Efficacy and Safety of Rilmenidine, a Selective Imidazoline I_1 Receptor Binding Ligand, in Mild-to-Moderate Thai Hypertensive Patients

Rilmenidine Thai Study Group
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Abstract

Background : Rilmenidine is an antihypertensive agent that selectively binds to imidazoline I_1 receptor located in the brainstem and kidney. It acts both centrally by reducing sympathetic over-activity and in the kidney by decreasing water and sodium overload. This dual action leads to the immediate and delayed control of blood pressure caused by this drug.

Objective : The aim of this study was to assess the efficacy and safety of rilmenidine as monotherapy in mild-to-moderate essential hypertensive patients.

Method : An 8-week, open-labeled, multicenter study was conducted in Thai patients with mild-to-moderate essential hypertension. Rilmenidine 1 mg/day was given for 8 weeks. The dose could be titrated up to 2 mg/day according to the patient's blood pressure response at week 4. The primary efficacy parameters were the mean reductions in systolic and diastolic blood pressure. The proportions of patients whose blood pressure normalized or responded were evaluated as secondary efficacy parameters. Safety parameters were assessed by the changes in heart rate and reported side effects during the treatment period.

Results : 103 subjects (44.7% men) with a mean age of 53 ± 9.7 years completed the 8-week follow-up. At baseline, 46.6 per cent and 53.4 per cent of the patients were classified with mild and moderate hypertension, respectively. The mean blood pressure was 154/93 mmHg. After the 8-week treatment, there was a significant decrease in blood pressure to 140/86 mmHg ($p < 0.001$), with mean pressure reduction of 14/7.5 mmHg. The normalization rate was 44 per cent and the response rate was 68 per cent. No significant changes were found for mean heart rate and any laboratory parameters tested. Only 17 patients reported mild and transient side effects such as drowsiness and dryness of the mouth and throat, which required no treatment.

Conclusion : This study has shown that rilmenidine is an effective and well tolerated monotherapy in Thai patients with mild-to-moderate essential hypertension.

Key word : Rilmenidine, Essential Hypertension, Imidazoline I_1 Receptor

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The autonomic imbalance due to overactivity of the sympathetic system in most patients with essential hypertension leads to many of the metabolic, hemodynamic, trophic, and rheologic abnormalities[1, 2]. Therefore, drugs that reduce sympathetic overactivity are a reasonable clinical choice in these patients[3, 4]. However, the utilization of centrally acting drugs such as α-methyldopa and clonidine have reduced in popularity due to their adverse effects and the availability of better tolerated alternative agents.

The discovery of I_1 imidazoline binding sites [5-8] and the findings that imidazoline derivatives may lower sympathetic tone by a different mechanism compared with α-methyldopa have led to the development of a new generation of centrally acting agents with a better tolerability profile[9-12]. Rilmenidine is a prototype drug selective for imidazoline I_1 receptor. Rilmenidine given systemically reduces the sympathetic tone from the rostral ventrolateral medulla of the brainstem leading to reduced total peripheral resistance and thus decreases blood pressure[5,10]. In the kidney, its effects are due to indirect sympathoinhibition at the renal level and a direct effect through selective binding to renal I_1 receptors in the proximal convoluted tubule leading to inhibition of the Na^+/H^+ antiport[7,8], and thus, decrease sodium and water retention[12]. This dual action gives rilmenidine both the sympathetic-mediated and the natriuretic effects leading to its immediate and sustained benefits in the long-term treatment[12]. Because of its much higher selectivity to I_1 receptor than to α_2-adrenoceptor, rilmenidine has less sedative and mouth dryness effects and no demonstrated capacity to produce rebound hypertension[1]. Thus, rilmenidine provides a better safety profile compared to the classical centrally acting drugs.

Rilmenidine is as effective in monotherapy as other first-line antihypertensive drugs[12,13]. There were no significant differences in the effects of rilmenidine on blood pressure compared with diuretics [14], β-blockers[15], α_2-agonists[9,16], calcium antagonists[17] and ACE inhibitors[18]. Incidences of adverse events were reported to be comparable between rilmenidine and placebo[12] and were significantly less frequent with rilmenidine than comparable drugs. Reports of reduction in left ventricular hypertrophy[19] and microalbuminuria[20] as well as improvement of glucose tolerance[17], insulin sensi-

tivity[17] and lipid parameters[18] suggested that rilmenidine could represent an important new development in antihypertensive therapy and the prevention of cardiovascular disease.

In Thailand, rilmenidine has just been marketed and clinical data in Thai patients is not yet available. Therefore, the objective of this study was to assess the efficacy and safety of rilmenidine in mild-to-moderate essential hypertension in Thai patients.

Study population and method

An eight-week, open-labeled, multicenter study was conducted in 8 hospitals in Bangkok (Siriraj, Police, Pramongkutklao, Bhumipol Adulyadej and Thammasat Hospitals) and upcountry (Chon Buri, Maharaj Nakorn Chiang Mai and Srinakarin Khon Kaen Hospitals). Patients were included when the following criteria were met; male or female, age over 18 years, having mild-to-moderate essential hypertension defined by WHO-ISH guidelines 1999 (systolic blood pressure 140-179 mmHg or diastolic blood pressure 90-109 mmHg)[21] and had taken no more than two concomitant antihypertensive drugs during the past 3 months prior to selection. Exclusion criteria were secondary hypertension, high degree atrioventricular block, any persisting chronic arrhythmia, myocardial infarction, severe heart, renal and hepatic failure, renal insufficiency or any severe or progressive disease. Breast-feeding women or women of childbearing potential without appropriate contraception were not eligible to participate in the present study. The study protocol was approved by the ethical committee of each participating center and the patients' informed consents were obtained prior to enrollment.

The eligible patients underwent a single blinded placebo control period for 2 weeks to washout the effects of previous antihypertensive medications and to allow them to be stabilized with lifestyle modifications. Following the washout period, blood pressure, heart rate and laboratory parameters (complete blood count, blood chemistry and urine analysis) were measured. Patients were treated with rilmenidine 1 mg to be taken as once daily for 8 weeks. Dose adjustment to rilmenidine 1 mg twice daily was allowed from week 4 in patients whose blood pressure higher than 140/90 mmHg.

Patients were monitored for blood pressure, heart rate and adverse events at weeks 4 and 8. Blood pressure measurement and clinical evaluation were carried out according to the recommendations of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)[22]. Blood chemistry parameters (glucose, creatinine, liver functions and lipid profiles) and routine urinalysis were also assessed at weeks 0 and 8 for safety monitoring. All data, particularly blood pressure and adverse events were registered on a case record form.

The primary efficacy parameters were blood pressure reduction in mmHg for both systolic and diastolic blood pressure. The secondary efficacy parameters were the percentage of patients whose blood pressure could be normalized (< 140/90 mmHg) and the percentage of those who responded (blood pressure normalized and/or reduced $\geq$ 15 mmHg for systolic and/or $\geq$ 10 mmHg for diastolic). The incidence of adverse events, and changes in heart rate and laboratory parameters from baseline were evaluated as safety parameters.

RESULTS

A total of 115 mild-to-moderate hypertensive patients were initially recruited, of whom 10 were lost to follow-up at the last visit and 2 had protocol violations. The remaining 103 patients were validated as eligible for analysis at the end of the 8-week follow-up period. Of these patients, 44.7 per cent were men. The mean age was 53 ± 9.7 years (range 33-72 years), with 26 patients (25.2%) over 60 years old. Demographic data of all patients is shown in Table 1. According to WHO-ISH Guidelines[21], 48 patients (46.6%) were classified as having mild hypertension and 55 patients (53.4%) as having moderate hypertension. Thirty-four patients (33.0%) were newly diag-

Table 1. Patient demographic data.

Parameter	Value*	%
Mean age (years)	53 ± 9.7 (range 33-72)	
Male	46	44.7
Female	57	53.4
Mild hypertension	48	46.6
Moderate hypertension	55	53.4
Mean weight (kg)	65 ± 10.2	
Mean height (cm)	159 ± 7.8	
BMI (kg/m^2)	25.5 ± 3.3	
Mean SBP (mmHg)	154.5 ± 10.7	
Mean DBP (mmHg)	93.6 ± 9.7	
Mean heart rate (bpm)	77.9 ± 10.0	

* Value expressed as mean ± SD

nosed and the others 69 (67.0%) had already been under treatment for hypertension. The duration with high blood pressure was in the range of 1 month to 20 years, with 32 patients (46.4%) being diagnosed for less than one year previously. The mean blood pressure at baseline was 154.5±10.7 mmHg for systolic and 93.6 ± 9.7 mmHg for diastolic. Mean heart rate was 77.9 ± 10.0 bpm.

Twenty-eight patients (27.2%) were not having any associated clinical condition, whereas the others were reported to have at least one additional concomitant disease (Table 2). The most commonly associated clinical conditions were hyperlipidaemia (38.8%), obesity (13.6%), and diabetes mellitus (8.7%). Twenty-two patients (21.4%) had more than one associated clinical condition.

At the end of the study, 51 patients (49.5%) received rilmenidine at the initial dose of 1 mg/day, whereas the others (50.5%) received the twice daily (2 mg) dosage regimen. After 4 weeks of treatment, mean blood pressure was progressively decreased from the baseline (Fig. 1) and mean diastolic blood pressure was controlled below 90 mmHg. At week 8, the blood pressure was significantly decreased from 154.5/93.6 mmHg to 140.5/86.1 mmHg ($p < 0.001$) with mean pressure reduction of 14 mmHg for systolic and 7.5 mmHg for diastolic (Table 3). Mean heart rate was 77.6 ± 11 bpm with no significant change from baseline of 77.9 ± 10 bpm.

At week 8, 43.7 per cent of patients had blood pressure normalized (< 140/90 mmHg). The overall response rate (blood pressure normalized and/or reduced ≥ 15 mmHg for systolic and/or ≥ 10 mmHg for diastolic) was 68 per cent. Of these responding patients, 61.4 per cent remained on rilmenidine at the dose of 1 mg/day.

Table 2. Associated clinical conditions in the study population.

Concomitant diseases	Number of patients	%
Hyperlipidaemia	40	38.8
Obesity (BMI > 30 kg/m^2)	14	13.6
Diabetes mellitus	9	8.7
Ischaemic heart disease	2	1.9
Others	19	18.4
More than one associated clinical condition	22	21.4

Only 17 patients reported adverse events during the study period (Table 4). Moreover, no patient was withdrawn because of these side effects. The most common side effects were drowsiness (8.7%), dryness of mouth and throat (4.9%) and headache (4.9%). These side effects normally occurred during the first few days of treatment and were mild and transient requiring no treatment. Blood chemistry parameters (glucose, creatinine, liver functions and lipid profile) and urine analysis results were not significantly different from those of the baseline values (data not shown).

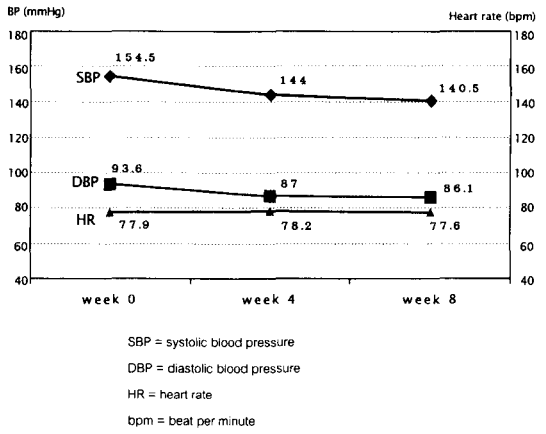

Fig. 1. Means of systolic and diastolic blood pressure and heart rate in patients receiving rilmenidine from week 0 to week 8 (n = 103).

SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, bpm = beat per minute

Table 3. Results at the end of 8-week treatment with rilmenidine (n = 103).

Parameters	Value*
Mean SBP (mmHg)	140.5 ± 14.6
Mean DBP (mmHg)	86.1 ± 9.5
Mean SBP/DBP reduction (mmHg)	14/7.5
Mean heart rate (bpm)	77.6 ± 11.0
Normalization rate (%)	43.7
Response rate (%)	68.0

* Value expressed as mean ± SD

Table 4. Reported side effects during treatment with rilmenidine (n = 103).

Adverse event	Number	%
Drowsiness	9	8.7
Dryness of mouth and throat	5	4.9
Headache	5	4.9
Others (hot flushes, constipation, and dizziness)	3	2.9
More than one reported side effect	4	3.9

DISCUSSION

The results from this open labeled, multicenter study confirmed the efficacy of rilmenidine in Thai patients with mild-to-moderate essential hypertension. After 8 weeks of treatment, rilmenidine significantly reduced blood pressure from 154/93 to 140/86 mmHg. Mean reductions of systolic and diastolic blood pressure were 14 and 7.5 mmHg, respectively. The response rate was 68 per cent with 43.7 per cent of the patients having normalized (blood pressure < 140/90 mmHg). This rate seems to be lower than other published results recently reviewed[12]. This may due to the fact that different guidelines and criteria were used. In other publications, normalization was considered when blood pressure was less than 160/90 mmHg or diastolic blood pressure was < 90 mmHg. However, the present study followed JNC VI guidelines[22] in which blood pressure should be lower than 140/90 to be considered normalized. Therefore, the efficacy of rilmenidine in this study should be comparable with other studies[9,12-16]. In addition, when rilmenidine at the doses of 1 and 2 mg per day were compared, it was found that both efficacy and side effects were not significantly different (data not shown).

It was also found from the present study that the effect of rilmenidine could be observed after 4 weeks of treatment with mean blood pressure reduction of 10/6 mmHg (Fig. 1). With increasing time of treatment and dosage adjustment, blood pressure was further decreased to the mean reduction of 14/7.5 mmHg (Table 1). This also corresponded with the increase in normalization rate from 32 to 43.7 per cent and response rate from 54 to 68 per cent of the patients after 4 and 8 weeks of treatment, respectively (data not shown). Moreover, with increasing time of treatment but without dosage adjustment, rilmenidine should also further reduce blood pressure. This might be explained by its selective binding to imidazoline I_1 receptor in the two key organs of blood pressure control leading to an immediate response through its reduction of sympathetic overactivity and a delayed response through its reduction of water and sodium overload in hypertensive patients[23].

In a HEAT study conducted in a Filipino population using the same normalization criteria, the normalization rate was 84 per cent after treatment with rilmenidine for 10 weeks[24]. This difference may be related to the fact that most of their patients (79%) were new cases with moderate hypertension at the inclusion. These factors might contribute to the greater reduction in blood pressure and higher normalization rate after rilmenidine treatment. However, the efficacy of rilmenidine in the present study was comparable when subgroup analyses were carried out between mild *versus* moderate hypertension, and newly diagnosed cases *versus* old cases (data not shown).

The most frequent side effects in this study were drowsiness and dryness of the mouth. However, the incidence was low with mild intensity and transient in duration compared to those found with first-generation centrally acting drugs[9]. Rilmenidine was found to have no effect on heart rate and all laboratory parameters tested.

SUMMARY

Results from the present study showed that after 8 weeks of treatment, rilmenidine in monotherapy was effective in the treatment of mild-to-moderate essential hypertension in a Thai population. The overall response rate was 68 per cent and 44 per cent of the patients were normalized (BP < 140/90). These results confirm that rilmenidine is an effective and

well tolerated medication as well as being an alternative choice of antihypertensive drug in the treatment of mild-to-moderate essential hypertension.

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การศึกษาประสิทธิภาพและความปลอดภัยของยาริลเมนนิดีน ซึ่งเป็นยาที่ออกฤทธิ์เฉพาะเจาะจงต่อ ตัวรับ I_1-อิมิดาโซลีน ในผู้ป่วยไทยที่มีภาวะความดันโลหิตสูงชนิดไม่รุนแรงถึงรุนแรงปานกลาง

กลุ่มผู้ร่วมทำการวิจัยริลเมนนิดีน

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ภูมิหลัง : ริลเมนนิดีนเป็นยาลดความดันโลหิตสูงที่ออกฤทธิ์เฉพาะเจาะจงต่อตัวรับ I_1-อิมิดาโซลีน ที่บริเวณสมองส่วนกลางและที่ไต โดยผลต่อการจับกับตัวรับที่สมองทำให้เกิดการลด sympathetic overactivity และผลที่ไตทำให้ลดการดูดกลับของน้ำและโซเดียม ด้วยกลไกดังกล่าว ริลเมนนิดีนสามารถควบคุมความดันโลหิตได้ทั้งแบบรวดเร็วและในระยะยาว

วัตถุประสงค์ : เพื่อประเมินประสิทธิภาพและความปลอดภัยของการใช้ยา ริลเมนนิดีน เป็นยาเดี่ยวในการรักษาผู้ป่วยไทยที่มีภาวะความดันโลหิตสูง ชนิดไม่รุนแรงและรุนแรงปานกลาง

วิธีการศึกษา : เป็นการศึกษาแบบเปิด ระยะเวลา 8 สัปดาห์ในผู้ป่วยไทย ที่มีภาวะความดันโลหิตสูงชนิดไม่รุนแรงถึงรุนแรงปานกลาง โดยผู้ป่วยจะได้รับยาริลเมนนิดีนขนาด 1 มก/วัน ตลอดเวลา 8 สัปดาห์ ขนาดของยาสามารถปรับเป็น 2 มก/วัน ได้หากผู้ป่วยไม่สามารถควบคุมความดันโลหิตได้ที่เวลา 4 สัปดาห์ ปัจจัยหลักในการประเมินประสิทธิภาพของยาได้แก่ ค่าเฉลี่ยของการลดความดันโลหิตทั้งซิสโตลิค และไดแอสโตลิค ปัจจัยรองได้แก่ สัดส่วนของผู้ป่วยที่ตอบสนองต่อยาและสามารถควบคุมความดันโลหิตได้ดี ในแง่ของความปลอดภัยจะประเมินค่าการเปลี่ยนแปลงอัตราการเต้นของหัวใจและรายงานอาการข้างเคียงตลอดเวลาที่ได้รับการรักษา

ผลการศึกษา : มีผู้ป่วยจำนวน 103 คน (44.7% เป็นเพศชาย) อายุเฉลี่ย 53 $\pm$ 9.7 ปี ที่ได้รับยาจนครบ 8 สัปดาห์ เมื่อเริ่มต้นการศึกษา 46.6% และ 53.4% ของผู้ป่วยมีภาวะความดันโลหิตสูงชนิดไม่รุนแรงและรุนแรงปานกลางตามลำดับ ค่าเฉลี่ยของความดันโลหิต 154/93 มม.ปรอท หลังได้รับยาริลเมนนิดีนเป็นเวลา 8 สัปดาห์ ความดันโลหิตของผู้ป่วยลดลงอย่างมีนัยสำคัญ โดยมีค่าเฉลี่ยที่ 140/86 มม.ปรอท ($p < 0.001$) และค่าเฉลี่ยของความดันโลหิตที่ลดลงคือ 14/7.5 มม.ปรอท ในจำนวนนี้มีผู้ป่วย 44% ที่สามารถควบคุมระดับความดันโลหิตได้เป็นอย่างดี และมีผู้ป่วย 68% ที่ตอบสนองต่อยา ในแง่ความปลอดภัยในการใช้ยา ไม่พบความเปลี่ยนแปลงของอัตราการเต้นของหัวใจและค่าผลตรวจทางห้องปฏิบัติการต่าง ๆ มีผู้ป่วยจำนวน 17 ราย รายงานอาการข้างเคียง ซึ่งเป็นอาการที่ไม่รุนแรงและหายได้โดยไม่ต้องรักษา

สรุป : การศึกษานี้แสดงให้เห็นว่า ริลเมนนิดีนเป็นยาที่มีประสิทธิภาพและความปลอดภัยในการใช้เป็นยาเดี่ยว เพื่อรักษาภาวะความดันโลหิตสูงชนิดไม่รุนแรงถึงรุนแรงปานกลาง ในผู้ป่วยคนไทย

คำสำคัญ : ริลเมนนิดีน, ความดันโลหิตสูง, ตัวรับอิมิดาโซลีน I$_1$

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