SHORT COMMUNICATION

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Risk Factors for Rhabdomyolysis with Simvastatin and Atorvastatin

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Abstract

Objective: To assess the frequency of risk factors for rhabdomyolysis with simvastatin and atorvastatin in cases reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC).

Design: Reports meeting the definition of rhabdomyolysis were reviewed for risk factors including age ≥70 years, dose ≥40mg, hepatic dysfunction, diabetes mellitus, hyperkalaemia, hypothyroidism and the use of concomitant interacting medications.

Results: Only one report associated with simvastatin and five reports associated with atorvastatin did not list any risk factors for rhabdomyolysis. Interacting medicines featured in 77% of reports of rhabdomyolysis associated with simvastatin and 44% of reports associated with atorvastatin.

A comparison of the age profile for reports of atorvastatin- and simvastatin-associated rhabdomyolysis with that for all adverse drug reaction reports received, and for all reports of muscle disorders, suggested a trend towards an increasing risk of rhabdomyolysis with increasing age with simvastatin but not with atorvastatin. Similarly, comparing prescribed tablet strengths from Pharmaceutical Benefits Scheme data with the HMG-CoA reductase inhibitor ('statin') doses in reports of rhabdomyolysis suggested a dose-related risk with simvastatin, but a less increased risk with high-dose atorvastatin.

Conclusion: Risk factors for rhabdomyolysis featured in nearly all of the reports of statin-associated rhabdomyolysis and the majority of reports listed multiple risk factors, although dependence on risk factors appeared to be stronger with simvastatin than atorvastatin. The multiplication of risk factors in patients taking simvastatin and atorvastatin should be minimised.

Introduction

The HMG-CoA reductase inhibitors or 'statins' are a well established treatment used for the reduction of cholesterol levels. In Australia, simvastatin was approved in 1990 and atorvastatin in 1997. In the year ending June 2005, atorvastatin and simvastatin were ranked first and second, respectively, for both their volume of use and cost to the Pharmaceutical Benefits Scheme (PBS) [$A434 million for

atorvastatin and $A344 million for simvastatin].[1] Fluvastatin and pravastatin are also available, but their volume of use is much lower.

Several large-scale studies have demonstrated advantages from long-term statin use in terms of reductions in mortality and cardiovascular disease events in a range of patient groups.[2-4] Publication of this evidence of benefit is likely to result in even greater prescribing of the statins, and in use at high rather than low doses. This greater use is further supported by the evidence of safety. In the Heart Protection Study, a slight non-significant excess in the number of cases of myopathy was observed in the group receiving simvastatin, and some patients with myopathy developed rhabdomyolysis (defined in this study as a creatine kinase level >40 times the upper limit of normal; number of patients not stated).[2] The study protocol excluded those with prevalent hepatic or renal dysfunction or muscle disease or those who were being treated with ciclosporin, fibric acid derivatives (fibrates) or high-dose niacin, thus excluding some with risk factors for rhabdomyolysis.

Similarly, despite the high dose of atorvastatin (80mg) used in the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombosis in Myocardial Infarction 22) study,[4] no cases of rhabdomyolysis occurred, and the rate of muscle disorders was not significantly greater with atorvastatin than pravastatin (40mg). Patients taking fibrates or strong inhibitors of cytochrome P450 enzyme (CYP) 3A4 and those with hepatic or renal impairment or elevated creatine kinase levels were excluded from this study.

Rhabdomyolysis is a potentially fatal adverse reaction associated with the statins, but as the results of these studies indicate, it is rare if patients with risk factors are excluded. Nevertheless, many patients prescribed statins in clinical practice are elderly patients with multiple medical conditions, who require multiple medications and hence potentially have multiple risk factors for statin-associated rhabdomyolysis.

To date, case series have listed risk factors, particularly interacting medicines, that may have contributed to the risk of rhabdomyolysis associated with the statins in the reported cases.[5-7] However, no study has analysed cases of statin-associated rhabdomyolysis for the frequency of established risk factors, as a means to evaluate their importance in rendering the individual patient susceptible to rhabdomyolysis.

The purpose of the present study is to assess the frequency of previously identified risk factors for rhabdomyolysis associated with simvastatin and atorvastatin in cases reported to the Australian Adverse Drug Reactions Advisory Committee (ADRAC).

Methods

Australian cases of rhabdomyolysis with simvastatin and atorvastatin reported to ADRAC, some of which have been described elsewhere,[8,9] were reviewed. Reports to ADRAC are received from general practitioners, specialists, pharmacists, sponsors and consumers. These reports dated from 1991 for simvastatin and from 1999 for atorvastatin, and were accepted for analysis up until December 2005. Original reports were reviewed to ensure complete and accurate recording of data, and inclusion of only those cases that adhered to the definition of rhabdomyolysis.

After exclusion of duplicates, a total of 121 reports associated with simvastatin and 52 associated with atorvastatin met the definition of rhabdomyolysis: myoglobinuria OR muscle symptoms plus renal failure otherwise unexplained OR muscle symptoms plus a creatine kinase level ≥10 000 IU/L that was otherwise unexplained. In addition, reports designated rhabdomyolysis by the reporter but including no further details were accepted at face value.

Parameters extracted from the reports were age, sex, statin dose, concomitant medication, other medical conditions and other reaction terms. Reports were excluded from the analysis if they did not provide data on age, sex or statin dose, reducing the number of reports included in the analysis to 96 for simvastatin and 39 for atorvastatin.

Age ≥70 years and statin dose ≥40mg were treated as risk factors for rhabdomyolysis, as were pre-

Table I. Drugs interacting with simvastatin and atorvastatin to increase the risk of rhabdomyolysis

Interacting via CYP3A4	Interacting by other/unknown means
Amiodarone[10,11]	Clozapine[21]
Clarithromycin[10,11]	Gemfibrozil[10,11]
Clopidogrel[19]	Cyproterone
Colchicine[14]	Esomeprazole[18]
Ciclosporin[10,11]	Warfarin[5,7,20]
Danazol[10]	
Diltiazem[10]	
Erythromycin[10,11]	
Fusidic acid[12]	
Itraconazole[10,11]	
Mibefradil[13]	
Nefazodone[10]	
Quinine[15]	
Roxithromycin[11]	
Verapamil[10]	

CYP = cytochrome P450 enzyme.

existing hepatic dysfunction, diabetes mellitus, hyperkalaemia, hypothyroidism and interacting drugs. Renal dysfunction was not included because of the difficulty of ascertaining whether it was pre-existing or part of the event resulting in rhabdomyolysis.

Drug interactions were identified from the Australian Product Information[10-12] and a review of the literature (see table I). If evidence was found that a drug interacts with simvastatin, it was considered for the purposes of this analysis to interact with atorvastatin and vice versa. Mibefradil was withdrawn from the market internationally because of the potency of its interactions via CYP3A4, and was associated with rhabdomyolysis when co-prescribed with simvastatin.[13] Colchicine[14] and quinine[15] were included since they are known to be metabolised by CYP3A4, and colchicine is an independent cause of rhabdomyolysis.[16,17] Published case reports demonstrating a plausible temporal relationship were identified for esomeprazole[18] (but not omeprazole) and clopidogrel.[19] Warfarin has been included as an interacting medicine in previous case series,[5,7] and was implicated in a published case report.[20] Clozapine is a known cause of rhabdomyolysis, as seen in published literature[21] and reports to ADRAC. Cyproterone was implicated in cases in this series where it first caused hepatic dysfunction, which is a risk factor for rhabdomyolysis. Known interacting substances (such as grapefruit juice, ketoconazole, HIV protease inhibitors and tacrolimus) were not listed if they did not feature in this series. Digoxin has been listed as an interacting medication previously,[5,7,22] but it has not been included in the present analysis because of a lack of independent evidence to indicate that it increases the risk of rhabdomyolysis.

Results

All but one report of rhabdomyolysis associated with simvastatin listed a risk factor, and 58% of cases were associated with three or more risk factors (figure 1a). For atorvastatin, no risk factors were described in five reports, and 43% of reports specified only one risk factor. Seventy-seven percent of reports of rhabdomyolysis associated with simvastatin and 44% of such reports associated with atorvastatin involved interacting medicines, and 41% of reports of simvastatin-associated rhabdomyolysis listed two or more such medicines (figure 1b).

The most commonly implicated interacting medicines were gemfibrozil (27% of reports associated with simvastatin; 15% of reports associated with atorvastatin), diltiazem (21%; 13%) and ciclosporin (11%; 11%). Diabetes was present in 19 cases (20%) associated with simvastatin and six cases (15%) associated with atorvastatin.

In two reports associated with simvastatin, patients taking cyproterone developed hepatic dysfunction as a reaction to the cyproterone and this was then followed by rhabdomyolysis as a result of reduced metabolism of simvastatin.

In the absence of data on the age distribution of prescriptions of simvastatin and atorvastatin, the age profile for reports of rhabdomyolysis was compared with that for all adverse reaction reports and for all reports of muscle disorders. For simvastatin, the comparison shows a trend towards an increasing risk of rhabdomyolysis with increasing age, with 48% of cases of rhabdomyolysis occurring in patients aged ≥70 years, compared with 27% of all adverse reactions (figure 2a). In contrast, for atorvastatin the age profile for cases of rhabdomyolysis is similar to the age profile for all adverse reaction reports, with only

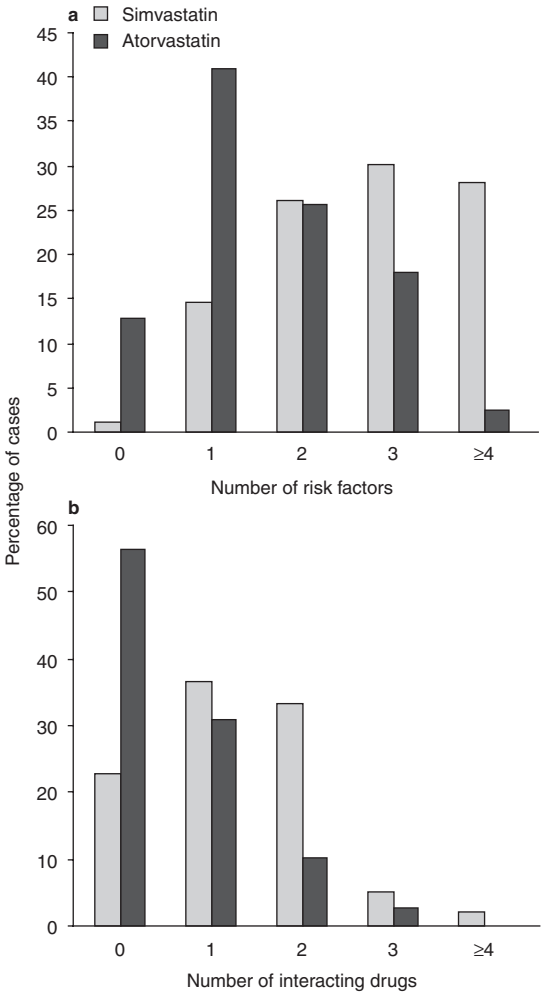

Fig. 1. Total number of risk factors (**a**) and number of interacting drugs (**b**) in reported cases of rhabdomyolysis associated with simvastatin and atorvastatin.

a small increase in the proportion of cases of rhabdomyolysis that occurred in the older age groups (figure 2b).

PBS data for the various tablet strengths for simvastatin and atorvastatin are presented in figure 3a.[23] The percentage of prescribing at each of the strengths is similar for each of these two statins. Although the tablet strength prescribed does not necessarily translate into dose taken, it should be a reasonable indication. Comparison of this bar graph with that showing the dose strengths associated with cases of rhabdomyolysis reveals a trend towards an increasing risk of rhabdomyolysis with increasing doses of simvastatin. For atorvastatin, the number of cases at each dose is reasonably constant, with a suggestion of an increase in risk with the 80mg dose (5% of usage; 23% of cases) [figure 3b].

Discussion

A case series of this type has limitations. First, case ascertainment will be incomplete and may be

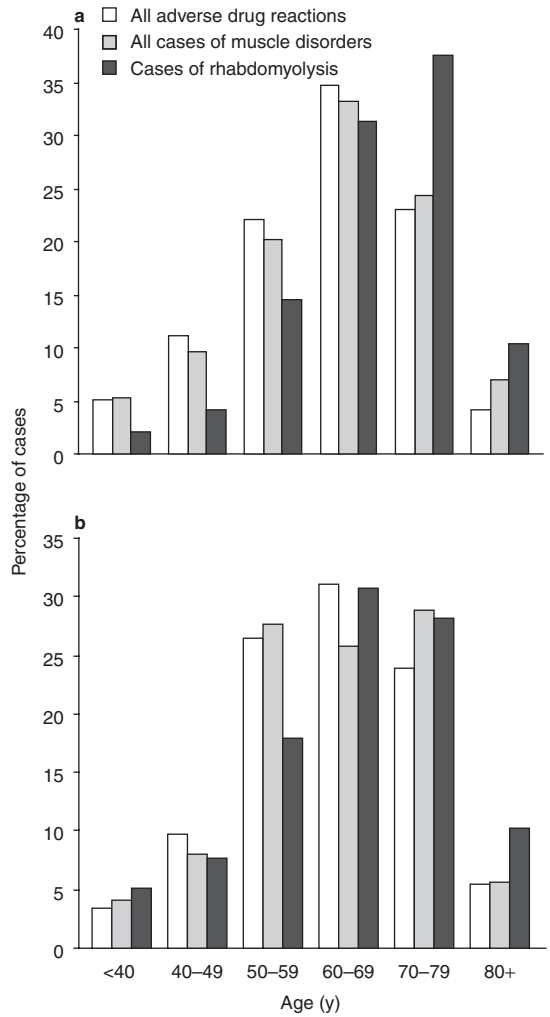

Fig. 2. Age distribution of all reported adverse drug reactions, all cases of muscle disorders and cases of rhabdomyolysis associated with simvastatin (**a**) and atorvastatin (**b**).

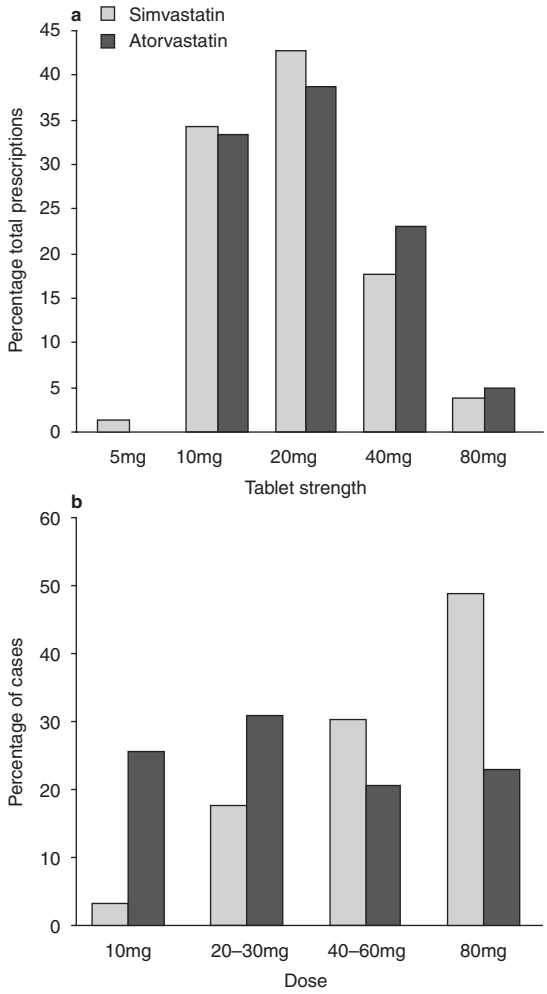

Fig. 3. Pharmaceutical Benefits Scheme prescriptions[23] for simvastatin and atorvastatin, January 1992 to December 2005 (**a**) and dose distribution of cases of rhabdomyolysis (**b**).

subject to bias. Secondly, although it is possible to obtain prescribing data from the PBS statistics, these do not provide data on the age distribution of patients, the frequency of exposure to concomitant medications or the use of the drugs of interest by patients with disease states that increase the risk of a certain adverse event. Hence, it is not possible to estimate the risk conferred by each factor or combination of factors. Thirdly, despite the exclusion of reports with specified data deficiencies, it is almost certain that potential risk factors, including interacting medicines, were incompletely described in the reports. Hence, risk factors may be even more strongly represented in the cases than this analysis suggests.

Using PBS data, and the total number of reports of rhabdomyolysis received by ADRAC (including those excluded because of incomplete data), the frequency of reports of rhabdomyolysis was 2.1 per million prescriptions for simvastatin and 1.3 per million prescriptions for atorvastatin. Even allowing for incomplete case ascertainment, these figures suggest that rhabdomyolysis with simvastatin or atorvastatin is a very rare adverse reaction.

In addition to the evidence from the long-term efficacy trials described in the Introduction section, calculations of incidence in studies focussing on muscle disorders are also indicative the rarity of statin-associated rhabdomyolysis. A cohort study using the UK General Practice Research Database that included 17 000 patients prescribed a lipid-lowering drug, of whom 10 000 were prescribed simvastatin, found a rate of myopathy of 2.3 per 10 000 person-years and no cases of rhabdomyolysis.[24] In the same study, no cases of myopathy were present in a control cohort of 29 000 patients with a diagnosis of hyperlipidaemia who received no medication to treat this condition. A further study[22] included a cohort of 181 patients taking simvastatin or atorvastatin plus potentially interacting medicines; none of these at-risk patients had signs or symptoms of myopathy. No information was provided on the statin dose or age for this patient group.

Another estimate of the risk with statin monotherapy comes from a cohort study[25] of patients hospitalised in the US for myopathy (creatine kinase level >10 × upper limit of normal, including rhabdomyolysis). Statin-usage data were obtained from prescription claims. In this study, myopathy occurred at rates of 0.49 (95% CI 0.06, 1.76) per 10 000 person-years with simvastatin and 0.54 (95% CI 0.22, 1.12) per 10 000 person-years with atorvastatin. Although there was only one such patient who developed myopathy, an estimate was made of the rate of myopathy when using gemfibrozil in combi-

nation with simvastatin: 19 (95% CI 0.47, 104) per 10 000 person-years or almost 40 times the risk associated with simvastatin monotherapy.

Another study conducted in the US,[26] also using data from prescription claims, found rates of hospitalisation for myopathy (identified using codes from the *International Classification of Diseases*) that were almost 10-times greater than those in the previous study: 3.5 (95% CI 2.1, 5.5) per 10 000 person-years for simvastatin and 2.5 (95% CI 1.9, 3.1) per 10 000 person-years for atorvastatin. In the age-matched case-control comparison, the risk of hospitalisation for myopathy with any lipid-lowering drug was increased by a factor of 6.0 (95% CI 2.18, 17.4) by co-administration of inhibitors of CYP 3A4 inhibitors. No individual drug analysis was conducted for this risk factor. In this study, 86% of the cohort were taking a statin as monotherapy for hyperlipidaemia.

An indication of the effect of a high statin dose can be seen from a trial with the usual range of exclusion criteria, including use of interacting drugs, and randomisation to simvastatin 20mg or 80mg daily. The proportion of patients developing rhabdomyolysis in association with simvastatin 80mg was 0.13% (three cases out of 2265 randomised to this group; six cases of myopathy).[27] The data provided permit the rate for all cases with creatine kinase levels >10 times the upper limit of normal to be calculated at 62 per 10 000 patient-years during the first 6 months on high-dose simvastatin. Twenty-five percent of patients in this study were aged ≥70 years.

Neither the published data nor the present analysis permit an estimate of the attributable risk of each identified risk factor. Nevertheless, the current analysis of case reports is suggestive of an escalating risk of rhabdomyolysis with each added risk factor, at least for simvastatin.

Interestingly, although risk factors were commonly featured in reports of rhabdomyolysis associated with atorvastatin, their influence was not as strong as for the cases associated with simvastatin. This was seen in the analyses of all risk factors and of interacting medicines, as well as in those for age and dose. Although these data may indicate that atorvastatin is safer than simvastatin in the presence of risk factors, conversely the data suggest that there is a greater risk of rhabdomyolysis associated with atorvastatin in the absence of risk factors. A recent study[28] of the effect of conversion of patients from simvastatin to atorvastatin for therapeutic reasons found lower creatine kinase levels associated with atorvastatin than simvastatin and all three patients who were given atorvastatin after developing rhabdomyolysis while being treated with simvastatin were able to continue the medication without ill effect. The reasons for these differences between simvastatin and atorvastatin seen in this recent study and the present analysis are unclear and may be more complex than the difference in potency or lipophilicity.

It is possible to identify from the data the interacting medicines most frequently implicated in cases of rhabdomyolysis, namely, gemfibrozil, diltiazem and ciclosporin, in decreasing order. However, without data on the frequency of use of these and other interacting medicines in the cohort of users of simvastatin and atorvastatin, it is not possible to determine the significance of this observation.

The most practical message to derive from this case series is the importance of minimising, where possible the multiplication of risk factors for rhabdomyolysis in those taking simvastatin or atorvastatin. For example, if the patient is aged ≥70 years and is taking ciclosporin to prevent transplant rejection, it may be advisable to not increase the dose of simvastatin above 30mg daily despite insufficient control of cholesterol levels. A patient with diabetes on atorvastatin and clopidogrel may be better treated with an alternative to a macrolide antibacterial in the event of an infection. There are many possible variations for minimising the number of risk factors, including reducing the dose of the statin if addition of an interacting medication is unavoidable. Patients prescribed statins, particularly those with risk factors for rhabdomyolysis who are taking simvastatin or atorvastatin, should be advised to report symptoms of muscle disorders, especially if these are severe or exacerbating.

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