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# Rilmenidine

Tony J. Verbeuren, *A. Tuan Dinh Xuan, †Elisabeth Koenig-Bérard, and †Philippe Vitou

*Department of Cardiovascular Pharmacology, Institut de Recherches Servier, Suresnes, France; *Laboratoire d'Explorations Fonctionnelles, Hopital Cochin, Paris, France; and †Institut de Recherches Internationales Servier, Neuilly-sur-Seine, France*

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Rilmenidine is a new antihypertensive agent, recently registered in France (1987); it is currently in phase III clinical investigations in several countries. Since initial studies using in vivo techniques or in vitro isolated organs have demonstrated affinity of rilmenidine for central $\alpha_2$-adrenoceptors (26,53), the drug is currently classified as an $\alpha_2$-adrenoceptor agonist (54). Consequently, it has been compared in many instances with the classical $\alpha_2$-agonist, clonidine. However, rilmenidine, being an oxazoline derivative, has a chemical structure that differs considerably from those of clonidine or guanfacine, the two classical $\alpha_2$-adrenoceptor agonists (an imidazoline and guanidine derivative, respectively). Furthermore, the pharmacological and clinical effects of rilmenidine, though comparable in some instances, are not always identical to those of clonidine in humans. The differences may be explained by recent discovery of specific imidazoline receptors in brain and kidney (5a,10,40). They differ from classical $\alpha_2$-adrenoceptors. Rilmenidine seems to have a higher affinity for these receptors (7). In this respect, rilmenidine may be regarded as the first representative of a new family of pharmacological compounds. Some of the properties of rilmenidine that distinguish this drug from other $\alpha_2$-adrenoceptor agonists in animals and in humans are reviewed below.

## CHEMISTRY

Rilmenidine, or 2-(dicyclopropylmethyl)amino-2-oxazoline phosphate, is a white powder. Its chemical structure differs from that of known $\alpha_2$-agonists: the compound possesses a dicyclopropyl group instead of a phenyl ring and an oxazoline nucleus instead of the imidazoline or guanidine group. Rilmenidine has a molecular weight of 180.25. Its solubility in water increases when the pH decreases from 12 to 6.9. It is

Address correspondence to Dr. T. J. Verbeuren at IDRS, 11 rue des Moulineaux, 92150 Suresnes, France. Address reprint requests to Dr. E. Koenig-Berard at IRIS, 22 rue Garnier, 92200 Neuilly-sur-Seine, France.

a weak base with a $pK_a$ of approximately 9. At physiologic pH (7.4), only 1% is in the ionized form. Rilmenidine is easily soluble in water, soluble in methanol, poorly soluble in ethanol (95% *v/v*), and mildly soluble in lipids. The true partition coefficient between water and octanol at pH 7.4 is about 0.47. Studies by infrared spectrophotometry and differential calorimetry of several batches of rilmenidine crystallized in various solvents showed the absence of polymorphism. The water-soluble phosphate salt is used clinically. The tablet contains 1 mg of rilmenidine (expressed as base).

## TOXICOLOGY

The oral $LD_{50}$ values of rilmenidine in Swiss mice and Wistar rats are 375 and 295 mg/kg, respectively, suggesting a high therapeutic index when compared to the maximal daily therapeutic dose. By repeated administration (in concentrations approximately 43 times higher than the therapeutic dose) to rats and monkeys for 1 year, rilmenidine produced no hematological, biochemical, or histological changes. Rilmenidine, even at very high doses, caused no fetal toxicity and did not affect fertility of treated animals or of their offspring. Although genetic malformations have not been observed in animals, rilmenidine is contraindicated in pregnant women since no appropriate clinical data are available. Furthermore, rilmenidine has no carcinogenic activity in the Fisher rat and in the B6C3F1 mouse after 125 and 80 weeks of treatment, respectively, with doses 100 times higher than the human therapeutic dose.

## PHARMACOKINETICS

The human pharmacokinetic profile of rilmenidine was determined after single intravenous and single or repeated oral administrations of the drug to 65 healthy subjects (23). In all studies, the dose administered was 1 mg of base (1.54 mg of phosphate salt). In the radiolabeled studies ([$^{14}$C]rilmenidine), the dose was approximately 1 mg. Since antihypertensive drugs are used widely, not only in the elderly but also in hypertensive patients with other diseases, it was of interest to study the effects of age, renal failure, and hepatic insufficiency on the basic pharmacokinetic profile of rilmenidine (47).

A sensitive and specific quantitative analysis for determination of rilmenidine levels in blood and urine was used; it combined gas chromatography (negative ion chemical ionization) and mass spectrometry (18,42,51).

### Healthy Subjects

No difference was found in the pharmacokinetic profiles of rilmenidine in men and women. Table 1 summarizes the main parameters following intravenous or oral administration. Absorption of rilmenidine (tablet form) was characterized by a $t_{max}$ of approximately 2 h, a $C_{max}$ of 3.5 ng/ml, and total bioavailability ($F = 1$). Distribution was characterized by a large volume (5 L/kg), reflecting an extensive tissue affinity and a large free fraction (plasma protein binding of <10%). Elimination was characterized by total clearance (Cl) of approximately 460 ml/min, an elimination half-life ($t_{1/2}$) of 8 h, and a mean residence time (MRT) of 12 h. Approximately 70% of

**TABLE 1.** *Pharmacokinetic parameters of rilmenidine in healthy subjects (n = 12) after intravenous and oral administration of 1 mg (mean ± SEM)*

| | Intravenous route | Oral route |
|---|---|---|
| $t_{lag}$ (h) | — | 0.25 ± 0.07 |
| $C_{max}$ (ng/ml) | — | 3.49 ± 1.79 |
| $t_{max}$ (h) | — | 1.79 ± 0.21 |
| $F$ (%) | — | 100.1 ± 5.3 |
| AUC (ng h/ml) | 38.61 ± 3.31 | 38.33 ± 3.55 |
| $V$ (L) | 314.44 ± 18.31 | 324.68 ± 20.67 |
| $T_{\frac{1}{2},z}$ (h) | 8.31 ± 0.77 | 8.51 ± 0.86 |
| MRT (h) | 11.77 ± 1.11 | 12.28 ± 0.99 |
| Cl (ml/min) | 463.58 ± 35.05 | 475.17 ± 41.32 |
| $Cl_R$ (ml/min) | 296.81 ± 33.56 | 330.13 ± 27.42 |
| $f_e$ (%) | 63.74 ± 5.14 | 71.18 ± 4.49 |

AUC = area under the plasma concentration curve; Cl = total plasma clearance; $Cl_R$ = renal clearance; $C_{max}$ = maximum plasma concentration; $F$ = bioavailability factor; $f_e$ = fraction of the unchanged drug excreted in urine; MRT = mean residence time; SEM = standard error of the mean; $t_{lag}$ = lag time of absorption; $t_{max}$ = time to reach the maximum plasma concentration; $t_{\frac{1}{2},z}$ = terminal half-life; $V$ = volume of distribution.

For the oral route, Cl and $V$ were calculated assuming $F$ (bioavailability factor) = 1.

the administered dose was recovered as unchanged compound in urine. Renal clearance ($Cl_R$) of approximately 300 ml/min represented two-thirds of the total clearance, indicating that the drug is eliminated largely by renal excretion. This latter conclusion is supported by oral and intravenous studies with [$^{14}$C]rilmenidine. In these studies, during a 7 day period of recovery, approximately 87% of the total radioactivity was found in the urine and less than 1% in the feces. Similarly inactive metabolites represented less than 5% of the total radioactivity in the urine. No metabolites were identified in the blood.

The limited metabolism of rilmenidine along with its total bioavailability allows the assumption that no hepatic first-pass effect occurs after oral administration of this drug. The large free fraction and the high rate of renal clearance indicate that rilmenidine undergoes not only glomerular filtration but also an active secretion process that is greater than reabsorption. It is likely that reabsorption is pH-dependent, since rilmenidine is a weak base ($pK_a$ = 9).

After oral administration of rilmenidine at 0.5 to 3 mg, $C_{max}$ and area under the curve (AUC) followed a significant linear relation. At the same range, $t_{max}$, elimination half-life, and mean residence time were independent of the dose administered. Total clearance and volume of distribution were slightly decreased at the 3 mg dose.

As expected for a drug with an elimination half-life of 8 h, plasma levels of rilmenidine reached steady state on the third day of repeated administration. There were no significant differences in pharmacokinetic parameters after single administration of the drug and at steady state.

There was also no significant difference in the pharmacokinetic parameters when

different formulations of rilmenidine were used (tablet or solution and tablet or capsule).

Food intake decreased the absorption rate but did not modify the disposition of rilmenidine.

### Patients

Pharmacokinetic parameters of rilmenidine were not modified by hypertension. In hypertensive patients, the absorption, distribution, or elimination of rilmenidine at single oral doses of 1 and 2 mg were similar to those in normal subjects.

The pharmacokinetic parameters in elderly hypertensive patients as compared with healthy subjects or young hypertensive patients revealed a delayed absorption phase (2.5 h), a decrease in the volume of distribution (251 L), a decrease in total clearance (234 ml/min), an increase in the elimination half-life (13 h), and an increase in the mean residence time (18 h). These differences can be explained by a decreased renal function in the elderly subjects. They have no clinical significance and changes in the dosage regimen in the elderly patients are not required.

In patients with renal failure, the elimination parameters of rilmenidine, 1 mg, single oral dose ($t_{1/2}$, MRT, Cl/$F$, and $Cl_R$) were directly correlated to the degree of renal failure. These results justify the reduction of the daily dose of rilmenidine in patients with severe renal failure (creatinine clearance < 15 ml/min).

In patients with hepatic insufficiency, absorption, and biodisposition of rilmenidine (1 mg single oral dose) were decreased although this effect remained without clinical significance and confirmed the minimal hepatic first-pass effect. The main alteration concerned the elimination phase in which the total clearance was decreased by approximately 20%. However, no decrease in the daily dose of the drug was required, even in these patients.

In summary, following oral administration, rilmenidine is rapidly and extensively absorbed with a bioavailability factor close to 1. Rilmenidine is weakly bound to plasma proteins; its distribution is independent of the free fraction. The risk of pharmacokinetic interaction of rilmenidine with other drugs is minimal. Rilmenidine is not extensively metabolized; it is excreted, largely unchanged, by the kidney. In patients with severe renal failure, the dose of rilmenidine should therefore be decreased.

## PHARMACOLOGICAL STUDIES

### Binding

In the rat brain, rilmenidine inhibits binding of a selective $\alpha_2$-adrenoceptor agonist, [$^3$H]*p*-aminoclonidine ($K_i$ values range from 25 to 144 n$M$). Rilmenidine has a 10 times lower affinity for the central $\alpha_2$-adrenoceptors than clonidine (26,53). In the rat brain and in cardiac membranes, rilmenidine weakly inhibited binding of the selective $\alpha_1$-adrenoceptor antagonist, [$^3$H]prazosin (27).

Other binding studies performed on the rat brain indicate that rilmenidine has no affinity for muscarinic, $\beta$-adrenergic, dopamine, serotonin, GABA, opioid, and histamine $H_2$ receptors ($IC_{50}$ values > $10^{-4}$ $M$); at histamine $H_1$ receptors, a low affinity binding has been detected ($IC_{50} = 3.2 \times 10^{-6}$ $M$).

**TABLE 2.** *Comparison of the $pD_2$ values of rilmenidine and clonidine in different isolated blood vessels*[a]

| Blood vessel | Receptor | Rilmenidine | Clonidine | Ratio[c] of clonidine/rilmenidine |
|---|---|---|---|---|
| Rat aorta | | | | |
| + Endothelium | $\alpha_1$-post | 4.55 ± 0.06 | 6.77 ± 0.11 | 166 |
| − Endothelium | $\alpha_1$-post | 4.82 ± 0.15 | 7.00 ± 0.18 | 151 |
| Rabbit aorta | | | | |
| + Endothelium | $\alpha_1$-post | 4.57 ± 0.03 | 6.58 ± 0.09 | 102 |
| − Endothelium | $\alpha_1$-post | 4.56 ± 0.05 | 6.55 ± 0.13 | 98 |
| Rabbit pulmonary artery | $\alpha_1$-post | 4.15 ± 0.08 | 6.34 ± 0.20 | 156 |
| Dog saphenous vein[b] | $\alpha_2$-post | 5.81 ± 0.10 | 7.18 ± 0.09 | 23 |
| Rabbit pulmonary artery[b] | $\alpha_2$-pre | 5.45 ± 0.17 | 6.88 ± 0.03 | 27 |
| Rabbit saphenous vein | $\alpha_2$-pre | 5.34 ± 0.12 | 6.86 ± 0.11 | 33 |

[a] Values shown as means ± SEM; data from ref. 56.
[b] From ref. 55.
[c] From the data shown, the mean ratio for the $\alpha_1$-adrenoceptors averages 135 and for the $\alpha_2$-adrenoceptors 28. Thus, rilmenidine appears to be 4.8 times more specific for the $\alpha_2$-adrenoceptors than clonidine.

In human brain membrane preparations, rilmenidine was 2.5 to 3.5 times more selective (when compared to clonidine and guanfacine) for medullary imidazoline prefering receptor (IPR) than for cortical $\alpha_2$-adrenoceptor (7). In basolateral membranes from rabbit renal proximal tubules, rilmenidine displayed higher affinity and selectivity for IPR than either clonidine or guanfacine (10).

### Isolated Vascular Tissues

The effects of rilmenidine on $\alpha$-adrenoceptor-mediated responses were investigated in a variety of isolated blood vessels in the guinea pig atria, and in the isolated perfused rat kidney. Postjunctional effects have been investigated in rat and rabbit aorta (56), rabbit pulmonary artery, and dog saphenous vein (55). At the postjunctional $\alpha_1$-adrenoceptor level, rilmenidine is a weak agonist, on average 135 times less potent than clonidine (Table 2). At postjunctional $\alpha_2$-adrenoceptors, rilmenidine is about 23 times less potent than clonidine. Rilmenidine and clonidine are 19.2 and 3.4 times, respectively, more selective for the postjunctional $\alpha_2$- than $\alpha_1$-adrenoceptors. Thus, rilmenidine appears to be 5.6 times more specific than clonidine at postjunctional $\alpha_2$-adrenoceptors.

Prejunctional effects have been studied in rabbit pulmonary artery (55), rabbit saphenous vein (56), and guinea pig atria (38). From the $pD_2$ values in Table 2, rilmenidine and clonidine are 7.4 and 1.7 times, respectively, more selective for the prejunctional $\alpha_2$- than for the postjunctional $\alpha_1$-adrenoceptors. Thus, rilmenidine appears to be 4.5 times more selective than clonidine though less potent for the $\alpha_2$ subtype of receptors.

Partial agonist activity has been investigated in the guinea pig atria, where rilmenidine enhances electrically stimulated norepinephrine release (38), and in the isolated perfused rat kidney, where rilmenidine at low concentrations inhibits the vasoconstriction induced by $\alpha$-adrenoceptor activation (56).

These data suggest that rilmenidine under certain circumstances may become an

"antagonist" at the $\alpha_2$-adrenoceptor; at the postjunctional level, this effect could imply a prevention of spasm induced by $\alpha$-adrenoceptor activation.

### Cardiovascular Effects

In normotensive anesthetized dogs, rilmenidine (0.3 mg/kg i.v.) produced an initial transient increase in mean arterial pressure, followed by a pronounced long-lasting decrease (35). Similar responses were obtained with rilmenidine at 0.1–1 mg/kg i.v. in normotensive or hypertensive rats anesthetized with pentobarbital (33,53). Both effects of rilmenidine were accompanied by bradycardia. The initial pressor response due to peripheral vasoconstriction caused by stimulation of postjunctional $\alpha_1$- and $\alpha_2$-adrenoceptors was evident in pithed rats (33,35,53).

In conscious spontaneously hypertensive rats, rilmenidine at single oral doses of 0.15 to 0.60 mg/kg decreased blood pressure without any effect on the heart rate (33). With chronic treatment (50 or 100 $\mu$g/kg/h for 10 days), rilmenidine dose-dependently reduced blood pressure in Wistar–Kyoto (WKY) rats (37). A more pronounced effect was obtained in active spontaneously hypertensive rats with a high level of sympathetic tone (30). In another model of high sympathetic activity, the sinoaortic baroreceptor denervated dog, rilmenidine at 1 mg/kg/day for 2 weeks decreased blood pressure and heart rate without affecting the number of platelet $\alpha_2$-adrenoceptors (52).

The decrease in blood pressure caused by rilmenidine is most likely due to the centrally induced reduction of sympathetic tone. Thus, in dogs, rilmenidine at a low dose (0.03 mg/kg) administered into the vertebral artery reduced blood pressure (35,53) and at 0.3 mg/kg decreased splanchnic nerve discharges (35). Plasma norepinephrine levels were reduced after treatment with rilmenidine (33,52).

In part, the antihypertensive effect of rilmenidine may involve an action on peripheral presynaptic $\alpha_2$-adrenoceptors, since in the pithed and bilaterally vagotomized dog, rilmenidine reduced tachycardia produced by stimulation of cardioaccelerator nerves. In the pithed rat, rilmenidine reduced tachycardia and pressor responses caused by electrical stimulation of sympathetic outflow (35). In addition, rilmenidine acts on the neuroadrenal sympathetic axis, reducing plasma epinephrine levels (33,52).

From these studies, it was assumed that the hypotensive action of rilmenidine was due to a mechanism similar to that of clonidine and related drugs and involves a sympathoinhibitory process that causes hypotension and bradycardia (32,54). However, recent findings suggest that other mechanisms may be involved in the hypotensive action of rilmenidine as well (5a).

Since Greenberg reported beneficial effects of clonidine on cardiac hypertrophy (25), the effects of rilmenidine 10 mg/day for 6 weeks on the left ventricular hypertrophy have been investigated in desoxycorticosteroid acetate (DOCA)–salt rats. In these animals, rilmenidine decreased the left ventricular weight and reduced collagen content without modifying the left ventricular weight/body weight ratio or isomyosines (9).

### Renal Effects

Rilmenidine, administered to spontaneously hypertensive rats at 0.3 mg/kg/day i.p. for 5 days, did not significantly modify plasma creatinine levels, glomerular filtra-

tion rate, or renal plasma flow. It had also no effects on the excretion of sodium, potassium, or chloride. At 0.3 mg/kg/day i.p. for 5 days or at 0.6 mg/kg/day for 12 weeks, rilmenidine decreased plasma renin activity (PRA) in spontaneously hypertensive (but not in the normotensive WKY rats) by 50% (22,24). The release and urinary excretion of vasodilatatory prostaglandins [6-keto-$PGF_{1\alpha}$ and $PGE_2$ (but not of $TxB_2$)] were decreased by rilmenidine. Plasma antidiuretic hormone (ADH) levels were significantly decreased, while ADH content in hypothalamus and hypophysis was nonsignificantly decreased by the drug (24). These results are consistent with the $\alpha$-adrenergic-mediated inhibition of synthesis and secretion of ADH in the hypothalamus (3).

The effects of rilmenidine (0.3 mg/kg i.v.) on glomerular filtration, renal blood flow, diuresis, and excretion of sodium and chloride in dogs were similar. PRA was reduced by 37% irrespective of the level of sodium in the diet (low: 2 mEq/day; normal: 40 mEq/day; or high: 120 mEq/day) (35). In contrast, plasma aldosterone levels were significantly reduced only in animals on a high sodium diet when PRA was low (35). It is conceivable that reductions in ADH levels and of PRA by rilmenidine could contribute to its hypotensive action.

### Central Nervous System Effects

Several studies in experimental animals have suggested that, at the effective antihypertensive doses, rilmenidine does not cause sedation. In the 2-day-old chick, which has a poorly developed blood–brain barrier (57), rilmenidine at doses up to 3.75 mg/kg did not inhibit the righting reflex. At higher doses of rilmenidine, the bell-shaped dose–response curve seen with partial $\alpha_2$-agonists (46) or the linear dose–response curve observed with full agonists was not observed (33,35). At doses up to 10 mg/kg, rilmenidine did not prolong the hexobarbital-induced sleeping time in mice (53) and had no effect on the barbiturate-induced sleeping time in rats (33). Moreover, rilmenidine inhibited clonidine-induced prolongation of barbiturate-induced sleeping time (33,35,53). At doses of 5 mg/kg and higher, rilmenidine reduced locomotor activity in rats; in this respect, it was 80 times less potent than clonidine (31,33). The firing rate of noradrenergic neurons in the locus ceruleus was inhibited by rilmenidine but its potency was about 60 times lower than that of clonidine. These monoaminergic neurons are believed to be involved in wake/sleep mechanisms (16,17). In the mouse, rilmenidine at doses up to 2.5 mg/kg had no antinociceptive effects (35), and in the rat at doses up to 10 mg/kg, rilmenidine had no anxiogenic effects (31).

Like clonidine, rilmenidine reduced the morphine withdrawal syndrome; but in this respect, rilmenidine was 100 times less potent than clonidine. Rilmenidine did not exhibit dose-dependent reinforcing properties and, unlike clonidine, had no addictive potential (48).

Thus, the central nervous system effects of rilmenidine differ from those of clonidine and related compounds.

## CLINICAL STUDIES

### Hemodynamic and Electrophysiologic Effects

The relationship between doses of rilmenidine and its effects on arterial blood pressure has been studied in normotensive subjects as well as in hypertensive patients

(15). In both groups, rilmenidine, administered at doses of 0.5, 1, 2, and 3 mg, decreased blood pressure in a dose-dependent manner. At the dose of 1 mg, rilmenidine seems to provide, in all patients, the optimal balance between a satisfactory antihypertensive activity and an acceptable level of side effects (15).

Acute hemodynamic and electrophysiologic effects of rilmenidine at single oral doses of either 25 or 50 μg/kg were studied in hypertensive patients (58). In the first group of eight patients treated with rilmenidine at 25 μg/kg, both systolic and diastolic blood pressures were significantly reduced at 2 h after treatment. The effect persisted for 8 h. The systemic peripheral resistance decreased starting from the third hour after treatment, with a significant effect at 5 h; the duration of action was in excess of 10 h. Cardiac index, pulmonary arterial pressure, pulmonary arterial resistance, and stroke volume were unchanged at 2 h after treatment. Heart rate did not vary significantly during the 10-h period after oral administration of the drug. During the first 2 h after treatment, there was a slight decrease in cardiac output with a concomitant increase in peripheral resistance. Reduction in preload, i.e., pulmonary capillary pressure, may account for the observed initial decrease in cardiac output. The stimulation of putative peripheral postjunctional $\alpha_2$-adrenoceptors is probably responsible for the increase in peripheral resistance. These effects were modest and did not reach statistical significance. In a second group of eight patients treated with 50 μg/kg of rilmenidine, cardiac index, pulmonary arterial pressure, and stroke volume were significantly reduced at 2 h after treatment in parallel with the decrease in both systolic and diastolic blood pressure.

Cardiac tolerance of the drug was satisfactory, since none of the electrophysiological parameters, such as sinus function, conduction parameters, and atrial, nodal, and ventricular refractory periods, were altered by rilmenidine at either 25 or 50 μg/kg (58). Treatment of mild to moderate hypertensive patients with rilmenidine (1 or 2 mg/day) for 28 days resulted in a prolonged antihypertensive effect, which was maintained for 24 h after drug administration and was accompanied by an acute vasodilator effect (43).

In a double-blind, randomized, placebo-controlled study on 14 hypertensive patients rilmenidine, 1 mg, produced a significant improvement in brachial artery wall stress without any effect on the diameter of the brachial artery or on carotidofemoral pulse wave velocity. This effect may contribute to the antihypertensive activity of rilmenidine (45).

In a group of 10 hypertensive patients, who were exercised on a cycle ergometer in a supine position, rilmenidine (1 mg) lowered the mean arterial blood pressure at rest but had no effect on the exercise-induced increase in blood pressure and cardiac output (11). In healthy subjects, the hemodynamic response to erect posture was not adversely affected by rilmenidine (28). The symptomatic orthostatic hypotension occurred only in 2 of 316 patients enrolled in a 1-year trial (4). Orthostatic hypotension is attributed to a decrease in baroreflex sensitivity (29), which in turn is responsible for the modification of the hemodynamic response to erect posture. The low incidence of symptomatic orthostatic hypotension with rilmenidine may be due to previously described enhancement of baroreflex sensitivity (28).

**TABLE 3.** *Side effects in patients on single therapy with rilmenidine (RIL), cumulative incidence from month 1.5 to month 12*

| | RIL, 1 mg/day (%)[a] | RIL, 2 mg/day (%)[b] |
|---|---|---|
| Asthenia | 7 (5.8) | 7 (6.5) |
| Gastric pain | 4 (3.3) | 6 (5.6) |
| Palpitations | 4 (3.3) | 4 (3.7) |
| Fatigue during exercise | 3 (2.5) | 4 (3.7) |
| Diarrhea | 3 (2.5) | 4 (3.7) |
| Cramps | 3 (2.5) | 2 (1.9) |
| Skin rash | 2 (1.7) | 6 (5.6) |
| Depression | 3 (2.5) | 3 (2.8) |
| Edema | 2 (1.7) | 2 (1.9) |
| Cold extremities | 2 (1.7) | 1 (0.9) |
| Dizziness | 2 (1.7) | 1 (0.9) |
| Sexual disorders | 4 (3.3) | 2 (1.9) |
| Memory disturbances | 1 (0.8) | 2 (1.9) |
| Nausea | 1 (0.8) | 1 (0.9) |
| Hot flushes | 1 (0.8) | 1 (0.9) |
| Paresthesia | 0 — | 1 (0.9) |

[a] n = 121.
[b] n = 107.

## Long-Term Studies

Long-term studies demonstrated in several multicenter trials the safety and efficacy of rilmenidine, 1 mg once or twice daily (19–21,44,50). In lowering arterial blood pressure, rilmenidine is more effective than placebo (44). Its effects on blood pressure are comparable to those of clonidine (19), methyldopa (21,50), or hydrochlorothiazide (20). Long-term follow-up studies over a period of 1 year demonstrated that rilmenidine is effective and well tolerated (4). The reported adverse effects of rilmenidine included dry mouth, drowsiness, asthenia, gastralgia, constipation, and palpitations. Side effects were observed mainly at the beginning of treatment. In general, they were rare with rilmenidine; their frequency was less than 8% (4) (Table 3). The central nervous system side effects usually observed with $\alpha_2$-agonists were less common in patients treated with rilmenidine than with clonidine (19) or methyldopa (50). Furthermore, discontinuation of the treatment due to intolerance was less frequent with rilmenidine than with clonidine (19) or methyldopa (50).

## Renal Effects

While lowering blood pressure, rilmenidine did not alter water and electrolyte balance (36). Combined therapy with rilmenidine (1 mg) and hydrochlorothiazide (25 mg) did not modify the diuretic effect of the latter (36). Monotherapy with rilmenidine at doses of 1 or 2 mg daily over a period of 2 months in hypertensive patients had no effect on blood volume, body weight, or renal function (unpublished data). By acute administration to healthy volunteers, rilmenidine (1 mg) significantly reduced blood pressure but had no effect on renal plasma flow or glomerular filtration rate (unpublished data). A significant fall in plasma renin activity has been found after

either acute administration of rilmenidine to healthy subjects or after chronic administration (over 2 months) to hypertensive patients (unpublished data). Thus, with acute or chronic administration, rilmenidine caused no detectable changes in renal function.

The above-described results were observed in healthy subjects or hypertensive patients with normal renal function. In view of the results obtained, the effects of rilmenidine were studied in patients with renal failure. Such a study has been completed in a group of 17 hypertensive patients with renal failure [mean creatinine clearance of 35 ± 4 (SD) ml/min/1.73 $m^2$] treated with rilmenidine at 1 mg twice daily over a period of 6 months (39). Creatinine and urea clearances did not vary throughout the treatment period. Plasma creatinine, plasma electrolytes, and body weight did not vary also in medium and long-term clinical trials. Although over a period of 6 months rilmenidine has been shown to be effective and well tolerated in patients with moderate renal insufficiency (39), the linear correlation between the degree of renal impairment and the half-life of the drug (47) indicates the need for caution in patients with severely impaired renal function. Since no clinical data are available in patients with creatinine clearance less than 15 ml/min/1.73 $m^2$, rilmenidine is contraindicated in this high-risk population.

### Endocrine and Metabolic Effects

Effects of rilmenidine on hypothalamopituitary axis have been assessed in healthy subjects (unpublished data). By acute administration, rilmenidine, 2 mg did not modify plasma cortisol, luteinizing hormone, and thyroid-stimulating hormone levels. A significant, though transient, increase in the growth hormone plasma level was observed in two healthy subjects. There was a moderate decrease in plasma levels of prolactin after acute administration of rilmenidine. This decrease was within the normal range and physiological variability; this conclusion was confirmed in 157 hypertensive patients treated with the drug for 12 weeks (50).

Rilmenidine did not alter carbohydrate metabolism in diabetic patients (41). Glycemic control carefully assessed by home glucose monitoring and determination of 24-h glucosuria, postprandial plasma glucose, and glycosylated hemoglobin in insulin-treated diabetic patients with mild to moderate hypertension has been found to remain stable throughout the 16-week treatment period (41).

A decrease in total and low-density lipoprotein cholesterol has been found in a group of 78 hypertensive patients after 12 weeks of treatment with rilmenidine (50); a decrease of total cholesterol has been noted in a group of 120 patients treated for 4 weeks (20). No such changes were noted in the diabetic patients. The changes in lipid metabolism, if any, appear to be beneficial but small; they have to be investigated in more detail.

### Respiratory Effects

The occurrence of either spontaneous asthma attack (1) or aggravation of the bronchial obstruction induced by inhaled histamine (12) in subjects treated with clonidine has occasionally been reported. Such aggravation is thought to be mediated through an increase in parasympathetic tone with a concomitant decrease of sympathetic tone

resulting from the stimulation of central $\alpha_2$-adrenoceptors (14). In this respect, rilmenidine has been found to be, in asthmatic subjects, less harmful than clonidine; it produced less aggravation of the histamine-induced bronchial obstruction (13).

### Effects on the Central Nervous System

The usual side effects of centrally acting antihypertensive agents, sedation and dry mouth, are assumed to be mediated by $\alpha_2$-adrenoceptors located in the brainstem (49). It would therefore appear to be difficult to develop a centrally acting $\alpha_2$-adrenoceptor agonist that does not cause sedation and dry mouth. Data from animal experiments and human studies highlighted a clear dissociation between the neuropharmacological effects and the antihypertensive properties of rilmenidine. Thus, at equipotent antihypertensive doses, sedation and dry mouth are two to three times less frequent with rilmenidine than with clonidine (19) or methyldopa (50). The occurrence of drowsiness with rilmenidine was not statistically different from that observed with placebo (44) or hydrochlorothiazide (20). The lower occurrence of centrally induced side effects differentiates rilmenidine from other available $\alpha_2$-agonists and raised questions about the nature of the receptors involved in its pharmacological effects.

## PUTATIVE MECHANISMS OF ACTION OF RILMENIDINE

The therapeutic effects of rilmenidine appear to be related to the stimulation of central adrenoceptors. Data from radioligand binding and pharmacological studies have shown a higher selectivity of rilmenidine for $\alpha_2$- than for $\alpha_1$-adrenoceptors (26,27). Rilmenidine has a greater affinity for $\alpha_2$-adrenoceptors than clonidine (55,56). Since drowsiness is thought to be mediated by stimulation of central $\alpha_2$-adrenoceptors (49), results from studies performed in both animals and humans are unexpected, since they indicate a very low incidence of central side effects after rilmenidine administration. To explain these findings, several hypotheses have been proposed.

A relatively selective stimulation of peripheral presynaptic $\alpha_2$-adrenoceptors could explain a lower incidence of central side effects of rilmenidine. Although a presynaptic effect of rilmenidine was observed in isolated blood vessels (55,56) and in studies involving measurements of plasma catecholamines levels in humans (unpublished data), it is still uncertain whether or not such a peripheral component is involved in the mechanism of the antihypertensive action of rilmenidine in humans. A putative process triggered by rilmenidine that tends to counteract its sedative effects has been proposed (53,54) but remains to be confirmed.

Perhaps the most attractive hypothesis is based on the newly described imidazoline preferring receptors (5a,40). It was shown that direct infusion of imidazoline derivatives into the nucleus reticularis lateralis results in hypotensive effects irrespective of their selectivity for different $\alpha$-adrenoceptor subtypes (5a); infusion of norepinephrine and epinephrine into the same site did not modify blood pressure. This has led to the proposition by Bousquet and co-workers of a new class of receptors that more specifically recognize imidazolines (5a). These receptors may be responsible for the

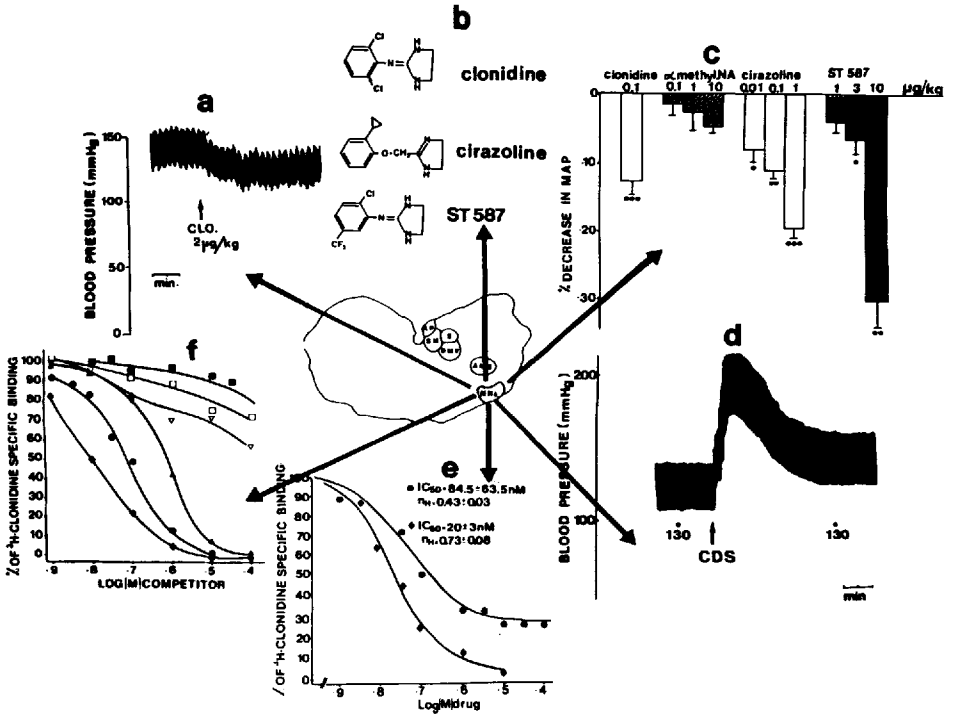


**FIG. 1.** This figure shows the available evidence for the existence of imidazoline receptors. The central part represents a slice of the medulla oblongata of the cat. (**a**) Microinjection of clonidine (2 µg/kg) in the lateral vasopressor area (NRL) of the anesthetized cat causes a decrease in arterial pressure. (**b**) Chemical structure of some imidazolines. (**c**) The imidazolines (clonidine, cirazoline, ST587), when injected into the lateral vasopressor area, evoke a decrease in mean arterial pressure (MAP) while catecholamines such as α-methylnorepinephrine have no effect. (**d**) Augmentation of arterial pressure caused by microinjection of an extract from the bovine brain that contains a substance that displaces the binding of clonidine in the lateral vasopressor area of the anesthetized cat. CDS = clonidine displacing substance, which has now been named endazoline. (**e**) Inhibition of [$^3$H]clonidine binding in membranes of the bovine lateral vasopressor area caused by clonidine (♦) and norepinephrine (●). Thirty percent of the [$^3$H]clonidine binding sites are insensitive to norepinephrine. (**f**) Inhibition of [$^3$H]clonidine binding in membranes of the human lateral vasopressor area by catecholamines: norepinephrine (■), epinephrine (□), methylnorepinephrine (▽); and imidazolines: ST587 (▲), clonidine (●), cirazoline (♦). The human lateral vasopressor area contains a homogeneous population of clonidine binding sites that are completely insensitive to catecholamines. (From ref. 5.)

hypotensive effect of imidazolines (Fig. 1). Subsequent studies using radioligand binding techniques have shown that imidazoline receptors can also be found in the lateroventral part of the medulla oblongata in several animal species and humans (8). The structure of the endogenous ligand (2) with vasopressor activities (6), which is an agonist at these receptors, is now being investigated.

Recently, rilmenidine has been found to bind to imidazoline preferring receptors in the brain (7) and in the kidney (34). An interesting observation is that rilmenidine appears to have a greater selectivity for these receptors than other imidazoline derivatives (7,10,34). Imidazoline preferring receptors are thought to be involved in blood pressure regulation and seem to be devoid of effects on vigilance, whereas activation

of central $\alpha_2$-adrenoceptors is most likely responsible for sedation. The greater affinity of rilmenidine for central imidazoline than for central $\alpha_2$-adrenoceptors could therefore explain the dissociation between its hypotensive and sedative effects.

## CONCLUSION

Among centrally acting antihypertensive drugs, rilmenidine is unique in being relatively free of centrally induced side effects usually observed with this class of drugs. Rilmenidine is not only a new, effective, and well-tolerated antihypertensive agent. Since its activity could be mediated through newly described imidazoline receptors, rilmenidine may be viewed as the first substance in a new family of pharmacological compounds.

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