Food and Chemical Toxicology 53 (2013) 168–173

Contents lists available at SciVerse ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Food–drug interactions: Effect of capsaicin on the pharmacokinetics of simvastatin and its active metabolite in rats

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ARTICLE INFO

Article history:
Received 6 April 2012
Accepted 27 November 2012
Available online 5 December 2012

Keywords:
Cytochrome P450
Capsaicin
Interaction
Pharmacokinetics
Rats
Simvastatin

ABSTRACT

Capsaicin (trans-8-methy-N-vanilly-6-nonenamide, CAP), the main ingredient responsible for the hot pungent taste of chilli peppers. However, little is known about the metabolic interactions between CAP and clinically used drugs. This study attempted to investigate the effect of CAP on the pharmacokinetics of simvastatin (SV), a cytochrome P450 (CYP) 3A substrate and an important cholesterol-lowering agent. CAP (3, 8 or 25 mg/kg), ketoconazole, dexamethasone or 5% CMC-Na was given to rats for seven consecutive days and on the seventh day SV (80 mg/kg) was administered orally. The results showed that when a single dose of SV was administered to rats fed with CAP over one week, $AUC_{0\to\infty}$, C_{max} of SV and its acid metabolite was significantly decreased in comparison to the control treatment. Pretreatment of rats with CAP resulted in an decrease in the $AUC_{0-\infty}$ of SV of about 67.06% (CAP 3 mg/kg, $P < 0.05$), 73.21% (CAP 8 mg/kg, $P < 0.01$) and 77.49% (CAP 25 mg/kg, $P < 0.01$) compared with the control group. The results demonstrate that chronic ingestion of high doses of CAP will decrease the bioavailability of SV to a significant extent in rats.

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1. Introduction

For a long time hot pepper fruit that belong to the plant genus *Capsicum* (Solanaceae family) are among the most heavily consumed spices throughout the world. It is used as a delicious spice with a characteristic smell and taste. The primary pungent principle in *Capsicum* fruits called capsaicin (CAP) that is typical of this plant is responsible for spiciness of pepper fruit (Bode and Dong, 2011; Perucka and Oleszek, 2000). The content of CAP in green and red peppers ranges from 0.1% to 1% (Hayman and Kam, 2008).

CAP evokes numerous biological effects and thus has been the target of extensive, investigations since its initial identification (Díaz-Laviada, 2010; Gooding et al., 2010; Reyes-Escogido et al., 2011). Many studies demonstrated that CAP has effects to promote energy metabolism and to suppress accumulation of body fat (Josse et al., 2010; Belza et al., 2007). Studies in humans confirm that CAP elevates body temperature and increases oxygen consumption (Hachiya et al., 2007; Lim et al., 1997). Ingestion of large amounts of CAP has been reported to cause histopathological and biochemical changes, including erosion of gastric mucosa and hepatic necrosis (Monsereenusorn et al., 1982). Moreover, there are several reports indicating that pretreatment with CAP might influence the activity of drug metabolizing enzymes (Pawlowska and Augustin, 2011; Chen et al., 2011; Zhou et al., 2004). Many consumers of CAP as a food additive take prescribed drugs concomitantly. This undoubtedly may raise the risk of drug–CAP interactions in these patients. Considering the frequent consumption of CAP and its current therapeutic application, correct assessment of this compound is important from the public health standpoint.

Among the drug metabolizing enzymes the cytochrome P450 monooxygenase isoform 3A (CYP3A) plays a prominent role and is responsible for the metabolism of the majority of all prescribed drugs (Zhou et al., 2007). One important drug metabolized by CYP3A is simvastatin (SV), a 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitor used for the treatment of hypercholesterolaemia, hyperlipidaemia and to reduce the risk of cardiovascular events (Neuvonen, 2010; Wang et al., 2011). SV, which is an inactive prodrug, transformed into the active form simvastatin acid (SVA) in plasma, liver and intestinal mucosa (Zhang et al., 2010a,b). The major enzyme responsible for metabolism of the parent prodrug SV and of its active form SVA is CYP3A; a minor part of SVA is also metabolized by CYP2C8 (Neuvonen et al., 2006). CYP-dependent hydroxylation in turn increases the rate of subsequent conjugation (phase II reactions) and excretion; thus, potent CYP3A inhibitors are able to increase plasma level and area under the plasma concentration–time curve (AUC) of SV and SVA several fold. Concomitant use of SV with drugs that inhibit CYP3A can even lead to toxic side effects of the statin like myopathy and rhabdomyolysis.

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http://dx.doi.org/10.1016/j.fct.2012.11.045

Studies revealed that the pharmacokinetics of the substrate for CYP3A was altered by oral administration of CAP to rats, suggesting that any possible interactions between CAP and other drugs which was mainly metabolized by CYP3A may occur *in vivo*, as well (Hirotani et al., 2007). Statins are commonly used to treat several forms of hypercholesterolemia. However, there is little information about the effects of CAP on the *in vivo* pharmacokinetics of the statin such as SV in animals or humans.

CAP was shown to inhibit CYP3A activity *in vitro* (Takanohashi et al., 2010). It can be concluded that high doses of the CAP might be able to increase the bioavailability of SV and SVA and lead to toxic side effects of the statin *in vivo*. An average daily per capita consumption of CAP may reach 50 mg in some south-east Asian countries (Buck and Burks, 1983). In some areas of China, the average daily intake of CAP reaches 150 mg (An et al., 1996). If people consume an excess of CAP compared to ordinary intake levels, significant regulation of CYP enzymes may occur. In order to test such a potentially harmful effect of the CAP, rats were pretreated with CAP at 3, 8 and 25 mg/kg that can be reached with dietary supplements. Therefore, we attempted to evaluate whether chronic dietary supplementation of CAP over one week might alter SV pharmacokinetics in rats in this study.

2. Materials and methods

2.1. Chemicals and reagents

CAP, SV and lovastatin were purchased from the National Institute for Control of Pharmaceutical and Biological Products (Beijing, China). SVA and lovastatin acid were supplied by Sichuan pharmaceutical preparations Co., Ltd. (Chengdu, China). HPLC-grade acetonitrile was obtained from Tedia (Tedia, Fairfield, OH, USA). Other reagents were analytical-grade or better. The water used for HPLC was purified by use of a Milli-Q system (Millipore, Milford, MA, USA).

2.2. Animal experiments

SD rats, female, 180–220 g, were obtained from the Laboratory Animal Center of the Tongji Medicine College of Huazhong University of Science and Technology (Wuhan, Hubei, China). Experimental protocols were approved by the Animal Care Committee of Huazhong University of Science and Technology. The rats were housed six per cage and given free access to food and water in a temperature-controlled room (25 °C) with a 12 h light/dark cycle.

The rats were randomly divided into six groups: (1) control group (pretreated with 5% CMC-Na, p.o., $n = 6$); (2) low dose group (pretreated with CAP in 5% CMC-Na, 3 mg/kg, p.o., $n = 6$); (3) middle dose group (pretreated with CAP in 5% CMC-Na, 8 mg/kg, p.o., $n = 6$); (4) high dose group (pretreated with CAP in 5% CMC-Na, 25 mg/kg, p.o., $n = 6$); (5) inhibition group (pretreated with ketoconazole in 5% CMC-Na, 100 mg/kg, p.o., $n = 6$); (6) induction group (pretreated with dexamethasone in 5% CMC-Na, 100 mg/kg, p.o., $n = 6$). All the rats were given vehicle (control group) or drug (other groups) daily by gastrogavage for 6 days. Six hours after the last treatment with CAP, access to the diet was removed and only water was provided. On the seventh day, the rats were treated with vehicle or drug. Thirtty minutes later after treatment, SV (80 mg/kg) was administered to rats. After administration, 300 μL blood samples were collected from caudal veins at different times (0, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300 and 360 min). The plasma samples were separated by centrifugation at 3000*g* for 10 min and stored at −20 °C until analysis.

2.3. Analytical methods

An aliquot of 50 μL internal standard solution (lovastatin 9.6 ng/mL and lovastatin acid 19.2 ng/mL in mobile phase) was added to a 100 μL plasma sample in a screw-cap glass tube. After vortex mixing for 30 s, the mixture was added 300 μL ammonium acetate buffer (0.5 M pH 4.0) and then vortexed for 60 s. After standing for 30 min, the sample was vortex mixed for 30 s and extracted with 3.0 ml methyl tert-butyl ether. After vortex-mixing for 3 min and centrifugation at 5000 rpm for 5 min, the organic layer was separated and evaporated to dryness at 40 °C under a gentle stream of nitrogen. The residue was reconstituted in 150 μL acetonitrile:ammonium acetate buffer pH 4.0 (75:25; v/v).

HPLC analysis was on an Agilent 1200 HPLC system using a Inertsil ODS-3 column (5 μm, 2.1 × 150 mm) for separation. The mobile phase was composed of acetonitrile:ammoniumacetate 2.5 mM (containing 0.1% formic acid) (75:25; v/v) and was pumped at a flow rate of 300 μL/min under 35 °C. An Agilent 6410B Triple Quadrupole LC/MS system equipped with an electrospray (ESI) source was used for the mass analysis and detection. The turbo ion-spray temperature was maintained at 350 °C. The precursor/product ion transitions were monitored at *m/z* 419.2 → *m/z* 199.2 (+Ion-mode) for SV and *m/z* 435.2 → *m/z* 319.2 for SVA (−Ion-mode). The internal standard lovastatin was monitored at *m/z* 405.2 → *m/z* 199.2 (+Ion-mode) and lovastatin acid was monitored at *m/z* 421.4 → *m/z* 319.2 (−Ion-mode). The total run time was 5.5 min per sample, the retention times were 3.32, 2.50 min for SV, SVA and 2.73, 2.14 min for the internal standard lovastatin, lovastatin acid, respectively (Figs. 1 and 2). Calibration curves were linear ranging from 0.1 to 5000 ng/mL for SV and SVA in plasma. As LLOQ a concentration of 0.1 ng/mL was determined for SV and SVA. Accuracy measured at three concentration levels was acceptable both for SV (varied from 86.00% to 107.14%) and for SVA (varied from 86.08% to 108.04%) and the R.S.D. values were all less than 3.79%. Precision was likewise acceptable (between 1.52% and 3.76% for SV; between 2.07 and 3.77 for SVA). The assay was sufficiently robust, there was no influence of plasma matrix from different rats on the outcome of the assay; stability of the samples under the assay conditions was secured. Data acquisition, peak integration and calculations were performed using Agilent Masshunter Workstation.

2.4. Pharmacokinetic analysis

Pharmacokinetic analysis was performed based on a noncompartmental description of the data observed. The Drug And Statistics (DAS) 2.0.1 pharmacokinetics fitting software were used to calculate the model-independent pharmacokinetic parameters. These parameters were the area under the plasma concentration–time curve (AUC), the clearance (CL/F) and the half-life ($T_{1/2}$). Maximum plasma concentrations (C_{max}) and times to achieve maximum plasma concentrations (T_{max}) were obtained directly from the individual plasma concentration–time curves.

2.5. Statistical analysis

The different parameters (AUC, C_{max}, T_{max}, CL/F and $T_{1/2}$) of SV and SVA were compared between blank solution pretreatment and pretreatment with different doses of CAP, ketoconazole or dexamethasone, respectively. All statistics were calculated using GraphPad Prism 4.0 software (San Diego, CA) designed for one-way ANOVA. The significance of difference between groups was analyzed by one-way ANOVA followed by Fisher's Protected Least Significance Difference (PLSD) test. Differences were considered significant when $P < 0.05$.

3. Results

The plasma concentration–time curves of SV after oral administration at the dose of 80 mg/kg, with different pretreatments, are shown in Fig. 3a. In the pre-administration with the CYP3A inhibitor, ketoconazole (KTZ), $AUC_{0\to\infty}$ of SV was increased by 1.60-fold ($P < 0.05$), and the CYP3A inducer, dexamethasone (DEX), significantly decreased the bioavailability of SV.

Upon pretreatment with CAP, the peak plasma concentrations of SV after administration were significantly lower compared to the pretreatment with vehicle. The pharmacokinetic parameters of SV indicated that pretreatment of rats with CAP at daily dosages of 3, 8 and 25 mg/kg for seven consecutive days resulted in a 67.06% ($P < 0.05$), 73.21% ($P < 0.01$) and a 77.49% ($P < 0.01$) reduction in the $AUC_{0-\infty}$ of SV, respectively. The difference in T_{max} and $T_{1/2}$ did not quite reach statistical significance but CL/F was significantly increased following pretreatment with CAP ($P < 0.05$). Other parameter like C_{max} was significantly different between groups (Table 1).

The peak plasma concentrations of SVA were higher than those of the parent compound. Again, the peak plasma concentrations of the metabolite showed a significant decrease after the pretreatment of CAP (Fig. 3b). When a single dose of SV was administered to rats fed with CAP over one week, pharmacokinetic parameters of this active metabolite were significantly different between groups (Table 1). $AUC_{0\to\infty}$ and C_{max} of SVA was significantly decreased in comparison to the control group using the same dose of the statin. However, $T_{1/2}$ and T_{max} were not significantly different between the different treatments.

AUC values of SV averaged approximately 12% of those of the active metabolite SVA after both vehicle and CAP pretreatment. The CAP pretreatment also did not alter the plasma ratio of SV and SVA ($P > 0.1$, Fig. 4). However, the ratios of plasma concentration of SV and SVA were significant higher after pretreatment with ketoconazole or dexamethasone ($P < 0.01$).

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