Saudi Pharmaceutical Journal 25 (2017) 823–829

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Prevalence of potential drug interactions in Thai patients receiving simvastatin: The causality assessment of musculoskeletal adverse events induced by statin interaction

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ARTICLE INFO

Article history:
Received 15 January 2016
Revised 11 November 2016
Accepted 11 December 2016
Available online 23 December 2016

Keywords:
Simvastatin
Drug interaction
Musculoskeletal adverse effects
Drug Interaction Probability Scale (DIPS)

ABSTRACT

Drug-drug interactions are one of the major risk factors associated with statin-induced myopathy. Although simvastatin is widely used in Thailand, studies investigating the prevalence of potential simvastatin-drug interactions (SDIs) and its clinical relevance in Thai population are still limited. We aimed to investigate the prevalence of potential SDIs (phase 1 study) and musculoskeletal adverse effects (AEs) associated with those interactions (phase 2 study). A phase 1 study was retrospectively conducted with outpatients at a 60-bed hospital who received simvastatin between July 1, 2012 and June 30, 2013. In phase 2, study was cross-sectionally conducted in outpatients whose prescriptions contain potential SDIs. Musculoskeletal AEs were evaluated by using symptom checklist questionnaires and measuring plasma creatinine kinase (CK). The causal relationship between the AEs and the potential SDIs was assessed using a Drug Interaction Probability Scale.

Out of 3447 simvastatin users, potential SDIs were found in 314 patients (9.1%). The prevalence of prescriptions containing potential SDIs was in the range of 4.7–6.0%. Two-thirds of the potential SDIs were rated to be highly significant while more than 70% were in contraindication list. The most common precipitant drugs were gemfibrozil (382 prescriptions), colchicine (171 prescriptions) and amlodipine (152 prescriptions). Of 49 patients recruited into phase 2 study, we found that 31 patients (63.3%) had myopathy. Myalgia was the most frequently identified AEs (n = 18, 58.1%), followed by asymptomatic rising CK (n = 8, 25.8%), and myositis (n = 5, 16.1%). Musculoskeletal AEs associated with SDIs were found in 16 patients (51.6%). Of these, we found 50.0%, 31.3% and 18.8% had asymptomatic rising CK, myalgia, and myositis, respectively. Precipitant drugs associated with myopathy were amlodipine (2 possible cases), colchicine (3 possible cases), gemfibrozil (8 possible and 1 probable cases), nevirapine (1 possible case), and nicotinic acid (1 possible case).

Potential SDIs have been found in the Thai population with a prevalence that is consistent with previous reports. Half of the musculoskeletal AEs identified were associated with SDIs. Systematic screening and management with interdisciplinary co-operation are needed to increase awareness of potential SDIs.

1. Introduction

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), are the cornerstones of dyslipidemia treatment. There is strong evidence supporting statin use for primary and secondary prevention of cardiovascular diseases (Stone et al., 2013). Statin use is generally safe and well tolerated; however, musculoskeletal adverse effects (AEs) are important causes of statin intolerance and discontinuation (Kashani et al., 2006; Law and Rudnicka, 2006; Armitage, 2007). In 2001, cerivastatin was withdrawn from the

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2016.12.006
1319-0164/

market because of the high report of fatal rhabdomyolysis, which was found to be associated with the patients who concomitantly received gemfibrozil (Furberg and Pitt, 2001; Staffa et al., 2002). Although a low incidence of statin induced myopathy was identified in clinical trials (Pasternak et al., 2002; Kashani et al., 2006), higher rates have been reported in clinical setting (de Sauvage Nolting et al., 2002; Franc et al., 2003; Bruckert et al., 2005). Many risk factors, including statin-drug interactions, were associated with higher incidences reported in clinical practice. To date, the computerized screening program has been developed and implemented in several hospitals to increase awareness of potential drug interactions. However, the co-prescription of statin, in particular simvastatin, with potential interacting drugs has been reported in several studies (Piacentini et al., 2005; Ratz Bravo et al., 2005; Tirkkonen et al., 2008; Bakhai et al., 2012). In Thailand, Boonmuang et al. (2013) reported that 40% of patients with statin induced myopathy received at least one potential interacting drug.

Among other statins, simvastatin has the highest potential for statin-drug interactions, in particular pharmacokinetic drug interactions. Simvastatin is a substrate of transporters including P-glycoprotein (P-gp) and organic anion transporting polypeptide (OATP) 1B1, and largely metabolized in the liver by CYP3A4 (Neuvonen et al., 2006; Shitara and Sugiyama, 2006; Chatzizisis et al., 2010; Bellosta and Corsini, 2012). Co-administration of simvastatin with interacting drugs that can inhibit these proteins may increase simvastatin exposure and potentiate its musculoskeletal AEs. In 2011, the US Food and Drug Administration (USFDA) changed the safety label of simvastatin (http://www.fda.gov/drugs/drugsafety/ucm256581.htm). Specifically, some changes include the addition of an interacting drug list for potential simvastatin-drug interactions. Simvastatin is mostly prescribed in Thailand, as it is in the Thai National List of Essential drugs and available in all hospitals. However, studies investigating the prevalence of potential simvastatin-drug interactions and their clinical relevance in Thailand are still limited. Thus, this study aims to investigate the prevalence of potential simvastatin-drug interactions in Piboonmungsaharn Hospital, a 60-bed secondary care setting, and to investigate the prevalence of musculoskeletal AEs associated with those interactions.

2. Methods

2.1. Study design

This study was divided into two phases. In phase 1, we retrospectively investigated the prevalence of potential simvastatin-drug interactions. Data were retrieved from hospital electronic medical records of outpatients who received simvastatin between July 1, 2012 and June 30, 2013. Potential simvastatin-drug interactions were screened based on the two references, Drug Interaction Facts 2011 (Tatro, 2011) and the USFDA safety communication 2011 (http://www.fda.gov/drugs/drugsafety/ucm256581.htm). According to Drug Interaction Fact 2011 reference, potential drug interactions were identified when the documentation level was in the level of possible or higher. In phase 2, we further investigated the prevalence and severity of the musculoskeletal AEs among the prescriptions containing potential simvastatin-drug interactions. Myopathy was evaluated by obtaining symptom checklist questionnaires and measuring plasma creatinine kinase (CK) levels. Myopathy was classified as asymptomatic rising CK, myalgia, myositis, and rhabdomyolysis (Pasternak et al., 2002). Causal relationships between musculoskeletal AEs and simvastatin-drug interactions were further evaluated with the Drug Interaction Probability Scale (DIPS).

2.2. Instruments

A musculoskeletal AEs questionnaire was used in this study to evaluate patient symptoms. The questionnaire is a symptom checklist that was modified from a previous study (Bruckert et al., 2005). The checklist consists of type, location, severity, duration, interruption of daily routine, onset of symptoms, other possible causes, management of the symptoms, and family history of myopathy. The questionnaire was tested for content validity in three health professionals containing one doctor and two pharmacists. The index of consistency was 0.95. The questionnaire was further tested in 10 patients to assure that they understand the questions. The causal relationship between a potential simvastatin-drug interaction and musculoskeletal AEs was performed with the Drug Interaction Probability Scale (DIPS), a tool that has been previously used to evaluate causation in potential drug interactions (Horn et al., 2007). The scale consists of 10 questions with the three answer options "yes", "no", or "unknown/not applicable". The total score is used to estimate the probability that the interaction is causally related to the AEs (Horn et al., 2007). In this study, we indicated that drug interaction is associated with AEs when the DIPS score is higher than or equal to 2. The probability can be classified as possible (2–4 scores), probable (5–8 scores) or highly probable (>8 scores) (Horn et al., 2007). The association is classified as doubtful if the total DIPS score is less than 2.

2.3. Data analysis

Data were evaluated with SPSS version 19 for Windows. The prevalence of potential simvastatin-drug interactions and musculoskeletal AEs associated with drug interactions was evaluated with descriptive statistics. The demographic data of patients in phase 2 with and without musculoskeletal AEs were compared with Mann-Whitney U tests and Chi-square tests for continuous and categorical variables, respectively.

2.4. Ethical approval

Both phases of study were approved by the Khon Kaen University Ethics Committee for human research (Institutional review board number: IRB00001189). Research was conducted in accordance with the principle of the Declaration of Helsinki and International Conference on Harmonization for Good Clinical Practice.

3. Results

3.1. Demographic data of patients in phase 1

All 3447 simvastatin users were screened for potential simvastatin-drug interactions. Demographic data are shown in Table 1. There were 2428 females (70.4%), and the average age was 60.8 ± 11.7 years old with the one-third of the patients being over 65 years old. Approximately 80% of the patients were agriculturists and used a universal coverage scheme for health payment. Most patients used 20 mg/day simvastatin (average dose 17.4 ± 6.5 mg/day); however, 122 patients used simvastatin at a dose of greater than 40 mg/day. More than half of the patients had underlying diabetes and/or hypertension.

3.2. Prevalence of potential simvastatin-drug interaction

Of 3447 simvastatin users, potential simvastatin-drug interactions were found in 314 patients (9.1%) (Table 2). We found potential simvastatin-drug interactions in 271 cases (7.9%) based on the information in Drug Interactions Facts 2011 and in 236 cases (6.8%)