

INFLUENCE OF KINNOW JUICE ON THE PHARMACOKINETICS OF SUSTAINED RELEASE THEOPHYLLINE IN HEALTHY MALE VOLUNTEERS

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(Received on May 16, 2000)

Abstract : The effect of kinnow juice on the pharmacokinetics of a single dose of sustained release theophylline was investigated in healthy male volunteers. In a two phased open cross-over randomized study, ten healthy male volunteers were given sustained release theophylline (300 mg) along with 300 ml of water or kinnow juice, a routinely used citrus juice in India. Blood samples were collected at different time points from 0-48 hours. Plasma was assayed for theophylline by a HPLC method and various pharmacokinetic parameters were calculated and compared. The theophylline levels were lower at all the time points with kinnow juice co-administration as compared to water but were significantly so only during the absorption phase from 1-4 hours. The values for all the pharmacokinetic parameters evaluated were on the lower side with kinnow juice except T_{max} which was slightly delayed. None of these alterations was found to be significantly different. The results indicate that since there is an interference with the absorption of the drug, the patients may be advised not to consume kinnow juice when taking a slow release theophylline preparation and the monitoring of plasma concentrations of theophylline in patients who routinely consume kinnow juice in their diet might be helpful in better management of these patients.

Key words : kinnow juice theophylline naringin

INTRODUCTION

Citrus juice of grape fruit has been reported to increase plasma concentration of several dihydrophyridine calcium channel antagonists (1-5) and a number of other drugs of diverse chemical and pharmacological characteristics (6-11). While no such interaction was detected when felodipine and nifedipine were co-

administered with orange juice (12). Inhibition of cytochrome P450 enzymes has been considered to be responsible for these interactions. Grapefruit juice contains a variety of bioflavonoids (13) and furanocoumarins (14). Naringin, its aglycone naringenin and bergamottin, a furanocoumarin have been shown to be inhibitors of dihydrophyridine oxidation (15, 16). In addition, naringenin has been

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reported to be a potent competitive inhibitor of CYP1A2 mediated demethylation of caffeine (17).

Recently a new variety of citrus fruit, known as kinnow has been developed in India, which is a hybrid of king mandarin and willow leaf mandarin (*Citrus nobilis* × *Citrus deliciosa*). Kinnow is one of the most popular citrus fruit of India because of its superior characteristics like taste, large production potential and lower price as compared to orange. Currently kinnow is also being exported to Afghanistan, Pakistan and United Kingdom. The major active principles of kinnow juice are limonin and naringin (18), which is also present in grapefruit juice and have been considered to be responsible for pharmacokinetic interactions with number of drugs.

Theophylline, one of the principal agents in long term treatment of chronic asthma shows concentration dependent effects. Since theophylline is mainly metabolised by cytochrome P450 isoform 1A2 (19), it may also be a subject to inhibitory effects of the citrus juice of grapefruit and kinnow. This food drug interaction has potential clinical significance because citrus juices are often consumed at breakfast or lunch time when drugs are also taken. The present study was designed to find out whether there is any pharmacokinetic interaction of kinnow juice co-administration with sustained release theophylline in healthy male volunteers.

METHODS

Subjects and study protocol

The study was carried out in ten healthy male volunteers (Median age 31 years; range between 26 to 42 years) and (Median weight-61; range between 57 to 73 Kg). None of the subjects had any history of drug allergy and all were non-alcoholic and non-smokers. All the subjects underwent clinical examination and hematological and biochemical tests, which were within normal limits. A written informed consent was obtained from all the volunteers and the study protocol was approved by the institute's ethics committee. The subjects were asked not to consume any medication or citrus fruits or juices for at least 15 days prior and during the study period. The trial was conducted in a cross-over randomized design with a two week wash-out period between the treatments. After an overnight fast, each volunteer received a single oral dose (300 mg) of sustained release theophylline [Tab. Theobid-Okasa Pharma Ltd. Dadra (India)] along with 300 ml of either water or freshly prepared kinnow juice. Food was withheld for next 4 hours and no caffeinated beverages or alcoholic drinks were allowed during the study period. 2.0 ml of blood was drawn at 0, 1, 2, 4, 6, 9, 12, 24 and 48 hours after the drug administration in heparinised tubes. Plasma was separated and stored at -20°C until assayed for theophylline using a PHLC technique (20). Calibration curves were prepared with methylxanthine free human plasma with known theophylline concentrations and were treated in the same

way as the samples. Limit of detection was 0.2 µg/ml and the intra-assay coefficient of variation was 6.78%.

Pharmacokinetic analysis

The pharmacokinetic data was obtained using an open one-compartment model after oral administration. Peak plasma concentration (C_{max}) and time to reach peak plasma concentration (T_{max}) were calculated from the observed plasma data of each volunteer. Area under the plasma concentration time curve up to the time period samples were taken (AUC_{0-48}) was calculated by the trapezoidal rule and $AUC_{t-\infty}$ by dividing the last plasma concentration by the elimination rate constant (Kel). The sum of AUC_{0-48} and $AUC_{48-\infty}$ was taken as $AUC_{0-\infty}$.

The apparent $t_{1/2e}$ (elimination half life) was calculated by the formula $0.693/Kel$ and Kel was calculated by the least square regression analysis of the monexponential declining plasma concentration time curve. Absorption rate constant (Ka) was calculated by residual method and the absorption half life ($t_{1/2a}$) was calculated from the formula $t_{1/2a} = 0.693/Ka$.

Mean residence time (MRT) was calculated by the formula $MRT = AUMC_{0-\infty} / AUC_{0-\infty}$, $AUMC$ being the area under the moment curve. The results are expressed as Mean \pm SEM and paired students 't' test applied for statistical analysis. $P < 0.05$ was considered to be statistically significant.

RESULTS

Figure 1 shows the mean theophylline levels at different time points when given with either water or kinnow juice. The plasma concentration of theophylline was significantly lower from 1.0 to 4.0 hours when given with kinnow juice as compared to when given with water. Thereafter also, the plasma theophylline levels were lower with kinnow juice but the difference was not statistically significant.

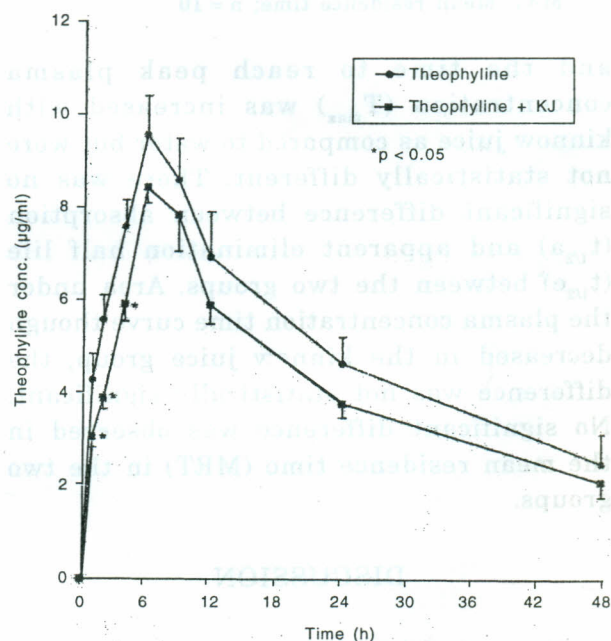


Fig. 1: Concentration time profile of theophylline (Mean \pm SEM) in plasma following oral administration of 300 mg theophylline with water or kinnow juice in 10 healthy male subjects.

Table I shows comparison of pharmacokinetic parameters of theophylline when given with kinnow juice or water. The peak plasma concentration (C_{max}) was lower

TABLE I: Pharmacokinetic characteristics of theophylline (Mean \pm SEM) following administration of 300 mg theophylline with water or with kinnow juice.

Pharmacokinetic parameters	Theophylline kinetics	
	With water	With kinnow juice
T _{max} (h)	5.90 \pm 0.43	6.6 \pm 0.4
C _{max} (μ g/ml)	9.54 \pm 0.85	8.43 \pm 0.66
T _{1/2} a (h)	2.03 \pm 0.52	2.16 \pm 0.29
T _{1/2} e (h) (Apparent)	25.13 \pm 2.43	21.69 \pm 3.08
AUC _{0-∞} (μ g.g/ml)	372.12 \pm 51.26	284.96 \pm 21.0
MRT (h)	25.96 \pm 1.83	21.94 \pm 1.61

MRT—Mean residence time; n = 10

and the time to reach peak plasma concentration (T_{max}) was increased with kinnow juice as compared to water but were not statistically different. There was no significant difference between absorption (t_{1/2}a) and apparent elimination half life (t_{1/2}e) between the two groups. Area under the plasma concentration time curve though decreased in the kinnow juice group, the difference was not statistically significant. No significant difference was observed in the mean residence time (MRT) in the two groups.

DISCUSSION

Recently kinnow juice has been shown to cause an increased concentration of carbamazepine in human volunteers because of an inhibitory action on cytochrome isoenzyme CYP3A (21). Naringin which is present in grapefruit juice has been shown to cause an inhibition of caffeine metabolism which requires cytochrome isoform CYP1A2 for its metabolism. Kinnow juice also contains naringin and it was expected to cause an inhibition of theophylline metabolism.

Kinnow juice (KJ) administration alongwith sustained release theophylline did not cause and major alteration in most of the pharmacokinetic parameters except for a significant lowering in the plasma concentration of theophylline at 1, 2 and 4 hours during the absorption phase. This lack of pharmacokinetic interaction in this study can be because of several reasons. Cytochrome isoform CYP1A2 has been shown to be involved in metabolism of both theophylline and caffeine, and much higher fraction of caffeine is metabolised as compared to theophylline (17). So theophylline metabolism would be influenced by kinnow juice to a lesser extent. Additionally, it has also been reported that chronic smokers have a two fold higher CYP1A2 activity than the non-smokers (17). All the volunteers in this study were non-smokers, so would be likely to have less CYP1A2 activity and hence less vulnerable to the effects of kinnow juice.

The lower plasma concentration of theophylline during the absorption phase only may well be as a result of food drug interaction between kinnow juice and

theophylline. A decrease in the rate as well as extent of theophylline absorption from a sustained release form has been reported by several workers (22–24). It has also been reported that food ordinarily slows the rate of absorption of theophylline without affecting the extent of absorption (25). A diet rich in carbohydrates has been shown to cause a lowering of plasma theophylline concentration (26). Kinnow juice with its high carbohydrate content approximately 14 gm/100 gm of kinnow juice responsible for reduced absorption of theophylline (27).

KJ may cause a delayed T_{max} and a lower C_{max} along with lower plasma concentration during the absorption phase because of a pH dependent effect also which in turn would affect dissolution of the sustained release formulation of theophylline. An increase in the gastric pH after food which persisted for a considerable time has earlier been reported in young healthy men and women (28). So kinnow juice with a pH 4–6 (27) could also cause an increase in pH and thereby a slower dissolution of the sustained release formulation as was used in this study.

T_{max} is dependent upon the rates of absorption and elimination. Since there was no significant change in $t_{1/2}$ elimination and MRT of the drug in the body, it would suggest that food ingestion i.e. KJ along with the drug administration slowed the absorption of drug without affecting the elimination of the drug. KJ produced a change in the rate of absorption but not in the extent is also evident by the fact that there was no significant change in AUC in the two groups.

Naturally occurring flavonoids present in vegetables and citrus juices have been shown to be potent activators of mono-oxygenases in human liver microsomes (29). Flavone, a flavonoid has been reported to stimulate metabolism of zoxazolamine both *in vitro* and *in vivo* (30). This activation process is in contrast to enzyme inductin as it does not require synthesis of the new enzymatic proteins. KJ also contains several bioflavonoids which may cause direct activation of the enzymes. Since the changes were limited only to absorption phase and theophylline is known not to undergo first pass metabolism in the gut this process of activation of enzymes may not be of any great consequence.

The findings of the study show that kinnow juice can significantly affect the rate of absorption of theophylline from a sustained release formulation though it may not affect the extent of absorption. Studies in a larger number of subjects might throw more light on this potential interaction. However, it may be advised to the patients not to consume kinnow juice or other citrus juices at the time theophylline administration. It may also be of use to carry out plasma concentration monitoring of theophylline in the patients who routinely consume kinnow juice or citrus juices in their diet.

ACKNOWLEDGEMENTS

Authors wish to thank Mr. K. J. Thomas for the technical assistance and also the volunteers who consented to participate in the study.

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