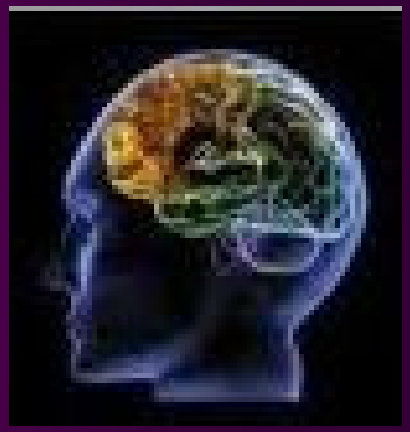
STUDY ON VARIATIONS OF THEOPHYLLINE PLASMA CONCENTRATIONS WITH RESPECT TO TIME OF ADMINISTRATION



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INTRODUCTION

- It is well established fact that the time of administration of the drugs influences the response but is often neglected in pharmacokinetic studies.

- Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24hours and are synchronized according to internal biologic clocks related to the sleep-wake cycle.

- Knowledge of circadian rhythm dependencies in the kinetics is of great importance. The same medication when dosed in the evening rather than morning need not have the same pharmacokinetics or efficacy.

- In individuals suffering from asthma and COPD, recurrent episodes of wheezing, breathlessness, chest tightness, and coughing are observed particularly at night or in the early morning.

- Theophylline is a methyl xanthine (bronchodilator) with proven efficacy as a element of the therapy in asthma & COPD.

- Theophylline exhibits marked inter-patient variability with regard to the rate and extent of absorption and the rate of elimination.

- Fatal intoxications with theophylline are very frequent sometimes resulting in sudden death.

- Both oral and parenteral routes have exhibited toxicity. Convulsions have occurred at plasma concentrations as low as 25 mg/ml.

- Thus it is necessary to calibrate the given preparation in a given patient and to avoid toxicity or under-dosing.



OBJECTIVES

- To estimate the peak and trough concentrations of theophylline at 8am and 8pm after oral administration

- To estimate the peak and trough concentrations of theophylline at 6am and 6pm after IV administration

- To assess, if the time of administration has any effect on the plasma levels of the drug.



METHODOLOGY

- The study was conducted for a period of 9 months where data was obtained from prospective series of patients, who were admitted to medicine wards of St. Martha's Hospital, Bangalore. Ethical committee approval was obtained from the Institutional Ethics Committee of the Hospital.

- **Inclusion Criteria:**

In-patients above the age of 18 years, which includes adults and geriatrics who were on theophylline therapy.

- **Exclusion Criteria:**

Pregnant/lactating ladies and pediatric patients.

- **Study design:**

The study was a prospective open blind single patient group design where patients were treated with deriphylline throughout the study.

- Blood samples were collected from patients enrolled in the study, upon attaining steady state.

- 1ml of the blood was withdrawn 30 mins prior to both oral and intravenous administration of theophylline, to determine the trough plasma levels of the drug.

- After 15 mins post intravenous administration and 3.0 hrs post oral administration 1 ml of blood was withdrawn to determine the peak plasma levels of the drug.

- Student's paired t-test and unpaired t- test was used to compare time and plasma concentrations of theophylline statistically.

- All the separations were performed on HPLC, consisting of Shimadzu LC-10AT liquid chromatographic pump, SIL-10A manual injector and SPD-10A UV-VIS absorbance detector.

- Chromatographic separations were performed using Phenomenex Luna C18 ODS 2 reversed-phase column and a guard column containing ODS cartridge insert.

- Isocratic elution with methanol-acetonitrile-tetrahydrofuran phosphate buffer was carried out at a flow rate of 1.5 ml/min. Detection was at a wavelength of 273 nm.



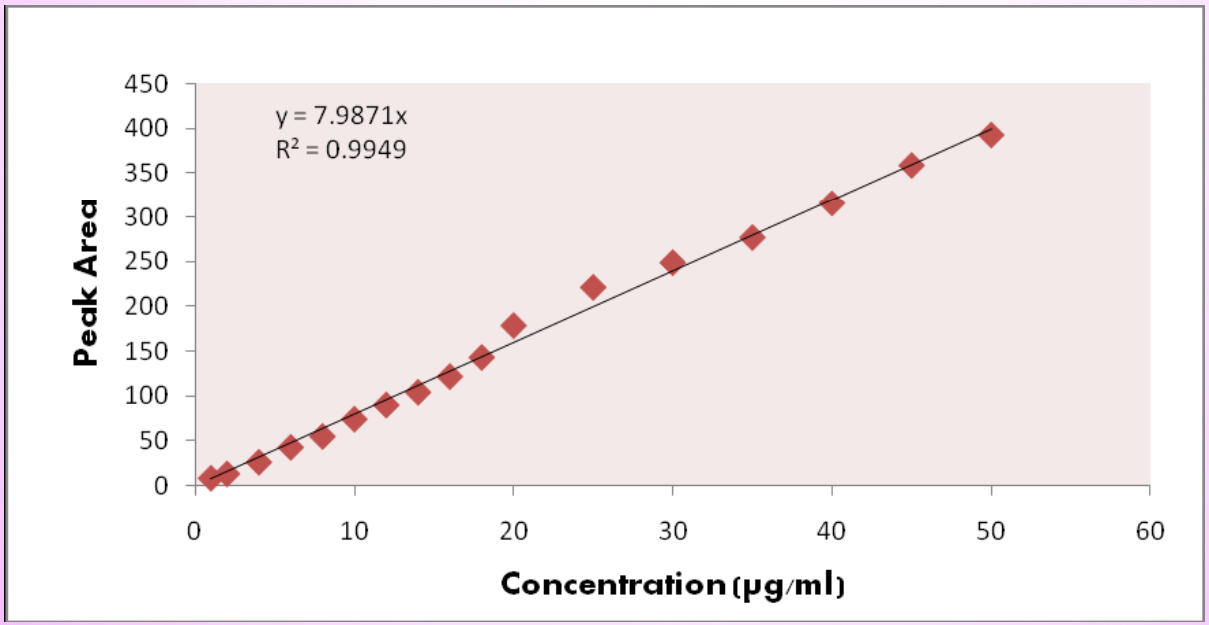
RESULTS & DISCUSSION

- Theophylline has a narrow therapeutic plasma concentration range of 5 to 20µg/ml.

- In-appropriate dosage regimens may result in either significant sub-therapeutic or toxic plasma concentrations of the drug.

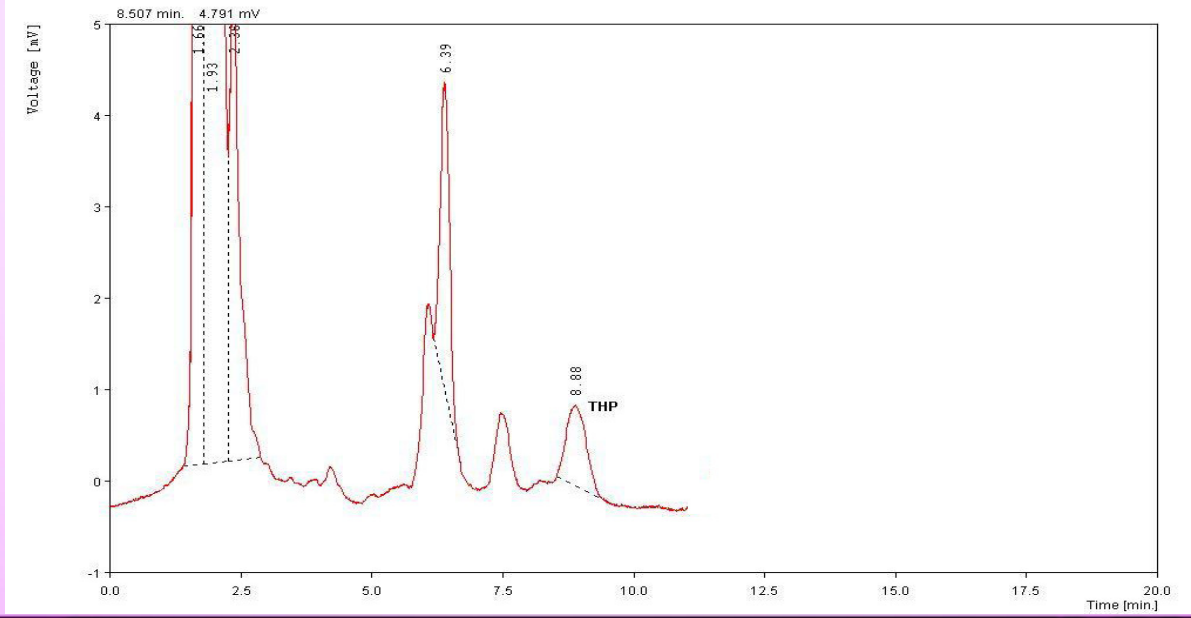
- Therefore, it is necessary to maintain the plasma theophylline concentration at therapeutic range.

The standard calibration curve of theophylline indicates linearity over the concentration range investigated (1.0-50µg/ml). The correlation coefficient was found(R^2) to be 0.9949.



➢HPLC chromatograms were obtained by spiking the HPLC column with patient plasma containing unknown concentration of theophylline.

➢From the HPLC chromatograms the retention time of theophylline was found to be 8.88mins. From the chromatogram it was also evident that peaks of theophylline were well resolved and do not show any signs of fronting or tailing.



During the study, 36 patients, receiving theophylline therapy were enrolled and their demographic details are as follows;

SL.NO	DEMOGRAPHIC DETAILS	NUMBER (n)	PERCENTAGE (%)
1	**GENDER**		
	Male	21	58.33
	Female	15	41.67
2	**AGE**		
	51-60 Yrs	9	25
	61-70 yrs	9	25
3	**HABITS**		
	Smokers	13	36.2
	Non Smokers	23	63.8
4	**DIAGNOSIS**		
	Asthma	9	25
	COPD	27	75
5	**CO-MORBIDITIES**		
	Hypertension	14	38.89
6	**ROUTE OF ADMINISTRATION**		
	Oral	8	22.22
	I V Bolus	28	77.78

Theophylline peak concentration 3hrs after 8am oral administration

Maximumconcentration (µg/ml)	11.74
Minimum concentration (µg/ml)	4.68
Mean concentration (µg/ml)	8.914
Standard deviation	2.139

Theophylline peak concentration 3hrs after 8pm oral administration

Maximumconcentration (µg/ml)	11.26
Minimum concentration (µg/ml)	4.82
Mean concentration (µg/ml)	8.569
Standard deviation	1.992

Theophylline peak concentration 11.5hrs after 8am oral administration

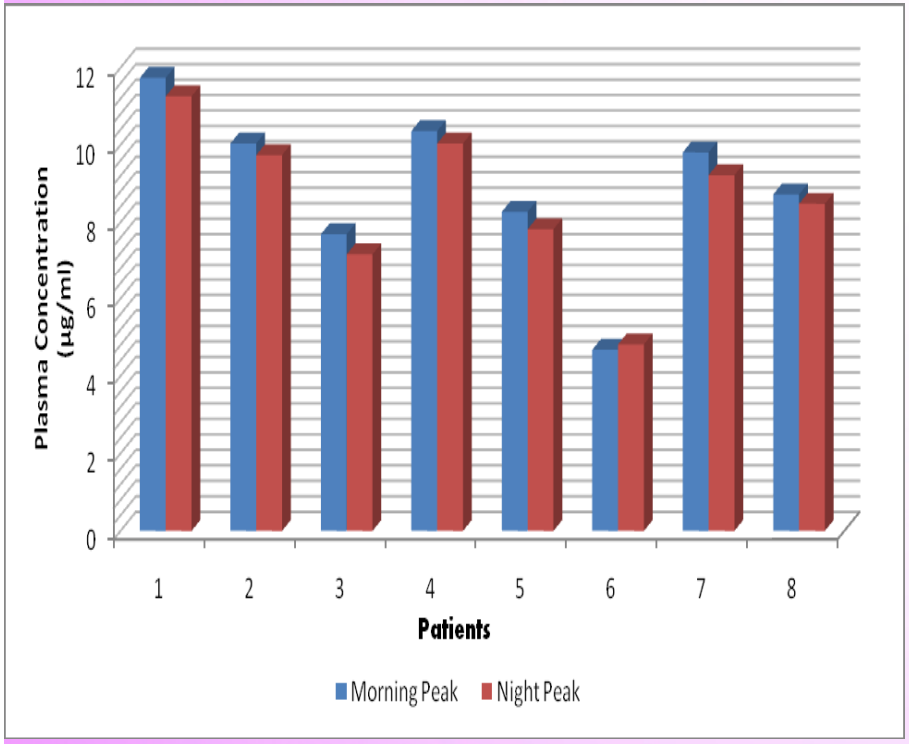
Maximumconcentration (µg/ml)	6.010
Minimum concentration (µg/ml)	2.93
Mean concentration (µg/ml)	4.735
Standard deviation	1.215

Theophylline peak concentration 11.5 hrs after 8pm oral administration

Maximumconcentration (µg/ml)	6.480
Minimum concentration (µg/ml)	3.43
Mean concentration (µg/ml)	5.089
Standard deviation	1.211

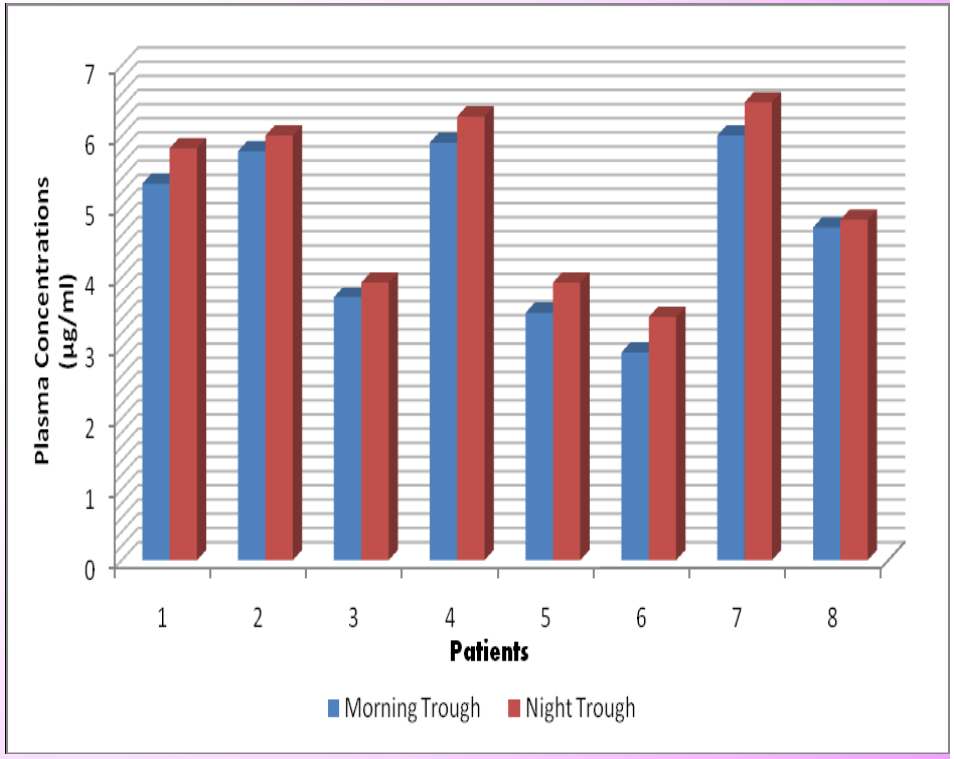
Statistical analysis between plasma peak concentrations after 8am and 8pm dose

P value	0.0038



Statistical analysis between plasma trough concentrations after 8am and 8pm dose

P value	0.0003



- Patients showed increased peak plasma concentrations after the morning dose (8am) when compared to the peak plasma concentrations after the night dose (8pm).

- Higher plasma peak concentrations after the morning dose (8am) may be due to faster absorption of the drug at daytime when compared to night time (8 pm)

- All the 8 patients on the oral dose depicted higher trough plasma concentrations after the night dose (8pm) compared to the morning dose (8am) this finding can be attributed to slower elimination of the drug at night time.

Theophylline peak concentration 15mins after 6am IV administration

Maximumconcentration (µg/ml)	18.48
Minimum concentration (µg/ml)	7.630
Mean concentration (µg/ml)	12.89
Standard deviation	2.371

Theophylline peak concentration 15mins after 6pm IV administration

Maximumconcentration (µg/ml)	18.39
Minimum concentration (µg/ml)	7.810
Mean concentration (µg/ml)	12.86
Standard deviation	2.338

Theophylline peak concentration 11.5 hrs after 6am IV administration

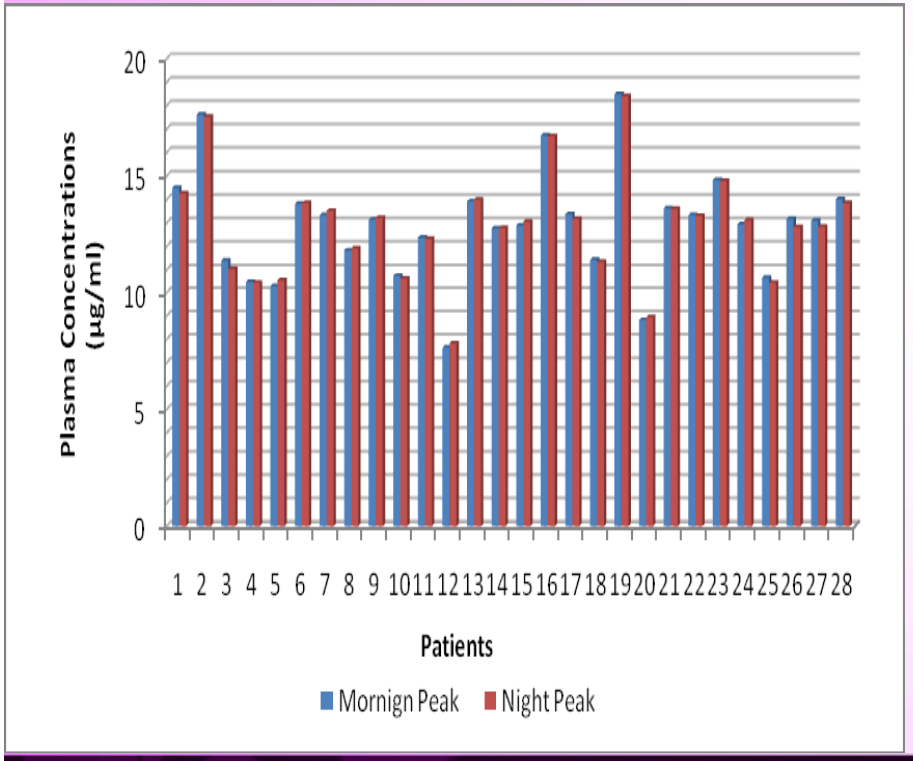
Maximumconcentration (µg/ml)	9.940
Minimum concentration (µg/ml)	5.170
Mean concentration (µg/ml)	7.260
Standard deviation	1.383

Theophylline peak concentration 11.5 hrs after 6pm IV administration

Maximumconcentration (µg/ml)	10.37
Minimum concentration (µg/ml)	5.620
Mean concentration (µg/ml)	7.655
Standard deviation	1.354

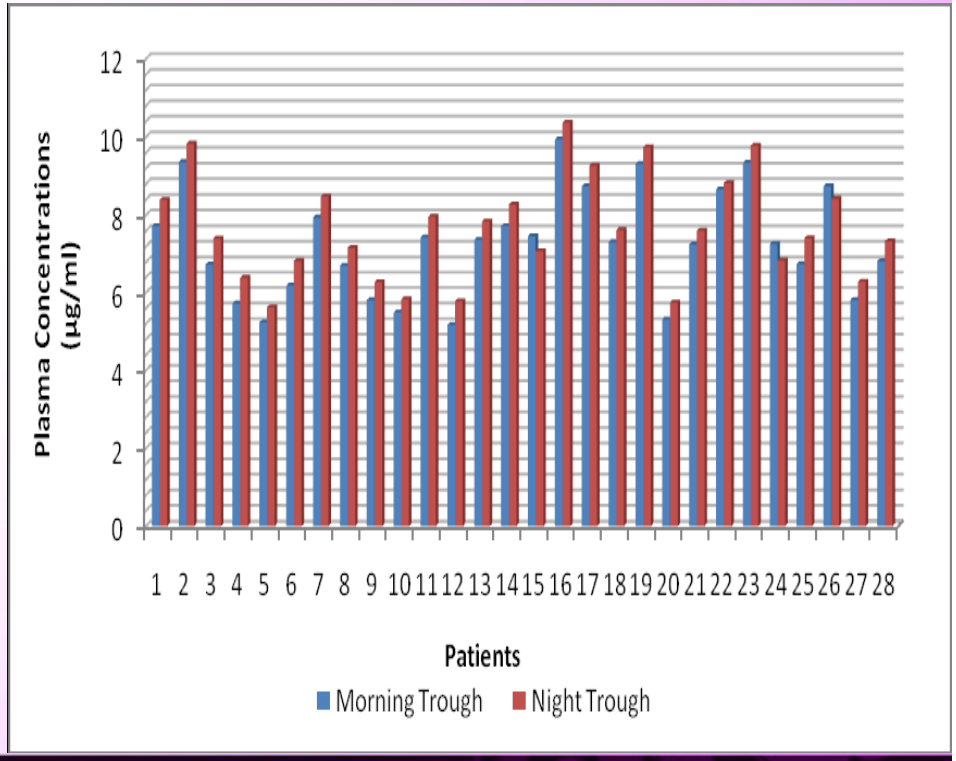
Statistical analysis between plasma peak concentrations after 6am and 6pm IV dose

P value	0.2474



Statistical analysis between plasma trough concentrations after 6am and 6pm IV dose

P value	<0.001



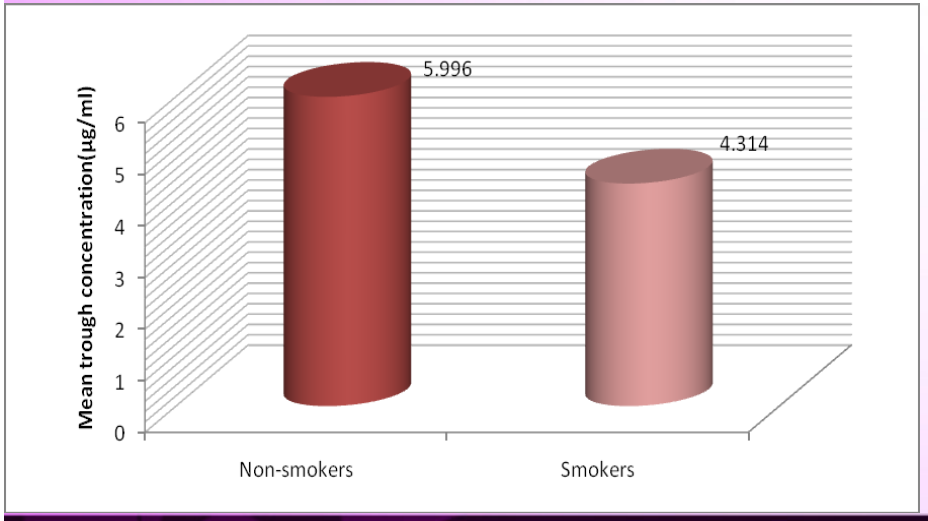
- In patients receiving IV dose at 6am and 6pm, there was no significant difference observed in plasma peak concentrations after morning and night dose. This may be due to the direct entry of the drug into the systemic circulation on intravenous administration.

- Higher plasma trough concentrations after the night dose indicate that the drug is eliminated slowly after night dose when compared to the elimination of the drug after morning dose.

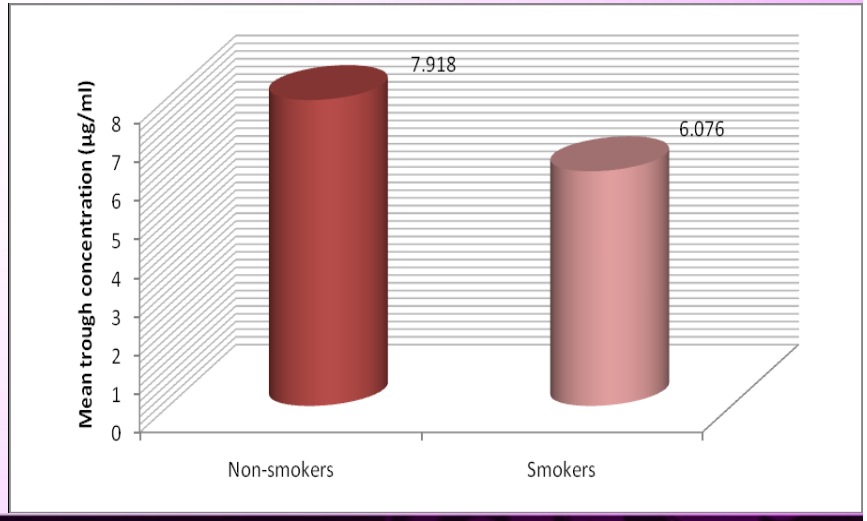
ADRs observed during the study period

ADRs	No. of Patients	Percentage
Tachycardia	2	5.56%
Restlessness	2	5.56%

Comparing mean trough concentration and Smoking habit of the patients - Oral dose



Comparing the mean trough concentrations and Smoking habit of the patients – IV dose





CONCLUSIONS

- Peak plasma concentration after oral administration showed a higher value after morning dose as compared to night dose, which was statistically significant.

- Peak plasma concentration after IV administration did not show any statistically significant difference between morning and night dosing.

- Higher trough plasma concentrations were observed after the night administration when compared to morning administration of theophylline in case of both oral and IV administration. This may clinically benefit the asthma patients in helping to control early morning bronchial obstructions.

- Thus, it can be concluded that the plasma concentration of theophylline is influenced by the time of administration.



QUESTIONS ???



Thank You

