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Brief Report

Pharmacokinetic Properties of Pravastatin in Mexicans: An Open-Label Study in Healthy Adult Volunteers

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ABSTRACT

Background: The pharmacokinetic properties of pravastatin, particularly AUC and C_{max}, are variable by population. A description of the pharmacokinetic properties of pravastatin in Mexican mestizos was not found in a search of MEDLINE/PubMed (key terms: *pravastatin, Mexican,* and *pharmacokinetics*; years: 1966–2005). Because Mexicans and Japanese have common ancestors (Mongoloid group), they also have a common gene pool. This gene pool was modified by genetic "bottlenecks" that occurred when these populations migrated to the Americas and when the Mexican population mixed with the Spanish population during the 16th and 17th centuries. Previous studies in Japanese subjects showed 5 main mutations on the hepatic drug transporter *OATP-C,* resulting in higher C_{max} and AUC values compared with whites. In the Japanese population, the rates of expression of the **1b* and **15* alleles were 46% and 15%, respectively.

Objective: The aim of this study was to evaluate the pharmacokinetic properties of pravastatin in healthy Mexican mestizo volunteers and to compare them with those in white and Japanese populations described in the literature.

Methods: This open-label, uncontrolled pilot study of the pharmacokinetic properties of pravastatin was conducted at the Division of Pharmacology, Center for Research and Advanced Studies, Mexico City, Mexico. Healthy, adult, Mexican volunteers received a single dose of pravastatin 10 mg PO (tablet). High-performance liquid chromatography was used to determine plasma pravastatin concentrations between 15 minutes and 12 hours after dosing.

Results: Twenty-four subjects (15 women, 9 men; mean age, 30.6 years) participated in the study. The mean (SD) C_{max} was 9.5 (2.4) ng/mL; T_{max}, 0.8 (0.3) hours; $AUC_{0-\infty}$, 35.7 (19.7) ng/mL · h; $t_{1/2}$, 2.7 (1.1) hours; and mean residence time, 3.1 (1.1) hours. One volunteer (4%) had an AUC value that differed substantially from the rest of the study population, producing a bimodal distribution of the pharmacokinetic parameters. No adverse events were observed or reported during the trial.

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Conclusions: In this small pilot study of the pharmacokinetic properties of pravastatin in Mexican mestizos, AUC was not statistically significantly different from previous studies, either in a white or Japanese population. However, we did not find the high values reported for C_{max} in some Japanese subjects carrying recently reported mutations on the pravastatin transporter. (*Curr Ther Res Clin Exp.* 2005;66:238–246)

Key words: pravastatin, pharmacokinetics, oral administration, AUC.

INTRODUCTION

Pravastatin is a cholesterol-lowering inhibitor of hydroxymethylglutaryl coenzyme A reductase (statin), which is involved in the de novo synthesis of cholesterol.[1,2] The first available statin, mevastatin, was isolated from the fungus *Penicillium citrinum* but was not marketed due to safety concerns (eg, hepatotoxicity).[3] Pravastatin is indicated for the treatment of hypercholesterolemia and the prevention of cardiovascular disease, diabetes mellitus,[4] and renal disease.[5,6] Once absorbed, pravastatin undergoes the first-pass effect as it enters the enterohepatic circulation, resulting in poor bioavailability (18%).[7] Pravastatin is metabolized in the stomach and duodenum.[2]

A previous study[8] in Japanese subjects showed 5 main mutations on the hepatic drug transporter *OATP-C,* resulting in higher C_{max} and AUC values compared with those in whites. In the Japanese population, the rates of expression of the **1b* and **15* alleles have been found to be 46% and 15%, respectively.[8] Because Mexicans and Japanese have common ancestors (Mongoloid group), they also have a common gene pool. This gene pool was modified by genetic "bottlenecks" that occurred when these populations migrated to the Americas and when the Mexican population mixed with the Spanish population during the 16th and 17th centuries.[9]

Although the clinical efficacy of pravastatin in Mexican patients has been shown,[10] a MEDLINE/PubMed search (key terms: *pravastatin, Mexican,* and *pharmacokinetics*; years: 1966–2005) revealed no published pharmacokinetic data for pravastatin in the Mexican population. Therefore, the aim of this study was to evaluate the pharmacokinetic properties of pravastatin in healthy Mexican mestizo volunteers and to compare them with those in white and Japanese populations described in the literature.

SUBJECTS AND METHODS

This open-label, uncontrolled pilot study of the pharmacokinetic properties of pravastatin was conducted at the Division of Pharmacology, Center for Research and Advanced Studies, Mexico City, Mexico. The local ethics committee revised and approved the study protocol.

Healthy subjects (as determined by physical examination and laboratory tests [complete blood count, biochemistry, creatinine clearance]) aged 18 to

50 years who could read, understand, and sign an informed-consent form were eligible for the study. Subjects were excluded from the study if they had any known pathology, had ingested any drug in the previous 8 days, used any psychotropic drug, abused drugs or alcohol, or were unwilling to provide written informed consent. Women who were pregnant, possibly pregnant, or breastfeeding were also excluded from the study.

Eligible subjects were recruited from a typical middle-class neighborhood in northern Mexico City. This middle-class group consists mainly of people of mestizo origin (the ancestry of this group is ~60% Native American, ~38% white, and ~2% African[11,12]) in Mexico City.[13] A correlation between middle economic income and mestizo origin in Mexico City has been found in a previous work.[13]

After an overnight fast, a 10-mg tablet of pravastatin was administered to each subject at 8:00 AM. A light lunch was served 3 hours later. High-performance liquid chromatography (HPLC) was used to determine plasma pravastatin concentrations between 15 minutes and 12 hours after dosing. Blood samples were collected from the cubital vein by a qualified nurse at 0, 15, and 30 minutes and 1, 2, 4, 8, 10, and 12 hours using Vacutainer heparin tubes (Becton, Dickinson and Co., Franklin Lakes, New Jersey). Seven milliliters of whole blood was kept after discarding 3 mL. Plasma was immediately separated by centrifugation (3500*g* at room temperature for 10 minutes) and kept frozen at –20°C until analysis (within 3 months). Pharmacokinetic properties were compared with data from published studies in white and Japanese populations. Spontaneous reports of adverse events were recorded.

Vital signs (blood pressure, heart rate, and body temperature) were monitored before, during, and at the end of the trial.

Equipment and Reactives

An Agilent series 1100 with automatic degassing system, quaternary pump, heated column, and diode array was used for HPLC. The column was a Zorbax XDB-C18 4.6 × 150 mm (Waters, Milford, Massachusetts). The reagents were Milli-Q deionized water, acetonitrile (Tecsiquim, Mexico City, Mexico), monobasic sodium phosphate ($NaHPO_4$), and dibasic potassium phosphate (K_2HPO_4) (J.T. Baker, Mexico City, Mexico).

Extraction and Chromatography

Pravastatin was extracted from 1 mL of plasma with C18 extra-clean columns (Alltech, Mexico City, Mexico). Conditioning was carried out with 2 mL of methanol and 1 mL of water. The internal standard was dicloxacillin. Extraction and chromatography were based on the published method of Otter and Mignat.[14] A washing step with 1 mL of water preceded the elution with 0.5 mL of acetonitrile:water 50:50.

The mobile phase was phosphate buffer (20 mmol/L):acetonitrile 56:44 at 1.0 mL/min. The temperature of the column was maintained at 40°C and run

time was 8 minutes. The detector was set to 239 nm, and the method was validated according to Causon's procedures.[15]

AUC was chosen as the response function. Correlation coefficients were always >0.999; precision was 14.5% at the lower limit of quantification (5 ng/mL) and 12.1% at the higher limit (200 ng/mL). The intraday and interday biases were always <13%.

Pharmacokinetic and Statistical Analysis

Basic pharmacokinetic model–independent parameters were calculated. Quartiles and frequency histograms were used to observe the distribution of C_{max} and AUC. Data are given as mean (SD). Best fits were chosen using Akaike criteria[16] provided by the P-Pharm program (Innaphase, Philadelphia, Pennsylvania), which measures the weighted sum of squares considering the number of parameters and number of observations taking the natural logarithm. Statistical comparisons of AUC values were performed using raw data estimations based on SDs and CIs. We compared our data with those from previous studies[8,17–20] using 1-way analysis of variance and the Tukey test. Statistical calculations were performed using Minitab version 14 (Minitab Inc., State College, Pennsylvania).

RESULTS

Twenty-four healthy volunteers (15 women, 9 men; mean age, 30.6 years) participated in the study, and all of them completed it. In the women, mean (SD) age was 33.6 (11.1) years and mean (SD) body weight was 56.0 (24.4) kg; in the men, the mean (SD) age was 29.1 (11.5) years and the mean (SD) body weight was 67.6 (27.8) kg.

Baseline mean (SD) values for the vital signs were as follows: systolic/diastolic blood pressure, 101/65 (33/21) mm Hg; heart rate, 82 (17) bpm; and body temperature, 36.5°C (0.2°C). No significant changes in the mean values were observed after pravastatin administration.

The mean plasma pravastatin concentrations are shown in **Figure 1**. Mean (SD) C_{max} and T_{max} values were 9.5 (2.4) ng/mL and 0.8 (0.3) hours, respectively, giving an $AUC_{0-\infty}$ of 35.7 (19.7) ng/mL · h (**Table I**). One volunteer had an outlier $AUC_{0-\infty}$ value, producing a bimodal distribution of the pharmacokinetic parameters. The $t_{1/2}$ of subject 24 was not possible to fit, so the AUC is shown as AUC_{0-12}. The mean Akaike value for individual fittings was 13.3.

The mean $t_{1/2}$ in the present study (2.7 [1.1] hours) was numerically greater than in previous studies (**Table II**).[8,17–20] The mean variability of the parameters between patients in this study was 44% (**Figure 2**). The variability in AUC (55%) is explained in part by the subject with the outlying value. No adverse events were reported.

DISCUSSION

Several studies of the pharmacokinetic parameters of pravastatin 10 mg have been published (**Table II**).[8,17–20] Because the Mexican mestizos have a gene pool similar to that of Asian populations,[10–12] the results of this study were compared

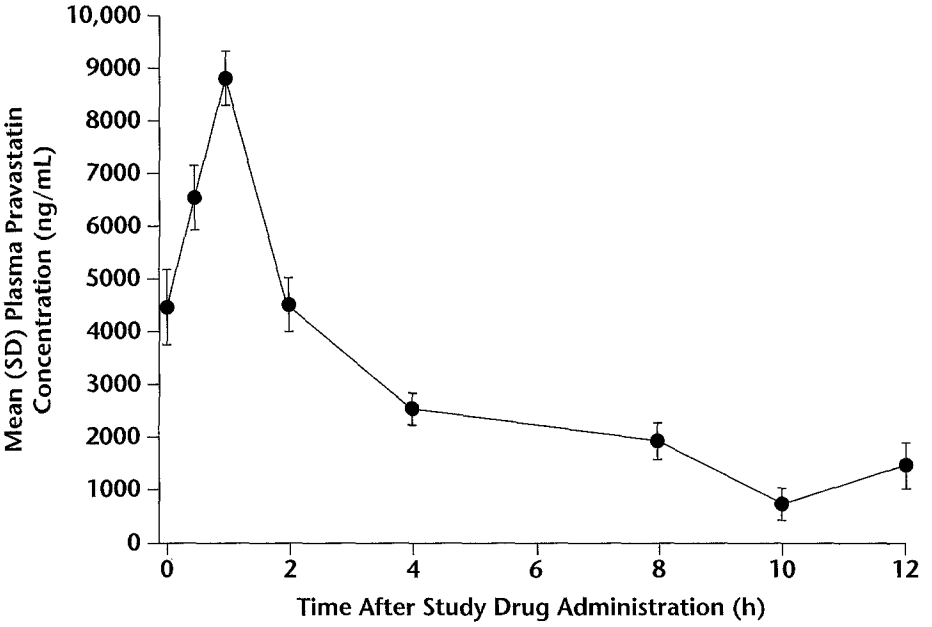

Figure 1. Plasma pravastatin concentrations after a single 10-mg dose. The profile is similar to previous reports in white patients with hypercholesterolemia and numerically lower than levels observed in Japanese volunteers receiving the same dose.

with Asian studies. One study[8] in Japanese subjects found 5 common mutations on *OATP-C* that produce a 5-fold increase in C_{max} and AUC. The expression rates of the **1b* and **15* alleles in the Japanese population have been found to be 46% and 15%, respectively.[8] In a white population, the expression rate of the **15* allele was found to be 0%.[8] Our literature search revealed no data for the *OATP-C* genotype in Mexicans. A previous comparison[9] found the AUC of nifedipine to be more similar between Mexican and Japanese populations than between either of these 2 populations and whites. Ogawa et al[18] evaluated the pharmacokinetic properties of pravastatin 10 mg in 84 healthy Japanese volunteers. They found that the C_{max} values were 4.8% higher in these subjects compared with the rest of the study population. In the present study, AUC was increased in 4% of subjects, whereas C_{max} was not increased in any of the subjects. In a study of 23 healthy Japanese volunteers, Nishizato et al[8] reported 3 *OATP-C* phenotypes (1b, 1b/15, and 15/15). In these individuals, the C_{max} values were 14, 27, and 49 ng/mL (**Table II**). All 3 values were numerically higher than the mean in the present study. Fukazawa et al[19] reported a geometric mean C_{max} of 13.3 ng/mL (range, 8.2–21.3 ng/mL) and an AUC of 40.0 ng/mL · h (range, 28.1–57.0 ng/mL · h) in Japanese subjects. In the present study, the geometric mean of C_{max} was 9.1 ng/mL (range, 4.1–13.7 ng/mL), and the geometric mean of AUC was 31.4 ng/mL · h (range,

Table I. Pharmacokinetic properties of pravastatin 10 mg after PO administration.

Patient No.	C_{max}, ng/mL	T_{max}, h	Ka	$AUC_{0-\infty}$, ng/mL · h	$t_{1/2}$, h	MRT, h
1	13.7	1.0	1.74	28.8	2.4	2.5
2	13.3	1.0	2.10	40.4	3.5	2.5
3	10.3	0.3	2.60	26.6	3.5	1.4
4	11.3	0.5	2.31	33.2	3.5	2.9
5	10.2	1.0	1.94	35.7	3.5	2.8
6	8.9	1.0	10.19	18.7	0.8	2.8
7	7.1	0.5	2.04	20.3	3.5	2.1
8	7.8	1.0	2.21	19.2	1.2	3.4
9	7.9	1.0	2.04	32.1	3.5	2.9
10	6.0	1.0	2.25	12.9	1.1	3.2
11	6.9	0.5	2.08	20.2	3.5	1.6
12	4.1	0.5	1.89	19.2	3.5	1.8
13	9.5	0.5	2.48	18.7	3.5	1.2
14	8.7	1.0	2.29	51.0	3.6	4.6
15	7.8	0.3	13.18	32.6	2.7	3.5
16	10.0	1.0	2.38	45.1	1.7	3.8
17	10.3	1.0	1.28	33.3	1.0	3.1
18	8.0	1.0	3.01	42.6	2.5	4.8
19	9.2	1.0	2.01	32.6	3.5	2.9
20	11.9	1.0	2.38	67.3	3.6	3.6
21	9.7	0.5	2.57	34.2	1.2	4.0
22	13.3	1.0	1.52	53.7	1.7	4.1
23	12.3	0.5	2.57	105.8	4.0	5.3
24	9.0	1.0	1.59	31.8	*	4.3
Mean	9.5	0.8	2.95	35.7	2.7	3.1
SD	2.4	0.3	2.76	19.7	1.1	1.1
CV, %	25	36	94	55	40	34

Ka = absorption rate constant; MRT = mean residence time; CV = coefficient of variation.
*This value was an outlier and so has been omitted here.

5.7–93.8 ng/mL · h). Based on these results, it is likely that no mestizo subjects included in the present study expressed the **1b* or **15 OATP-C* alleles because these alleles produce phenotypes of C_{max} of 14 and 49 ng/mL, respectively, and an AUC of 44.2 and 62.1 ng/mL · h, respectively (**Table II**).

On the other hand, Pan et al[17] reported a mean C_{max} of 11.6 ng/mL; $t_{1/2}$, 2.6 hours; and AUC, 31.3 ng/mL · h after administering pravastatin 10 mg to white patients with hypercholesterolemia. Data from the present study in healthy Mexican mestizo volunteers are similar to those from the study by Pan et al.[17]

Table II. Comparison of pharmacokinetic properties of pravastatin found in this study versus previous studies.

Study	C_{max}, ng/mL	$AUC_{0-\infty}$ ng/mL · h	$t_{1/2}$, h
This study	9.5	35.7	2.7
Ogawa et al[18]	14.0	36.0	2.5
Pan et al[17]	11.6	31.3	2.6
Nishizato et al[8] 15/15	49.0	111.8	3.3
Nishizato et al[8] 1b/15	27.0	62.1	2.7
Nishizato et al[8] 1b/1b	14.0	44.2	2.2
Fukazawa et al[19]	13.3	40.0	–
Sugimoto et al[20]	36.5	109.4	–

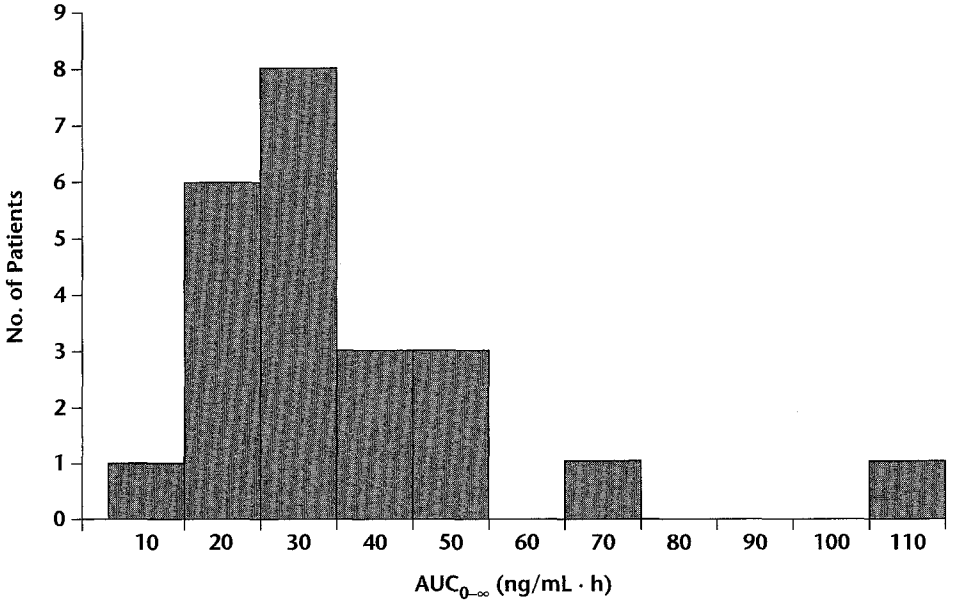

Figure 2. Histogram for the distribution of $AUC_{0-\infty}$ of pravastatin. $AUC_{0-\infty}$ shows polymorphic behavior, but did not reach the values observed in Japanese populations.

Because the methods for pharmacokinetic analysis in most published articles use mass spectrometry linked to HPLC, these studies are comparable.[1,2] Furthermore, the pharmacokinetic properties of pravastatin have been shown to be similar between men and women.[20]

With pravastatin 10 mg, no accumulation has been reported when the drug is administered BID. The $t_{1/2}$ of pravastatin 10 mg reported in most studies is between 1.6 and 3.3 hours.[16–20] In the present study, $t_{1/2}$ fell within that range in 20% of subjects. One subject showed a $t_{1/2}$ between 4 and 6 hours. The mean $t_{1/2}$ in the present study was slightly numerically higher compared with those of previous studies, with the exception of the study by Mazzu et al,[21] in which the authors reported a $t_{1/2}$ of 5.5 hours with pravastatin 40 mg. Pravastatin has "flip-flop" pharmacokinetic properties (ie, absorption is slower than elimination),[7] so the observed $t_{1/2}$ in all studies mainly represent drug absorption, and in some cases drug distribution, both of which can be influenced by the polymorphism on *OATP-C*.

We recommend conducting genomic studies on the Mexican population to verify the presence of an *OATP-C* genotype.

This study is considered a pilot study due to the small sample size and limited statistics compared with previous studies, and because no genomic data were determined. However, it provides an indication of the pharmacokinetic properties in this mestizo population.

CONCLUSIONS

In this small pilot study of the pharmacokinetic properties of pravastatin in healthy Mexican mestizo volunteers, the AUC values were statistically similar to those previously reported in white and Japanese populations. On the other hand, C_{max} and $t_{1/2}$ were numerically similar to those in a white population but not to those in some Japanese populations, which was due to the presence of allele **15* in *OATP-C*.

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REFERENCES

1. Quion JA, Jones PH. Clinical pharmacokinetics of pravastatin. *Clin Pharmacokinet.* 1994;27:94–103.
2. Hatanaka T. Clinical pharmacokinetics of pravastatin: Mechanisms of pharmacokinetic events. *Clin Pharmacokinet.* 2000;39:397–412.
3. Haruyama H, Kuwano H, Kinoshita T, et al. Structure elucidation of the bioactive metabolites of ML-236B (mevastatin) isolated from dog urine. *Chem Pharm Bull (Tokyo).* 1986;34:1459–1467.

4. Prisant LM. Preventing type II diabetes mellitus. *J Clin Pharmacol.* 2004;44:406–413.
5. Halstenson CE, Triscari J, Devault A, et al. Single-dose pharmacokinetics of pravastatin and metabolites in patients with renal impairment. *J Clin Pharmacol.* 1992;32: 124–132.
6. Jandeleit-Dahm K, Cao Z, Cox AJ, et al. Role of hyperlipidemia in progressive renal disease: Focus on diabetic nephropathy. *Kidney Int Suppl.* 1999;71:S31–S36.
7. Singhvi SM, Pan HY, Morrison RA, Willard DA. Disposition of pravastatin sodium, a tissue-selective HMG-CoA reductase inhibitor, in healthy subjects. *Br J Clin Pharmacol.* 1990;29:239–243.
8. Nishizato Y, Ieiri I, Suzuki H, et al. Polymorphisms of OATP-C (SLC21A6) and OAT3 (SLC22A8) genes: Consequences for pravastatin pharmacokinetics. *Clin Pharmacol Ther.* 2003;73:554–565.
9. Castaneda-Hernandez G, Hoyo-Vadillo C, Palma-Aguirre JA, Flores-Murrieta FJ. Pharmacokinetics of oral nifedipine in different populations. *J Clin Pharmacol.* 1993; 33:140–145.
10. Aldrete-Velasco J, Casanova JM, Mejia P, Martinez P. Efficacy of pravastatin as a hypolipidemic agent in patients with polygenic hypercholesterolemia. *Arch Med Res.* 1992;23:117–122.
11. Lisker R, Ramirez E, Briceno RP, et al. Gene frequencies and admixture estimates in four Mexican urban centers. *Hum Biol.* 1990;62:791–801.
12. Lisker R, Ramirez E, Babinsky V. Genetic structure of autochthonous populations of Meso-America: Mexico. *Hum Biol.* 1996;68:395–404.
13. Lisker R, Perez-Briceno R, Granados J, et al. Gene frequencies and admixture estimates in a Mexico City population. *Am J Phys Anthropol.* 1986;71:203–207.
14. Otter K, Mignat C. Determination of pravastatin in human plasma by high-performance liquid chromatography with ultraviolet detection. *J Chromatogr B Biomed Sci Appl.* 1998;708:235–241.
15. Causon R. Validation of chromatographic methods in biomedical analysis. Viewpoint and discussion. *J Chromatogr B Biomed Sci Appl.* 1997;689:175–180.
16. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr.* 1974;AC-19:716–723.
17. Pan HY, DeVault AR, Swites BJ, et al. Pharmacokinetics and pharmacodynamics of pravastatin alone and with cholestyramine in hypercholesterolemia. *Clin Pharmacol Ther.* 1990;48:201–207.
18. Ogawa K, Hasegawa S, Udaka Y, et al. Individual difference in the pharmacokinetics of a drug, pravastatin, in healthy subjects. *J Clin Pharmacol.* 2003;43:1268–1273.
19. Fukazawa I, Uchida N, Uchida E, Yasuhara H. Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. *Br J Clin Pharmacol.* 2004;57:448–455.
20. Sugimoto K, Ohmori M, Tsuruoka S, et al. Different effects of St John's wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther.* 2001;70:518–524.
21. Mazzu AL, Lasseter KC, Shamblen EC, et al. Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. *Clin Pharmacol Ther.* 2000;68:391–400.

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