Myopathy Due to Statin/Fibrate Use in the Netherlands

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OBJECTIVE: To estimate the number of expected cases of myopathy based on the prevalence of lipid-lowering drug use, and to compare this number with the observed number of cases of myopathy due to lipid-lowering drug use in the Netherlands.

METHODS: Prevalence of lipid-lowering drug use in 1998 was estimated by using data from the PHARMO record linkage system comprising pharmacy records linked to hospital admission data. The expected number of cases of myopathy was calculated by multiplying the total number of person-years of lipid-lowering drug use by the excess incidence rates of myopathy due to those drugs as reported in the literature. The observed number of cases was obtained from PHARMO and the Dutch Pharmacovigilance Foundation Lareb.

RESULTS: Based on the estimated prevalence of lipid-lowering drug use in the Netherlands in 1998 (n = 520 800), we expected 60 cases of idiopathic myopathy due to hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) or fibric acid derivatives (fibrates). This low number was confirmed by data from PHARMO (n = 11; none of these were related to current use of lipid-lowering drugs) and Lareb (n = 43).

CONCLUSIONS: The expected number of statin- or fibrate-related idiopathic myopathy is low and observed numbers are even lower in the Netherlands. This should, therefore, not compromise continued use of lipid-lowering drugs.

KEY WORDS: fibrate, myopathy, statin.

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Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have proven to be safe and effective in reducing fatal and nonfatal cardiovascular events in both primary[1,2] and secondary prevention[3-5] and produce a reduction in total mortality of approximately 30%.

In August 2001, the lipid-lowering drug cerivastatin was withdrawn from the market after its use was associated with the deaths of 52 patients due to rhabdomyolysis in Europe and the US.[6] In 12 of the 31 US deaths, cerivastatin was used in combination with a fibric acid derivative (fibrate), in all cases, gemfibrozil.[7]

Myopathy and rhabdomyolysis, however, have been reported[8-10] for all statins and fibrates. Additional risk factors for myopathy include increased age, female gender, renal or liver disease, diabetes, hypothyroidism, debilitated status, surgery, trauma, excessive alcohol intake, and heavy exercise,[10] as well as interacting comedication.[8] Although the use of statins and fibrates is associated with an increased risk of myopathy, the absolute risk of myopathy is low in patients using these lipid-lowering drugs.[11]

The aim of this study was to estimate the expected number of cases of statin- and fibrate-related myopathy based on the prevalence of lipid-lowering drug use, and to compare this number with the observed number of cases of idiopathic myopathy due to the use of statins and fibrates in the Netherlands.

Methods

PREVALENCE OF LIPID-LOWERING DRUG USE

Data on lipid-lowering drug use were obtained from the PHARMO database, a record linkage system containing drug-dispensing records

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from community pharmacies and linked hospital discharge records of approximately 300 000 subjects. This database covers a well-defined population of residents of 6 medium-sized cities in the Netherlands. Clustering of all pharmacies within each city results in medication histories that contain >95% of all prescriptions dispensed to a particular patient.[12]

We estimated the 1-year prevalence rates of lipid-lowering drug use in 1998. A patient was defined as a prevalent user at that time if he or she filled at least 1 prescription for a statin available in the Netherlands (atorvastatin, cerivastatin, fluvastatin, pravastatin, simvastatin) or fibrate (bezafibrate, ciprofibrate, clofibrate, gemfibrozil) between January 1, 1998, and December 31, 1998. The absolute number of people using these drugs in the Netherlands was subsequently calculated using data from Statistics Netherlands.

To compare dosing of different lipid-lowering drugs, we expressed the prescribed daily dose as the number of defined daily doses (DDDs; Table 1). This unit corresponds to the average daily dose of a drug for its main indication in adults and is recommended by the World Health Organization.[13]

EXPECTED CASES OF MYOPATHY

To estimate the expected number of cases, we used data from an observational study[11] on the risk of myopathy. The estimated incidence of myopathy in the general population shown in that investigation was 0.2 (95% CI 0.1 to 0.4) per 10 000 person-years. The incidence rates for current use of statins and fibrates were 1.2 (95% CI 0.3 to 4.7) and 6.6 (95% CI 3.0 to 14.3) per 10 000 person-years, respectively. For the statin–fibrate combination, we assumed an additive effect on the incidence rate. Based on these rates, we calculated the excess rates due to statin or fibrate use, defined as the difference between the drug-specific incidence rates and the rate in the general population.

The number of person-years of lipid-lowering drug use was calculated by multiplying the absolute number of users by the average duration of use. The expected number of cases of idiopathic myopathy was subsequently calculated by multiplying the number of person-years by the excess incidence rates.

OBSERVED CASES OF MYOPATHY

To assess the observed number of cases of myopathy and rhabdomyolysis in the PHARMO database, we selected all cases with ICD-9 codes 359 (muscular dystrophies and other myopathies) and 728.89 (other disorders of muscle, liagament, and fascia, including rhabdomyolysis) during 1998. We excluded ICD codes 359.0 and 359.1, which represent hereditary forms of muscular dystrophy.

Additionally, reports of myopathy in the Netherlands in 1998 were obtained from the Netherlands Pharmacovigilance Foundation Lareb. Lareb maintains the national spontaneous reporting system on behalf of the Dutch Medicines Evaluation Board. Health professionals send reports to Lareb on a voluntary basis. Information is collected on the patient, the suspected adverse drug reaction, and concomitantly used medication.[14]

STATISTICAL ANALYSIS

All prevalence rates were adjusted for the age and gender distribution of the general Dutch population. Prevalence rates and their 95% CIs were calculated according to Altman,[15] using binomial distribution. Excess incidence rates and their 95% CIs were calculated according to Rothman and Greenland.[16]

Table 1. Defined Daily Doses for Statins and Fibrates

Atorvastatin	10 mg	Bezafibrate	600 mg
Cerivastatin	0.2 mg	Ciprofibrate	100 mg
Fluvastatin	40 mg	Clofibrate	2000 mg
Pravastatin	20 mg	Gemfibrozil	1200 mg
Simvastatin	15 mg		

Results

In 1998, we identified 10 390 prevalent users of lipid-lowering drugs in the PHARMO database. Of these patients, 9569 (92.1%) used a statin alone, 435 (4.2%) used a fibrate alone, and 386 (3.7%) used a statin–fibrate combination. The majority of the patients were male, and the mean age was approximately 60 years (Table 2).

Simvastatin was the most frequently used statin in monotherapy (59.4%), followed by pravastatin (16.0%) and atorvastatin (13.8%). Gemfibrozil was used most frequently (70.0%) by patients on fibrate monotherapy, followed by ciprofibrate (22.7%). These statins and fibrates were also the drugs included most often in combination therapy. The simvastatin–fibrate combination was used by 30.8% of patients on combination therapy. Average prescribed daily doses were close to 1 DDD for both statin and fibrate use alone (1.2 and 0.9 for statins and fibrates, respectively). In patients using combination therapy, the average prescribed daily doses were higher; the prescribed daily dose for statins was 1.9 DDD and, for fibrates, 1.2 DDD. Most of the patients used lipid-lowering drugs for >250 days that year, which was longer with length of use of statins alone and combination therapy than use of fibrates alone (Table 2).

One-year prevalence rates adjusted for the age and gender distribution of the Dutch general population resulted in an absolute number of users of approximately 480 000, 21 600, and 19 200 in the Netherlands in 1998, for statins, fibrates, and combinations, respectively.

Combination of the estimated number of users of statins or fibrates and the excessive incidence rates of myopathy yields a total of 60 expected cases of possible statin- or fibrate-related idiopathic myopathy in 1998 in the Netherlands.

In 1998, 36 cases of myalgia or myopathy and 7 cases of rhabdomyolysis possibly attributable to the use of statins or fibrates were spontaneously reported to Lareb. In PHARMO, among the 11 patients admitted to the hospital for myopathy (n = 2) and rhabdomyolysis (n = 9), none of the patients used a statin or fibrate at admission and only 1 had ever used a statin before the date of the event.

Discussion

The 1-year prevalence of the use of fibrates alone or statin–fibrate combination therapy is very low in the Netherlands, resulting in a low expected number of patients with idiopathic myopathy due to the use of these drugs. Although the use of statin monotherapy is substantial, the number of expected cases of idiopathic myopathy remains low, because an estimated 10 000 patients must be treated for the occurrence of 1 case of myopathy due to statin therapy. This low expected number of cases of myopathy or

rhabdomyolysis was confirmed by data from PHARMO and Lareb.

Data on the prevalence of lipid-lowering drug use were derived from a large, population-based database[12] comprising virtually complete medication histories on a patient level, resulting in a valid estimate of lipid-lowering drug use in the Netherlands.

Myopathy is a rare adverse drug effect of statins and fibrates and, until recently, reports on the occurrence of this adverse drug effect mainly consisted of case reports.[17] To estimate the number of expected cases of myopathy due to lipid-lowering drug use, we used data from the first, large epidemiologic study[11] on the risk of myopathy in patients using these agents. Although this study may have some limitations, great effort was made by the authors to validate their cases of myopathy and to control for potential confounders.

To compare the number of expected cases of idiopathic myopathy due to the use of statins and fibrates with the observed number of cases in general practice, we used data from multiple sources available in the Netherlands. In PHARMO, medication histories are linked to hospital discharge records. Rhabdomyolysis is a severe disease for which hospitalization is necessary. However, we may have missed less severe cases of myopathy for which hospitalization is unnecessary.

Pharmacovigilance is mainly based on spontaneous reporting of observations by health professionals. Due to the spontaneous character of the reporting, the method has some limitations. The most noticeable problem is (selective) underreporting.[18,19] Unfortunately, too many factors are involved in underreporting to make a general estimate of its extent. Since not all adverse drug events are reported, the spontaneous reporting system is not necessarily a valid representation of the adverse drug reactions occurring in daily practice, but often remains the only information for regulatory bodies to act on.

The observed number of cases of idiopathic myopathy due to lipid-lowering drug use as reported by both PHARMO and Lareb is far lower than expected. Underreporting may account for a large part of this difference, but both sources still confirm the low absolute risk of myopathy due to the use of statins and fibrates.

Although the occurrence of statin- or fibrate-related myopathy is rare and the case-fatality rate is low, fear of patients and physicians for this adverse effect, raised by broad lay media attention, might threaten the continuation of lipid-lowering therapy.[20,21] To reassure statin users, the American Heart Association and the American College of Cardiology[22] issued a statement that the benefits of the use of statins still far outweigh any risks. A recent meta-analysis[23] based on 3 placebo-controlled clinical trials including >112 000 person-years of exposure to pravastatin did not reveal any case of myopathy.

Our main concern should be to closely monitor patients with multiple risk factors for myopathy and to prevent patients from discontinuation of their lipid-lowering medication.

Table 2. Prevalence Rates of Prescribing Lipid-Lowering Therapy and Expected Number of Patients Developing Idiopathic Myopathy

Parameter	Statins (n = 9569)	Fibrates (n = 435)	Statins–Fibrates (n = 386)
Women (%)	4334 (45.3%)	148 (34.0%)	113 (29.3%)
Age (mean ± SD)	60.9 ± 11.2	58.4 ± 10.7	57.5 ± 9.9
Days of therapy (mean ± SD)	293 ± 113	263 ± 128	293 ± 110
Defined daily dose (d)	1.2	0.9	1.9 (statins) 1.2 (fibrates)
1-y prevalence[a] (95% CI)	3.0% (3.0 to 3.1)	0.14% (0.12 to 0.15)	0.12% (0.11 to 0.13)
Absolute number of users	479 997	21 620	19 194
Person-years of use	385 313	15 578	15 408
Expected number of cases of idiopathic myopathy (95% CI)	39 (–24 to 105)	10 (2 to 18)	11 (NE)

NE = not estimable.
[a]1-year prevalence rates adjusted for the age and gender distribution of the general Dutch population.

Summary

In this study, the expected number of cases of idiopathic myopathy due to the use of statins or fibrates was low. The number of observed cases of myopathy in the Netherlands was even lower. This low risk of myopathy should not compromise continued use of lipid-lowering drugs.

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EXTRACTO

OBJETIVO: Estimar el número esperado de casos de miopatía secundaria a medicamentos antilipémicos, inhibidores de reductasa de HMG-CoA, y fibratos, basado en la prevalencia del uso de estos fármacos y compararlo con el número de casos de miopatía observados en Los Paises Bajos, Holanda (The Netherlands).

MÉTODOS: En 1998, se estimó la prevalencia del uso de medicamentos que reducen las concentraciones de lípidos utilizando la información obtenida del sistema de datos PHARMO. Este sistema interconecta datos de registros de la dispensación de medicamentos de farmacias de comunidad con datos de hospitalización, de aproximadamente 300 000 personas. El número esperado de casos de miopatía se calculó multiplicando el número total de personas-años usando agentes antilipémicos por el exceso en las razones de incidencia de miopatía asociadas al uso de estos medicamentos según informadas en la literatura. El número de casos observados se obtuvo a través de PHARMO y de la Fundación Holandesa de Farmacovigilancia Lareb.

RESULTADOS: En 1998, se identificaron 10 390 personas que usaban agentes antilipémicos. El 92.1% de éstos usaban estatinas, el 4.2% usaban fibratos, y el 3.7% usaban la combinación de estatina y fibratos. El número de casos esperados de miopatía inducida por estatinas o por fibratos se calculó en 60. Este número se obtuvo a base del estimado de prevalencia de uso de estos medicamentos en 1998 (n = 520 800). Este número estimado se confirmó con los datos de PHARMO (n = 11; ninguno de los cuales se relacionaron con el uso concurrente de antilipémicos) y datos de Lareb (n = 43). Entre los casos informados a Lareb, hubo 36 casos de mialgia o miopatía y 7 casos de rabdomiólisis posiblemente atribuídos a estatinas o a fibratos.

CONCLUSIONES: La miopatía inducida por agentes antilipémicos es un evento adverso raro. El número estimado de miopatía idiopática relacionada con el uso de estatinas o fibratos en Los Paises Bajos es bajo. El número de casos observados es todavía más bajo. Los autores concluyen que este efecto no debe comprometer la continuación en el uso de los agentes que reducen los niveles de lípidos.

Mirza D Martínez

RÉSUMÉ

OBJECTIF: Estimer le nombre potentiel de cas de myopathies associées aux hypolipémiants d'aprés la prévalance de leur utilisation, et comparer cette valeur à celle rapportée dans la région de Pays-Bas.

MÉTHODOLOGIE: La prévalence d'utilisation des hypolipémiants en 1998 a été estimée avec les données obtenues à partir du système PHARMO qui établit des liens entre les dossiers pharmaceutiques et les raisons d'admission hospitalière de patients. Le nombre potentiel de cas de myopathies a été calculé en multipliant le nombre total de patients sous hypolipémiants-année par les taux d'incidence de myopathies, dues aux hypolipémiants, rapportés dans la littérature. Le nombre de cas observés provient du systéme PHARMO et de la fondation Lareb (cas de pharmacovigilance)

RÉSULTATS: Selon la prévalence estimée d'utilisation d'hypolipémiants aux Pays-Bas en 1998 (n = 520 800), les chercheurs s'attendaient à 60 cas de myopathies idiopathiques associées a ux statines ou aux fibartes. Les donnés obtenues par PHARMO (n = 11; aucun cas n'était relié à l'usage courani d'hypolipémiants) et par Lareb (n = 43) confirment ce faible nombre.

CONCLUSION: Le nombre potentiel de cas de myopathies associées aux statines ou aux fibrates est peu élevé et le nombre obtenu aux Pays-Bas est encore plus faible. Ainsi, ces données ne devraient pas compromettre l'usage actuel des hypolipémiants.

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