DISCUSSION
Treatment of infection with antimicrobial agents given orally had always been a difficult task to accomplish because of the inaccessible efficacy measurement. In treatment of most of the infections therapeutic drug monitoring is seldom employed because, it is impractical and also not cost effective, apart from the inconvenience to the patient and the tedious procedure involved in the measurement of drug concentrations. Oral route is the most commonly advocated route of drug administration although, the absorption of the drug is influenced by a number of factors.

Assuming that the drug reaches its adequate concentration in the desired target site has been the cause of number of therapeutic failures, in the treatment of infections with antibiotics. Antimicrobial agents are either concentration dependent i.e., the concentration of the drug in the target site reflects its clinical efficacy or time dependent i.e., the time above a certain concentration decides the clinical cure. The objective behind prescribing these drugs has been to administer the concentration dependent drugs using widely spaced intervals and time dependent ones with short dosing intervals.

There has been a proliferation in the literature on the oral absorption of drugs because of the complexity involved due to the influence of various factors. Among the various factors, which influence the absorption of drugs, food plays a very important role.

Present evidence indicates that food substances are capable of altering the rate and efficiency with which orally closed antimicrobial or antifungal agents are absorbed. The numerous inconsistencies between reports from different laboratories illustrate the difficulty of developing general guidelines for correct management of food-drug interactions.

The clinical significance of food-drug interactions is difficult to assess. The clinical effect of reduced or delayed absorption depends on the type of antimicrobial agents and the minimum inhibitory concentration for particular pathogens, and the degree to which drug absorption is reduced. Clearly, in any situation when circulating drug levels are close to the minimum inhibitory concentration then reduced
absorption, whatever the cause, is likely to be clinically significant. The absorption of the most penicillins, tetracyclines, some oral cephalosporins and some erythromycin products may be markedly reduced by food, and the likelihood of therapeutic failures in these situations is high.\(^5\)

In order to obtain maximum circulating drug levels for a given dose of antibacterial agent and to maintain reproducible drug levels between doses, it becomes utmost important to define the drug-food interaction. Cefaclor being a time dependent antibiotic it become further more important to define its interaction with food so as to enable the prescribing physician to decide on the correct dosing interval.

With this background, a literature search was carried out for food interaction of Cefaclor. A computer search on EMBASE; Drugs and Pharmacology, Medline and International Pharmaceutical Abstracts (IPA) disks gave information on three reported Cefaclor food interactions as described below (the computer search was updated periodically and the latest search was done on April 2000 with the key words, Cefaclor and food / diet(s) / interaction / meal / meat / fat / protein / carbohydrate / adsorption / juice / rice / wheat / calcium / milk / diary / lipid(s), which also did not reveal any new findings).

Glynne A, et al.,\(^{273}\) have studied the effects of food on Cefaclor 250 mg capsules in 6 subjects in fasting and fed (breakfast consisting of scrambled eggs, toast and tea or coffee) conditions. The blood samples were analyzed by microbiological assay method using disc plates. Food reduced the absorption, as the peak levels were lower and the AUC were smaller with food. The Tmax was also delayed by food. The authors concluded that Cefaclor might be more effective when taken before meals.

Barbhaiya R H, et al.,\(^{16}\) have reported the effects of food on the pharmacokinetics of Cefaclor 250 mg capsule in 12 subjects under fasting and fed (standard breakfast consisting of two eggs, one slice of toast, butter and jelly, two links of sausage, and 200 ml of orange juice) conditions. Plasma samples were analyzed by validated HPLC method. The pharmacokinetic parameters are tabulated in table - DC1.
**TABLE - DC 1**

Pharmacokinetic parameters for Cefaclor 250 mg capsules after fasting and fed treatments in 12 subjects (Barbhaiya et al.,).\textsuperscript{15}

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Tmax (h)</th>
<th>Cmax (µg/mL)</th>
<th>AUC (0-inf.) (µg.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefaclor – Fasting</td>
<td>0.6</td>
<td>8.70 (2.72)</td>
<td>8.60 (1.43)</td>
</tr>
<tr>
<td>Cefaclor – Food</td>
<td>1.3</td>
<td>4.29 (1.52)</td>
<td>7.57 (1.20)</td>
</tr>
</tbody>
</table>

The values in the parenthesis indicate standard deviation.

**TABLE - DC 2**

Pharmacokinetic parameters for Cefaclor 500 mg capsules after fasting and four different fed treatments in 8 subjects (Oguma et al.,).\textsuperscript{14}

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Cmax (µg/mL)</th>
<th>AUC (0-6) (µg.h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>14.8 (5.3)</td>
<td>18.6 (3.6)</td>
</tr>
<tr>
<td>Rice – 350 Calories</td>
<td>9.11 (2.19)</td>
<td>19.9 (2.6)</td>
</tr>
<tr>
<td>Rice – 700 Calories</td>
<td>5.91 (1.04)</td>
<td>16.6 (2.9)</td>
</tr>
<tr>
<td>Bread – 500 Calories</td>
<td>7.88 (1.65)</td>
<td>15.4 (4.0)</td>
</tr>
<tr>
<td>Bread – 1000 Calories</td>
<td>6.79 (2.11)</td>
<td>17.7 (3.7)</td>
</tr>
</tbody>
</table>

The values in the parenthesis indicate standard deviation.
The mean \( C_{\text{max}} \) of Cefaclor decreased significantly from 8.70 \( \mu g/mL \) under the fasting conditions to 4.29 \( \mu g/mL \) after breakfast. The corresponding values for \( T_{\text{max}} \) increased significantly from 0.6 to 1.3 hours. The mean Cefaclor \( AUC_{(0-\infty)} \) were 8.60 \( \mu g/mL \) under the fasting conditions and 7.57 \( \mu g/mL \) after breakfast and were not significantly different from each other. The author concluded that the presence of food significantly decreased the rate of Cefaclor absorption but the extent was not affected.

Oguma T, et al.,\(^{14}\) have reported the pharmacokinetic analysis of the effects of different foods on absorption of Cefaclor 500 mg capsules in 8 volunteers after overnight fasting, after two rice meals (350 and 700 calories), and two bread meals (500 and 1000 calories). The rice meal (700 calories) consisted of 300 gm of rice with 160 ml of bean paste soup, 20 gm of pickles, and 200 ml of milk. The bread meal (500 cal) consisted of one and one-half slices of bread with 10 gm of margarine, one boiled egg and 200 ml of milk. The 350 calories rice meal was half of the 700 calories rice meal and the 1000 calories wheat meal was double the quantity of 500 calories wheat meal. The pharmacokinetic parameters are tabulated in table - DC 2. The mean \( C_{\text{max}} \) of Cefaclor in plasma after fasting, rice meal 350 cal, rice meal 700 cal, bread meal 500 cal and bread meal 1000 cal was 14.8, 9.11, 5.91, 7.88 and 6.79 \( \mu g/mL \) respectively. The mean \( C_{\text{max}} \) values of Cefaclor under the four conditions in which subjects were fed were reduced to less than one-half of that under fasting conditions. There was little difference among mean \( AUC_{(0 \text{ to } 6)} \)'s for the five administrations. The authors conclude that the absorption of Cefaclor was delayed, but the extent of absorption was not affected by food intake.

The duration of time that serum drug levels remain above the \( \text{MIC}_{90} \) (Time above the \( \text{MIC}_{90} \)) for the pathogen has been shown to be the most significant parameter determining the efficacies of beta lactam antibiotics including cephalosporins.\(^{290}\) Optimization of both dose and time above the \( \text{MIC}_{90} \) appears to be necessary for the treatment of infections with Cefaclor to achieve adequate clinical efficacy.
It is a known fact that compliance affects clinical response and outcome. The two most important factors to ensure good compliance are clear instructions to the patient and the simplest regimen consistent with continuous drug action. Medication that must be taken not more than twice daily, as compared three or four times daily, improves patient compliance with treatment in a number of disease settings.

Extended release Cefaclor is a modified form of the immediate release formulation designed to have a slower rate of dissolution, that produces a decreased but longer lasting maximal plasma concentration. The pharmacokinetics of the extended release formulation permit less frequent dosing than with immediate release Cefaclor formulation. The pharmacokinetic parameters of Cefaclor 500 mg conventional (immediate) release formulations are tabulated in table – DC 3. The Mean Tmax, Cmax, AUC(0 to t) and Half-life values ranges from 30 to 60 minutes, 9.9 to 17.3 µg/mL, 966 to 1768 µg.min/mL and 35 to 60 min, respectively.

Surprisingly, there is only one paper published comparing immediate release capsule and extended release tablet formulation of Cefaclor 500 mg, where the food interaction and pharmacokinetic details are poorly provided.

The comparative pharmacokinetics of Cefaclor immediate and extended release formulation (500 mg) after fasting and fed conditions as described in Product Information Sheet of Ceclor CD® is tabulated in table - DC 4.

Recently, some evidence that a greater increase in rate of absorption of Cefaclor was observed after Ceclor CD® (Cefaclor extended release 500 mg tablet formulation) was administered with non-vegetarian breakfast as compared to vegetarian breakfast. A difference of 23% existed when the mean Cmax of these two diets are compared simultaneously.
**TABLE - DC 3**

**Pharmacokinetic parameters for Cefaclor 500 mg conventional release formulation in normal human subjects after fasting conditions.**

<table>
<thead>
<tr>
<th>Tmax (min)</th>
<th>Cmax (µg/mL)</th>
<th>AUC (0 to t) (µg.min/mL)</th>
<th>Half life (min)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 - 60</td>
<td>12.4 (1.3)*</td>
<td>NA</td>
<td>48 (6)</td>
<td>Levison et al(^{263})</td>
</tr>
<tr>
<td>42 (12)</td>
<td>17.3 (3.6)</td>
<td>1050 (126)</td>
<td>42 (6)</td>
<td>Barbhaiya et al(^{15})</td>
</tr>
<tr>
<td>54 (24)</td>
<td>15.9 (5.7)</td>
<td>1236 (204)</td>
<td>42 (12)</td>
<td>Nix et al(^{284})</td>
</tr>
<tr>
<td>60 (18)</td>
<td>9.9 (1.4)</td>
<td>966 (150)</td>
<td>38</td>
<td>Welling et al(^{285})</td>
</tr>
<tr>
<td>60</td>
<td>15.2 (2.4)</td>
<td>1768 (337)</td>
<td>60 (11)</td>
<td>Hodges et al(^{271})</td>
</tr>
<tr>
<td>NA</td>
<td>14.8 (5.3)</td>
<td>1116 (216)</td>
<td>35 (8)</td>
<td>Oguma et al(^{14})</td>
</tr>
<tr>
<td>NA</td>
<td>12.4 (1.3)</td>
<td>NA</td>
<td>48</td>
<td>Santoro et al(^{292})</td>
</tr>
</tbody>
</table>

The values in the parenthesis indicate standard deviation (SD) except * which is standard error (SE). NA: Data not reported
TABLE - DC 4

The comparative pharmacokinetics of Cefaclor extended release (Ceclor CD) and immediate release (Ceclor Pulvules) formulation (500 mg dose) after fasting and fed conditions.²⁶¹

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ceclor CD</th>
<th>Ceclor Pulvules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500 mg</td>
<td>2 X 250 mg</td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>Fasting</td>
</tr>
<tr>
<td>N</td>
<td>N = 16</td>
<td>N = 16</td>
</tr>
<tr>
<td>Cmax</td>
<td>8.2 (4.2)</td>
<td>5.4 (1.6)</td>
</tr>
<tr>
<td>Tmax</td>
<td>2.5 (0.8)</td>
<td>1.5 (0.7)</td>
</tr>
<tr>
<td>AUC</td>
<td>18.1 (4.2)</td>
<td>14.8 (4.0)</td>
</tr>
</tbody>
</table>

The values in the parenthesis indicate standard deviation (SD)
The following differences in the pharmacokinetics of Cefaclor-food interaction were interesting:

1. Food decreased and delayed the rate of absorption with Cefaclor immediate release formulations\(^\ddagger\) while it increased and delayed the rate of absorption with Cefaclor extended release formulations.\(^\ddagger\)

2. Oguma et al.\(^\ddagger\) reported that rice diet decreased the rate of absorption of Cefaclor more than the bread diet. However, a close look at the constitution of rice and bread diet reveals an imbalance in their fat content, which these authors have not taken into account when drawing their conclusions.

3. A difference of 23% existed when the mean Cmax of vegetarian and non-vegetarian diets were compared after oral administration of Ceclor CD\(^\ddagger\) (Cefaclor) 500 mg.\(^\ddagger\)

4. The Cmax is decreased and the Tmax is prolonged when Cefaclor conventional (immediate release) formulation is administered with food, though the AUC is not much different, while the Cmax and AUC are increased, and the Tmax prolonged when Cefaclor extended release formulation is administered with food. The product information sheet of Cefaclor extended release formulation (Ceclor CD) therefore states that Ceclor CD should be taken with food.\(^\ddagger\) However, there are no directions regarding the source and content of the food.

Since a vast majority of the Indian population is vegetarian, it seemed prudent to further define the interaction with the administration of Ceclor CD\(^\ddagger\) (Cefaclor) 500 mg along with equicaloric diets which varied both in content and source. Hence this study was planned to compare the effect of five different diets, viz. High Fat Vegetarian, High Fat Non Vegetarian, Low Fat Vegetarian (wheat based), Low Fat Non Vegetarian and Low Fat Vegetarian (rice based) diets, and the fasting
state on the bioavailability of Cefaclor CD in normal human subjects. The fasted treatment served as the reference for comparison.

The conduct of the study has a number of aspects that merit discussion. Most of the principles envisaged in the Good Clinical Research Practice were adhered to. All the diets (breakfasts) were constituted with the help of Clinical Nutritionist and standard reference texts. They were all equicaloric, the high fat diets contained more than 50% of fat calories, the low fat diets less than 25% of fat calories. Percentage of proteins was maintained between 13 to 15% in all the diets. Rice diet was a low fat vegetarian diet. The study protocol and Informed Consent Form (ICF) were approved by the Jamia Hamdard Institutional Review Board.

Each of the subjects was required to understand and affix his signature on the written Informed Consent Form. The signed original ICF was retained. The standard SOPs of the Clinical Pharmacology and Pharmacokinetics department including Clinical Pharmacology Unit have been adhered to in the clinical, analytical, pharmacokinetic and statistical procedures.

Randomization schedule was computer generated by SAS software. The different diets (breakfasts) treatments were allotted to the subjects according the randomization.

All the 5 different diets (breakfasts) were standardized with a trial run. In all the six periods the preparation of the diets (including measurement of individual ingredients before preparation) was supervised. Compliance of breakfast intake by subjects after serving was ensured.

The subjects were highly co-operative throughout the study by following the instructions of overnight fasting, 1 hour water restriction before dose, and 2 hours post dosing, reporting for blood sampling and vital sign measurements very promptly, abstaining from tobacco, alcohol during the study period and from caffeine 48 hours before dosing in each period. They were also instructed not to take any medication during the study period without informing the investigator.
Serum separated from blood samples was stored in properly labeled polypropylene capped tubes at -70±10°C. The analytical HPLC method was validated for selectivity, linearity, sensitivity, accuracy, precision, recovery and stability (including freeze thaw, bench top and in-injector). All the columns used were checked for the column performance test and the HPLC systems for the system suitability before their use in the analysis. The working standards for Cefaclor and Internal standard (cephalexin) were checked for their actual content (assay - potency), revalidation date and expiry date. Correction was made with the actual amount weighed for the potency.

All the chemicals reagents used were of either AR grade or HPLC grade and all the glassware and equipments used were calibrated.

All the six periods study samples (90 samples) of one subject were processed along with one set of calibration standard samples (11 samples) and 3 sets of quality control samples (9 samples). The processed calibration samples and the quality control samples which were interspersed with the subject samples were injected.

The chromatograms were processed using Class LC 10/VP software and the pharmacokinetic analysis was done using WinNonlin Software Version 1.5 (SCI, USA). Statistical analysis was performed using SAS Version 6.12 (SAS Institute Inc., Cary NC, USA). The result are presented as ratios of means with confidence Intervals as required by FDA and also as statistically significance at P<0.05.

FDA Guidelines for Food-Effect Bioavailability (BA) studies states that "A food effect will be concluded when the 90% Confidence Interval (CI) for the ratio of means (population geometric means based on log transformed data) of fed and fasted treatments fall outside 80-125% for AUC and Cmax. It also states that "In food-effect BA studies, the fasted treatment serves as the reference".

According to these FDA guidelines, the results of the present study are tabulated in table - DC 5. It is evident that High Fat Non Vegetarian breakfast exhibits a food effect while the food effect of low fat vegetarian, high fat vegetarian and Rice based breakfasts was
indeterminant. A significant (P<0.05) food-effect resulted with High Fat Non-Vegetarian diet (breakfast) while the food-effect with Low Fat Vegetarian diet (breakfast) marginally failed to reach the significance level (0.05<P<0.1), and the food-effect of High Fat Vegetarian, Low Fat Non Vegetarian and Rice diets (breakfasts) are not statistically significant.

The above mentioned results show that there exists a food effect with High Fat Non Vegetarian diet. This may be due to increase in the viscosity of gastric contents, increase dissolution and increased bile secretion resulting in better absorption from duodenum and jejunum.

The reason for the negligible food-effect with Low Fat Non Vegetarian breakfast may be due to the adsorption of Cefaclor to the non vegetarian (meat) component and hence lesser amount of Cefaclor being available for absorption in the duodenum and jejunum. The indeterminant food effect of High Fat Vegetarian is in agreement with one of the Ranbaxy studies,\textsuperscript{29} which had concluded that significant food effect was not noticed with High Fat Vegetarian diet (breakfast) with Cefaclor CD. The indeterminant food effect with Low Fat Vegetarian wheat based and Rice based diets can be explained with the help of reported food effect by Oguma et al.\textsuperscript{14} Oguma et al have reported that rice diet decreased the rate of absorption more than the bread diet with Cefaclor immediate release formulation. It is understood that food behaves in a opposite way with Cefaclor CD,\textsuperscript{28} hence the increased rate of absorption with rice diet more than the bread diet in this study with Cefaclor CD is understandable.

**EFFECT OF DIETS AND FASTING CONDITIONS**

All the dietary treatments studied increased the Tmax, as compared to the fasting state. There were, however, differences in the increase produced by different diets. This is in agreement with the results reported by other workers.\textsuperscript{14,15} The increase was inversely related to the fat content of the diet. Both high fat vegetarian and non-vegetarian diets produced a smaller increase in Tmax (37.5\%) as compared to the respective low fat vegetarian and non-vegetarian diets (100\%). These results are unexpected, since high fat diets are reported
to prolong the gastric emptying time and hence $T_{\text{max}}$ of immediate release drug formulations.\textsuperscript{5, 36} This effect may be a characteristic of sustained release drug formulation i.e. Cefaclor CD. Rice based diet had the least effect on $T_{\text{max}}$ (+25%).

There was a 50% increase in $C_{\text{max}}$ when Rice diet was compared with fasting ($P<0.001$) this was followed by 33% increase with Low Fat Vegetarian diet ($P<0.001$) and 29% with High Fat Non Vegetarian diet ($P<0.01$). The increase in $C_{\text{max}}$ by Rice diet, followed by High Fat Non Vegetarian diet is in agreement with the reported food effect by Oguma et al.\textsuperscript{14} and Barbhaiya et al.\textsuperscript{15} respectively as explained before. The $C_{\text{max}}$ of High Fat Vegetarian diet and Low Fat Non Vegetarian diet were increased by 12% and 7% respectively, which was not statistically significant. This is in agreement with the High Fat Vegetarian diet showing little food effect in the Ranbaxy study.\textsuperscript{28} The Low Fat Non Vegetarian diet showing little food effect may be due to adsorption of Cefaclor to the non vegetarian content (meat). The significant increase in $C_{\text{max}}$ with high fat non-vegetarian diet may be due to decrease in adsorption of Cefaclor to meat in the presence of fat and an increase in release of Cefaclor from the CD formulation produced by fat-induced increase in biliary secretion as reported by Williams et al.\textsuperscript{23} The increase in $C_{\text{max}}$ however, is not relevant to the pharmacodynamic effect (efficacy) of Cefaclor since it is a time – dependent antibiotic.

All diets studied increased the AUC (0 to $t$) and AUC (0 to $\text{inf.}$) as compared to fasting state. This confirms the data contained in Product Information Sheet on Cefaclor CD. The Product Information Sheet, however, contains no information about the nature of food or its fat content. In the present study, low fat non-vegetarian food had very little effect on AUC, as compared to the fasting state, while high fat non-vegetarian that produced the maximum increase in AUC ($P<0.05$). The effect of low fat vegetarian diet was nearly as much as that produced by high fat non-vegetarian diet but the effect just failed to reach the significance level ($0.05<P<0.1$)
### TABLE - DC 5

Ratio of means (geometric means (LSM) based on Log transformed data) and 90 % confidence intervals for all the diet treatments versus fasting treatment for Cmax, AUC(0 to t) and AUC(0 to inf.).

<table>
<thead>
<tr>
<th>TREATMENT COMPARISON</th>
<th>Cmax</th>
<th>AUC(0 to t)</th>
<th>AUC(0 to inf.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ratio (%)</td>
<td>CI (%)</td>
<td>Ratio (%)</td>
</tr>
<tr>
<td>Fasting (A) Vs High Fat Veg. (B)</td>
<td>96.11</td>
<td>77.63* to 106.87</td>
<td>97.49</td>
</tr>
<tr>
<td>Fasting (A) Vs High Fat Non Veg. (C)</td>
<td>90.07</td>
<td>66.07* to 90.96</td>
<td>95.83</td>
</tr>
<tr>
<td>Fasting (A) Vs Low Fat Veg. (D)</td>
<td>89.98</td>
<td>65.91* to 90.74</td>
<td>97.05</td>
</tr>
<tr>
<td>Fasting (A) Vs Low Fat Non Veg. (E)</td>
<td>99.77</td>
<td>84.77 to 116.70</td>
<td>100.05</td>
</tr>
<tr>
<td>Fasting (A) Vs Rice based diet (F)</td>
<td>85.07</td>
<td>56.83* to 78.24*</td>
<td>97.03</td>
</tr>
</tbody>
</table>

* CI not within 80 ~ 125 % for log transformed data

** CI not within 80 ~ 120 % for untransformed data
EFFECT OF SOURCE (VEGETARIAN OR NON VEGETARIAN) OF DIETS (BREAKFASTS)

There exists a difference of 371% in Cmax 197% in AUC\(_{(0 \to t)}\) and 121% in AUC\(_{(0 \to \infty)}\) when percent difference against fasting of Low Fat Non Vegetarian diet was compared with percent difference against fasting of Low Fat Vegetarian diet. The statistically significant difference in Cmax may be due to adsorption of Cefaclor to Non Vegetarian (meat) component.

EFFECT OF FAT (HIGH OR LOW) OF DIETS

There exists a difference of 319% in Cmax (P<0.05), 286% in AUC\(_{(0 \to t)}\) and 146% in AUC\(_{(0 \to \infty)}\) when percent difference against fasting of Low Fat Non Vegetarian diet was compared with percent difference against fasting of High Fat Non Vegetarian diet. The statistically significant difference in Cmax shows marked fat effect amongst the Non Vegetarian diet, which may be attributed to the fact that fat diet increases the gastric retention time and bile secretion and hence more dissolution of the drug occurs in the stomach and in the duodenum facilitating increased absorption from small intestine. The low fat vegetarian diet fared better than high fat vegetarian diet with Cmax which may be due to less viscid gastrointestinal contents and hence more drug release enabling increased absorption from small intestines with low fat diet. The differences in AUCs between low and high fat vegetarian diets were not significant (P>0.05). This is in agreement with Zhi et al\(^{179}\) who have reported that the difference in the magnitude of the effects of dietary fats on drug absorption between two meals that are different in fat content (e.g., low fat versus high fat meals) is smaller than that between fasting and intake of meals that contain fat.

EFFECT OF RICE DIET

There was no significant difference between the Rice based diets and the Low Fat Vegetarian wheat based indicating that both the diets were equivalent. This is in agreement with the observations of Oguma et al, as explained earlier.\(^{14}\)
Cefaclor being a time dependent antibiotic the Time above MIC\textsubscript{90} directly reflects the clinical efficacy. Hence Cefaclor is prescribed with short dosing intervals so as to maintain the concentration of the drug above MIC\textsubscript{90} for long time periods.

Various studies\textsuperscript{286, 287, 288, 290} have reported the MIC values for Cefaclor and MIC\textsubscript{90} values of 8 \mu g/mL (in which over 90\% of the strains of susceptible microorganisms are inhibited) was used for calculating Time above it. According to the mean Time > MIC\textsubscript{90} (8 \mu g/mL) parameter, the Low Fat Vegetarian diet showed a very long duration of action with 107 minutes (P<0.05) followed by High Fat Non Vegetarian with 102 minutes (P<0.1) then by high fat vegetarian and Rice diet both with 101 minutes (P<0.1) and then low fat non vegetarian with 86 minutes (P>0.1) which works out to be an increase in Time>MIC\textsubscript{90} of 41.6\%, 35.2\%, 34.5\%, 33.7\% and 14.6\% respectively, as compared to the fasting state. Hence, Cefaclor CD given with Low Fat Non Vegetarian breakfast (fed) is no better than when it is administered in the fasting state.

**LIMITATIONS OF THE PRESENT STUDY**

This study was not designed to study the mechanism(s) of Cefaclor CD-food interactions. The mechanisms proposed to explain the observed effects are hence speculative. Further studies on bioavailability of Cefaclor CD using (i) hyosine hydrobromide to delay gastric emptying, (ii) ranitidine to increase gastric pH and (iii) dehydrocholic acid to increase biliary secretion, are warranted.

The results obtained clearly bring out that with drugs like Cefaclor CD, the customary Drug Regulatory requirement of determining bioavailability by kinetic parameters (Tmax, Cmax and AUC) may not translate in totality to clinical efficacy which is depended on a pharmacodynamic end-point, i.e., Time above MIC\textsubscript{90} in case of time dependent antimicrobials. Based on kinetic parameters, the maximum increase in bioavailability of Cefaclor CD was obtained with high fat non-vegetarian diet, while in the analysis based on pharmacodynamic parameter the low fat vegetarian diet yielded the
best results. Further, studies with other time-dependent antimicrobial agents are warranted.

CONCLUSIONS OF THE PRESENT STUDY

The following main conclusions may be drawn based on the discussion of the results obtained in this study.

1. A marked food effect, an increase in both rate and extent of absorption was observed with high fat non-vegetarian and low fat vegetarian breakfasts. The effect with the latter treatment just failed to reach the level of statistical significance.

2. Low fat vegetarian and non-vegetarian diets produced a 100% increase in Tmax. The increase in Tmax produced by high fat diets was much less (37.5%). This effect was unexpected and appears to be a peculiar feature of Cefaclor CD.

3. The source of diet (non-vegetarian and vegetarian) has nearly the same effect on bioavailability.

4. Using FDA guidelines for determining bioavailability of Cefaclor CD, high fat non vegetarian diet yielded better results, as compared to low fat vegetarian diet. However, when a pharmacodynamic end – point of clinical efficacy i.e. time above MIC$_{90}$ was used, a diametrically opposite result was obtained i.e. the low fat vegetarian diet fared better than the high fat non vegetarian diet.

Hence the present data clearly seems to favour Low Fat Vegetarian diet (breakfast) to be taken with Cefaclor CD to achieve maximum benefit in terms of clinical efficacy. This finding is of great significance for the Indian population since a vast majority of us are vegetarians and consume relatively less fat, as compared to developed countries. Non-vegetarians need to consume high fat content diet for obtaining optimal results.
Drug food interaction is a hotly debated topic in the scientific research community. The interaction is clinically significant in the case of (i) drugs with a narrow window of absorption in the upper part of the intestine, (ii) drugs in which peak plasma concentration (Cmax) achieved determines their efficacy or toxicity and (iii) drugs in which the time above a critical plasma concentration determines their efficacy or lack of it. Cefaclor CD falls in the last category.

Food plays an important and interesting role in the oral absorption of Cefaclor from the gastrointestinal tract. Food delays and decreases the rate of absorption but it extent not affected, has been well documented. Interestingly, the outcome of food interaction of Cefaclor is reversed with an extended release formulation (Ceclor CD®) i.e., the rate and extent of absorption is increased along with a delay in absorption, when it is administered with food. Though the Product Information Sheet of Ceclor CD® states that it should be consumed with food, there is no mention regarding the type and source of food to be used.

Hence, this study was planned to investigate the effect of 5 different dietary treatments, viz., high fat vegetarian, high fat non vegetarian, low fat vegetarian, low fat non vegetarian and rice diet on the bioavailability of Cefaclor CD. The bioavailability determined under fasting condition was used as the reference point for comparison.

The study design was open label, balanced, randomized, six period, six treatment, six sequence, single dose, crossover bioavailability study on Ceclor CD® in 24 healthy, adult, male, human volunteers. A wash out period of 7 days was maintained between the six periods. One subject dropped out in the second period. The remaining 23 volunteers completed all the six periods of the study.

The analytical HPLC method used was validated for selectivity, linearity, sensitivity, accuracy, precision, recovery and stability (including freeze thaw, bench top and in-injector). The chromatograms were processed using class LC 10/VP software and the pharmacokinetic analysis was done using WinNonlin Software Version
1.5 (SCI, USA). Statistical analysis was performed on the pharmacokinetic parameters using SAS software Version 6.12 (SAS Institute Inc., Cary NC, USA).

Under Fasting and Fed Conditions

The Tmax of Cefaclor CD was increased by 100% (low fat diets), 37.5% (high fat diets) and 25% (rice diets) when compared against fasting state.

A significant increase in Cmax was observed as compared to fasting state with rice (52%), low fat vegetarian (33%) and high fat non vegetarian (29%) diets. The increase with high fat vegetarian (12.5%) and low fat non vegetarian (7%) diets was not statistically significant.

A considerable increase in AUC(0 to t) and AUC(0 to inf.) as compared to fasting state was observed with high fat non vegetarian and low fat vegetarian diets. The increase in the case of high fat non vegetarian was statistically significant (P<0.05) while the increase marginally failed to reach the significance level (0.05<P<0.1). The increase with other treatments as compared to fasting was not statistically significant.

Comparative Effect of Source (Vegetarian or Non Vegetarian) of Diet (Breakfast)

Low fat vegetarian diet produced a statistically significant increase in Cmax (371.12%) as compared to low fat non vegetarian diet. The increase in AUC(0 to t) (196.91%) and AUC(0 to inf.) (120.52%) were not statistically significant.

Comparative Effect of High and Low Fat Diets (Breakfasts)

High fat non vegetarian diet produced a statistically significant increase in Cmax (319.11%) as compared to low fat non vegetarian diet, but the increase in AUC(0 to t) (285.67%) just failed to reach the significance level (0.05<P<0.1), and the increase in AUC(0 to inf.) (146.41%) was not statistically significant.
High fat vegetarian diet produced an unexpected but not statistically significant decrease in Cmax (-61.91%) and AUC \(_{(0 \text{ to } \infty)}\) (-9.03%) as compared to low fat vegetarian diet and a negligible increase in AUC\(_{(0 \text{ to } t)}\) (2.93%).

**Comparative Effect of Wheat based and Rice based diets (breakfasts)**

Rice diet produced an increase in Cmax (57.85%) and a decrease in AUC\(_{(0 \text{ to } t)}\) (-22.8%) and AUC\(_{(0 \text{ to } \infty)}\) (-45.35%) produced as compared to low fat vegetarian diet. The differences were not statistically significant.

**PHARMACOKINETIC - PHARMACODYNAMIC ANALYSIS**

A marked increase in the time above MIC\(_{90}\) (8 \(\mu\)g/mL) for low fat vegetarian diet (41.6%), high fat non vegetarian diet (35.2%), high fat vegetarian diet (34.5%) and rice diet (33.7%) as compared to fasting state was observed. The increase with low fat non vegetarian diet (14.7%) was marginal.

Based by the FDA Bioequivalence guidelines, Cefaclor CD exhibits best food effect with high fat non vegetarian diet. However, what actually matters is determining is the clinical efficacy of the antibiotic Cefaclor, i.e., the maximum time the drug level is above the MIC\(_{90}\). Hence, according to the latter end point the best diet (breakfast) to be taken along with Cefaclor CD would be low fat vegetarian. The significance of the results in the Indian population has been discussed.

This study was not designed to investigate the mechanism(s) of Cefaclor CD – food interaction. The possible mechanisms have been discussed. Further work is warranted to confirm it.


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