

Journal of Clinical and Basic Cardiology

An Independent International Scientific Journal



Journal of Clinical and Basic Cardiology 2003; 6 (Issue 1-4), 45-47

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Comparative Effects of Fosinopril and Irbesartan on Haematopoiesis in Essential Hypertensives

N. R. Robles¹, E. Angulo¹, J. Grois¹, A. Barquero²

Objective: To compare the response of erythropoiesis to an angiotensin receptor blocker, irbesartan with an angiotensin converting enzyme inhibitor, fosinopril, in essential hypertensive patients with normal renal function.

Design and Methods: Thirty patients were randomized to receive either irbesartan (150 mg once daily) (n = 15, mean age 65.2 ± 8.7 years) or fosinopril (20 mg once daily) (n = 15, mean age 57.4 ± 11.5 years, difference is not significant) during 12 weeks. Plasma erythropoietin, haemoglobin (Hb) and haematocrit (Hc) levels were measured at start and monthly after receiving the treatment. All values are expressed as mean ± 1 SD.

Results: Irbesartan decreased erythropoietin levels (baseline 20.7 ± 1.3 vs. 18.1 ± 3.7 mU/ml, p = 0.019), but they remained unchanged with fosinopril (baseline 18.8 ± 1.3 vs. 18.6 ± 1.6 mU/ml). Hb levels were lowered in the irbesartan group (baseline 13.8 ± 1.2 vs. 13.5 ± 1.1 g/dl, p = 0.029), but they did not change in fosinopril treated patients (baseline 14.6 ± 1.3 vs. 14.5 ± 1.3 g/dl). Hc did not show any change either in the irbesartan group (baseline 40.9 ± 3.7 vs. 40.8 ± 3.3 %) or in the fosinopril group (baseline 14.6 ± 1.3 vs. 14.5 ± 1.3 %).

Conclusions: Irbesartan lowered erythropoietin secretion and haemoglobin levels in essential hypertensives. Fosinopril can neither influence erythropoietin secretion nor decrease haemoglobin levels. Angiotensin receptor blockers seem to get higher efficacy for antagonizing angiotensin effects. Safety of angiotensin receptor blockers in anaemic hypertensive patients should be studied. *J Clin Basic Cardiol* 2003; 6: 45–7.

Key words: angiotensin, haematopoiesis, angiotensin converting enzyme inhibitors, angiotensin receptor antagonist

Experimental and clinical data suggest that there is an association between the renin-angiotensin system and haematopoiesis in several clinical conditions such as kidney transplantation [1, 2], chronic haemodialysis [3], renovascular hypertension [4], chronic obstructive pulmonary disease [5] and severe heart failure [6]. Increased erythropoietin secretion has been reported following the administration of renin or angiotensin to experimental animals [7, 8]. On the other hand, administration of angiotensin converting enzyme inhibitors (ACEI) caused a decrease in erythropoietin levels and haemoglobin values in uraemic patients [3, 9, 10], kidney transplant recipients [11, 12] and patients with congestive heart failure [13].

Little is known about the relationship between the renin-angiotensin axis and erythropoietin secretion in essential hypertensives without renal failure. Moreover, the possible effects of blocking the renin-angiotensin system in this kind of patient have never been evaluated to our knowledge. The recent introduction of angiotensin receptor antagonists (ARA) has introduced a new approach to this therapeutic objective. Although ARA and ACEI prevent the untoward effects of angiotensin II, each does it in a distinct manner. ACEI repress the production of angiotensin II, ARA blocks the angiotensin-II AT1 receptor. This different mechanism of action may confer the ARA a therapeutic advantage over the ACEI [14].

The objective of the present study was to assess whether blocking the renin-angiotensin system may decrease erythropoietin secretion in essential hypertensives. Moreover, we compared the effect of an ARA (irbesartan) with an ACEI (fosinopril) to assess the distinct ability of each drug to reduce haematopoiesis.

Material and Methods

Patients and Definitions

Thirty patients were randomized to receive either irbesartan (150 mg once daily) (n = 15, mean age 65.2 ± 8.7 years, 6 male and 9 female) or fosinopril (20 mg once daily) (n = 15, mean age 57.4 ± 11.5 years, 9 male and 6 female, differences are not significant). Eligible patients (men or women) presented a diagnosis of mild or moderate essential hypertension (blood pressure > 140/90 mmHg and < 180/110 mmHg). The presence of creatinine > 1.5 mg/dl, unstable angina, myocardial infarction or stroke in the last three months, heart failure, hyperkalaemia, COPD, haematological diseases, haemoglobin < 13 g/dl or > 17 g/dl, were considered as exclusion criteria, as well as pregnancy and known hypersensitivity to any of the tested drugs. Only postmenopausal women were included.

Study Design

After withdrawal of any antihypertensive therapy, if needed, eligible patients entered a 2-week washout phase. At the end of the run-in phase, patients were randomly assigned to one of the two arms of the study: irbesartan 150 mg/day or fosinopril 20 mg/day. All medications were administered o.d. during the following 4 weeks. After 4 weeks of active treatment, these were titrated by adding 12.5 mg/day if BP > 140/90 mmHg. At the 8th week, non-controlled patients under combined treatment were excluded. Patients were followed until the 12 weeks of follow-up were completed. All the patients were recommended to limit sodium intake.

Outcome Measures

At baseline and after 4, 8, and 12 weeks the following parameters were recorded: blood pressure, heart rate, and body weight. Completed blood cell counts were collected in the

Received: July 8th, 2002; accepted: August 19th, 2002.

From the ¹Servicio de Hematología and the ²Servicio de Análisis Clínicos, Unidad de Hipertensión Arterial, Infanta Cristina Hospital, Badajoz, Spain.

Correspondence to: Nicolás Roberto Robles, MD, Unidad de HTA, Hospital Infanta Cristina, Carretera de Portugal s/n, 06080 Badajoz, Spain; e-mail: nroblesp@meditex.es

morning after the patients had remained supine for at least 30 minutes and processed using automated standard techniques. Erythropoietin was measured by enzyme-immunoassay (R & D System, Minneapolis, Minnesota).

Statistical Analysis

Results are expressed as mean $\pm$ 1 standard deviation. Paired and non-paired Student's *t*-test was used for continuous data and the chi square test was used for discrete data. All statistical tests were two-sided. *P* values lower than 0.05 were considered as significant. Analysis was developed with the statistical package SPSS 9.0.

Results

Blood Pressure

A reduction of SBP and DBP was observed in both treatment groups throughout the study. In order to obtain further BP reduction, hydrochlorothiazide was added in 6 patients with inadequate BP response in the 4th week (3 patients in the irbesartan group) and 8th week (2 patients in the irbesartan group and 1 patient in the fosinopril group). SBP was reduced in the irbesartan group from 157.7 ± 11.2 to 131.0 ± 8.7 mmHg (12th week, $p < 0.001$). DBP decreased from 94.1 ± 5.6 to 82.7 ± 4.2 mmHg ($p < 0.001$). In the fosinopril group SBP was reduced from 147.9 ± 11.7 to 132.2 ± 12.4 mmHg ($p < 0.001$) and DBP decreased from 92.3 ± 6.3 to 84.0 ± 5.4 mmHg ($p < 0.001$).

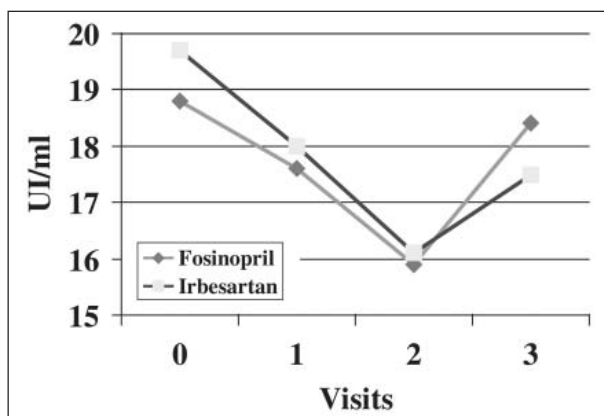


Figure 1. Erythropoietin levels decreased under irbesartan treatment ($p < 0.05$) and this effect remained until the end of follow-up. Fosinopril showed only a transient decrease of erythropoietin levels.

Erythropoietin

The patients treated with irbesartan showed a reduction of plasma haemoglobin levels (Figure 1). This decrease was significant in the second visit (baseline, 19.6 ± 4.3 ; 4th week, 17.7 ± 2.0 UI/l, $p = 0.027$) and the haemoglobin levels remained reduced along the study (8th week 15.5 ± 3.1 , $p = 0.012$ vs. baseline; 12th 17.0 ± 3.2 , $p = 0.013$ vs. baseline). In the fosinopril group haemoglobin levels showed only a transient decrease in the 8th week of follow-up (15.9 ± 3.1 , $p = 0.027$ vs. baseline 18.8 ± 3.5 UI/l, and afterwards plasma haemoglobin increased to the previous level (17.5 ± 3.6 UI/l, not significant). There was no change in the 4th week (17.8 ± 2.0 UI/l) vs. baseline level.

Red Blood Cells

During therapy with irbesartan, haemoglobin decreased from 13.8 ± 1.2 (baseline) to 13.5 ± 1.1 ($p = 0.03$). The patients treated with fosinopril did not show any change in haemoglobin. Haematocrit, red blood cell count and reticulocyte count did not change neither in the irbesartan group nor in the fosinopril group.

Mean corpuscular haemoglobin (MCH) did not change after treatment with either fosinopril or irbesartan. Mean corpuscular haemoglobin concentration (MCHC) decreased in the irbesartan group (30.0 ± 0.5 , $p = 0.027$ vs. baseline 33.7 ± 0.8) but not in the fosinopril group. Mean corpuscular volume (MCV) increased in both groups at the end of follow-up. All values are shown in Tables 1 and 2.

Discussion

In essential hypertensives irbesartan significantly decreased erythropoietin secretion. Simultaneously, a small but statistically significant reduction in plasma haemoglobin and MCHC was shown after irbesartan treatment. Fosinopril showed only a transient lowering in plasma erythropoietin levels without showing any effect on plasma haemoglobin and MCHC. No changes were detected of either haematocrit or red blood cell count. To our knowledge this is the first report of this kind of effect of ARA on essential hypertensives, though there are some reports on this action in kidney graft recipients with erythrocytosis.

So, the clinical effect of using ARA (or ACE inhibitors) seems to be small and not clinically dangerous in a selected population of essential hypertensives: men and postmenopausal women without anaemia. Nevertheless, the possible effect of this kind of drugs (ARA) on women with normal ovarian function and/or anaemia is still not known. The ability of ARA to reduce haematopoiesis should raise some concerns on the safety of its use in these two latter groups of patients. Indeed, it has been shown that use of ACE inhibitors may

Table 1. Red blood cells under irbesartan treatment

	Baseline	4 th week	8 th week	12 th week
RBC Count	4,655 $\pm$ 439	4,563 $\pm$ 382	4,601 $\pm$ 322	4,539 $\pm$ 301
Haematocrit	41.0 $\pm$ 3.9	40.4 $\pm$ 3.5	40.8 $\pm$ 2.7	40.8 $\pm$ 3.3
Haemoglobin	13.8 $\pm$ 1.2	13.6 $\pm$ 1.2	13.6 $\pm$ 1.0	13.5 $\pm$ 1.1
MCV	88.0 $\pm$ 4.0	88.5 $\pm$ 3.9	88.5 $\pm$ 4.0	89.8 $\pm$ 3.7
MCH	29.7 $\pm$ 1.4	29.9 $\pm$ 1.3	29.6 $\pm$ 1.4	29.6 $\pm$ 1.3
MCHC	33.7 $\pm$ 0.8	33.8 $\pm$ 0.7	33.5 $\pm$ 0.7	30.0 $\pm$ 0.5
Reticulocytes	12.9 $\pm$ 0.5	13.1 $\pm$ 0.6	13.3 $\pm$ 0.6	13.1 $\pm$ 0.6

RBC = red blood cells; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration

Table 2. Red blood cells under fosinopril treatment

	Baseline	4 th week	8 th week	12 th week
RBC Count	4,703 $\pm$ 440	4,658 $\pm$ 436	4,705 $\pm$ 441	4,660 $\pm$ 356
Haematocrit	43.2 $\pm$ 3.9	42.8 $\pm$ 3.4	43.3 $\pm$ 3.2	43.8 $\pm$ 3.3
Haemoglobin	14.6 $\pm$ 1.3	14.3 $\pm$ 1.3	14.4 $\pm$ 1.1	14.5 $\pm$ 1.3
MCV	91.2 $\pm$ 3.1	91.8 $\pm$ 3.4	91.9 $\pm$ 3.6	92.7 $\pm$ 3.0
MCH	31.1 $\pm$ 1.1	31.2 $\pm$ 1.4	31.1 $\pm$ 1.3	31.1 $\pm$ 1.2
MCHC	34.0 $\pm$ 0.9	34.0 $\pm$ 0.9	33.7 $\pm$ 0.7	33.6 $\pm$ 0.8
Reticulocytes	12.7 $\pm$ 0.6	12.9 $\pm$ 0.7	12.9 $\pm$ 0.6	12.9 $\pm$ 0.6

RBC = red blood cells; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration

worsen chronic renal failure anaemia in uraemic patients [3, 9, 10]. New studies will be needed to define this issue in anaemic or anaemic prone patients.

Conversely, this is a positive effect which has therapeutic use in polyglobulic transplant recipients [11, 12, 15–17] and, more recently, in patients with chronic pulmonary disease [1, 8]. Posttransplantation erythrocytosis is a phenomenon limited to renal transplant recipients, and although some aspect of its pathogenesis remain obscure, the use of ACE inhibitors or ARA can significantly lower haematocrit by decreasing red cell production in patients with posttransplantation erythrocytosis. A variety of possible mechanisms has been suggested, including abnormal bone marrow production of angiotensin II and increased sensitivity of erythroid precursor to angiotensin II [19].

There is a considerable amount of experimental evidence linking the renin-angiotensin system to haematopoiesis. Both renin and angiotensin stimulate erythropoietin production when injected into experimental animals [20–22]. It has been shown that renin, renin substrate and angiotensin II are correlated to erythropoietin levels in the hypoxaemic rat model. These rats produced a threefold increase in erythropoietin secretion when renin was injected subcutaneously. This effect was abolished when rats were pretreated with a single oral dose of an ACE inhibitor, an effect which was reversed with angiotensin II administration [7]. On the other hand, type I diabetes subjects with hyporeninaemic hypoadosteronism had low haemoglobin concentration and inappropriately low serum erythropoietin levels [23].

The renin-angiotensin system seems to be involved in erythropoiesis at the progenitor cell level [19]. Erythroid burst-forming units (BFU-E) from healthy humans expressed the angiotensin AT₁ receptor after 6 to 9 days of growth in culture. Angiotensin II, in the presence of erythropoietin, stimulated BFU-E colony formation when added to the cell culture medium, and this effect was eliminated by the addition of losartan, an ARA, to the medium. Conversely, ACE inhibitors failed to show this effect [24]. In another study, enalapril added to a cell culture inhibited BFU-E colony formation in posttransplant erythrocytosis patients, but there was no evidence of colony inhibition in the cultures from control patients [2]. Taken altogether this data suggest that ARA, but not ACE inhibitors, could inhibit haematopoiesis in normal patients.

In vivo studies have shown that ACE inhibitors and ARA can lower haematocrit in posttransplant recipient erythrocytosis [11, 12, 15–17]. It has been reported that losartan can achieve a more pronounced decrease of haematocrit in posttransplant recipient erythrocytosis non-responders than ramipril [17]. Hence, ARA might get a higher haematopoiesis inhibition than ACE inhibitors in posttransplant clinical settings. Our results suggest that in essential hypertensives ARA are also more efficient than ACE inhibitors in blocking erythropoietin production.

It has been suggested that angiotensin may act by direct stimulation of erythroid progenitors. Angiotensin II has been recognized as a growth factor for a variety of cells types, including renal tubular epithelial cells, vascular smooth muscle cells, heart myocytes and fibroblasts [25]. This raises the possibility that angiotensin II could act directly in the bone marrow as a growth factor to stimulate production or maturation of erythrocyte progenitors. As a matter of fact, it has been shown that angiotensin II enhances erythropoietin-stimulated erythroid proliferation [24]. Our data suggest an indirect effect of angiotensin II on haematopoiesis by lowering erythropoietin secretion, but they can exclude a direct effect of angiotensin II on erythroid progenitors. Maybe angio-

tensin II acts by a double mechanism on erythroid progenitors.

Irbesartan, an ARA, seems to decrease erythropoietin secretion in essential hypertensives. Fosinopril can only achieve a transient similar effect. This decrease in erythropoietin secretion induces minor haematological changes in essential hypertensives without anaemia (including postmenopausal women) and, hence, its clinical use seems to be safe. The safety of treatment with ARA in anaemic patients and women with normal ovarian function needs to be tested.

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