Pharmacokinetics of tenidap sodium administered with food or antacid in healthy volunteers

P. E. COATES1 & R. MESURE2
1Early Clinical Research Group, Pfizer Central Research, Ramsgate Road, Sandwich, Kent CT13 9NJ, UK and
2Clinique St Remi, 29 Rue Vandernoot, B-1020, Brussels, Belgium

1 The effects of food and antacid on the pharmacokinetics of tenidap were investigated in this randomised, 3-way cross-over study.
2 Twenty-one healthy young men, mean age 27.4 years, received single oral doses of tenidap sodium 120 mg at weekly intervals after either an overnight fast, with food or with 20 ml of the antacid Maalox® (aluminium hydroxide 1.8 g and magnesium hydroxide 1.2 g). Plasma samples collected immediately before and up to 96 h after each tenidap dose were assayed for tenidap using a validated h.p.l.c. method. The assay data were used to determine the pharmacokinetic parameters of tenidap in each group.
3 Co-administration of tenidap with food produced a statistically significant delay in the rate of absorption ($t_{\text{max}}$, 4.4 h) ($P < 0.001$). There was no statistically significant change in $C_{\text{max}}$. However, co-administration with the antacid significantly decreased both the mean rate and extent of absorption of tenidap compared with the fasting state: AUC, 420.93 μg ml⁻¹ h (antacid), 476.31 μg ml⁻¹ h (fasting) ($P = 0.026$); $C_{\text{max}}$ 14.3 μg ml⁻¹ (antacid), 18.0 μg ml⁻¹ (fasting) ($P = 0.001$); $t_{\text{max}}$ 4.5 h (antacid), 2.9 h (fasting) ($P < 0.001$). Neither food nor the antacid had any effect on the elimination of tenidap. These changes in $t_{\text{max}}$ are unlikely to be of any clinical significance owing to the long half-life of tenidap.
4 Treatment was well tolerated. Only two adverse events were reported that were considered by the investigator to be related to tenidap. There were no reports of laboratory or cardiovascular abnormalities.
5 The reduced rate of absorption with food is probably a consequence of delayed stomach emptying, whereas the reduced extent of absorption with antacid (11%) probably results from adsorption. These reductions are unlikely to be of clinical significance.

Keywords tenidap sodium antacid food pharmacokinetics bioavailability

Introduction

Tenidap sodium is a novel anti-rheumatic drug, currently undergoing clinical trials for the treatment of rheumatoid arthritis (RA) and osteoarthritis. In a placebo-controlled study, tenidap at a daily dose of 120 mg has displayed efficacy in the treatment of RA [1]. Tenidap, unlike non-steroidal anti-inflammatory drugs (NSAIDs), has also been found to modulate the production of cytokines, particularly interleukin-6, interleukin-1 and tumour necrosis factor [2]. Like NSAIDs, however, tenidap inhibits the enzyme cyclo-oxygenase [3].

In RA patients, tenidap 120 mg day⁻¹ also induces a significant, rapid and sustained reduction in the serum concentrations of the acute phase proteins, C-reactive protein (CRP) and serum amyloid A, and reduces erythrocyte sedimentation rate [4]. The observed reduction in serum CRP concentration has been linked with the modulation of cytokines [4]. Tenidap is a highly protein-bound, low clearance compound which attains steady-state plasma concentrations by the eleventh daily dose [5]. It was necessary to determine whether food would affect the bioavailability of tenidap, and
thus have an impact on either the time taken to reach steady-state or the final plasma tenidap concentration. Many anti-rheumatic drugs are known to have gastrointestinal side effects; consequently it is important to know whether co-administration of an antacid to control these effects will have any effect on the pharmacodynamics of the therapeutic agent.

The aim of the present study, therefore, was to compare the pharmacokinetics of single oral doses of tenidap 120 mg given to healthy young men after fasting, with food and with a combination aluminium hydroxide/magnesium hydroxide antacid, Maalox®.

Methods

Subjects

Healthy males, aged between 21 and 45 years were eligible for entry into the study. They were to be within the weight range 60–90 kg, and be within 15% of their ideal weight for age and height. Subjects were excluded if they presented with any of the following: evidence or history of haematological, renal, endocrinological, pulmonary, gastrointestinal, cardiovascular, hepatic, or neurological disease; allergy: any condition possibly affecting drug absorption; intolerance to NSAIDs or antacids; or alcohol or drug dependence. All subjects underwent routine laboratory tests at screening and throughout the study. Additionally, a 12-lead ECG was performed at screening, and again at the end of the study. Blood pressure and pulse rate were recorded at screening and on treatment days. Concomitant medication was not permitted during the study and before the study began subjects were not permitted to take prescription, over-the-counter, or recreational drugs for at least 2 weeks, or investigational drugs for at least 8 weeks. The study was approved by the Independent Ethics Committee of the Clinique St Remi and conducted in accordance with the Declaration of Helsinki (1964) and the Tokyo (1975) and Venice (1983) revisions. All subjects gave written, informed consent.

Protocol

This was an open, single-centre, randomised, three-way crossover study. Subjects were randomised to receive one of the following treatments, separated by 7 days: a single oral dose of one capsule of 120 mg tenidap (as tenidap sodium) on three occasions after either a 12 h overnight fast, within 30 min of eating a standard breakfast of milk, bread, butter, bacon, two fried eggs and coffee, or within 30 min of receiving a 20 ml dose of the antacid, Maalox® (aluminium hydroxide 1.8 g and magnesium hydroxide 1.2 g) after an overnight fast. Subjects were not permitted to lie down, smoke, drink caffeinated beverages or eat any food for 4 h immediately after each tenidap dose.

Pharmacokinetic assessments

Tenidap plasma concentrations were determined from plasma prepared from blood collected immediately before, and 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72 and 96 h after each tenidap dose. The samples were stored at -20 °C and were assayed for tenidap using h.p.l.c. with a calibration range of 0.5–30 μg ml⁻¹ and u.v. detection at 365 nm [6].

The following parameters were estimated from the individual plasma tenidap concentration-time curves: Cmax, maximum plasma tenidap concentration; tmax, time to first occurrence of Cmax; λz, terminal phase rate constant calculated by linear regression of those data points visually assessed to be on the terminal log-linear phase; t½, mean terminal half-life calculated by In2/mean λz; AUC(0,τ), area under the curve from immediately pre-dose to the time of the last detectable concentration (τ), calculated using the trapezoidal rule; and AUC, area under the curve between zero and infinity, calculated as AUC(0,τ) + C/λz for extrapolation to infinity, where C, is the last measured plasma concentration.

Statistical evaluation

The derived pharmacokinetic parameters were subjected to parametric analyses of variance (ANOVA) appropriate to the three-way cross-over design. Standard diagnostic plots were produced in order to examine the appropriateness of the model used. The SAS statistical package was used to calculate the Tukey 90% confidence limits and Genstat® was used for all other calculations. Due to the imbalance of sequences, the means were adjusted according to the level of contribution from each sequence.

Results

A total of 21 men were enrolled into the study and all successfully completed it. Demographic data are shown in Table 1. The following deviations from the protocol occurred but were not considered to have a substantial impact on the results and, therefore, did not cause any subject to be excluded from the analyses. Two subjects presented with marginal eosinophilia (8.6% and 6.6%), two had ECG abnormalities which were considered not to be clinically significant, one had a history of reaction to dextropropoxyphene and

Table 1. Baseline characteristics of healthy male volunteers treated with 120 mg day⁻¹ tenidap sodium after food, antacid or fasting

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects (all male)</td>
<td>21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.4</td>
</tr>
<tr>
<td>Mean</td>
<td>21–43</td>
</tr>
<tr>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.1</td>
</tr>
<tr>
<td>Mean</td>
<td>60.0–81.7</td>
</tr>
<tr>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>14</td>
</tr>
<tr>
<td>Oriental</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 2 Summary of mean pharmacokinetic values for healthy volunteers treated with a single dose of 120 mg day\(^{-1}\) tenidap after food or antacid or fasting

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Fasting</th>
<th>With food</th>
<th>With antacid</th>
<th>Fed-fasting</th>
<th>90% confidence limits</th>
<th>Antacid-fasting</th>
<th>90% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(^{\circ}) (µg ml(^{-1}) h(^{-1}))</td>
<td>473</td>
<td>466</td>
<td>424(^{\circ})</td>
<td>-10.90</td>
<td>-70.25, 48.45</td>
<td>-55.37</td>
<td>-116.11, 5.36</td>
</tr>
<tr>
<td>C(_{\text{max}}) (µg ml(^{-1}))</td>
<td>18.0</td>
<td>18.3</td>
<td>14.3(^{\circ})</td>
<td>0.4052</td>
<td>-1.94, 2.75</td>
<td>-3.4376</td>
<td>-5.78, -1.09</td>
</tr>
<tr>
<td>t(_{\text{max}}) (h)</td>
<td>2.9</td>
<td>4.4(^{\circ})</td>
<td>4.5</td>
<td>1.5714</td>
<td>0.41, 2.73</td>
<td>1.4762</td>
<td>0.66, 2.291</td>
</tr>
<tr>
<td>λ(_{1}) (h(^{-1}))</td>
<td>0.0320</td>
<td>0.0322</td>
<td>0.0332</td>
<td>0.000130</td>
<td>-0.005, 0.004</td>
<td>0.001270</td>
<td>-0.005, 0.004</td>
</tr>
<tr>
<td>t(_{1/2}) (h)</td>
<td>21.7</td>
<td>21.7</td>
<td>21.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{\circ}\)Adjusted means. \(^{\circ}\)Significantly different from fasting and with food \(P = 0.026\). \(^{\circ}\)Significantly different from fasting and with food \(P = 0.001\). \(^{\circ}\)Significantly different from fasting \(P < 0.001\). P values based on the overall F-test between the three treatments.

ibuprofen, and one subject used a hexetidine gargle for pharyngitis during the antacid treatment period. Moderate and increasingly severe stomatitis and gingivitis occurred in one subject 5 days after the second (fasting) tenidap dose, which progressed to oral candidiasis 8 days later when miconazole was prescribed. Another subject experienced mild abdominal pain following the first (antacid) tenidap dose which resolved after 1 h. The adverse events reported in these two subjects were considered to be treatment related. None of these events required withdrawal from the study. No clinically significant laboratory abnormalities or changes in ECG, blood pressure or pulse rate were reported.

The terminal log-linear phases were not well-defined for three subjects after fasting, for four subjects after food intake and for four subjects after taking antacid; therefore, AUC and λ\(_{1}\) could not be calculated for these subjects and the mean pharmacokinetic parameters were adjusted. The mean pharmacokinetic data are shown in Table 2.

When tenidap was administered with antacid, the mean values for both AUC and C\(_{\text{max}}\) were significantly lower when compared with the mean values for both the fasting and fed groups \((P = 0.026\) for AUC and \(P = 0.001\) for C\(_{\text{max}}\)). In the presence of either antacid or food, t\(_{\text{max}}\) was significantly higher compared with the fasting state \((P < 0.001\) in both cases). No other significant differences in pharmacokinetic parameters were observed and there was no evidence of any treatment carryover effects or order of treatment interaction.

Discussion

The present study was designed to compare the effects of fasting, food and antacids on the pharmacokinetics of single oral doses of tenidap 120 mg. The results indicate that co-administration of the antacid (Maalox\(^{\circ}\)) delayed absorption, as reflected by the increase in t\(_{\text{max}}\) compared with the fasting group. There was also a significant decrease in AUC in the antacid group, indicating a corresponding decrease in amount absorbed.

The presence of food was also found to result in a significant delay in the absorption of tenidap. This was probably a result of delayed stomach emptying, as there was no significant effect on either C\(_{\text{max}}\) or AUC, although there was a significant delay in t\(_{\text{max}}\) compared with the fasting group.

Neither food nor the antacid were found to have an effect on tenidap elimination.

The clinical implications of the decrease in bioavailability of tenidap induced by antacid co-administration are unlikely to be profound. As the presence of food did not alter tenidap bioavailability, even though it did delay absorption, it is unlikely that tenidap administration with, or shortly after, food would have clinical implications.

References

5 Gardner M. The pharmacokinetics of tenidap following single and multiple 120 mg doses to healthy, male volunteers. Clin Pharmac Ther 1993; 53: 211.