A Comparative Study of the Side Effects Between Pseudoephedrine in Loratadine Plus Pseudoephedrine Sulfate Repetabs Tables† and Loratadine + Pseudoephedrine Tablet in Treatment of Allergic Rhinitis in Thai Patients

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Abstract

The objective of the study was to evaluate the adverse reactions of Loratadine plus Pseudoephedrine Sulfate Repetabs Tables (LTD+PSE Repetabs) (Loratadine 5 mg + Pseudoephedrine 120 mg) twice daily with that of loratadine (5 mg) twice daily and pseudoephedrine (60 mg) quarter daily in the treatment of patients with allergic rhinitis. The study was designed as an investigator-blind, parallel group study. In this study, 56 patients were equally separated into 2 groups and treated for 14 days with either LTD+PSE Repetabs or loratadine + pseudoephedrine tablet. Both groups were comparable in age, gender, weight; baseline systolic blood pressure, diastolic blood pressure and pulse rate. The change of systolic blood pressure, diastolic blood pressure, and pulse rate did not reach clinical significance throughout the study period. There was no significant difference in occurrences of insomnia, palpitation, mouth dryness and anxiety. However, the incidence of patients with tremor at day 14 in the loratadine + pseudoephedrine tablet group was significantly higher than the LTD+PSE Repetabs group (39% *vs* 10.7%, p-value = 0.03). Furthermore, one patient in the loratadine + pseudoephedrine tablet group had to discontinue medication at day 7 due to insomnia. In conclusion, LTD+PSE Repetabs is well tolerated and has fewer adverse effects when compared to the loratadine + pseudoephedrine tablet.

Key word : Pseudoephedrine, Loratadine, Drug Side Effects, Allergic Rhinitis

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J Med Assoc Thai 2002; 85: 722-727

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† Loratadine plus Pseudoephedrine Sulfate Repetabs Tables = Clarinase Repetab® (Schering-Plough Ltd.)

Allergic rhinitis is an IgE-mediated inflammatory disease of the nasal mucosa characterized by symptoms of sneezing, rhinorrhea, nasal congestion, and nasal pruritus. The disease has been estimated to affect as many as 20 per cent of the general population and has a trend to increase. Allergic rhinitis may be seasonal as a result of the pollination patterns of a variety of air borne allergens or year-round as a result of chronic exposure to other environmental allergens such as house dust or animal dander. Avoiding exposure to the allergens is the most efficacious means of controlling allergic rhinitis; nevertheless, avoidance may not be practical or even impossible in some cases. Therapy with pharmacologic agents represents the standard approach in the management of allergic rhinitis. H1-receptor antagonists (antihistamine) and alpha-adrenergic agonists (decongestants) are generally prescribed as the first-line therapy for most patients with allergic rhinitis. Second-generation H_1-receptor antagonists are often prescribed instead of the first-generation to avoid sedation and unwanted anticholinergic effects. The commonly prescribed oral decongestant is pseudoephedrine, an α-adrenergic agonists, which primarily reduces nasal congestion and to some extent rhinorrhea. The recommended dose of this drug is 60 mg three to four times a day with a maximum dose of 240 mg/day. Most common side effects of pseudoephedrine include insomnia, nervousness, irritability, and palpitations. Formerly, prescription of these drugs was usually concomitant, but in a separate tablet. Nevertheless, allergic rhinitis is a chronic disease. Some patients may need to use these drugs for a long period of time. The combination of non-sedating antihistamine with long acting pseudoephedrine should provide more convenience(1,2).

LTD+PSE Repetabs is a combination of loratadine (5 mg), a non-sedating antihistamine, and pseudoephedrine (120 mg). Within the two-layered tablet, loratadine is in the immediate-release coating and pseudoephedrine is in the extended-release core, which is pH-sensitive. Loratadine has been shown to be effective in the treatment of allergic rhinitis and to be as effective as terfenedine(3-5) and astemizole(6) with fewer side effects. This study was intended to compare the safety and adverse effect between a combination of loratadine-pseudoephedrine (LTD+PSE Repetabs) and their individual components (loratadine 5 mg bid and pseudoephedrine 60 mg qid) in Thai patients with allergic rhinitis.

MATERIAL AND METHOD

Subjects

Patients with a diagnosis of perennial allergic rhinitis were recruited. All patients had had symptoms of allergic rhinitis for at least 1 year. Their ages were between 15 to 45 years. Their allergic status was confirmed by a positive skin prick test. All were healthy, having no other underlying illness and were in the normal weight range. Eligible patients were required to stop regular coffee drinking for two days and discontinue any sympathomimetic and anti-cholinergic drugs for at least one week before entering the study. The exclusion criteria were as follows: having abnormal value of blood pressure or pulse rate upon screening; having a history of hypertension or cardiac problems, current medication which might precipitate side effects of the study drugs could not discontinue; pregnancy; history of allergy to the study drugs. The ethic committee of Chulalongkorn University approved the study protocol and informed consent. Written informed consent was obtained from all patients or from the parents or legal guardians if the patient was younger than 18 years.

Study design

The study was conducted as an investigator-blind, parallel group study performed in the Department of Otolaryngology, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Eligible subjects were randomized to receive either a sustained-release formulation of loratadine 5 mg plus pseudoephedrine 120 mg (LTD+PSE Repetabs; Schering-Plough Corp, Thailand) 1 tablet twice a day, or loratadine (10 mg) half a tablet twice a day concomitant with pseudoephedrine (60 mg) 4 times a day orally for 14 days. Subjects returned to the clinic every 7 days after starting the study medication for evaluation of blood pressure, heart rate and review of adverse events and medication compliance.

Symptom score measurement

All symptoms were classified as follows: 0, had no symptoms of adverse reaction; 1, had symptoms of adverse reaction but did not interfere with normal life activities; 2, had moderate magnitude of symptoms but did not interfere with normal life activities; 3, had severe magnitude of symptoms

Table 1. Demographic characteristics of studied patients.

	Loratadine + Pseudoephedrine (N = 28)	LTD+PSE Repetabs (N = 28)	P-value
Sex (% male patients)	12 (42.9%)	10 (35.7%)	0.6
Age (year) (SD)	33.2 (12.3)	32.6 (12.6)	0.8
Weight (kg) (SD)	55.8 (9.8)	52.4 (8.6)	0.2
Baseline systolic blood pressure (mmHg) (SD)	114.3 (11.3)	108.6 (10.4)	0.06
Baseline diastolic blood pressure (mmHg) (SD)	72.1 (7.9)	71.4 (8.5)	0.7
Baseline pulse rate (BPM) (SD)	74.9 (9.6)	75.7 (12.1)	0.8

LTD+PSE Repetabs = Loratadine plus Pseudoephedrine Sulfate Repetabs Tables

Table 2. Adverse events.

Adverse events	Severity	Day 7				Day 14			
		Loratadine + Pseudoephedrine (N = 28)		LTD+PSE Repetabs (N = 28)		Loratadine + Pseudoephedrine (N = 28)		LTD+PSE Repetabs (N = 28)	
			%		%		%		%
Insomnia	0	17	60.7	16	57.1	15	53.6	15	53.6
	1	7	25	11	39.3	6	21.4	11	39.3
	2	2	7.1	1	3.6	5	17.9	2	7.1
	3	1	3.6	0		2	7.1	0	
	4	1	3.6	0		0		0	
		p-value = 0.6				p-value = 0.2			
Palpitation	0	18	64.3	21	75	17	60.7	22	78.5
	1	7	25	6	21.4	10	35.7	5	17.9
	2	3	10.7	1	3.6	1	3.6	1	3.6
	3	0		0		0		0	
	4	0		0		0		0	
		p-value = 0.7				p-value = 0.3			
Tremor	0	19	67.9	25	89.3	17	60.7	25	89.3
	1	9	32.1	3	10.7	10	35.7	3	10.7
	2	0		0		0		0	
	3	0		0		0		0	
	4	0		0		0		0	
		p-value = 0.05				p-value = 0.03			
Mouth dryness	0	19	67.9	21	75	20	71.4	20	71.4
	1	9	32.1	7	25	7	25	7	25
	2	0		0		0		0	
	3	0		0		0		0	
	4	0		0		0		0	
		p-value = 0.4				p-value = 1			
Anxiety	0	27	96.4	26	92.9	26	92.8	26	92.8
	1	0		2	7.1	1	3.6	0	
	2	1	3.6	0		1	3.6	0	
	3	0		0		0		0	
	4	0		0		0		0	
		p-value = 0.5				p-value = 1			

0, had no symptoms of adverse reaction;
1, had symptoms of adverse reaction but did not interfere with normal life activities;
2, had moderate magnitude of symptoms but did not interfere with normal life activities;
3, had severe magnitude of symptoms of side effects but can continue medication;
4, had severe magnitude of symptoms of side effects and discontinued medication
LTD+PSE Repetabs = Loratadine plus Pseudoephedrine Sulfate Repetabs Tables

of side effects but can continue medication; 4, had severe magnitude of symptoms of side effects and discontinued medication.

Statistical analysis

Data of symptoms from adverse reaction were analyzed by either Chi square test or Fisher exact test, compared between the two groups of treatment in each subsequent 7 days of study. The data of heart rate and blood pressure were analyzed by means of repeated measure analysis of variance between the treatment groups and each visit. All tests of hypotheses were two-tailed and performed at the 0.05 significance level.

RESULTS

Fifty-six patients were enrolled in the study. Twenty-eight patients were randomized to receive LTD+PSE Repetabs, and 28 were assigned to receive loratadine and pseudo-ephedrine. Demographic characteristics of patients in both groups are shown in Table 1. There were no significant differences in distribution of sex, mean age, mean weight, baseline blood pressure and baseline heart rate.

Occurrence of adverse events (insomnia; palpitation; mouth dryness; and anxiety) was not comparable between treatments throughout the study period. On repeated measure basis, no significant difference in blood pressure and heart rate among the three visits of the study period and between treatments was detected. However, there was a significantly higher incidence of tremor in the group treated with loratadine and pseudoephedrine (39%), compared with the LTD+PSE Repetabs group (10.7%) on day 14 of the study (p-value = 0.03). Furthermore, one patient treated with loratadine and pseudoephedrine had to discontinue the medication because of severe insomnia on day 7 of the study. Two patients treated with loratadine and pseudoephedrine also had to reduce the dose of pseudoephedrine to 3 times a day because of severe headache on day 7 of the study.

DISCUSSION

Combination of H1-receptor antagonists with decongestants have been clinically used and proved to be effective in the treatment of allergic rhinitis[7,8]. This study is one of the few studies intended to evaluate the side effects of an antihistamine-decongestant combination medication, LTD+PSE Repetabs, compared with the conventional prescription in a separate tablet. There was a significant increase in the incidence of the symptom of tremor in the separated loratadine and pseudoephedrine group when compared to the LTD+PSE Repetabs group. Other adverse reactions were comparable between the groups.

The adverse events reported by Bronsky et al[9] were lower than in the present study. In their study, mouth dryness was reported to be 8 per cent in SCH 434 QD (a combination of 10 mg of loratadine in the coating and 240 mg of pseudoephedrine sulfate in an extended released core) group and 3-7 per cent in loratadine and pseudoephedrine group, insomnia was 5 per cent and 9 per cent respectively, while nervousness was found in about 5 per cent of both groups. Corren et al[10] also reported that insomnia was found in 10 per cent in the combination of loratadine plus pseudoephedrine group. Differences in incidence of adverse effects may be explained by racial difference and difference in drug dosage compared to body weight. Furthermore, use of severity grading in the present study should add more knowledge about adverse events in clinical use of the combination medication of loratadine plus pseudoephedrine. In conclusion, LTD+PSE Repetabs was well tolerated and has fewer adverse effects when compared to loratadine and pseudoephedrine in a separate tablet.

ACKNOWLEDGEMENT

The authors would like to thank to Schering-Plough Ltd. For providing the studied medications.

(Received for publication on December 29, 2001)

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การศึกษาเปรียบเทียบผลข้างเคียงของ Pseudoephedrine ในยา Loratadine Plus Pseudoephedrine Sulfate Repetabs Tables (LTD+PSE Repetabs) กับการให้ยา Loratadine ร่วมกับ Pseudoephedrine ในการรักษาผู้ป่วยไทยที่เป็นโรคจมูกอักเสบจากภูมิแพ้

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การศึกษานี้มีวัตถุประสงค์เพื่อต้องการศึกษาผลข้างเคียงของการให้ยา LTD+PSE Repetabs (Loratadine 5 mg + Pseudoephedrine 120 mg) รับประทานวันละสองครั้ง เปรียบเทียบกับการใช้ยาเม็ด Loratadine 5 mg รับประทานวันละสองครั้ง ร่วมกับยาเม็ด Pseudoephedrine 60 mg รับประทานวันละ 4 ครั้งในการรักษาผู้ป่วยโรคจมูกอักเสบจากภูมิแพ้ การศึกษานี้เป็นการศึกษาแบบไปข้างหน้า เปรียบเทียบระหว่างยาสองกลุ่ม โดยผู้ตรวจไม่ทราบว่าผู้ป่วยได้รับยาชนิดใด มีผู้ป่วยเข้าร่วมการศึกษาทั้งสิ้น 56 คน แบ่งเป็น 2 กลุ่มเท่า ๆ กัน (กลุ่มละ 28 คน) กลุ่มหนึ่งได้รับการรักษาด้วยยา LTD+PSE Repetabs อีกกลุ่มหนึ่งได้รับยา Loratadine ร่วมกับ Pseudoephedrine ผลการศึกษาพบว่าก่อนทำการรักษา ลักษณะข้อมูลพื้นฐานทางด้านอายุ เพศ น้ำหนัก ความดันโลหิต และชีพจรของผู้ป่วยทั้ง 2 กลุ่มไม่มีความแตกต่างกัน การเปลี่ยนแปลงของความดันโลหิตและชีพจรหลังได้รับการรักษาไม่มีความแตกต่างกัน ส่วนผลข้างเคียงของยาที่ทำให้นอนไม่หลับ ใจสั่น ปากแห้ง และความกังวลในผู้ป่วยไม่มีความแตกต่างกันระหว่าง 2 กลุ่ม อย่างไรก็ตาม อุบัติการณ์การเกิดมือสั่นในวันที่สิบสี่ของการรักษาในกลุ่มผู้ป่วยที่ได้รับยาเม็ด Loratadine ร่วมกับยาเม็ด Pseudoephedrine สูงกว่าในกลุ่มที่ได้รับยา LTD+PSE Repetabs อย่างมีนัยสำคัญทางสถิติ ($p=0.03$) นอกจากนี้ผู้ป่วย 1 รายที่ได้รับยาเม็ด Loratadine ร่วมกับยาเม็ด Pseudoephedrine ต้องหยุดยาในวันที่ 7 หลังการรักษาเนื่องจากปัญหานอนไม่หลับ

โดยสรุป ยา LTD+PSE Repetabs มีผลข้างเคียงต่ำกว่าการให้ยาเม็ด Loratadine ร่วมกับยาเม็ด Pseudoephedrine และผู้ป่วยในกลุ่มที่ได้รับยา LTD+PSE Repetabs สามารถทนต่อผลข้างเคียงของตัวยา Pseudoephedrine ที่บรรจุอยู่ใน Repetab ได้ดีกว่า

คำสำคัญ : Pseudoephedrine, Loratadine, ผลข้างเคียงของยา, จมูกอักเสบจากภูมิแพ้

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