Do trandolapril and indomethacin influence renal function and renal functional reserve in hypertensive patients?

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Aims To assess the effect of trandolapril (2 mg once daily) and indomethacin (25 mg three times daily), alone and in combination, on renal function and renal functional reserve in hypertensive patients (DBP 95–115 mmHg) requiring regular non-steroidal anti-inflammatory drugs (NSAIDs).

Methods Randomized, double-blind, placebo-controlled, four way crossover design. After 3 weeks treatment renal plasma flow (RPF) and glomerular filtration rate (GFR) were measured using the *p*-aminohippurate (PAH) and inulin methods. Renal functional reserve was estimated by measuring RPF and GFR at the end of an intravenous infusion of dopamine 2 $\mu g\,kg^{-1}$ and 10% amino acid solution.

Results There was no significant difference in RPF between treatments: $-22.79\ ml\ min^{-1}$ (95% CI −54.82, 9.24) for placebo and trandolapril, $-10.37\ ml\ min^{-1}$ (95% CI −30.7, 9.96) for placebo and indomethacin, $-14.78\ ml\ min^{-1}$ (95% CI −50.33, 20.77) for placebo and trandolapril with indomethacin. There was no significant difference in functional reserve RPF between treatments: $-34.96\ ml\ min^{-1}$ (95% CI −119.8, 49.88) for placebo and trandolapril, $29.78\ ml\ min^{-1}$, −15.18, 74.74) for placebo and indomethacin, and $-25.84\ ml\ min^{-1}$ (95% CI −87.62, 35.94) for placebo and trandolapril with indomethacin. There was no significant difference in GFR between treatments: $-1.01\ ml\ min^{-1}$ (95% CI −7.45, 5.42) for placebo and trandolapril, $-7.88\ ml\ min^{-1}$ (95% CI −15.08, −0.68) for placebo and indomethacin, and $-0.36\ ml\ min^{-1}$ (95% CI −7.58, 6.86) for placebo and trandolapril with indomethacin. There was no significant difference in functional reserve GFR between treatments: $5.13\ ml\ min^{-1}$ (95% CI −4.97, 15.23) for placebo and trandolapril, $6.31\ ml\ min^{-1}$ (95% CI −1.88, 14.5) for placebo and indomethacin, $7.21\ ml\ min^{-1}$ (95% CI 1.26, 13.16) for placebo and trandolapril with indomethacin.

Conclusion In hypertensives chronic treatment with NSAIDs or ACEI alone or in combination did not change RPF or GFR and did not change renal functional reserve capacity of RPF or GFR.

Keywords: trandolapril, indomethacin renal function, renal functional reserve, PAH/inulin

Introduction

The renin-angiotensin system is one of the mechanisms involved in renal autoregulation. Angiotensin II (AII) elicits a dose dependent reduction in renal blood flow (RBF), and a variable effect upon GFR, such that filtration fraction increases. AII causes afferent and efferent arteriolar vasoconstriction, but has slightly more effect on the efferent arteriole. AII stimulates intrarenal production of vasodilator prostaglandins, which in turn, help protect the renal circulation from the vasoconstrictor effects of AII. ACE inhibitors (ACEI) prevent conversion of angiotensin I (AI) to AII, thereby dissociating renal blood flow from glomerular filtration and affecting renal autoregulation [1]. For their full antihypertensive effect ACEI require an intact prostaglandin system, and if this is blocked by an NSAID, their antihypertensive effect is attenuated [2]. Due to their effect on renal autoregulation the co-administration of ACEI and NSAIDs may also adversely affect renal function [3].

Glomerular filtration rate (GFR) and renal plasma flow (RPF) in the normal kidney increases in response to a protein load. The greatest increases are obtained with a combined infusion of dopamine and amino acids [4]. The difference between the unstimulated GFR and the maximal GFR achieved, which can be an increase of 20–40%, is called the renal functional reserve (RFR). The increments in GFR and RPF are usually parallel such that filtration fraction remains unchanged [5–7]. The main mechanisms involved in eliciting the RFR are: alteration of tubulo-glomerular feedback, modification of AII circulating concen-

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tration, growth hormone or other hypophyseal hormone release, glucagon release and prostaglandin synthesis [8]. Assessment of RFR in hypertensive patients has produced conflicting results, with Cottone *et al.* [5] demonstrating an increased GFR, and Losito *et al.* reporting diminished renal functional reserve [9].

The present study tested the hypothesis that chronic NSAID treatment would blunt and ACEI would improve renal function at steady state and renal functional reserve capacity in hypertensive patients. We therefore studied the interaction between indomethacin and the non-sulphydryl ACEI, trandolapril, on RPF and GFR, and upon functional reserve RPF and GFR, using the *p*-aminohippurate (PAH) and inulin clearance methods [10].

Methods

Approval for the study was obtained from the Grampian Health Board Ethics Committee. Twenty-three patients (10 male, aged 36–66 years, mean age 53.5 years) were recruited from the Aberdeen Blood Pressure Clinic and gave informed written consent. All had hypertension (untreated DBP 95–115 mmHg, mean BP 162.8/103.7 mmHg) and a musculoskeletal disorder requiring regular NSAID treatment. Patients were excluded if they had a serum creatinine $>110\ \mu mol\ l^{-1}$, grade III hypertensive retinopathy, cerebrovascular, renovascular or peripheral vascular disease, ischaemic heart disease, active peptic ulceration, asthma, significant hepatic dysfunction, diabetes mellitus, known intolerance of ACEI or indomethacin, or were women of childbearing potential.

All patients discontinued NSAID and antihypertensive therapy 3 weeks prior to randomization. Paracetamol up to $4\ g\ day^{-1}$ was substituted as an analgesic to control their symptoms. There was a 3 week single-blind run-in period during which patients took no antihypertensive treatment but took placebo and paracetamol as required. If patients remained hypertensive (untreated diastolic blood pressure (DBP) 95–115 mmHg) they proceeded to the double-blind phase. Patients were withdrawn from the study if their systolic blood pressure (SBP) > 180 mmHg, or DBP > 115 mmHg, or if their musculoskeletal symptoms were inadequately controlled with paracetamol. The study was a double-blind, placebo-controlled, randomized, four way crossover design. The four treatments were:

(1) trandolapril 2 mg once daily and indomethacin 25 mg three times daily in combination (plus paracetamol as required),

(2) trandolapril 2 mg once daily plus placebo (plus paracetamol as required),

(3) indomethacin 25 mg three times daily plus placebo (plus paracetamol as required),

(4) placebo and placebo (plus paracetamol as required).

Each week serum creatinine levels were measured. At the end of each 3 week treatment period renal plasma flow (RPF) and glomerular filtration rate (GFR) were measured using the *p*-aminohippurate (PAH) and inulin clearance methods [10]. Renal functional reserve was measured at the end of the PAH and inulin clearance methods during a 2 h i.v. infusion of dopamine ($2\ \mu g\ kg^{-1}$) and 10% amino acid solution [4]. Salt intake was not restricted during the study.

Renal function measurements

Patients attended the ward having eaten a light breakfast. Height and weight were recorded for estimation of body surface area. Cannulae were inserted into both arms, one for infusion of PAH and inulin and the other for venous sampling. Patients passed urine before dosing. Trandolapril, indomethacin or placebo were given orally with simultaneous i.v. bolus injections of PAH (0.5 g in 2.5 ml) (aminohippurate sodium, MSD, Rahway, New Jersey, USA) and inulin (2.5 g diluted to 30 ml with 0.9% saline) (Inutest, Laevosan-Gesellschaft, Linz, Austria), followed by a continuous infusion of PAH ($19.8\ mg\ min^{-1}$) and inulin ($19.5\ mg\ min^{-1}$) for 6 h. Overhydration was achieved by drinking 1 l water during the first hour of the PAH/inulin infusion, and maintained, by drinking a volume of water equivalent to the volume of urine passed at each time point up to 6 h post dose. Two aliquots (20 ml each) of urine collected at each time point were stored at -45° C. Blood (10 ml) was collected into a lithium heparin tube at each time point up to 6 h after the start of the PAH/inulin infusion. After centrifugation the plasma was stored at -45° C. PAH and inulin samples collected 2, 3 and 4 h after the start of the infusions were used to calculate static RPF and GFR.

Renal functional reserve was stimulated by infusing dopamine ($2\ \mu g\ kg^{-1}\ min^{-1}$) (Intropin, Du Pont, Letchworth, Herts., UK) and 10% amino acid solution (Vamin 9, Kabi Pharmacia, Milton Keynes, UK) for 2 h. The dopamine/amino acids infusion started 4 h after commencing the PAH/inulin infusion. Plasma and urine samples were collected 5, 5.5 and 6 h post dose for measurement of PAH and inulin levels from which RPF and GFR were calculated. A colorimetric method was used to determine PAH and inulin concentrations [11].

Both RPF and GFR were corrected for body surface to $1.73\ m^2$. RPF and GFR were calculated from the mean of the 2, 3 and 4 h time points. The mean and peak functional reserve RPF and GFR were calculated from the 5, 5.5 and 6 h time points. Filtration fraction (FF) was calculated as a ratio of GFR : RPF for baseline and mean functional reserve renal function for each treatment. Analysis of variance suitable for crossover design (SAS, Version 6.08 for Windows) was used to evaluate any change in RPF and GFR and renal functional reserve during the four treatment periods.

The study was designed with 80% power to detect a $90\ ml\ min^{-1}$ difference in RPF and a $20\ ml\ min^{-1}$ difference in GFR between treatments at the 5% significance level.

Results

Twenty-three eligible patients were recruited to the study. Six patients withdrew from the study after randomization due to; patients request (2), increased symptoms on withdrawal of NSAID (2), DBP > 115 mmHg (1) and failure to attend unit (1). At recruitment four patients were newly diagnosed hypertensives, seven patients were taking one and six were taking two antihypertensive drugs. Bendrofluazide (7) and calcium antagonists (5) were the drugs most commonly used. All patients required an NSAID, the most common being ibuprofen (3), sulindac (3) and azapropazone (3). The commonest indications for NSAID treatment were

osteoarthritis (10) and gout (4). Other indications were rheumatoid arthritis (1), deQuervain's tenosynovitis (1) and ankylosing spondylitis (1). The present analyses are based on the 17 patients (7 male) who completed the study. Renal functional reserve was not measured in four patients, either due to headache and nausea during dopamine/amino acid infusion (2), or voluntary withdrawal from this part of the study (2).

End of treatment clinic blood pressures were 152.9/98.6 mmHg (95% CI 147.2, 158.6/95.8, 101.4) with placebo and placebo, 150.4/94.9 mmHg (95% CI 144.7, 156.1/92.1, 97.7) with trandolapril and indomethacin, 148.2/96.5 mmHg (95% CI 142.5, 153.9/93.7, 99.3) with trandolapril and placebo, and 156.6/97.4 mmHg (95% CI 150.9, 162.3/94.6, 100.2) with indomethacin and placebo. There were no significant interactions between trandolapril and indomethacin for clinic SBP ($P=0.79$) or clinic DBP ($P=0.87$). When trandolapril treatments (placebo or with indomethacin) were compared with treatments without trandolapril (placebo or indomethacin), trandolapril lowered clinic SBP by 5.4 mmHg ($P=0.047$) and DBP by 2.3 mmHg ($P=0.08$) [12].

Renal plasma flow, glomerular filtration rate and filtration fraction

All data are presented in Table 1. Figures 1 and 2 show RPF and GFR respectively at each time point up to 6 h post dose.

Renal plasma flow was 309.2 ml min^{-1} (95% CI 246.8, 371.5) on placebo and placebo, 338.24 ml min^{-1} (95% CI 275.4, 401.1) on trandolapril and placebo, 335.4 ml min^{-1} (95% CI 267.9, 402.8) on indomethacin and placebo, and 327.0 ml min^{-1} (95% CI 260.5, 393.4) on trandolapril and indomethacin. There was no significant interaction between trandolapril and indomethacin ($P=0.10$). Neither trandolapril ($P=0.45$) nor indomethacin ($P=0.67$) had any effect on RPF.

There was no significant difference in RPF between treatments: -22.79 ml min^{-1} (95% CI -54.82, 9.24) for placebo and trandolapril, -10.37 ml min^{-1} (95% CI -30.7, 9.96) for placebo and indomethacin, -14.78 ml min^{-1} (95% CI -50.33, 20.77) for placebo and trandolapril with indomethacin.

During dopamine/amino acid infusion RPF rose to 547.6 ml min^{-1} (95% CI 403.8, 691.4) on placebo and placebo, 559.6 ml min^{-1} (95% CI 370.6, 748.5) on trandolapril and placebo, 409.3 ml min^{-1} (95% CI 249.3, 569.4) on indomethacin and placebo, and 560.4 ml min^{-1} (95% CI 409.9, 711.0) on trandolapril and indomethacin. There was no significant interaction between trandolapril and indomethacin ($P=0.53$). Neither trandolapril ($P=0.83$) nor indomethacin ($P=0.31$) had any significant effect on RPF.

There was no significant difference in functional reserve RPF between treatments: -34.96 ml min^{-1} (95% CI -119.8, 49.88) for placebo and trandolapril, 29.78 ml min^{-1} -15.18, 74.74) for placebo and indomethacin, and -25.84 ml min^{-1} (95% CI -87.62, 35.94) for placebo and trandolapril with indomethacin.

Glomerular filtration rate was 73.8 ml min^{-1} (95% CI 60.8, 86.7) on placebo and placebo, 76.3 ml min^{-1} (95% CI 63.2, 89.4) on trandolapril and placebo, 81.8 ml min^{-1} (95% CI 66.1, 97.5) on indomethacin and placebo, and 74.6 ml min^{-1} (95% CI 61.5, 87.6) on trandolapril and indomethacin. There was no significant interaction between trandolapril and indomethacin ($P=0.08$). Neither trandolapril ($P=0.49$) nor indomethacin ($P=0.31$) had any effect on GFR.

There was no significant difference in GFR between treatments: -1.01 ml min^{-1} (95% CI -7.45, 5.42) for placebo and trandolapril, -7.88 ml min^{-1} (95% CI -15.08, -0.68) for placebo and indomethacin, and -0.36 ml min^{-1} (95% CI -7.58, 6.86) for placebo and trandolapril with indomethacin.

During dopamine/amino acid infusion, GFR rose to 95.5 ml min^{-1} (95% CI 78.8, 112.3) on placebo and placebo, 84.0 ml min^{-1} (95% CI 62.5, 105.3) on trandolapril and placebo, 86.45 ml min^{-1} (95% CI 65.0, 107.9) on indomethacin and placebo, and 85.4 ml min^{-1} (95% CI 66.3, 104.5) on trandolapril and indomethacin. There was no significant interaction between trandolapril and indomethacin ($P=0.39$). Neither trandolapril ($P=0.63$) nor indomethacin ($P=0.20$) had any effect on GFR.

There was no significant difference in functional reserve GFR between treatments: 5.13 ml min^{-1} (95% CI -4.97, 15.23) for placebo and trandolapril, 6.31 ml min^{-1} (95% CI -1.88, 14.5) for placebo and indomethacin, 7.21 ml min^{-1} (95% CI 1.26, 13.16) for placebo and trandolapril with indomethacin.

Baseline FF was similar between treatments: 23.9% on placebo and placebo, 22.6% on trandolapril and placebo,

Table 1 Renal function (RPF and GFR) ± S.E. mean and filtration fraction (%) for each treatment.

	Trandolapril and indomethacin	*Indomethacin*	*Trandolapril*	*Placebo*
RPF (ml min^{-1})	326.92 ± 30.24	335.38 ± 31.81	338.24 ± 29.65	309.16 ± 29.41
RPF mean reserve (ml min^{-1})	560.43 ± 69.69	505.94 ± 74.10	559.56 ± 86.72	547.63 ± 66.58
% rise in RPF	41.66	18.06	39.55	43.55
RPF peak reserve (ml min^{-1})	567.27 ± 73.94	555.82 ± 109.48	583.89 ± 109.58	558.89 ± 64.23
GFR (ml min^{-1})	74.56 ± 5.84	81.76 ± 7.41	76.29 ± 6.18	73.79 ± 6.11
GFR mean reserve (ml min^{-1})	85.37 ± 8.54	86.45 ± 9.94	83.9 ± 9.84	92.52 ± 7.49
% rise in GFR	12.66	5.43	9.07	20.24
GFR peak reserve (ml min^{-1})	88.36 ± 12.74	93.79 ± 14.61	88.35 ± 13.20	96.99 ± 8.39
Baseline filtration fraction (%)	22.64	24.37	22.58	23.91
Reserve filtration fraction (%)	15.10	17.01	15.00	16.93

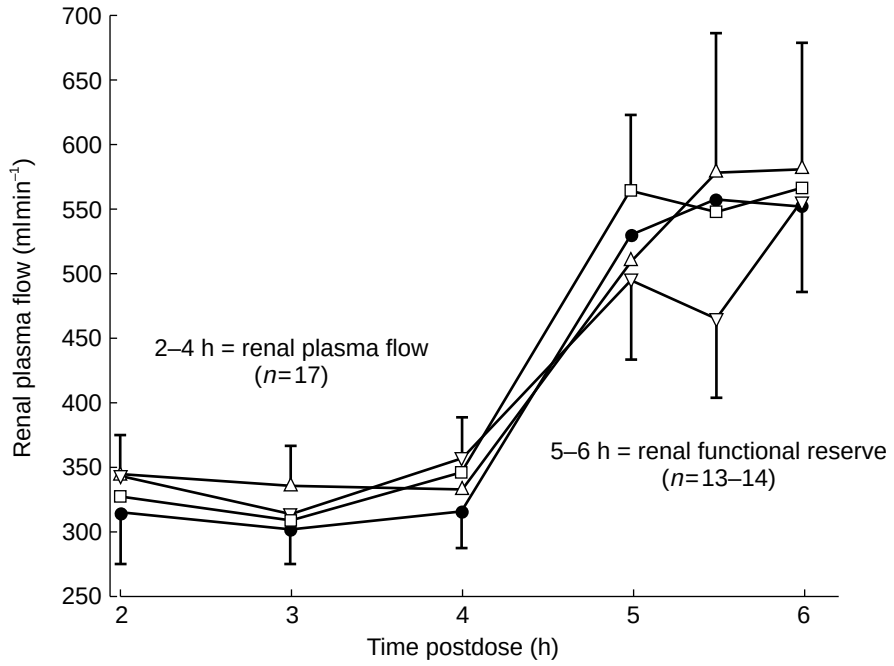

Figure 1 Renal plasma flow (±s.e.mean) by *p*-aminohippurate method. □ trandolapril and indomethacin, ▽ indomethacin, ● placebo, △ trandolapril.

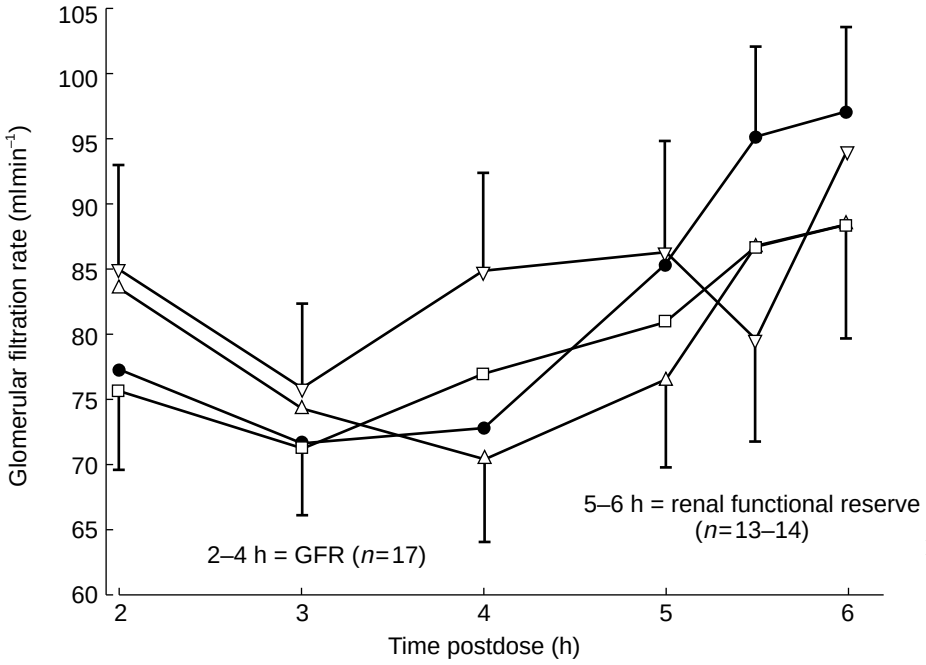

Figure 2 Glomerular filtration rate (±s.e.mean) by inulin method. □ trandolapril and indomethacin, ▽ indomethacin, ● placebo, △ trandolapril.

24.4% on indomethacin and placebo, and 22.6% on trandolapril and indomethacin. Following dopamine/amino acid infusion FF fell to 16.9% on placebo and placebo, 15.0% on trandolapril and placebo, 17.0% on indomethacin and placebo and 15.1% on trandolapril and indomethacin.

Discussion

Hypertension and musculoskeletal disorders commonly coexist, and with increasing use of ACEI in the treatment of hypertension, NSAIDs and ACEI may be co-prescribed. This study compared the effect of trandolapril alone and in combination with indomethacin on RPF and GFR, and functional reserve RPF and GFR in a group of hypertensive patients who had an indication for chronic NSAID use. Baseline RPF and GFR, although lower than expected, were similar to other data from the same laboratory [13, 14].

In the present study mean GFR (placebo and placebo) rose from 72.79 ml min^{-1} to 92.52 ml min^{-1} following dopamine/amino acid infusion. A rise in GFR of 48 ml min^{-1} has been reported by Juncos *et al.* [15], Rodríguez-Iturbe [7] and Cottone *et al.* [5]. However, Cottone *et al.* studied younger (mean age 40 years) patients with newly diagnosed hypertension, who may respond differently to dopamine/amino acid stimulation than the older (mean age 53.5 years) patients with established hypertension in the present study. Tack *et al.* [16] evaluated renal functional reserve in renal transplant recipients and found that hypertensive patients had a greater increase in RFR than normotensive patients (23±10 *vs*

11 ± 5 ml min^{-1} 1.73 m^{-2}). This increment in RFR is comparable with that seen in our study.

The present study did not show a significant interaction between indomethacin and trandolapril on either RPF or GFR. Passmore *et al.* [17] reported no effect of indomethacin on baseline RPF or GFR in healthy volunteers, and Dibona [18] reported no change in either RPF or GFR in salt replete healthy subjects receiving indomethacin.

When renal function is normal FF varies between 22–28% and falls by 2–3% following dopamine/amino acid infusion [4]. Baseline FF in the present study was similar for all treatments, and fell by approximately 7% following dopamine/amino acid infusion with all treatments. Low dose dopamine increases renal perfusion and explains the rise in RPF observed in the present study. FF falls because the rise in RPF is relatively larger than the increase in GFR.

This is the first study to investigate the possible interaction between such drugs on renal function in hypertensive patients. RPF and GFR were measured using the well established PAH/inulin method which gives a reliable measurement of renal function provided urinary output is maintained [10]. Although a type II error may have prevented it, our data did not show any interaction between trandolapril or indomethacin on RPF or GFR, and we could exclude a difference of 20 ml min^{-1} for GFR and 90 ml min^{-1} for RPF. Whilst these are quite large differences, they are the clinically important differences that would be sought in drug induced renal impairment.

Acute ACE inhibition has previously been shown to enhance [19] and indomethacin to inhibit [20] a frusemide-induced natriuresis and the frusemide-induced rise in renal plasma flow. The mechanisms are thought to be prostaglandin dependent. Frusemide also inhibits the frusemide induced rise in GFR [20]. These findings lend support to the hypothesis that renal functional reserve might be altered by ACEIs and indomethacin. In the present study we did not detect a clinically significant change in reserve capacity and thus we cannot support this hypothesis.

These data provide some reassurance that the combination of ACEI and NSAIDs does not produce clinical deterioration in baseline renal function. In addition, renal functional reserve appears to be preserved.

In conclusion, it would appear that the combination of indomethacin and trandolapril does not adversely affect renal function and can be used safely in combination in hypertensive patients.

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