Eur J Clin Pharmacol (1993) 45: 157–160

European Journal of Clinical Pharmacology

Dose-effect relationship of rilmenidine after chronic administration

R. Luccioni[1], M. Lambert[1], P. Ambrosi[1], and M. Scemama[2]

[1] Department of Cardiology, CHU la Timone, Marseille, France
[2] IRIS, Courbevoie, France

Reveived: July 16, 1992/Accepted in revised form: April 5, 1993

Summary. The antihypertensive efficacy and acceptability of 3 doses of rilmenidine (0.5, 1 and 2 mg, once daily) and a placebo over a 4 week period have been compared in a randomised, double-blind, parallel-group trial in 60 mild to moderate hypertensive patients. Six patients dropped out: 4 in the 2 mg-group and one in the 1 mg-group because of adverse events, and one in the placebo group for personal reason. The blood pressure was significantly decreased after the 1 and 2 mg doses with the maximum antihypertensive effect already being obtained after 1 mg. A significant dose-effect relationship was shown for supine systolic blood pressure ($P = 0.05$) but not for the supine diastolic blood pressure.

The most beneficial efficacy/acceptability ratio was achieved at the dose of 1 mg once daily, which demonstrated the maximum antihypertensive effect associated with a low incidence of adverse events.

Key words: Hypertension, Rilmenidine; dose-effect relationship, chronic administration

Rilmenidine is an oxazoline derivative which lowers blood pressure mainly through central modulation of the sympathetic tone. Its antihypertensive activity can be explained by its actions on imidazole-preferring receptors (IPR) in the brainstem C1 area [1].

Previous dose ranging studies after a single dose of rilmenidine [2] showed that within the range of doses tested (0.5, 1, 2 and 3 mg), the best efficacy/acceptability (E/A) ratio was obtained after 1 mg, both in normotensive and hypertensive subjects.

To determine the optimal repeated dose of rilmenidine, i.e. the dose providing the most beneficial E/A ratio, a 4 week, double blind parallel group study was carried out in 60 mild to moderate hypertensive patients given rilmenidine 0.5 mg, 1 mg or 2 mg once daily, or placebo.

Patients and methods

The study was carried out in 60 patients suffering from a mild to moderate primary hypertension (WHO I–II). It was sponsored by the International Research Institute of Servier.

The study was approved by the Ethics Committee of the University of La Timone, Marseille. Informed written consent was obtained from all patients, in accordance with the revised Helsinki Declaration (Hong Kong, 1989), and the french regulations.

General design of the study

The study began with a 2 week open wash-out period, in which any previous antihypertensive drug was withdrawn. After a further 2 week placebo run-in period if the blood pressure was stable (reduction in diastolic blood pressure (DBP) less than 10 mm Hg), patients were randomised if the inclusion criteria were fullfilled. Patients were assigned to treatment according to a computer generated, randomised, parallel group design. Treatments were administered once-a-day, in the morning, for 4 weeks.

Sample size

The sample size was calculated to demonstrate a difference of 9 mm Hg in supine DBP between each dose of rilmenidine and the placebo. The Type I error allowed was 0.05 and the power was 0.80. The a priori standard deviation was 6 mm Hg and was derived from a previous comparative study versus placebo [3]. This standard deviation is in accordance with the value recently published by Chalmers et al. [4]. The number of patients required was calculated to be 60, not including drop-outs.

Inclusion and exclusion criteria

Sixty outpatients, aged 59.9 (1.2) y, with uncomplicated primary hypertension (WHO grade I or II) were studied. Their demographic characteristics are shown in Table 1. All patients had a supine DBP > 95 mm Hg on two consecutive visits, two weeks apart.

Patients with secondary or malignant hypertension were excluded from the study, as well as patients with heart failure (NYHA grades II to IV), evolutive exertional angina, unstable angina, atrioventricular block (2nd and 3rd degree) or bradycardia (< 50 beats $\cdot$ min^{-1}).

Table 1. Baseline characteristics of the 60 patients (mean with (SEM))

	Placebo ($n = 15$)	Ril 0.5 mg ($n = 15$)	Ril 1 mg ($n = 15$)	Ril 2 mg ($n = 15$)
Age (y)	59.1 (2.3)	60.7 (1.9)	60.2 (2.6)	59.7 (3.0)
Sex m/f	10/5	6/9	11/4	10/5
Weight (kg)	76.5 (2.8)	65.9 (3.6)	70.3 (4.1)	67.1 (3.5)
WHO class I/II	12/3	8/7	7/8	6/9
Smokers/non smokers	2/13	1/14	2/13	2/13
Supine SBP (mm Hg)	162 (4.8)	164 (3.4)	172 (5.4)	170 (3.9)
Supine DBP (mm Hg)	104 (3.4)	104 (1.7)	106 (1.7)	105 (1.8)
Standing SBP (mm Hg)	158 (5.1)	156 (3.7)	168 (6.0)	166 (4.7)
Standing DBP (mm Hg)	100 (2.0)	105 (1.7)	109 (2.6)	108 (3.0)
Supine HR (beats $\cdot$ min^{-1})	78.3 (3.2)	69.9 (2.7)	75.9 (2.5)	72.4 (2.4)
Standing HR (beats $\cdot$ min^{-1})	82.8 (3.0)	76.7 (2.0)	79.8 (2.0)	75.4 (2.2)

SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate

Other exclusion criteria were severe liver disease, renal failure (serum creatinine $> 180\ \mu mol \cdot l^{-1}$), myocardial infarction or stroke within the previous 6 months, other severe disabling diseases, alcohol or drug abuse, poor compliance with treatment and absence of effective contraception. Drugs which could potentially interfere with rilmenidine were not allowed, namely tricyclic antidepressants and monoamine oxidase inhibitors.

Drugs were prepared according to the double dummy method. According to their allocated treatment, patients received once daily two placebo capsules in the placebo group; one rilmenidine 0.5 mg capsule and one matching placebo capsule in the 0.5 mg group; one rilmenidine 1 mg capsule and one matching placebo capsule in the 1 mg group; and two rilmenidine 1 mg capsules in the 2 mg group.

Patients were withdrawn from the study if their supine DBP increased above 120 mm Hg, if they asked to stop the trial, if they were lost to follow-up, or if they experienced any severe adverse events.

Assessment of blood pressure and heart rate

Blood pressure (BP) and heart rate (HR) were measured at two week intervals (in weeks W-2, W0, W4, W8), 5 h after drug intake in the morning.

Systolic BP (SBP) and diastolic BP (DBP, Korotkoff Phase V) were measured with a mercury sphygmomanometer in the supine (after a 5 min rest) and standing positions. Three consecutive measurements were made in the supine position and two measurements in the standing position. The mean of the measurements carried out in each position was used for the analysis. HR was recorded by cardiac auscultation over 1 min, both in the supine and standing positions.

Adverse reactions

Adverse reactions (ARs) were recorded at the end of the placebo run-in period (at W0) and then every two weeks (W2 and W4) following non-leading questioning. The investigator recorded his own opinion on the severity of the AR, and on their relationship to the test drug. Adverse reactions were graded from 1 = "mild" to 4 = "severe and frequent". Only ARs arising or deteriorating during the test period are described in the "Results".

ECGs and blood samples for routine safety tests were obtained before and at the end of the test period. Plasma rilmenidine concentrations were assessed on Day 28 2 h after drug intake, in patients who completed the study. They were measured only in patients treated with rilmenidine.

Data analysis

Changes in BP and HR over the 4 weeks were analysed in patients who completed the study. The Day 14 measurements of BP and HR were not used in the analysis of BP and HR. Changes in BP were analysed as the mean reduction (D28-D0) in each group, using the non parametric Kruskall-Wallis test. Heart rate was analysed by two way analysis of variance (time x group) with repeated measures over time.

The response rate, i.e. the number of patients whose supine DBP was controlled (supine DBP < 90 mm Hg) or decreased by at least 10 mm Hg, was analysed by a chi-squared test.

Variations in haematology/biochemistry values and in ECG parameters were analysed by two way analysis of variance (time x group).

The relationship between the logarithm of the plasma rilmenidine concentration and BP reduction was assessed by linear regression.

Adverse reactions and drop-outs were described.

Results

Blood pressure and heart rate

Blood pressure and heart rate were comparable between groups at the time of inclusion (Table 1).

Six patients withdrew from the study during active therapy; in the 2 mg-group 4 patients withdrew: two (1 on Day 1 and 1 on Day 15) because of dry mouth and asthenia, one because of dry mouth on Day 24, and one because of severe headaches due to an increase in BP on Day 21. In the 1 mg-group, one patient withdrew on Day 14 because his cardiac impairment worsened and he felt strained. In the placebo group, 1 patient withdrew for personal reason on Day 21.

Analysis of the antihypertensive activity was carried out, therefore on the 54 fully documented cases. The blood pressure measurements on Day 14 were not taken into account in the statistical analysis, since the full antihypertensive effect of rilmenidine was only anticipated on Day 28 according to a previous study against placebo [3]. The blood pressure on Day 14 was measured for safety reasons only.

Significant differences between groups were observed in the change in supine SBP ($P < 0.001$), standing SBP ($P < 0.001$) and standing DBP ($P < 0.001$). A similar but not significant trend was observed in supine DBP ($P = 0.11$). Compared to the change in the placebo group, the reduction in supine DBP was as expected, namely 9 and 9.8 mm Hg in the 1 mg and 2 mg groups, respectively (Table 2 and Fig. 1).

A dose-effect relationship was demonstrated for supine SBP ($P = 0.05$) but not for supine DBP ($P = 0.51$).

Table 2. Changes in blood pressure after treatment

(D28–D0) difference in blood pressure	Placebo	Ril 0.5 mg	Ril 1 mg	Ril 2 mg	Group time interaction	Intragroup analysis[a]	
Supine SBP (mmHg)	5.0 (4.5)	−6.9 (37)	−23.2 (5.2)	−15.6 (5.6)	$P < 0.001$	Placebo	0.5 mg: NS 1 mg: S 2 mg: S
Supine DBP (mm Hg)	1.3 (2.2)	−3.5 (2.4)	−7.7 (3.7)	−8.5 (3.9)	$P = 0.11$	–	
Standing SBP (mm Hg)	4.2 (4.3)	−7.6 (4.9)	−27.2 (6.0)	−21.0 (6.8)	$P < 0.001$	Placebo	0.5 mg: NS 1 mg: S 2 mg: S
Standing DBP (mm Hg)	4.3 (2.3)	−4.6 (2.9)	−11.0 (2.9)	−11.1 (3.5)	$P < 0.001$	Placebo	0.5 mg: NS 1 mg: S 2 mg: S

[a] Intragroup analysis: S, Significant time effect; NS, Non-significant time effect

The log (concentration)-effect relationship was significant both for supine SBP ($r = 0.446$, $P = 0.004$) and supine DBP ($r = 0.334$, $P = 0.032$). Intragroup analysis of supine SBP, standing SBP and standing DBP, showed a significant reduction of BP in the 1 and 2 mg groups (Table 2). No significant decrease in BP was observed in the 0.5 mg group. The response rate was also dose-dependent: a supine DBP lower than 90 mm Hg, or a 10 mm Hg decrease in supine DBP, was observed in 7%, 27%, 43% and 47% of patients in the placebo, 0.5 mg, 1 mg and 2 mg groups, respectively. The heart rate did not change significantly in any group.

Adverse reactions

Among the 54 fully documented patients, 13 complained of adverse reactions (ARs). Four patients in the 2 mg group complained mainly of both dry mouth and asthenia as did one in the 1 mg group. The severity of symptoms was always mild or moderate and tended to improve over time.

In the 0.5 mg group, one patient complained of a mild and transient dry mouth and two patients of drowsiness. In the placebo group, one patient complained of mild asthenia and one of mild drowsiness.

Dry mouth and drowsiness did not appear to be related to the reduction in BP, since patients who complained of ARs did not exhibit the greatest falls in BP.

No change was noticed in routine haematology/biochemistry parameters or in ECG parameters.

The effects on blood pressure and heart rate were not assessed following drug withdrawal, since patients were immediately shifted to another antihypertensive drug at the end of the study.

Discussion

A significant, dose-dependent decrease in blood pressure was observed after repeated administration of rilmenidine. Compared to the change in the placebo group, supine SBP/DBP decreased by 11.9/4.8, 28.2/9.0 and 20.6/9.8 mm Hg in the 0.5 mg, 1 mg and 2 mg groups, respectively. The blood pressure lowering activity of rilmenidine was mild at the dose of 0.5 mg, while both the 1 and 2 mg doses exhibited a maximal and comparable antihypertensive activity. These results are partly in contrast to those observed after single administration [2] where the dose-effect relationship was linear for doses ranging between 0.5 and 3 mg, with no plateau effect at doses above 1 mg.

Regarding clinical acceptability, adverse reactions leading to drop-out were principally seen in the 2 mg-group, from which 4 patients withdrew from the study because of adverse reactions; only 1 patient withdrew from the 1 mg-group, and none from the 0.5 mg- and placebo groups. These results confirmed the findings after a single dose of rilmenidine: dry mouth and sedation did not differ after 1 mg and placebo, and were only increased after the 2 and 3 mg doses [2]. This had been confirmed in a 4 week

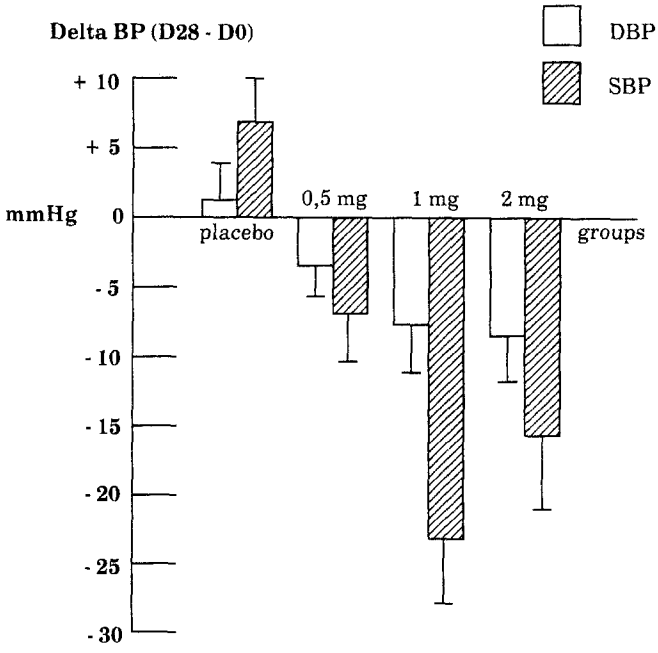

Fig. 1. Reduction (D0–D28) in supine blood pressure (expressed as mean with SEM, in mm Hg)

placebo-controlled study [3], in which the rate of adverse events was no different from placebo at the once-a-day dose of 1 mg. In controlled studies against reference drugs, the clinical acceptability of rilmenidine was also very satisfactory and compared favourably with that of clonidine [5] and methyldopa [6, 7]. The acceptability of rilmenidine did not differ from that of atenolol [8] and hydrochlorothiazide [9] administered in equihypotensive doses. In particular, dry mouth and drowsiness were as frequent after rilmenidine as after atenolol and hydrochlorothiazide [8, 9].

The present study strongly supports the fact that the most beneficial efficacy/acceptability ratio was achieved at the dose of 1 mg. The unit doses of 0.5 and 2 mg did not appear appropriate for the treatment of essential hypertension: the dose of 0.5 mg did not demonstrate antihypertensive activity significantly different from that of placebo, while the 2 mg unit dose led to a marked increase in adverse reactions with no additional antihypertensive effect compared to the 1 mg dose. This once-a-day dose of 2 mg differs from the highest recommended dosage of rilmenidine (1 mg bd) and has certainly increased the incidence of ARs. The dose of 1 mg bd is only administered if blood pressure is inadequately controlled by 1 mg/day. In the present study, patients were randomly allocated to the dose of 2 mg without prior assessment of their response to the 1 mg.

Dissociation between the antihypertensive and central nervous system (CNS) – related effects of rilmenidine were best obtained at the unit dose of 1 mg. These results support recent knowledge of the pharmacology of Imidazoline Preferring Receptors (IPRs). In fact, the hypotensive effect of rilmenidine is now explained by modulation of sympathetic tone through IPRs located in the rostral ventrolateral medulla [10]. Other subtypes of IPRs have been recognized in many tissues of different species [11, 12, 13, 14], although their physiologic functions remain unclear. Like imidazoline derivatives, including clonidine, rilmenidine can bind to α_2-adrenoceptors, but binds preferentially to IPRs [1, 15]. This selectivity explains the dissociation observed in animal [16] and in human studies [3, 5, 6, 7, 8, 9] between the antihypertensive and CNS-related effects of rilmenidine.

The relevance of the study to clinical practice was restricted by the lack of BP measurements over 24 h periods. The 24 h antihypertensive activity of rilmenidine 1 mg once daily has previously been assessed by home BP measurements [17].

In conclusion, the most beneficial efficacy/acceptability ratio was obtained at the dose of 1 mg, once daily. At this dose the maximal antihypertensive efficacy of rilmenidine was comparable to that of reference antihypertensive drugs [18], and was associated with satisfactory clinical acceptability.

References

1. Gomez RE, Ernsberger P, Feinland G, Reis D (1991) Rilmenidine lowers arterial pressure via imidazole receptors in brainstem C1 area. Eur J Pharmacol 195: 181–191
2. Dollery CT, Davies DS, Duchier J, Pannier B, Safar ME (1988) Dose and concentration-effect relations for rilmenidine. Am J Cardiol 61: 60D–66D
3. Ostermann G, Brisgand B, Schmitt J, Fillastre JP (1988) Efficacy and acceptability of rilmenidine for mild to moderate systemic hypertension. Am J Cardiol 61: 76D–80D
4. Chalmers J, Wing L, Taylors S (1990) Analysis of time trends, individual subject responses and background variation in crossover factorial studies with antihypertensive drugs. J Hypertens 8 [Suppl 4]: S27–S35
5. Fillastre JP, Letac B, Galinier F, Le Bihan G, Schwartz J (1988) A multicenter double-blind comparative study of rilmenidine and clonidine in 333 hypertensive patients. Am J Cardiol 61: 81D–85D
6. Galley P, Manciet G, Hessel JL, Michel JP (1988) Antihypertensive efficacy and acceptability of rilmenidine in elderly hypertensive patients. Am J Cardiol 61: 86D–90D
7. United Kingdom Working Party on Rilmenidine (1990) Rilmenidine in mild to moderate essential hypertension. A double-blind, randomised, parallel-group, multicenter comparison with methyldopa in 157 patients. Current Therap Res 47: 194–211
8. Dallochio M, Gosse P, Fillastre JP, Grollier G, Morand P, Drici M, Corcoran C (1991) La rilmenidine, un nouvel antihypertenseur dans le traitement de première intention de l'hypertension artérielle essentielle. Presse Med 20: 1265–1271
9. Fiorentini C, Guillet C, Guazzi M (1989) A multicentre coubleblind trial comparing rilmenidine 1 mg and hydrochlorothiazide 25 mg in 244 patients. Arch Mal Coeur 82: 39–46
10. Bousquet P, Feldman J, Schwartz J (1984) Central cardiovascular effect of alpha-adrenergic drug: differences between catecholamines and imidazoles. J Pharmacol Exp Ther 230: 232–236
11. Coupry I, Lachaud V, Podevin RA, Koenig E, Parini A (1989) Different affinities of α2 agonist for imidazoline and α2 adrenergic receptors. Am J Hypertens, 2: 468–470
12. Langin D, Paris H, Dauzats M, Lafontan M (1990) Discrimination between alpha 2-adrenoceptors and [3H]idazoxan – labelled non-adrenergic sites in rabbit white fat cells. Eur J Pharmacol, 188: 261–272
13. Lachaud-Pettiti V, Podevin RA, Chretien Y, Parini A (1991) Imidazoline-guanidinium and alpha 2 adrenergic binding sites in basolateral membranes from human kidney. Eur J Pharmcol, 206: 23–31
14. Tesson F, Prip-Buus C, Lemoine A, Pegorier JP, Parini A (1991) Subcellular distribution of imidazoline-guanidinium-receptive sites in human and rabbit liver. J Biol Chem 266: 155–160
15. Bricca G, Dontenwill M, Molines A, Feldman J, Tibirica E, Belcourt A, Bousquet P (1989) Rilmenidine selectivity for imidazoline receptors in human brain. Eur J Pharmacol 163: 373–377
16. Van Zwieten PA, Thoulen JMC, Jonkman FAM, Wilffert B, De Jonge A, Timmermans PBMWM (1986) Central and peripheral effects of S3341 [(N-dicyclopropylmethyl)-amino-2-oxazoline] in animal models. Arch Int Pharmacodyn Ther, 279: 130–149
17. Beau B, Mahieux F, Paraire M, Laurin S, Brisgand B, Vitou P (1988) Efficacy and safety of rilmenidine for arterial hypertension. Am J Cardiol 61: 95D–102D
18. Gould BA, Mann S, Davies AB, Altman DG, Raftery EB (1981) Does placebo lower blood pressure? Lancet II: 1377–1381

Prof. Dr. R. Luccioni
Department of Cardiology
CHU la Timone
Chemin de l'armée d'Afrique
F-13005 Marseille
France