Farmacia Hospitalaria
ISSN: 1130-6343
farmhosp@grupoaulamedica.com
Sociedad Española de Farmacia Hospitalaria
España

Márquez-Peiró, J.F.; Porta-Oltra, B.; Borrás-Almenar, C.
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Farmacia Hospitalaria, vol. 33, núm. 2, 2009, pp. 66-71
Sociedad Española de Farmacia Hospitalaria
Madrid, España

Farm Hosp. 2009;**33(2)**:66-71

Farmacia
HOSPITALARIA

www.elsevier.es/farmhosp

ORIGINAL ARTICLE

Therapeutic exchange of angiotensin II receptor antagonists in patients hospitalised in a traumatology unit

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Received April 24, 2008; accepted February 10, 2009

KEYWORDS
Angiotensin II receptor antagonists;
Therapeutic exchange;
Arterial hypertension

Abstract
Objective: To analyse the proportion of patients whose blood pressure values have remained within the established therapeutic aim, so as to reduce cardiovascular risk following therapeutic exchange of angiotensin II receptor antagonists (AIIRA).
Methods: Analytical, observational, prospective, longitudinal study with pre-post analysis. Patients undergoing AIIRA treatment who were not included in the hospital's pharmaco-therapeutic guide were included in the study over those who had undergone a normalised therapeutic exchange of AIIRA. Variable response: proportion of patients whose blood pressure levels (BP levels) remained within the established therapeutic aim for the prevention of cardiovascular accidents. Other variables: systolic and diastolic blood pressure values (SBP and DBP) in the month prior to hospitalisation and after therapeutic exchange, antihypertensive medication, comorbidities.
Results: Thirty-seven patients were included in the study. Following therapeutic exchange, 81.08% maintained BP values within the range established by the European Society of Hypertension-European Society of Cardiology Committee. SBP difference: 4.82 (95% confidence interval [CI], −1.09 to 10.74; *P*=.107); DBP difference: −0.15 (95% CI, −3.27 to 2.97; *P*=.924), and therefore not clinically significant.
Conclusions: The normalised procedure for therapeutic exchange of AIIRA is effective and safe for patients in terms of maintaining BP, which allows for adequate control of BP during the hospital stay.

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1130-6343/$ - see front matter

PALABRAS CLAVE
Antagonistas del receptor de angiotensina II;
Intercambio terapéutico;
Hipertensión arterial

Intercambio terapéutico de antagonistas del receptor de angiotensina II en pacientes hospitalizados en una unidad de traumatología

Resumen
Objetivo: Analizar la proporción de pacientes que mantiene los valores de presión arterial (PA) dentro del objetivo terapéutico establecido para reducir el riesgo cardiovascular tras el intercambio terapéutico de antagonistas del receptor de angiotensina II (ARA-II).
Métodos: Estudio observacional, analítico, prospectivo y longitudinal, con análisis pre-post. Se incluyeron pacientes en tratamiento con ARA-II no incluidos en la guía farmacoterapéutica del hospital en los que se realizó un intercambio terapéutico normalizado de ARA-II. Variable respuesta: proporción de pacientes que mantienen los valores de PA dentro del objetivo terapéutico establecido para la prevención de accidentes cardiovasculares. Otras variables: valores de PA sistólica (PAS) y diastólica (PAD) el mes previo al ingreso y tras el intercambio terapéutico, medicamentos antihipertensivos, comorbilidades.
Resultados: Se incluyó a 37 pacientes. Tras el intercambio terapéutico el 81,08% de los pacientes mantiene los valores de PA dentro del objetivo establecido por la European Society of Hypertension-European Society of Cardiology Committee. Diferencia PAS: 4,82 (intervalo de confianza [IC] del 95 %, −1,09 a 10,74; p = 0,107); diferencia PAD: −0,15 (IC del 95 %, −3,27 a 2,97; p = 0,924) y, por tanto, sin significación clínica.
Conclusiones: El procedimiento normalizado para intercambio terapéutico de ARA-II es efectivo y seguro para los pacientes en términos de mantenimiento de la PA, permitiendo un adecuado control de la PA durante la estancia hospitalaria.

Introduction

One of the functions of a hospital pharmacist is the selection and objective review of drugs, as well as the development of directives outlining the basics for the rational use of drugs via protocols and explicit criteria, which increase the possibility of obtaining optimal pharmacotherapeutic results in patients.[1]

The application of a pharmacotherapeutic guide system in hospitals requires the establishment of criteria for action in the event of the prescription of treatments from the outpatient sphere which are not included in the pharmacotherapeutic guide. This has led to the development of therapeutic exchange programmes in addition to the pharmacotherapeutic guide, with the aim of suggesting the use of the best therapeutic alternative available between the drugs selected within an institution, where a therapeutic alternative is understood as the possibility of exchanging drugs, in a consensual way, for different chemical structures from the same pharmacological or therapeutic class, which are hoped will have similar therapeutic effects and adverse reactions when administered in therapeutically equivalent doses.[2]

According to the GENESIS group forming part of the Spanish Society of Hospital Pharmacy, therapeutic exchange may be defined as the substitution of therapeutically equivalent drugs by the pharmacist based on consensual and previously established criteria.[3] In this respect, the objective of therapeutic exchange is continuity in the patient's treatment and promotion of the efficient use of drugs.[4] Furthermore, standard procedures for therapeutic exchange must be constantly updated and it is recommended that studies are carried out to assess the efficacy and safety of these, as well as determine the degree of patient satisfaction with respect to the therapeutic exchange.

With regard to the specific case of the treatment of arterial hypertension (AH), there are currently 6 main drug groups (diuretics, beta-blockers, calcium blockers, angiotensin-converting enzyme inhibitors [ACE inhibitor], angiotensin II receptor antagonists [AIIRAs], and alpha blockers), and in total there are 62 active ingredients and more than 100 pharmaceutical products including specialties with established antihypertensive associations. In addition to this, within these therapeutic groups, there has been an increase in the so-called *me-too* drugs (drugs with similar chemical structures that are not any more effective than those on the market for the same indication), which does not contribute to the rational use of drugs.[5] As a consequence, AIIRAs are one of the main drug groups included in the therapeutic exchange programmes.

The theory put forward in the present article is that the therapeutic exchange protocol implemented for AIIRA in this hospital is effective and safe in terms of maintaining blood pressure (BP) in patients hospitalised in a traumatology unit. To confirm this theory, the main objective established was the analysis of the proportion of patients that maintain BP levels within the therapeutic aim established to reduce cardiovascular risk following the therapeutic exchange of AIIRA. The secondary objectives were to analyse variations in the BP values in patients following the therapeutic exchange of AIIRA in the treatment of AH and their potential clinical significance.

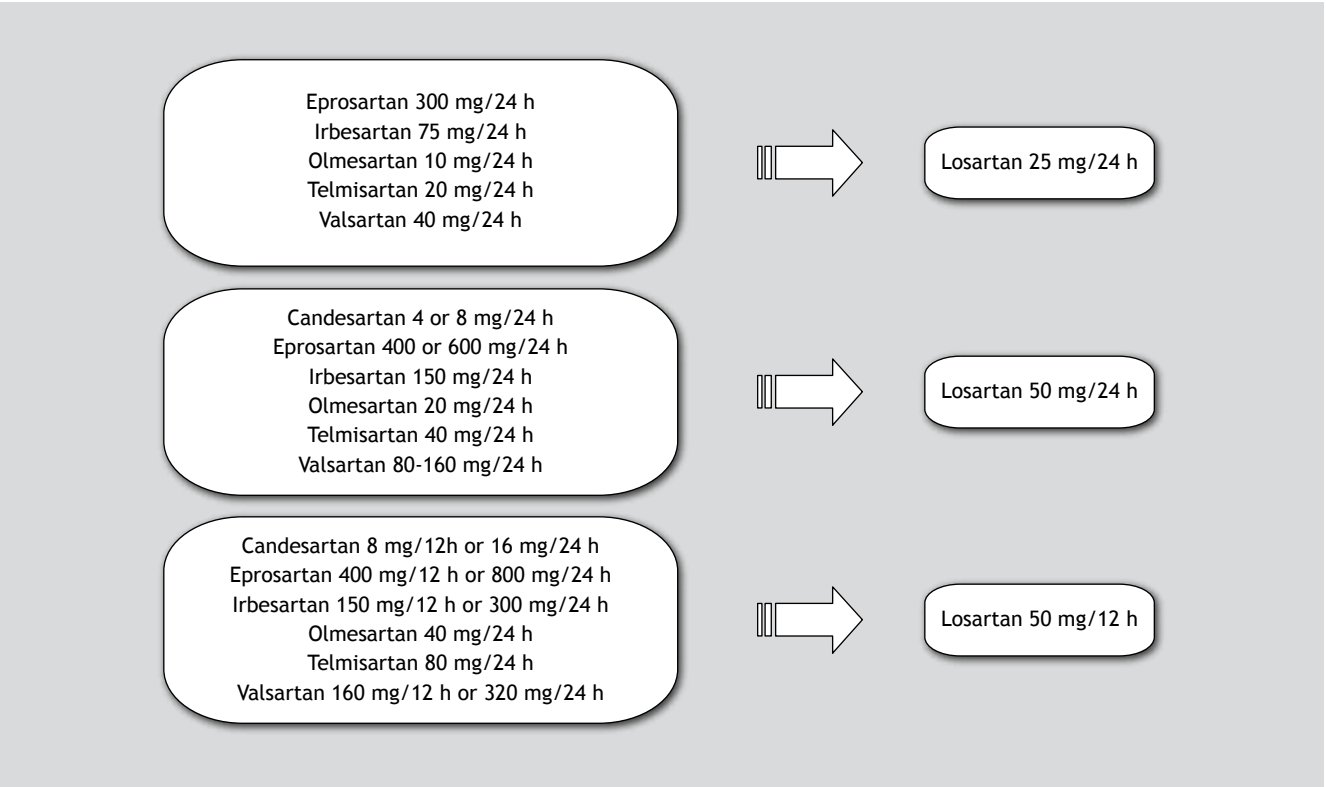

Figure 1 Standard procedure for therapeutic exchange of angiotensin II receptor antagonists implemented in the hospital.

Methods

To evaluate the efficacy of the therapeutic exchange of AIIRA, an observational, analytical, prospective, and longitudinal study was performed, with within subject analysis, using the history of BP values provided by the patients.

The study included all patients aged 18 and above, with AH and undergoing treatment with AIIRA, who were admitted to the orthopaedic surgery and traumatology departments, and who gave verbal consent to participate in the study. The study excluded patients in whom the therapeutic exchange of AIIRA was not performed, those for whom therapeutic exchange of other antihypertensive drugs was performed, as well as patients who remained in hospital for less than 5 days and those who could not provide a history for their BP values from the month prior to admission. The recruitment of patients was performed following a consecutive sampling system (nonprobability sampling). The therapeutic exchange of AIIRA was performed according to the standard procedure in the hospital (Figure 1) taking into account that the only AIIRA included in the pharmacotherapeutic guide is losartan 50 mg.

The main response variable was the *percentage of patients who maintained values of BP within the therapeutic aim established for the prevention of strokes*. The secondary response variable was the *difference between systolic BP (SBP) and diastolic blood pressure (DBP) values following therapeutic exchange*. The objective SBP and DBP values of the antihypertensive treatment considered in the study are those indicated by the European Society of Hypertension and the European Society of Cardiology, where the reduction in BP values was considered the aim for patients with comorbidities such as diabetes, etc.[6]

Other variables considered in both groups of patients were:

- Outpatient SBP and DBP values, obtained from the patient's own register from routine controls carried out in pharmacies and/or health centres. The mean of the values from the month prior to admission to hospital were obtained
- Antihypertensive treatment: active ingredients used
- Main diagnosis
- Age, sex, and body mass index

According to the consensus guides regarding chronic treatment in the perioperative period,[7] suspension of AIIRA treatment is recommended in the immediate perioperative period, with home treatment normally reintroduced 24-48 h after surgery if there are no complications. Consequently, although BP values were collected on a daily basis, they were only considered valid as of 24 h after the reintroduction of the drug and always 48 h after surgery. In this way a lavage period was ensured to eliminate the effect of the AIIRA taken chronically by the patient as an outpatient.

BP was measured daily at the same time interval (first thing in the morning) and using a correctly calibrated automatic arm tension meter. The remaining information was collected indirectly via an interview with the patient.

Table 1 Basal characteristics of the patients included in the study (n=37)

Variables	Results (n; %)
Sex, male/female	17/20
Age,[a] mean (SD)	65.67 (10.26)
BMI, mean (SD), kg/m^2	29.55 (5.98)
Stage of hypertension[b] (n; %)	
Stage 0	26 (70.3)
Stage 1	7 (18.9)
Stage 2	4 (10.8)
Comorbidities (n; %)	
No comorbidities	18 (48.6)
Dyslipemia	17 (46)
Diabetes	2 (5.4)
AIIRA in chronic treatment	
Valsartan	25 (67.6)
Irbesartan	6 (16.2)
Eprosartan	4 (10.8)
Candesartan	2 (5.4)
Other antihypertensives (n; %)	
None	15 (40.5)
Diuretics	10 (27)
Calcium antagonists	9 (24.3)
ACE inhibitor	3 (8.2)

ACE inhibitor indicates angiotensin-converting enzyme inhibitors; AIIRA, angiotensin II receptor antagonists; BMI, body mass index; SD, standard deviation.
[a]Age in years.
[b]Classification of blood pressure (BP) values according to guidelines from the European Society of Hypertension-European Society of Cardiology Committee.
[c]The *z* test for comparison of proportions or exact tests were performed for categorical variables (if conditions for applying the *z* test were not met) and for quantitative variables, the *t* test for independent samplesor the Wilcoxon signed-rank test. In all cases a Fisher's *P* value of .05 was considered to determine the significant differences.

The sample size was calculated and an alpha error of 5% was considered, with a potential to detect differences of 80%, taking into account 20% of conflicting pairs as clinically significant. As a result, it was necessary to include 37 patients in the study.

Statistical analysis

The categorical variables were studied based on the absolute and relative frequency of their appearance. Quantitative variables were studied based on their central tendency measurements (mean or median) and dispersion (standard deviation). The normality of the distribution of the variables was studied via the Shapiro-Wilk test, where assumed normality was accepted if *P*>.05.

For the comparison of within subject measurements, the McNemar test was used for categorical variables, applying the Yates correction (if the number of changing pairs was lower than 10), and for quantitative variables, the Student *t* test was used for matching data or the Wilcoxin signed-rank test for matching data if the distribution of the variables did not follow normal distribution.

In all cases a Fisher's *P* value of ≤.05 was established to determine significant differences. The confidence interval (CI) of the difference (d_o) was determined to evaluate the true magnitude of the difference found and its clinical significance. The CIs used were 95% in all cases.

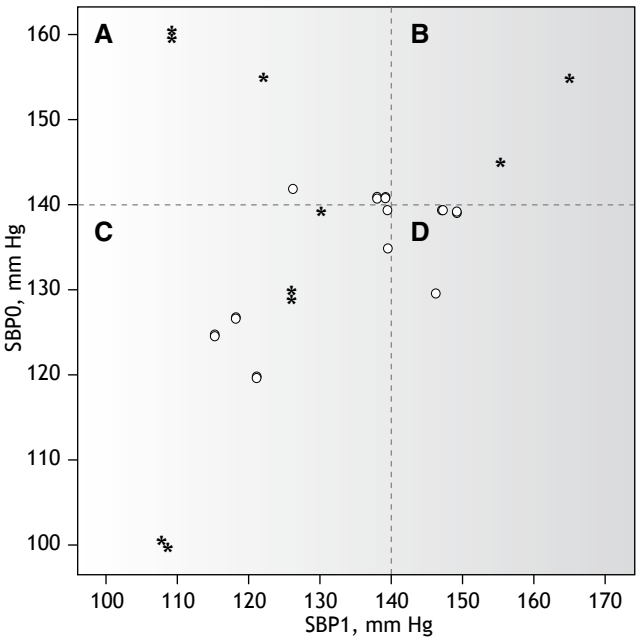

Figure 2 Relationship between systolic blood pressure values before (SBP0) and after (SBP1) therapeutic exchange.

Results

The study was performed over 3 months. During this period, a total of 37 patients were included based on the calculation of the sample size performed. The results of the normality tests indicate that the variables studied are adjusted to normal distribution (*P*>.05 in the Shapiro-Wilk test), and therefore parametric tests were used in the statistical analysis (McNemar, *z* and *t* test depending on the type of variable and measurement).

Table 1 shows the basal characteristics of the patients included in the study. The main reasons identified for the admission of patients included in the study were hip fracture (63.6%) and femur fracture (22.7%). The mean stay of the patients was 8.55 days (95% CI, 2.75-14.35 days) with a median of 6 valid BP measurements per patient. The pre-post analysis performed shows how 81.08% (n=30/37) of patients maintained normal BP values following therapeutic exchange, with a non-significant increase of 8% with respect to the outpatient period (McNemar test with Yates' correction for continuity: χ^2=0.5000 and *P*=.239). Reduction in SBP was more marked than in DBP values. Figure 2 shows the relationship between SBP before and after therapeutic exchange. It can be observed that, in general, there is a reduction in SBP values allowing the majority of patients to

Table 2 Results of the within subject significance test between blood pressure (BP) values at home and during the hospital stay (mean, maximum, minimum) in patients included in the study (n=37)

	BP0	BP1	d_o	95% CI d_o	Student *t* test[a]	*P*
SBP, mm Hg	135.14 (100-160)	130.32 (108-165)	4.82	−1.09 to 10.74	1.658	.107
DBP, mm Hg	73.91 (60-100)	74.05 (64-92)	−0.15	−3.27 to 2.97	−0.096	.924

BP0 indicates outpatient blood pressure; BP1, blood pressure following therapeutic exchange; DBP, diastolic blood pressure; d_o, difference observed between blood pressure values (BP0-BP1); SBP, systolic blood pressure.
[a]Result of the statistical Student *t* test for related samples, where *P*=.05 to find significant differences.

reduce the stage of hypertension (squares A and C). However, in 5 patients (13.51%) with controlled values of BP as outpatients, at least in the month prior to admission, an increase in the SBP values was observed, and the stage of AH also increased (square D). However, of the 11 patients with uncontrolled AH as outpatients, 24.32% (n=9/37) improved their BP values following therapeutic exchange (square A) and no change was observed in BP control in 2 patients (square B).

Table 2 shows the results of the within subject analysis of SBP and DBP values. In this respect, it is observed that following therapeutic exchange an average reduction in SBP of 5 mm Hg was observed, and around 1 mm Hg in DBP. The values of 95% CI show a reduction of almost 11 mm Hg in the SBP values.

Discussion

Standardisation and normalisation of processes leads to better quality services and patient care. In this respect, the standardisation of therapeutic exchange procedures reduces possible errors in drugs associated with the variability observed in this procedure.[8] The standard procedure for the therapeutic exchange of AIIRA in this centre was implemented following an exhaustive bibliographical review, in which a series of studies comparing the efficacy of the AIIRA with other antihypertensive drugs were analysed. Given that articles comparing the activity of the different AIIRAs on the market are scarce and if the possible differences that exist may generate greater clinical efficiacy,[9] this study was carried out based on the premise that all AIIRAs are equally effective in the treatment of AH, with a very similar hypotensive action in terms of the start of the action, maximum antihypertensive effect, and duration of the action.[10]

Although these drugs continue to be considered as an alternative to ACE inhibitors in the treatment of AH,[11-13] the consumption of AIIRAs in Spain has increased in recent years[14]; valsartan has been the AIIRA of greatest consumption in the last five years.[14-16] This situation is in line with the results obtained in the present study, in which valsartan was the AIIRA used in the outpatient sphere for the majority of patients included in the study (Table 1), and in the majority of cases (80%), this was associated with thiazide diuretics.

Following the therapeutic exchange, significant changes in BP values were observed in 43.24% (n=16/37) of cases and, in particular, reductions in SBP values which facilitated a reduction in the stage of AH (Figure 2). Furthermore, an increase in the number of patients with BP values within the therapeutic aim (8%) was observed, which may be due to the combined effect of diet, change in treatment and possible improved adherence to treatment during the hospital stay. Lower control of BP was only observed in 5 patients following the therapeutic exchange. However, given that patients with stage 2 AH did manage to obtain normal values of AH following therapeutic exchange, the stage of hypertension does not appear to limit the application of the therapeutic exchange protocol to this type of patient.

Following the within subject analysis performed, no significant differences were found between mean values of SBP and DBP following therapeutic exchange and BP values in the outpatient sphere. In the case of DBP, the differences found are not clinically relevant since the upper interval limit obtained is lower than 5 mm Hg, which experts have established as the value indicating a clinically significant difference in the efficacy of antihypertensive drugs.[17,18] However, in the case of SBP, the upper interval limit is 11 mm Hg, and therefore this difference could become clinically relevant since it could involve an excessive reduction in SBP following therapeutic exchange, with the risk of causing hypotension in patients. However, low SBP values are better tolerated than low DBP values, since the latter is the pressure in the arteries when the heart is resting and, therefore, diastolic hypertension could affect the perfusion of blood to the tissue, in particular to the myocardium. As a result, the reduction of around 11 mm Hg observed in SBP values does not present, in our opinion, clinical significance in terms of morbidity and, in any case, it has facilitated a reduction in the stage of AH in some patients. Indeed, no patient required modifications in the dose of any antihypertensive drug or the addition of another drug during the hospital stay, nor did they present any hypertensive crises or situations of hypotension.

Although this study was not performed with surgical patients, there are several studies with non-surgical and non-hospitalised patients which have obtained similar results. Consequently, while a study performed by Fogari et al[19] in non-hospitalised hypertensive patients observed that valsartan reduced the BP values faster and to a greater extent than losartan and telmisartan, another study performed by Eliot et al[20] on a similar patient population did not observe differences between losartan and valsartan in terms of the reduction of AH. However, a meta-analysis including 43 placebo controlled clinical trials (n=11 281 patients), in which losartan was compared with valsartan, irbestarn, and candesartan, did not find any significant

clinical differences in terms of SBP or DBP. The 4 drugs presented similar efficacy in the reduction of AH.[21] All of these studies support our results, despite the fact that they were performed in non-hospitalised patients. However, the study performed by Peris Mati et al[22] with elderly institutionalised patients shows that the therapeutic exchange of AIIRA by lasartan is effective and safe, with minimal differences in the values of SBP and DBP, in accordance with the results obtained in the present study. To conclude, based on the results obtained and taking into account the possible uncontrolled bias and limitations of the study, it may be concluded that the values of SBP and DBP do not present clinically significant alterations following the therapeutic exchange of AIIRA for losartan, and therefore the therapeutic exchange protocol for AIIRA available in the hospital is effective and safe, and does not lead to less control of AH nor situations of hypertension in patients. Although the use of this therapeutic exchange protocol could be extended to other types of patients, strict monitoring of the patient would be required, as well as studies in these patients to evaluate its efficacy and safety.

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