Cimetidine does not alter the clearance or plasma binding of tenidap in healthy male volunteers

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1 An open-label, placebo-controlled study was conducted to examine the effect of cimetidine on the steady-state pharmacokinetics of tenidap.

2 Twenty-four healthy volunteers received tenidap sodium (120 mg) each morning throughout the study. On day 14 plasma levels of tenidap had reached steady state; half of the subjects were treated concomitantly with cimetidine 800 mg at night, while the other half received placebo. Allocation of cimetidine or placebo was randomised. Plasma profiles of tenidap were measured on days 14 and 16.

3 The addition of cimetidine did not significantly affect the \( C_{\text{max}} \), \( t_{\text{max}} \), or \( \lambda_z \) of tenidap. The AUC(0,24h) increased by 4% between days 14 and 16 in the cimetidine treatment group, compared with a decrease of 2% in the placebo group. This small difference is statistically significant (\( P = 0.047 \)), but it is not considered to be clinically relevant.

4 It is concluded that concomitant administration of cimetidine does not significantly affect the pharmacokinetics of tenidap at steady state.

Keywords tenidap sodium cimetidine interaction pharmacokinetics

Introduction

Tenidap sodium is a novel cytokine-modulating, anti-rheumatic agent which is currently undergoing clinical evaluation in the USA and Europe for the treatment of rheumatoid arthritis (RA) and osteo-arthritis (OA). Tenidap, unlike non-steroidal anti-inflammatory drugs (NSAIDs), inhibits the synthesis of interleukins (IL) 1 and 6 and tumour necrosis factor (TNF) [1, 2]. It has also been shown to inhibit cyclo-oxygenase [3].

The release of acute phase proteins from the liver has been shown to be mediated by TNF, IL-1 and IL-6 [4]. The rat adjuvant arthritis model showed tenidap to dampen the acute phase response and relieve the symptoms of arthritis [5]. In vitro studies have shown that tenidap suppresses IL-1-induced proteoglycan loss from cartilage [6, 7]. It has also been demonstrated that tenidap lowers the amount of C-reactive protein (CRP) in patients with RA [8, 9].

Tenidap is more effective than standard NSAIDs, such as piroxicam, naproxen and diclofenac in the treatment of RA, and more effective than the NSAID/disease-modifying anti-rheumatic drug (DMARD) combinations of auranofin plus diclofenac and hydroxychloroquine plus piroxicam [10–13]. These studies also indicate that tenidap decreases the acute phase response: significant reductions in erythrocyte sedimentation rate (ESR) and levels of CRP and serum amyloid protein (SAA) have been associated with tenidap treatment.

Treatment with tenidap can cause gastrointestinal effects, the incidence being similar to that with NSAID treatment. These symptoms are often controlled with cimetidine, a drug which binds to the cytochrome P450 isozyme thereby inhibiting the breakdown of other drugs metabolised by this system. Although it is not known whether tenidap is metabolised by this system, medication with tenidap is likely to be long-term and it is probable that some patients will be treated concomitantly with cimetidine. It is therefore essential to investigate whether there is any pharmacokinetic interaction between steady-state tenidap and cimetidine.

Methods

Subjects

Healthy male volunteers aged 18–45 years were enrolled in this double-blind, placebo-controlled
study. Volunteers were to weigh between 61 and 91 kg, and to be within 10% of normal weight for age and height. General medical examination and laboratory tests were carried out prior to the study to exclude significant illness, allergies, drug or alcohol dependence, or conditions which may affect absorption or metabolism of the study drugs. No medication other than the study drugs was permitted for 2 weeks prior to or during the study. The study was approved by the Research Consultants’ Review Committee, Austin, Texas, and all volunteers gave written, informed consent before taking part.

Protocol

All subjects received tenidap sodium 120 mg (as 3 × 40 mg capsules), orally, each morning from day 1 to day 16. Cimetidine 800 mg or matching placebo was administered orally once daily at bedtime from day 14 to day 20. On days 14 and 16, subjects remained in the clinical research unit overnight for 12 h before and 24 h after tenidap administration while blood samples were collected.

Pharmacokinetic assessments

Plasma was prepared from individual blood samples collected on days 12, 13 and 14 to ascertain that tenidap had reached steady state. Plasma was frozen at −20°C until analysis of 50 μl aliquots by h.p.l.c. with u.v. detections at 360 nm [14]. The assay had a dynamic range of 0.1–40 μg ml⁻¹.

Pharmacokinetic parameters

From the individual plasma concentration-time curves obtained on days 14 and 16 the following pharmacokinetic parameters were calculated: the area under the plasma concentration curve from time zero to 24 h post-dose (AUC(0,24h)), estimated using linear trapezoidal approximation; the maximum observed plasma concentration (Cmax); the terminal phase rate constant λz, estimated from day 16 measurements only, using least squares regression analysis of the plasma concentration-time curve obtained during the terminal log-linear phase; and the half-life (t1/2), calculated as 0.693/λz.

Statistical analysis

Power calculations demonstrated that 12 subjects were required in each treatment group in order that a 30% difference between the AUC(0,24h) between groups could be detected with 80% power at a 5% level of significance.

Mean pharmacokinetic parameters were calculated for each treatment group. Differences in each of the parameters between days 14 (baseline) and 16 within each treatment group were compared between groups using the two-sample t-test, and 95% confidence intervals were calculated.

Results

The demographic characteristics of the two treatment groups were similar (Table 1) and all 24 enrolled volunteers completed the study. There were several minor protocol deviations, but none was considered sufficiently serious to warrant withdrawal from the study or to affect the final results.

Pharmacokinetic results

Tenidap plasma concentrations at days 12, 13 and 14 confirmed that steady state had been attained prior to the initiation of concomitant treatment with cimetidine or placebo (data not shown). The mean pharmacokinetic parameters of tenidap during concomitant treatment and differences between the cimetidine and placebo groups in the day 14 (baseline) and day 16 values are shown in Table 2.

The AUC(0,24h) increased by 14.4 μg ml⁻¹ h (4%) in the cimetidine group when compared with the 6.0 μg ml⁻¹ h (−2%) decrease in the placebo group, and this difference was found to be statistically significant ($P = 0.047$).

In the cimetidine-treated group $C_{\text{max}}$ increased by 1.7 μg ml⁻¹, a non-statistically significant increase of 7% from baseline compared with placebo. There was a slight decrease from 3.0 h to 2.2 h in the mean $t_{\text{max}}$ of tenidap in the cimetidine group. Again, this was not considered statistically significant compared with the zero change observed in the placebo group.

Values for the elimination constant ($\lambda_z$) and $t_{1/2}$ for tenidap are also shown in Table 2. These data are derived from day 16 alone. Mean $\lambda_z$ values for the two groups were also compared using a two-sample t-test and a 95% confidence interval. Neither parameter showed a statistically significant difference between the two groups.

Adverse events

Tenidap was well tolerated during the 20 days of continuous administration and there were no drug-related
Table 2 Mean pharmacokinetic profile of steady state tenidap (days 14 and 16) on concomitant treatment with cimetidine or matching placebo and comparison between groups

| Parameter          | Day 16-day 14 | Tenidap + cimetidine | Tenidap + placebo | Day 16-day 14 difference | P value | 95% CI  
|--------------------|---------------|----------------------|-------------------|--------------------------|---------|--------
| AUC(0,24h)         | 14            | 342.8                | 364.8             | −6.0                     | 20.4    | 0.047  
| (µg ml⁻¹ h)       | 16            | 357.2                | 358.8             | 0                        | −0.8    | NS     
| Cₘₐₓ (µg ml⁻¹)    | 14            | 25.8                 | 26.8              | 0                        | 1.8     | NS     
| tₘₐₓ (h)          | 14            | 3.0                  | 2.8               | 0                        | −0.8    | NS     
| λ₁ (h⁻¹)          | 16            | 0.0257               | 0.0301            | NS                       | (−0.0096, 0.0007) | NS     
| t½a,b (h)         | 16            | 27.0                 | 23.0              | NS                       |         | NS     

a λ₁ and t½a,b values were only determined on day 16 of the study, so the day 16 - day 14 differences and differences in these changes between groups, are not shown.
b Mean t½a,b estimated as 0.693/mean λ₁.

adverse effects considered to warrant withdrawal. Several subjects had minor laboratory abnormalities prior to the study, and three reported abnormally dark-coloured urine during the study. One subject developed enlarged lymph nodes (unrelated to treatment). There were no abnormalities or changes in blood pressure, pulse rate or ECG, and no subject complained of adverse effects.

Discussion

This open, randomised, parallel-group study involving 24 healthy volunteers evaluated the effects of multiple dose cimetidine administration on the pharmacokinetics of tenidap sodium at steady state. Results from this study indicate that there is a marginal increase in the AUC(0,24h) value in the cimetidine group which, although statistically significant, is not considered to be clinically relevant. Of the other pharmacokinetic parameters measured none showed any statistically significant differences between the tenidap plus placebo and tenidap plus cimetidine groups, and tenidap was well tolerated.

Cimetidine, which is commonly used to control the gastrointestinal side-effects of anti-rheumatic agents is known to bind to various isozymes of cytochrome P450 [15]. This can potentially inhibit the breakdown of drugs metabolised by this system. For example, cimetidine has been shown to modify the oxidation metabolism of sulindac [16] but not paracetamol [17]. Pharmacokinetic interactions between cimetidine and anti-rheumatic drugs have also been demonstrated; administration of cimetidine and sulindac results in a significant reduction in sulindac clearance. This suggests that H2-receptor antagonists may decrease the volume of distribution of NSAIDs [16, 18]. Cimetidine can also influence the hepatic elimination of salicylates [19]. However, there is no effect of cimetidine on the pharmacokinetics of piroxicam [20].

It can be concluded from the present data that, in healthy male volunteers, multiple doses of cimetidine 800 mg day⁻¹ do not interact with tenidap at a dose of 120 mg day⁻¹ at steady state.

References

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