Effect of danshen extract on the activity of CYP3A4 in healthy volunteers

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Many cytochrome P450 mediated interactions have been reported between drug and herbal medicines. In particular, CYP3A4 is known to play a critical role in several clinically relevant herb-drug interactions. Midazolam has been reported to be one of the preferred *in vivo* CYP3A probes.
- It has been reported that the lipophilic components of danshen could induce CYP3A in C57BL/6J mice, that cryptotanshinone and tanshinone IIA of danshen extract could activate human PXR and consequently induce the expression of the CYP3A4 gene.

WHAT THIS STUDY ADDS

- Co-administration of multiple doses of danshen tablets caused an increase in apparent oral clearance of midazolam by 35.4%, a corresponding decline in C_{max} by 31.1% and a decline in $AUC(0,\infty)$ by 27.0% in human volunteers. The $t_{1/2}$ of midazolam and 1-hydroxymidazolam were not changed, and the C_{max} and $AUC(0,\infty)$ ratio of midazolam to 1-hydroxymidazolam were not affected. The results suggested that multiple dose administration of danshen tablets could induce CYP3A4 in the gut, thereby increasing the clearance of midazolam. Therefore, caution should be taken when danshen products containing lipophilic components are used in combination with therapeutic drugs metabolized by CYP3A.

AIMS

To assess the effect of danshen extract on CYP3A4 activity using midazolam as an *in vivo* probe.

METHODS

A sequential, open-label, two-period pharmacokinetic interaction study design was used to compare midazolam pharmacokinetic parameters before and after 14 days of administration of danshen tablets. Twelve healthy volunteers received a single oral dose (15 mg) of midazolam followed by danshen tablets (four tablets orally, three times a day) for 14 days. On the last day of the study they received four danshen tablets with a 15 mg midazolam tablet and plasma concentrations of midazolam and its corresponding metabolite 1-hydroxymidazolam were measured prior to and after the administration of danshen tablets periodically for 12 h.

RESULTS

The 90% confidence intervals of C_{max} , $t_{1/2}$, CL/F and $AUC(0,\infty)$ of midazolam before and after administration of danshen tablets were (0.559, 0.849), (0.908, 1.142), (1.086, 1.688) and (0.592, 0.921), respectively; and those of C_{max} , $t_{1/2}$ and $AUC(0,\infty)$ of 1-hydroxymidazolam after vs. before administration of danshen tablets were (0.633, 0.923), (0.801, 1.210) and (0.573, 0.980), respectively. Ratios of geometric LS means of $C_{max(1OHMid)} : C_{max(Mid)}$ and $AUC_{max(1OHMid)} : AUC_{max(Mid)}$ (after vs. before 14-day danshen) were 1.072 and 1.035, respectively.

CONCLUSIONS

Our findings suggest that multiple dose administration of danshen tablets may induce CYP3A4 in the gut. Accordingly, caution should be taken when danshen products are used in combination with therapeutic drugs metabolized by CYP3A.

Introduction

Many cytochrome P450 (CYP) mediated interactions have been reported between drugs and herbal medicines [1–3]. CYP3A4 is the most important human enzyme in the CYP family due to its high relative abundance in the body and its broad substrate specificity [4]. For example, St John's wort has been found to induce the expression of CYP3A4 [2, 3] and consequently accelerate the clearance of several clinically important drugs including midazolam, amitriptyline [2], cyclosporin [3], and the oral contraceptive [5].

Danshen, the dried root of *Salvia miltiorrhiza*, has been used for more than 2000 years in China for the treatment of numerous ailments [6]. Danshen extract contains both hydrophilic components (danshensu, protocatechuic aldehyde and salvianolic acid B, etc.) and lipophilic components (tanshinone I, tanshinone IIA and cryptotanshinone, etc.). Hydrophilic components exhibit strong antioxidant and antithrombotic activities, which are able to protect the brain and heart from the damage caused by ischaemia reperfusion and avoid hepatic damage [7]. The biological effects of the lipophilic components mainly include antibacterial, anti-oxidant, antitumour activities, prevention of angina pectoris and myocardial infarction [8, 9]. In China, as well as other countries, danshen is widely used either alone or in combination with other drugs for the treatment of cardiovascular disease [10]. At present, many danshen preparations are commercially available; a danshen extract in the form of a danshen tablet is one of the most commonly used danshen products in clinical practice.

In recent years, some studies have revealed the effect of danshen extract on CYP3A4. Kuo *et al.* reported that the ethyl acetate extract (lipophilic components) of danshen could induce expression of CYP3A in C57BL/6J mice [11]. Using the reporter gene assay and polymerase chain reaction (PCR) Yu *et al.* [12] found that tanshinone IIA and cryptotanshinone were efficacious pregnant X receptor (PXR) agonists, and that constitutive androstane receptor (CAR) and glucocorticoid receptor (GR) were, to a lesser extent, involved in the induction of CYP3A4 expression by tanshinones. Yu's group also found that treatment of LS174T cells with cryptotanshinone or tanshinone IIA resulted in a significant increase of CYP3A4 mRNA and concluded that activation of PXR and the resultant CYP3A4 induction was mediated by cryptotanshinone and tanshinone IIA. Our previous findings indicated that seven (three lipophilic and four hydrophilic) components of danshen extract had no inhibitory effect on CYP3A4 enzyme activity in liver microsomes [13]. Although these findings suggested that the lipophilic components of danshen extract might account for danshen-mediated CYP3A4 induction, no human studies have investigated the potential of danshen to alter drug metabolism of CYP3A substrates. The probable interaction between the lipophilic components of

danshen tablets and substrates of CYP3A has not been investigated.

The purpose of this study was to investigate whether danshen tablets could induce CYP3A4 activity using midazolam, which is recognized as one of the preferred *in vivo* probes [14], in healthy volunteers. This finding could provide useful insight into the safe and effective use of danshen preparations in clinical practice.

Methods

Study drugs

Danshen tablets used in this study were produced according to the method in the Chinese Pharmacopoeia (2005) [15] and contained an extract of 1 g danshen (lot no. 071005), manufactured by Shanghai Leiyongshang Pharmaceutical Limited Company (China).

The main lipophilic components (cryptotanshinone, tanshinone I and tanshinone IIA) and hydrophilic components (danshensu, salvianolic acid B and protocatechuic aldehyde) of danshen tablets were separately determined by HPLC on a C₁₈ column according to a previously published method [16]. For determination of hydrophilic components, elution with a mobile phase (0.5% acetic acid: methanol 80:20) was carried out at a flow rate of 1 ml min⁻¹. The detection wavelength was set to 282 nm. For determination of the lipophilic components, the mobile phase (0.5% acetic acid: methanol 17:83) was eluted at a flow rate of 1.0 ml min⁻¹. The detection wavelength was set to 254 nm.

Midazolam tablets (15 mg/tablet, lot SH0027) were manufactured by Shanghai Roche Pharmaceuticals Ltd.

Clinical study

Subjects Healthy male volunteers were enrolled in the study after obtaining written informed consent. The clinical protocol and informed consent form were approved by the independent YiJiShan hospital medical ethics committee.

Subjects were excluded from participation if they had any relevant medical history or had consumed any known or suspected inhibitors or inducers of CYP enzymes within 4 weeks of the commencement of the study. The use of any other drugs, herbal or dietary supplements, and grapefruit juice was prohibited throughout the study.

Study design The study design was a sequential, open-label, two-period trial [13] conducted at the Drug Clinical Research Organization of YiJiShan Hospital. On the morning of day 1, after fasting overnight, a single dose of 15 mg midazolam was administered orally. The volunteers were provided a light standard meal at 4 h and 10 h after medication intake. At 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 h after drug administration 4 ml of blood were obtained from forearm veins for measurement of midazolam and

1-hydroxymidazolam. The blood samples were centrifuged and plasma separated and stored at -70°C until the time of analysis. Beginning on day 2, the volunteers received four danshen tablets, three times a day for 14 days. On day 16, after fasting overnight, the volunteers received four danshen tablets together with 15 mg midazolam. Blood sampling to determine midazolam, 1-hydroxymidazolam and danshen lipophilic components, and meals followed the same scheme used on day 1. Smoking and consumption of alcohol, coffee, tea, and any drugs were prohibited during the test days.

Analysis of midazolam and 1-hydroxymidazolam in plasma [17]

The liquid chromatograph-mass spectrometer (Shimadzu, Kyoto, Japan) consisted of a DGU-14 AM degasser, Shimadzu 10ADvp Pump, a high pressure mixer, a CTO-10Avp column oven and a Shimadzu 10ATvp autoinjector equipped with an electrospray ionization (ESI) probe.

Extraction of midazolam and 1-hydroxymidazolam was performed with 0.2 ml plasma, diluted with 30 μl of 1 M NaOH solution and 10 μl of diazepam (IS) solution, to which 1 ml of ethyl acetate was added. The samples were centrifuged, evaporated and reconstituted in the mobile phase (0.01% of ammonium acetate : methanol 70:30). The gradient elution, using two mobile phases: (i) 0.01% of ammonium acetate and (ii) methanol (v : v), was as follows: 70A : 30B to 5A : 95B in 0.5 min, then 5A : 95B for 1 min, next 5A : 95B to 70A : 30B and for 6 min. The flow rate was 0.2 ml min^{-1} . Separation by HPLC on a C_{18} column (5 μm , 2.1 mm $\times$ 150 mm) was followed by mass spectrometric detection (LC/MS). This assay had a lower limit of quantitation (LLOQ) of 1.0 ng ml^{-1} , with a calibration curve range from 1.0 to 500.0 ng ml^{-1} . Intra- and interday CV of midazolam and 1-hydroxymidazolam were below 15%.

Analysis of danshen components in plasma [18, 19]

The liquid chromatograph-mass spectrometer (Thermo Electron, San Jose, CA, USA) consisted of an HPLC system and a Finnigan TSQ Quantum Discovery max system equipped with an ESI probe.

Lipophilic analytes (tanshinone I, tanshinone IIA and cryptotanshinone) were extracted from 0.5 ml plasma, diluted with 10 μl of diazepam (IS) solution, with 4 ml ethyl acetate. The samples were centrifuged, evaporated and reconstituted in the mobile phase (acetonitrile : 0.05% of ammonium acetate 80:20). Separation by HPLC on a C_{18} column (5 μm , 2.1 mm $\times$ 150 mm) was followed by tandem mass spectrometric detection (LC/MS/MS). The mass spectrometer was operated in positive ion mode and quantification was thus performed using selected reaction monitoring (SRM) of the transitions of m/z 295 $\rightarrow$ 277 for tanshinone IIA, m/z 297 $\rightarrow$ 251 for cryptotanshinone, m/z 277 $\rightarrow$ 249 for tanshinone, and m/z 285 $\rightarrow$ 193 for the diazepam (IS), respectively. This assay had a LLOQ of 0.1 ng ml^{-1} ,

with intra- and interday CV of tanshinone I, tanshinone IIA and cryptotanshinone being below 15%.

Hydrophilic analytes (danshensu and protocatechuic aldehyde) were extracted from 0.5 ml plasma, diluted with 10 μl of protocatechuic acid (IS) solution, with 1 mol l^{-1} HCl 30 μl and then 4 ml ethyl acetate. The samples were centrifuged, evaporated and reconstituted in the mobile phase (0.1% formic acid : methanol 60:40). Separation by HPLC on C_{18} column (2 μm , 2.0 mm $\times$ 250 mm) was followed by electrospray ionization tandem mass spectrometric detection. The mass spectrometer was operated in negative ion mode and quantification was thus performed using selected reaction monitoring (SRM) of the transitions of m/z 197.1 $\rightarrow$ 135.0 for danshensu, 137.1 $\rightarrow$ 108.0 for protocatechuic aldehyde and 153.0 $\rightarrow$ 108.0 for IS, respectively. This assay had a LLOQ of 0.1 ng ml^{-1} , and intra- and interday CV of danshensu and protocatechuic aldehyde were below 15%.

Pharmacokinetic and statistical analysis

The plasma concentration-time data of analytes obtained on days 1 and 16 were analyzed by model independent approaches. The peak plasma drug concentration (C_{max}) and time to C_{max} (t_{max}) were directly obtained from the plasma concentration-time data. The elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$, where λ_z , the elimination rate constant, was calculated from the terminal phase of the semi-log regression of the plasma concentration-time curve (at least three points). The area under curve from time 0 to infinity ($\text{AUC}(0,\infty)$) was estimated as $\text{AUC}(0,t) + C_t/\lambda_z$, where C_t is the plasma concentration of the last measurable sample and $\text{AUC}(0,t)$ was calculated according to the linear trapezoidal rule. Total plasma clearance (CL/F) was calculated as $\text{dose}/\text{AUC}(0,\infty)$.

Descriptive statistics of pharmacokinetic parameters included geometric means, arithmetic means and standard deviation (SD). 90% confidence intervals (CIs) were constructed for the ratios of with to without danshen treatment using the log-transformed data for the geometric least-squares (LS) means of C_{max} , $\text{AUC}(0,\infty)$, $t_{1/2}$ and CL/F . The resulting confidence limits were transformed by exponentiation and reported on the original measurement scale. The statistical limits were set at 0.80–1.25. t_{max} was analyzed using Wilcoxon's signed rank test. The DAS statistical analysis system (version 1.0) was used.

Results

Content analysis of the danshen tablets

Each danshen tablet contained 0.26 ± 0.05 mg cryptotanshinone, 0.5 ± 0.1 mg tanshinone I and 0.37 ± 0.04 mg tanshinone IIA, 0.67 ± 0.01 mg protocatechuic aldehyde, 1.7 ± 0.3 mg danshensu and 13.5 ± 1.1 mg salvianolic acid B.

Figure 1

Mean ($\pm$ SD, $n = 12$) plasma concentrations of midazolam following a single 15 mg oral dose of midazolam before and after 14 days of danshen tablet administration. midazolam (—○—); midazolam + danshen (—●—)

Figure 2

Mean ($\pm$ SD, $n = 12$) plasma concentrations of 1-OH-midazolam following a single 15 mg oral dose of midazolam before and after 14 days of danshen tablet administration. 1-OHMDZ (—○—); 1-OHMDZ + Danshen (—●—)

Clinical study

Twelve healthy male Chinese subjects with a mean age of 24 years (range 21–28 years), a mean weight of 62.8 kg (range 57–77 kg) and a mean height of 172 cm (range 165–180 cm) participated in this study. All subjects tolerated danshen and midazolam tablets well during the study. Complete pharmacokinetic data for both sampling periods were available for 12 subjects and were included in the pharmacokinetic analyses.

Mean plasma midazolam and 1-hydroxymidazolam concentration–time profiles before and after 14 days of danshen tablets are presented in Figures 1 and 2. Table 1 summarizes the pharmacokinetic parameters of midazolam and 1-hydroxymidazolam before and after 14 days of treatment with danshen tablets.

For midazolam, values of $C_{\max}$ (before vs. after 14 days treatment with danshen) were 113.98 and 72.50 ng mL⁻¹,

CL/F was 48.72 and 64.69 l h⁻¹ and $t_{\max}$ was 0.79 and 0.92 h, $t_{1/2}$ was 3.05 and 3.11 h, AUC(0,∞) was 353.62 and 254.96 ng mL⁻¹ h, respectively. Ratios of geometric LS means of $C_{\max}$, AUC(0,∞), $t_{1/2}$ and CL/F (after vs. before 14 days of treatment with danshen) were 0.689, 0.739, 1.018 and 1.354, respectively. For 1-hydroxymidazolam, values of $C_{\max}$ were 21.42 and 16.20 ng mL⁻¹, $t_{\max}$ was 0.88 and 0.96 h, $t_{1/2}$ was 2.70 and 2.29 h, AUC(0,∞) was 74.36 and 51.24 ng mL⁻¹ h, respectively. Ratios of geometric LS means of $C_{\max}$, AUC(0,∞), and $t_{1/2}$ (after vs. before 14 days of treatment with danshen) were 0.764, 0.750, and 0.910, respectively. Ratios of geometric LS means of $C_{\max(1\text{OHMid})} : C_{\max(\text{Mid})}$ and AUC_{max(1OHMid)} : AUC_{max(Mid)} (after vs. before 14 days of treatment with danshen) were 1.072 and 1.035, respectively.

Ninety percent (90%) CIs of $C_{\max}$ and AUC(0,∞) of midazolam and 1-hydroxymidazolam were under the lower statistical limit set (<0.80) but 90% CIs of $t_{1/2}$ were within the range of statistical limit set (0.80, 1.25). A Wilcoxon signed rank test for midazolam and 1-hydroxymidazolam indicated that $t_{\max}$ was not significantly different ($P > 0.05$).

Danshensu reached its maximal concentration (34.92 ± 5.13 ng mL⁻¹) at 4 h post-dosing and decreased to about 1.2 ng mL⁻¹ at 24 h post-dosing. AUC(0,∞) and $t_{1/2}$ of danshensu were 86.2 ± 22.0 ng mL⁻¹ h, and 1.20 ± 0.38 h, respectively. $C_{\max}$ of cryptotanshinone, tanshinone I and tanshinone IIA were 0.35 ng mL⁻¹, 0.3 ng mL⁻¹ and 1.0 ng mL⁻¹ at 0.5 h after administration of danshen tablets, respectively. The plasma concentrations of protocatechuic aldehyde were not determined.

Discussion

Danshen tablets, which contain hydrophilic and lipophilic components of danshen extract, are one of the most commonly used danshen extract products in clinical practice. The effect of danshen extract on CYP3A activity *in vivo* by an established CYP3A probe midazolam was evaluated in healthy volunteers treated with danshen tablets for 14 days.

To our knowledge, this is the first report to evaluate the effect of danshen extract on CYP3A activity *in vivo* by administering midazolam as a CYP3A probe to human volunteers. Due to the fact that midazolam is predominantly metabolized to 1-hydroxymidazolam by CYP3A4 and/or CYP3A5, this drug is referred to as an *in vivo* marker of CYP3A activity [14]. In this study, administration of multiple doses of danshen tablets caused a significant increase (35.4%) in apparent oral clearance, a corresponding significant decline (31.1%) in $C_{\max}$ from 113.98 ng mL⁻¹–72.50 ng mL⁻¹ and a significant decline (27.0%) in AUC(0,∞) from 353.62 ng mL⁻¹ h to 254.96 ng mL⁻¹ h. The results suggested that chronic administration of danshen tablets may induce the CYP3A enzyme *in vivo*. The $t_{1/2}$ of midazolam and 1-hydroxymidazolam and the $C_{\max}$ and AUC(0,∞) ratio

Table 1

Pharmacokinetic parameters of midazolam and 1-hydroxymidazolam after administration of a single oral dose of 15 mg midazolam in 12 healthy volunteers before and after 14 days of danshen tablet administration

PK parameter	Before danshen	After danshen	Geometric mean ratio	90%CI	P value
Midazolam (MID)					
t _{1/2} (h)	3.05 ± 0.60	3.11 ± 0.59	1.018	(0.908, 1.142)	–
t _{max} (h)	0.79 ± 0.45	0.92 ± 0.36	–	–	0.79
C _{max} (ng ml ⁻¹)	113.98 ± 48.52	72.50 ± 10.72	0.689	(0.559, 0.849)	–
CL/F (l h ⁻¹)	48.72 ± 19.11	64.69 ± 32.26	1.354	(1.086, 1.688)	–
AUC(0,∞ (ng ml ⁻¹ h)	353.62 ± 131.83	254.96 ± 72.90	0.739	(0.592, 0.921)	–
1-hydroxymidazolam (1-OHMID)					
t _{1/2} (h)	2.70 ± 1.09	2.29 ± 0.64	0.910	(0.802, 1.033)	–
t _{max} (h)	0.88 ± 0.43	0.96 ± 0.45	–	–	0.60
C _{max} (mg ml ⁻¹)	21.42 ± 8.11	16.20 ± 5.03	0.764	(0.633, 0.923)	–
AUC(0,∞ (ng ml ⁻¹ h)	74.36 ± 37.70	51.24 ± 14.10	0.750	(0.573, 0.980)	–
C _{max} (1OHMid) : C _{max} (Mid)	0.22 ± 0.06	0.24 ± 0.08	1.072	(0.979, 1.173)	–
AUC _{max} (1OHMid) : AUC _{max} (Mid)	0.22 ± 0.06	0.20 ± 0.04	1.035	(0.940, 1.141)	–

of midazolam to 1-hydroxymidazolam were not significantly affected by 14 days of danshen tablet administration, suggesting the induction of CYP3A was mainly in the wall of the small intestine.

Our findings suggest that the C_{max} of danshensu was 34.92 ± 5.13 ng ml⁻¹, and concentrations of tanshinone IIA, tanshinone I and cryptotanshinone were below 1 ng ml⁻¹ following administration of four danshen tablets. Salvianolic acid B is absorbed into the blood stream to a greater extent than other components due to its abundance in danshen tablets. This result indicated that salvianolic acids (danshensu and salvianolic acid B, etc.) were the main active pharmacological components of danshen tablets.

In the present study, although concentrations of tanshinones were below 1 ng ml⁻¹ following administration of four danshen tablets, the three lipophilic components of danshen were presumably present in higher concentrations in the small intestine. The poor absorption of tanshinones may have been due to their low aqueous solubility and limited membrane permeability [20]. Yu *et al.* [21] reported that cryptotanshinone is a substrate for P-gp, and that P-gp mediated efflux of cryptotanshinone into the gut lumen. Thus low oral bioavailability was also attributed to the first-pass effect. At an estimated gut concentration of approximately 10 μM (four tablets of herbal mixture 1.0 mg, intestinal volume is 500 ml [22]), the concentration of cryptotanshinone and tanshinone IIA could induce the intestinal CYP3A4 enzymes. Therefore, the results of this study could be due to the induction of intestinal CYP3A4 by a higher concentration of cryptotanshinone and tanshinone IIA in the intestine.

The xenobiotic-mediated induction of the human CYP3A gene is known to be regulated by PXR, CAR, GR as well as other receptors [23, 24]. PXR is a key regulator of xenobiotic-inducible CYP3A gene expression. PXR and CAR have the potential to cross-regulate CYP3A gene expres-

sion. Another nuclear receptor GR can be activated to increase the expression of PXR, CAR and retinoid X receptor (RXR), which in turn function as transcriptional regulators of the CYP3A gene [25, 26]. CYP3A4 and CYP3A5 are two CYP3A family members present in adult intestine. In the CYP3A4 5'-upstream region, the induction by PXR or CAR can occur either by the proximal everted repeat separated by six base pairs (ER6) motif or by a direct repeat separated by three base pairs (DR3) site within the XREM. Additionally, the PXR-and CAR-dependent induction of CYP3A4 is enhanced by GR [25, 26]. Compared with CYP3A4, CYP3A5 may be a relatively minor enzyme in the human small bowel, and appears to be less sensitive to induction by PXR activators because it lacks the distal PXR-response element cluster shown to enhance the transcription of CYP3A4 by xenobiotics [27, 28]. Yu *et al.* [12] found that tanshinone IIA and cryptotanshinone were efficacious activators for human PXR, GR was also involved in the *trans*-activation of the CYP3A4 promoter by cryptotanshinone and tanshinone IIA, and CAR played a role in tanshinone IIA-mediated CYP3A4 induction. The *in vitro* study results reported are consistent with our *in vivo* findings here. The lack of an association of the CYP3A5 genotype with *in vivo* pharmacokinetics of midazolam, as well as the demonstrated unimodally distributed clearance of the drug [29, 30], suggests only a minor role of CYP3A5 for midazolam metabolism *in vivo*. Altogether, the increased clearance of midazolam *in vivo* should be mainly attributed to induction of tanshinones on CYP3A4 in gut wall.

Furthermore, P-gp and CYP3A4 have considerable overlap in inducers *in vitro* and share common regulatory mechanisms (PXR and CAR) [31]. P-gp can be induced by tanshinone IIA and cryptotanshinone. Thus, co-administration of tanshinones and a drug substrate for P-gp leads presumably to drug interactions. The inducing effects would decrease their intestinal absorption and so

increase first pass clearance of CYP3A4 and/or P-gp substrates. In future studies other danshen preparations containing a higher content of cryptotanshinone and tanshinone IIA should be evaluated for their ability to induce *in vivo* CYP3A4 and P-gp. Confirmation of the results of this study will require larger, controlled trials.

In conclusion, chronic administration of danshen tablets resulted in a significant decline in oral bioavailability of midazolam, which may be the consequence of the induction of intestinal CYP3A4. If an orally administered drug is a substrate of CYP3A and has low oral bioavailability because of extensive pre-systemic metabolism by enteric CYP3A4, then administration of danshen tablets may have a significant effect on systemic exposure. Use of CYP3A substrates with concurrent danshen tablet use may call for caution, depending on the drug's exposure-response relationship. Dose adjustment of CYP3A substrates may be necessary in patients receiving concomitant therapy with danshen preparations containing lipophilic components.

Competing interests

There are no competing interests to declare.

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