Is Simvastatin harmful in children? A case report

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Abstract
Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease in children living in Western countries. Hyperlipidemia, obesity and insulin resistance are common components of the metabolic syndrome, which is frequently associated with NAFLD. Since patients with NAFLD are at high risk to develop cardiovascular disease (CVD), statins are frequently prescribed to patients with NAFLD and hyperlipidemia. The 3-Hydroxy-3-methylcoenzyme A reductase (HMG-CoA reductase) is the rate limiting enzyme in cholesterol biosynthesis. Simvastatin is a lactone that is readily hydrolyzed “in vivo” to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Under treatment with simvastatin, an improvement of enzymatic antioxidant parameters has been described in subjects with hypercholesterolemia. The safety and effectiveness of statins in pediatric patients with NAFLD or non-alcoholic steatohepatitis (NASH), and their effect on hepatic fat infiltration or tachyphylaxis, are among the most widely prescribed drugs in the pediatric NAFLD population. NAFLD and their effect on hepatic fat infiltration or the extent of hepatic fibrosis are not known. Also, no evidences of the effects of a non-therapeutic ingestion of this drug on the glutathione homeostasis and in children have been reported. We describe the case of an obese 4-year-old girl in whom an accidental overdose of simvastatin led to decrease levels of glutathione in blood with increase of the GSSG/GSH ratio. No adverse reactions were registered. All laboratory tests were normal during the follow up. Only a 35% decrease of Glutathione was observed such as a possible mechanism of mitochondrial toxicity and depletion of the glutathione pool after the intake of excessive dose of HMG-CoA reductase inhibitors. Further RCTs are needed in order to establish the safety and efficacy to use of statin for pediatric NAFLD or NASH.

Keywords: Steatohepatitis, Statins, Drug safety, Metabolic Syndrome

1. Introduction
The epidemics of overweight and obesity has resulted in a significant increase of non alcoholic fatty liver disease (NAFLD), a potentially progressive condition. NAFLD is an asymptomatic disease that can progress to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma. Obesity, hyperlipidemia and diabetes mellitus are common components of the metabolic syndrome, which is frequently associated with NAFLD. The pathogenesis of NAFLD is currently unknown, but accumulating data suggest that insulin resistance, oxidative stress, lipotoxicity, and altered redox balance play a crucial role in the pathogenesis of steatosis, steatohepatitis, and fibrosis.

Currently, the treatment of pediatric NAFLD focuses on lifestyle modification and gradual weight loss. However, there is mounting interest in other multitarget pharmacological agents as potential treatment for liver steatosis that has been tested not only in animal models but also in human adults and in children.

Since patients with NAFLD are at high risk to development cardiovascular disease (CVD), statins are frequently prescribed to patients with NAFLD and dyslipidemia. Statins, which are among the most widely prescribed drugs in the world, play a significant role in decreasing cardiovascular risk associated with nonalcoholic steatohepatitis (NASH), including the metabolic syndrome and type 2 diabetes mellitus.

Statins (hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors) are the mainstay of lipid lowering drug therapy in patients with hyperlipidemia. Simvastatin (SMV) is a competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which catalyzes the rate limiting step in cholesterol biosynthesis.
This enzyme converts 3-hydroxy-3-methylglutaryl- coenzyme A (HMG CoA) to mevalonate, a precursor of both cholesterol and ubiquinone, a central compound of the mitochondrial chain. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells stimulating the synthesis of LDL receptors and thereby increasing the uptake of LDL particles. The final result is a reduction of the plasma cholesterol concentration.

The available data indicate that statins can be usefully and well tolerated in adult. Over the last decade, several retrospective and prospective studies and one randomized clinical trial (RCT) have established that statins are safe in patients with liver disease, and there is no evidence that patients with chronic liver disease, including at NAFLD and NASH, are at higher risk for serious liver injury from statins than those without liver disease. The safety and effectiveness of statins in pediatric patients with NAFLD or NASH, and their effect on hepatic fat infiltration or the extent of hepatic fibrosis are not known. Clinical use of statins is common but there are few reports of children overdoses in literature. Given the lack of evidence to show that patients with NAFLD and NASH are at increased risk for serious drug-induced liver injury from statins, statins can be used to treat dyslipidemia in adult patients with NAFLD and NASH. We report the case of an accidental overdose of simvastatin in a 4 years old obese girl.

2. Case report

A 4 year old female was brought to Emergency Department of Bambino Gesù Children’s Hospital, Rome, Italy after 90 minutes from an accidental ingestion of 8 tablets of Simvastatin, which contained 40 mg of Simvastatin per tablet. Her physical examination revealed normal findings, with a body weight and height of 25 kg (>97°centile) and 110 cm (95°centile) respectively. Laboratory parameters showed: aspartate aminotransferase (AST) 35 IU/L, alanine aminotransferase (ALT) 27 IU/L, g-glutamyltransferase (GGT) 14 IU/L, lactate dehydrogenase (LDH) 488 UI/L, total cholesterol 155 mg/dl, (90-97°pc), triglycerides 101 mg/dl, glicemia 82 mg/dl, uric acid 3.2 mg/dl. Bilirubin, albumin, creatin kina and prothrombin time were within the reference range. The blood pressure, the respiration rate, pulse rate and body temperature were 100/60 mmHg, 112/min, 24/min and 35.5°C respectively. A total of 20 grams of activated charcoal were administrated (0.8 gram/kilogram body weight) at her arrival to Emergency Department.

Laboratory analyses were performed after 2 hours from ingestion (complete blood count, liver and renal function test, serum electrolytes, creatine kinase (CK), blood lactate, arterial blood gas analyses). We also measured Simvastatin level in the blood at 2, 4 and 6 hours after simvastatin ingestion.

The patient’s serum statins level, performed using high-pressure liquid chromatography/mass spectrometry (HPLC/MS) technique, was 60 ng/ml in the first sample, while in the other two samples resulted undetectable.

A clinical follow-up at 2 weeks and at 3 months from admission was performed. No adverse reactions were registered. All laboratory tests were normal. Our attention has been especially focused on CK levels because, even if statins are well tolerated, they can cause myopathy that ranges from transient increases in CK to serious muscle toxicity, including rhabdomyolysis. CK was always normal.

Glutathione levels were also evaluated on blood samples at the first follow up after 15 days (T1) and after 3 months (T2) from the ingestion. Furthermore, as simvastatin toxicity may occur through several mechanisms, such as the inhibition of mitochondrial respiratory chain with increased oxidative stress, and/or the depletion of mitochondrial glutathione pool, during the follow up we also assayed Glutathione in lymphocytes and the ratio between its reduced (GSH) and oxidized form (GSSG), which are good indicators of the tissue redox environment. Interestingly, after two weeks from ingestion we found a 35% decrease of Glutathione that was associated with a 60% increase of the GSSG/GSH ratio, respect to normal values. After 3 months, however, both levels were normalized (Table 1), indicating a transient and reversible response of the antioxidant system to the acute toxic insult.

### Table 1: Glutathione levels and ratio between its reduced (GSH) and oxidized form (GSSG) during the follow up

<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutathione (nmol/mg proteins)</td>
<td>15</td>
<td>27</td>
<td>23-68</td>
</tr>
<tr>
<td>GSSG/GSH ratio</td>
<td>0.16</td>
<td>0.10</td>
<td>0.04-0.10</td>
</tr>
</tbody>
</table>

3. Discussion

NAFLD is progressive liver disease recognized as the hepatic manifestation of metabolic syndrome. Recent studies demonstrated that NASH may be a leading cause of cryptogenic cirrhosis, so effective therapies are needed to ameliorate inflammation, hepatic steatosis, and fibrosis, and to prevent the progression to cirrhosis and hepatocellular carcinoma.

Statins have been proposed as therapy for patients with either NAFLD or NASH in view of their anti-inflammatory and anti oxidative mechanisms. Statins are an important class of agents to treat dyslipidemia that have been considered to exert pleiotropic effects on cardiovascular system. As reported by different studies statins reduce the risk of cardiovascular events in patients with diabetes mellitus, and other causes of atherosclerosis in adult. Independently of their hypocholesterolemic activity, statins have anti-inflammatory, immunomodulatory, antioxidative, anti thrombotic actions, as well as an antibacterial effects such as reported by different studies in vitro and in vivo. Several studies have suggested that statins may improve liver biochemistries and histology in adult patients with NASH.
These studies consisted of small number of patients and have not been rigorously designed\textsuperscript{27-29}. Compared to that found in the placebo-treated patients, Nelson et al., in a randomized double blind placebo-controlled trial, reported no significant improvement in the serum aminotransferase activity, the severity of hepatic steatosis, and the degree of hepatic inflammation\textsuperscript{28}. In a small group of 26 patients with NAFLD and metabolic syndrome (without liver histology), who were treated daily with 20 mg simvastatin for 6 months, Abel et al. show that simvastatin was safe and effective to decreases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities and in serum LDL-cholesterol levels\textsuperscript{29}.

Safety of statins in pediatric population has been evaluated in controlled studies and at therapeutic dosage\textsuperscript{29,30}. The largest double blind randomized placebo controlled multicenter trial with simvastatin in children aged 10 to 17 years by De Jongh and colleagues demonstrated no serious adverse drug events\textsuperscript{31}. Another recent double blind randomized, placebo-controlled, multicenter trial involved lovastatin in 54 postmenarchal females with familiar hyperlipidemia. There were no clinically significant adverse effects observed over a 6 month period\textsuperscript{32}.

In this study, we report the case of a simvastatin overdose (320 mg) in a 4 year old obese girl without any side effects. The therapeutic dose of simvastatin is from 5 to 80 mg daily in adults\textsuperscript{33,34}. Single doses up to 200 mg of lovastatin are well tolerated without significant adverse inflammatory and oxidative mechanisms are involved in the pathogenesis of NAFLD or NASH, effects in adult human volunteers. Overdoses up to 5-6 grams of lovastatin are well tolerated in adults without any symptoms\textsuperscript{35}. The maximum reported dose of simvastatin ingestion in adults is 3.6 g with no specific symptoms. Simvastatin is a lipophilic compound showing antioxidant effect both in vitro and in vivo\textsuperscript{34}. Its pharmacologically active form is a potent inhibitor of 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A reductase, the rate limiting enzyme in cholesterol biosynthesis\textsuperscript{34,36}. Under treatment with simvastatin, an improvement of enzymatic antioxidant parameters has been described in subjects with hypercholesterolemia\textsuperscript{34}, but so far no evidences of the effects of a massive ingestion of this drug on the glutathione homeostasis have been reported.

In the medical there is limited experience with overdosage of statins in children\textsuperscript{35,37}. Only case reports of suspected overdose with fluvastatin sodium in children including a 2 year old and 3 years of age. The maximum amount of fluvastatin sodium that could be ingested was 80 mg. Neither child experienced any adverse symptoms\textsuperscript{35,37}.

Glutathione plays an important role in detoxification of free radicals\textsuperscript{38}. It is required for the recycling of vitamin C and acts as a substrate for several enzymes involved in preventing the deleterious effect of free radicals. The balance between the reduced (GSH) and oxidized (GSSG) glutathione forms (GSSG/GSH ratio) is critical for the tissue redox environment and its increase may be a marker of oxidative stress/damage\textsuperscript{39,40}. The measurement of free glutathione in blood samples is essential for evaluating the redox and detoxification status of cells in relation to its protective role against oxidative-mediated cell injury.

Poisoning of drugs like statins may induce mitochondrial toxicity and depletion of the glutathione pool\textsuperscript{19}. Upon acute simvastatin ingestion, we found an imbalance of the glutathione homeostasis, with a decrease of GSH levels and an increase of the GSSG/GSH ratio. Thus, the organism reacts to high concentrations of simvastatin by activating the first line of antioxidant defense represented by the glutathione system. The observed GSH decrease may be due to its increased utilization as scavenger of free radicals, or as a co-substrate for antioxidant enzymes (such as glutathione-peroxidase, glutathione S-transferase, glutathione reductase). In addition, GSH may be also conjugated to simvastatin, leading to the formation of glutathione-adducts\textsuperscript{20}. Noteworthy, after 3 months we however observed a recovery of glutathione levels, indicating the effectiveness of the buffering response to the drug. At this stage, we have not carried out the research of simvastatin in the blood, because it was already absent at the sixth hour after taking.

Nevertheless, the patient presented no clinical signs of myopathy or rhabdomyolysis or other clinically adverse experiences such as reported in the literature\textsuperscript{18}. We cannot exclude that promptly treatment with activated charcoal after 90 minutes from the ingestion of simvastatin may have a role in the reduction of the drug absorption.

4. Conclusion

There are several studies about the therapeutic use of simvastatin in pediatric patients, but literature has not revealed specific studies of pharmacodynamics of simvastatin in children. There are no descriptions of the range of toxicity for children. In our report we demonstrate that a total of 320 mg of simvastatin ingested from a 4 years old obese girl, treated with activated charcoal at 90 minutes from her arrival in Emergency Department, was fairly safe without any clinical signs, except for a temporary decrease in the antioxidant capacity of the cell and that the Glutathione level on blood can be helpful to identify cell-injury simvastatin-induced.

On the basis of the results of studies on adult patients, statins are safe and efficacious in patients with either NAFLD or NASH, and some of these agents can induce significant decreases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities and in serum LDL-cholesterol levels, a reduction in the extent of the hepatic steatosis, and a to reduce the degree of hepatic inflammation and the extent of hepatic fibrosis. To date, there are no study on efficacy and safety of simvastatin in pediatric NAFLD. More RCTs are needed in order to establish the suitable statin for patients with NAFLD or NASH with or without hyperlipidemic. Another purpose of these RCTs should also assess whether combination therapy of statin with agents antioxidants such as omega-3 fatty acids, insulin sensitizing agents or ursodeoxycholic acid, can achieve better clinical results than those achieved with monotherapy. Further studies are necessary to confirm these results.
References


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