European Journal of Pharmaceutical Sciences 100 (2017) 163–175

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Hyperlipidaemia alone and in combination with acidosis can increase the incidence and severity of statin-induced myotoxicity

Dhiaa A. Taha [a], Atheer Zgair [a,b], Jong Bong Lee [a], Cornelia H. de Moor [c], David A. Barrett [c], Kimberley D. Bruce [d], Mitchell Sungelo [d], Robert H. Eckel [d], Pavel Gershkovich [a,*]

[a] Division of Medicinal Chemistry and Structural Biology, School of Pharmacy, University of Nottingham, Nottingham, UK
[b] College of Pharmacy, University of Anbar, Anbar, Iraq
[c] Division of Molecular and Cellular Science, School of Pharmacy, University of Nottingham, Nottingham, UK
[d] Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

ARTICLE INFO

Article history:
Received 9 September 2016
Received in revised form 9 January 2017
Accepted 16 January 2017
Available online 16 January 2017

Chemical Compounds Studied in This Article:
Simvastatin lactone (PubChem CID: 54454)
Simvastatin hydroxy acid (PubChem CID: 64718)
Pravastatin lactone (PubChem CID: 9931182)
Pravastatin hydroxy acid (PubChem CID: 54687)

Keywords:
Acidosis
Chylomicrons
Hyperlipidemia
Lipoproteins
Myotoxicity
Statins

ABSTRACT

The association of lipophilic statins with plasma lipoproteins in the presence of disturbed acid-base balance can modify the pharmacokinetics and tissue distribution of these drugs, resulting in alteration in their efficacy and toxicity profiles. The purpose of this study is to elucidate the role of hyperlipidaemia alone or in combination with acidosis/alkalosis in the development and potentiation of statin-induced myotoxicity. Statins association with plasma lipoproteins was examined under conditions of physiological and altered pH levels. The effect of this association on cellular uptake and myotoxicity of statins was also assessed at different pH levels using C2C12 cells that overexpress lipoprotein lipase. Lipophilic simvastatin displayed considerable association with the non-polar lipoprotein fractions (triglyceride-rich lipoproteins and low-density lipoprotein). This association contributed to increased cellular uptake of simvastatin by C2C12 cells through lipoprotein lipase-mediated process, resulting in enhanced muscle toxicity in hyperlipidaemic conditions. Furthermore, a combination of low pH environment (representing acidosis) and hyperlipidaemia increased the association of simvastatin with plasma lipoproteins causing potentiation of cellular uptake and myotoxicity of this drug. Comorbidities such as hyperlipidaemia, especially when coincident with acidosis, can enhance statin-associated muscle toxicity, and therefore require extra caution by prescribing clinicians. Hydrophilic rather than lipophilic statins could be a preferable choice in this patient population.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Statins are essential pharmacotherapy for patients with ischemic heart disease and dyslipidaemia (Perk et al., 2012; Stone et al., 2014). However, these drugs have the potential to cause serious side effects such as muscle-related toxicity and hepatotoxicity. Statins are classified into hydrophilic or lipophilic compounds based on their physicochemical properties and tissue selectivity (Hamelin and Turgeon, 1998; Joshi et al., 1999). These drugs are available either as lactone or hydroxy acid forms. In general, the lactone forms of statins are more lipophilic, and indeed, more myotoxic than the corresponding hydroxy acid forms owing to their lipophilicity (Schirris et al., 2015; Skottheim et al., 2008).

It has been estimated that, in clinical practice, about 10% of patients receiving high-dosage statin therapy develop statin-induced myotoxicity (Bruckert et al., 2005). The exact mechanism of statin-induced myotoxicity remains largely unclear. Comorbidities including conditions such as hepatic or renal failure, hypothyroidism, and diabetes mellitus are among the most important risk factors that have been shown to predispose patients to statin-induced myotoxicity (Taha et al., 2014). We have previously reported that disturbances in acid-base balance, such as acidosis or alkalosis, could influence the toxicity profile of statins. Acidosis increases the proportion of lipophilic lactone form,

Abbreviations: hLPL, human lipoprotein lipase; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; LPDP, lipoprotein-deficient plasma; mLPL, mouse lipoprotein lipase; MTT, thiazolyl blue tetrazolium bromide; MSCV, murine stem cell virus; SV-LDL, simvastatin-loaded low-density lipoprotein; SV-Sol, simvastatin solution; SV-TRL, simvastatin-loaded triglyceride-rich lipoproteins; TRL, triglyceride-rich lipoproteins.

* Corresponding author at: School of Pharmacy, Centre for Biomolecular Sciences, University Park, The University of Nottingham, Nottingham NG7 2RD, UK.
E-mail address: pavel.gershkovich@nottingham.ac.uk (P. Gershkovich).

http://dx.doi.org/10.1016/j.ejps.2017.01.018
0928-0987/© 2017 Elsevier B.V. All rights reserved.

promotes accumulation of statins in skeletal muscle cells and enhances statin-induced myotoxicity in vitro (Taha et al., 2016).

Association with plasma lipoproteins has been shown to modify the pharmacokinetics, tissue distribution and pharmacological activity of lipophilic drugs (Wasan and Cassidy, 1998; Yeganeh and Mclachlan, 2002). For example, increased association with low-density lipoproteins (LDL) has been linked to higher nephrotoxicity of amphotericin B and cyclosporine (Luke et al., 1992; Wasan and Conklin, 1997).

Transient elevation in triglyceride-rich lipoproteins (TRL), mainly chylomicrons, occurs following the ingestion of a high-fat meal (Gershkovich and Hoffman, 2007). These lipoproteins are the major carriers of lipids in the systemic circulation, and can also serve as potential carriers for lipophilic statins (Simon et al., 1997; Wasan and Cassidy, 1998). Similarly, pathological hyperlipidaemia is associated with elevated levels of some lipoproteins (very low-density lipoprotein [VLDL] and LDL). Lipophilic statins can associate with plasma lipoproteins in the general circulation, and this, in turn, can facilitate their delivery to peripheral tissues. Lipoprotein lipase (LPL) present at the surface of the capillary endothelium of cardiac and skeletal muscle and adipose tissue mediates the hydrolysis of triglycerides within the TRL to fatty acids and monoacylglycerol. Released free fatty acids are then transported across cell membranes to the tissues of LPL synthesis and secretion (Wang and Eckel, 2009). This process could be accompanied by an increase in the uptake of lipoprotein-associated lipophilic statins by the skeletal muscle. In addition, LPL also mediates the internalisation of LDL into cells as reported in several studies (Obunike et al., 1994; Rumsey et al., 1992), which could be an additional mechanism of enhanced intracellular accumulation and toxicity of statins in hyperlipidaemic state. Therefore, the administration of lipophilic statins to patients with pathological or postprandial hyperlipidaemia could potentially contribute to enhanced muscle toxicity.

The coincidence of hyperlipidaemia with acidosis could augment the myotoxicity of statins even further. This is because acidosis, as we have previously demonstrated (Taha et al., 2016), increases the proportion of lipophilic lactone form of statins in the general circulation and skeletal muscle. This can contribute to statin-induced muscle toxicity by increasing the association of lactone form with plasma lipoproteins, and increasing the intracellular concentration of statins by LPL-mediated mechanism.

Both acidosis and hyperlipidaemia are quite common among statin users. Most patients using statins have abnormal plasma lipoproteins levels. It is common for clinicians to recommend such patients to use unsaturated fat and fatty acids such as olive oil for prevention of cardiovascular and atherosclerotic diseases (Buttar et al., 2005). The use of these oils is associated with transient elevation in plasma TRL, mainly chylomicrons (Jespersen et al., 2001). In addition, many patients on statins have multiple co-morbidities such as diabetes mellitus, cardiovascular and renal diseases. These conditions are risk factors for development of metabolic acidosis (Köse et al., 2014).

To the best of our knowledge, there are no previously reported studies which examined the influence of hyperlipidaemia, or a combination of hyperlipidaemia and acidosis, on the myotoxic potential of statins. Therefore, the aim of this study is to assess the effect of hyperlipidaemia alone and in combination with acidosis/alkalosis on development and severity of statin-induced myotoxicity.

2. Materials and Methods

2.1. Materials

Simvastatin lactone (99.3%) and pravastatin hydroxy acid sodium (99.4%) were purchased from Kemprotec Ltd. (Lancashire, UK). Pravastatin lactone (98%) and simvastatin hydroxy acid ammonium salt (98.0%) were obtained from Toronto Research Chemicals Inc. (Toronto, Canada). Thiazolyl blue tetrazolium bromide (MTT) was purchased from Alfa Aesar (Lancashire, UK). Dulbecco's modified eagle medium (42430025-DMEM, high glucose, HEPES without sodium pyruvate) was purchased from GIBCO-Invitrogen. Pooled hyperlipidaemic human plasma was obtained from Biological Specialty Corporation (Pennsylvania, USA). LPL activity fluorometric assay kit and total cholesterol and cholesteryl ester colorimetric assay kit were purchased from T/A Source BioScience Ltd. (Wiltshire, UK). Microsep™ advance centrifugal device with Omega™ membrane was obtained from VWR International Ltd. (Leicestershire, UK). Triglyceride reagent, free glycerol reagent, and glycerol standard were obtained from Sigma-Aldrich (Dorset, UK). Pierce™ lactate dehydrogenase (LDH) Cytotoxicity Assay kit was purchased from Thermo Fisher Scientific (Loughborough, UK). All other reagents were of high-performance liquid chromatography (HPLC) grade.

2.2. In Silico Prediction of Statins Association With Chylomicrons

A previously reported in silico model was applied to predict the degree of association of simvastatin lactone, simvastatin hydroxy acid, pravastatin lactone and pravastatin hydroxy acid with chylomicrons (Gershkovich et al., 2009). The model relies on physicochemical parameters calculated using ACD/I-Lab (Advanced Chemistry Development Inc.) for each compound (Supplementary Table 1).

2.3. Association of Statins With Plasma-derived Human Chylomicrons

Chylomicron fractions were obtained from human plasma following induction of transient postprandial hypertriglyceridaemia. The study was approved by the Faculty of Medicine and Health Sciences Research Ethics Committee, Queens Medical Centre, Nottingham University Hospitals (BT12102015 CBS SoP). Three healthy male volunteers (25–35 years old) were recruited for this study after giving informed consents. Participants were instructed not to use any over the counter medication for one-week prior to the study. Following 12 h overnight fasting, participants had long-chain triglyceride-rich breakfast (full English breakfast or olive oil-fried eggs). 3 to 4 h following the meal [expected time of peak plasma chylomicron levels (Cohn et al., 1988; Cohn et al., 1989)] blood samples (30 ml) were collected and plasma was separated by centrifugation (800*g*, 10 min, 15 °C). Chylomicrons were separated from human plasma by density gradient ultracentrifugation using Sorvall® Discovery 100 SE Ultracentrifuge (TH-641 Rotor, 35 min, 274,044*g*, 15 °C) as described previously (Gershkovich et al., 2009; Gershkovich and Hoffman, 2005). The top 1 ml, white milky layer representing the chylomicron fraction was collected, and triglyceride content was measured using triglyceride colorimetric kit. Chylomicrons emulsion was diluted with PBS to a triglyceride level of 100 mg/dl and the emulsion was kept at 4 °C pending association experiments (<24 h).

The uptake of simvastatin lactone, simvastatin hydroxy acid, pravastatin lactone and pravastatin hydroxy acid by human chylomicrons was evaluated as previously described (Gershkovich et al., 2009; Gershkovich and Hoffman, 2005). All incubation experiments were carried out at physiological pH 7.4 in addition to pH levels that correspond to acidosis (pH 6.8) and alkalosis (pH 7.8) as describe previously (Taha et al., 2016). The selection of this range was based on extreme but clinically relevant disturbances in acid-base balance that are encountered in patients with long-term diuretics use (Tripathy, 2009), prolonged vomiting (Galla, 2000), diabetic ketoacidosis (Wathen and Starkey, 1986), lactic acidosis (Winocour et al., 1989), renal tubular acidosis (Kraut and Kurtz, 2005), hypovolemic shock (Zimmer, 2014), and ethylene glycol intoxication (Lundgaard, 2009). It should be noted that significant effects of milder plasma pH alterations on statin interconversion between lactone and hydroxy acid forms were also reported in our previous works (Taha et al., 2016).

Stock solutions of four statins (350 μM) were prepared in propylene glycol and an appropriate volume of each solution was added to 1 ml of human chylomicron emulsions of different pH to achieve a final

Download English Version:

https://daneshyari.com/en/article/5547851

Download Persian Version:

https://daneshyari.com/article/5547851

Daneshyari.com