DOI:10.1111/j.1365-2125.2004.02044.x

Professional athletes suffering from familial hypercholesterolaemia rarely tolerate statin treatment because of muscular problems

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Keywords
creatine phosphokinase, familial hypercholesterolaemia, muscle pains, oxidation injury, professional athletes

Received
17 July 2003
Accepted
30 October 2003

Aims
Muscular problems are the major group of side-effects during statin treatment. They are known to occur much more frequently during and after exercise.

Methods and results
For the last 8 years we have monitored 22 professional athletes in whom, because of familial hypercholesterolaemia, treatment with different statins was attempted. Only six out of the 22 finally tolerated at least one member of this family of drugs. In three of these six the first statin prescribed allowed training performance without any limitation. Changing the drug demonstrated that only two tolerated all the four or five statins examined (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin). Cerivastatin was not among the statins prescribed.

Conclusions
These findings indicate that in top sports performers only about 20% tolerate statin treatment without side-effects. Clinical decision making as to lipid lowering therapy thus becomes a critical issue in this small subgroup of patients.

Introduction

Statins are one of the most widely used drugs worldwide because of their clinical effectiveness [1]. Although rare, top sports performers suffering from familial hypercholesterolaemia (FH) may require drug treatment even at a young age. Muscular symptoms are the major group of adverse side-effects among statin users, totaling about 5% in multicentre-controlled studies [2]. The HPS-Study reported muscular symptoms at a rate of 32.9% in the active treatment group and 33.2% in the placebo

group [3]. The number of more severe side-effects is quite low, ranging below 0.1% [4, 5]. However, some years ago we found that muscular side-effects during exercise clearly are related to statin treatment even in the absence of elevated creatine kinase (CK) [6]. In another study examining the role of exercise in patients with statin treatment we realized that in those people performing regular strenuous exercise side-effects, characterized as ache- and cramp-like symptoms as well as muscular weakness, may increase, raising the possibility that as many as 25% may suffer. In recent reviews [7, 8] exercise-induced pain and the problem of statin use in top athletes is not even mentioned. Throughout the years we have monitored a number of professional athletes in whom FH had been diagnosed and at different stages statin treatment was initiated. In this paper we describe the individual cases and response to attempts to treat with various members of this family of compounds.

Methods

Patients were considered as professional athletes when they had attended an Austrian championship at any age class during the last 2 years or were playing in the top two leagues of their respective discipline (for characteristics of athletes see Table 1). They all were suffering from FH as diagnosed at the receptor level. No other drugs including vitamins were taken for at least 4 weeks. Testing for anabolic steroids was done in all athletes to exclude any possible influence. According to a recommendation of the Austrian Cholesterol Consensus [9] the starting dose of the respective statin was always the lowest available dose. Logic for switching patients who tolerated a statin was that they did not achieve target values. The shortest duration of treatment before switching was 8 weeks.

Blood samples for CK and liver enzymes (GOT, GPT, γGT) were regularly drawn at each monitoring interval.

Table 1
Athletes characteristics and the statin tolerated and not tolerated by each

Number	Age (years)	Sex (M/F)	Height (cm)	Weight (kg)	Discipline	FH (years)	Total CH (mmol)	Lp(a) (mg/dl)	Statins adverse event	Statins tolerated
1	15	F	160	38	Running	10	8.78	9	L, P, S	F, A
2	13	M	150	38	Fencing	8	10.63	13	P, L, S	F, A
3	17	F	172	70	Swimming	6	7.71	69	P, S, A, F, L	None
4	23	M	196	93	Volleyball	4	7.92	106	P, S, A, F, L	None
5	19	M	194	91	Basketball	4	8.26	17	P, S, A	L, F
6	33	M	180	83	Skiing	14	7.63	21	P, S, A, F, L	None
7	26	M	174	73	Soccer	9	8.97	4	P, L, S, A, F	None
8	29	F	174	67	Handball	7	9.47	165	P, L, S, A, F	None
9	20	M	174	76	Skiing	5	7.78	51	L, P, S, F, A	None
10	17	M	175	75	Bicycling	10	9.68	44	P, L, S, A, F	None
11	26	M	194	102	Football	6	9.73	124	–	L, S, A, P, F
12	29	F	175	70	Handball	7	7.94	171	S, A, P, F, L	None
13	24	M	169	71	Soccer	4	7.83	16	S, P, A, L, F	None
14	25	M	167	57	Running	8	7.50	207	S, P, A	None
15	32	M	190	92	Basketball	11	9.13	71	–	L, P, S, A
16	35	M	178	74	Soccer	10	8.81	9	A, S, P, L, F	None
17	28	F	166	69	Skating	9	8.47	41	A, S, P, F, L	None
18	23	M	186	83	Tennis	8	9.34	94	A, S, P, F	None
19	21	F	166	57	Hockey	6	9.05	3	A, S, P, F	None
20	26	M	177	76	Soccer	8	8.18	7	L, S	P, A
21	22	F	177	71	Tennis	7	8.52	83	S, A, P, F, L	None
22	27	M	188	93	Ice hockey	14	9.65	9	A, S, P, F, L	None

FH familial hypercholesterolaemia; CH cholesterol (mmol); A atorvastatin, F fluvastatin; L lovastatin; P pravastatin; S simvastatin.

Results

Except for cerivastatin all the other statins available were tried. Some of the athletes refused to try a further compound (Table 2). When initiating a statin therapy only three (numbers 5, 11, 15) out of 22 athletes (11%) tolerated the chosen drug (Table 2). Another three patients (numbers 1, 2, 20) tolerated at least one statin, while only two athletes (numbers 11 and 15) tolerated all the compounds used. Switching to other compounds we realized that toleration was rare and 16 (78%) athletes did not tolerate any of the compounds tested (Table 2). Symptoms experienced on the different statins in one and the same athlete were very similar. The delay in reporting onset of symptoms was longer during the first drug attempt, possibly because the athletes were more alert to the possible emergence of muscle problems. After drug withdrawal, symptoms in most of the patients disappeared within a few days (< 1 week) and in all of them within 3 weeks. Patients 1 and 2 were already reported in part in our earlier work describing statin associated exercise-induced muscle pain without CK-alteration for the first time [6]. An increase in CK above the value usually found in professional athletes was not seen. In the present study an increase in any of the liver enzymes was not observed in any of the athletes. Testing for anabolic steroids was negative in all of them. Fenofibrate given finally mainly to those athletes with extremely elevated Lp(a) did not produce any adverse reaction in the six athletes treated so far.

Discussion

Thompson *et al.* first described exercise-induced skeletal muscle injury with CK-elevation but in the absence of symptoms after lovastatin [10]. Prevalence of muscle pain without exercise may increase in hobby athletes and even further in professional athletes. Regardless of the biochemical background statin therapy and top athletics seem to be almost incompatible. Whether top athletes are more likely to report side-effects affecting the results remains open. Switching to nonstatin lipid reduction therapy or (in less severe FH) to postpone treatment seemed to be the only options available. As biopsy studies [2] and blood examination [11] revealed an oxidation injury which may be further aggravated by heavy exer-

Table 2
Individual problems top athletes exhibited on the respective statins, time to onset and the drug prescribed finally

Patient	1st statin	2nd	3rd	4th	
1	L: MP(a), D7	P: MP(a), D7	S: MP(a), D3	F, A: tolerated	A →
2	P: MP(a), D10	L: MP(a), D7	S: MP(a), D5	F, A: tolerated	A →
3	P: CK,MP(a), D6	S: CK,MP(a), D3	A: CK,MP(a),D2	F: MP(a), D5	L: MP(a), D5 → 0
4	P: MP(w), D18	S: MP(w,a), D12	A: MP(w), D11	F: MP(w), D17	L: MP(w), D14→ 0
5	L: tolerated	P: MP(c,o), D3	F: tolerated	S: MP(w,a), D12	A: MP(c,o) → L
6	P: MP(c), D6	S: MP(c), D9	A: MP(c), D6	F: MP(c), D5	L: MP(c), D7 → 0
7	P: MP(w), D16	L: MP(w), D14	S: MP(w), D10	A: MP(w), D10	F: MP(w), D7 → 0
8	P: MP(o), D12	L: MP(o), D14	S: MP(o), D8	A: MP(o), D5	F: MP(o), D4 → Fe
9	L: CK,MP(a), D4	P: CK,MP(a), D4	S: MP(a), D4	F: MP(a), D3	A: MP(a); D3 → Fe
10	P: MP(a,w), D18	L: MP(a,w), D14	S: MP(a), D9	A: MP(a), D8	F: MP(a), D7 → 0
11	L: tolerated	S: tolerated	A: tolerated	P: tolerated	F: tolerated; → A
12	S: MP(a), D6	A: MP(a), D8	P: MP(a), D10	F: MP(a), D7	L: MP(a), D6 → Fe
13	S: MP(c), D3	P: MP(c), D3	A: MP(a), D8	L: MP(w), D12	F: MP(a,w), D5 → 0
14	S: MP(w,a), D9	P: MP(w,a), D7	A: MP(a), D5	–	→ Fe
15	L: tolerated	P: tolerated	S: tolerated	A: tolerated	→ A
16	A: MP(a), D6	S: MP(a), D8	P: MP(a), D9	L: MP(a), D5	F: MP(a), D4 → 0
17	A: MP(w,c), D11	S: MP(w,c), D14	P: MP(w), D10	F: MP(w,c), D8	L: MP(w), D10 → Co
18	S: MP(w), D5	A: MP(w), D7	P: MP(w), D9	F: MP(w), D6	→ Fe
19	A: MP(o), D16	S: MP(o), D13	P: MP(o,w) D8	F: MP(o), D12	→ 0
20	L: MP(c,w), D5	P: tolerated	A: tolerated	S: MP(c,w), D4	→ A
21	S: CK,MP(a,c),D4	A: MP(a,c), D5	P: MP(a), D6	F: MP(a), D8	L: MP(a,c), D5 → 0
22	A: MP (w,o), D12	S: MP(w,o), D10	P: MP(w), D8	F: MP(o), D10	L: MP(o,w), D7 → Fe

A atorvastatin; Co colestyramine; F fluvastatin; Fe fenofibratre; L lovastatin; P pravastatin; S simvastatin; 0 no drug; CK CK-elevation; MP muscle pain (a = ache-like,c = cramp-like, w = weakness, o = others); Dx onset in × days.

cise (the underlying pathogenesis being unknown), withdrawal of statins until after finishing an athletic career considering the usually high HDL these patients have may be advisable. The decision, however, remains a very individual one based only on experience and risk calculation rather than facts or recommendations available.

The case report that incidental vitamin E administration improved statin-induced muscle pains [12] led to the discovery that many of these patients show increased lipid peroxidation while normally statin therapy causes a decrease [13]. It has been described that in patients with muscle problems on all the statins a withdrawal of the drug results in cessation in muscular symptoms [14] as also seen in the athletes.

In the original description on exercise-induced muscle pain on statins [6] problems in all the eight patients (six of them performing hobby sports activities) disappeared after fluvastatin; in our group of top athletes, however, the prevalence of side-effects on all the compounds examined seemed to be comparable. The limitation of this observation is the lack of a control. However, at least six of them tolerated some statin. Our data are raising a concern on the use of statins in elite professional athletics. In order to definitely test the hypothesis, however, there is a strong need for a placebo-controlled trial of statins in subjects undergoing intensive exercise.

In conclusion, our findings demonstrate that the great majority of professional athletes with severe FH do not tolerate any of the statins available.

The valuable help of Eva Unger in preparing and typing the manuscript is gratefully acknowledged.

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