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O. Kourilsky

ITERIUM: CLINICAL BENEFITS FROM AN INNOVATIVE ANTIHYPERTENSIVE TREATMENT

INTRODUCTION

The renaissance of interest in sympathetic overactivity as a candidate link between blood pressure elevation, insulin resistance and other cardiovascular risk factors further underlined the potential of I_1-imidazoline receptors as therapeutic targets for antihypertensives.

It was against background that rilmenidine began its clinical development, and hence became the first I_1-imidazoline receptor selective antihypertensive to enter the therapeutic arena. Rilmenidine's selective binding to I_1-imidazoline receptors in the lateral reticular nucleus of the brainstem [1] leads to a reduction in systemic sympathetic tone. Rilmenidine exerts its antihypertensive effect mainly through reduced total peripheral resistance, mediated by reduction in sympathetic overdrive [2].

Sympathoinhibition at renal level and a direct effect through selective binding I_1 receptors [3] combine to inhibit the Na^+/H^+ antiport in the proximal convoluted renal tubule. Rilmenidine's renal effects lead to a decrease in sodium and water retention, contributing to maintenance of blood pressure control in the long term [4–8].

ANTIHYPERTENSIVE EFFICACY

Rilmenidine's antihypertensive efficacy has been extensively tested in double-blind, randomized trials versus placebo and against reference antihypertensive drugs.

Versus Placebo

126 hypertensive patients were included in this multicenter trial. Patients were divided into those with mild and those with moderate hypertension. After a placebo run-in period, rilmenidine was given in monotherapy for 4 weeks. Reduction in blood pressure by rilmenidine was significant in both the mild and moderate hypertension group. Of all rilmenidine treated patients, 61 % were normalized (target SBP/ DBP $\leq$ 160/90 mmHg) after 4 weeks treatment. In the mild hypertension group, the normalization rate at 4 weeks on, rilmenidine was 84 % [9].

Versus Diuretics

In a study including 244 placebo-resistant mild-to-moderate hypertensive patients, rilmenidine was compared with hydrochlorothiazide over a period of 8 weeks. The 2 antihypertensive treatments were equally effective, each normalizing (target DBP $\leq$ 90 mmHg) 57 % of patients in monotherapy [10].

These findings were broadly reproduced in another study in elderly patients, with rilmenidine normalizing 67 % of patients over 8 weeks, and no significant difference between rilmenidine and hydrochlorothiazide in terms of either absolute reduction or normalization rate [11].

Versus Beta-blockers

Rilmenidine (1–2 mg daily) was compared with atenolol (50 to 100 mg daily) in 90 mild-to-moderate hypertensive patients. Normalization rates at 12 weeks (target SBP/DBP $\leq$ 160/90 mmHg) were 66 % on rilmenidine and 65 % on atenolol. Fewer patients in the rilmenidine group (12 %) than in the beta-blocker treated group (16 %) required of a second antihypertensive for inadequate blood pressure control [12].

Versus Calcium-channel blockers

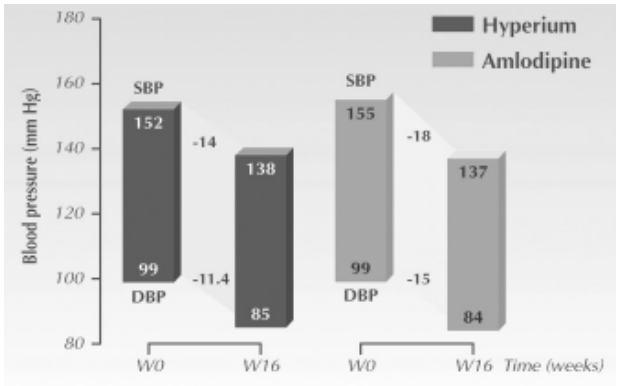
Trials of rilmenidine versus both nifedipine and amlodipine have been performed in placebo-resistant hypertensives. Fifty-six patients completed the study per protocol in a comparison between rilmenidine (1 to 2 mg daily) and nifedipine (40 mg daily). At the end of a year of treatment, blood pressure was adequately controlled on rilmenidine (DBP from 102.7 ± 4.6 at baseline to 88.5 ± 7.1 mmHg) and on nifedipine (DBP from 102.7 ± 5.1 at baseline to 85.6 ± 7.9). No significant difference was observed in the antihypertensive efficacy of the treatments [13].

In a recent trial, 43 mild-to-moderate hypertensives with risk factors comprising the metabolic syndrome were treated with rilmenidine (1 to 2 mg daily) or amlodipine (5 to 10 mg daily) for 4 months. The treatments were comparable in their reductions of blood pressure (SBP/DBP) (rilmenidine from 152/99 mmHg to 138/85 mmHg and amlodipine from 154.1/ 98.5 mmHg to 136.5 ± 84.1 mmHg), which were not statistically different (Fig. 1) [14].

Versus ACE-Inhibitors

Rilmenidine was compared with captopril in 51 mild-to-moderate placebo-resistant hypertensives over 8 weeks' treatment. The reductions in blood pressure in the rilmenidine (1 to 2 mg daily) and captopril (50 to 100 mg daily) groups were significant, and there was no significant difference between them. The number of patients requiring dose adaptation for nonresponse was the same for rilmenidine treated as for captopril treated patients. Normalization (target DBP $\leq$ 90 mmHg) was achieved in 79 % of patients in the rilmenidine group [15]. Comparability of the antihypertensive efficacy of rilmenidine and captopril is also demonstrated by recent results showing similar blood pressure reductions (SBP/DBP = –18/–14 on rilmenidine, –13/–19 on captopril) over 6 months treatment (Fig. 2) [16].

Figure 1



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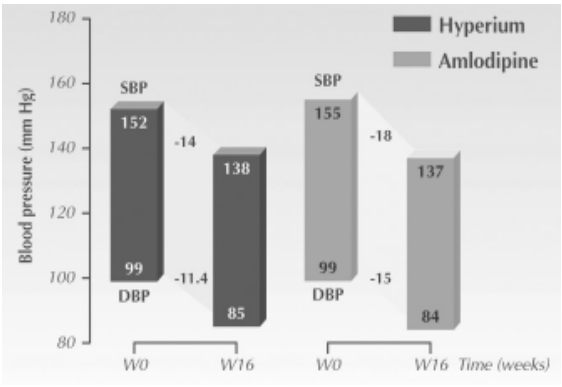


Versus α_2 agonists

Studies against both clonidine and α-methyl-dopa have been performed in placebo-resistant, mild-to-moderate hypertensives, and these demonstrated both that rilmenidine is as effective as these older agents, and that it has a superior tolerance profile. Three hundred and thirty-three patients were randomized to rilmenidine (1 to 2 mg daily) or clonidine (0.15 to 0.3 mg daily) for 6 weeks' treatment. At the end of treatment identical blood pressure reductions were seen in the two groups (–19 mmHg systolic, –12 mmHg diastolic). Normalization rates (target SBP/DBP ≤ 160/90) were 57 % and 56 % for rilmenidine treated and clonidine treated patients respectively [17]. Another study compared rilmenidine (1 to 2 mg daily) and α-methyl-dopa 0.5 to 1 g daily in 157 hypertensives. There was no significant difference in blood pressure normalization rates between the groups, fewer patients in the rilmenidine group requiring addition of a second antihypertensive agent (hydrochlorothiazide) for inadequate response [18]. Rilmenidine and α-methyl-dopa were also comparable in their antihypertensive efficacy in fragile elderly hypertensive requiring long-term geriatric admission. Normalization (target DBP < 90 mmHg) was achieved in 83 % and 85 % of patients on rilmenidine and α-methyl-dopa respectively. Fewer patients required dose adaptations for nonresponse in the rilmenidine group [19].

Long-term maintenance

Rilmenidine's longer term antihypertensive efficacy has been studied in two non-comparative trials. Maintenance of blood pressure control in rilmenidine-treated placebo-resistant mild-to-moderate hypertensives was studied over 1 year. Eight percent of all study patients were controlled (to DBP ≤ 90 mmHg) at 6 months (66 % of them on rilmenidine monotherapy), and 84 % controlled at 1 year (60 % on rilmenidine monotherapy) [20]. A second study of 12 months treatment included 18,235 unselected hypertensive patients. No fading of effect was seen, with both the reductions in pressure and the rate of normalization on rilmenidine (60 % at 1 mg daily) being maintained throughout. Furthermore, antihypertensive efficacy was comparable in several defined at-risk subpopulations – those with isolated systolic hypertension, aged over 70 with severe hypertension, diabetes mellitus, dyslipidemia, coronary disease, arrhythmias, heart failure, and renal failure (Fig. 3) [21].

The antihypertensive efficacy of rilmenidine is thus entirely comparable with that of reference representatives of the four most prescribed antihypertensive classes. Efficacy is demonstrated in both uncomplicated and at-risk hypertensives, control being satisfactorily maintained in the long term without fading of effect.

Clinical Tolerance Profile

Lack of α_2 adrenoceptor-mediated side effects

Rilmenidine is pharmacologically distinguished from antihypertensives acting either entirely or predominately through α_2-adrenoceptors such as clonidine and α-methyl-dopa. Many of the undesirable effects of these central agents are α_2-adrenoceptor-mediated (such as sedation via α_2-agonism in the locus ceruleus, drying of the mouth via α_2-agonism in the salivary glands).

Rilmenidine's good tolerance, through selective binding to I_1-imidazoline receptors has been demonstrated in a large number of clinical studies.

A double-blind comparison of rilmenidine and placebo showed no difference in incidence of adverse effects between placebo-treated patients and those taking rilmenidine at the usual 1 mg daily dose [9]. Head-to-head comparisons of rilmeni-

Figure 3

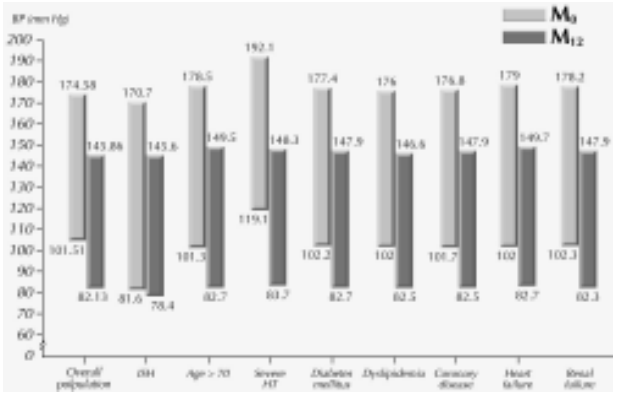
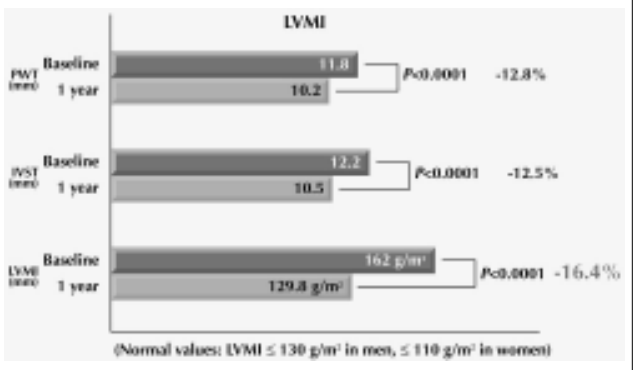


Figure 4



dine against clonidine and α-methyldopa show a clear differentation in terms of side-effect profile. Against clonidine, the incidence of dry mouth and drowsiness induced by rilmenidine was 2 to 3 times less and of weaker intensity than that of the comparator. These differences were statistically significant, and clinically relevant as no rilmenidine treated patient stopped treatment, whereas 10 % of clonidine-treated patients left the study due to side effects [17]. Versus α-methyl-dopa, in a study including 157 patients, no clinically significant side effects were observed during 4 months of rilmenidine treatment. The marked difference between rilmenidine and α_2-agonist antihypertensive was therefore again underlined [18].

Clinical tolerance in long-term treatment

Further strong support for the good tolerance of rilmenidine can be found in the results of a very large pharmacoepidemiological study. Luccioni reported this trial, including 18,235 unselected hypertensive patients. Despite more than 35,000 coprescriptions, only 3,6 % of patients withdrew due to any adverse effect during a year of treatment with rilmenidine 1 to 2 mg daily [21].

Lack of rebound phenomena

The lack of clinical rebound phenomenon on cessation of rilmenidine treatment is well documented. In a comparative, double-blind, controlled trial, 59 patients were randomized to clonidine (0.15 to 0.30 mg) or rilmenidine (1 to 2 mg daily). After 8 weeks of active treatment the antihypertensive effects of the two treatments were similar. Active treatment was then ceased and all patients switched to placebo. Cessation of clonidine treatment was associated with significant tachycardia, whereas there was no evidence of rebound phenomenon on cessation of rilmenidine treatment [22]. This lack of clinical symptoms on withdrawal of rilmenidine treatment was reproduced in other clinical studies, including placebo periods at the end of treatment [12, 18, 19].

Lack of sodium and water retention

Clinical evidence for lack of sodium and water retention during rilmenidine treatment is provided by the trends in patients' weight in clinical studies. In contrast experience of centrally acting α_2-adrenoceptor agonists, which induce sodium and water retention due to their effects on the Na^+/H^+ antiport rilmenidine was weight-neutral in a number of controlled trials lasting between 4 weeks and 1 year [9, 11, 12, 15, 18].

Preserved cardiovascular adaptation

Cardiovascular responses to posture and exercise during rilmenidine treatment were specifically assessed and shown to be preserved in a double-blind trial versus atenolol. This was in contrast to the impaired responses seen in the atenolol-treated group [23]. Preservation of postural and exercise responses is of importance in the treatment of elderly, and of young and active hypertensive patients respectively. Lack of postural hypotension during rilmenidine treatment has been noted in trials specifically treating elderly patients. No cases arose during 6 weeks' rilmenidine treatment of patients aged over 70 years and requiring long-stay inpatient care [19], and another trial including 46 elderly patients in the rilmenidine group produced no symptomatic orthostatic hypotension during 8 weeks of treatment [11]. Hence, review of the study evidence provides clinical proof that none of the classic α-mediated adverse effects of centrally acting agents is clinically significant during rilmenidine treatment. The reduction of sympathetic overdrive by rilmenidine is achieved without compromising postural or exercise responses.

Preservation of Metabolic Parameters

In uncomplicated hypertensive patients

In a comparison with atenolol over 12 weeks' treatment, rilmenidine significantly reduced low-density lipoprotein (LDL) and preserved high-density lipoprotein (HDL). This lipid neutrality contrasted with the classic pattern of lipid abnormalities produced by beta-blocker therapy, in the atenolol group there was a significant reduction of HDL and a tendency to increase triglycerides [12].

In another controlled study, patients treated with hydrochlorothiazide show significant elevations in total cholesterol and uric acid, and a reduction in potassium level. Rilmenidine's preservation of lipid profile is confirmed in this study, as well as its respect for electrolyte and lipid profiles. Rilmenidine treatment in fact produced a small statistically significant reduction in total cholesterol (TC). Rilmenidine's neutrality regarding these parameters was therefore highlighted against the adverse effects of a reference diuretic [10]. Rilmenidine treatment was associated with significant reductions in TC and LDL levels in mild-to-moderate hypertensives over a 12 weeks' treatment in another study. There was a parallel but non-significant tendence for fasting plasma glucose to improve (5.63 to 5.39 mmol/L) in this population. The glucose trend was significantly different ($p < 0.05$) from that observed with α-methyldopa – a comparator agent (5.38 to 5.60 mmol/L) [18].

In long-term treatment

Open studies provide further incidence of the metabolic neutrality of rilmenidine, and confirm the persistence of this benefit in long-term treatment. Measured lipid parameters (TC and TG) were unchanged during a year of rilmenidine treatment of mild-moderate hypertensives [20] and in the study population, neither fasting glucose, lipids, electrolytes, nor uric acid were significantly altered over 1 year of treatment in more than 18,000 hypertensives [21].

In elderly patients

Lipid profiles were unchanged in a study in elderly patients over 6 weeks of treatment [19], a finding confirmed in a second study over 8 weeks [11]. In this second study the fact rilmenidine did not alter electrolyte and uric levels contrasted with the significant reduction in potassium and chloride, and increase in uric acid produced by the comparator, hydrochlorothiazide.

The elderly subpopulation analysis of the Luccioni study confirmed rilmenidine's neutrality as regards electrolytes, lipids, glucose, and uric acid [21]. These tolerance data support the role of rilmenidine as a first-line antihypertensive choice in this fragile and frequently polymedicated population.

In diabetic patients

Rilmenidine's efficacy and acceptability were studied over 4 months in 29 hypertensive insulin-dependent diabetes. Neither random blood glucose values, urine glucose excretion, insulin requirements, nor glycosylated hemoglobin were significantly changed during treatment [24].

Results in non-insulin-dependent diabetics were similar, 3 months' treatment with rilmenidine (1 to 2 mg daily) changed neither requirements for hypoglycemic medication, nor any parameters of glucose or lipid metabolism in hypertensive type 2 diabetic patients [25].

Additional data confirm the stability of glucose and lipid parameters in type 2 diabetics over 6 months' treatment in a comparative study versus captopril treatment [16]. Metabolic tolerance in the longer term was seen in the diabetic population in the Luccioni study, where a small but non-significant tendency for fasting glucose to decrease was observed after 1 year of rilmenidine therapy (7.2 to 6.8 mmol/L) [21].

In dyslipidemic patients

In mild-to-moderate placebo-resistant hypertensives with type 2α or 2β hyperlipidemia, who were not taking lipid-lowering agents, rilmenidine (1 to 2 mg daily) was compared with captopril (50 to 100 mg daily) over 1 year of treatment. Total cholesterol (TC), HDL, LDL, apoprotein A1, and apoprotein B remained stable in the two groups, with no significant intergroup differences observed [15]. In patients, with high triglycerides as part of the metabolic syndrome, rilmenidine's neutrality with respect to lipids was further demonstrated TC, HDL, and TG were stable throughout the 4 months of treatment [14]. The validity of these observations in chronic administration is confirmed by analysis of lipid parameters in the dyslipidemic subpopulation of a large pharmacoepidemiological study, where no changes in TG or TC arose over 1 year of treatment [21].

Hence, rilmenidine does not alter lipid, glucose or electrolyte profiles in long-term treatment, in any population of hypertensive patients, including the elderly, diabetics, and with established dyslipidemia.

Additional Benefits in at Risk Hypertensives

Reduction of left ventricular hypertrophy

One year of treatment with rilmenidine (1 to 2 mg daily) reversed left ventricular hypertrophy (LVH) (from 152 ± 5 to 131 ± 4 g/m², p < 0.05). This significant 14 % reduction in left ventricular mass index (LVMI) was accompanied by decreases in intraventricular septum and posterior wall thicknesses, and without changes in endsystolic or end-systolic internal diameters [16]. These findings were reproduced in a double-blind placebo controlled trial against nifedipine, where rilmenidine reduced LVMI by 12.5 % over 1 year. This reduction was not significantly different from that produced by slow-release nifedipine (40 mg per day) [13].

These results have been reinforced by a-year multicenter study involving 219 mild-to-moderate hypertensive patients with left ventricular hypertrophy and/or left ventricular diabetic dysfunction treated with rilmenidine 1 to 2 mg/ day. After a 1-year treatment, rilmenidine in monotherapy significantly decreased the left ventricular mass index (LVMI) by 16.4 %. This decrease was related to the significant cumulative decrease of the posterior wall thickness (PWT) of 11.8 % and the intervention septum thickness (IVST) of 12.5 %. More over these results have been accompagnied by an improvement of the ventricular diastolic function in both E/A ratio of peak velocities (from 0.78 ± 0.1 to 0.92 ± 0.2, P < 0.001) and DT value (deceleration time of the E-wave, from 232 ± 23.1 to 217 ± 27.1 ms, P < 0.01) echo parameters (Fig. 4) [27].

Reduction of microalbuminuria

Rilmenidine has recently been compared with captopril in type 2 diabetics with placebo resistant mild-to-moderate hypertension and microalbuminuria (30 < microalbuminuria < 300 mg/24 h). Median microalbuminuria level reduction over 6 months on rilmenidine (160 to 56 mg/24 h) was similar to that observed on captopril (144 to 54 mg/24 h). There was no significant difference between the two treatment groups. Rilmenidine's use first-line in the hypertensive diabetic is hence further supported by a potentially nephroprotective treatment (Fig. 5) [16].

Improvement in insulin resistance

The effects of rilmenidine were studied recently in patients with metabolic syndrome (syndrome X). Fifty-two patients with obesity, hypertension, impaired glucose tolerance, and hypertriglyceridemia (body mass index (BMI) ≥ 29 kg/m², 95 ≤ DBP ≤ 114 mmHg, TG ≥ 2 mmol/L 6.1 ≤ fasting plasma glucose ≤ 7.0 mmol/L or 7.8 ≤ plasma glucose at 2 hours on an oral glucose tolerance test (OGTT) ≤ 11 mmol/L) were included. They were treated with rilmenidine (1 to 2 mg daily) for 6 months.

Rilmenidine significantly improved glucose metabolism compared with the comparator amlodipine, as judged on the oral glucose tolerance test by significant reduction in plasma glucose at 2 hours and in the area under the curve. These findings suggest a specific effect of rilmenidine on insulin resistance, most likely mediated by reduction in sympathetic overdrive (Fig. 6) [14].

Thus in addition to the well-demonstrated antihypertensive efficacy, clinical and metabolic tolerability of rilmenidine, use in at-risk hypertensive patients is supported by specific benefits in those with ventricular hypertrophy, diabetic microalbuminuria, and impaired glucose tolerance.

Conclusion

Rilmenidine, the first antihypertensive with high selectivity for brainstem and renal I_1-imidazoline receptors, has amply shown its suitability for first-line use in the treatment of mild-to-moderate essential hypertension. Experience in both controlled trials and in conditions of daily practice confirm the very good efficacy, acceptability, and tolerability of this agent. Clinical development is ongoing, as evidenced by recent studies in specific at-risk populations.

New results showing improvement in pressure-independent cardiovascular risk factors during treatment with rilmenidine reinforce both the important role of the sympathetic overdrive in pathogenesis of the syndrome of hypertension, and draw attention to the therapeutic value of this original molecule.

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Figure 5

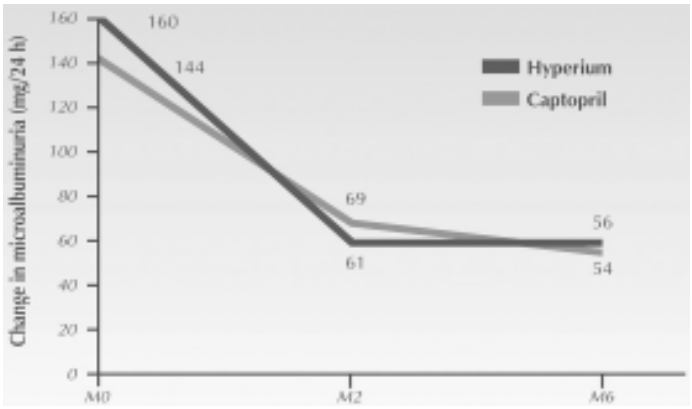
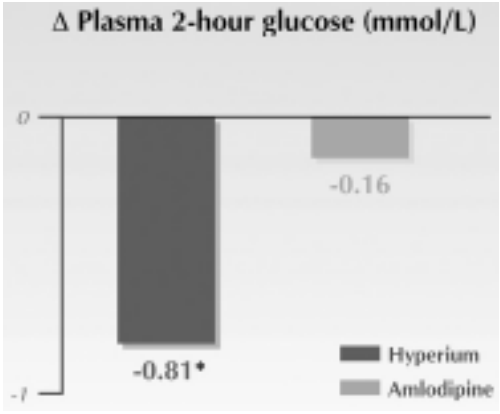


Figure 6



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