Rilmenidine: A Clinical Overview
J.L. Reid

Rilmenidine is an antihypertensive agent with selectivity for I$_1$ imidazoline receptors that acts both centrally by reducing sympathetic overactivity and in the kidney by inhibiting the Na$^+$/H$^+$ antiport.

Rilmenidine provides antihypertensive efficacy comparable with that of diuretics, β-blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors.

Experience from trials and clinical practice highlights rilmenidine’s clinical and metabolic acceptability in hypertensive populations, including those at special risk because of old age, renal impairment, diabetes mellitus, or dyslipidemia.

In the at-risk hypertensive, rilmenidine reduces left ventricular hypertrophy to a similar degree to other reference agents. New studies show a significant improvement in glucose metabolism in metabolic syndrome patients treated with rilmenidine, and a significant reduction in microalbuminuria during rilmenidine treatment of hypertensive type 2 diabetics.

Thus the efficacy/tolerance ratio of rilmenidine supports its role as a first-line antihypertensive option for all groups of hypertensive patient, with specific advantages in some at-risk populations.

From the Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow, United Kingdom.

Address correspondence and reprint requests to Professor J.L. Reid, DM, FRCP, FRSE, Regius Professor of Medicine and Therapeutics, Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow, G11 6NT United Kingdom; e-mail: j.l.reid@clinmed.gla.ac.uk

HISTORICAL PERSPECTIVE

The discovery of I$_1$ imidazoline binding sites in mammalian brainstem and kidney, and the first descriptions of the physiologic effects of molecules binding to these sites, suggested the possibility of therapeutic modulation of sympathetic tone dissociated from classic α$_2$-adrenoceptor-mediated secondary effects.

The renaissance of interest in sympathetic overactivity as a candidate link among 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 this background that rilmenidine began its clinical development, and became the first I$_1$ imidazoline receptor-selective antihypertensive agent to enter the therapeutic arena.

MECHANISM OF ACTION

Rilmenidine’s selective binding to I$_1$ imidazoline receptors in the lateral reticular nucleus of the brainstem leads to a reduction in systemic sympathetic tone. Rilmenidine appears to exert its antihypertensive effect mainly through reduced total peripheral resistance, mediated by a reduction in sympathetic activity.

Sympathoinhibition at the renal level and a direct effect through selective binding to renal I$_1$ receptors 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 the maintenance of blood pressure control in the long term.4–8

ANTIHYPERTENSIVE EFFICACY

Rilmenidine’s antihypertensive efficacy has been extensively evaluated in double-blind, randomized trials versus placebo and against other classes of antihypertensive.

**Versus Placebo** One hundred twenty-six hypertensive patients were included in this multicenter trial. Patients were divided into those with mild and those with moderate hypertension. After a 4-week placebo run-in period, patients were randomized to receive either rilmenidine or placebo, double-blind, for 4 weeks’ treatment. Reduction in blood pressure by rilmenidine was significant in both the mild and moderate hypertension groups. Of all rilmenidine-treated patients, 61% were normalized (target SBP/DBP ≤ 160/90 mm Hg) after 4 weeks’ treatment. In the mild hypertension group, the normalization rate at 4 weeks with rilmenidine was 84%. The blood pressure reductions, responder rates, and normalization rates were all significantly greater with rilmenidine treatment than in those receiving placebo.9

**Versus Diuretics** In a study including 244 mild-to-moderate hypertensive patients, rilmenidine was compared with hydrochlorothiazide over a period of 8 weeks. The two antihypertensive treatments were equally effective, each normalizing (target DBP ≤ 90 mm Hg) 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 pressure reduction or normalization rate.11

**Versus β-Blockers** Rilmenidine (1 to 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 ≤ 160/90 mm Hg) were 64% with rilmenidine and 63% with atenolol. Fewer patients in the rilmenidine group (12%) than in the β-blocker–treated group (16%) required the addition 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 hypertensive patients. 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 with rilmenidine (DBP from 102.7 ± 5.1 at baseline to 85.6 ± 7.9 mm Hg). No significant difference was observed in the antihypertensive efficacy of the two 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 mm Hg to 138/85 mm Hg and amlodipine from 154.1/98.5 mm Hg to 136.5/84.1 mm Hg), which were not statistically different.14

**Versus Angiotensin-Converting Enzyme (ACE) Inhibitors** Rilmenidine was compared with captopril in 51 mild-to-moderate 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 ≤ 90 mm Hg) was achieved in 79% of patients in the rilmenidine group.15

**Versus α₂ Agonists** Studies against both clonidine and α-methyl dopamine have been performed in 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 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 mm Hg systolic, −12 mm Hg diastolic). Normalization rates (target SBP/DBP ≤ 160/90 mm Hg) 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 dopamine 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) because of an inadequate response.18 Rilmenidine and α-methyl dopamine were also comparable in their antihypertensive efficacy in fragile elderly hypertensives requiring long-term geriatric admission. Normalization (target DBP ≤ 90 mm Hg) was achieved in 83% and 85% of patients taking rilmenidine and α-methyl dopamine respectively. Fewer pa-
patients required dose changes for nonresponse in the rilmenidine group.19

Long-Term Maintenance Treatment Rilmenidine’s longer-term antihypertensive efficacy has been studied in two noncomparative trials. Maintenance of blood pressure control in rilmenidine-treated, placebo-resistant, mild-to-moderate hypertensives was studied over 1 year. Eighty percent of all study patients were controlled (to DBP ≤ 90 mm Hg) at 6 months (66% of them with rilmenidine monotherapy), and 84% were controlled at 1 year (60% with rilmenidine monotherapy).20 A second study of 12 months’ treatment included 18,235 unselected hypertensive patients. No loss of effect was seen, with both the reductions in pressure and the rate of normalization with 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; those aged > 70 years; those with severe hypertension, diabetes mellitus, dyslipidemia, coronary disease, arrhythmias, heart failure, and renal failure.21

The antihypertensive efficacy of rilmenidine is thus entirely comparable to 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 $\alpha_2$-Adrenoceptor-Mediated Side Effects Rilmenidine is pharmacologically distinguished from antihypertensives acting either entirely or predominately through $\alpha_2$-adrenoceptors such as clonidine and $\alpha$-methyldopa. Many of the undesirable effects of these central agents are $\alpha_2$-adrenoceptor-mediated (such as sedation and mouth dryness).

Rilmenidine’s good tolerance, through selective binding to $I_1$ imidazoline receptors, has been amply 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 rilmenidine against clonidine and $\alpha$-methyldopa showed a clear differentiation in terms of side-effect profile. Compared with clonidine, the incidence of dry mouth and drowsiness induced by rilmenidine was 2 to 3 times less and of weaker intensity. These differences were statistically significant and clinically relevant, as no rilmenidine-treated patient stopped treatment, whereas 10% of clonidine-treated patients left the study because of side effects.17 Versus $\alpha$-methyldopa, 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 $\alpha_2$ agonist antihypertensives 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 pharmacoepidemiologic study. Luccioni reported this trial, which included 18,235 unselected hypertensive patients. Despite more than 35,000 coprescriptions, only 3.6% of patients withdrew because of 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 phenomena 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 phenomena 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 with clinical experience of centrally acting $\alpha_2$-adrenoceptor agonists, which induce sodium and water retention because of 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 also been noted in trials specifically treating elderly patients. No cases arose during 6 weeks’ rilmenidine treatment of patients aged > 70 years and requiring long-stay inpatient care,19 and another trial including 46 elderly patients in the rilmenidine group produced no symp-
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) levels. This lipid neutrality contrasted with the classic pattern of lipid abnormalities produced by β-blocker therapy: in the atenolol group there was a significant reduction in HDL and a tendency to increase triglycerides (TG).12

In another controlled study, patients treated with hydrochlorothiazide showed significant elevations in total cholesterol and uric acid, and a reduction in potassium levels. Rilmenidine’s preservation of lipid profile was confirmed in this study, as was its respect for electrolyte and lipid profiles. In fact, rilmenidine treatment produced a small but statistically significant reduction in total cholesterol (TC). Rilmenidine’s neutrality with regard to these parameters was therefore highlighted against the adverse effects of a reference diuretic.8

Rilmenidine treatment was associated with significant reductions in TC and LDL levels in mild-to-moderate hypertensives over 12 weeks’ treatment in another study. There was a parallel but nonsignificant tendency for fasting plasma glucose to improve (5.63 to 5.39 mmol/L) in this population. The glucose trend was significantly different (P < .05) from that observed with α-methyldopa—the comparator agent (5.38 to 5.60 mmol/L).16

In Long-Term Treatment  Open studies provide further evidence 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-to-moderate hypertensives,20 and in the Luccioni study population, neither fasting glucose, lipids, electrolytes, nor uric acid were significantly altered over 1 year of treatment of 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 that rilmenidine did not alter electrolyte and uric acid levels contrasted with the significant reduction in potassium and chloride and increase in uric acid produced by the 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 population, who are frequently treated with several different drugs.

In Diabetic Patients  Rilmenidine’s efficacy and acceptability were studied over 4 months in 29 hypertensive insulin-dependent diabetics. Neither random blood glucose values, urine glucose excretion, insulin requirements, nor glycosylated hemoglobin were significantly changed during treatment.22 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 parameter of glucose or lipid metabolism in hypertensive type 2 diabetic patients.25

Recent 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 nonsignificant fall in fasting glucose 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 2a or 2b 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, 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, LDL, 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 pharmacopeidemiological 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 those 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 < .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 end-systolic or end-diastolic internal diameter.26 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

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). The median microalbuminuria level reduction over 6 months with rilmenidine (160 to 56 mg/24 h) was similar to that observed for 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 renoprotective treatment.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 ≥ 29 kg/m², DBP ≤ 114 mm Hg, TG ≥ 2 mmol/L, 6.1 ≤ fasting plasma glucose ≤ 7.0 mmol/L or 7.8 ≤ plasma glucose at 2 h on an oral glucose tolerance test ≤ 11 mmol/L) were included. They were treated with rilmenidine (1 to 2 mg daily) for 5 months. Rilmenidine significantly improved glucose metabolism compared with amloidipine, as judged on the oral glucose tolerance test by significant reduction in plasma glucose at 2 h 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.14

Thus, in addition to the well-demonstrated antihypertensive efficacy, and 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 selectivity for brainstem and renal I1 imidazoline receptors, is suitable for first-line use in the treatment of mild-to-moderate essential hypertension. Experience in both controlled trials and in conditions of daily practice confirms the 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 markers during treatment with rilmenidine reinforce both the important role of sympathetic overdrive in the pathogenesis of the syndrome of hypertension, and draw attention to the therapeutic value of this original molecule.

REFERENCES


