Journal of Applied Pharmaceutical Science Vol. 5 (12), pp. 001-007, December, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.501201
ISSN 2231-3354

Pharmacokinetics interaction of dapoxetine with different doses of green tea extract in male healthy volunteers using midazolam as CYP3A4 enzyme probe

Khaled Sobhy Abdelkawy[1*], Ahmed M Donia[2], Mahmoud S Abdallah[3]

[1]Clinical Pharmacy Department, Faculty of Pharmacy, Kafrelsheikh University, Kafr El Sheikh Governorate, Egypt. [2]Faculty of pharmacy, Tanta Unviersity, Tanta, Egypt. [3]Faculty of Pharmacy, Badr University, Cairo Governorate 11829, Egypt.

ARTICLE INFO

Article history:
Received on: 18/09/2015
Revised on: 16/10/2015
Accepted on: 15/11/2015
Available online: 27/12/2015

Key words:
dapoxetine, green tea, midazolam, CYP3A4, pharmacokinetic, interaction.

ABSTRACT

Objective: This study aimed to investigate the pharmacokinetics interaction of dapoxetine with different doses of green tea extract in healthy volunteers using midazolam (CYP3A4 probe).
Method and materials: Twelve healthy males were included in a random three-way crossover study. Each volunteer received dapoxetine 60 mg and midazolam 7.5 mg concurrently after drinking 250 ml of water, 250 ml of fresh extract of 2 gram of green tea or 250 ml of fresh extract of 4 gram of green tea with one week washout period. Plasma samples were analyzed for dapoxetine and midazolam using HPLC.
Results: The co-administration of dapoxetine with 4 gm green tea extract significantly increased dapoxetine AUC∞ (from 3218.74 µg.hr/L to 4207.65 µg.hr/L, P<0.05) and dapoxetine Cmax (from 433.1 µg/L to 601.1 µg/L,P<0.05) with a decrease in CL and $t_{1/2}$ only after administration of 4 gm green tea extract. There was a significant increase in midazolam AUC∞ (from 41.123 µg.hr/L to 58.55 µg.hr/L, P<0.05) and midazolam Cmax (from 36.07 µg/L to 53.53 µg/L,P<0.05) with a decrease in CL and $t_{1/2}$only after administration of 4 gm green tea extract. However, the intake of 2 gram green tea extract showed no significant change in either dapoxetine or midazolam AUC or Cmax (p≥0.05).
Conclusion: High dose of green tea intake increases dapoxetine bioavailability by the inhibiting CYP3A4 enzyme as indicated by the change in midazolam pharmacokinetic. Taking high dose of green tea with dapoxetine should be avoided. However, normal dose of green tea is safe for dapoxetine co-administration.

INTRODUCTION

Premature ejaculation (PE) is a common male sexual disorder which is associated with substantial personal and interpersonal negative psychological factors. The off–label use of anti-depressant SSRIs including paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine has revolutionized the approach to PE treatment (Salonia *et al*., 2009). However, the lack of an approved drug and total reliance on off–label treatment represents a substantial unmet treatment need. Dapoxetine was the first safe drug developed for PE (McMahon, 2011). Dapoxetine is a potent SSRI structurally similar to fluoxetine (Sorbera *et al.*, 2004). Dapoxetine binds to 5–HT, norepinephrine (NE) and dopamine (DA) re–uptake transporters and inhibits uptake in the following order of potency: 5–HT> NE >DA (Gengo *et al.*, 2005). Dapoxetine was rapidly absorbed, Dapoxetine has a Tmax of 1.0–2.0 hours and rapidly achieves peak plasma concentration (Cmax) following oral administration. Both plasma concentration and area under the curve (AUC) are dose dependent up to 100 mg (Dresser *et al.*, 2004). Elimination was biphasic, with an initial half–life of approximately 1.4 hours and a terminal half–life of approximately 15 hours (Modi *et al.*, 2006).

** Corresponding Author*
Khaled Sobhy Abdelkawy, PhD of Clinical Pharmacy, Clinical Pharmacy Department, Faculty of Pharmacy, Kafrelsheikh University, Kafr El-Shaikh, Egypt.
Email: khaledabdelkawy79@yahoo.com

Dapoxetine is metabolized extensively in the liver and kidney by multiple enzymes mainly CYP3A4 or CYP2D6. The major product at the end of the metabolic pathway is circulating dapoxetine N– oxide, which is a weak SSRI and contributes no clinical effect. The other products presented less than 3% in the plasma are desmethyl dapoxetine and didesmethydapoxetine, which are equipotent to dapoxetine. Although didesmethyldapoxetine is equipotent to the parent dapoxetine, its substantially lower plasma concentration, compared with dapoxetine, limits its pharmacological activity and it exerts little clinical effect (Dresser *et al.,* 2006). Dapoxetine 30 and 60 mg were well tolerated with a low incidence of adverse effects (AEs). The most frequently reported AEs were nausea, diarrhea, headache, dizziness, insomnia, somnolence, fatigue, and nasopharyngitis (Montejo *et al.,* 2001). Green tea has been widely used as antioxidant and chemo-preventive agents against vascular risk factors, sexual disorders, and cancer (Mostafa *et al.,* 2013). Green tea is derived from *Camellia sinensis* plant (Graham, 1992). The major catechins in green tea are epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG) which is the most abundant, accounting for 50–80% of the total catechins in green tea (Feng, 2006). Previous study showed that green tea extract inhibited CYP3A4 activity in human liver microsomes (Nishikawa *et al.,* 2004). For this reason, the wide variety of medical uses of green tea suggests that the possibility for potential drug interaction is high. Drug-drug interactions (DDI) of CYP3A4 are of particular importance because of the number of marketed drugs that are cleared by this enzyme. Multiple probe substrates are often used for in CYP3A4 DDI studies, including midazolam, felodipine/ nifedipine, and testosterone (Foti *et al.,* 2010). Patients receiving dapoxetine for the treatment of PE could potentially take grean tea as a beverage for its multiple benefits. Green tea can inhibit CYP 3A4 and Dapoxetine undergo CYP3A4 metabolism and the potential for interactions must be evaluated. So, this study aimed to investigate the pharmacokinetic interaction of dapoxetine and different doses of green tea extract in normal healthy male volunteers using midazolam as CYP3A4 probe

MATERIAL AND METHODS

Materials

Dapoxetine was obtained from SEIDICO "South Egypt for Drug Industries Co. (Ismailia, Egypt), midazolam was obtained Amoun pharmaceutical company (cairo, Egypt), and clonazepam was obtained from Sigma chemical Co. (St.Louis, MO, USA). Acetonitrile, methanol, and ammonium dihydrogen phosphate, and phosphoric acids were purchased from (Riedel–De Haen, Germany). All solvents were HPLC grade. Diethyl ether of analytical grade was obtained from Honil Limited (London, UK).

Subjects

Twelve healthy males were included in the study. The average age of the volunteers range (25–45) and the average weight was 78 kg (range 60–93). The study was carried out in the Pharmaceutical Research Center of Faculty of Pharmacy, Tanta University, Egypt, from April 2015 to July 2015. The study protocol was approved by the ethical committee of Tanta University in accordance with the Declaration of Helsinki. Participants signed for a written consent form. All volunteer had vital signs, normal kidney and liver functions free from ischemic heart disease and liver disorders.

Study design

A random crossover single dose study was employed. Participants abstain taking any drug for at least 3 days before and till the end of the study period. They were fast for 8 hours before drug intervention. On the day of the study, each volunteer received Dapoxetine tablet 60 mg (Joypox® 60 mg, SEDICO "South Egypt for Drug Industries Co.", Cairo, Egypt), midazolam tablet 7.5 mg (Mediathetic® 7.5 mg, Amoun pharmaceutical company, Cairo, Egypt) concurrently after drinking 250 ml of water, after drinking 250 ml of fresh extract of 2 gram of green tea (one Green tea packets 2 grams, Mepaco, Anshas El-raml, Sharqia), or after drinking 250 ml of fresh extract of 4 gram of green(two Green tea packets 2 grams, Mepaco, Anshas El-raml, Sharqia). After one week washout period, each volunteer received the second intervention followed by another one week washout period, then each volunteer received the third intervention as shown in the study flow (Table 1). All volunteers take the same standardized meal 4 hours after dapoxetine intake and no smoking was allowed during blood sampling period.

Table 1: Study flow for volunteers after co-administration of dapoxetine 60 mg and midazolam 7.5 mg.

4 participants take 250 ml water	7 day washout period	4 participants take 250 ml extract of 4 gm green tea leaves powder	7 day washout period	4 participants take 250 ml extract of 2 gm green tea leaves powder
4 participants take 250 ml extract of 2 gm green tea leaves powder		4 participants take 250 ml water		4 participants take 250 ml extract of 4 gm green tea leaves powder
4 participants take 250 ml extract of 4 gm green tea leaves powder		4 participants take 250 ml extract of 2 gm green tea leaves powder		4 participants take 250 ml water

Sampling

Blood samples were obtained after the insertion of peripheral cannula into the forearm by a skilled certified nurse. Samples were obtained before dapoxetine and midazolam intake (blank) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 5, 8, 12,24, and 48 hours after sildenafil and midazolam administration. The samples were collected in clean heparinized tubes. Plasma was obtained by centrifugation (Hettich EAB 12 Centrifugator, Germany) and was stored at –20° until assay. Plasma samples were analyzed for dapoxetine and midazolam using HPLC (Shimadzu HPLC LC2010HT, Shimadzu Corporation, Japan). Tolerability was assessed throughout the study using vital–sign measurements,

physical examinations, and monitoring of adverse events (AEs) that were recorded in terms of symptoms and signs, duration, and seriousness.

Determination of dapoxetine and midazolam by HPLC

Plasma samples were analyzed for dapoxetine and midazolam in one run using validated HPLC method developed in the laboratory of pharmaceutical research center of faculty of pharmacy, Tanta University, Egypt. A clean test tube were spiked with 50 µl of the internal standard solution "5 µg/ml clonazepam in methanol" and the methanol was left to evaporate in a water bath adjusted at 50°. To this tube, 0.5 ml of the collected plasma sample was added and the tube contents were vortex mixed for 3 min. The plasma samples already spiked with the internal standard were extracted with 4 ml of ether following mixing by vortex for 3 minutes. After centrifugation for 10 min, the ether layer was transferred to a clean test tube and was evaporated in a water bath at 50°. The residue was dissolved in 150 µl of the mobile phase and 50 µl of the resulting solution was injected into the HPLC.

The mobile phase consisted of acetonitril and 50 mmol ammonium dihydrogen phosphate buffer (PH adjusted at 2.5 with phosphoric acid) at a ratio 30:70. Separation was achieved at ambient temperature using column C8 (C_8 150*4.6) at a flow rate of 1.0 ml/min. The column effluent was monitored by UV detector at 220 nm. The retention time (RT) for dapoxetine was 3.3 and (RT) for midazolam was 8.79 as shown in the following chromatogram (Figure 1).

Standard Curve for dapoxetine

Blank plasma was spiked with the internal standard and known amounts of dapoxetine to produce standard samples with concentrations in the range of 50µg/L – 1000 µg/L. Calibration curves were constructed from the obtained peak area and the concentration of dapoxetinein each standard sample. The concentrations of dapoxetine in the unknown samples were determined from the calibration curves. The assay was fully validated for linearity, selectivity, precision, accuracy and stability.

Standard Curve for midazolam

Blank plasma was spiked with the internal standard and known amounts of midazolam to produce standard samples with concentrations in the range of 5 µg/L-100 µg/L. Calibration curves were constructed from the obtained peak area and the concentration of midazolam in each standard sample. The concentrations of midazolam in the unknown samples were determined from the calibration curves. The assay was fully validated for linearity, selectivity, precision, accuracy and stability.

Pharmacokinetic and statistical calculations

The plasma concentration–time profiles of dapoxetine, and midazolam of each subject were analyzed by a non–compartmental method using WinNonlin® software (v 6.1; Pharsight Corporation, Mountain View, CA, USA). Pharmacokinetic values for peak concentration (Cmax) and time to Cmax (Tmax) were taken directly from the observed data. Individual concentration–versus time profiles were plotted, and the terminal elimination rate constant (k) was determined by the log–linear regression of at least three data points judged to be in the terminal phase. The half–life ($t_{1/2}$) equal to 0.693/k. Area under curve (AUC) was determined by the trapezoidal rule from time zero to the time of the last observed concentration (C_{last}) plus C_{last}/k.

The total body clearance (CL/F) was obtained as dose/AUC. Statistical comparisons of the estimated pharmacokinetic values were performed using ANOVA with Tukey's test. P–values < 0.05 were considered significant.

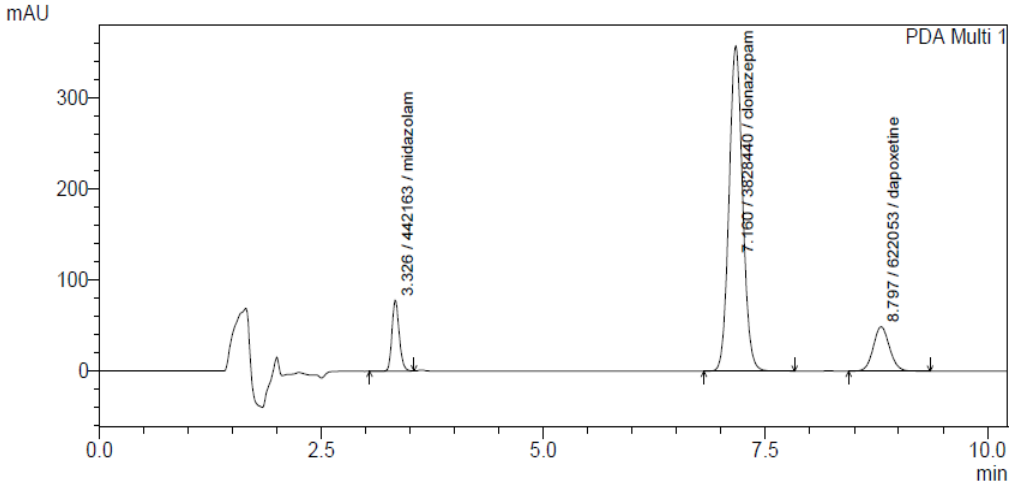

Fig. 1: HPLC Chromatogram for both dapoxetine and midazolam in one single run using clonazepam as internal standard. Retention time for midazolam is 3.328 min, for dapoxetineis 8.797 min, for clonazepam (invernal standard) 7.16 min.

RESULTS

Vital signs were similar after dapoxetine alone as well as with different doses of green tea extract. Dapoxetine was absorbed rapidly after oral administration reaching a maximum plasma concentration in about 1hr. The mean plasma concentration–time profile after a single dose of dapoxetine 60 mg without, after 2 gm, or after 4 gm green tea were shown in Figure (2). There was a significant increase in dapoxetine AUC∞ (from 3218.74µg.hr/L to 4207.65µg.hr/L, P<0.05) and dapoxetine Cmax (from 433.1µg/L to 601.1µg/L, P<0.05) only after co-administration of 4 gm green tea extract with dapoxetine. However, the intake of 2 gram green tea extract with dapoxetine showed no significant increase in dapoxetine AUC or Cmax (p≥0.05). Table (2) showed the pharmacokinetic analysis for dapoxetine in the three cases. After 4gm intake of green tea with dapoxetine. The CLtot/F was significantly reduced from 18.64 L/hr to 14.25 L/hr (p<0.05) and the elimination of dapoxetine was also significantly delayed. The elimination rate constant was decreased from 0.046hr^{-1} to 0.034h-^{1} (p<0.05) and the elimination half life was prolonged from15.06 h to 20.38 h (p<0.05).

On the other hand, the Tmax showed no significant change after either 2 gm or 4 gm intake of green tea extract (p≥0.05). Regarding midazolam, the mean plasma concentration–time profile after a single dose of midazolam 7.5 mg without, after 2 gm, or after 4 gm green tea were shown in Figure (3). There was a significant increase in midazolam AUC∞ (from 41.123 µg.hr/L to 58.55 µg.hr/L, P<0.05) and midazolam Cmax (from 36.07 µg/L to 53.53µg/L, P<0.05) only after co-administration of 4 gm green tea extract with midazolam. However, the intake of 2 gram green tea extract showed no significant increase in midazolam AUC or Cmax (p≥0.05).

Table (3) showed the pharmacokinetic analysis for midazolam in the three cases. After 4gm intake of green tea with midazolam. The CLtot/F for midazolam was significantly reduced from 182.37 L/hr to 128.09 L/hr ((p<0.05) and the elimination of midazolam was also significantly delayed. The terminal elimination rate constant was decreased from 0.643hr^{-1} to 0.389hr^{-1} (p<0.05) and the terminal elimination half life was prolonged from 1.096hr to1.758hr (p<0.05). On the other hand, the Tmax showed no significant change after either 2 gm or 4 gm intake of green tea extract (p≥0.05).

Table 2: The Effect of the intake of green tea extract on dapoxetine (60 mg) pharmacokinetic parameters.

Treatment	AUC∞ (µg.hr/L)	Cmax (µg/L)	tmax (hr)	T½ (hr)	K (hr-1)	CLtot/F (L/hr)
Dapoxetine	3218.74±645	433.1±41	1 (0.75-1.5)	15.06±6.5	0.046±0.0052	18.64±3.5
Dapoxetine with 2 gm green tea extract	3380.67±542	455.3±64	1(0.5-1. 5)	14.74±5.5	0.047±0.0061	17.74±4.3
% change	5.03	5.12		-2.2	2.17	-4.9
Dapoxetine with 4 gm green tea extract	4207.65±611*	601.1±75*	1(0.75-1.5)	20.38±6.9*	0.034±0.0077*	14.25±4.5*
%change	30.72	38.79		35.32	-26.1	-23.56

Data are presented as mean ± S.E, except for tmax for which median is shown, n=12. *significantly different from dapoxetine (paired t test, p<0.05). k= elimination rate constant, AUC∞=area under the curve, t½= half-life, tmax= time required to achieve maximum plasma concentration, Cmax=maximum plasma concentration, CLtot= total body clearance and F= bioavailability.

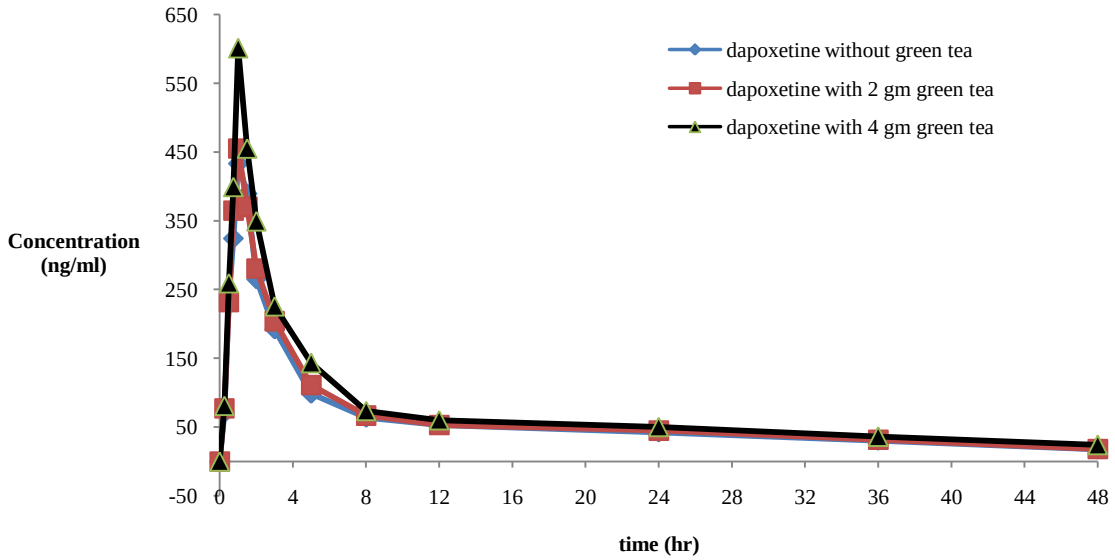

Fig. 2: The mean plasma concentration-time profile after a single dose of dapoxetine 60 mg without, after 2 gm, or after 4 gm green tea.
* significant increase AUC and Cmax after co-administration with 4 gm green tea extract compared to dapoxetine alone (paired t test, P<0.05).

Table 3: The Effect of 2gm and 4 gm intake of green tea on midazolam (7.5 mg) pharmacokinetic parameters.

Treatment	AUC∞ (µg.hr/L)	Cmax (µg/L)	tmax (hr)	T½ (hr)	K (hr-1)	CLtot/F (L/hr)
midazolam	41.123±6.1	36.07±4.9	0.5 (0.25-1)	1.096±41	0.643±0.08	182.37±38
midazolam with 2 gm green tea extract	43.555±5.4	38.43±5.3	0.5 (0.25-0.75)	1.17±41	0.589±0.07	172.196±52
% change	5.9	6.54		6.75	-8.4	-5.6
midazolam with 4 gm green tea extract	58.555±5.9*	53.53±5.4*	0.5 (0.25-0.75)	1.7588±41*	0.394±0.05*	128.09±44*
% change	34.44	48.4		60.4	38.8	-29.8

Data are presented as mean ± S.E, except for tmax for which median is shown , n=12. *significantly different from control ($p<0.05$). k= elimination rate constant, AUC∞=area under the curve, t½= half-life, tmax= time required to achieve maximum plasma concentration, Cmax=maximum plasma concentration, CLtot= total body clearance and F= bioavailability.

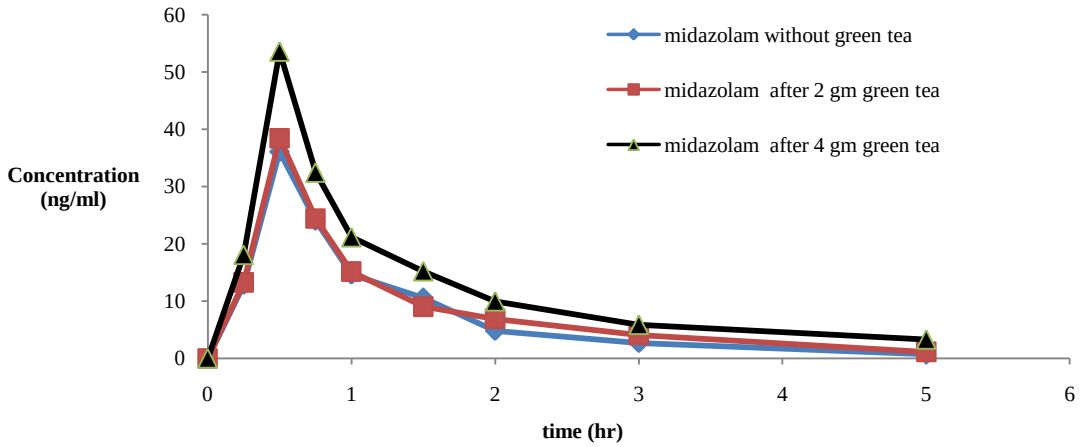

Fig. 3: The mean plasma concentration-time profile after a single dose of midazolam 7.5 mg without, after 2 gm, or after 4 gm green tea.
* significant increase AUC and Cmax after co-administration with 4 gm green tea extract compared to midazolam alone (paired t test, $P<0.05$).

DISCUSSION

Dapoxetine is the first effective and safe treatment for premature ejaculation that represents a major advance in sexual medicine. So, the use of dapoxetine is expected to increase. For this reason, it is very important to ensure the safety of this drug in a variety of conditions (McMahon, 2011).Recently, the use of herbal supplements has increased dramatically as an alternative to chemical drugs, making drug interactions with these supplements a major concern to researchers specially that herbal supplements are not subject to the same regulations as prescription drugs (Wanwimolruk *et al.*, 2009).

In this study, the primary pharmacokinetic parameters were the AUC, Tmax, and C_{max} of dapoxetine and midazolam. The results of current study indicated that co-administration of 4 gm green tea extract (high dose than normal) produced a significant increase in the extent of dapoxetine absorption but not the rate of dapoxetine absorption. This was apparent from the significant increase in dapoxetine AUC without any change in Tmax. However, the co-administration of 2 gm green tea extract (normal green tea dose) showed no change in dapoxetine pharmacokinetics. In addition, the current study showed an increase in half life of dapoxetine. This prolongation of the half life by high dose of green tea resulted from decreasing the total body clearance which is attributed to the decrease in dapoxetine metabolism by inhibiting CYP3A4 (Walsky and Obach, 2004). The inhibition of CYP3A4 was confirmed by the increase in midazolam concentration. Midazolam is the most reliable standard substrate for evaluation of the in vivo inhibition of CYP3A4 (Ohno *et al.*, 2007). The change in midazolam bioavailability after dapoxetine intake indicate the possible inhibition of CYP3A4 by dapoxetine.

The most common form of green tea in the market is packet of 2gm green tea leave powder which is considered the normal dose. In contrast, high dose of green tea may be found in some dietary supplement in the market or from taking two packets of 2 gram green tea simultaneously. So, patients taking this high dose should be warranted about the possible drug interaction with dapoxetine and reducing dapoxetine dose may be recommended or seeking physician for advice. Yang and Pan were the first to report that The effect of green tea on drug metabolism is dose dependant supporting current results and that the of tea catechins from dietary supplements containing large doses may produce more profound effects on drug metabolism while normal doses may be safe on drug metabolism (Yang and Pan, 2012).

The green tea used in this study was tested for content in polyphenols (Catechins represent 90 % of polyphenol) by the manufacturing company which reported that the used green tea is

the Chinese species of green tea and one gram of green tea leaves powder contain 0.3 gram of catchins. In our laboratory, qualitative standardization for the composition of green tea leaves was carried out by comparing their TLC fingerprints with authentic sample of green tea leaves. The amount is automatically adjusted by the manufacturing company so variation in amount is reduced to minimum. In the current study, 60 mg dose of dapoxetine were selected because they are the highest recommended dosage. Generally, these drugs are used on–demand; for this reason, this study was conducted after a single oral administration of dapoxetine (Hatzimouratidis *et al.,* 2010).

Limited studies are available for dapoxetine pharmacokinetic interactions. Currently, there are no documented drug–drug interactions associated with dapoxetine except for ketoconazole which is potent CYP3A4 inhibitor. Ketoconazole increased dapoxetine exposure to a greater extent. There was a 23% increase in C_{max} and 88% increase in the AUC of dapoxetine. However, other drug interaction studies on dapoxetine and other PDE–5 inhibitors, including tadalafil, sildenafil or udenafil as well as with ethanol reported no clinically significant pharmacokinetic interactions. Despite that contraindication to dapoxetine include that Dapoxetine should not be used in men receiving CYP3A4 inhibitors such as ritonavir, ketoconazole, and telithromycine (Dresser *et al.,* 2006; Kim *et al.,* 2015)

The effects of green tea extract on enzyme metabolism is not completely proven. Many previous studies indicated that green tea extract use caused significant interactions with drugs metabolism by inhibiting CYP3A4 and Tea whether used for leisure or medicinal purposes has the potential to inhibit CYP3A4 (Vischini *et al.,* 2011; Tam *et al.,* 2014).On the other hand, few studies indicated that green tea extract might not change or even increase the CYP3A4 activity.

Regarding supporting studies, Mooiman *et al*. stated that green tea is a potent inhibitor of CYP3A4–mediated metabolism of midazolam (Mooiman *et al.,* 2014) and the effect on CYP3A4 varied among different brands of green tea, possibly due to variations in their content of the herbal product's active ingredients (Wanwimolruk *et al.,* 2009). Engdal and Nilsen stated that although Agaricus, noni juice, mistletoe and green tea inhibited CYP3A4 metabolism in vitro, clinically relevant systemic or intestinal interactions with CYP3A4 were considered only for the green tea (Engdal and Nilsen, 2009). In addition, Chow *et al.,* revealed that four weeks of green tea catechin intervention did not alter the CYP1A2, CYP12D6, and CYP12C9 activities, but resulted in increasing AUC of buspirone concentration through the reduction in CYP3A4 activity (Chow *et al.,* 2009). A recent study showed that, green tea inhibited CYP3A activity in a noncompetitive manner (Misaka *et al.,* 2012). Moreover, green tea extract alters the pharmacokinetics of simvastatin by 3.3 fold increase, probably by inhibiting intestinal CYP3A (Misaka *et al.,* 2013). In another study, the repeated intake of green tea extract aggravated cyclophosphamide–induced body weight loss and malformations of fetuses by modulating CYP2B and CYP3A mRNA (Park *et al.,* 2009). In the opposite side, Donovan was the first to report that green tea is unlikely to alter the disposition of medications primarily dependent on the CYP2D6 or CYP3A4 pathways of metabolism (Donovan *et al.,* 2004). A recent study showed that green tea extract decreased the bioavailability of quetiapine but the exact mechanism was unknown (Asiri and Iqbal, 2015).

Boušová *et al*. who showed that green tea decreased insulin and leptin levels and Long–term administration of green tea extract caused an increase in the activity and mRNA level of CYP3A4 ortholog in the liver as well as in the small intestine in obese individuals and these unexpected result may be related to obese people only (Boušová *et al.,* 2015). The use of Midazolam enabled us to investigate the possible mechanism for this interaction at high dose. Midazolam is considered the clinical standard probe for CYP3A4 enzyme (Ohno *et al.,* 2007). The increase of midazolam AUC and Cmax at the high dose of green tea indicated that the expected mechanism of this interaction is the inhibition of CYP3A4 enzyme in both the intestine and the liver.

In conclusion, at normal doses of green tea, dapoxetine has no clinically important pharmacokinetic interactions with green tea, and the combinations are well tolerated. But, at high doses of green tea, green tea may cause moderate increase in dapoxetine plasma concentration by inhibiting CYP3A4 enzyme as indicated by the significant increase in midazolam AUC and Cmax. Patients taking high dose of green tea should take smaller doses of dapoxetine or should contact physician first before taking dapoxetine therapy. However, further controlled studies for larger numbers of patients may be required.

REFERENCES

Asiri Y, Iqbal M. Effects of green tea extracts on the pharmacokinetics of quetiapine in rats. Evid. Based. Complement. Alternat Med, 2015; 61: 5285-9.

Boušová I, Matoušková P, Bártíková H, Szotáková B, Hanušová V, Tománková V, Anzenbacherová E, Lišková B, Anzenbacher P, Skálová L. Influence of diet supplementation with green tea extract on drug–metabolizing enzymes in a mouse model of monosodium glutamate–induced obesity. Eur J Nutr, 2015 [Epub ahead of print].

Chow S, HakimI, Vining D, Crowel J, Cordova C, Chew, W, Xu M, Hsu C, Ranger–Moore J, Alberts, D. Effects of Repeated Green Tea Catechin Administration on Human Cytochrome P450 Activity. Cancer.Epidemiol. Biomarkers Prev, 2006; 15: 2473-7.

Donovan J, Chavin K, Devane C, Taylor R, Wang J, Ruan Y, Markowitz J. Green tea (*Camellia sinensis*) extract does not alter cytochrome p450 3A4 or 2D6 activity in healthy volunteers. Drug Metab Dispos, 2004; 32(9): 906-8.

Dresser M, Kang D, Staehr P, Gidwani S, Guo C, Mulhall J. Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: Impact of age and effects of a high–fat meal. J Clin Pharmacol, 2006; 46: 1023-9.

Dresser M, Lindert K, Lin D, Gidwani S, Gupta S, Modi N. Pharmacokinetics of single and multiple escalating doses of dapoxetine in healthy volunteers. Clin Pharmac Therap, 2004; 75(2): 32-7.

Engdal S, Nilsen O. In vitro inhibition of CYP3A4 by herbal remedies frequently used by cancer patients. Phytother Res, 2009; 23(7): 906-12.

Feng W. Metabolism of green tea catechins: an overview. Curr Drug Metab, 2006; 7: 755-809.

Foti R, Rock D, Wienkers L, Wahlstrom J. Selection of alternative CYP3A4 probe substrates for clinical drug interaction studies

using in vitro data and in vivo simulation. Drug Metab Dispos, 2010; 38(6):981-7.

Gengo R, Giuliano F, McKenna K, Chester A, Lovenberg T, Bonaventure P. Monoaminergic Transporter Binding and Inhibition Profile of Dapoxetine, A medication for the Treatment of Premature Ejaculation J Urol, 2005; 173: 230-3.

Graham, H. Green tea composition, consumption and polyphenol chemistry. Prev Med, 1992; 21: 334-50.

NakamuraH, Kimura N, Kimura M, Hasegawa A, Kusu F, Ohmori S, Nakazawa K, Kitada M,. Effects of continuous ingestion of green tea or grape seed extracts on the pharmacokinetics of midazolam. Drug Metab Pharmacokinet, 2004; 19: 280-9.

Hatzimouratidis K, Amar E, Eardley I. European Association of Urology Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol, 2010; 57(5): 804-14.

Kang K, ParkY, Hwang H, Kim S, Lee J, Shin H.Antioxidative properties of brown algae polyphenolics and their perspectives as chemopreventive agents against vascular risk factors. Arch Pharm Res, 2003; 26(4): 286-93.

Kim Y, Choi H, Lee S, Jeon H, Lim H, Bahng M, Bae K. Pharmacokinetic interaction between udenafil and dapoxetine: a randomized, open–labeled crossover study in healthy male volunteers. Drug Des Devel Ther, 2015; 9: 1209-16.

McMahon C. Efficacy of dapoxetine in the treatment of premature ejaculation. clinicalmedicine insights. Reprod Health, 2011; 5: 25-39.

Misaka S, Kawabe K, Onoue S, Werba J, Giroli M, Tamaki S, Kan T, Kimura J, Watanabe H, Yamada S. Effects of green tea catechins on cytochrome P450 2B6, 2C8, 2C19, 2D6 and 3A activities in human liver and intestinal microsomes.Drug Metab Pharmacokinet, 2012; 25: 232-44.

Misaka S, Kawabe K, Onoue S, Werba J, Giroli M, Watanabe H, Yamada S. Green tea extract affects the cytochrome P450 3A activity and pharmacokinetics of simvastatin in rats. Drug Metab Pharmacokinet, 2013; 28(6): 514-8.

Modi N, Dresser M, Simon M, Lin D, DesaiD, Gupta S. Single–and multiple–dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. J Clin Pharmacol, 2006; 46(3):301-9.

Montejo A, Lorca G, Izquierdo J, Rico–Villademoros F . Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic–Related Sexual Dysfunction. J Clin Psychiatry, 2001; 62: 10-21.

Mooiman K, Maas–Bakker R, Hendrikx J, Bank P, Rosing H, Beijnen J, Schellens J, Meijerman I. The effect of complementary and alternative medicines on CYP3A4–mediated metabolism of three different substrates: 7–benzyloxy–4–trifluoromethyl–coumarin, midazolam and docetaxel. J Pharm Pharmacol, 2014; 66(6): 865-74.

Mostafa T, Sabry D, Abdelaal A, Mostafa I, Taymour M. Cavernous antioxidant effect of green tea, epigallocatechin–3–gallate with/without sildenafil citrate intake in aged diabetic rats. Andrologia, 2013; 45(4): 272-7.

Nishikawa M, Ariyoshi N, Kotani A, Ishii I, Nakamura H, Nakasa H, Ida M, Ohno Y, Hisaka A, Suzuki H. General framework for the quantitative prediction of CYP3A4–mediated oral drug interactions based on the AUC increase by coadministration of standard drugs. Clin Pharmacokinet, 2007; 46(8): 681-96.

Park D, Jeon J, Shin S, Joo S, Kang D, Moon S, Jang M, Cho Y, Kim J, Ji H, Ahn B, Oh K, Kim Y. Green tea extract increases cyclophosphamide–induced teratogenesis by modulating the expression of cytochrome P–450 mRNA. Reprod Toxicol, 2009; 27(1): 79-84.

Salonia A, Rocchini L, Sacca A, Pellucchi F, Ferrari M, Carro U. Acceptance of and discontinuation rate from paroxetine treatment in patients with lifelong premature ejaculation. J Sex Med, 2009; 6: 2868-77.

Sorbera L, Castaner J, Castaner R. Dapoxetine hydrochloride. Drugs Future, 2004; 29:1201-5.

Tam T, Liu R, Saleem A, Arnason J, Krantis A, Foster B. Cytochrome 3A4 and 2D6–mediated metabolism of leisure and medicinal teas. J. Pharm. Pharm. Sci.2014; 17(3): 294-301.

Vischini G, Niscola P, Stefoni A, Farneti F. Increased plasma levels of tacrolimus after ingestion of green tea. Am J Kidney Dis, 2011; 58(2): 329-34.

Walsky R, Obach R. Validated assays for human cytochrome P450 activities. Drug Metab Dispos, 2004; 32(6): 647-60.

Wanwimolruk S, Wong K, Wanwimolruk P. Variable inhibitory effect of different brands of commercial herbal supplements on human cytochrome P–450 CYP3A4. Drug Metabol Drug Interact, 2009; 24(1):17-35.

Wanwimolruk S, Wong K, Wanwimolruk P. Variable inhibitory effect of different brands of commercial herbal supplements on human cytochrome P–450 CYP3A4. Drug Metabol Drug Interact, 2009; 24(1): 17-35.

Yang C, Pan E.The effects of green tea polyphenols on drug metabolism. Expert Opin Drug Metab Toxicol, 2012; 8(6): 677-89.

How to cite this article:

Abdelkawy KS, Donia A, Abdallah M. Pharmacokinetics interaction of dapoxetine with different doses of green tea extract in male healthy volunteers using midazolam as CYP3A4 enzyme probe. J App Pharm Sci, 2015; 5 (12): 001-007.