Abstract: Bioavailability studies with single oral doses of omeprazole 20 mg (enteric coated formulation) and felodipine 10 mg (extended release formulation) were performed in Indian volunteers to confirm that adequate plasma concentrations are obtained in Indian subjects. Plasma samples were analysed by chromatographic methods. The AUCs of omeprazole were about 3 fold higher and those of felodipine 2 fold higher than AUCs reported in Western subjects. This has no toxicological implications with respect to omeprazole, but whether lower dose of omeprazole may be sufficient in Indian patients with acid related diseases would require acid inhibition studies. In the case of felodipine the higher AUCs in Indian subjects suggest a need for a lower strength formulation (2.5 mg) to fine-titrate the dosage to obtain optimal antihypertensive effects with minimal adverse effects.

Key words: ethnic differences, omeprazole, bioavailability, felodipine

INTRODUCTION

Omeprazole, a substituted benzimidazole has been shown to suppress gastric acid secretion by inhibiting the H+K+ATPase in the parietal cell. To overcome its susceptibility to degradation at low pH, an acid resistant formulation of omeprazole has been developed. This formulation which has been used in clinical evaluations of omeprazole, consists of enteric coated (EC) granules (1).

Felodipine is a vascular selective calcium antagonist of the dihydropyridine class used in the treatment of hypertension. In order to obtain sustained plasma levels of felodipine in the antihypertensive range on once daily dosing, felodipine has been formulated as an extended release (ER) preparation based on the gel matrix principle of drug release (2).

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Oral bioavailability studies with the above formulations were undertaken to confirm that adequate plasma concentrations are obtained in Indian subjects.

METHODS

The study was performed in healthy Indian volunteers (10 subjects for omeprazole and 8 for felodipine) who were chosen according to the following criteria of inclusion and exclusion: age between 18-40 years, bodyweight between 50-70 kg, no significant abnormality in the physical examination and laboratory screen, no significant clinical illness in the past two weeks, no investigational drug administered in the past two weeks, no need for any concurrent medication, no history of allergy, cardiac, renal or gastrointestinal disease that could modify the absorption of the study drugs, no history of
abuse of alcohol or other drugs. All subjects gave written consent to participate in the study after being informed about the purpose and attendant risks. The protocols were approved by the Ethics Committee of St. John's Medical College, Bangalore.

Alcohol, tobacco and all medication including 'over the counter' drugs were not permitted from 2 days prior to and during the study period. Standardised snacks were served 3.5 hr after intake of study medication. Care was taken to exclude flavinoid containing foods which are known to enhance the absorption of felodipine (3).

After an overnight fast, subjects were administered a hard gelatin capsule of 20 mg of enteric coated granules of omeprazole (LOSEC Astra) or one extended release (ER) tablet containing 10 mg of felodipine (PLENDIL Astra) with a glass of water. Blood samples (7 ml) were drawn before drug administration and at various time points in the next 24 hr in heparinised tubes. Plasma was separated and stored at –20°C until analysis. The analysis of plasma samples were performed at the Department of Bioanalytical Chemistry of AB Hassle, Sweden. Omeprazole content was analysed according to the method of Lagerstrom and Persson using high pressure liquid chromatography (4). The minimum determinable omeprazole concentration by this method is 20 nmol/l; the separation of the parent drug from its metabolites is adequate and the recovery is over 95%.

Felodipine was assayed according to the procedure of Ahnoff et al (5, 6) using gas chromatography. The minimum felodipine concentration detectable by this method is 1 nmol/ml, and the recovery above 98%.

The area under the plasma concentration – time curve (AUC) was determined by the trapezoidal rule from the time of dosing until the last detectable plasma concentration. Time to reach maximal concentration (Tmax) and maximum concentration reached (Cmax) were observed values.

RESULTS

In Table I are given the (mean ± SEM) AUC's, Tmax and Cmax and in Table II the Geometric mean (GM) 90% confidence intervals on GM, mean, maximum and minimum values of AUC, Tmax and Cmax of omeprazole and felodipine. For omeprazole Tmax was achieved in 1-3 hr with a median of 1.75 hr. The median Cmax was 1.17 μmol/L (range 0.469-3.260) and the mean AUC 2.294 μmol/hr/L with 90% confidence intervals of 1.428–3.687.

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Tmax</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole 20 mg</td>
<td>3.065 ± 0.862</td>
<td>1.75 ± 0.24 h</td>
<td>1.294 ± 0.27 μmol/L</td>
</tr>
<tr>
<td>Felodipine ER 10 mg</td>
<td>107.29 ± 12.40</td>
<td>4.88 ± 1.25</td>
<td>8.750 ± 1.11 nmol/hr/L</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM
TABLE II: Geometric mean (GM) 90% confidence intervals Median, maximum and minimum values of AUC, Tmax and Cmax after single oral doses of omeprazole 20 mg (n = 10) and felodipine ER 10 mg (n = 8) in healthy volunteers.

<table>
<thead>
<tr>
<th></th>
<th>Omeprazole</th>
<th>Felodipine</th>
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<tbody>
<tr>
<td></td>
<td>AUC (umol/hr/L)</td>
<td>Tmax (hr)</td>
</tr>
<tr>
<td>Geometric Mean (GM)</td>
<td>2.294</td>
<td>1.60</td>
</tr>
<tr>
<td>90% confidence intervals on GM</td>
<td>1.428-7.64</td>
<td>1.24-15.45</td>
</tr>
<tr>
<td>Median</td>
<td>2.302</td>
<td>1.75</td>
</tr>
<tr>
<td>Maximum</td>
<td>10.267</td>
<td>3.00</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.739</td>
<td>1.00</td>
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</table>

For felodipine Tmax was achieved in 1-10 hr with a median of 4 hr. The median Cmax was 9.2 nmol/L (range 4.30-13.00) and the mean AUC 103.00 nmol/hr/L with 90% confidence intervals of 84.61-125.50.

DISCUSSION

In Western subjects, the (mean ± SEM) AUCs obtained after a single 20 mg dose of omeprazole have been reported to be 1.022 ± 0.138 umol/L (7) and 1.10 ± 0.033 umol/hr/l (8). The (mean ± SEM) AUC in Indian subjects with the same dose of omeprazole used in the present study was 3.065 ± 0.862 umol/hr/l, i.e. about 3 fold higher than in Western subjects.

All available evidence suggests that high AUCs of omeprazole observed in this study are devoid of toxicological significance. Omeprazole has a high margin of safety due to specific action at a localised target site. The proton pump (H-K+ ATPase enzyme) is unique to the parietal cell and has not been found in any other organ/tissue in the body. The drug is pharmacologically inactive at physiological pH and the active form is generated at the target site. Omeprazole has a short half life (about 1 hr) and in this respect, free from the tendency to accumulate. The difference between the toxic dose of omeprazole in animal experiments (12000 m.mol/kg/day) and the therapeutic dose in man (0.3 to 0.6 m.mol/kg/day) is several thousand fold. In Zollinger Ellison syndrome omeprazole has been well tolerated at doses 16 times as high (320 mg/kg) as the standard daily dose of 20 mg per day used in duodenal ulcer. It may therefore be inferred that the higher AUCs of omeprazole observed in Indian volunteers has no toxicological implications. Acid inhibition studies would however, be required to address the question of whether lower doses would be adequate, since clinically adequate plasma omeprazole AUC's are attained in Indian subjects after oral administration of the standard daily dose of 20 mg.

The AUCs of felodipine in Indian subjects (mean ± SEM) 107.29 ± 12.40 nmol/l are about twice as higher than the AUC of 60.00 ± 21.00 nmol/hr reported in Western subjects by Harris (9). Most of the clinically observed side effects of felodipine are pharmacodynamic in nature, and would be plasma concentration dependent. Thus the higher felodipine concentrations observed in Indian subjects could be clinically important. A 2.5 mg of felodipine ER has been shown to produce an antihypertensive effect significantly greater than that of placebo (10). A formulation of felodipine ER 2.5 mg may be useful in fine titrating felodipine dosage in Indian hypertensives especially in hypertensives with cardiac failure, hepatic impairment or advanced age in whom plasma concentrations after felodipine tend to be high (2).

In conclusion, therapeutically adequate plasma concentration of omeprazole and felodipine are obtained in Indian volunteers with the formulations tested. The AUC is taken
to reflect the amount of drug that is absorbed. The higher AUCs of both omeprazole and felodipine in Indians compared to Western subjects may indicate great interindividual variations in absorption or in drug metabolism due to the ethnic variability of the Indian subjects. This is without toxicological implications for omeprazole; however a formulation incorporating a lower strength of felodipine seems desirable in our country for fine titration of dosage in individual hypertensive.

REFERENCES