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EFFECT OF FATTY DIET ON PHARMACOKINETICS AND PHARMACODYNAMICS OF A LIQUID THEOPHYLLINE PREPARATION IN VOLUNTEERS

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Abstract : The effect of a standard breakfast and a fatty breakfast on the pharmacokinetics and pharmacodynamics of a theophylline liquid preparation (160 mg - single dose) was examined in 6 healthy, non-smoking male volunteers. The plasma theophylline concentrations after both standard and fatty diet were found to be comparable at each point of time and pharmacokinetic parameters like Cmax, Tmax, $T_{1/2}a$, $T_{1/2\beta}$ and $AUC_{0-\infty}$,were also comparable. However, the time taken to attain the therapeutic plasma concentration was earlier and sustained along with the standard breakfast in comparison to that with fatty breakfast. Peak change in PEFR and pulse rate was also observed earlier with the standard diet than with fatty diet. The plasma theophylline concentrations produced after both diets were insufficient to produce any detectable change in subjective symptoms like tremor palpitation, heart burn, nausea, restlessness and tenseness. However, theophylline after fatty breakfast was better tolerated than that after a standard breakfast.

Key words : theophylline fatty diet pharmacokinetics Peak expiratory flow rate pulse

INTRODUCTION

There is a significant relationship between serum theophylline concentrations and efficacy and toxicity. Many patients, such as children and smokers have a rapid elimination which produces a rapid decline in theophylline concentrations, resulting in large fluctuations of drug concentrations in plasma (high peaks, low troughs) and clinical response (1). Sustained release preparations of theophylline have been designed to decrease peak-to-trough fluctuations, allowing less frequent dosage administration and improved compliance (1). However, in India, the use of liquids (elixirs) or plain tablets of theophylline is popular (2) and is also considered economical (3).

Several studies have demonstrated intrasubject variability in absorption which may effect the efficacy of theophylline. Apart from circadian variation in theophylline absorption (4), food has been reported to alter the absorption kinetics of theophylline, although there is no consensus of opinion. Rate of absorption of theophylline with food has been shown to be decreased (5,6), increased (7) or unaffected (8). A markedly lower absorption rate and a longer Tmax have been observed in subjects given relatively high dose of 'Theo-Dur' after a meal high in fat (9,10). However, the effect of high fat meal on the absorption kinetics of liquid or plain theophylline tablets is not known. In rabbits, high fat diet was found to reduce the bioavailability of liquid theophylline when compared the standard pellet diet or fasting conditions (11).

In view of the fact that liquid and plain tablets of theophylline are in widespread use, the effect of high fat diet on the absorption of single dose of theophylline 'elixir' in comparison with a standard diet was studied. The effect of the theophylline on peak expiratory flow rate (PEFR), pulse rate and psychomotor performance was also noted.

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METHODS

Subjects - Six healthy male volunteers participating in the study gave informed consent. The mean (±S.D.) age of the volunteers was 32±3.41 years, mean (±SD) weight being 68±4.1 kg. All 6 volunteers were non-smokers.

Protocol - To eliminate any intake of theophylline from other sources and possible formation of theophylline *in vivo* following intake of caffeine, the subjects were instructed to abstain from beverages containing xanthine derivatives for 24 hr prior to each study day. The volunteers had not taken any other medications 7 days prior to the study.

After an overnight fast, the subjects reported at 8.00 hr and their baseline pulse rate, PEFR and visual analog scales (VAS) for subjective symptoms were recorded. Each performed a 6 digit cancellation test. They were given a standard light breakfast (75 g of bread and 60 g of jam) followed by administration of 160 mg of theophylline (liquid formulation). Blood samples were collected at 0.5, 1, 1.5, 2, 3, 4 and 6 hr after drug administration along with recording of pulse rate, PEFR, VAS and 6 digit cancellation test.

After a wash out period of 72 h, the same procedure was repeated with theophylline being administered after a high fat containing breakfast (75 g of bread, 60 g of jam and 33 g of butter).

Serum was separated from the blood samples collected and frozen at —20°C till assayed for theophylline. The concentration of theophylline was determined by high pressure liquid chromatorgraphy (12). Samples were analyzed in duplicate.

Pulse rate was recorded on all occasions by a single observer. PEFR was recorded as mean of 3 attempts on each occasion with a Wright Peak Flowmeter (Airmed Limited, Harlow, England). Six digit cancellation was performed as described by Stone (13) and a digit cancellation index (DCI) was calculated.

For subjective assessment of symptoms of VAS, the extremes of scales were: Extreme palpitation - no feeling of palpitation, extreme tremor - no feeling of tremor, extreme nausea - no nausea, extreme heartburn - no heartburn, extreme restlessness - no restlessness, extremely tense - completely relaxed. Any other spontaneously reported side effects were also recorded.

Analysis of data - From the pharmacokinetic data, Cmax, Tmax, absorption half-life ($t_{1/2}a$)and area under the curve ($AUC_{0-\alpha}$) were calculated. From the pharmacodynamic experiments, percentage of baseline of pulse rate, PEFR, DCI and VAS were calculated. Data obtained after standard and high fat breakfast were compared using Student's paired t-test.

RESULTS

The effects of standard and fatty breakfast on various pharmacokinetic parameters of a liquid theophylline preparation are shown in Table I. The mean Cmax, Tmax, $t\frac{1}{2}a$, $t\frac{1}{2}$ and $AUC_{0-\alpha}$ were comparable despite different composition of diet.

TABLE I : Single dose kinetics of theophylline in plasma with fatty and standard breakfast. Values represent mean ±S.E. of 6 volunteers.

	C_{max} (mg/ml)	T_{max} (hr)	$T_{1/2}a$ (hr)	$T_{1/2}$ (hr)	$AUC_{0-\alpha}$
Theophylline with fatty breakfast	6.61 ± 0.77	3.08 ± 0.45	1.03 ± 0.33	8.12 ± 1.75	125.76 ± 42.79
Theophylline with standard breakfast	7.05 ± 0.48	3.25 ± 0.45	0.63 ± 0.15	11.37 ± 3.90	101.73 ± 21.50

With standard breakfast the maximum change in PEFR was observed at 1 hr. Thereafter the effect of the drug decreased and stabilised between 103 to 104% of baseline till the end of the observation period. The increase in PEFR after a fatty breakfast has a slow onset and gradually reached a maximum at 4 hr. However, the changes with both fatty and standard diets were comparable at each point of time (Fig. 1). PEFR after theophylline was significantly increased from control ($P < 0.05$) at 1 hr with standard breakfast and at 4 and 6 hr with fatty breakfast. With a standard breakfast the peak increase in pulse rate was seen at 1.5 hr but with fatty breakfast, the peak increase was seen at 4 hr. The increase in pulse rate seen with standard breakfast was significantly more

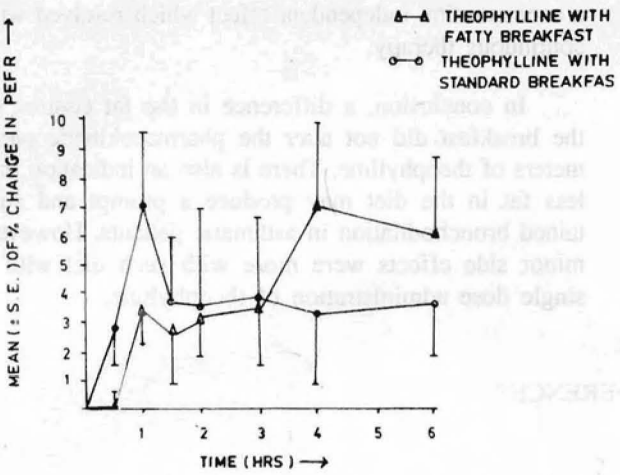

Fig. 1 : **The effect of fatty and standard breakfast on the expiratory flow rate (PEFR) at different time intervals after 160 mg of theophylline in 6 volunteers.**

than the increase observed with the fatty breakfast ($P < 0.05$). The pulse rate with fatty breakfast at 1 and 4 hr were comparable, thus demonstrating two peaks (Fig. 2).

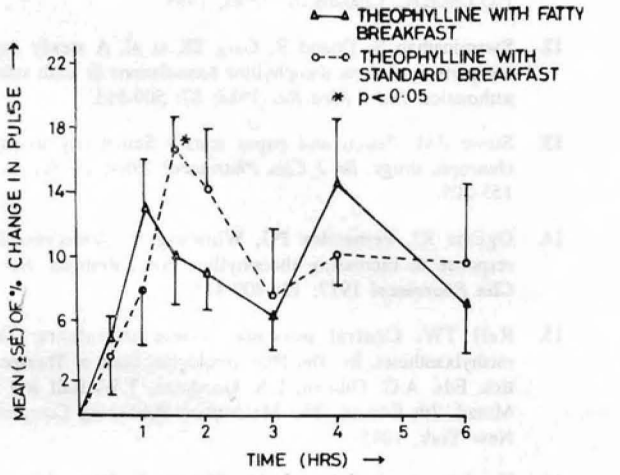

Fig. 2: **The effect of fatty and standard breakfast on the pulse rate at different time intervals after 160 mg of theophylline in 6 volunteers.**

Theophylline did not produce any improvement in the DCI of the volunteers. There was no difference between the subjective symptoms after theophylline as measured by the VAS, after standard and fatty breakfast. However, the six volunteers spontaneously reported a total of 23 adverse drug events in the 6 hr study period with theophylline after standard breakfast like headache, heaviness in head while after fatty food, there were only 3 adverse drug events reported.

DISCUSSION

The present study shows that fatty food does not affect the pharmacokinetic parameters in comparison to that with a standard breakfast. The therapeutic plasma concentration of theophylline that produces effective bronchodilation in asthmatic patients lies between 5 and 20 µg/ml. With standard breakfast the plasma theophylline concentration was above 5 mg/ml at 1.5 hr and was maintained above 5 µg/ml till 6 hr. However, with fatty breakfast the mean plasma theophylline concentration above 5 µg/ml was attained only after 3 hr. The maximum change a PEFR after standard breakfast was noted early in comparison with that with fatty breakfast. The peak increase in pulse with standard breakfast was noted at 1.5 hr. However, with fatty diet, 2 peaks in the percentage change in pulse rate observed. The reason for this is largely unknown; but it is possible that the increase in pulse rate is directly proportional to the rate of change of theophylline concentration in the plasma. In the present study, it was seen that theophylline had caused 15-17% peak increase in pulse rate when the corresponding theophylline levels were between 5-6 µg/ml. This is in contrast to that reported by Ogilvie et al. (14) who noted a modest increase of 3-16 beats/min in heart rate in normal individuals at theopylline plasma concentrations of more than 10 µg/ml.

There was no overt stimulation of the central nervous system with administration of 160 mg of theophylline in this study, as there was no improvement in the performance of the volunteers in the six-digit cancellation test. Although the exact serum levels of theophylline for stimulation of CNS have not been thoroughly investigated, this effect has been reported principally as side effect in the therapy of bronchial asthma in which the adult dose was above 250 mg (15).

No diference could be detected in the subjective symptoms as measured by VAS both after standard and fatty diet. The reason for this could be that the

subjective symptoms occur only at much higher serum theophylline levels (15). The relatively large number of minor adverse drug events reported spontaneously with theophylline after a standard breakfast in comparison to that after a fatty breakfast (23 vs 3) in the presence of comparable Cmax may be due to a more rapid increase in plasma theophylline concentration after standard breakfast. Moreover, Hendeles et al (16) identified minor side effects due to central nervous system stimulation at start of theophylline therapy as a concentration independent effect which resolved with continuous therapy.

In conclusion, a difference in the fat content of the breakfast did not alter the pharmacokinetic parameters of theophylline. There is also an indication that less fat in the diet may produce a prompt and sustained bronchodilation in asthmatic patients. However, minor side effects were more with such diet with a single dose administration of theophylline.

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