Effect of tenidap sodium on digoxin pharmacokinetics in healthy young men

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- 1 The effects of tenidap sodium and placebo on digoxin pharmacokinetics were compared in 14 healthy young men, in a double-blind, parallel-group study lasting for 24 days.
- 2 Subjects were administered digoxin alone for the first 10 days and digoxin plus tenidap 120 mg day⁻¹ or placebo for the remaining 14 days.
- 3 Changes in the means between day 10 (digoxin monotherapy) and day 24 (combined therapy) for renal clearance, area under the plasma concentration-time curve during the dosing interval, and the minimum and maximum plasma digoxin concentrations did not differ significantly between the tenidap and placebo groups. There was a small but statistically significant increase (0.5 h) in the time taken to reach maximum plasma digoxin concentration following 14 days' continuous tenidap co-administration compared with placebo, but this was not considered to be clinically meaningful.
- 4 Co-administration of tenidap and digoxin was well tolerated. No subject withdrew from the study during combination treatment. Treatment-related adverse events were of mild to moderate severity and were reported by four subjects on digoxin monotherapy, four on tenidap and digoxin, and by two on digoxin and placebo. Those reported by the tenidap group predominantly affected the gastrointestinal system and were mild in severity. There were no reports of laboratory test abnormalities or cardiovascular abnormalities related to combined digoxin and tenidap administration.
- 5 The results of this study indicate that, in healthy young men, co-administration of tenidap with digoxin does not have any apparent clinically significant effects on the pharmacokinetic profile of digoxin, and the treatment is well tolerated.

Keywords tenidap digoxin interaction pharmacokinetics healthy volunteers

Introduction

Tenidap sodium is a novel anti-rheumatic agent which has been found to be effective and well tolerated in the treatment of rheumatoid arthritis (RA) [1]. Like non-steroidal anti-inflammatory drugs (NSAIDs) *in vitro*, tenidap has been shown to inhibit prostaglandin synthesis through inhibition of cyclooxygenase [2]; however, tenidap can be differentiated from NSAIDs by its ability to modulate human peripheral blood monocyte production of the cytokines, interleukin-1 (IL-1), tumour necrosis factor and, particularly, interleukin-6 (IL-6) [3]. Tenidap has also been found to

reduce significantly the level of IL-1 in synovial fluid in RA patients with previously elevated levels [4]. In a placebo-controlled study involving RA patients, tenidap 120 mg day⁻¹ but not naproxen 1000 mg day⁻¹ was found to decrease rapidly, persistently and significantly the plasma concentrations of the acute phase protein, C-reactive protein (CRP) [5]. This finding is consistent with the *in vitro* effects of tenidap on cytokine production: a correlation between CRP levels and IL-6 activity has been reported [6] and the cytokines, particularly IL-6, have been found to

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mediate the release of acute phase proteins [7]. Tenidap 120 mg attains steady-state plasma concentration after 11 daily doses and is highly protein-bound [8].

Digoxin is extensively prescribed in elderly patients for the treatment of atrial fibrillation and is still used for the treatment of heart failure. It is excreted mainly unchanged in the urine, excretion being directly proportional to glomerular filtration rate. Co-administration of any drug which significantly alters the pharmacokinetic profile of digoxin could lead to digoxin toxicity or sub-therapeutic digoxin plasma levels, with profound clinical consequences. As digoxin and anti-rheumatics are extensively co-prescribed, particularly in the elderly, this potential interaction is of particular importance. The aim of this study was to investigate the pharmacokinetic interaction between tenidap sodium 120 mg day⁻¹ at steady state and digoxin 0.25 mg day⁻¹ in healthy young men.

Methods

Subjects

Healthy men aged 18–45 years were eligible for entry into this single-centre, double-blind, placebo-controlled study approved by the Simbec Independent Ethics Committee. Written, informed consent was required from each subject in order to take part. At screening, all subjects underwent questioning and a full medical, haematological and biochemical examination, to establish that they had no evidence or history of disease, allergic condition, or known hypersensitivity to drugs. A 12-lead electrocardiogram (ECG) and a 24 h Holter ECG were performed to ensure that no subject had an arrhythmia or a conduction defect. The ECG was performed on several occasions throughout the study prior to the morning dose of medication, on day 25 (after completion of digoxin and tenidap therapies) and at the follow-up visit 2 weeks after the final dose. Subjects were required to have a resting heart rate of 50–90 beats min⁻¹. Blood pressure was recorded at screening, on days 1, 5, 10, 11, 15, 19 and 24 prior to the morning dose of study medication, as well as on day 25 and at follow-up. Sitting pulse rate was measured in duplicate following a 5 min rest, prior to receiving the study medication each day. In addition, a two-lead rhythm strip was recorded 1 h after digoxin administration on days 11–24. Any abnormal results were monitored until they returned to normal or study entry values, or a clinical diagnosis of intercurrent illness was confirmed.

Subjects were excluded if they had taken over-the-counter or prescribed medication in the 2 weeks prior to the study, or experimental drugs in the 3 months prior to entry. Further exclusion criteria were smoking more than five cigarettes per day, evidence of drug abuse and consumption of more than 14 units of alcohol per week.

Protocol

Oral digoxin (Lanoxin®, Wellcome, 0.25 mg tablets) was administered from days 1 to 24 starting with a loading dose of 1.0 mg on day 1, followed by 0.5 mg on day 2 and continuing with 0.25 mg once daily until day 24. On days 11–24, in addition to digoxin treatment, subjects were randomised to receive single daily oral doses of either tenidap sodium 120 mg or matching placebo. All drugs were administered in the research unit, and subjects stayed in the research unit overnight on days 9–11 and 23–25.

Pharmacokinetic assessments

On days 10 and 24, blood samples were collected 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 8, 12, 16 and 24 h after digoxin administration. Enough blood was collected to prepare 5 ml plasma for assay of plasma digoxin concentrations. Plasma samples were frozen in two aliquots within 20 min of blood collection. On days 10 and 24, complete urine collections were made. The total volume was measured and two 10 ml aliquots were taken, one for measurement of creatinine and one for measurement of digoxin. Trough plasma digoxin concentrations were measured using blood samples taken immediately prior to digoxin administration on days 8–24 and the results were reviewed immediately prior to the next day's dose of digoxin. A trough plasma digoxin concentration ≥ 2.5 ng ml⁻¹ was considered toxic. Plasma and urine samples were analysed for digoxin at L.A.B. (GmbH) Ltd using a validated radioimmunoassay (Amersham Amerlex Digoxin r.i.a. kit, Amersham Buchler GmbH & Co), with detection ranges of 0.058–6.43 nM for plasma, and 8–512 nM for urine.

Digoxin concentration-time curves were produced from which the following pharmacokinetic parameters were estimated: minimum and maximum plasma digoxin concentrations ($C_{\min}$ and $C_{\max}$, respectively), the time taken to reach maximum plasma digoxin concentration ($t_{\max}$) and the area under the plasma digoxin concentration-time curve (AUC(0,24h)). Renal clearance of digoxin (CL_R) was determined by calculating the ratio between the total amount of digoxin excreted in urine over 24 h and the AUC(0,24h).

Statistical analysis

The differences between the day 10 and day 24 means for each pharmacokinetic parameter were compared between treatment groups using a two-sample *t*-test with 95% confidence limits. These analyses were carried out using the SAS statistical package. Graphical examination was undertaken visually to ensure that there were no outlying data points exerting undue influence on the results and to ensure that the assumption of equal variances was met. The study was designed to have sufficient statistical power (80% power to detect a 20% difference in digoxin AUC) if 14 subjects completed.

Table 1 Baseline demographic data of healthy male Caucasian subjects randomised to receive oral digoxin and concomitant oral tenidap 120 mg day⁻¹ or matching placebo

	Tenidap sodium (n = 7)	Placebo (n = 7)
Age (years)		
Range	21–43	22–30
Mean	28.7	26.0
Weight (kg)		
Range	64.7–85.1	56.7–78.5
Mean	74.0	64.8

Results

Subjects

All the 15 male subjects who entered into the study were Caucasian. One subject entered with an ECG showing a PR interval of > 210 ms. This increased to 256 ms on day 9 digoxin treatment and therefore this subject was withdrawn from the study on day 11, having received no concomitant double-blind therapy. The baseline demographic details for the seven subjects in each treatment group who completed the study showed no statistical differences between groups (Table 1).

Pharmacokinetics

The mean pharmacokinetic parameters for digoxin for each treatment group, before and after 14 days of continuous tenidap or placebo administration, are shown in Table 2.

There were no statistically significant differences between treatment groups in the day 24 to day 10 changes in the mean AUC(0,24h), $C_{\min}$, $C_{\max}$ and CL_R within each treatment group. The day 24 minus day 10 difference in mean $t_{\max}$ was significantly greater in the tenidap group (increase by 0.5 h) than in the placebo group (decrease by 6 min) ($P = 0.03$).

There were no reports of digoxin toxicity or abnormalities in either the 12-lead or 24 h Holter ECGs in subjects who completed the study, and no reports of clinically significant changes in mean plasma creatinine concentrations between days 10 and 24. Adverse events, considered by the investigator to be treatment-related were reported by four subjects on digoxin monotherapy, four on combined digoxin and tenidap,

and by two on combined digoxin and placebo. All adverse events were of mild to moderate severity and none led to patient withdrawal.

Discussion

The results of this study demonstrate that co-administration of tenidap sodium 120 mg with digoxin had no significant effect on renal clearance (CL_R) or on any pharmacokinetic parameter of digoxin apart from $t_{\max}$ compared with placebo. The change in $t_{\max}$ was significantly greater after 14 days' continuous co-administration with tenidap (increase of 0.5 h) than after 14 days of placebo (decrease of 6 min). This is unlikely to be clinically significant since it was not accompanied by a significant change in either $C_{\max}$ or steady-state digoxin concentrations.

There were no reports of toxic digoxin plasma concentrations. These findings indicate that tenidap co-administration did not affect digoxin clearance and, therefore, is unlikely to lead to the development of either digoxin toxicity or sub-therapeutic digoxin plasma concentrations. However, care should still be taken in co-administering tenidap and digoxin to the elderly or those with impaired cardiovascular status.

Tenidap was well tolerated. All adverse events were of mild to moderate severity and no subject withdrew from the study while taking combined tenidap and digoxin. The number of subjects experiencing adverse events that were considered by the investigator to be treatment-related was the same during digoxin monotherapy as during combined digoxin and tenidap administration. This suggests that combining tenidap with digoxin does not affect the tolerability of either drug. During combined tenidap and digoxin administration, there were no reports of cardiovascular abnormalities.

Numerous interactions between digoxin and other drugs have been identified. These include changes in digoxin bioavailability (antacid gels, kaolin-pectate, cancer chemotherapeutic agents, antibiotics), steady-state serum levels (anti-arrhythmic drugs such as quinidine) and alterations in renal function (potassium-sparing diuretics) [9]. Interactions between digoxin and currently available antirheumatic treatments have also been reported. The disease-modifying anti-rheumatic drug, cyclosporin, interacts with digoxin with a resultant increase in serum levels and enhanced

Table 2 Mean pharmacokinetic data taken from the plasma digoxin concentration-time curve following concomitant therapy of healthy male Caucasians with digoxin and either 120 mg day⁻¹ tenidap or matching placebo

	Tenidap		Placebo		Between group difference in the day 24–day 10 change	95% confidence limits	P value
	Day 10 (n = 7)	Day 24 (n = 7)	Day 10 (n = 7)	Day 24 (n = 7)			
AUC(0,24h) (nmol l ⁻¹ h)	26.6	26.7	26.2	22.4	3.8	–0.3, 8.0	NS
$C_{\max}$ (nmol l ⁻¹)	3.32	2.91	3.02	2.87	–0.26	–1.17, 0.65	NS
$C_{\min}$ (nmol l ⁻¹)	0.84	0.87	0.83	0.71	0.14	–0.03, 0.31	NS
$t_{\max}$ (h)	0.7	1.2	1.0	0.9	0.6	0.1, 1.2	0.03
CL_R (l h ⁻¹)	7.17	6.38	6.74	6.81	–0.98	–2.02, 0.06	NS

NS: not significant ($P \geq 0.05$).

toxicity [10], whereas sulphasalazine produces a decrease in serum digoxin of approximately 20% [11]. In ambulatory patients during the early stages of ibuprofen therapy, serum digoxin concentrations have been found to increase by more than 30% during the first 7 days of treatment [12]. Although the clinical relevance of this interaction was uncertain, it was considered due, at least in part, to decreased digoxin clearance.

The findings of this study indicate that the co-administration of tenidap and digoxin in healthy young men is safe and well tolerated, and although the results cannot be extrapolated to predict safety in patients treated with these two drugs, it seems unlikely that such a combination would be contraindicated.

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