Comparison of antihypertensive and metabolic effects of losartan and losartan in combination with hydrochlorathiazide – a randomized controlled trial

Patrick Owens[a], Linda Kelly[b], Ruth Nallen[b], Daire Ryan[b], Desmond Fitzgerald[b] and Eoin O'Brien"

Introduction **Losattan is an angiotensin II receptor blocker indicated for treatment of hypertension. It also inhibits platelet agreggation through blockade of thromboxane A_2/prostaglandin H_2 receptors, and has a uricosuric effect. We determined the effect on ambulatory blood pressure (ABP) of 100 mg losartan monotherapy (L100) versus 50 mg losartan/12.5 mg hydrochlorothiazide (HCTZ) combination therapy (L50H12.5C), in patients uncontrolled on 50 mg losartan. We also assessed the effects of losartan on platelet aggregation and serum urate at these clinically relevant doses.**

Methods This was a randomized, double-blind trial of L100 versus L50H12.5C, in moderate hypertensives (sitting diastolic blood pressure (DBP) ⩾ 95 mmHg and < 120 mmHg). After 4 weeks of placebo run-in, patients received 50 mg losartan for 6 weeks; patients uncontrolled (sitting DBP ⩾ 95 mmHg) were randomized to L100 or L50H12.5C for a further 6 weeks. Platelet function was assessed by measuring percentage inhibition of platelet aggregation, and serum uric acid was also measured.

Results Monotherapy with 50 mg losattan reduced ABP by 16.0/9.9 mmHg during the day and 9.8/5.5 mmHg at night. However, 16 out of 24 (66%) patients had uncontrolled blood pressure on this treatment. L50H12.5C further reduced daytime ABP by 10.7(10.7)/8.4(6.5) mmHg mean (SEM) compared with L100 (−5.3(9.7)/−2.3(4.8), $P = 0.013$). 50 mg losartan and L100 did not affect platelet function or uric acid levels beyond placebo values; treatment with L50H12.5C was associated with a significant rise in serum urate above levels obtained on 50 mg losartan (366.9(67.6) versus 331.6(65.0), $P = 0.006$), to levels similar to placebo (358.8(80.9)).

Conclusion L50H12.5C is an effective antihypertensive regimen in patients with moderate hypertension that is uncontrolled on 50 mg losartan monotherapy, and is the preferred treatment option in these patients compared with increasing the dose of losartan. The additional benefit of losartan on platelet inhibition was not evident in our population at these dopes; however, there was evidence to suggest that the uricosuric effects of losartan might ameliorate the uric acid retention effects of therapy with hydrochlorothiazide. *J Hypertens* **2000, 18:339–345 © Lippincott Williams & Wilkins.**

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[a]Blood Pressure Unit, Beaumont Hospital, and [b]Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, Dublin, Ireland.

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Correspondence and requests for reprints to Dr P Owens, Blood Pressure Unit, Beaumont Hospital, PO Box 1297, Beaumont Road, Dublin, Ireland.
Tel: +353-1-8092160; fax: +353-1-8093098;
e-mail: pomod@genie.co.uk

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Introduction

Losartan potassium is an angiotensin II receptor antagonist that is indicated for the treatment of hypertension. A newer compound in the field of hypertension treatment, it *was* introduced after the angiotensin converting enzyme (ACE) inhibitors, and was felt to provide antihypertensive efficacy with a lower incidence of side effects, especially cough [1]. It has been shown that at a daily dose of 50 mg losartan, trough blood pressure is equivalent to that achieved with 20 mg enalapril [2]. It is known that the antihypertensive effect of ACE inhibitors can be augmented with the simultaneous administration of a diuretic [3]; similarly, co-administration of a diuretic improves the antihypertensive effect of losartan [4,5].

Losartan is also known to inhibit platelet aggregation by blockade of the thromboxane A_2/prostaglandin H_2 (TxA_2/PGH_2) receptor [6]. It could be postulated that this drug would therefore have beneficial anti-platelet effects in patients with concomitant ischaemic heart disease. Finally, losartan has been shown to be uricosuric [7], and this property could be beneficial in patients with hyperuricaemia, and might offset the uric acid retention effects of diuretic therapy for hyper-

tension. This study was therefore carried out to compare the antihypertensive efficacy of losartan given in a dose of 100 mg daily, with 50 mg losartan in combination with 12.5 mg hydrochlorothiazide (HCTZ), in patients whose blood pressure was not controlled on 50 mg losartan monotherapy, and to determine the effects of losartan on platelet aggregability, and finally to determine the effect of losartan and losartan and HCTZ in combination on serum uric acid.

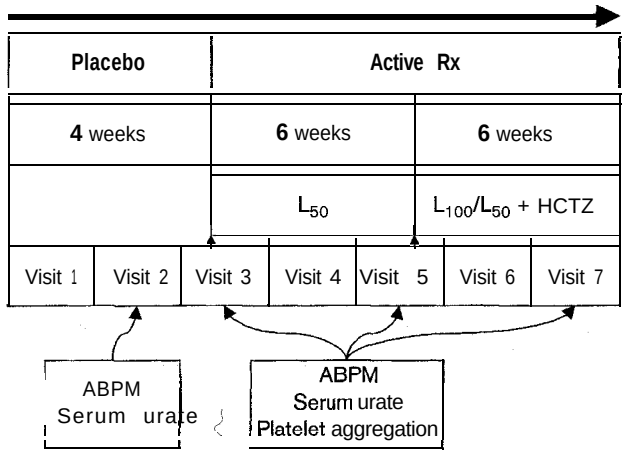
Methods

A flow chart of the study protocol is given in Figure 1.

Patient population

Patients were enrolled from the hypertension clinic in Beaumont Hospital. Patients were entered into the study if they had a history of essential hypertension before entry, and a mean sitting diastolic pressure in the range 95–120 mmHg after placebo visits 2 and 3. Suitable patients were between 40 and 75 years of age, and had to be free of intercurrent medical illnesses that might themselves or by their treatment affect the patients' blood pressure. Patients were not included if they failed to give informed consent, or had any of the following exclusion criteria: secondary hypertension (excluded on clinical grounds); malignant hypertension or a sitting systolic blood pressure > 210 mmHg; history of acute renal failure or evidence of significant renal impairment (i.e. serum creatinine > 180 μmol/l or proteinuria $>2+$ on urine dipstick); heart failure, stroke, myocardial infarction, transient ischaemic attack or hypertensive encephalopathy within the previous 12 months; uncontrolled diabetes mellitus; uncontrolled hyperthyroidism or hypothyroidism; or any condition deemed by the attending clinician to warrant exclusion from the trial.

Fig. 1



Study design. APBM, ambulatory blood pressure monitoring; HCTZ, hydrochlorothiazide; L, losartan.

Study design

At the initial screening visit, patients were included provided the conditions outlined above were met and they signed their consent to be enrolled into the study. If they-were already taking antihypertensive medication (which by definition was not adequately controlling their blood pressure), they were asked to discontinue this. Patients were issued with placebo at this visit, which they continued to take for 4 weeks, and if at visit 2 and 3 their sitting diastolic blood pressure was still in the range 95-120 mmHg, they were entered into the active treatment phase of the study.

Patients still eligible for inclusion at visit 3 were issued with a bottle of 50 mg losartan tablets. One tablet was taken daily for 6 weeks. If at the end of this treatment phase, patients remained uncontrolled, that is, had a sitting diastolic blood pressure $\geqslant 90$ mmHg, they were randomly separated into two groups: one to receive 100 mg lgartan daily, the other 50 mg losartan and 12.5 mg HCTZ daily. The treatment period was 6 weeks. Patients who were controlled on 50 mg losartan remained on this until the conclusion of the study.

Blood pressure measurement

Blood pressure was measured at each clinic visit, after 5 min quiet sitting. The diastolic pressure was recorded as phase V of the Korotkov sounds. At least three measurements were taken per patient, and were continued at l-min intervals until three stable diastolic readings were obtained (i.e. three consecutive measurements deviating by no more than 5 mmHg from the average of the three measurements). Blood pressure measurements were taken in accordance with the recommendations of the British Hypertension Society [8].

Ambulatory blood pressure measurements

Ambulatory blood pressure (ABP) monitoring was performed using the SpaceLabs 90207 (SpaceLabs Inc, Redmond Washington, USA) ambulatory blood pressure monitor, which has been validated for accuracy [9]. Measurements were performed at visits 2, 3, 5 and the final visit, 7. The monitor was applied to the nondominant arm between 0900 and 1200 h, and the patient was instructed to carry on as normal between measurements but to rest the arm at heart level during measurements. Monitors were programmed to measure blood pressure at 30-min intervals throughout the day and night. The monitor was removed the following day, and the data was transferred into a personal computer and loaded into a specialized software package (DABL) [10]. The daytime and night-time systolic, diastolic and mean blood pressures were calculated. 'Daytime' was defined as the hours between 0900 and 2100 h (excluding the first hour, when blood pressure is still affected by the white coat effect [11]), and night-time as the hours

between 0100 and 0600 h. Transition times (2101 to 0059 h, and 0601 to 0859 h) were not included in the estimation of day and night mean pressures, as these periods represent times during which bed rest is inconsistent and therefore cannot reliably be categorized [12]. Erroneous measurements identified by the editing software were removed from the recording, and all others were included in the data set [13].

Platelet function and urate assay

Fasting blood was drawn at clinic visits 3, 5 and 7 from each patient, taking 4.5 ml blood into a 3.8% sodium citrate blood tube. This was spun to give a platelet-rich plasma (PRP) supernatant, which, after calibration with platelet poor plasma from the same patient, was assessed for platelet function in a Biodata Pap 4 aggregometer (MI, Inc., Minnesota, USA). The agonists used were 50 μl of 2 X 10^{-4} mol/l adenosine diphosphate (ADP), added to 4.50 μl PRP, and 50 μl U46619 added to 450 μl PRP. Platelet function was assessed as the mean percentage aggregation from two successive trials of each agonist. At visits 2, 3, 5 and 7 fasting blood was drawn from each patient and the serum urate concentration was determined.

Definitions and statistical methods

The primary endpoint of the study was the change in ABP at the end of the randomized part of the study, to compare the relative efficacy of losartan alone and losartan in combination with HCTZ for patients uncontrolled on 50 mg losartan alone. Assuming a = 0.05 and 80% power, eight patients in each group were required to show a difference of 10 mmHg between visit ABP measurements, assuming also a standard deviation of the differences in blood pressure of 10 mmHg. Baseline ABP parameters and serum urate were taken as the mean of the two placebo phase measurements. Secondary objectives were change in platelet aggregation and serum urate between placebo and losartan monotherapy, and the randomized phase of the trial. Additionally, trough/peak (T/P) ratio estimation of the 24-h blood pressure lowering efficacy of the treatments used was determined after the method described by Omboni *et al.* [14]. Briefly, peak pressure reduction was determined by identifying and averaging the greatest reduction in blood pressure between the placebo phase and treatment phase ABP measurements over a Z-h period in a window of between 2 and 7 h after dosing. The trough pressure reduction was calculated by averaging the blood pressure reduction between 0600 and 0800 h on the second day of monitoring. The trough value was divided by the peak value to give the T/P ratio.

The institutional ethics committee reviewed and approved this study. Differences between continuous variables were compared using the Student's *t* test; differences across groups were compared using one-way analysis of variance.

Results

A total of 31 patients entered the placebo phase of the study. Seven patients were withdrawn during the placebo phase; one was withdrawn because of normalization of blood pressure over the placebo period; six either withdrew voluntarily or were withdrawn because of noncompliance with drugs, defined as the failure to take 80% of prescribed placebo pills; this was determined by counting the pills at the final placebo clinic visit. A further eight patients normalized their clinic diastolic pressure on 50 mg losartan, and were not included in the randomized part of the study; these patients continued to take 50 mg losartan until the end of the study. Therefore a total of 16 patients successfully completed the randomized stage of the study.

Blood pressure

The baseline clinical data for the 24 patients who completed the'single-blind phase of the trial are shown in Table 1. Ambulatory blood pressure was significantly reduced by 50 mg losartan between the placebo phase and after 6 weeks of losartan treatment (Table 2; Figs 2 and 3). However, only three patients (12.5%) had normal ABP, and only eight patients (33%) had normal clinic pressure on treatment with 50 mg losartan monotherapy.

Sixteen patients whose blood pressure remained uncontrolled at the end of the single-blind phase of the trial

Table 1 Baseline clinical characteristics for the 24 patients completing the single-blind phase of the trial

Age (years)	51.4 ± 6.9
Sex (m/f)	13/10
Height (cm)	168.3 ± 10.7
Weight (kg)	80.8 ± 15.7
cSBP (mmHg)	**172.0 ± 16.7**
cDBP (mmHg)	104.6 ± 8.1
Day SBP (mmHg)	160.2 ± 13.1
Day DBP (mmHg)	101.4 ± 9.0
Night SBP (mmHg)	133.0 ± 13.2
Night DBP (mmHg)	81.9 ± 12.2

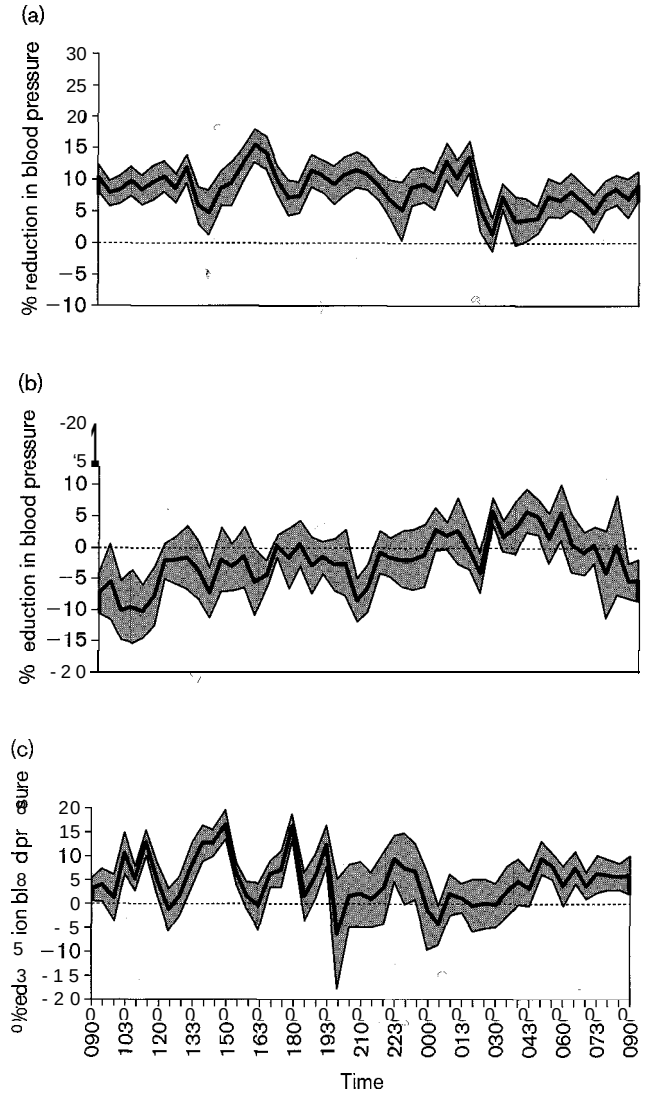
Values are means ± SEM. cDBP, clinic diastolic blood pressure; cSBP, clinic systolic blood pressure.

Table 2 Antihypertensive efficacy of losartan: comparison between placebo and after 6 weeks treatment with 50 mg losartan daily

	Placebo	50 mg Losartan	*P*
Day SBP (mmHg)	160.2 ± 13.1	144.2 ± 12.9	< 0.001
Day DBP (mmHg)	101.4 ± 9.0	91.5 ± 8.6	< 0.001
Night SBP (mmHg)	133.0 ± 13.2	123.2 ± 13.4	< 0.001
Night DBP (mmHg)	81.9 ± 12.2	76.4 ± 10.2	0.004

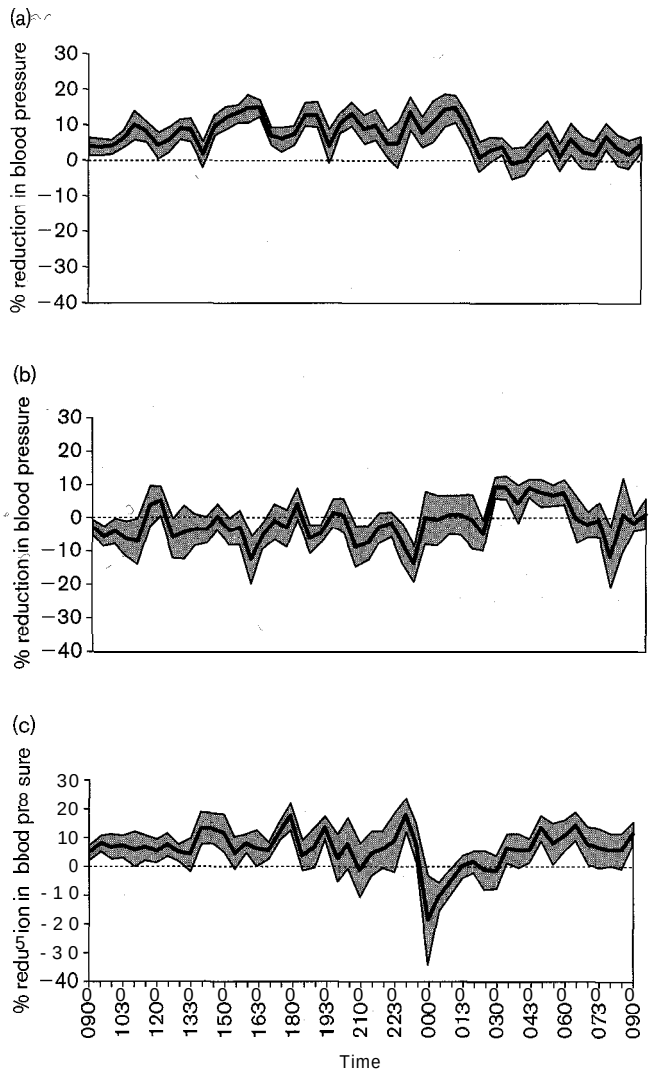
Values are means ± SEM. DBP, diastolic blood pressure; SBP, systolic blood pressure.

Fig. 2



(a) Percentage systolic blood pressure reduction after treatment with 50 mg losartan compared with placebo-only phase. Further percentage change in systolic blood pressure compared with blood pressure on 50 mg losartan (b) with 100 mg losartan and (c) with 50 mg losartan/ 12.5 mg hydrochlorothiazide. Bold line represents mean percentage blood pressure reduction according to time of day for all subjects. Grey band represents ± SEM.

Fig. 3



(a) Percentage diastolic blood pressure reduction after treatment with 50 mg losartan compared with placebo-only phase. Further percentage change in diastolic blood pressure compared with blood pressure on 50 mg losartan (b) with 100 mg losartan and (c) with 50 mg losartan/ 12.5 mg hydrochlorothiazide. Bold line represents mean percentage blood pressure reduction according to time of day for all subjects. Grey band represents ± SEM.

were randomly assigned either 100 mg losartan or 50 mg losartan/12.5 mg HCTZ. Their data at the time of randomization is presented in Table 3. There was a nonsignificant trend for slightly lower nocturnal pressures in the group subsequently randomized to combination therapy.

Treatment with 100 mg losartan daily for 6 weeks resulted in no further reduction in blood pressure from the values recorded on 50 mg losartan daily, except for a small (3.6 mmHg) nonsignificant (P = 0.055) fall in mean night-time diastolic pressure (Figs 2 and 3). Treatment with 50 mg losartan/12.5 mg HCTZ for 6 weeks resulted in significant further reductions in systolic and diastolic daytime pressures compared with treatment with 50 mg losartan alone (Table 4; Figs 2 and 3). There was no significant effect on nocturnal systolic or diastolic blood pressures in either treatment group.

The T/P ratio for treatment with 50 mg fosartan was

Table 3 Comparative clinical data from randomized cohorts to the double-blind phase of the study

	100 mg losartan	50 mg losartan/12.5 mg HCTZ	P
Age (years)	50.2 ± 5.6	49.5 ± 5.5	0.27
Sex (m/f)	5/3	5/3	
Weight (kg)	83.8 ± 21.2	83.3 ± 14.5	0.95
Height (cm)	169.1 ± 14.3	170.3 ± 9.9	0.87
Day SBP (mmHg)	145.7 ± 13.5	144.6 ± 15.0	0.89
Day DBP (mmHg)	93.1 ± 6.0	93.4 ± 11.7	0.96
Night SBP (mmHg)	130.0 ± 8.0	119.0 ± 15.2	0.11
Night DBP (mmHg)	82.1 ± 8.4	75.4 ± 10.8	0.20

Values are means ± SEM. Ambulatory blood pressure data refers to blood pressure documented at the end of the single-blind losartan treatment phase, just before randomization. DBP, diastolic blood pressure; SBP, systolic blood pressure; HCTZ, hydrochlorothiazide.

Table 4 Blood pressure reductions with 100 mg losartan monotherapy, and combination therapy with 50 mg losartan/12.5 mg HCTZ compared with baseline ambulatory blood pressure (on 50 mg losartan)

Δ in BP	100 mg Losartan	50 mg Losartan/12.5 mg HCTZ	P
Day SBP	−5.3 ± 9.7	10.7 ± 10.7	0.013
Day DBP	-2.3 ± 4.8	8.4 ± 6.5	0.006
Night SBP	3.4 ± 7.6	4.6 ± 9.2	0.80
Night DBP	3.6 ± 3.7	3.9 ± 6.6	0.92

Values are means ± SEM. A in BP, change in blood pressure. A negative value indicates a rise in blood pressure, HCTZ, hydrochlorothiazide.

0.31 (0.33) for systolic blood pressure and 0.34 (0.76) for diastolic pressure; 100 mg losartan showed a mean T/P of 0.33 (0.83) for systolic and 0.31 (0.43) for diastolic pressures. Combined treatment with losartan/HCTZ gave a T/P of 0.51 (0.28) and 0.53 (0.27) for systolic and diastolic pressures, respectively. Variation was wide, however, and this trend for a more favourable T/P in the combined treatment group was not statistically significant.

Platelet function

Platelet aggregation did not differ significantly at baseline between the two reagents used. Comparing platelet function on placebo and after single-blind treatment with 50 mg losartan for 6 weeks, platelet function remained unchanged for both reagents used (80.8 ± 9.1 versus 80.6 ± 7.7, P = ***0.22*** for ADP, 86.1 ± 8.8 versus 84.1 ± 5.7, P = 0.63 for U46619). In patients receiving 100 mg losartan, platelet function was unaltered at the end of the trial (78.6 ± 11.6 versus 87.1 ± 11.2, P = 0.27 for ADP, 88.8 ± 3.4 versus 89.7 ± 10.8, P = 0.80 for U46619). Finally, no change in platelet function was evident between placebo and patients receiving 50 mg losartan/12.5 mg HCTZ (78.4 ± 4.5 versus 80.4 ± 6.6, P= 0.59 for ADP, 82.7 ± 4.7 versus 88.3 ± 11.0, P = 0.25 for U46619).

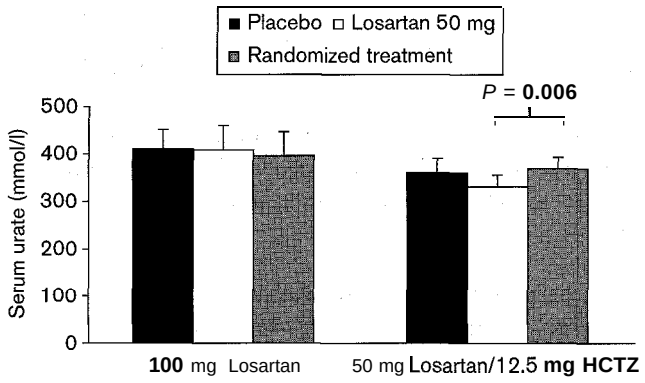
Serum urate

The serum urate levels are shown in Figure 4. There was no significant change in serum urate between placebo and the end of the 50 mg losartan single-blind phase (385.3 ± 122.4 versus 376.2 ± 123.6, P = 0.33). In patients receiving 100 mg losartan, urate did not fall significantly compared with placebo (408.9 ± 114.9 versus 396.5 ± 135.9, P = 0.314), nor did urate change significantly in those receiving the losartan/HCTZ combination (358.7 ± 80.9 versus 366.9 ± 67.6, P = 0.31). However, those receiving combination treatment did exhibit significantly higher serum urate levels than those receiving 50 mg losartan monotherapy (366.9 ± 67.6 versus 331.6 ± 65.0, P = 0.006).

Discussion

Losartan is a relatively new treatment option in the management of hypertension, and was the first drug in the class of angiotensin II receptor antagonists to be used clinically. It has been shown to be an effective antihypertensive agent compared with the established antihypertensives. It also compares well with ACE inhibitors, calcium channel blockers and β-blockers in terms of its effect on lowering blood pressure [15], and compares favourably with respect to the incidence of cough [16]. Losartan also has been shown to inhibit platelet aggregation by blockade of the TxA_2/PGH_2 receptor, leading to speculation that it may have additional benefit in patients with ischaemic heart disease. Finally, it is uricosuric, and this may be of benefit in patients with hyperuricaemia. This study therefore addresses the antihypertensive efficacy of losartan and losartan in combination with HCTZ, and examjnes the potential effects of these treatments on platelet function and serum urate levels.

Fig. 4



Change in serum urate concentration after 6 weeks monotherapy and either 100 mg losartan or losartan 50 mg/12.5 mg hydrochlorothiazide (HCTZ) treatment. Addition of hydrochlorothiazide (HCTZ) to 50 mg losartan was associated with a significant rise in serum urate levels, to levels comparable with placebo values.

Our data confirm that 50 mg losartan as monotherapy significantly reduces blood pressure after 6 weeks of treatment. However, monotherapy failed to normalize blood pressure in 66% of our patient cohort as defined using clinic diastolic pressure, and failed to normalize 87.5% of our cohort as defined using ABP definitions of normality [17]. In the randomized limb of the study, we have shown that combination therapy with 50 mg losartan and 12.5 mg HCTZ is a more efficacious antihypertensive treatment regimen than 100 mg losartan in mild to moderate hypertensive patients whose blood pressure is not controlled on losartan monotherapy alone. Previous work has suggested that losartan/HCTZ treatment is an efficacious combination in non-responders to 50 mg losartan monotherapy [4], and our work would confirm that indeed combination therapy is preferable to incremental doses of losartan. There is evidence to suggest that the dose-response of losartan plateaus after 50 mg daily [18], and the results here support the conclusion that doses beyond this do not significantly contribute to blood pressure reduction [19].

The recommendations of the Food and Drug Administration are that for an antihypertensive drug to be acceptable, its T/P should be greater than 0.5 [20]. Interestingly, the T/P for losartan 50 and 100 mg monotherapy was 0.31/0.34 and 0.33/0.31 (systolic/diastolic), respectively. Combination therapy had a T/P of 0.51/0.53, and although this difference was not statistically significant, it does suggest a trend towards better 24-h cover with combination treatment.

At these doses, no pharmacokinetic interaction between losartan and HCTZ has been noted [21]. In our study population no patients dropped out as a result of side effects or adverse metabolic reactions to the study medication. Although our study population was small, our results support the safety and tolerability of losartan/thiazide combination therapy. However, our study population specifically excluded patients with uncontrolled diabetes – in fact, no patients with diagnosed diabetes mellitus were actually enrolled – so we therefore cannot generalize the safety of this drug combination in diabetic patients, on the basis of our current data.

What pathophysiological mechanisms might explain the combined benefit of an angiotensin II receptor antagonist and a diuretic? Thiazide diuretics cause loss of sodium and potassium ions in the urine, and as such would tend to activate the renin–angiotensin–aldosterone axis. The co-administration of an angiotensin II receptor blocker would therefore offset potential compensatory vasoconstrictive and aldosterone-dependent salt retention mechanisms.

As for the effects of losartan on platelet function, no changes in platelet aggregation were noted in our population, at 50mg or 100mg doses, compared with patients on placebo treatment. The low numbers in the study mean that it was relatively under-powered for detecting subtle changes in platelet function; however, the study was large enough to detect a 50% inhibition in platelet aggregation ($\alpha = 0.80$, $1 - \beta = 0.05$) between treatment groups and placebo. This figure is close to the level of platelet inhibition seen with the use of aspirin [22]. We can therefore conclude from this study that inhibition of platelet aggregation to this degree is not induced by losartan at clinically relevant doses. Losartan has been shown to reduce platelet aggregation in spontaneously hypertensive rats [6], and in normotensive humans [23]; the lack of effect found in this study may reflect different platelet receptor properties in hypertensive humans, in whom the known increase in platelet activity may reflect biochemical pathways insensitive to angiotensin II/thromboxane A_2 receptor blockade.

The uricosuric properties of losartan have been shown in previous work, and this activity is important in the context of treating hypertensive populations who have an increased incidence of hyperuricaemia [7]. The potential to exacerbate gout by treatment of hypertension with diuretics is well recognized, so the possible beneficial effect of adding a uricosuric agent to diuretic treatment to offset the possible precipitation of gout is important. We have shown that in our small sample size, serum urate was not significantly altered by administration of losartan at the 50 mg dose; similarly, the increased dose of 100 mg per day did not appreciably change the level of uric acid. The level of urate did, however, increase significantly in patients treated with 50 mg losartan/12.5 mg HCTZ compared with those receiving 50 mg losartan monotherapy. This reflects the powerful uric acid retention effects of thiazide diuretics [24]. The rise in serum urate was to a level similar to that found on placebo treatment, suggesting that in combination preparations, the tendency for urate levels to rise with thiazide diuretics is offset by the known uricosuric effects of losartan [25]. This effect has been documented by other workers, showing that over doses of HCTZ ranging from 6.25 to 25 mg given in addition to 50 mg losartan, urate levels did not increase over placebo [4]. Again the small sample size reduces the power of the study to detect subtle differences; however, the study was sufficiently powered to detect a difference of 50 mmol/l in serum urate between the placebo and the two treatment limbs.

In conclusion, we have shown that combination losartan/diuretic treatment is a more appropriate treatment option than increasing the dose of losartan in patients

unresponsive to 50 mg losartan alone, and would therefore recommend that a practical maximum dose of losartan in a clinical context- should be 50 mg, with combination diuretic therapy as the appropriate next treatment step.

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