Safety and tolerability of isradipine in Phase I trial in Chinese population

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Abstract: Hypertension is one of the well-established risk factor for cardiovascular diseases. Calcium channel blockers (CCBs), chemicals that could block voltage-gated calcium channels (VGCCs) in cardiac muscle and blood vessels, has been widely used for the treatment of hypertension. Isradipine, a second-generation CCB with high affinity for voltage-operated calcium channels, has not been marked in China. The purpose of this study was to investigate the efficacy, safety and tolerability of isradipine in a phase I clinical trial including 31 healthy Chinese subjects. All subjects received different doses of isradipine at 2.5, 5.0 and 10.0 mg in single-dose study. When the test is completed, subjects treated with 5.0 mg isradipine stayed at the research center for multiple-dose study (5.0 mg isradipine twice daily for 9 d). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured pre-dose and post-dose (1, 2, 4, 6, 8, 12, 24, 36 and 48 h after isradipine treatment). Electrocardiography (ECG) and peripheral edema were monitored pre-dose and 4, 8, 24 and 48 h after isradipine treatment. SBP and DBP in single-dose study decreased after isradipine treatment. SBP reached the lowest values 8 h after dosing with a decrease of (7.0±9.7) mmHg (5.4%, $P = 0.111$) in 2.5 mg group, (7.0±6.9) mmHg (6.0%, $P = 0.008$) in 5.0 mg group, and (14.0±10.5) mmHg (12.7%, $P = 0.005$) for 10.0 mg group respectively. Similarly, DBP also reached the lowest values 8 h after dosing with a decrease of (10.0±7.9) mmHg (12.8%, $P = 0.004$) in 2.5 mg group, (6.0±7.0) mmHg (8.6%, $P = 0.003$) in 5.0 mg group, and (11.0±4.1) mmHg (15.1%, $P = 0.000$) in 10.0 mg group respectively. No significant changes of SBP and DBP were observed in multiple-dose study. We detected mild adverse events (AEs), such as increased transaminase and headache that resolved rapidly and spontaneously without intervention. No serious or potentially life-threatening AE was detected. Our results indicate that isradipin has a good safety and tolerability in Chinese healthy subjects. Long-term study with larger sample size is needed to confirm our conclusion.
Keywords: Isradipine capsule; Tolerance; Safety; Phase I clinical trial

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1. Introduction

Hypertension is one of the well-established risk factor for cardiovascular diseases. Calcium channel blockers (CCBs) are chemicals that could block voltage-gated calcium channels (VGCCs) in cardiac muscle and blood vessels. This decrease of intracellular calcium leads to a reduction in muscle contraction[1]. CCBs are divided into three generations[1,2]. The first-generation agent, such as nifedipine, has short duration of action and poor vascular selectivity.The second-generation agent has longer duration of action and better vascular selectivity but poor bioavailability, such as nifedipine controlled-release tablet. The third-generation agent, such as amlodipine, has longer half time, better bioavailability, stability and tolerability, and lower risk of side effect than the first- and second-generation agents. Currently, the second- and the third- generation CCBs are commonly prescribed hypertension drugs.

Isradipine, a second-generation CCB with high affinity for voltage-operated calcium channels (slow channel or L-channel), was developed by Sandoz in 1989 and marketed by Ciba-Geigy for the treatment of hypertension. It selectively dilates arteries with little effect on cardiac filling pressure, thus reducing systemic resistance and blood pressure with little or no negative inotropic effect[3]. It also processes mild natriuretic effect to increase renal plasma flow and glomerular filtration rare, which can result in decreased renal vascular resistance while protecting kidneys from glomerular hyperfiltration[3–5]. The major adverse events (AEs) of isradipine were related to its vasodilatory effect, the most common effect in all CCBs, such as headache, facial flushing, peripheral edema, dizziness and tachycardia[3,6]. In 2006, two isradipine types, COBALT LABS and ACTAVIS TOTOWA, have

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been approved by FDA. Because isradipine has not been marked in China, studies in Chinese population remains very limited. In this phase I clinical trial, we examined the efficacy, safety and tolerability of isradipine in 31 hypertension patients at Beijing Hospital, China.

2. Methods

2.1. Isradipine treatment and design

Isradipine capsule (2.5 mg) was manufactured by Sichuan Baili Pharmaceutical Co. Ltd. (Sichuan, China). The trial was approved by the Medical Ethics Committee of Beijing Hospital of Ministry of Health. Individual written informed consent and Institutional Review Board Approval was obtained prior to the study. Based on the isradipine's prescribing information published by abroad, initial, maintenance and maximum dose of isradipine was 2.5, 5.0, and 10.0 mg twice daily for the treatment of hypertension. Patients would not benefit from enhanced antihypertensive effect, but may have higher risk of AEs by increasing dose when the daily maximum dosage is reached[7,8]. In our study, we planned to enroll 32 healthy subjects and divide them into three groups with the treatment of isradipine at different doses, including 2.5 mg (n = 10), 5.0 mg (n = 12) and 10.0 mg (n = 10) perspectival. When the single-dose study is completed, subjects treated with 5 mg isradipine stay at the research center for multiple-dose study by treatment of 5.0 mg of isradipine twice daily for 9 d.

2.2. Study population

Healthy nonsmokers aged at 18 to 40 years were included in this study. The other inclusion criteria are body mass index (BMI) (19.0 to 25.0 kg/m^2), body temperature (35.0 to 37.0 ℃), systolic blood pressure (SBP) (100.0 to 139.0 mmHg) and diastolic blood pressure (DBP) (60.0 to 89.0 mmHg). All female subjects must have negative pregnancy test results at screening. All male subjects must agree to use two acceptable methods of contraception for the entire duration of the study, up to the study completion visit. Exclusion criteria are any disease or condition that might interfere with the absorption, distribution, metabolism, or excretion of isradipine, drug history or alcohol abuse, blood donation (more than 400.0 mL) within the past 8 weeks, consumption of other prescribed or over the counter drugs (vitamins or calcium supplements allowed) within 4 weeks before the study, participation in a similar study within the past 4 weeks, and a history of immunodeficiency disease, including a positive HIV test result, or a positive hepatitis B surface antigen or hepatitis C antibody. Patients who met the criteria were confirmed by blood test and patient reports. Routine clinical chemistry tests were performed for all patients, including hemoglobin, hematocrit, total white blood cell count, blood glucose, triglycerides, total cholesterol, albumin, direct and indirect bilirubin, creatinine, aspartate aminotransferase, alkaline phosphates, lactic dehydrogenase, potassium, sodium, calcium, magnesium, inorganic phosphorus and urinalysis.

2.3. Efficacy, safety and tolerability assessments

AEs were graded using the table for grading the severity of adult and pediatric AEs (DAIDS 1.0) issued by the United States National Institutes of Health (NIH) on December 28, 2004[9].

In the single-dose study, the general physical examination and laboratory tests were implemented in screening and after dosing. SBP and DBP were measured pre-dose and post-dose (1, 2, 4, 6, 8, 12, 24, 36 and 48 h after isradipine treatment). Electrocardiography (ECG) and peripheral edema were monitored pre-dose and 4, 8, 24 and 48 h after isradipine treatment. In the multiple-dose study, study plans and monitoring projects of the 1st and 2nd days were similar to the 1st and 2nd days of single-dose study, and these of the 7th, 8th and 9th days were similar to the 1st, 2nd and 3rd days of single-dose study respectively. From 3rd to 6th days, BP was measured pre-dose and 2 h after dosing every day. ECG was obtained before the morning dose from 3rd to 6th days and before the evening dose on the 5th and 6th days. From 3rd to 6th days, peripheral edema was monitored before the morning dose. The whole processes of experiment were closely monitored by doctors. We defined the day that subjects taken study drug for the first time as the first day of study.

2.4. Statistical analysis

Descriptive and inferential statistics were performed using SPSS 16.0. For continuous variables, the arithmetic mean and standard deviation (SD) were used. The baseline was defined as the last measurement before the first dose of isradipine, and changes in SBP, DBP, heart rate (HR) and body weight from baseline were all recorded. For the single-dose study, the changes within and between groups were analyzed by paired t-test and ANOVA perceptively. For the multiple-dose study, the changes were analyzed by paired t-test. P<0.05 was considered statistically significant. For categorical data, the number and percentage were used in the data summaries.

3. Results

3.1. Characteristics of study population

Totally, 31 subjects were enrolled in single-dose study for tolerance and safety evaluation in fact, including 10 subjects treated with 2.5 mg isradipine, 12 subjects treated with 5.0 mg isradipine, and 9 subjects treated with 10.0 mg isradipine. The characteristics of all subjects are shown in Table 1.

3.2. Safety and tolerability

3.2.1. Adverse events

Table 2 summarizes all AEs observed in single-dose and multiple dose study. All AEs were mild or moderate intensity, and resolved rapidly and spontaneously without intervention. No serious or potentially life-threatening AE was detected.

In single-dose study, mild AEs were observed in groups treated with 5.0 or 10.0 mg isradipine. In 5.0 mg group, one female subject reported headache 2 h after dosing and recovered 2 h later. In 10.0 mg group, facial flushing appeared in three men at 0.5–1 h after dosing and lasted about 3–5 h. Urine test showed WBC (3–6)/HP 48 h after dosing and recovered the next day in one woman.

In multiple-dose study, the female subject reporting headache in single-dose study at 5.0 mg encountered headache and facial flushing after the morning and evening dose on the 3rd day. One male subject complained of skin itch in the evening on the 4th day. Physical examination showed congestion rash at the anterior skin. Itch on the back and anterior skin was reported before the morning dose on the 6th day, and a similar sign was detected by physical examination in this subject. One female subject complained of skin itch at noon on the 4th and 6th days, showed congestion rash at back, and the symptom disappeared 1 h later of each attack. Urine test in one male subject showed protein positive on the 5th day and recovered on the 8th day. Because urine test showed protein positive in this man on the last day of the study, a follow-up urine test was performed 18 d after the day leaving site and the man recovered without any treatment. One man with protein positive in urine test was lost for follow-up.

Table 1. Characteristics of study population

Characteristic	Isradipine dose		
	2.5 mg (n = 10)	5.0 mg (n = 12)	10.0 mg (n = 9)
Sex			
Male (n)	7	10	7
Female (n)	3	2	2
Age (Mean±SD)	28.0±4.4	29.5±4.9	27.0±5.0
Ethnic			
Han	9	10	9
Others	1	2	0
Height (cm±SD)	166.0±5.0	168.4±7.2	166.3±9.8
Weight (kg±SD)	62.6±4.9	63.4±6.8	63.7±8.1
SBP (mmHg±SD)	111.0±5.7	107.5±6.7	106.9±8.3
DBP (mmHg±SD)	78.0±4.2	67.7±6.7	70.7±6.1

Table 2. Adverse events

Adverse events	Single-dose (n = 31)	Multiple-dose (n = 12)	Severity	Drug relation
Laboratory examination abnormity, n (%)				
Trace urinary protein	0	2 (16.7)	Mild[b]	No
Urine WBC[a] positive	1 (3.2)	0	Mild[b]	No
Elevated transaminase	0	3 (25.0)	Mild~moderate[b]	Possibly
Dermal system abnormity, n (%)				
Skin itch and rash	0	2 (16.7)	Mild[b]	Possibly
Nervous system abnormity, n (%)				
Headache	1 (3.2)	1 (8.3)	Mild[b]	Possibly
Facial rushing	3 (12.9)	1 (8.3)	Mild[b]	Possibly
Total, n (%)	5 (16.1)	9 (75.0)		

[a] WBC: white blood cells; [b] defined according to the table for grading the severity of adult and pediatric AEs (DAIDS 1.0) issued by the United States National Institutes of Health (NIH) on December 28, 2004.

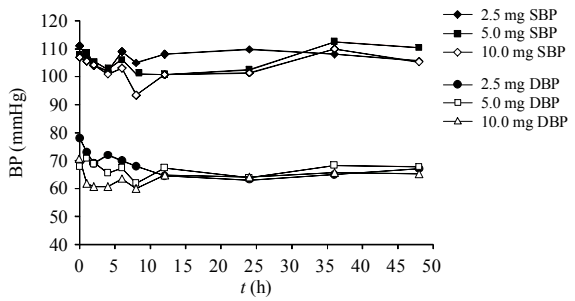

Figure 1. The time-blood pressure curve of single-dose study.

Slight increase in alanine amino-transferase (ALT) and aspirate amino-transferase (AST) were observed in three subjects, including grade II damage in one subject and grade I damage in two subjects according to the criterion[9]. The subject with grade II damage recovered 18 d later. For the two subjects with grade I damage, one recovered 13 d later, and one was lost for follow-up. No other symptoms accompanied with laboratory abnormalities were found in all subjects.

3.2.2. Changes in BP, HR, ECG and edema

SBP and DBP in single-dose study in three groups all decreased after isradipine administration (Fig. 1). SBP reached the lowest values 8 h after dosing with a decrease of (7.0±9.7) mmHg (5.4%, P = 0.111) in 2.5 mg group, (7.0±6.9) mmHg (6.0%, P = 0.008) in 5.0 mg group, and (14.0±10.5) mmHg (12.7%, P = 0.005) in 10.0 mg group, respectively. Similarly, DBP also reached the lowest values 8 h after dosing with a decrease of (10.0±7.9) mmHg (12.8%, P = 0.004) in 2.5 mg group, (6.0±7.0) mmHg (8.6%, P = 0.003) in 5.0 mg group, and (11.0±4.1) mmHg (15.1%, P = 0.000) in 10.0 mg group, respectively. No significant changes of SBP and DBP were observed in multiple-dose study. We did not observe significant changes in HR, ECG and edema (data not shown).

4. Discussion

We observed the maximum antihypertensive effect of isradipine (2.5, 5.0, and 10.0 mg) 8 h after dosing in single-dose study. The antihypertensive effect at 2.5 mg was better than 5.0 mg. The activity of subjects and errors in measurement may all contribute to the observed short-term effect. However, we observed only slight fluctuation but no significant changes in multiple-dose study. The stable antihypertensive effects of some CCBs, such as nifedipine and lacidipine, have been reported to occur 2 weeks after dosing[10]. Therefore, our study might be too short to observe the antihypertensive effect of isradipine. In term of isradipine pharmacokinetics in plasma, the $T_{1/2}$ was [(10.5–13.2)±(2.3–4.4)] h and the T_{max} was [(1.0–1.5)±(0.4–0.6)] h. Plasma concentrations declined to less than 15.0% of C_{max} within the 12 h after dosing (data were conducted in our lab, not published). Therefore, antihypertensive effect of the study drug might appear near the time of T_{max} and attenuate when the plasma concentrations declined to less than 15.0% of C_{max} according to those data and the trend of changes of BP.

We observed mild and transient AEs, such as headache and facial flushing, which is in line with previous reports[3,6]. It is hypothesized that these AEs might be caused by experimental medicine with great possibility. Facial flushing might be dose-related. The observed skin itch and congestion rash in two subjects might be related to study drug, dry environment and high room temperature. Peripheral edema, a common and dose-dependent AE of CCBs, which need a long-term observation did not occur in our study[11,12], further suggesting that a long-term study should be performed. Abnormalities and trace protein in urine were observed in few subjects, however, it was confirmed that it is not isradipine-related. At the late stage of multiple-dose study, we observed increased transaminase level, a possible isradipine-related AE that has been reported in other CCBs, such as nifedipine[1].

In summary, in the phase I clinical trial, we demonstrated that isradipin has a good efficacy, safety and tolerability in Chinese healthy subjects. We also detected mild AEs, such as increased transaminase and peripheral edema. No serious or potentially life-threatening AE was detected. Long-term study with a larger sample size is needed to confirm the conclusion.

References

[1] Coca, A.; Mazón, P.; Aranda, P.; Redón, J.; Divisón, J.A.; Martínez, J.; Calvo, C.; Galcerán, J.M.; Barrios, V.; Coll, A.R. *Exp. Rev. Cardiovasc. Ther*. **2013**, *11*, 91–105.

[2] Takahara, A. *Cardiovasc. Ther*. **2009**, *27*, 124–139.

[3] Brogden, R.N.; Sorkin, E.M. *Drugs*. **1995**, *49*, 618–649.

[4] Persson, B.; Andersson, O.K.; Wysocki, M.; Hedner, T.; Aurell, M. *Am. J. Med.* **1989**, *86*, 60–64.

[5] Francischetti, E.A.; Barroso, I.; da Silva, A.; Fagundes, V.G. *J. Cardiovasc. Pharmacol.* **1992**, *19*, 90–92.

[6] Cheung, B.M.; Lau, C.P.; Wu, B.Z. *Clin. Ther.* **1998**, *20*, 1159–1169.

[7] Dynacirc® (isradipine) Capsules. *Last Reviewed on RxList*: *4/22/2009*. This artical can be found online at http://www.rxlist.com/dynacirc-drug/indications-dosage.htm.

[8] Novartis Pharmaceuticals UK Ltd. Prescal. *Last updated on the eMC*: *18/11/2011*.

[9] United States National Institutes of Health (NIH). *Publish date*: *12/28/2004*. This article can be found online at http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/daidsaegradingtable.pdf

[10] Cherubini, A.; Fabris, F,; Ferrari, E.; Cucinotta, D.; Antonelli Incalzi, R.; Senin, U. *Arch. Gerontol. Geriatr.* **2003**, *37*, 203–212.

[11] Makarounas-Kirchmann, K.; Glover-Koudounas, S.; Ferrari, P. *Clin. Ther.* **2009**, *31*, 1652–1663.

[12] Makarounas-Kirchmann, K.; Glover-Koudounas, S.; Ferrari, P. *Am. J. Hypertens.* **2002**, *15*, 932–940.

伊拉地平胶囊I期临床安全性和耐受性评价

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摘要: 本文旨在评价国产伊拉地平胶囊在中国健康受试者体内的耐受性和安全性。单次给药的剂量递增顺序依次为2.5 mg, 5 mg, 10 mg。其中5 mg剂量组的受试者在完成单次给药试验后需继续留在研究中心, 进行多次给药试验。医学观察指标包括生命体征、心电图、水肿及医学实验室检查。结果显示单次给药各组受试者的血压在服药后均有下降趋势。不良事件主要包括头痛、面部潮红、皮肤瘙痒和转氨酶升高。因此, 按照试验设计的给药剂量和方案, 受试者对伊拉地平有较好的耐受性。

关键词: 伊拉地平胶囊; 耐受性; 安全性; I期临床试验