Journal of Basic and Applied Pharmacology
Vol.1 No.1 July - December 2021

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Original research article

Unusual pharmacokinetic herb-drug interactions between turmeric crude extract and digoxin in male volunteers

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Received 15 September 2021; Received in revised form 4 November 2021
Accepted 29 December 2021; Available online 31 December 2021

ABSTRACT

Curcuminoids, the major components of *Curcuma longa* L. (turmeric), have inhibitory properties against P-glycoprotein, an efflux transporter found in the intestine. It is reasonable to hypothesize that the inhibition of P-glycoprotein-mediated transport by curcuminoids can cause an increase in plasma concentrations of P-glycoprotein substrates, such as digoxin, in the human body. In our previous randomized crossover study, we observed an increase in digoxin plasma concentrations following concomitant use of a turmeric crude extract equivalent to 1,000 mg of curcuminoids *per* day in a majority of healthy male volunteers. However, there were two volunteers whose pharmacokinetic changes were opposite to those of the other volunteers; that is, digoxin plasma concentrations were markedly decreased after the concomitant use of the turmeric crude extract. In the present article, we report the results of our repeated experiment with these two volunteers using a different digoxin formulation (*i.e.*, digoxin elixir). With digoxin elixir, the unusual pharmacokinetic pattern was somewhat similar to that observed in the corresponding experiment with digoxin tablets. The consistent results between initial and repeated experiments ensured that the unusual pharmacokinetic herb-drug interaction was not mainly attributable to an abnormal disintegration or dissolution of the digoxin tablets. Precaution should be taken when the turmeric crude extract is concurrently taken with P-glycoprotein substrates. Not only an increase in plasma concentrations of P-glycoprotein substrates, but also a decrease in plasma concentrations of such substrates could occur.

Keywords: curcuminoids, turmeric, P-glycoprotein, drug interactions, digoxin

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1. Introduction

Turmeric (*Curcuma longa* L.) is a perennial herbaceous plant belonging to the ginger family (*Zingiberaceae*). It is commonly used in traditional medicine thanks to its multiple therapeutic benefits, several of which have scientific evidence supporting the health claim.[1-3] The major components of *Curcuma longa* L. are curcuminoids, which typically consist of curcumin, demethoxycurcumin, and bisdemethoxycurcumin.[4,5] It is well documented that curcuminoids have inhibitory properties against P-glycoprotein, an ATP-dependent efflux transporter found in the intestine.[6] Lines of non-clinical evidence have demonstrated the P-glycoprotein inhibitory property of curcumin, demethoxycurcumin, and/or bisdemethoxycurcumin in both *in vitro* and *in vivo* experiments.[7-10] Due to the P-glycoprotein inhibitory property of curcuminoids, further development of such compounds are of great interest to the scientists with the aim of translating basic knowledge into clinical application.[11]

Several studies have demonstrated a beneficial effect of curcuminoids as a modulator of P-glycoprotein function in various conditions.[12-14] For example, it is shown that curcumin can reverse the P-glycoprotein-mediated multidrug resistance (MDR) of cancer cells,[15] can promote cell cycle arrest and induce apoptosis in the MDR cell line,[16] and can cause a reversal of anticancer drug resistance.[17] As such, curcumin and its derivatives have been extensively studied in clinical studies, many of which display promising clinical effects of curcumin and/or its derivatives in cancer therapy.[18,19]

It is reasonable to hypothesize that the inhibition of P-glycoprotein-mediated transport by curcuminoids in the turmeric crude extract can cause an increase in the plasma concentrations of P-glycoprotein substrates in humans. Digoxin, a type of medicine called a cardiac glycoside, is one of the reference P-glycoprotein substrate probes, commonly used to investigate the P-glycoprotein-mediated pharmacokinetic drug-drug/herb-drug interactions in the human body.[20,21] There are a number of clinical studies investigating the effect of certain drugs/substances on P-glycoprotein activity using digoxin as a probe.[22-24] An increase in digoxin plasma concentrations can be observed following the concurrent use of digoxin with a drug known as a P-glycoprotein inhibitor (*e.g.*, quinidine).[25] In contrast, a decrease in the digoxin plasma concentrations can be seen when digoxin is concomitantly prescribed with a drug known as a P-glycoprotein inducer (*e.g.*, rifampin).[26]

We previously conducted a randomized crossover study to study the effects of the turmeric crude extract on P-glycoprotein activity using digoxin as a probe in healthy male volunteers.[27] The pharmacokinetic changes following the concurrent use of the turmeric crude extract in the majority of the volunteers are in line with our hypothesis; that is, the inhibition of P-glycoprotein-mediated transport by curcuminoids could lead to increased digoxin plasma concentrations. However, there were two male volunteers whose pharmacokinetic alterations were unanticipated; that is, digoxin plasma concentrations were markedly decreased when digoxin was co-administered with the turmeric crude extract. Since this unexpected finding was conflicting with the hypothesis and opposite to the observation in the majority of the volunteers in the same cohort, we conducted a further investigation to confirm the finding and to explore some conceivable causes or explanations for it. In the present article, we report the results of our repeated experiment in these two volunteers with a different digoxin formulation (*i.e.*, digoxin elixir).

2. Materials and Methods

The study protocol of the previous crossover study investigating the effects of the turmeric crude extract on P-glycoprotein activity using digoxin as a probe in healthy male volunteers is described in Koonrungsesomboon *et al*.[27] In brief, it was an open-label, randomized, two-period, crossover study, with a washout period of at least 15

days. In study phase I, the volunteers were asked to take a single oral dose of 0.5 mg digoxin (0.25 mg/tablet) (Lanoxin®, Glaxo SmithKline, Boronia, Australia). Blood samples (3 mL each) were collected to follow the level of digoxin plasma concentrations at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 60, and 72 hours. In study phase II, the volunteers took two capsules of the turmeric crude extract (GPO-Curcumin®, manufactured by the Government Pharmaceutical Organization of Thailand; each capsule contained a turmeric crude extract equivalent to 250 mg of curcuminoids), twice daily (1,000 mg curcuminoids/day) after meals for seven days. On Day 5 of the turmeric crude extract intake, the volunteers were asked to take a single oral dose of 0.5 mg digoxin, and blood samples were collected following exactly the same protocol as done in the study phase I.

The two male volunteers whose pharmacokinetic parameters of digoxin were unexpectedly observed during the initial experiment were asked to undergo further investigation. The study protocol was repeated with them after a washout period of more than 20 days. During the repeated experiment, the formulation of digoxin was changed from tablet formulation to elixir formulation (Lanoxin™ Paediatric/Geriatric Elixir, Aspen Bad Oldesloe GmbH, Bad Oldesloe, Germany) in order to ensure that the unusual interaction was not attributable to an abnormal disintegration or dissolution of the digoxin tablets. The volunteers underwent all processes exactly as previously done, with the exception of substituting 10 mL of digoxin elixir (equivalent to 0.5 mg digoxin) orally for the two digoxin tablets, and blood samples taken up to 24 hours after the initiation of digoxin. Protocol amendment received ethical approval from the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University, prior to the conduct of this repeated experimental phase. Written informed consent was obtained from the volunteers prior to any study procedures.

Plasma concentrations of digoxin were determined by the AxSYM Digoxin assay, a microparticle enzyme immunoassay [MEIA]. The Digoxin III assay kits were purchased from Abbott Diagnostics (Abbott Park, IL, USA) and the assay was run using the AxSYM analyzer. The lower limit of quantification (LLoQ) of digoxin plasma concentrations was 0.30 ng/mL; any values less than the lower limit of detection were considered as none detected.

The pharmacokinetic parameters were calculated by means of the non-compartmental model, using the TopFit software version 2.0 for PC. Maximum plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were obtained by direct visual examination of the plasma concentration-time profile of digoxin. Area under the concentration-time curve from time 0 to the last quantifiable point (AUC_{0-t}) was calculated using the trapezoidal rule, while area under the concentration-time curve from time t to infinity ($AUC_{t-\infty}$) was mathematically extrapolated. Area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) is the sum of $AUC_{0-t} + AUC_{t-\infty}$. Since no digoxin plasma concentrations were detected at a time point later than 12 hours after digoxin ingestion in both volunteers, the calculation of the elimination half-life ($t_{1/2\beta}$) could not be accomplished.

3. Results

A 21-year-old male volunteer (Volunteer A) and a 20-year-old male volunteer (Volunteer B) had a body mass index of 20.62 and 18.04 kg/m^2, respectively. Both of them had never smoked nor lately drunk alcohol-containing beverages. No adverse events were observed following oral administration of 0.5 mg digoxin (either tablet formulation or elixir formulation) with and without concomitant use of the turmeric crude extract (equivalent to 1,000 mg curcuminoids/day). The pharmacokinetic parameters of digoxin in Volunteer A and Volunteer B are described in Table 1. The pharmacokinetic patterns of digoxin in both volunteers are depicted in Fig. 1.

In Volunteer A, oral administration of 0.5 mg digoxin tablets achieved a C_{max} of 4.64

ng/mL in one hour and an $AUC_{0-\infty}$ of 12.46 ng.h/mL, with the last quantifiable digoxin level at 8 hours following digoxin ingestion. The C_{max} and $AUC_{0-\infty}$ were decreased by 45.91% and 47.03%, respectively, when 0.5 mg digoxin tablets were concomitantly taken with the turmeric crude extract. In the repeated experiment with 10 mL digoxin elixir, the C_{max} and $AUC_{0-\infty}$ of Volunteer A were 4.84 ng/mL and 11.96 ng.h/mL, respectively. Both pharmacokinetic parameters were decreased by 60.95% and 28.01%, respectively when 10 mL digoxin elixir was concurrently administered with the turmeric crude extract.

In Volunteer B, oral administration of 0.5 mg digoxin tablets reached a C_{max} of 4.42 ng/mL in one hour and an $AUC_{0-\infty}$ of 12.07 ng.h/mL, with the last quantifiable digoxin level at 8 hours following digoxin ingestion. The C_{max} and $AUC_{0-\infty}$ were decreased by 66.29% and 47.31%, respectively, when 0.5 mg digoxin tablets were concomitantly taken with the turmeric crude extract. When Volunteer B took 10 mL digoxin elixir, the C_{max} was 4.58 ng/mL and the $AUC_{0-\infty}$ was 13.09 ng.h/mL. The former value was decreased by 14.85%, while the later value was decreased by 31.40% when 10 mL digoxin elixir was concurrently administered with the turmeric crude extract.

Table 1. Pharmacokinetics of digoxin in Volunteer A and Volunteer B.

Pharmacokinetic parameters	Volunteer A				Volunteer B			
	Digoxin tablets		Digoxin elixir		Digoxin tablets		Digoxin elixir	
	Phase I (D)	Phase II (D+T)	Phase I (D)	Phase II (D+T)	Phase I (D)	Phase II (D+T)	Phase I (D)	Phase II (D+T)
C_{max} (ng/mL)	4.64	2.51	4.84	1.89	4.42	1.49	4.58	3.90
T_{max} (h)	1	1	1	1	1	1.5	0.5	0.75
AUC_{0-t} (ng.h/mL)	9.54	5.48	8.84	6.26	10.15	4.73	10.39	7.37
$AUC_{0-\infty}$ (ng.h/mL)	12.46	6.60	11.96	8.61	12.07	6.36	13.09	8.98

D, digoxin alone; D+T, digoxin with concurrent use of the turmeric crude extract.

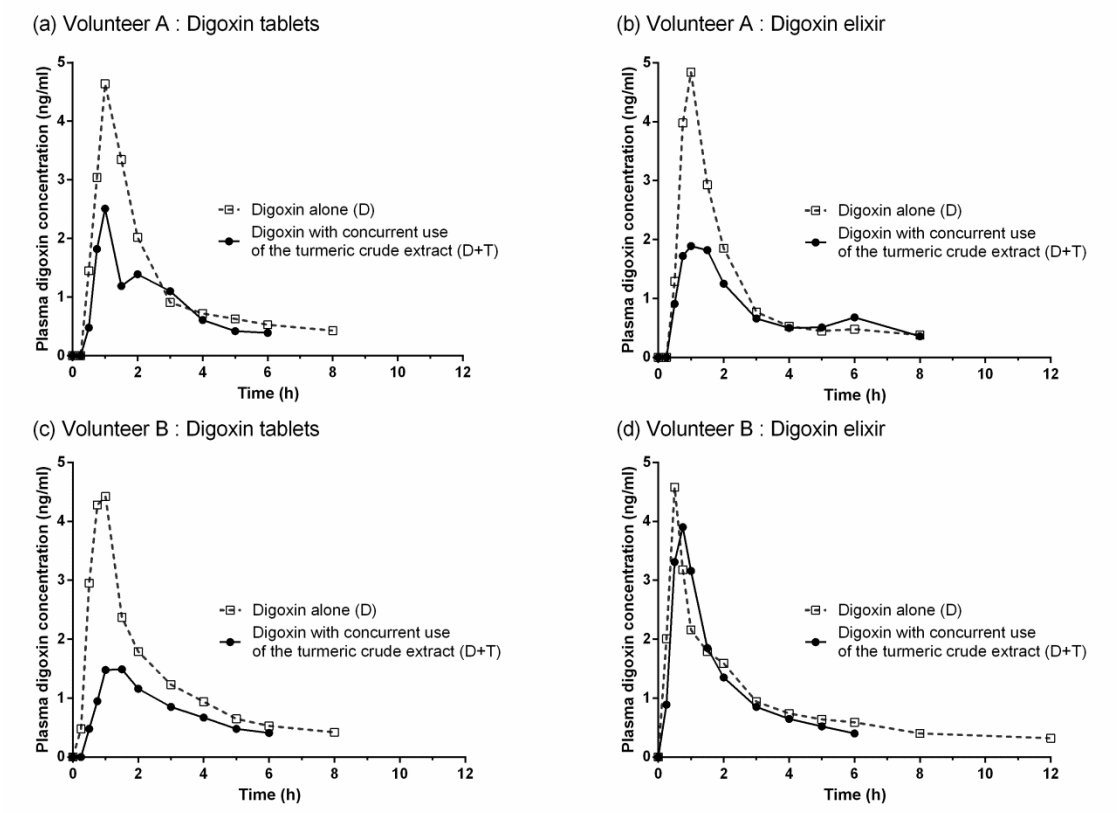

Fig. 1. Plasma digoxin concentration-time curves of Volunteer A and Volunteer B.

4. Discussion

The observation in the two volunteers was unexpected and contrary to our initial hypothesis. It suggests that the turmeric crude extract (equivalent to 1,000 mg curcuminoids/day) might be able to modulate the intestinal P-glycoprotein in the opposite direction than what had been initially anticipated.[27] We thus further explored certain plausible explanations for this unanticipated finding by repeating the study in these two volunteers with a different digoxin formulation (*i.e.*, digoxin elixir), with the aim of ensuring that the unusual pharmacokinetic herb-drug interaction was not attributable to an abnormal disintegration or dissolution of the digoxin tablets initially used. With digoxin elixir, the unusual pharmacokinetic pattern was somewhat similar to that observed in the corresponding experiment with digoxin tablets. The results were consistent between initial and repeated studies, indicating that the concurrent use of the turmeric crude extract remarkably reduced oral bioavailability of digoxin in these two volunteers, regardless of the digoxin formulation.

The literature provides some possible explanations for this unusual herb-drug interaction. Quite a few investigations have observed the same, unexpected findings as what we observed in these two volunteers.[28-30] Chearwae *et al*. previously observed an inhibitory effect of curcuminoids at high concentrations on the P-glycoprotein-mediated efflux, whereas they found that relatively low concentrations of curcuminoids (0.5-1 μM) could rather stimulate P-glycoprotein ATPase activity in an *in vitro* experiment.[31] This observation was replicated in human studies where the consumption of low-dose curcumin

(300-600 mg/day) reduced oral bioavailability of the P-glycoprotein probe talinolol,[32,33] whereas a relatively higher dose of curcumin (1,000 mg/day) increased oral bioavailability of talinolol in healthy volunteers.[34] Based on the above-mentioned studies, the dose and/or concentration of curcuminoids in the turmeric crude extract given to the volunteers should be taken into account. In our initial experiment, all the healthy volunteers took the same dose of the turmeric crude extract, but the unanticipated finding was observed in only two volunteers.[27] Hence, the dose of curcuminoids itself is less likely to be the cause of unusual pharmaco-kinetic herb-drug interactions in this study. Rather, there is a possibility that the two male volunteers might have had relatively low concentrations of curcuminoids in the gastrointestinal tract when compared to other volunteers, because a large portion of curcuminoids entering the intestinal epithelium might have undergone extensive metabolism differently among individuals.[35] However, this is only our presumption and further investigations are required before a solid conclusion can be drawn.

It is also possible that some other compounds in the turmeric crude extract (other than curcuminoids) may have P-glycoprotein inductive activity and be a contributing factor responsible for this unusual herb-drug interaction. Hou *et al*. reported an effect of turmeric crude extract on P-glycoprotein activity contrary to that of curcumin in Caco-2 cells.[36] Yue *et al*. subsequently demonstrated that aromatic turmerone, a sesquiterpenoid isolated from the turmeric crude extract, significantly increases P-glycoprotein mRNA expression levels and enhances efflux activity in Caco-2 cells.[37] Juan *et al*. also reported a significant up-regulation of P-glycoprotein expression and function effect from tetrahydrocurcumin, a metabolite of curcumin, in an *in vitro* experiment.[33] Hence, the effects of the turmeric crude extract (containing several compounds), rather than curcuminoids alone, on P-glycoprotein activity may be more complicated than what was expected.

There is also the possibility that some pathways other than P-glycoprotein may partly contribute to such an unusual herb-drug interaction.[38] For example, Hsieh *et al*. revealed that curcumin metabolites, including glucuronides/sulfates of curcumin and demethoxycurcumin, could activate CYP3A4 activity in rats and significantly decrease the oral bioavailability of a P-glycoprotein/CYP3A4 substrate probe.[39] Although the cytochrome P450 system does not play a major role in digoxin metabolism, CYP3A4 is a minor pathway responsible for digoxin biotransformation.[40] Hence, it is not unreasonable to assume that intestinal CYP3A4-mediated metabolism of digoxin in the two volunteers might largely differ from other volunteers, so that the effect of CYP3A4 activation by curcumin metabolites apparently overrode the inhibitory effects of curcuminoids on P-glycoprotein.[41]

Last but not least, the turmeric crude extract might alter the gastrointestinal tract environment, thereby reducing the absorption of digoxin in these two volunteers. Administration of the turmeric crude extract containing lipophilic polyphenols and essential oils might have had some influence on solubility and dissolution rate of digoxin, thereby affecting the oral bioavailability of digoxin.[42] It is also possible that curcumin and its derivatives might decrease gastric acid secretion and, as a result, alter the extent of digoxin absorption.[43,44] Furthermore, the curcumin-rich turmeric crude extract might be able to alter the composition of the gut microbiota, hence affecting digoxin biotransformation and absorption.[45-47] As such, the alteration of the gastrointestinal tract environment following co-administration of the turmeric crude extract with digoxin might interfere with the absorption of digoxin to a certain extent.

5. Conclusion

Based on the available data, the mechanism underlying the unusual pharmacokinetic interaction between digoxin and the turmeric crude extract in these two male volunteers has not yet been discovered. At least, the repeated experiment can confirm that this unanticipated observation is not mainly attributable to an abnormal disintegration or dissolution of digoxin tablets. Further investigations are required to elucidate the effects of curcuminoids, their metabolites, and/or any other active compounds in the turmeric crude extract on P-glycoprotein-related drug efflux transporters or any related possible mechanisms in humans. In addition, individual host factors affecting intestinal metabolism of curcuminoids and other active compounds in the turmeric crude extract warrant further investigation. Available information suggests that precaution should be taken when the turmeric crude extract is concurrently taken with drugs known as P-glycoprotein substrates because either an increase or decrease in oral bioavailability of such substrates, leading to toxicity or inefficacy, is possible.

Acknowledgements

This work was supported by Faculty of Medicine, Chiang Mai University, grant number 052/2557. We would like to thank Ms. Sujitra Techatoei and Ms. Rapheephorn Khatsri for their secretarial support.

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