



Review Article

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Relationship between Statins Adverse Events and Pharmacokinetic Variables



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Abstract

Background: Statins are a widely used class of drugs very effective in reducing the levels of cholesterol and the mortality for cardiovascular events. Despite these drugs are usually well tolerated, adverse events, such as diabetes type II and myopathy can arise and cause a significant limitation to the therapy adherence. Statins pharmacokinetics (PK) characteristics may have an impact on the determination of these adverse events.

Methods: 14 reviews and 92 papers reporting the PK data were analyzed for the correlation between PK variables and: a) the risk of diabetes type II [DRR] as reported in the Ontario Diabetes Database; b) the myopathies as reported in MAERS (Adverse Events Reporting System between 2005-2011) of FDA. The correlation coefficient "r" and the Ellipses Density were used to calculate the relationship between the variables.

Results: DRR seems to be directly correlated with t_{1/2} (r = 0.921 p < 0.05) and potency of statins (r=0.894 p<0.05), whereas impairment of muscle coordination/weakness seems directly correlated with fecal excretion (r = 0.817 p < 0.05) mirroring the gastrointestinal recycling. Among the statins pravastatin, lovastatin and fluvastatin were shown safer for the diabetes recurrence and lovastatin was found less myotoxic.

Conclusion: Theoretically for every statin an equilibrium between activity and side effects may exists. Lovastatin seems to be the safer. Since age and concomitant therapies can interfere with PK variables, it is important to reduce the dosage at the minimal effective amount, favoring the bed time administration and the physical exercise.

Keywords : Statins; Myopathy; Diabetes type II; Pharmacokinetics

Introduction

There are no doubts that statins together with steroids, antibiotics and diuretics are among the most important drugs of the last two centuries. Despite the improvement of the life expectancy, statins have to be used carefully to avoid any misuse that could bring the patients from the benefit to the risk of damaging side effects [1,2].

Statins (hydroxymethyl-glutaryl coenzyme A reductase inhibitors or HMG-CoA reductase inhibitors) are characterized by different potency [3] which is reflected by the daily dosage, ranging between 2mg (pitavastatin) and 80mg (fluvastatin), with intermediate dosages of 10, 20 and 40mg respectively for atorvastatin, simvastatin, and lovastatin.

Table 1: Main pharmacokinetics variables of statins and the risk of diabetes and my toxicity.

Variable	Measure	Statins							
		Atorva	Ceriva	Fluva	Lova	Pitava ^e	Prava	Rosuva	Simva
Absorption (AB)	%	30	98	90-98	30	90	32-35	50	70-85
Bioavailability (F)	%	Dec-41	60	20-25	5	51-60	18	20	5

Protein Binding (PB)	%	85-98	99	98-99	80-95	99	45-50	88-90	90-96.5
Half Live (T ^{1/2})	h	12.6-32.6	2-5 ^d	0.75-3	1.4-3	Jun-14	1.6-2	19-20.8	1.9-5.6
Renal Excretion (RE)	%	2.3-5	30	4.9-6	13-30	15	20-60	10	13
Fecal Elimination (FE)	%	70-98	70	90-95	64-83	79	45.5-71	90	58
Clearance (CL/F) ^A	mL/min/kg	4.2	3.3	8.8-16.2	9.7 -10	2.5-8	11.3-11.7	10.5	7.5
Potency ^b (P)	mg	10	0.3	80	40	2	40	5	20
Risk of Diabetes (DRR)	Odd ratio	1.22	NA	0.95	0.99	NA	1	1.18	1.1
Risk of Myopathy (Maers)	Primary ^c	58	NA	84	10	NA	21	88	43
a=the values were present in 1 to 4 reviews only ; b=Dosage needed to obtain 31-35% reduction of LDL;									
c=Primary suspect AE; d=the references (100) was added to the values reported in the reviews; e= the values were taken from references 15, 101-110 since the complete set of data was reported in one review only.									

Recently the incidence of side effects, such as diabetes [1] and myopathy [2], have been focused respectively on population based cohort studies for the diabetes risk [DRR] and following a survey of the FDA's Adverse Events Reporting System for Myopathies [MAERS]. In terms of diabetes, pravastatin was taken as the reference drug with DRR = 1 and compared to the other five statins with available risk data. No significant DRR increase was found for lovastatin and fluvastatin, whereas atorvastatin, rosuvastatin, and simvastatin resulted associated with a significantly higher DRR (Table 1).

For the myopathy, MAERs were indicated aligning with potency since rosuvastatin showed the higher risk, atorvastatin and simvastatin intermediate risk, whereas pravastatin and lovastatin appeared to bring the lowest risk rates. No data for DRR and MAERs were available for pitavastatin, whereas cerivastatin was withdrawn from the market few years ago and they were not listed into the published FDA report.

Although the structural characteristics and the metabolic pattern may determine some important difference in the activities of statins, the pharmacokinetics (PK) variables were never taken into account for a systematic analysis of their possible correlation with these two specific side effects. For these reasons we tried to correlate all the most common PK variables with the diabetogenic and myotoxic risk currently available [1,2] for 6 different statins.

Methods

Data sources

We have at first analyzed 14 of the published reviews on the PK of statins [4-17] focusing the usual common variables (e.c. absorption, bioavailability, protein binding, see Table 1). Most

of the times the half-life of statins reported in the reviews was not differentiating between the lacton and the acidic forms, in particular for lovastatin and simvastatin that may have a different impact on the adverse reactions. For these reasons we re-analyzed 92 publications available on Medline [18-110]. We reviewed also the clearance values (CL/F) that were re-calculated for all the products according to a common formula, based upon the non-compartmental methodology and consisting of FD/AUC [0-∞]. FD is the dosage fraction measured in ng (nanograms) and represented the absorbed quantity of the given statin; AUC [0-∞] was the area under the plasma curve in terms of ng/mL/h. According to this formula, CL/F was expressed in mL/min/kg. In case the body weight of the subjects was not reported (surprisingly!) a standard body weight of 70kg was considered, with the exclusion of Chinese and Korean volunteers for whom the standard body weight was fixed to 60kg. Since for the majority of the PK trials single data were not available, all the correlations between variables were calculated on the base of the average data. The potency of statins was based upon the dosage to be administered to obtain a similar reduction of LDL as reported in Goodman & Gilman's "The Pharmacological Basis of Therapeutics" 12th Ed. p.895.

Statistical analysis

The statistical analysis was based on the correlation coefficient "r" between the PK variables and DRR or MAERs was also applied.

Result

PK variables

The PK variables reported on the 14 reviews were summarized in Table 1. They were related to apparently healthy

volunteers, following a single administration, and represented the average values or ranges as described in the reviews. Last two rows of the Table 1 report the side effects in terms of DRR for diabetes and MAERs for myotoxicity.

^aP < 0.01; ^bp < 0.05

Absorption [AB]; Bioavailability [F]; Protein binding [PB]; Half live [$t^{1/2}$]; Renal excretion [RE]; Fecal elimination [FE]; Clearance [CL/F]; Potency [P]; Risk of diabetes [DRR]; Risk of myopathy [MAERs].

All the reviews indicate that most of the PK variables may change according to age, sex, race, time of administration (morning Vs evening), fasting, and polymorphism. Furthermore, there were also indications that some of the statins were sensible

to liver and kidney impairment, and to the concomitant therapies which can interfere because of some metabolic competition.

Potency of statins was considered using as co-variable the dosages equivalent approximately to the 31-35% reduction of LDL, defining the potency as follows: cerivastatin > pitavastatin > rosuvastatin > atorvastatin > simvastatin > pravastatin=lovastatin > fluvastatin.

The correlation matrix is reported in Table 2 and was based upon the average data listed in Table 1. For those variables consisting of range values, the average value was taken as covariate for the calculations. Some of the correlations were statistically significant, both with positive (direct) and negative (indirect) values and the signs were most of the time coherent. The following indications can be drawn:

Table 2: Correlations (“r”) between pharmacokinetics variables of statins and diabetes risk (DRR) or Adverse Events Report System (MAERs). Values correspond to “r”.

	AB	F	PB	$t^{1/2}$	RE	FE	CL	P	DRR	MAERs
AB	1	-0.042	0.499	-0.352	-0.44	0.239	0.184	0.545	-0.334	0.577
F		1	0.002	0.569	-0.302	0.701	-0.098	0.084	0.24	0.496
PB			1	0,269	-0.924 ^a	0.599	-0.455	0.008	0.242	0.536
$t1/2$				1	-0.537	0.497	-0.682	-0.724	0.921 ^a	0.496
RE					1	-0.714	-0.595	0.109	-0.462	-0.728
FE						1	-0.062	0.141	0.188	0.755
CL							1	0.636	-0.806	-0.149
P								1	-0.894 ^a	-0.009
DRR									1	0.355
MAERs										1

1. the inverse relationship between RE and PB was significant (p<0.01) indicating that the renal excretion of statins is limited by the PB;
2. the DRR was directly correlated with the $t1/2$ (0.921; p<0.01) standing for a more pronounced diabetogenic tendency in relation to the drug permanence in the plasma;
3. DRR showed a direct correlation with potency also (-0.894; p<0.05), the negative value was because the

covariate was the dosage;

4. despite RE and FE were not significantly correlated with MAERs, the values (respectively -0.728 and 0.755) were close to be significant (p<0.07);
5. the analysis of myotoxicity in relation to FE was extended to every symptom using as covariate the primary AEs as they were reported in the FDA's database (see Table 3);

Table 3: Correlations (r) between fecal excretion (FE) and primary MAERs of FDA database related to statins drug class. 6

	Atorva	Fluva	Lova	Prava	Rosu	Simva	R Vs FE
							correlation
Myalgia	57	69	5	20	100	18	0,802
Myopathy	67	100	17	21	78	54	0,738
Myositis	63	91	7	25	81	100	0,284
Rhabdomyolysis	38	100	14	16	91	71	0,549
Joints & Tendoms	56	60	8	18	100	18	0,790
Muscle Atrophy	73	100	10	31	69	24	0,804
Muscle Coord/Weak*	51	68	7	14	100	18	0,817 ^a

6. among the various MAERs only muscle coordination and weakness was found significantly correlated with FE, whereas myalgia, myopathy, joint & tendon, muscle atrophy were close to be significant (r between 0.738 and 0.804 $p < 0.07$), and myositis and rhabdomyolysis were found to be independent;

7. The same analysis was conducted for UE (data not reported), and for myalgia only an inverse correlation was found close to the statistical significance ($r = -0.809$ $p < 0.06$).

As usual, FE was expressed as % of the product that was absorbed and then excreted through the bile into the intestine.

In kinetics terms this excretion should be part of the total CL which essentially is the combination of the renal and hepatic clearances. The lack of correlation between CL values and both DRR and MAERs was considered as a discrepancy, and stimulated the re-analysis of almost all PK data published (abstract were excluded).

Among all the studies [18-110] only those reporting PK data pertinent to the original product and/or lacton plasma levels were analyzed (see Table 4). In the reviewed studies there was a large prevalence of males (678 M and 311 F) for all statins, with the exclusion of pravastatin (139 M; 114 F). The body weight and age range were almost similar for all the products (see Table 4).

Table 4: PK general characteristics of the pertinent original statins (as acid/lacton).

Statin	CL/F a mL/min/kg	$t^{1/2}$ h	N of trials (references)	N of cases (M;F)	mean age range (years)	Mean BW range (kg) ^a
Atorva acid	22±9.2	9.5±3.72	4 (18,19,23,26)	48 (35 M; 13F)	23-35	67-77
Atorva lacton		10.4± 3.31				
Fluva acid	31 ±16.4	1.8±1.14	10(31-40)	20 (137 M; 66 F)	22-65	65-75
Lova lacton	34±22.8	2.9±1.43	14 (20,42-47, 49, 51,52, 55-58)	239 (173 M; 66 F)	22-65	64-73
Lova acid		2.6±0.48				
Prava acid	25±13.8	2.0±1.11	14 (19,26,31,34, 41,48,50,60,61, 65,67,68,70,71)	280 (150 M; 130 F)	22-79	56-82
Rosuva acid	22±13.8	16.3 ±5.33	14 (58,72-79,81-85)	184 (157 M; 27 F)	24-49	59-87
Simva lacton	124±48.1	2.8±0.80	9 (67,86-92)	100 (61M;39 F)	22-51	62-84
Simva acid		3.1±0.51				

a) The CL/F was calculated on the base of the average “absorbed dosage” (as reported in Table 1): in the general formula: FD/AUC . AUCs of atorvastatin, lovastatin and simvastatin were represented by the sum of lacton and acid area.

b) 60 Kg were taken as a standard value for trials conducted in China and Corea that were not indicating the body weight, in all the other studies not reporting the body weight 70kg were taken as standard value.

Some discrepancies were found between the values reported in the reviews and our calculations. In particular the half life of atorvastatin and rosuvastatin resulted much lower than those indicated by the other authors (reported in Table 1). For atorvastatin, the averages of our analysis were 9.5-10.4 h respectively for acid and lacton, whereas a combined range between 12.6 and 32.6 h was found in the reviews. For rosuvastatin the average value in our analysis was 16.3h compared to a range of 19-20.8h of the reviews. However, even considering our data the correlation between DRR and half life still remained significant (0.835 $p < 0.05$).

The highest discrepancy came out from the CL values. This was because our calculations were based upon the average “absorbed dosage” (see Table 1) that end up with higher values than those calculated using the bioavailable dosage. In any case, the correlation between our CL values and both DRR and MAERs did not became significant.

Discussion

Despite many limitations, some practical indications came out from this analysis:

1. The power of statins is correlated with the diabetogenic side effects
2. the diabetogenity is in relation to a longer half life
3. The impairment of muscle coordination and weakness are correlated to the fecal excretion.

The first point doesn't need much explanation, since this side effects can be taken as part of the pleiotropic effects of statins that basically are all dose related. However, lovastatin came out to be less toxic than the other statins although it can

reduce cholesterol levels in the same way. This indicates that an equilibrium exists between activity and side effects that theoretically can be found for every statin.

The second point indicates that product with longer half live (atorvastatin and rosuvastatin) can cause diabetes II with relatively higher frequency than short half life statins. This can be due in part to some accumulation of the drug following repeated administration. Lipophilic molecules represented by the lactonic form can have a more consistent penetration in the tissues than the acidic moieties. The more diabetogenic statins such as atorvastatin and rosuvastatin, despite administered as acidic forms were shown to be transformed into the lactonic forms that usually are characterized by a longer half life than the parent drug. This last point is consistent with the long permanence in the liver and other tissue (as muscles and pancreas) that may be determinant for this specific side effect.

The relationship between fecal excretion and myotoxicity needs a more complex “explanatory hypothesis”. During the first pass effect, both the intestine and the liver acting as a barrier do not allow the given statin to reach the circulation. However, the product cannot flow immediately into the liver because the enterocytes takes up part of the drug, and then they release it back to the intestinal fluid (apparently as it happens with phytosterols). The consequence of this “cycling” is such that the statin will be theoretically absorbed diffusing within the intestine without reaching the liver. The part of the statin crossing the intestine and getting to the liver can follow four ways only: part will inhibit the HMG-CoA reductase, part will be metabolized (via CYPs or other pathways such as sulfation), part will be “exported” in the tissues, and all the remaining part (free or bound to the bile salts) will be excreted via the biliary system into the gut. Once in the intestine the statin and/or the metabolites can be reabsorbed for a “second” first pass effect, recycling between and gut and liver.

In a different perspective, the fecal excretion mirrors the gut/liver recycle and the gut/liver metabolic burden also. This “circle” cannot be picked up by the classical CL measurement that stands for the amount of blood cleared out from the drug (in mL/min/kg or equivalents), simply because the product doesn't arrive to the extra-hepatic circulation.

This could mean that myotoxicity and diabetogenic tendency belong to the liver/gut burden mainly and only to the concentration in muscles and pancreas. For what concerns cerivastatin, one may say that its potency could give some suspect about the diabetogenicity, but fecal excretion was not higher than other safer statins and consequently myotoxicity should not be more prominent than with the other statins. This may indicate that, as supposed by many authors, the interference with the concomitant therapies such as gemfibrozil could be the cause of rhabdomyolysis and other myotoxic symptoms.

Pitavastatin is lacking of monitoring data on both diabetes and myotoxicity. The potency and the relative long half-life of the

product may give some suspect for diabetes, whereas in terms of MAERs the fecal excretion seems to be close the one observed for safer statins.

Indications for the Therapy with Statins

One may not argue about the activity of statins or about their efficacy in controlling cardiovascular events. The arguments concerning primary or secondary prevention of cardiovascular diseases has been clarified in hundred of clinical trial, and doctors can easily tailor any statin to the patient's need [93]. The real threat of statins is the misuse, and the relative side effects cannot be denied. The risk benefit ratio could be improved substantially if the patient's therapy will follows some very simple rules.

Because of the underlined mechanisms of toxicity, the suggestions for the doctors could be: a) to reduce the dosage as much as possible; b) to give the treatment in the evening (cholesterol synthesis is peaking between midnight and the first hours of the morning), no matter if in some author was showing that the evening and morning administration end up with identical activity. The evening administration (just before sleeping) will have a favorable impact on oxidative stress. During sleep the oxidative stress become minimal, and the liver, the gut, and all the tissues interested by the statin's pleiotropic effect can use their metabolic energy to get a rid of the drug excess and relative toxic metabolites. Finally the gut/liver recycle will be minimal for the reduction of bile secretion.

Similarly, physical exercise will improve the antioxidant defense, since trained muscles are extremely efficient in producing enzymatic antioxidants that can help in controlling the oxidative stress deriving from the statin's metabolic burden. According to the evening scheme of treatment, the morning intake of grape fruit juice should not compromise the plasma levels of statins with short half live (fluvastatin, lovastatin, pravastatin, simvastatin).

There are also alternative therapies based upon the lovastatin, that was found to be safer than the other statins, but still may have same side effects. Lovastatin can be administered as a “food supplement” in formulations containing *Monascus purpureus* [94-97]. However, doctors have to prescribe the product (not TV or advertising) and should be minded to give dosages (in the evening) not exceeding 10mg/day of monakolin K (which is lovastatin). Furthermore, products containing *Monascus p.* plus berberine should be avoided, since the latter has about 30h of half-life [98], tends to accumulate following repeated administration, and can be potentially toxic [99].

Limitations and Strengths

The main limitation of this study was that all the variables reported consist of average values. The use of average values does not allow to determine the variance, which was quite large for all the products. The PK variances of statins suffer of multiple interferences for absorption, transportation in and out of the liver, polymorphism, and finally for the involvement

of different CYPs. During the analysis we have noted that differences on the variables can derive also from morning and evening administration, fasting, age and sex. The race difference is also known, particularly for some Asiatic people that need to be treated with lower dosages. Furthermore, most of the studies were conducted in healthy volunteers and the concomitant therapies may have an important impact on the PK variables. However, these were the same problems that had to be faced by the authors of the 14 reviews.

Some of PK data reported in the literature of the seven statins were lacking of important information such as body weight of volunteers, and the measure of the apparent distribution volumes (VD) was very rare for all the products and impossible to be re-calculated. This last point was due to the lack of the values of the drug absorption (for pitavastatin was not reported in any paper), and because the data on plasma concentrations were presented only as figures and not as values.

In same study was also difficult to end up with precise calculation of AUC [0 to infinity], particularly for those statins with higher half-life. Since the CL measure belongs to the ratio D/AUC, sometimes was hard to make a precise determination of AUC $[[0-\infty]]$ that in our calculations may contain estimation errors up to the 10 %. However, even an errors up to 10% of AUC will not change the CL in a sensible way.

Another limitation belongs to the different methodology used both for chemical analysis of the same statin (inter-laboratory variations), for the blood sampling time (sometimes too short) and for the evaluation of PK variables that were calculated applying different models (compartmental or non-compartmental). However, the variable we used for the reanalysis ($t^{1/2}$ and AUC) were very solid and made our evaluation sufficiently precise.

The few number of correlation couples available, 6 points only, implies that data have to be considered carefully. In the future the side effect records with pitavastatin (in case they will appear) may improve the power of the correlations. The strength of the study was the complete review of most of the available PK data on statins. At the end of the analysis we were wandering if doctors that are not very well skilled in PK can come out from the fog generated by all the information given that sometimes is redundant, and with no practical explanation. This could mean that the doctor has to rely on his experience only, no matter about polymorphisms and drug interferences, that although important, most of the time seem more oriented to the commercial differentiation.

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