



EFFECT OF RHODODENDRON FLOWER JUICE ON THE BIOAVAILABILITY OF AMLODIPINE IN RATS

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Received for publication: December 23, 2013; Accepted: January 11, 2014

Abstract: The aim of the study was to determine the effect of rhododendron flower juice on the bioavailability of Amlodipine in rats. This study was carried out in rats as a parallel design study. After the analysis of blood samples, it has been concluded that a component (s) of rhododendron flower juice inhibits the CYP3A4 mediated metabolism of Amlodipine. AUC was determined with the help of Trapezoidal rule. C_{max} and T_{max} were determined from the area under the plasma concentration-time curve. Statistical analysis was performed on the data obtained from both the group of rats. One way Analysis of Variance (ANOVA) from which Tukey-Kramer Multiple Comparisons Test was applied to the data obtained. This test compared all the parameters such as AUC, C_{max} and T_{max} without flower juice and after giving flower juice and the standard deviation of AUC of amlodipine with and without juice was found to be 14.25 and 10.44 respectively. AUC of the amlodipine after giving rhododendron flower juice to rats was significantly increased in comparison to the control group. The Overall result indicates that the oral bioavailability of amlodipine after giving rhododendron flower juice was increased as compared to the amlodipine with water.

Keywords: Rhododendron, Bioavailability, Metabolism

INTRODUCTION

The desirable and undesirable effects of a drug arising from its concentrations at the sites of action are usually related either to the amount administered (dose) or to the resulting blood concentrations, which are affected by its absorption, distribution, metabolism, and/or excretion¹. Elimination of a drug or its metabolites occurs either by metabolism, usually by the liver or gut mucosa, or by excretion, usually by the kidneys and liver. Drugs and other exogenous lipophilic compounds usually have to be metabolized before they can be excreted from the body. This metabolism occurs by phase I and phase II reactions. In phase I, the majority of drugs undergo biotransformation reactions that are generally mediated by CYP enzymes, oxidative reactions being the most common. In phase II reactions, drug molecules or their metabolites are usually conjugated². Metabolic drug interactions between drugs represent a major concern for the pharmaceutical industry, for regulatory agencies and clinically for health care professionals and their patients. Many drug interactions are a result of induction or inhibition of CYP enzymes³.

Drug and Juice Interaction

Several forms of juice are intended to be safe for human consumption, but at the same time, few juices can produce an interaction with the drugs by altering their pharmacokinetics and subsequent clinical response. Serendipitous findings about 10 years ago in

clinical drug study, when grapefruit juice used to mask the taste of ethanol, led to the discovery of a grapefruit juice felodipine interaction. Felodipine is a dihydropyridine calcium channel antagonist used for the treatment of hypertension; simultaneous administration of felodipine with a single glass of grapefruit juice increased significantly the plasma concentration of felodipine and also increased its hypotensive effect³. Since then, grape fruit juice has been shown to increase the plasma concentration of several drugs e.g. cyclosporine, midazolam, and terfenadine. The inhibitory effect of juice is believed to depend on the components which are present in the fruit species⁴. Pharmacokinetic interactions are most frequent mechanism of interactions among medicines and interactions in the metabolic processes are particularly important⁵. Inhibition of drug metabolism by specific drugs, chemicals, fruit species or herbal medications causes increased levels of parent drug, prolonged drug activity and an increased potential for drug toxicity. However there is a little information based on scientific evidence concerning the interaction between other fruit juices and drug metabolized by CYP3A4. This led to conduct further studies on drug and juice interaction⁶.

Rhododendron flower juice contains ursolic acid, resins, certain species of flavonoid glycosides like quercetrin, and anthocyanins, having the activity to

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inhibit the enzyme CYP3A4. Same as that of grape fruit juice which inhibits the CYP3A4 enzyme. Rhododendron flower juice is normally taken by the patients for good health in northern parts of India, as this flower juice has much medicinal importance⁷.

MATERIALS AND METHODS

The drug sample amlodipine was procured from Ranbaxy laboratories, paonta sahib. Rhododendron flower juice was purchased from the northern parts of Uttarakhand as it was available commercially. Two groups i.e. Group-I and Group-II of Wistar rats (n=6) of either sex or weighing between 150-200g were used in this study. The animals were housed under standard laboratory, maintained on a natural light and dark cycles and given free access to food and water. Animals were acclimatized to laboratory conditions before the experimentation. All experiments were carried out between 0 to 24 hrs. The experimental protocols were approved by the Institutional Ethics Committee and conducted according to the Indian National Science Academy Guidelines for the use and care of experimental animals. The rats were fasted overnight before the experiment. The drug Amlodipine was orally administered at a dose of 1mg/kg body weight to the rats⁸. At the start of the study, first six animals (group-I) were given 2ml of rhododendron flower juice orally; afterwards each animal was given amlodipine at a dose of 1mg/kg body weight in water. To the group-II of six animals, were given the drug amlodipine alone. Blood samples were taken at 0, 4, 8, 12, 16, 20, 24 hrs. After blood sampling, it was centrifuged immediately at 1600g and separated. Plasma was stored at -20°C until analysis. The analysis was performed using gradient high performance liquid chromatographic system. The data obtained from HPLC was treated to get AUC, C_{max} and T_{max} . Fig. 1 shows HPLC graph showing area of standard amlodipine. Fig. 2 shows HPLC graph showing area of amlodipine without rhododendron flower juice. Fig. 3 shows HPLC graph showing area of amlodipine with rhododendron flower juice.

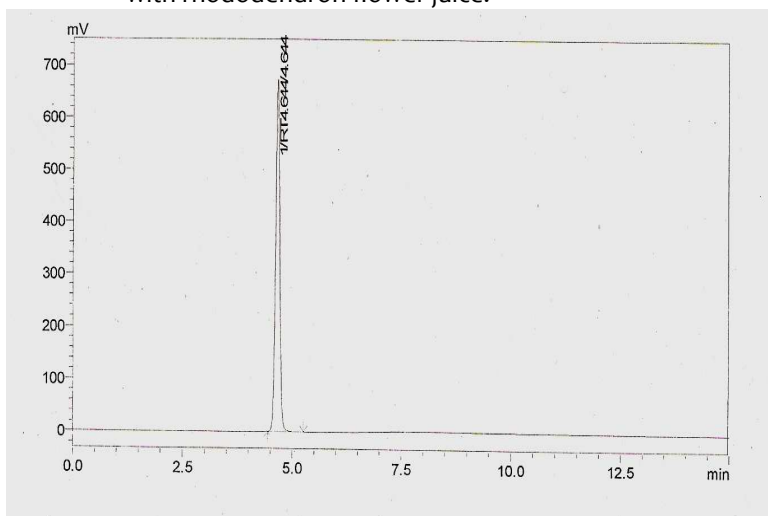


Fig.1: HPLC graph showing area of standard amlodipine

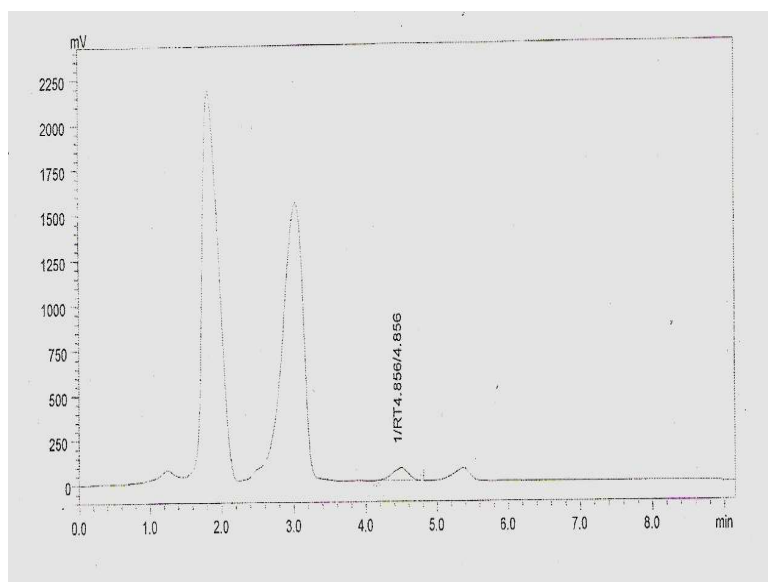


Fig.2: HPLC graph showing area of amlodipine without rhododendron flower juice

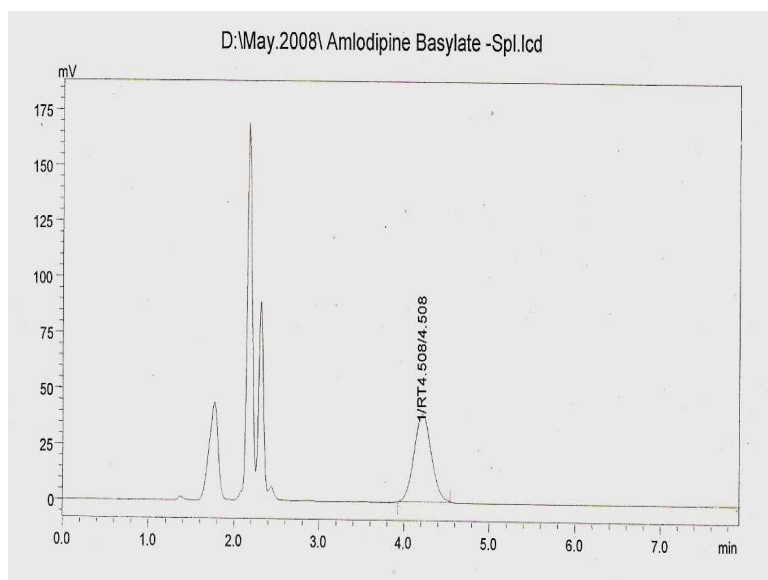


Fig.3: HPLC graph showing area of amlodipine with rhododendron flower juice

RESULT AND DISCUSSION

Statistical analysis was performed on the data obtained from both the group of rats. One way Analysis of Variance (ANOVA) from which Tukey-Kramer Multiple Comparisons Test was applied to the data obtained. This test compared all the parameters such as AUC, C_{max} and T_{max} without flower juice and after giving flower juice (Table 1). Table 2 shows the value obtained after statistical analysis. The standard deviation of AUC of Amlodipine with and without juice was found to be 14.25 and 10.44 respectively. In case of C_{max} of amlodipine the standard deviation with and without rhododendron flower juice was found to be 0.80 and 0.86 respectively. For T_{max} , standard deviation was found to be 0.00 with and without juice. For AUC, the standard error of mean (SEM) was found to be

4.265 without and 5.818 with the rhododendron flower juice. For C_{max} , standard error of mean (SEM) was found to be 0.3291 with juice and 0.3517 without juice. AUC of the amlodipine after giving rhododendron flower juice to rats was significantly increased in comparison to the control group. Table 2 shows the comparison of the pharmacokinetic parameters. Comparison of AUC with and without juice compared with C_{max} and T_{max} after giving the flower juice and the control group was found to be significant. In this comparison p value was observed as <0.001. The Overall result indicates that the oral bioavailability of amlodipine after giving rhododendron flower juice was increased as compared to the amlodipine with water.

Table 1: Determination of Amlodipine AUC, C_{max} , T_{max}

Animal		Without flower juice			Animal		With flower Juice		
No.	AUC	C_{max}	T_{max}	No.	AUC	C_{max}	T_{max}		
1	212.28	14.38	8	1	351.78	21.87	8		
2	193.78	13.16	8	2	345.44	21.55	8		
3	201.82	14.04	8	3	327.22	20.62	8		
4	204.12	14.90	8	4	337.30	21.72	8		
5	182.00	12.50	8	5	316.10	21.24	8		
6	203.58	13.70	8	6	319.94	19.75	8		

Table 2: Values obtained after statistical application

Animal No.	Without Flower Juice			With flower juice		
	AUC	C_{max}	T_{max}	AUC	C_{max}	T_{max}
Mean	199.59	13.78	8	332.96	21.12	8
S.D.±	10.44	0.86	0.0	14.25	0.80	0.0
Sample Size (N)	6	6	6	6	6	6
Std. error of mean	4.265	0.3517	0.0	5.818	0.3291	0.0
Lower 90% confi.limit	188.6	12.87	8	318.01	20.27	8
Upper 95% confi.limit	210.56	14.68	8	347.92	21.97	8
Minimum	182.00	12.50	8	316.10	19.75	8
Median	202.70	13.87	8	332.26	21.39	8
Maximum	212.28	14.9	8	351.78	21.87	8

CONCLUSION

Inhibition of metabolism is probably the most common cause of clinically important pharmacokinetic drug interactions, because it can lead to a dramatic increase in the plasma concentrations of an affected drug. Therefore it is very important for us to determine the identity of component (s) in juice that exhibits potent inhibition of CYP3A activity. By understanding the nature of these chemical components (s) would enable us and other healthcare professionals to avoid any food-drug interactions. Furthermore, such information will be helpful in identifying situations where the inhibition of CYP3A activity may be therapeutically useful.

ACKNOWLEDGMENT

Authors are very thankful for the financial support received from Science and Engineering Research Board (SERB), Department of Science and Technology, Government of India (Registration No. SERB/LS-172/2013).

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Source of support: Department of Science and Technology, India

Conflict of interest: None Declared