Eur J Clin Pharmacol (1992) 42: 333–335

European Journal of Clinical Pharmacology

Short communications

Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects

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Received: April 15, 1991/Accepted in revised form: August 21, 1991

Summary. The uricosuric effect of DuP-753, a novel, specific angiotensin II receptor antagonist, has been explored in a healthy male Japanese volunteers, given single oral doses of 25, 50, 100 or 200 mg ($n = 6$), or 100 mg ($n = 6$) or placebo ($n = 3$) once daily for 7 consecutive days.

In the single-dose study, serum uric acid measured at 4 h after dosing showed a dose dependent decrease; the reductions from the corresponding pre-dose values were: 0.32 (25 mg), 0.77 (50 mg), 1.25 (100 mg) and 1.33 mg · dl^{-1} (200 mg). The urinary excretion of uric acid within the first 4 h after treatment was also increased in a dose-dependent manner, whereas the urinary excretion of creatinine remained unchanged.

In the multiple-dose study, DuP-753 significantly decreased the serum uric acid concentration measured 4 h both after the first (pre-dose value: 5.68 vs 4 h after: 4.48 mg · dl^{-1}) and last administrations (4.42 mg · dl^{-1}). Simultaneously, the ratio of urinary uric acid to creatinine excretion was significantly increased within the first 4 h both after the first (DuP-753: 1.190 vs placebo: 0.576) and last administrations (1.02 vs 0.576).

The findings suggest that DuP-753 posesses a uricosuric effect both after single and multiple doses in healthy subjects. The effect should be further examined in hypertensive patients.

Key words: DuP-753, Uricosuria; angiotensin II receptor antagonist; healthy volunteers

DuP-753, the potassium salt of 2-n-butyl-4-chloro-1-[2′-(tetrazol-5-yl)-1,1′-biphenyl-4-ylmethyl]-1H-imidazole-5-methanol, is a novel, specific non-peptide angiotensin II receptor antagonist, which has promise as an antihypertensive agent with no effect on bradykinin metabolism [1–3]. During the Phase I clinical study of this agent, by chance attention was drawn to a reduction of serum uric acid due to the increased urinary excretion of uric acid. With this further effect DuP-753 would have additional merit as an antihypertensive agent, because hyperuricaemia is reported to be found in 26 % to 33 % of patients with untreated mild hypertension [4, 5], and it may contribute to the deterioration of renal function associated with hypertensive vascular disease [6]. It is also true that increased excretion of uric acid may give rise to nephrotoxicity. Haematologists have suggested that hyperuricaemia may modify platelet function by increasing platelet adhesiveness and thereby promoting atherosclerosis [7, 8].

In the present experiment attention was focused on the uricosuric effect of DuP-753 in healthy male Japanese volunteers.

Materials and methods

Subjects

Thirty-three healthy male volunteers participated in the study after giving informed consent. Twenty-four of the subjects (aged 31.3 (1.3) y; body weight 64.6 (1.9) kg) were allocated to the single dose-study and the other nine (age 36.0 (2.2) y; body weight: 63.9 (3.6) kg) to the placebo-controlled multiple dose study. Prior to participating in the study, all subjects had been confirmed to be in good health by physical examination, electrocardiography and routine clinical laboratory tests.

Study protocol

In the single dose study the subjects were divided into 4 groups each of 6 subjects. Each group was given 25, 50, 100 or 200 mg DuP-753 after an overnight fast. In the multiple dose study 6 subjects received DuP-753 100 mg and 3 subjects received placebo once a day for 7 days. During the 30 h (single-dose study) or 48 h (multiple-dose study) all volunteers were hospitalized just before the commencement of drug administration, and control data on the diurnal changes in blood pressure were obtained.

Blood samples for the analysis of uric acid were taken before, 4 and 24 h after treatment in the single-dose study and before and 4 h after the first and last doses, and also 24 h after the last dose, in the multiple-dose study. Urine was collected: 0–4, 4–8, 8–12, 12–24 and 24–30 h after the administration in the single-dose study; and after 0–4, 4–12 and 12–24 h on the first and last days, and 0–12 and 12–24 h on the other days in the multiple-dose study.

The protocol was approved by the local Ethics Committee.

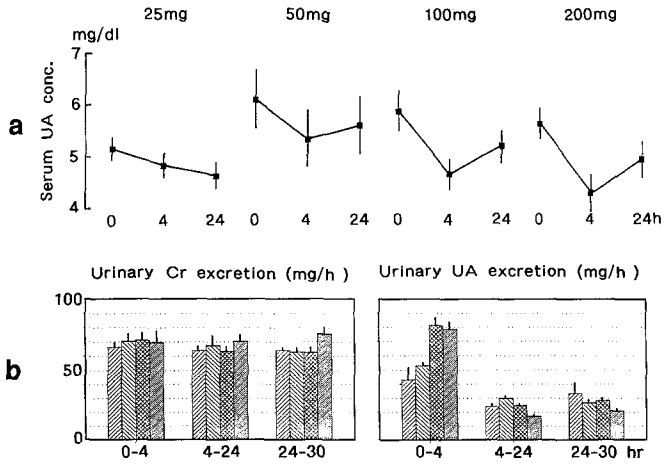

Fig. 1 a, b. The reduction of serum uric acid and the uricosuric activity of single doses of DuP-753 25, 50, 100 and 200 mg. **a** Serum uric acid concentrations (UA conc.) just before (0 h), 4 and 24 h after the administration of DuP-753 are shown. Each symbol and bar shows mean with (SEM) ($n = 6$). **b** Urinary excretion of creatinine (Cr) and uric acid (UA) over 0–4, 4–24 and 24–30 h expressed in mg/h. Each column and bar shows mean with (SEM) ($n = 6$). ▨ 25 mg ▧ 50 mg ▩ 100 mg ▩ 200 mg

Assay procedures

Serum and urinary uric acid concentrations were measured by standard automated procedures based on a uricase-peroxidase method. Creatinine (Cr) concentrations were also measured by standard automated procedures.

Statistics

Data are expressed as mean with (SEM). Either parametric (Student's *t*-test and Scheffe's or Tukey's multiple comparison) or non-parametric methods (Wilcoxon's U-test) were employed for statistical analysis, as appropriate.

Results

Single-dose study

The serum uric acid concentration 4 h after the administration of DuP-753 was dose-dependently decreased. The decreases from the corresponding pre-dose level was 0.32 (0.08) (25 mg), 0.77 (0.04) (50 mg), 1.25 (0.14) (100 mg) and 1.33 (0.12) mg·dl^{-1} (200 mg). The differences between the doses were statistically significant (Scheffe's multiple comparisons) – 25 mg vs 50 ($P < 0.05$), 100 ($P < 0.01$) and 200 mg ($P < 0.01$); 50 mg vs 100 ($P < 0.01$) and 200 mg ($P < 0.01$) (Figure 1 a). The urinary excretion of Cr remained unchanged but that of uric acid was increased in a dose-dependent manner within the first 4 h after administration: 25 mg vs 100 ($P < 0.01$) and 200 mg ($P < 0.01$); 50 mg vs 100 ($P < 0.05$) by Tukey's multiple comparison test (Fig. 1 b).

Multiple-dose study

DuP-753 significantly decreased serum uric acid concentrations measured 4 h both after the first and last doses as compared to placebo. The ratio of uric acid to Cr excretion in urine was significantly increased on the same occasions (Table 1).

Discussion

Peptide analogues of angiotensin II [9] have been used as angiotensin II receptor antagonists, but they lack oral activity and retain significant agonistic effects. More recently, selective, non-peptide antagonists, lacking partial agonistic activity, have been reported, including DuP-753 [1–3, 10].

Table 1. Changes in serum uric acid and ratio of urinary excretion of uric acid to that of creatinine associated with multiple doses of DuP-753 and placebo

Serum uric acid (mg/dl)

	Day 1		Day 7	
	0 h	4 h	4 h	24 h
DuP-753	5.68 (0.44)	4.48** (0.36)	4.42* (0.30)	4.92 (0.20)
Placebo	6.00 (0.47)	5.60 (0.44)	5.53 (0.30)	5.67 (0.27)

Ratio of urinary excretion of uric acid to creatinine

	day 1			day 2		day 7				
	0–4 h	4–8 h	8–24 h	0–12 h	12–24 h	0–4 h	4–8 h	8–24 h	24–36 h	36–48 h
DuP-753	1.187* (0.113)	0.407 (0.032)	0.254 (0.011)	0.545 (0.041)	0.330 (0.024)	1.019* (0.047)	0.445 (0.031)	0.334 (0.017)	0.361 (0.018)	0.285 (0.013)
Placebo	0.576 (0.017)	0.384 (0.008)	0.319 (0.047)	0.455 (0.017)	0.405 (0.008)	0.576 (0.063)	0.404 (0.005)	0.381 (0.003)	0.414 (0.030)	0.323 (0.021)

Serum uric acid was decreased at 4 h after DuP-753 administration on both 1st and 7th day. The decreases from the pre-dose value of the 1st day are significantly larger in the DuP-753-treated group than the placebo-treated group (*: $P < 0.05$; **: $P < 0.01$ by Student's *t*-test). The ratios of urinary uric acid excretion to creatinine excretion within the first 4 h after both 1st and last administrations are significantly larger in the DuP-753-treated group than the placebo-treated group (*: $P < 0.05$ by Wilcoxon's U-test). Each value represents mean with (SEM) ($n = 6$ for DuP-753; $n = 3$ for placebo)

An uricosuric effect of DuP-753 and the consequent decrease in serum uric acid concentration was demonstrated by systemic measurements of uric acid, in both single and multiple dose studies. In the single-dose study, a dose-dependent reduction in serum uric acid after DuP-753 administration was apparent after 4 h, even though the study was not placebo-controlled. Compared to the dose of 25 mg, which was minimally effective in lowening the serum uric acid, the reducing effect on serum urate of DuP-753 increased with the dose, although 200 mg had almost the same activity as 100 mg. Paralleling the decrease in serum uric acid, the urinary uric acid excretion also increased dose-dependently, whereas that of Cr remained unchanged. The uricosuric effect could not really be observed after more than 4 h and serum urate 24 h after administration had returned to the pre-dose level. This can be explained by the facts that the concentration of DuP-753 in blood reaches its maximum 0.7–1.3 h after administration and the half-life in blood is short (1.5–2.5 h; unpublished observations). In the multiple-dose placebo-controlled study, DuP-753 100 mg was again shown to lower serum uric acid 4 h after the administration as compared to placebo. The effect was almost the same on the 1st and 7th days of administration. The effect was comparable to that of the single dose of 100 mg.

DuP-753 was not demonstrated to be uricosuric in laboratory animals. It is known that the purine metabolism differs in rats and dogs from that in humans, in that the final product of purine is not uric acid, but allantoin. This metabolic difference may contribute to the failure to demonstrate uricosuria in animal experiments.

Uric acid is almost completely ultrafilterable from human plasma, it is not lipid-soluble and there is little evidence of non-ionic diffusion. Changes in urine pH and urine volume are reported to have very little effect on urate excretion in urine. In the present study the urinary excretion of Cr remained unchanged, showing that any possible effect of DuP-753 on renal haemodynamics, especially on glomerular filtration, makes little, if any contribution to the increase in uric acid excretion. The proximal tubule seems to be the main site of uric acid transport, and it can be assumed that drugs influence the transport of uric acid there only by inhibiting secretion either or both and reabsorption. In fact, the uricosuria caused either by disease states or pharmacological intervention is considered to be due to stimulation of tubular secretion or, alternatively and more likely, to diminished reabsorption of secreted uric acid [11]. Increasing evidence suggests that angiotensin II controls renal sodium excretion, not only by affecting renal haemodynamics and aldosterone biosynthesis, but also by directly regulating epithelial sodium transport [12]. It has been reported that DuP-753 was more effective than captopril in inhibiting sodium chloride transport in the S_1 subsegment of proximal convoluted tubule, suggesting that it is the most potent diuretic ever described that acts on this segment to induce a substantial diuresis, natriuresis and chloruresis [13]. In addition, an active metabolite of DuP-753 with a carboxylic acid side chain has been identified in humans (unpublished observation). It is known that carboxylic acids are subject to reabsorption as well as secretion in the renal tubule. It is possible that the direct effects both of DuP-753 and its metabolite reduce the reabsorption of uric acid in the tubules, so causing an increase in urinary excretion, although the exact mechanism remains to be clarified.

In conclusion, DuP-753 possesses a uricosuric activity in healthy subjects. The potential clinical useful value of this effect should be further evaluated in hypertensive patients as well as its antihypertensive efficacy.

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