of interesting letters and authors’ responses addressing several issues of statin myotoxicity [1,2]. Among them, Toma reasoned that L-carnitine (LC) treatment might have a favorable impact on the incidence of statin-associated therapy [2]. We have recently completed a study in young rodents treated with myotoxic doses of simvastatin, a useful model for statin myotoxicity studies [3], in combination or not with LC and our results strengthen Toma’s proposal in addressing the preventive or therapeutic effect of LC on statin-associated myopathy in human clinical trials. Indeed, our study shows that, at the highest dose of simvastatin, creatine kinase (CK) plasma levels were significantly elevated in treated animals compared with controls and that carnitine coadministration efficiently counteracted plasma CK levels in the former group (Table 1). Statin treatment at the two highest doses also caused a significant elevation of glutamic oxalacetate transaminase (GOT) and glutamic pyruvate transaminase (GPT), which may reflect both hepatic and muscle insult. LC administration did not lead to a significant correction of these two enzymatic indices in statin-treated groups, although, at the highest dose of simvastatin, LC seems to oppose GOT and GPT elevations (Table 1). The beneficial effect of carnitine administration in the simvastatin-treated animals does not seem to be altered to the anation of the pharmacokinetic properties of the statin, since the cholesterol-lowering effect observed at the highest dose of simvastatin was not affected by carnitine (Table 1). Statin-treated animals were also treadmill-tested at a constant 15° angle and a speed of 10 m min⁻¹. As expected, their walking capacity was severely impaired at the highest statin dose (90% of rats fell more than three times overall a period of 5 min walking) compared with controls (no fall over a period of 5 min walking). A marked improvement by adding carnitine to statin treatment was observed (60% of rats fell more than three times over a period of 5 min walking).

The majority of the specific myotoxic actions described in the literature seem to indicate that muscle membrane represents a common pathogenetic target of statins’ mode of action [4]. Since several cellular functions rely on the integrity of biological membranes (i.e. ionic homeostasis, signal transduction, com-

<table>
<thead>
<tr>
<th></th>
<th>GOT  U L⁻¹</th>
<th>GPT  U L⁻¹</th>
<th>CK   U L⁻¹</th>
<th>Cholesterol mg dL⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (14)</td>
<td>140</td>
<td>45</td>
<td>1056</td>
<td>72.0 ± 6.5</td>
</tr>
<tr>
<td>Simvastatin 70 mg kg⁻¹ (10)</td>
<td>96–196</td>
<td>40–57</td>
<td>477–1616</td>
<td>98–237</td>
</tr>
<tr>
<td>Simvastatin 140 mg kg⁻¹ (8)</td>
<td>139–293.8</td>
<td>40–98</td>
<td>417–1836</td>
<td>139–293.8</td>
</tr>
<tr>
<td>Simvastatin 210 mg kg⁻¹ (9)</td>
<td>172–5288</td>
<td>35–495</td>
<td>880–4887</td>
<td>172–5288</td>
</tr>
<tr>
<td>Simvastatin 70 mg kg⁻¹ plus LC 200 mg kg⁻¹ b.i.d. (9)</td>
<td>100–204</td>
<td>38–77</td>
<td>442–1840</td>
<td>100–204</td>
</tr>
<tr>
<td>Simvastatin 140 mg kg⁻¹ b.i.d. (9)</td>
<td>209</td>
<td>57</td>
<td>762*</td>
<td>57.3 ± 14.8</td>
</tr>
<tr>
<td>LC 200 mg kg⁻¹ b.i.d. (9)</td>
<td>112–373</td>
<td>42–138</td>
<td>350–1455</td>
<td>112–373</td>
</tr>
<tr>
<td>Simvastatin 210 mg kg⁻¹ b.i.d. (9)</td>
<td>435</td>
<td>78</td>
<td>741*</td>
<td>45.2 ± 14.1</td>
</tr>
<tr>
<td>LC 200 mg kg⁻¹ b.i.d. (9)</td>
<td>134–2422</td>
<td>52–495</td>
<td>535–2425</td>
<td>134–2422</td>
</tr>
</tbody>
</table>

Young male Wistar rats weighing 45–50 g (about 23 days old) received three different doses of simvastatin (70, 140 and 210 mg kg⁻¹) alone and in combination with LC (200 mg kg⁻¹, b.i.d.) for 9 days. Twenty-four hours after the last treatment, blood was collected and plasma CK, GOT, GPT and cholesterol levels were analyzed with Roche diagnostic kit. Since serum enzymatic activities showed a highly skewed distribution, a non-parametric Wilcoxon signed rank test was used to evaluate statistically significance differences. Cholesterol data were evaluated with an analysis of variance followed by the Bonferroni t-test. P < 0.05 was the criterion for statistical difference. Groups’ comparison: control vs. simvastatin, and simvastatin vs. simvastatin plus LC. *P < 0.05; **P < 0.002. Data are expressed as median and range or mean ± SD. Numbers of animals are indicated between parentheses.

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plex lipid metabolism, etc.), any intervention affecting supramolecular organization of the membrane bilayer may lead to dramatic changes of those function/activities residing on muscle membranes. LC is one of the major drivers of mitochondria-based energy production processes. However, supraphysiological LC levels may alter cellular integrity and viability of cells exposed to a variety of adverse conditions by other mechanisms mainly operating through a dual metabolic and biophysical intervention on plasma membrane [5,6]. Statin treatment has also been shown to cause a moderate muscle LC deficiency in rabbits [7], though overt myotoxicity is only observed in much more severe LC deficiency conditions [8]. Irrespective of the precise nature of LC’s beneficial action, our rodent study further supports the concept that human studies should be performed to quantify the potential protective effect of LC administration in statin-associated myotoxicity in man.

Conflict of interest

The authors certify that they are affiliated to organizations with a direct financial interest in the materials discussed in the Letter to the Editor. A.A. is the CEO of Iperboreal Pharma Srl, A.P., F.G. and P.C. are employees of Sigma Tau Pharmaceuticals Spa.

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First identification and expression of a type 2N von Willebrand disease mutation (E1078K) located in exon 25 of von Willebrand factor gene

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In type 2N von Willebrand disease (VWD), von Willebrand factor (VWF) is characterized by a markedly decreased affinity for factor (F)VIII and a recessive inheritance pattern. The FVIII binding domain has been localized within a fragment corresponding to the first 272 amino acid residues of mature VWF (aa 764–1035) encoded by exons 18–23 [1]. Most of type 2N VWD patients have been found to harbor missense mutations in the VWF D’ domain (aa 769–865) encoded by exons 18–20 [http://www.shef.ac.uk/vwf/]. The R854Q mutation, in exon 20, is the most frequent mutation identified, on at least one allele, in 90% of type 2N VWD patients studied thanks to the French INSERM Network (unpublished data). Until now, only the Q1053H and C1060R mutations in exon 24 [2] and the C1225G mutation in exon 27 of VWF gene [3] have been identified outside the N-terminal FVIII binding domain of VWF.

We report here on the identification of a new VWF gene defect in a 24-year-old French male patient with a history of...