EFFECT OF MACROCOMPONENTS OF FOOD ON THE PHARMACOKINETICS OF A LONG ACTING PREPARATION OF ANHYDROUS THEOPHYLLINE

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Abstract: In a single dose crossover study, the effect of macrocomponents of food on the pharmacokinetics of a long acting preparation of anhydrous theophylline was investigated. Compared to fasting subjects, carbohydrate and fat rich diet caused an enhancement of absorption half life and a lower C_{max} with a delayed t_{max} and elimination of the bronchodilator. Protein coadministration decreased AUC_{0-∞} of the drug without significantly altering its absorption or elimination kinetics.

Key words: pharmacokinetics
food macro-components

INTRODUCTION

Theophylline, a bronchodilator widely used in chronic obstructive lung disease suffers from the disadvantage of a narrow margin of safety (7.5 – 15 mcg/ml) and sharp swings in the steady state levels (1). A short elimination half life of the drug dictates frequent dosing, thus further adding the factor of poor patient compliance. Whereas the long acting formulations of theophylline have been useful in reducing the fluctuations in steady state drug levels and in the improvement of patient compliance as a consequence of less frequent dosing, the spectrum and quantum of associated adverse effects have remained unaltered even with these preparations (2).

In order to overcome frequently occurring gastrointestinal symptoms thought to be mainly due to local irritant effect of oral theophylline (3), the drug is often recommended for use after food. However, during the recent past, alteration of theophylline kinetics by concomitant food administration has been reported (4).

Though several authors (5, 6, 7) have reported food induced alterations in pharmacokinetics of sustained action theophylline preparations, the data with regard to the effect of different macrocomponents on the pharmacokinetic behaviour of these preparations is scanty. Also no report on the components of the food in the form used by the Indian population on a commercially available long acting theophylline preparation in the country could be located. It was therefore thought interesting to investigate the problem by selecting a long acting anhydrous theophylline preparation commonly employed in the clinical practice.

In the present study, the effect of different macrocomponents of the food on the pharmacokinetics of a long acting theophylline preparation (Theo-SR) was evaluated wherein the contents, form and presentation of food items conformed more closely to the food taken by an Indian patient.

METHODS

Ten healthy non-smoker subjects (19-22 years and weight 50-75 kg) who did not exhibit any abnormal physical findings or abnormal biochemical/laboratory values consented voluntarily to participate in the study.
Alcohol and drugs other than those used in present study were restricted during and one week prior to experimentation. Xanthine containing foods were not permitted on the days of the study.

A single dose randomised crossover design was followed so that each subject received on the day of experimentation at 9.00 A.M. a single dose of two tablets of Theo-SR 200 (each tablet containing 200 mg of anhydrous theophylline) preceded 15 min earlier by one of the therapeutic regimens outlined in Table I.

Spectrophotometrically on UV-VIS microprocessor controlled 'Uvikron 810' spectrophotometer as per the method described by Jenne and coworkers (8).

The time-theophylline concentration curve was plotted and observed to be best described by a single compartment open model. Pharmacokinetic calculations were performed by the standard methods. Absorption and elimination half-lives (abs. \( t_{0.5} \) and elimin \( t_{0.5} \)) were obtained from the corresponding rate constants (\( K_a \) and \( K_e \)) calculated from the slopes obtained by the method of least squares (9) and method of residuals (10) respectively. Area under the curve (AUC\(^9\)) was determined by the trapezoidal method (11) and AUC from \( t \) to infinity was calculated by the expression \( \text{AUC}_{t-\infty} = C_t/K_e \) where \( C_t \) conformed to the last recorded concentration (11). \( C_{\text{max}} \) was read directly from the time concentration curve and value of \( T_{\text{max}} \) calculated from the equation (12):

\[
T_{\text{max}} = \frac{-2.303}{K_a - K_e} \times \log \frac{K_a}{K_e}
\]

by rotation on different occasions; each session separated from the other by a washout period of 2 weeks. On the day of experimentation the subjects were permitted water or fruit juice at \textit{lib} and lunch which was permitted 4h after drug administration, consisted of fruits and salad at \textit{lib}. All the subjects had a standard supper the evening previous to the day of experimentation and 10h after the drug administration.

Five ml of venous blood samples were obtained at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 and 24 h after drug administration. Serum theophylline was estimated spectrophotometrically on UV-VIS microprocessor controlled 'Uvikron 810' spectrophotometer as per the method described by Jenne and coworkers (8).

\[TABLE I : \text{Details of food components used in various regiments.}\]

<table>
<thead>
<tr>
<th>Diet</th>
<th>Protein (gm)</th>
<th>Fat (gm)</th>
<th>Carbohydrate (gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) High Protein Diet:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skimmed milk (200 ml)</td>
<td>7.30</td>
<td>-</td>
<td>9.70</td>
</tr>
<tr>
<td>Roasted liver (250 gm)</td>
<td>50.00</td>
<td>7.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Chapatis 2 (wheat flour 30 gm)</td>
<td>3.80</td>
<td>1.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Cauliflower curry (50 gm)</td>
<td>1.30</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Total</td>
<td>-62.4</td>
<td>11.5</td>
<td>31.3</td>
</tr>
<tr>
<td>B) High Carbohydrate Diet:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooked bengal gram (50 gm) + Potato curry (in oil)</td>
<td>8.8</td>
<td>12.8</td>
<td>41.3</td>
</tr>
<tr>
<td>Chapatis 4 (wheat flour 60 gm)</td>
<td>7.4</td>
<td>2.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Total</td>
<td>16.2</td>
<td>14.8</td>
<td>69.3</td>
</tr>
<tr>
<td>C) High Fat Diet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halwa (Suji 20 gm, ghee 15 gm) sugar 15 gm)</td>
<td>2.8</td>
<td>20.2</td>
<td>15.0</td>
</tr>
<tr>
<td>Puris (wheat flour 20 gm and ghee 15 gm)</td>
<td>2.2</td>
<td>15.2</td>
<td>10.0</td>
</tr>
<tr>
<td>Total</td>
<td>5.0</td>
<td>35.4</td>
<td>25.0</td>
</tr>
</tbody>
</table>
RESULTS

The mean time concentration curve obtained with a single dose of the theo-SR preparation in fasting subjects revealed a gradual and sustained upward slope with maximum concentrations attained at 6-8 h. The drug concentrations, thereafter followed a down-ward trend and serum levels at 24 h were observed to be almost within the therapeutic range.

The general behaviour of mean time theophylline concentration curve in fasting and non-fasting states who received the theo-SR preparation did not differ (Fig. 1). However, the co-administration of food was observed to alter the maximum serum theophylline concentration. While - as decreased theophylline levels were registered after protein administration, an enhancement in levels was observed with carbohydrate and fat rich food. The pharmacokinetic data obtained reveal that the values obtained in non-fasting subjects differ from the values obtained in fasting situations (Table II).

![Fig. 1: Time-concentration curve of theophylline after administration of a single oral dose of Theo-SR, 400 mg in fasting state and after food with high protein, high carbohydrate or high fat contents.](image-url)
TABLE II: Comparative pharmacokinetic data of theophylline in fasting and after high protein, carbohydrate and fat diets. (Values depict Mean ± SEM).

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Fasting</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K_a ) (h^{-1})</td>
<td>0.345 ± 0.013</td>
<td>0.371 ± 0.007</td>
<td>0.259 ± 0.02**</td>
<td>0.254 ± 0.012***</td>
</tr>
<tr>
<td>( t_{abs} ) (h)</td>
<td>2.0 ± 0.082</td>
<td>1.9 ± 0.06</td>
<td>2.82 ± 0.22**</td>
<td>2.79 ± 0.14***</td>
</tr>
<tr>
<td>( K_e ) (h^{-1})</td>
<td>0.045 ± 0.00003</td>
<td>0.043 ± 0.00001</td>
<td>0.052 ± 0.00000*</td>
<td>0.052 ± 0.00000*</td>
</tr>
<tr>
<td>( t_{elim} ) (h)</td>
<td>15.25 ± 0.56</td>
<td>16.0 ± 0.52</td>
<td>13.5 ± 0.72*</td>
<td>13.5 ± 0.69*</td>
</tr>
<tr>
<td>( C_{max}(\mu g/ml) )</td>
<td>15.37 ± 0.34</td>
<td>13.66 ± 0.39</td>
<td>17.30 ± 0.39**</td>
<td>16.87 ± 0.41**</td>
</tr>
<tr>
<td>( t_{max} ) (h)</td>
<td>6.79 ± 0.2</td>
<td>6.54 ± 0.11</td>
<td>7.95 ± 0.47*</td>
<td>7.96 ± 0.31**</td>
</tr>
<tr>
<td>( AUC_0^\infty (\mu g/ml/hr) )</td>
<td>376.492 ± 17.01</td>
<td>354.446 ± 14.84**</td>
<td>386.688 ± 17.09</td>
<td>380.434 ± 17.74</td>
</tr>
</tbody>
</table>

A. After high protein diet. B. After high carbohydrate diet. C. After high fat diet.

* \( P<0.05; **P<0.01; ***P<0.001 \) when compared with fasting group (A).

DISCUSSION

The \( C_{max} \) obtained in the fasting subjects in the present study with theo-SR conforms to the values obtained in an earlier investigation on another commercially available long acting theophylline preparation (13) (Deriphylline Retard' containing theophylline + hydroxyethyl theophylline with a theophylline content equivalent to 273.2 mg). However, the time to reach maximum concentrations was attained earlier with the latter long acting preparation and serum drug levels registered at 24 h dipped down to levels far lower than obtained with the theo-SR.

Our observations of decreased theophylline levels with protein coadministration and enhanced serum levels after carbohydrate and fat rich food agree with the data reported by Feldman and coworkers (14) and Thebault et al (15). Food has been generally reported to increase the time taken to attain maximum theophylline concentrations (5, 6, 7). Though the aforementioned authors did not investigate effect of individual components of food, our results in subjects who received carbohydrate/fat rich diet conform to these observations. The inability of a predominantly fat food to influence \( T_{max} \) reported by Thebault et al (15) is however at variance with our results.

An analysis of pharmacokinetic data reveals that carbohydrate/fat diets produce a delayed absorptive process and a prolonged elimination of theophylline.

Co-administration of protein diet did exhibit evidences of enhanced absorption and delayed elimination.

The influence of macronutrients like protein, carbohydrate and fat on drug metabolism in human subjects has been reported by Anderson (16). The aforementioned author altered one of the macronutrients keeping number of calories constant and observed an opposing effect of protein and carbohydrate on metabolism of theophylline and antipyrine (17). While as protein supplement increased rate of metabolism, the carbohydrate co-administration had an inhibitory effect.

The effect of carbohydrate and fat rich diet on elimination kinetics of theo-SR seems difficult to explain. In this context, it may be interesting to examine observations of effect of protein and carbohydrate on mixed function oxidase enzyme. Increased dietary protein augments hepatic microsomal P450 and this effect has been likened to the inducing effect of phenobarbitone on microsomal enzymes (18, 19). On the other hand, it is known that high carbohydrate intake decreases cytochrome P450 activity and rate of drug metabolism (19). Mechanism of decreased theophylline clearance as a consequence of carbohydrate rich diet in our study can be explained on the basis of above mentioned mechanism. Similarly, the altered elimination of theophylline due to high fat intake in our study can be correlated to effect of enhanced lipoprotein turnover on microsomal activity.
REFERENCES


