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RESEARCH ARTICLE

The effect of Pomegranate and Licorice on Pharmacokinetics of Theophylline in Rat Plasma

Alhuda ALANBAKI[*], Israa ALANI[**], Eyad Mallah[***], Zainab ZAKAREIA[*****], Tawfiq ARAFAT[******], Wael ABU DAYYIH[*********],°

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SUMMARY

Food or drinks may significantly alter the pharmacokinetics and pharmacodynamics of drugs which may lead to adverse events. A drug such as theophylline is widely used to treat asthma and chronic obstructive pulmonary disease. Pomegranate and licorice have been identified to help in cough management. However, the interactions of the later with theophylline pharmacokinetics were not studied. Therefore, we aimed to study the impact of pomegranate and licorice on theophylline pharmacokinetics in rats. An HPLC method of analysis was developed and partially validated successfully according to the European Medical Agency Guideline to measure theophylline in rat plasma. Pomegranate and licorice juices were given to rats for two days and half an hour before theophylline (5 mg/kg) was orally administered as solution. Blood samples, then, were collected at scheduled time intervals, processed and analyzed using the validated reliable HPLC method. Plasma profile of theophylline was obtained and pharmacokinetic parameters (Cmax, Tmax and Area under the curve (AUC)),were calculated for each group. Values of the pharmacokinetic parameters were compared statistically using ANOVA, t-test with corresponding control values on 95%confidence interval. It was found that consumption of pomegranate or licorice juice prior oral administration of theophylline did not result in significant pharmacokinetic interaction.

Key Words: *Theophylline, licorice ,pomegranate ,pharmacokinetics, rat, drug-food interaction*

Sıçan Plazmasında Nar ve Meyan Kökünün Teofilinin Farmakokinetiğine Etkisi

ÖZ

Yiyecek ve içecekler ilaçların farmakokinetiğini ve farmakodinamiğini ters etkiler oluşturacak kadar önemli ölçüde değiştirebilir. Teofilin gibi bir ilaç astım ve kronik obstruktif akciğer hastalığı tedavisinde yaygın olarak kullanılır. Nar ve meyan kökünün, öksürük yönetiminde yardımcı oldukları tanımlanmıştır. Ancak, teofilin ile sonraki farmakokinetik etkileşimleri çalışılmamıştır. Bu nedenle, bu çalışmada nar ve meyankökünün sıçanlarda teofilin farmakokinetiği üzerine etkilerini incelemeyi amaçladık.

Sıçan plazmasında teofilini ölçmek üzere Avrupa Sağlık Ajansı Kılavuzuna göre kısmen valide olmuş bir HPLC analiz yöntemi geliştirildi. Sıçanlara nar ve meyan suları teofilinin (5 mg / kg) oral larak uygulamasından yarım saat sonra olmak üzere iki gün süreyle verildi. Daha sonra kan örnekleri programlanmış zaman aralıklarında toplandı,güvenilir HPLC yöntemi ile teofilinin plazma profili elde edildi ve farmakokinetik parametreler (Cmax, Tmax ve Area eğri altında (AUC)), her grup için hesaplandı. Farmakokinetik parametreler ANOVA, t test ile % 95 güvenlikte karşılık gelen kontrol değerleriyle istatistiksel olarak karşılaştırıldı. Teofilinin oral yoldan verilmesinden önce meyve suyu olarak nar veya meyan kökü tüketiminin
önemli farmakokinetik etkileşime neden olmadığı bulundu.

Anahtar Kelimeler: *Teofilin, meyan kökü, nar, farmakokinetik, sıçan, gıda-ilaç etkileşmesi*

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[*] ORCİD:- Faculty of Pharmacy and Medical Sciences, University of Petra
[**] ORCİD:-Faculty of Pharmacy and Medical Sciences, Al-Ahliyya Amman University
[****] ORCİD:- Faculty of Pharmacy and Medical Sciences, University of Petra
[*****] ORCİD:- Faculty of Pharmacy and Medical Sciences, University of Petra
[******] ORCİD:- Faculty of Pharmacy and Medical Sciences, University of Petra
[*******] ORCİD: 0000-0003-2432-9356, Faculty of Pharmacy and Medical Sciences, Al-Ahliyya Amman University
° Corresponding Author; Dr . Wael Abu Dayyih (PhD, Bpharm) Associate Professor
Tel.: +962-6–5799555 Fax: +962-6–5715570 E-mail:wabudayyih@uop.edu.jo

INTRODUCTION

The consumption of herbs as beverages has increased in recent years. It has been estimated that approximately 1 out of 5 Asian take prescription medications concurrently with at least 1 herbal product or more (Shane-McWhorter,2001). In many cases, patients consume such products to treat various disorders such as anxiety, dementia and memory impairment, headache, weight loss, and others (Marcus and Grollman,2002). Concurrent use of herbal beverage with approved medications can result in therapeutic failures or adverse effects and may produce variable outcomes of clinical importance if this concomitant consumption is not controlled (Sinh and Saratchandra 2005, Hamad et al. 2017). In this regard, several juices have shown to alter enzymes and transporters that modulate the pharmacokinetic parameters (PKP) and thus might result in undesired pharmacodynamic (PD) outcomes (Abu Dayyih et al. 2016, Mima et al. 2017). Most of the previously reported drug– juice interactions focused mainly on grapefruit juice. On the other hand, interactions with several other juices with drugs are generally unnoticed which still need to be investigated and addressed (Garvan and Lipsky 2000).

Pomegranate (*Punica granatum* from the family-Lythraceae) has become highly recommended supplements as a natural antioxidant consumed as fruit or juce (Komperda 2009, Awad et al. 2017). However, it showed pharmacokinetic interaction with various drugs like antiarrythmic, calicium channel blokers and statins (Abu Dayyih et al, 2014). Studies proved that pomegranate inhibits CYP3A in the body, in addition, it was reported that pomegranate juice interfered with the intestinal absorption of certain drugs probably through an effect on transporters responsible for the absorption process (Hidaka et al.2005, Hamad et al.2017).

Licorice (*Glycyrrhiza glabra* of the Leguminosae Family), on the other hand, is one of the well-known traditional drinks particularly in the Middle East region. It is known for its antiinflammatory, hypocholesterolemic and antioxidant effects (Cantelli-Forti, et al. 1994). However, licorice was found to interact with some drugs' kinetics like digoxin, thiazides and spironolactone (Shaikhli, 2015). It was also reported that licorice significantly reduced cyclosporine bioavailability by interfering with P-glycoprotein and CYP3A4 (Chua, et al. 2015)

Theophylline (1,3-dimethylxanthine) is a naturally occurring alkaloid which has been classified as bronchodilator in the treatment of asthma and chronic obstructive pulmonary diseases (COPD) due to its effect in relaxation of bronchial smooth muscle. It has a narrow therapeutic index ranging from 5 to 20 mg/ml of serum concentration(Piafsky and Ogilvie 1975). Theophylline is mainly (85-90%) metabolized by liver cytochrome P-450 in both human and rats. Oxidation at carbon no. 8 is the major metabolic pathway in human performed mainly by CYP1A2 as well as N-demethylation to 3-methylxanthine and conjugation (Ogilive 1978, Khan and Jones 2014). CYP1A2 is stimulated by smoking and many drugs, and there is significant inter-individual variation in the level of this enzyme (Weinberger and Hendeles 1996). In rats, the 8-hydroxy derivative composes more than 95% of the total recovered metabolites. It was subjected to induction and inhibition by different xenobiotics as well (Kim et al, 2003). Furthermore, many studies showed interaction of the theophylline with other drugs, food, beverages or dietary supplements on its effect and activity (Khan and Jones 2014). Aqueous licorice and pomegranate root extract is one of the widely used juices worldwide as multi-target agents, and may exert a pronounced effect on several diseases. Therefore, we aimed here to study the impact of pomegranate and licorice on theophylline pharmacokinetics (PK) in rats.

MATERIALS AND METHODS

Chemicals and reagents

Theophylline and Paracetamol (the internal standard) were of analytical purity grade and purchased from United Pharmaceuticals. Phosphoric Acid was purchased from (Chromanorm), Perchloric acid 60% was obtained from (Scharlau), Triethylamine acid was obtained from (Tedia Company). Methanol, water, and acetonitrile were all of HPLC grade (Chromanorm). Pomegranate and licorice (fresh) were purchased from local markets.

Methods

Study design

Seventeen (17) male and female Sprague–Dawley rats average weight (250–300 g) were used in this study. The design of the study was to divide rats to four groups, two groups of equal number of 7 rats. One group receives theophylline solution orally after feeding it with pomegranate juice. And the other is control which received only theophylline solution by the same dose. And the other two groups each of 3 rats, one group received theophylline with licorice juice and the others only theophylline as a control group.

The rats were kept in conditioned environment with 12 hr light/dark cycles. Food and water were available until 12 h prior to an experiment. The animal experiments were performed in compliance with

FELASA guidelines (Federation of European Laboratory Animal Science Association) and the study protocol was approved by the Research Committee (June 2016) at the Faculty of Pharmacy and medical science, University of Petra, Amman, Jordan (certificate number 116). The animals were supplied by the animal house University of Petra.

Each rat received a calculated volume of theophylline solution by using a stainless steel oral gavage needle. Freshly prepared juices were given for 12 h in drinking water before the experiment and half an hour before the dose of theophylline, a booster dose (5 ml/kg) of juice was given just after theophylline. The rats were fasted for 12 hr prior theophylline dosing.

Blood sample were taken from the rats' optical vein and placed into EDTA-containing tubes at the following time points: 0.0, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 10.0, 24.0 hours. Samples were analyzed using the validated HPLC method and plasma level – time profile was constructed and the major PKP , maximum concentration in plasma (C_{max}), time to reach maximum concentration (T_{max}) and AUC_{0-24} hrs were calculated using Winnonlin software V 5.2.

Preparation of theophylline solution and Pomegranate and licorice juices

Theophylline solution was freshly prepared at the day of an experiment. (5 mg/kg) dose was chosen based on average human dose. Stock solution of 1 mg/ml was prepared by dissolving theophylline in distilled water and filtration of the solution.

Pomegranate and licorice juices were freshly prepared for each experiment, refrigerated at and supplied to rats as such without further treatment. Pomegranate fruits were purchased from a local market (Amman, Jordan). It was freshly hand-squeezed without any additives. Licorice root juice was prepared according to the traditional way by soaking in water for one hour, then the roots transferred to special perforated can usually supplied with the root. Cold water was then allowed to drizzle over it for 2 hours. 20 g of licorice roots and rhizomes were used to prepare 1L of the beverage. This method was described by Qiao et al.(Qiao et al.,**2014).**

HPLC analysis

An HPLC (FINNIGAN SURVEYOR) was used and composed of the following: ChromQuest software 4.2.34 Solvent delivery systems pump (LC Pump Plus), autosampler Plus, UV-VIS Plus Detector, Hypersil Thermo Electron Corporation, BDS C-18 Column (150 mm × 4.6 mm, 5 µm) and computer System, Windows XP, SP3.

The mobile phase consisted of 7% acetonitrile in water. 1 ml Triethylamine was added per 1 liter. It was circulated through a reversed-phase Thermo Scientific column (BDS HYPERSIL C18) at flow rate of 1.0 ml/minute. Absorbance was measured at wavelength 272 nm (Table 1).

The sample extraction method was as follows: 100 µl aliquot of each test sample (blank, zero, standards, quality control samples or rat samples) was added to 100 µl of Internal Standard (IS) (40 µg/ml of Paracetamol was prepared in 5% Perchloric acid) vortexed for 1. minute and then tubes were centrifuged at 14 000 rpm for 10 minutes

Table 1. Chromatographic conditions of theophylline HPLC assay.

HPLC Conditions	Pump Flow Rate	Column Oven Temp	Autosampler Temp	Autosampler Injection Volume
	1.0 ml/min	30 °C	10 °C 20 µl	
Chromatography	**Mobile phase**	93 % of Water Contains (1 ml Triethylamine per 1 liter) 7 % of Acetonitrile PH= 3 , adjust with H3PO4		
	Column type	Hypersil Thermo Electron Corporation, BDS C-18 Column (150 mm × 4.6 mm, 5µm)		
	Retention times	**Theophylline**		Paracetamol (Internal Std)
	(minutes)	4.0 _ 4.3	3.4 _ 3.6	
Detection conditions	**Wavelength**	272 nm		
Method	**isocratic elution**			

Method validation included measurement of linearity, precision, and accuracy, stability and recovery according to European Medical Agency (EMEA) guideline (EMEA/ CHMP/ EWP/192217/2009 Rev. 1 Corr. 2 ,2011). Linearity, inter and intra-day precision , accuracy, short term stability (freeze-thaw stability and autosampler stability) and absolute recovery, were all measured and compared to the guideline.

Regarding **linearity**, seven calibration points (0.5µg/ml ,1**µg/ml , 2µg/ml , 5 µg/ml, 10µg/ml , 18 µg/ml** and 30 µg/ml) were prepared and used. Concentrations were prepared from theophylline stock solution of 1mg/ml in water. A series of six injections of each calibration concentration level were performed. Peak areas of the calibration standards were plotted in the Y-axis against the nominal standard concentration.

The **intra-day precision and accuracy** were evaluated by analyzing six replicates of the quality control (QC) samples (low, mid, high) and lower limit of quantification (LLOQ) samples on a single day. The inter-day precision and accuracy were determined by analyzing three runs of QC samples and LLOQ samples on three different days. The accuracy (%) was calculated by dividing a measured mean concentration over the nominal concentration. Precision was presented as CV%. The acceptable values of accuracy and precision are below 15% except at the LLOQ, for which accuracy and precision should be below 20%.

In this study, a **short-term stability** were preformed, freeze-thaw stability and autosampler stability tests. Stability were tested using a low and a high concentration of QC samples. The short-term (bench top) stability was assessed by keeping the plasma samples at room temperature for 24 h. For the freeze and thaw stability test, the samples were shorted at -30 C for 24 h and kept at room temperature until the samples were thawed completely, then refrozen for 24 h. This cycle was repeated three times (three cycles) and then analyzed. The rack at 10 C° for 24 h after sample preparation. The analyte were considered stable if the assay values were within the acceptable limit of accuracy ±15%.

The **absolute recovery** was calculated by comparing the AUCs for plasma extracted samples with un-extracted samples (solution) those represent 100% recovery. Recovery of the analyte does not need to be 100%. However, extent of the recovery of the analyte and IS should be consistent and reproducible. The same method of validation was followed by Awad et al.(Awad et al.,2016)

Calculation of Pharmacokinetics parameters (PKP)

Plasma level-time profile of theophylline was plotted and PKP were calculated by noncompartmental analysis (NCA) model using Winnonlin software V 5.2. The following parameters were estimated: (AUC_{0-24}), (C_{max}) and (T_{max}). The statistical analysis was assessed on the difference between C_{max}, T_{max} and AUC_{0-24} between each 2 groups (test and control) using the independent samples Student's t-test using the same software. The *p*-value <0.05 is considered significant.

RESULTS AND DISCUSSION

Results of validation of method of analysis

Validation according to EMEA guidelines was carried out. The correlation coefficient (R) for the calibration curve of theophylline for each run was higher than 0.99. Furthermore, the intra-day and the inter-day accuracy values of theophylline were between (97.90%-105.19%) and (98.65%-105.88%), respectively, while the intra- and inter-day precision values were equal to or less than 3.175% and 3.653%, respectively (Table 2). This method of assay provides reasonable accuracy, precision, linearity for theophylline over the concentration range tested since all of the results were found within the acceptance criteria of validation guidelines.

Regarding stability and recovery, the method showed stability for short time in auto-sampler for 24 hr and 3 freezing thawing cycles. Percent recovery of test samples was 95.2±3.3% as shown also in table 2.

All results of validation parameters are within the limits specified by the EMEA guide line of analysis and validation.

Table 2. Validation results of the HPLC method used for analyzing theophylline in rats' plasma.

Parameter	Value
Linearity (R2)	0.999
linearity equation	Y=0.000725X–0.002026
Accuracy (%)	
intra-day accuracy (range)	(97.90–105.19%)
inter-day accuracy (range)	(98.65–105.88%)
Precision (CV%)	
intra-day precision (less than)	3.175%
inter-day precision (less than)	3.653%
Stability (%)	
Short term	Stable for 8 hr
Auto-sampler	Stable for 24 h
Freeze thaw	Stable for 3 cycles
Recovery (%)	95.2±4.3

Pharmacokinetics

Theophylline is metabolized both in man and rats mainly by CYP 1A2 oxidase (Kim et al, 2003). The major metabolites are to demethylated and hydroxylated products (Khan and Jone, 2014).

Figures (1) and (2) show the plasma level-time profile of theophylline when given alone and with pomegranate juice and licorice juice. Results shown

in table (3) shows the calculated PKP and results of statistical analysis. These results show nonsignificant change in basic PKP of theophylline when administered to rats pre-fed with either pomegranate or licorice juice, which indicated that there was no effect on its PKP and metabolism mainly by CYP1A2.

Although many studies proved that the most enzymes susceptible for induction and inhibition by fruits and herbs' juices are CYP1A1, CYP1A2, CYP1A4, CYP3A1, CYP3A4, CYP2C6, CYP2C9 and CYP2E1 (Mallhi, 2015) while other cytochromes are less affected. Although theophylline major metabolizing enzyme is CYP1A2, it shows good stability toward food and juices.

A study by Fuhr et al. since 1995 proved lack of grape fruit juice on theophylline pharmacokinetic (Fuhr et al.1995),but there was an effect on T_{max} after administration of modified release tablet of theophylline in adult human males as investigated by Gupta. (Gupta et al., 1999). It was found that grape fruit does not interfere either with the PK of caffeine which shares the xanthan nucleus with theophylline (Maish et al., 1996).

Many studied focused on grapefruit as famous beverage which is known to interact with several medication. But pomegranate juice and licorice juice are widely consumed and they might have potential interactions with medications. The metabolism of theophylline as mentioned above is highly similar between man and rat, that's why we can say that the result of this work give a good indication of this combination.

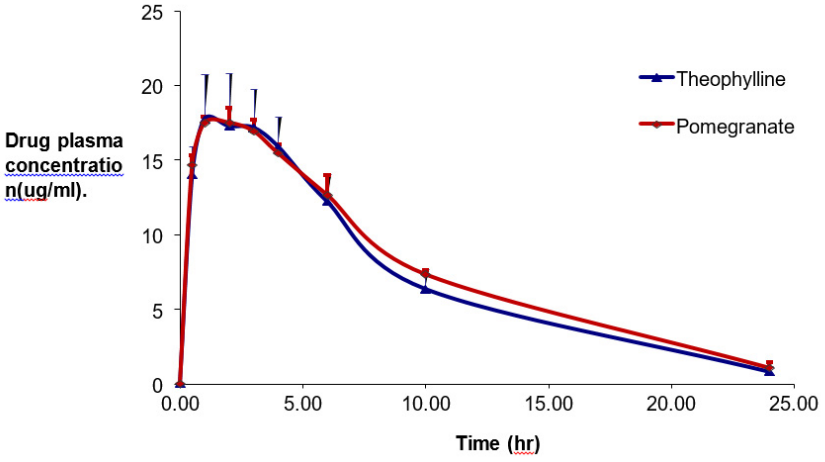

Figure 1. The effect of pre-administration of pomegranate juice on plasma metformin concentration–time profile following an oral dose of theophylline (5mg/kg). Results are shown as mean ± SEM (n=3 rats).

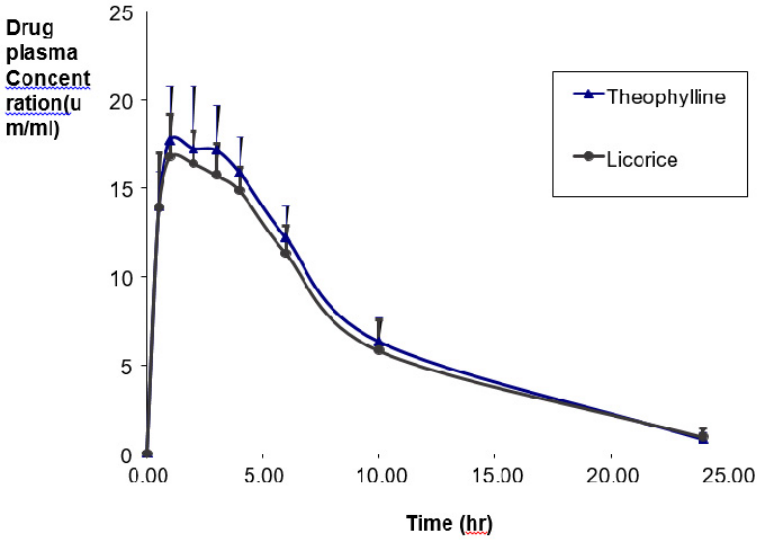

Figure 2. The effect of pre-administration of licorice juice on plasma theophylline concentration–time profile following an oral dose of theophylline (5mg/kg). Results are shown as mean ± SEM (n=7 rats).

Table 3. Pharmacokinetic parameters for theophylline in rat plasma after a single dose of theophylline compared to theophylline following pre-administration of pomegranate or licorice.

Drug and Combination	Cmax (µg/ml)	Tmax (hr)	$AUC_{(0-24)}$ (µg/ml*hr)
Theophylline	17.722±4	1	177.917±20.2
Theophylline with licorice juice	16.780±3.8	1	166.940±16.1
Theophylline with pomegranate juice	17.497±2.9	2	189.599±18.8

CONCLUSION

Results of this work show there is no a beverage - drug interaction between pomegranate or licorice and theophylline in rats. This was expressed by statistically nonsignificant differences between C_{max}, T_{max} and $AUC_{(0-24hr)}$ between groups of rats that received theophylline alone and those which received theophylline with pomegranate juice and licorice juice orally. This could be of important value if extended to human and can provide important information regarding theophylline administration and uses.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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