The effect of tenidap on the anti-hypertensive efficacy of thiazide diuretics in patients treated for mild to moderate hypertension

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- 1 This randomised, placebo-controlled, double-blind, parallel-group study was conducted to assess the effect of tenidap sodium 120 mg, a novel anti-arthritis cytokine modulating drug, on the hypotensive efficacy of the thiazide diuretics hydrochlorothiazide or bendrofluazide.
- 2 Twenty-three male and female patients, aged 41–78 years, with mild to moderate, uncomplicated, essential hypertension controlled with thiazide diuretic therapy, received either a single daily dose of tenidap sodium 120 mg or matched placebo for 22 days in addition to their diuretic therapy. Changes between baseline and endpoint in supine and standing systolic and diastolic pressures and pulse rate were compared between treatment groups.
- 3 Daily treatment with tenidap reduced the anti-hypertensive efficacy of the thiazide diuretics. Blood pressure tended to increase marginally and the increase in mean standing diastolic pressure observed with tenidap was significantly greater than the change in the placebo group. All pressures tended to decrease in the placebo group and all endpoint measurements were within 7 mm Hg of baseline in both groups.
- 4 Treatment-related side effects of mild to moderate severity were reported in two subjects receiving tenidap, but in neither case was treatment discontinued. Two subjects receiving placebo also experienced side effects considered to be treatment-related and both were withdrawn from the study.
- 5 The results of this study suggest that tenidap may be given to patients treated for mild to moderate essential hypertension controlled with thiazide therapy; however, the patient's blood pressure should be regularly monitored.

Keywords tenidap sodium hypertension thiazide diuretic hypotension drug interaction arthritis

Introduction

Co-existing arthritis and hypertension is a common medical problem particularly in mature and elderly patients [1]. Many of these patients receive non-steroidal anti-inflammatory drugs (NSAIDs) for rheumatoid arthritis (RA) or osteoarthritis as well as an anti-hypertensive regimen. It is estimated that, in the United States alone, some 20 million or more people receive concurrent NSAID and anti-hypertensive therapy [2].

Interactions between NSAIDs and several classes of anti-hypertensive drugs, including the thiazide diuretics, have been reported [3,4]. By inhibiting the cyclo-oxygenase pathway of arachidonic metabolism and renal synthesis of prostaglandins such as prostacyclin and prostaglandin E₂, NSAIDs are thought to attenuate the hypotensive effect of many thiazide diuretics [2]. The antagonistic effect of NSAIDs on blood pressure varies among individuals but significant

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interactions are thought to occur in about 1% of patients, with the elderly, black and those with low renin hypertension at greatest risk [5].

Tenidap sodium is a novel anti-rheumatic/anti-inflammatory drug undergoing clinical trials in the treatment of RA and osteoarthritis [6, 7]. It is chemically unrelated to either NSAIDs or disease modifying anti-rheumatic drugs (DMARDs), but shares with NSAIDs the ability to inhibit the cyclo-oxygenase pathway of arachidonic metabolism [8].

Tenidap is differentiated from NSAIDs by its ability to modulate cytokines which has been demonstrated *in vivo* in several models. It has been found to inhibit significantly the production of the cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor (TNF) in lipopolysaccharide (LPS)-stimulated human peripheral blood monocytes [9] and the production of IL-1 in LPS-stimulated murine macrophages [10]. Tenidap has also been found to inhibit cytokine-mediated bone resorption [11] and IL-1 stimulated cartilage degradation [12].

The aim of this study was to assess the effects of daily administration of either tenidap sodium or placebo for 22 days on the stable hypotensive response to a thiazide diuretic in subjects with uncomplicated essential hypertension.

Methods

Subjects

Male and female subjects aged between 18 and 79 years with uncomplicated essential hypertension could participate in this randomised, placebo-controlled, double-blind, parallel-group study. Females were to be either post-menopausal or to have been surgically sterilised.

Subjects were excluded if they had evidence of severe ventricular hypertrophy; a history of cerebrovascular accident, myocardial infarction within the previous 12 months, heart failure or heart block; diabetes mellitus requiring treatment with insulin or oral hypoglycaemic agents; severe dyspeptic symptoms associated with gastro-duodenal ulceration, haematemesis or melaena, or any condition likely to influence drug absorption; evidence of abnormal renal function or history of renal disease or renal artery stenosis; a history of asthma, eczema or previous hypersensitivity to any drug, especially NSAIDs, paracetamol or aspirin.

During the 3 weeks prior to the study, all subjects received a full physical examination, including electrocardiography with 12 lead electrocardiogram and routine laboratory analysis of blood and urine. Unless prior approval had been obtained from the study physician, subjects were excluded if their laboratory test results were not within 20% of the normal range.

Except for the thiazide diuretics, sublingual glyceryl trinitrate, and the occasional sanctioned use of codeine for headache, no concomitant medication, either prescribed or over-the-counter drugs, was

permitted in the 3 weeks prior to, or during the study. The use of other NSAIDs was strictly prohibited.

Subjects who had received any experimental drug within the previous 3 months, had evidence of drug or alcohol abuse, smoked more than 20 cigarettes a day or were positive for hepatitis B antigen (HbsAg) were also excluded. Subjects were not permitted to donate blood or blood products from a month before to completion of the study.

The study was conducted in accordance with the Declaration of Helsinki and received the approval of the North East Warwickshire Research Ethics Committee. All subjects gave written, informed consent.

Protocol

Subjects had a well-documented history of hypertension, defined as a diastolic blood pressure of 95–114 mm Hg before initiation of anti-hypertensive treatment. For at least 3 months before the start of the study subjects received regular treatment for their hypertension with a constant dose of either hydrochlorothiazide or bendrofluazide and were permitted to take potassium supplements, if needed. To ensure that pre-tenidap blood pressure levels were stable and influenced only by the thiazide diuretic, all other anti-hypertensive therapy was discontinued for 5 weeks before administration of tenidap.

During the 3 weeks prior to the start of the study, diastolic blood pressure was required to be within the range 80–97 mm Hg and within ± 4 mm Hg of the measurement taken at the start of this period. Subjects were then randomised to receive either a single oral daily dose of 120 mg tenidap sodium (Pfizer Central Research, Groton, CT, USA) or matched placebo, for 22 days whilst still maintaining treatment with their diuretic therapy. Subjects took their usual dose of thiazide therapy with water immediately before or during breakfast followed, at least 1 h later, by the study medication.

Blood pressure and pulse rates were measured at weekly intervals in the 3 weeks before day 1 of the study medication (baseline), and on days 7, 14 and 21. Blood pressure and pulse rate were both measured in triplicate after the subject had rested supine for 5 min and also after standing for 2 min. Ideally, both measurements were made at least 1 h after thiazide treatment but a delay of 1 h was permissible. If this was not possible the subject returned within 2 days to repeat the assessment.

Blood pressure was measured from the same arm, by the same investigator and at the same time of day relative to thiazide therapy. A conventional mercury sphygmomanometer was used, cuff size 14.5 cm, with diastolic pressure taken to phase V (the disappearance of the Korotkoff sounds).

Statistical evaluation

To detect a difference of 10% in standing diastolic blood pressure with a probability of 0.80 at the 5% significance level, a sample size of 20 subjects (10 per treatment group) was recommended [3].

An intent-to-treat analysis was used to compare baseline to endpoint (last visit on double-blind therapy) changes in supine and standing diastolic and systolic blood pressures and pulse rates between treatment groups. Data were analysed using a one-way analysis of variance, with treatment as the factor, and also using a two-way analysis of variance with treatment and centre, and their interaction as factors. Differences between treatment groups and 95% confidence intervals were calculated based on sample means from the one-way analysis of variance.

Graphical representation of the residual and fitted values was used to ensure that the underlying assumptions of normality and equal variance were met and that there were no outlying values exerting undue influence on the results.

Results

Twenty-five subjects were screened, of whom 23 (aged between 41 and 78 years) entered the study, 11 being randomised to tenidap and 12 to placebo. The two treatment groups were comparable demographically at baseline (Table 1). Except for one subject who received hydrochlorothiazide all others were treated with bendrofluzide.

Although protocol violations were reported they were balanced between groups and none warranted excluding any subject from the analysis. These included two patients who were outside the permitted weight range, and six subjects who took additional medication during the study.

Four subjects, two of whom received tenidap and two placebo, experienced side-effects that were considered to be treatment-related by the investigator. In the tenidap group one subject developed dyspepsia and the other dyspnoea with increased cough. These were of mild or moderate intensity and did not result in withdrawal from the study. In the placebo group one

Table 1 Baseline demographic information according to treatment group for subjects receiving 120 mg day⁻¹ tenidap with either a concomitant thiazide diuretic or matching placebo

	Tenidap		Placebo	
Number of subjects	11		12	
Age (years)				
Range	41–78		44–73	
Mean	65.6		57.7	
Weight (kg)				
Range	Men	64–93	Men	74–106
	Women	55–82.5	Women	52–78
Mean	Men	76.2	Men	87.4
	Women	70.4	Women	65.9
Ethnic origin				
White	11		11	
Asian	0		1	

subject experienced intermittent abdominal discomfort and the other a rash and both subjects were withdrawn from the study after 7 days. There were no reports of clinically significant treatment-related laboratory test abnormalities.

Pharmacodynamics

In the one-way ANOVA there was no significant difference between the two groups in the baseline to endpoint changes in either systolic pressure or pulse rate (Table 2). Comparison of the endpoint-baseline changes in mean standing diastolic blood pressure showed a statistical difference between the tenidap and placebo treatment groups ($P = 0.0023$). There were no other statistically significant differences for any of the other blood pressure or pulse measurements.

Occasional diastolic readings outside the limits of variance specified in the protocol were reported in some subjects during the run-in period, but these were not considered to have a significant impact on the

Table 2 Mean blood pressures and pulse rates at baseline and endpoint, and endpoint – baseline changes according to treatment group (one-way ANOVA)

	Tenidap (n = 11)			Placebo (n = 12)			Difference between changes	95% confidence limits
	Baseline mean	Endpoint mean	Endpoint–baseline change	Baseline mean	Endpoint mean	Endpoint–baseline change		
Supine diastolic BP (mm Hg)	85.9	87.8	1.9	84.4	83.3	–1.1	3.0	–1.08, 6.95
Standing diastolic BP (mm Hg)	86.8	90.3	3.5	87.2	83.9	–3.3	6.8*	2.75, –10.95
Supine systolic BP (mm Hg)	149.9	152.1	2.2	150.2	146.5	–3.7	5.9	–2.14, 13.95
Standing systolic BP (mm Hg)	151.5	151.5	0.0	150.3	143.8	–6.5	6.5	–5.22, 18.22
Supine pulse rate (beats min ⁻¹)	77.5	76.1	–1.4	74.5	74.3	–0.2	–1.2	–7.99, 5.65
Standing pulse rate (beats min ⁻¹)	78.7	77.1	–1.6	75.3	74.5	–0.8	–0.8	–6.93, 5.21

* $P = 0.0023$.

results. During treatment, mean systolic pressures from the tenidap group and diastolic pressures from both groups were within ± 5 mm Hg of their respective baselines. Mean systolic pressures in the placebo group were within 7 mm Hg of baseline. Mean pulse rates remained relatively constant throughout treatment (within 5 beats min^{-1} of baseline; Table 2). There was a tendency for all blood pressure measurements to decrease during placebo treatment and this was not seen during the 3 week period prior to the study.

When the treatment by centre interaction was analysed, a statistically significant difference between groups emerged for changes in supine and standing diastolic blood pressure and pulse rate but not for systolic pressure. This indicates that the tenidap minus placebo differences in the endpoint – baseline changes were not consistent among centres. Since the numbers of subjects in each of the five centres was small, the tenidap – placebo comparisons are difficult to interpret. Excluding the two smallest centres from the analysis, the results show that the treatment by centre inter-action was still statistically significant for supine and standing diastolic pressures. The treatment by centre interaction for pulse rate was attributed to an outlier whose pulse rate increased by 22 and 19 beats min^{-1} for supine and standing rates respectively, and the data were no longer significant when the results of this subject were excluded.

There were no within-subject changes in either blood pressure or pulse rate which could be attributed to tenidap.

Discussion

Once daily administration of 120 mg tenidap sodium to patients receiving concurrent therapy with the thiazide diuretics hydrochlorothiazide or bendrofluazide for control of mild to moderate uncomplicated hypertension, resulted in a statistically significant, yet marginal increase in diastolic blood pressure and no change in systolic blood pressure. However, the difference between tenidap and placebo was only significant for standing diastolic blood pressure. The results for

diastolic blood pressure should be interpreted with some care, however, since the differences in the effects of tenidap and placebo were not consistent among centres. When centre was included in the analysis both supine and standing diastolic pressures increased significantly under tenidap compared with placebo. All of the changes in mean blood pressures were relatively small. None exceeded 7 mm Hg and only rarely did any individual exceed 10% of baseline values.

Results from pooled studies of the effects of NSAIDs on anti-hypertensive drugs indicate that they produce an average increase in mean arterial pressure of 10 mm Hg which can be either short-lived or chronic [13]. NSAID attenuation of the hypotensive effects of thiazide diuretics has been demonstrated in a number of studies. Concurrent administration of indomethacin with several thiazide diuretics resulted in an increase in blood pressure in comparison with placebo [3]. A comparison of the effects of the NSAIDs sulindac, piroxicam and naproxen on hypertension control in patients stabilised on a β -adrenoceptor blocker and a combination diuretic of hydrochlorothiazide and amiloride showed naproxen and piroxicam significantly reduced renal synthesis of prostaglandins and produced significantly higher supine and standing diastolic blood pressures in comparison with sulindac and placebo [5]. Ibuprofen was found not to induce significant changes in blood pressure when administered at high doses and for a short period concomitantly with hydrochlorothiazide [14].

Given that tenidap shares with NSAIDs the ability to inhibit cyclo-oxygenase [8], the findings of this study should be considered in the light of previous experience of concomitant NSAID and thiazide administration. Thus the reduction in the hypotensive effect of the thiazide diuretics observed in this study is unlikely to be clinically important. Tenidap was well tolerated, the incidence of treatment-related side-effects being low and comparable with placebo.

The results of this study suggest that tenidap may be given concurrently with thiazide diuretic therapy to patients with mild to moderate hypertension, with regular monitoring of the patient's blood pressure.

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