Indian J Physiol Pharmacol 1991; 35(2): 130-134

A STUDY ON BIOAVAILABILITY OF THEOPHYLLINE IN RABBITS AS INFLUENCED BY FATTY DIET

ASHOK KUMAR S., A. CHAKRABARTI AND S. K. GARG*

Department of Pharmacology,
Postgraduate Institute of
Medical Education & Research,
Chandigarh - 160 012

(Received on January 7, 1991)

Abstract : The influence of fatty diet and standard diet on the bioavailability and plasma half life of conventional theophylline was studied in the rabbit. It was found that standard diet had significantly reduced the extent of oral bioavailability ($AUC_{0-\infty}$) of theophylline compared to the fasting state. The fatty diet resulted in a significantly increased extent of oral bioavailability ($AUC_{0-\infty}$ and Cmax) and significantly decreased rate of bioavailability (tmax and t1/2a) of theophylline compared to the standard diet group. The plasma half life was unaffected by either standard diet or the fatty diet. Therefore, dietary composition should be actively considered while titrating the dose of theophylline since theophylline is a drug of narrow therapeutic range and requires close monitoring of therapeutic plasma level.

Key words : theophylline rabbit fatty diet bioavailability

INTRODUCTION

Theophylline is a widely prescribed bronchodilator agent with a narrow therapeutic range. The pharmacokinetics of theophylline has been shown to be dependent on food composition (1, 2), quantity of food intake (3) and on dosing time relative food intake (4). Further it was reported (5) that the bioavailability of theophylline from a solid dosage form was greater when the drug was given immediately after a high protein meal than after a high carbohydrate meal. However, no information is available on the interaction of theophylline kinetics and fatty food. Hence, this study was undertaken to find out the influence of fatty food on the bioavailability and half life parameters of theophylline in rabbits.

METHODS

Ten healthy male rabbits (1.5 to 2.5 kg) were obtained from the Central animal house of the Institute and kept in individual cages for 30 days prior to the study in the departmental animal house for the purpose of acclimatization. They had free access to water and food (Hind Lever pellets) was given once a day at 13.00 h. A constant day-night cycle was maintained and the temperature of the animal room was constant at 23±2°C throughout the study period.

An open, cross-over design of study was adopted to study the following:

a) The efffect of fasting, standard diet and high fat diet on the bioavailability of single dose of aminophylline solution given orally through a intragastric tube to the rabbits.

Under the fasting condition the rabbits were fasted for 24 h, standard diet meant the adminstration of the usual daily ration of Hind Lever chow (70 g/rabbit) given at 13.00 h and high fat diet referred to standard diet fortified with 5 g of additional butter given through the orogastic tube directly into the stomach of the rabbit on the study day. In each of the three conditions i.e. fasting, standard diet and high fat diet, the drug (aminophylline solution) was given at a dose of 10 mg/kg (as the theophylline

*Corresponding Author

base) orally at 14.00 h as a single dose to ten rabbits with a washout period of ten days between two study days.

b) The effect of standard diet and high fat diet on the multiple dose kinetics of theophylline.

Aminophylline solution was given orally at a dose of 10 mg/kg four times a day at 08.00 h, 20.00 h and 02.00 h for five consecutive days while on the 6th day i.e. the study day, drug was given at 08.00 h and 14.00 h. Similar drug treatment protocol was maintained both during the standard and the high fat dietary regimes. Standard diet or the high fat diet was given daily once at 13.00 h for six consecutive days of drug treatment inclusive of the study day. A washout period of ten days was given between the two studies.

Venous blood samples (0.5 ml each) were collected by giving a cut on the marginal ear vein of rabbit at the following time intervals both in the single dose and the multiple dose kinetic study; 0 h (i.e. just before the 14.00 h drug administration) and 0.5, 0.75, 1, 2, 4 and 6 h after the drug administration. An additional sample at 0.25 h and 8 h after drug administration was taken in the single dose study. Blood samples were immediately centrifused at 3000 rpm for 15 min and the plasma was separated and stored at − 20°C till assay. Plasma theophylline was assayed by reverse-phase high performance liquid chromatography (HPLC) technique according to the method described earlier by Swaminathan et al (6). The sensitivity of the method was 0.2 μg/ml and the specificity as measured by the coefficient of variation was 6.78%.

Calculations: The plasma concentration versus time data was analysed by open one compartment model. The following kinetic parameters were calculated: Cmax (peak plasma concentration), tmax (time to peak plasma concentration) from the plasma data, t1/2 a (absorption half life) by the residual method, t1/2 (elimination half life) by the least square regression analysis, $AUC_{0-\infty}$ (area under the plasma concentration time curve) by trapezoidal rule, $C_{ss}max$ (steady state peak concentration) from the plasma data, C_{ss} min (steady state trough concentration) from the plasma data and percentage fluctuation by the formula

$$\frac{Cmax - Cmin}{Cmax} \times 100$$

Statistics: Plasma theophylline concentrations were expressed as Mean ± SEM. Statistical comparison was done by the analysis of variance and if the 'F' value was significant then paired 't' test was applied for inter group comparison. $P < 0.05$ was considered statistically significant.

RESULTS

Fig. 1 shows the plasma concentration versus time curves of theophylline after single dose administration under three different dietary situations. Each point represents Mean ± SEM from ten observations. Each curve showed a rapid rise to attain the peak followed by gradual fall in the plasma concentration of theophylline. The peak was delayed in the

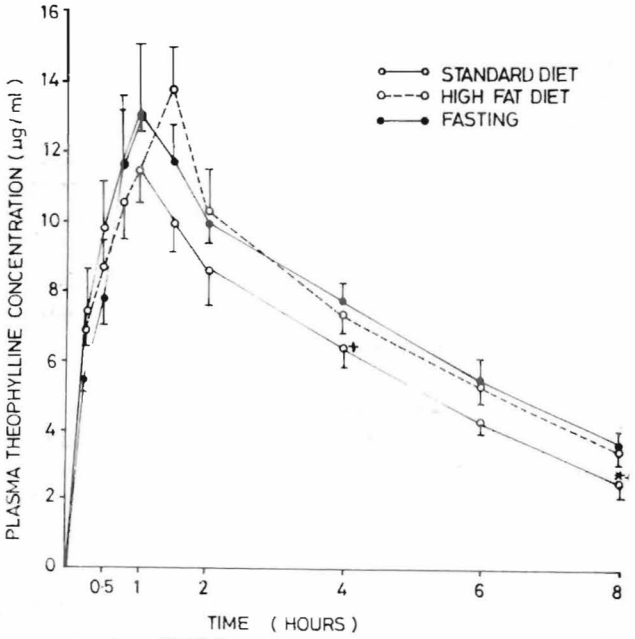

Fig. 1 : Plasma theophylline concentrations at different time intervals after single oral dose adminstration to 10 rabbits under three different dietary schedules.

*P < 0.05 between the standard diet and the high fat diet groups.

+P< 0.05 between the fasting and the standard diet groups.

TABLE I : Single dose study comparison of theophylline pharmacokinetic parameters.

Groups	*Cmax* (*μg/ml*)	*Tmax* (*h*)	*t1/2a* (*h*)	*t1/2el* (*h*)	$AUC_{0-\infty}$ (μg/ml, h)
1. Fasting	13.24±1.82	1.07±0.09§	0.49±0.12	4.22±0.34	82.64±6.37+
2. Standard diet	13.15±0.68	1.00±0.13	0.36±0.09	3.63±0.21	62.13±4.69
3. High Fat diet	13.76±1.15	1.45±0.08*	0.61±0.12	3.80±0.35	78.40±7.10

Values are Mean ± SEM (n=10)
§1 significantly different from 3 at $P < 0.05$.
*3 significantly different from 2 at < 0.05.
+1 significantly different from 2 at < 0.05.

high fat diet group compared to the other two groups. Plasma theophylline levels were significantly higher in the fasting group at 4 h and 8 h compared to the standard diet group while it was significantly higher at 8 h for the high fat diet group compared to the standard diet group. No significant difference was observed between the fasting and the high fat diet groups at any point of time.

Table I shows the kinetic parameters of single dose theophylline under three different dietary schedules. Tmax was significantly higher for the high fat diet group compared to the other two groups. Cmax and t1/2 elimination did not differ significantly amongst the three groups. $AUC_{0-\infty}$ was significantly higher for the fasting group compared to the standard diet group but did not differ significantly from the high fat diet group. $AUC_{0-\infty}$ for the high fat diet group was much higher compared to that of the standard diet group but failed to attain statistical significance due to wide scatter.

Fig. 2 shows the plasma concentration-time curves of theophylline at steady state condition under two different dietary schedules i.e. standard diet and high fat diet. The peak concentration was delayed in the high fat diet group. The concentration

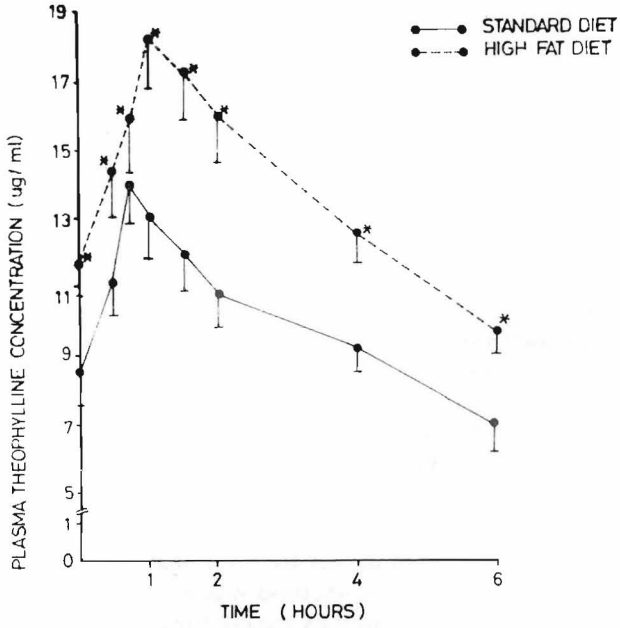

Fig. 2 : Plasma theophylline concentrations at different time intervals after multiple oral doses to rabbits under two different dietary schedules.

*P<0.05 between the two groups.

TABLE II : Multiple dose study comparison of theophylline pharmacokinetic parameters.

Groups	*Css max* (*μg/ml*)	*Tmax* (*h*)	*t1/2el* (*h*)	*Css min* (*μg/ml*)	$AUC_{0-\infty}$ (*μg/ml.h*)	*Percentage fluctuations*
Standard diet	14.04±1.13	0.81±0.04	5.92±0.46	7.02±0.69	120.6±10.49	46.24±1.77
High Fat diet	18.24±1.44*	1.16±0.10*	5.62±0.27	9.68±0.60*	160.8±10.40*	49.49±2.16

Values are Mean ± SEM (n=10)
*P< 0.05.

of theophylline at each point of time, though showed wide scatter, yet was significantly higher for the high fat diet group compared to the standard diet group.

Table II shows the comparative kinetic parameters of theophylline in the standard diet and the high fat diet groups of rabbits. The C_{ss}max, C_{ss}min, tmax and $AUC_{0-\infty}$ were significantly higher for the high fat diet group compared to the standard diet group. However, no significant difference was observed in the t1/2 el. and percentage fluctuation parameters of theophylline between the two groups under study.

DISCUSSION

Food and drug interaction is well known. Depending upon the type of food, the nature of drug and the degree of interaction, the drug absorption might be reduced, delayed, unaffected or increased. Whether the changes in drug absorption are clinically relevant or not depends both on the type of drug and the extent of the change. A small alternation in absorption characteristics would be unimportant for a drug which is effective over a wide concentration range but might be critical for a drug with a narrow therapeutic range or with a steep dose-response curve (7). Theophylline is a bronchodilator drug with a narrow therapeutic range (8-20 μg/ml) in the treatment of bronchial asthma. In the single dose study, it was found that the extent of oral bioavailability ($AUC_{0-\infty}$) was significantly reduced by standard pellet diet while the rate of bioavailability (measured by tmax and t1/2 a) was reduced by fatty diet. The slower absorption of theophylline after fatty diet could be due to prolonged gastric emptying time caused by the fatty diet (5) since theophylline is principally absorbed from the small intestine. The impaired extent of oral bioavailability of theophylline by pellet diet as observed in the present study was in contrast to that reported by Lagas and Jonkman (8) who showed an increased bioavailability of theophylline after meals. In contrast to aminophylline solution that was used in the present study, Lagas and Jonkman (8) had used sustained release theophylline formulation to the human beings in their study.

In the steady condition, it was observed that fatty diet had significantly increased the extent of oral bioavailability and significantly reduced the rate of bioavailability of theophylline compared to the standard diet group. The exact reason for the increased extent of oral bioavailability of theophylline by fatty diet is unclear. Similar increase in the bioavailability of several other drugs like griseofulvin (9), riboflavin and riboflavin-s-phosphate (10) by fatty food have also been reported earlier. The increased bioavailability ranged from 26-40% over that after standard diet, thereby, suggesting that considerations of dietary composition is crucial for dosage adjustment of theophylline. Neither the standard diet nor the fatty diet had any influence on the half life of theophylline. Short duration (of 6 days) of dietary intervention might be the limiting factor for evaluating the influence of fatty diet on theophylline disposition. Therefore, further studies on theophylline disposition with prolonged administration of fatty diet are warranted since hepatic mixed function oxidase system which metabolizes theophylline, is reported to be influenced by fatty acid content of diet given for three weeks to rats (11).

REFERENCES

1. Anderson KE, Conney AH, Kappas A. Nutritional influences on chemical biotransformation in humans. *Nutrition Reviews* 1982; 40: 161-71.
2. Osman MA, Patel RB, Irwin DS, Welling PG. Absorption of theophylline from enteric coated and sustained release formulations in fasted and non-fasted subjects. *Biophalm Drug Disp.* 1983; 4: 63-72.
3. Lagas M, Jonkman JHG. Influence of food on the rate and extent of absorption of theophylline after single dose oral adminstration of a controlled release tablet. *Int J Clin Pharmacol Ther Toxicol* 1985; 23: 424-26.
4. Karim A, Burns T, Jankey D, Hurwitz A. Food-induced changes in theophylline absorption from controlled release formulations. Part II. Importance of meal composition and

dosing time relative to meal intake in assessing changes in absorption. *Clin Pharmacol Ther* 1985b; 38: 642-47.

5. Welling PG, Lyons LL, Craig WA, Trochta GS. Influence of diet and fluid on bioavailability of theophylline. *Clin Pharmacol Ther* 1975; 17: 475-80.
6. Swaminathan S, Garg SK, Dhand R, Malik SK, Sharma PL. Measurement of plasma theophylline concentration by high pressure liquid chromatography. *Bull PGI* 1986. 20: 63-68.
7. Toothaker RD, Welling PG. The effect of food on drug bioavailability. *Ann Rev Pharmacol Toxicol* 1980. 20: 173-99.
8. Lagas M, Jonkman JHG. Greatly enhanced bioavailability of theophylline on postprandial administration of a sustained release tablet. *Eur J Clin Pharmacol* 1983; 24: 761-65.
9. Kabasakalian P, Katz M, Rosenkrantz B, Townley E. Parameters affecting absorption of griseofulvin in a human subject using urinary metabolite excretion data. *J Pharm Sci* 1970; 59: 595-600.
10. Jusko WJ, Levy G. Absorption, metabolism and excretion of riboflavin-s-phosphate in man. *J Pharm Sci* 1967; 56: 58-62.
11. Wade AE, Norred WP, Evans JS. Nutrition and drug inter-relations. Hathcock JN, Coon J. eds. New York: Academic Press, 1978; 478-503.