ORIGINAL ARTICLE

CME

Comparison of the Acute Antihypertensive Response to Telmisartan and Irbesartan in Spontaneously Hypertensive Rats

Comparación de la respuesta antihipertensiva aguda al telmisartán y al irbesartán en ratas espontáneamente hipertensas

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ABSTRACT

Background: Telmisartan and irbesartan, two of the main AT1 receptor antagonists available for the control of cardiovascular diseases, differ in their pharmacological properties, including time of dissociation from the AT1 receptor and the ability to activate other receptors, with potential impact on their relative clinical efficacy.
Objectives: The aim of this study was to compare the acute cardiovascular response to single dose administration of irbesartan or telmisartan in spontaneously hypertensive rats.
Methods: Twenty-four male spontaneously hypertensive rats, weighing 250-275 g, were used. The carotid artery and femoral vein were cannulated for direct mean arterial pressure measurement (MAP) and irbesartan 3-6 mg/kg or telmisartan 0,5-1 mg/kg administration. Changes in MAP, heart rate and short-term and beat-to-beat blood pressure variability were estimated.
Results: Although both antagonists reduced MAP, telmisartan induced a longer antihypertensive response than irbesartan, evidenced by greater MAP reduction after 180 min (-33.3%±4.1% vs. -16.3%±4%; $p<0.05$). Telmisartan and irbesartan induced sustained reduction of short-term blood pressure variability without significant differences between both experimental groups. At the lower dose level, telmisartan produced greater decrease of heart rate and beat-to-beat blood pressure variability at the different frequency domains compared with irbesartan.
Conclusions: In spontaneously hypertensive rats, telmisartan administration induces a more persistent antihypertensive response and a greater bradycardic response than irbesartan. Spectral analysis of beat-to-beat blood pressure variability suggests that low dose telmisartan produces greater attenuation of vascular sympathetic activity compared with irbesartan.

Key words: Telmisartan – Irbesartan - Blood pressure - Antihypertensive Agents - Angiotensin II Type 1 Receptor Blockers

RESUMEN

Introducción: El telmisartán y el irbesartán, dos de los principales antagonistas del receptor AT1 disponibles para el control de enfermedades cardiovasculares, difieren en sus propiedades farmacológicas, incluyendo el tiempo de disociación desde el receptor AT1 y la capacidad de activar otros receptores, con potencial impacto en su eficacia clínica relativa.
Objetivo: Comparar la respuesta cardiovascular aguda de la administración de una dosis única de irbesartán o de telmisartán en ratas espontáneamente hipertensas.
Material y métodos: Se utilizaron 24 ratas espontáneamente hipertensas macho de 250-275 g, a las que se les canuló la arteria carótida y la vena femoral para la medición directa de la presión arterial media (PAM) y la administración de irbesartán 3-6 mg/kg o de telmisartán 0,5-1 mg/kg. Se estimó el cambio en la PAM, la frecuencia cardíaca y la variabilidad de la presión arterial a corto plazo y latido-a-latido.
Resultados: Aunque ambos antagonistas redujeron la PAM, el telmisartán indujo una respuesta antihipertensiva más prolongada que el irbesartán, evidenciada por mayor reducción de la PAM luego de 180 minutos (-33,3% ± 4,1% vs. -16,3% ± 4%; $p < 0,05$). El telmisartán y el irbesartán atenuaron de manera prolongada la variabilidad de la presión arterial a corto plazo, sin diferencias entre ambos grupos experimentales. En el nivel de dosis más bajo, el telmisartán disminuyó en mayor medida la frecuencia cardíaca y la variabilidad latido-a-latido en los diferentes dominios de frecuencia en comparación con el irbesartán.
Conclusiones: En ratas espontáneamente hipertensas, la administración de telmisartán induce un efecto antihipertensivo más prolongado y una respuesta bradicardizante mayor que el irbesartán. El análisis espectral de la variabilidad latido-a-latido sugiere que el telmisartán, en la dosis más baja, atenúa en mayor medida la actividad simpática vascular en comparación con el irbesartán.

Palabras claves: Telmisartan - Irbesartan - Presión arterial - Antihipertensivos - Bloqueadores del Receptor Tipo 1 de Angiotensina II

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Abbreviations

ARB	AT1 receptor blockers	**PPAR**	Peroxisome proliferator-activated receptor gamma
BP	Blood pressure	**RAS**	Renin-angiotensin system
HR	Heart rate	**SD**	Standard deviation
LF	Low frequency	**SHR**	Spontaneously hypertensive rats
MAP	Mean arterial pressure	**VLF**	Very low frequency

INTRODUCTION

The renin-angiotensin system (RAS) is one of the main regulators of blood pressure (BP), renal hemodynamics and volume homeostasis in normal physiological conditions, and contributes to the development of cardiovascular and kidney diseases. (1) Since their introduction in 1995, AT1 receptor blockers (ARB) have become the pillars of hypertension and heart failure therapy, and of end-stage kidney disease prevention in patients with diabetes mellitus. (2, 3) At present, there are seven different ARB approved, and although they share the ability of selectively blocking the AT1 receptor, they differ in their different pharmacokinetic and pharmacodynamics properties with potential impact on their relative clinical efficacy. (4) In this context, the different components forming part of this therapeutic group vary in terms of liposolubility, dissociation velocity from the AT1 receptor, inverse agonism activity and actions on other molecular targets. (4)

Telmisartan and irbesartan, two of the main ARB available for the control of cardiovascular diseases, exhibit different pharmacokinetic and pharmacodynamic properties. (4) Although all ARB are liposoluble compounds, telmisartan presents higher affinity for lipids compared with irbesartan (logP 6.66 vs. 4.51) and would therefore have greater penetration in the central nervous system. (4, 5) Telmisartan also exhibits a longer elimination half-life than irbesartan (21-38 hours vs. 11-18 hours). (6) Telmisartan and irbesartan also differ in the antagonism profile of the angiotensin II-induced response; whereas irbesartan displaces the angiotensin II dose-response curve to the right, a phenomenon compatible with reversible, competitive antagonism, telmisartan is able to generate the progressive reduction of the maximum angiotensin II vasoconstrictor response, needing several hours to reestablish the peptide action. (7) This blockade pattern, known as insurmountable antagonism, is explained by its slow dissociation from the AT1 receptor. (7) In vitro studies have established that telmisartan dissociation half-life from its AT1 receptor is 75 minutes compared to only 17 minutes in the case of irbesartan. (7) Telmisartan also differs from irbesartan in its ability to act as partial agonist of the peroxisome proliferator-activated receptor gamma (PPAR-γ). (7) It is assumed that PPAR-γ contributes to different pharmacological effects of telmisartan, including the reduction of atrial arrhythmia susceptibility, glycemic regulation, protection against vascular dysfunction and renoprotection, among others. (8-11)

Considering the differences in ARB pharmacodynamic profile, the aim of this study was to compare the effects of single dose irbesartan or telmisartan administration on BP, heart rate (HR) and short-term BP variability in spontaneously hypertensive rats (SHR).

METHODS

Two-month old, inbred spontaneously hypertensive rats, weighing 220-250 g were used. Rats were randomly divided into two groups: irbesartan (n=12) and telmisartan (n=12). Following ketamine/xylazin anesthesia, the left carotid artery and left femoral vein were cannulated and the catheters were tunneled beneath the skin to emerge at the posterior part of the neck. Experiments were performed in conscious animals 24 hours after catheter placement.

On the day of the experiment, the arterial catheter was connected to a Spectramed P23XL (Spectramed, Oxnard, CA, USA) pressure transducer, coupled to a Grass 79D (Grass Instruments, Quincy, MA, USA) polygraph. This was in turn connected to a digital converter (Polyview, PVA 1, Grass-Astro Med, West Warwick, RI, USA), and BP recordings were stored and analyzed with Polyview 2.3 software (Astro-Med, West Warwick, RI, USA). Mean arterial pressure (MAP) and HR were monitored during a 60-minute period prior to drug administration, and were directly reported by the Polyview 2.3 software.

After baseline BP and HR measurement, intravenous irbesartan [3 mg/kg (n=6) or 6 mg/kg (n=6)] or telmisartan [0.5 mg/kg (n=6) or 1 mg/kg (n=6)] were administered for 30 minutes. Doses were selected according to the dosing range evaluated by Maillard et al. (12) Intravenous single dose administration of each ARB was selected to become independent of the absorption process and to better characterize the pharmacodynamic properties.

After ARB administration, a continuous 3-hour BP recording was performed, continuously assessing changes in the hemodynamic variables. At this point, it is important to consider that the elimination half-life of telmisartan and irbesartan reported in rats is 12-15 hours and 12 hours, respectively. (13-15)

The study quantified the effect of intravenous telmisartan and irbesartan administration on beat-to-beat and short-term variability. Short-term BP variability was established through BP standard deviation (SD) calculated during 3-minute periods. Beat-to-beat variability was evaluated by spectral analysis of continuous BP recordings during 3-minute periods at baseline and at regular intervals after ARB administration. According to previous studies from our and other laboratories, (16-18) spectral analysis of data was performed using the fast Fourier transform algorithm with Hamming window. Spectral densities were calculated in very low frequency (VLF) (0.1 to 0.2 Hz), low frequency (LF) (0.2 to 0.7 Hz) and high frequency (HF) (0.7 to 2.5 Hz) ranges.

Statistical analysis

The normal distribution of data and study variables was assessed with the Kolgomorov Smirnov test. Data were ex-

pressed as mean±SEM. Baseline cardiovascular parameters in both groups were compared using Student's t test. Two-way analysis of variance (ANOVA) with post-hoc Bonferroni test was used for the statistical analysis of telmisartan or irbesartan effects on MAP, HR, SD and beat-to-beat BP variability in the different frequency domains. GraphPad Prism, version 5.2 for Windows software package (GraphPad Software, San Diego, California, CA) was used for statistical analyses. A p value <0.05 was considered statistically significant.

Ethical considerations

Animal experiments were performed according to the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-3, revised 1985).

RESULTS

Baseline MAP, HR, short-term BP variability expressed as SD and the different components of beat-to-beat BP variability did not differ between the groups of animals receiving telmisartan or irbesartan (Table 1). Intravenous irbesartan or telmisartan administration induced a significant decrease of MAP (Figure 1). However, BP reduction was more sustained in the groups of animals that received telmisartan 0.5 or 1 mg/kg compared with those treated with irbesartan 3 or 6 mg/kg (Figure 1).

Table 1. Baseline blood pressure, heart rate and blood pressure variability values in SHR treated with telmisartan or irbesartan.

	Telmisartan (n=12)	Irbesartan (n=12)
MAP (mmHg)	157±7	152±7
HR (bpm)	396±9	389±7
SD (mmHg)	6.2±0.4	6.1±0.3
Beat-to-beat variability		
VLF (mmHg2)	42.0±2.4	45.5±3.5
LF (mmHg2)	33.6±2.5	34.1±3.2
HF (mmHg2)	8.7±0.6	10.2±0.7

MAP: Mean arterial pressure. HR: Heart rate. SD: Standard deviation. VLF: Very low frequency. LF: Low frequency. HF: High frequency.

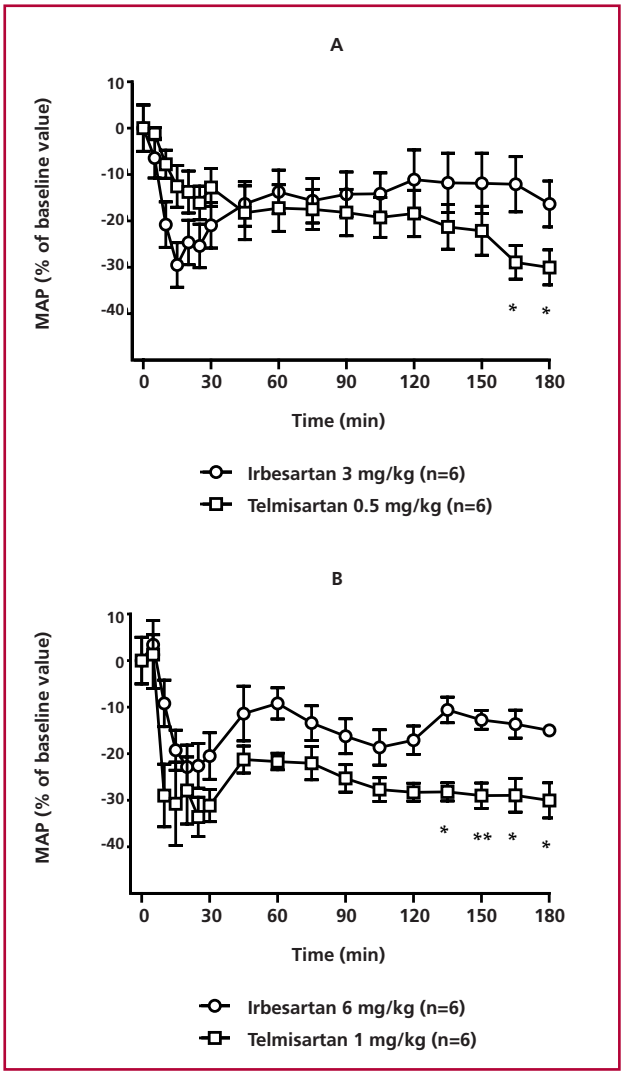

Fig. 1. Time course of mean arterial pressure change (ΔMAP, % of baseline values), after telmisartan 0.5 or 1 mg/kg or irbesartan 3 or 6 mg/kg in spontaneously hypertensive rats. Each point shows mean±SEM of six rats. * p<0.05 vs. irbesartan (two-way ANOVA followed by the Bonferroni test).

The HR time course analysis after intravenous injection of both ARB drugs detected differences in the chronotropic effect of telmisartan and irbesartan. Although no significant changes were registered in HR following the lowest dose of both ARB, telmisartan 1 mg/kg induced a significantly higher bradycardic response than irbesartan 6 mg/kg (Figure 2).

The present study evaluated the effect of intravenous irbesartan or telmisartan on short-term BP variability by means of SD change in the continuous recording of direct BP. At the lowest and highest dose level, both ARB produced a sustained SD reduction of MAP values without significant differences between telmisartan and irbesartan (Figure 3). At the highest dose level, telmisartan 1 mg/kg showed a trend to greater reduction of short-term MAP fluctuations compared with irbesartan 6 mg/kg (Figure 3).

The change in beat-to-beat BP variability at the different frequency domains obtained from spectral analysis of BP recordings is shown in Table 2. At the lowest dose level, telmisartan induced greater variability reduction in the VLF, LF and HF domains compared with irbesartan. After intravenous injection of the highest dose, telmisartan 1 mg/kg and irbesartan 6 mg/kg induced a comparable decrease of beat-to-beat variability at the different frequency ranges (Table 2).

DISCUSSION

Results show certain differences in the hemodynamic profile of SHR following acute intravenous administration of telmisartan or irbesartan. Specifically, telmisartan induced a more sustained MAP reduction, bradycardic effect and greater beat-to-beat variability

Table 2. Change of beat-to beat variability in the very low frequency (VLF), low frequency (LF) and high frequency (HF) domain in spontaneously hypertensive rats treated with telmisartan or irbesartan.

	Telmisartan (% of baseline)	Irbesartan (% of baseline)	Telmisartan (% of baseline)	Irbesartan (% of baseline)
	0.5 mg/kg (n=6)	1 mg/kg (n=6)	3 mg/kg (n=6)	6 mg/kg (n=6)
ΔVLF	49.5±7.9*	53.6±6.8	79.0±7.6	69.1±4.8
ΔLF	53.0±6.8*	53.2±6.4	89.1±5.9	71.1±7.6
ΔHF	51.0±8.6*	58.2±6.5	106.0±5.5	74.4±7.2

Values indicate mean±SEM of six animals
*p<0.05 vs. irbesartan (two-way ANOVA followed by the Bonferroni test).

reduction in the three frequency domains compared with irbesartan. In addition, both ARB demonstrated a significant reduction of short-term BP variability without statistical differences between them.

The most significant hemodynamic finding of this comparative study was the longer antihypertensive effect of telmisartan compared with irbesartan in an experimental model of genetic hypertension. Whereas rats treated with irbesartan showed partial recovery of MAP values during the 180-minute evaluation period at both dose levels, telmisartan 0.5 and 1 mg/kg allowed a persistent pressure reduction without return to the baseline level (Figure 1). As telmisartan and irbesartan elimination half-life is similar in rats, the more prolonged antihypertensive effect of telmisartan could be explained by various specific aspects of the mechanism of action, such as the low dissociation from the receptor and PPAR-γ partial agonist activity. In vitro comparative studies have established that telmisartan presents a longer dissociation time from the AT1 receptor than irbesartan (75 vs. 17 minutes), allowing a more prolonged antagonist effect on endogenous angiotensin II and a sustained antihypertensive effect. (7) Similarly, Maillard et al. established that telmisartan administration produces a more extended blockade of the pressor effect induced by angiotensin II administration compared with irbesartan. (12) Another mechanism that might explain the higher antihypertensive efficacy of telmisartan is its ability to activate the nuclear PPAR-γ receptor. Although still controversial, recent evidence suggests that PPAR-γ expressed in vascular smooth muscle cells have an important role in BP regulation. (19)

In order to establish the neurohumoral mechanisms involved in the higher antihypertensive response of telmisartan in SHR, the study assessed changes in beat-to-beat variability at different frequency ranges by means of BP spectral analysis. It is known that the identification of frequency components of BP beat-to-beat variability by spectral analysis provides information on the mechanisms involved in BP regulation. (20, 21) While RAS activity, myogenic vascular tone and endothelial nitric oxide regulate BP in the VLF range, sympathetic nervous system activity does it in the LF domain. (20) The results of the present analysis establish that intravenous telmisartan administration induces a higher reduction of beat-to-beat BP variability in the VLF and LF range compared with irbesartan. This finding suggests greater inhibition of neurohumoral mechanisms, including RAS and the sympathetic nervous system, and might potentially explain the increased hypertensive efficacy of telmisartan compared with irbesartan. Similar findings have been reported by other authors in studies performed in other experimental models. In this context, Sueta et al. (22) found that telmisartan induces a longer antihypertensive effect than valsartan in an experimental model of metabolic syndrome,

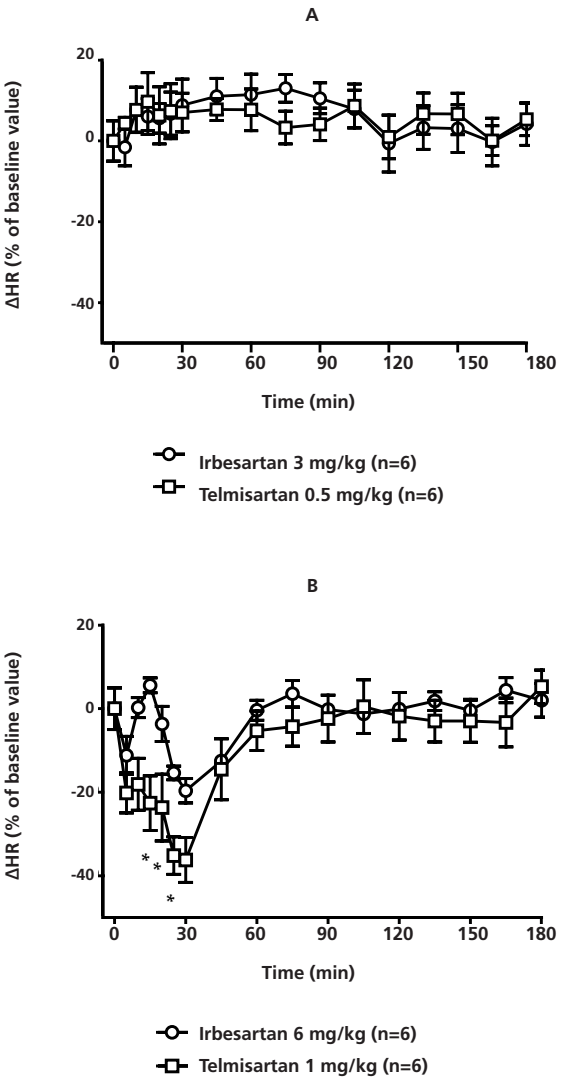

Fig. 2. Time course of heart rate change (ΔHR, % of baseline values), after telmisartan 0.5 or 1 mg/kg or irbesartan 3 or 6 mg/kg in spontaneously hypertensive rats. Each point shows mean±SEM of six rats. * p<0.05 vs. irbesartan (two-way ANOVA followed by the Bonferroni test).

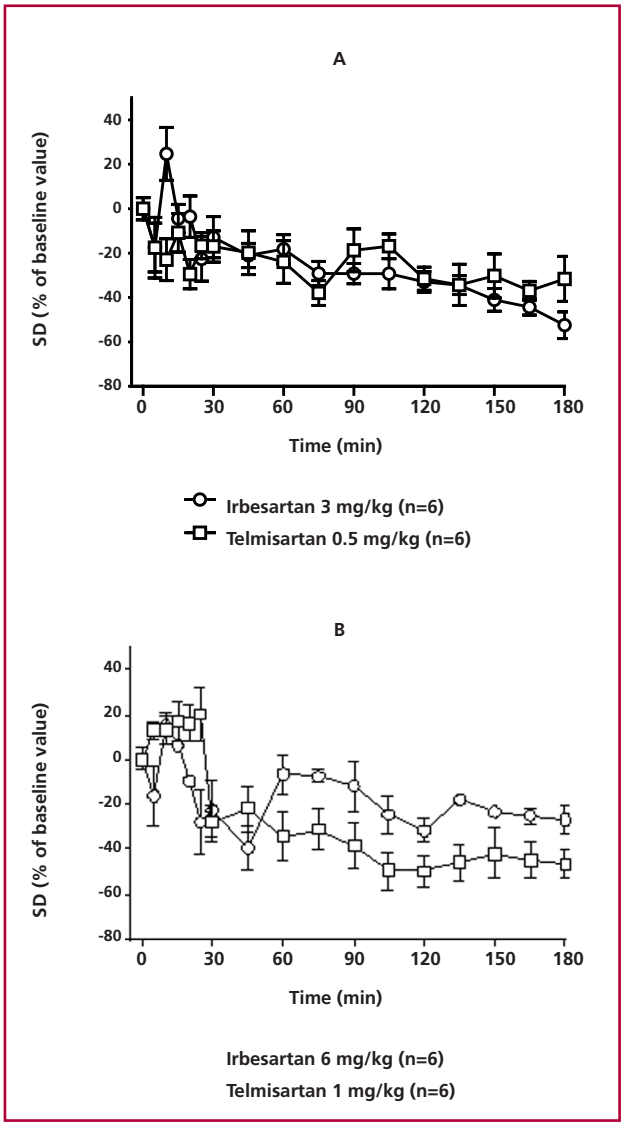

Fig. 3. Time course of short-term blood pressure variability change expressed as standard deviation (ΔSD, % of baseline values), after telmisartan 0.5 or 1 mg/kg or irbesartan 3 or 6 mg/kg in spontaneously hypertensive rats. Each point shows mean±SEM of six rats.

in part as a result of greater reduction of LF BP variability, an effect compatible with higher attenuation of sympathetic activity.

The present study also evaluated the HR effect of different telmisartan or irbesartan doses in SHR. Although both ARB did not evidence significant chronotropic effects at the lowest dose level, telmisartan 1 mg/kg produced greater HR reduction compared with irbesartan 6 mg/kg. These results suggest that telmisartan would have greater effect on the cardiac sympathovagal balance than irbesartan. Previous clinical studies have established telmisartan ability to improve cardiac autonomic balance. (23, 24) In hypertensive patients, telmisartan increases cardiac parasympathetic activity and produces greater attenuation of autonomic imbalance compared with enalapril. (23, 24) Moreover, Kishi et al. evidenced that oral telmisartan administration induces greater HR and cardiac sympathetic activity reduction than candesartan in stroke-prone SHR. (25)

Finally, we evaluated the effect of single dose telmisartan or irbesartan on short-term BP variability. The increase in BP variability has been established as a risk factor for the development of target organ injury not only in hypertensive patients, but also in normotensive subjects. (26, 27) Clinical studies have shown that the increase in BP fluctuation during 24 hours, day after day and between medical visits is associated with greater risk of major cardiovascular events in the hypertensive population. (21) Taking into account this relationship, it is now postulated that BP variability should be considered as a new therapeutic goal of antihypertensive therapy. (21, 25, 26) Clinical studies using the analysis of Smoothness Indexes have established telmisartan ability to reduce BP variability. (28) On the other hand, Masuda et al. reported that telmisartan treatment, contrary to losartan, reduces daytime, nighttime and 24-hour short-term BP variability in hypertensive patients. (29) The results of the present work confirm telmisartan ability to attenuate BP variability in a model of genetic hypertension. The efficacy in terms of SD reduction in BP recordings was equivalent between telmisartan and irbesartan at both dose levels.

CONCLUSIONS

In conclusion, intravenous telmisartan or irbesartan administration significantly reduces not only BP but also short-term BP variability in SHR, both factors that independently contribute to the development of the target organ injury associated to the hypertensive status. The comparison of both ARB hemodynamic effects establishes that telmisartan induces a more prolonged antihypertensive influence and a higher bradycardic response than irbesartan. Spectral analysis of beat-to-beat variability suggests that telmisartan at the lowest dose produces greater attenuation of vascular sympathetic activity compared with irbesartan.

Conflicts of interest

None declared. (See author´s conflicts of interest forms in the web / Supplementary Material)

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