When Nutraceuticals Reinforce Drugs Side Effects: A Case Report

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Abstract: Introduction: Nutraceutical is a term applied for a plethora of products ranging from isolated nutrients, herbal products to dietary supplements and recently, the interest for a nutraceutical approach to lipid and metabolic disorders is growing. Patients with metabolic conditions seem to appreciate a therapeutic management that does not involve drug treatment, particularly for the side effects due to statins, a class of drug used for lipid disorders. Statins directly induce skeletal muscle injury and in elderly patients, under polytherapy treatments, this risk relies to an increase of adverse drug reactions due to drug interactions.

Case Description: Herein we report a 70-year-old woman under polytherapy, who develops rhabdomyolysis after starting the administration of a dietary supplement containing monacolin K. Using the Drug Interaction Probability Scale we postulated that rhabdomyolysis was possibly related to a drug interaction between sertraline, rosuvastatin and monacolin K. These treatments were discontinued leading to a remission of both clinical symptoms and biochemical parameters.

Conclusion: This case report highlights how pharmaceutical treatment must be periodically reassessed, since elderly people could take drugs by themselves when they don’t need.

Keywords: Nutraceutical, interaction, rhabdomyolysis, rosuvastatin, sertraline, red yeast rice.

INTRODUCTION

Nutraceutical is a term applied for a plethora of products ranging from functional foods (i.e. products that beneficially affect one or more target functions in the body, beyond adequate nutritional effects), food supplements (i.e. concentrated source of nutrients or other substances with a nutritional or physiological effect) to dietary foods (i.e. complete foods with a standard nutrient formulation which may constitute the only source of nourishment for a designed person), able to provide health benefits [1].

Even if their use is increasing among the general population, very low data have been published concerning their safety. In a recent paper, Geller and coworkers [2] evaluating surveillance data from 63 emergency departments in the United States obtained from 2004 through 2013, estimated that 23,005 emergency department visits/year were attributed to adverse events related to dietary supplements.

The risk of an adverse event is related to age of the patient but also to the co administered drug. In fact, recently Felix et al. [3], reported that the potential for the development of adverse drug reactions during the treatment with dietary supplements can be amplified in elderly patients or those taking multiple prescription drugs; this may be related with the development of drug interactions (DI) involving all the phases of the pharmacokinetic of each drug.

It has been reported that hypolipidemic supplements, such as monacolin K, are also able to evoke myopathy and rhabdomyolysis [4]. Here we report a case where a nutraceutical (Armolipid plus®) reinforced drug side effects inducing rhabdomyolysis by DI in an elderly patient.

CASE SUMMARY

On 16th October 2013, a 70-year-old woman lamented acute muscular pain, with muscular weakness and reduced mobilization of limbs. Clinical examination performed by orthopedist excluded bone damage and neurological failure. Her clinical history revealed the presence of hypercholesterolemia, hypothyroidism, blood hypertension, Parkinson’s disease and depression, for that she was treated with rosuvastatin (5 mg o.d.; daily dose 5 mg), levothyroxine (100 mcg o.d.; daily dose 100 mcg), perindopril plus indapamide (2.5/0.625 mg o.d.; daily dose perindopril 2.5 mg and indapamide 0.625 mg) pramipexole (0.18 mg 1 and ½ tablets in the morning and two tablets at bedtime; daily dose 0.63 mg) and sertraline (150 mg o.d.; daily dose 150 mg), respectively. Biochemical laboratory parameters3 days
Table 1. Biochemical laboratory parameters recorded in a 70-year-old woman at the time of the first examination (16th October 2013), at the time of the hospital admission (19th October 2013) and one month after the discontinuation of rosvastatin and red yeast rice, and the change of sertraline with escitalopram (29th November 2013).

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>16th October</th>
<th>19th October</th>
<th>29th November</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine Phosphokinase</td>
<td>82</td>
<td>4,800</td>
<td>85</td>
<td>0-180 IU/L</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td>197</td>
<td>880</td>
<td>208</td>
<td>240-480 IU/L</td>
</tr>
<tr>
<td>Aspartate Aminotransferase</td>
<td>28</td>
<td>255</td>
<td>29</td>
<td>0-30 IU/L</td>
</tr>
<tr>
<td>Alanine Aminotransferase</td>
<td>22</td>
<td>80</td>
<td>31</td>
<td>0-34 IU/L</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>98</td>
<td>1000</td>
<td>101</td>
<td>&lt;106 mcg/L</td>
</tr>
<tr>
<td>Troponin I</td>
<td>-</td>
<td>0.09</td>
<td>-</td>
<td>&lt;0.013 mcg/L</td>
</tr>
</tbody>
</table>

Later the admission to hospital (19th October 2013) revealed the presence of muscular failure (Table 1). Cardiac failure was excluded. The patient reported that about 15 days before the admission she started one tablet/day of an oral dietary supplement containing natural substances: policosanol (10 mg/table), red yeast rice (200 mg/table), berberine (588 mg/table), folic acid (200 mcg/table) coenzyme Q10 (2 mg/table) and astaxanthin (0.5 mg/table).

Pharmacological assessment revealed the possible relationship among sertraline, rosvastatin and red yeast rice (present in the dietary supplement). Using the Drug Interaction Probability Scale (DIPS) [5], we estimated that the DI among the active ingredients mentioned above, was probably involved in the development of rhabdomyolysis (DIPS score: 5). Therefore both rosvastatin and the dietary supplement were discontinued, while sertraline was changed to escitalopram (10 mg o.d.; daily dose 10 mg) because it shows a low risk of drug interactions. One month later (29th November), during the follow-up, clinical and laboratory finding revealed a complete remission of both, clinical symptoms and biochemical parameters (see Table 1), but documented an increase in blood lipid plasma levels (total cholesterol: 285 mg/dL, normal values <200 mg/dL; LDL cholesterol 142 mg/dL, normal values: <100 mg/dL; HDL cholesterol 46 mg/dL, normal values >45 mg/dL), therefore rosvastatin (5 mg o.d.; daily dose 5 mg) was added. During the follow-up performed about 3 months later (06th March 2014), no symptoms of depression appeared (Geriatric Depression Scale score 8/30), plasma cholesterol levels were in normal range (total cholesterol: 198 mg/dL; LDL cholesterol 99 mg/dL), without increase in rhabdomyolysis markers (Creatinine Phosphokinase: 84 IU/L; Lactate Dehydrogenase 202 IU/L; Aspartate Aminotransferase 29 IU/L; Myoglobin 97 mcg/L). At the time of writing (November 2015, about two years later), no adverse drug reactions appeared.

**DISCUSSION**

In this case, we report the development of rhabdomyolysis possibly related to a drug-nutraceutical interaction. Previously, we documented the development of generalized dermatitis and itch induced by a possible drug-food interaction [6], moreover, we also reported that both sertraline and rosvastatin are able to induce rhabdomyolysis [7, 8].

In our patient, the co-administration of sertraline (150 mg/day), rosvastatin (5 mg/day) and of dietary supplement (1 table/day) containing red yeast rice induced the development of rhabdomyolysis.

Since benefits of statins are well documented [9], myopathy or rhabdomyolysis, have been associated with the use of statins; this effect is dose-related [10] and could be associated with pharmacokinetic interactions [8].

On the other hand, the development of myopathy and rhabdomyolysis was also described in patients treated with monacolin K [4]. It is worth to note that red yeast rice contains monacolin K that has the identical biochemical/pharmacological action of lovastatin and is able per se to induce rhabdomyolysis [11, 12].

Moreover, recently Philibert et al. [13] evaluating the French national pharmacovigilance database and in scientific literature, documented the development of muscular disorders in patients treated with monacolin K.

Even if yeast rice and rosvastatin, have a direct effect on skeletal muscle tissue, other drugs such as benzodiazepines, antihistamines, barbiturates and antidepressants, are also able to predispose patients to the development of rhabdomyolysis [14].

In the present case, our patient received a treatment with Selective Serotonin-Reuptake Inhibitors (SSRIs). Labotz and coworkers [15] reported the development of rhabdomyolysis in three patients treated with SSRIs after performing 15 sets of 15 repetitions of maximal eccentric contractions of the elbow flexors, suggesting that SSRIs may represent a predisposing factor to muscle injury after eccentric exercise. Moreover, Gareri and co-workers [7] reported a 71-year-old woman with co-morbidity that developed rhabdomyolysis after the administration of sertraline (50 mg/day), supporting a role of sertraline in the development of this ADR probably related to genetic factor (e.g. Genetic defects of sertraline demethylation and/or P-glycoprotein binding).

Finally, the development of rhabdomyolysis may also be related to drug overuse. In fact, in a retrospective study Wilson et al., [16] documented the development of acute muscle injury in patients who ingested larger quantities of venlafaxine (mean 2800 mg/day).

However, the development of rhabdomyolysis was also documented in a 21-year-old woman treated with low dosages of venlafaxine (37.5 mg/day) [17].
In our patient, we can exclude a role of exercise as a factor able to increase the risk of rhabdomyolysis. Furthermore we cannot rule out that this ADR might be related to genetic factors, involving the absorption and the metabolism and the of the drugs (e.g. cytochrome P450 and P-glycoprotein polymorphisms) [18]. However, we did not perform the therapeutic drug monitoring of drugs therefore we cannot exclude a drug overuse, and this represents a limit of this case, even if the patient and her parents referred to the use of standard dosage of each drug.

The discontinuation of both rosuvastatin and dietary supplement and the change of sertraline to escitalopram induced the complete remission of the clinical symptoms, and using the DIPS scale we postulated that a DI probable induced the development of rhabdomyolysis.

Although, nutraceuticals are over-the-counter drugs, without doubt they are not less dangerous than others due to their pharmacokinetic and pharmacodynamic interactions and our patient reported that she was taking the dietary supplement without her physician’s consultation. The present case is indicative for an inappropriate use of a dietary supplement to whoever was already under rosuvastatin and sertraline treatments.

The type of study, case report, represents another limit of this presentation and post-marketing drug safety surveillance data (e.g. voluntary spontaneous reports of adverse events from consumers and health care professionals) are necessary to validate this observation. However, we think that a surveillance system for a closer monitoring of the safety of nutraceutical substances may be useful to evaluate their safety in particular types of patients, i.e. elderly and patients in poly-therapy.

This case report highlights how pharmacological treatment must be periodically reassessed, since elderly people could take drugs by themselves when they do not need them. The reassessing of the therapy could also improve elderly patient’s psychosocial comfort, their quality of life and costs for their assistance. In fact, in agreement with our previously reports, the development of ADRs due to an inappropriate use, is an alert for physicians/pharmacists in order to carefully evaluate the co-administration of drugs and dietary supplements [19]. This concern is particularly important for elderly people, who often take a relevant daily number of drugs.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES


PATIENT’S CONSENT

Declared none.

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