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Pharmacokinetic and Pharmacodynamic Study Determines Factors Affecting Blood Pressure Response to Valsartan

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▌ABSTRACT▐

Background: Valsartan is an angiotensin II receptor blocker and is used for patient with hypertension. Although response to valsartan varies each individual, there is no study about factors affecting the variability of valsartan response. **Methods:** To investigate the effects of valsartan on the baseline characteristics of blood pressure, single group, open label, pre- and post-comparison clinical study was conducted. Total 21 male Korean volunteers were enrolled. Each subject was administered no drugs in first period and valsartan 80 mg (Diovan HCT) in second period. For pharmacodynamic analysis, 24 hours blood pressure changes were monitored by ambulatory blood pressure monitoring. Twenty-four hour blood pressure changes were matched to valsartan concentration and analyzed by correlation analysis. Changes in blood pressure pattern were also analyzed. Subjects were divided into responder, non-responder, and reverse responder according to pre- and post- 24 hours blood monitoring results. For determination of pharmacokinetic parameters, plasma concentration of valsartan was measured by a validated ultra-performance liquid chromatography-tandem mass spectrometry method. Pharmacokinetic parameters including area under the plasma concentration versus time curve from 0 hour to the last measurable concentration (AUC_t), area under the plasma concentration versus time curve extrapolated to infinity, maximum plasma concentration (C_{max}), and time required to reach maximum plasma concentration (T_{max}) were calculated by noncompartmental models in the BA-CALC 2008 program ver. 1.0.0. **Results:** There were no significant associations between blood pressure changes and pharmacokinetic parameters of valsartan. Blood pressure pattern change analysis showed significant results. For AUCt, total amount of absorbed valsartan was 25,808 ± 6,863.0 ng·hr/mL , 20,683 ± 8,782.7 ng·hr/mL, and 12,502 ± 5,566.6 ng·hr/mL in responder, non-responder, and reverse responder, respectively (p = 0.041). In C_{max}, maximum concentration of valsartan was 4,314 ± 1,522.6 ng/mL, 2,588 ± 1,273.9 ng/mL, and 2,056 ± 1,075.5 ng/mL, respectively. **Conclusions:** These results showed that response to valsartan was not associated with blood concentration in healthy volunteers and changes in blood pressure patterns to valsartan might be associated with the amount of drugs which are absorbed to subjects. **(J Korean Soc Hypertens 2012;18(3):88-96)**

Key Words: Valsartan; Pharmacokinetics; Pharmacology; Blood pressure monitoring

Introduction

Valsartan is an angiotensin II receptor antagonist with particularly high affinity for the type I angiotensin II

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receptor.[1] By blocking the action of angiotensin, valsartan reduces blood pressure and used for long time for treatment of hypertension, heart failure.[2-4] After a single oral morning dose, the onset of its blood pressure-lowering action started within 2 hours with peak effect occurring 4 to 6 hours. Morning once-a-day dosing ranging from 80 to 320 mg/day results in blood pressure reduction throughout the day.[5,6]

In most drugs, after administration of drugs patients are divided into responder and non-responder. The effect of valsartan is affected by various factors. These factors are including age,[9] sex,[10,11] genetic factors,[12] and so on.

In this study, we hypothesized that the individual differences in valsartan effect might be result from amount of drug absorbed. To prove this hypothesis, single group, two-sequence, open label, pre- and post-comparison clinical trial was conducted. Subjects were assigned to free of medication in the first period; in the second period, they received the valsartan 80 mg (Diovan HCT, Novartis Korea, Seoul, Korea). The blood concentration of valsartan was determined by rapid and sensitive ultra-performance liquid chromatography-electrospray ionization tandem mass spectrometric (UPLC-ESI-MS/MS) method. The effect of valsartan was monitored by ambulatory blood pressure monitoring (ABPM). The pharmacokinetic parameters including the area under the plasma concentration versus time curve from 0 hour to the last measureable concentration (AUC_t), area under the plasma concentration versus time curve extrapolated to infinity (AUC_{inf}), maximum plasma concentration (C_{max}), and time required to reach maximum plasma concentration (T_{max}) were analyzed.

The results of 24-hour blood pressure monitoring were used for further pharmacokinetic-pharmacodynamic analysis. Pre- and post-dose changes in blood pressure were matched to valsartan concentration and analyzed by Pearson correlation coefficient test. Pre- and post-dose changes in blood pressure patterns were also analyzed.

Subjects and methods

1. Subjects

Twenty-one healthy Korean male volunteers aged 20 to 45 years were enrolled in the study. Subjects underwent screening examinations including a medical history, physical examination, and laboratory tests (hematology, clinical chemistry, and urinalysis). Exclusion criteria included medically documented conditions, including cardiovascular, respiratory, renal, hepatic, or gastrointestinal disorders; a chronic disorder that might influence the absorption, disposition, metabolism, or excretion of valsartan; a history of disturbances of organ or acute illness; a history of hematologic disorder or blood donation within 2 months; a history of blood fraction donation within 1 month; a history of psychiatric disorder; a history of drug hypersensitivity; a history of alcohol or drug abuse; participation in another clinical trial within 3 months; consumption of over 5 glasses daily of beverages containing xanthine derivatives; smoking > 20 cigarettes daily; and use of any over-the-counter drug medication having the potential to affect the study results. The study purpose and procedures were explained before the study, and written informed consent was obtained from all subjects.

2. Study design and sample collection

The study was a single group, two-sequence, open label, pre- and post-comparison, with a 1-week washout between study days. The study protocol was reviewed by the institutional review board of Kyung Hee University Hospital. All study procedures were conducted in accordance with the principles of the Declaration of Helsinki and the Korean Good Clinical Practice guidelines. Subjects were assigned to free of medication in the first

period; in the second period, they received the valsartan 80 mg. In both periods, subjects were admitted to the Kyung Hee University Clinical Research Center at 5 p.m. on the day before administration of valsartan or study initiation. They received a standardized dinner, and no food was permitted after 8 p.m. The next day, subjects received no drug (baseline) or valsartan (treatment) along with 240 mL of tap water. Food and water were prohibited during the first 4 hours after dosing. At 4 hours after the oral administration, all subjects were given standardized meals. The subjects were not allowed to remain in a supine position or to sleep until 8 hours after the oral administration. Blood samples (7 mL) for valsartan concentration determination were obtained through a 22-guage indwelling catheter in a forearm vein or by direct venipuncture before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and 24-hour after dosing in each period. Each sample was collected in heparinized tubes. The blood samples were centrifuged immediately (3,000 rpm, 10 minutes), and were frozen at -80°C until UPLC -MS/MS analysis.

3. Pharmacokinetic assessment

To determine the valsartan plasma concentration, ACQUITY UPLC (Waters, Milford, MA, USA)-QTRAP 5500 (AB SCIEX, Foster City, CA, USA) were used as UPLC-ESI-MS/MS method.[11] The chromatographic separation was performed on a 2.1 × 50 mm, 3.5 μm xBridge C18 column (Waters) maintained at 25°C using a mobile phase of methanol-10 mM ammonium acetate (50:50, v/v), and the separation was under isocratic conditions with a flow rate of 0.3 mL/min. Valsartan form *m/z* 434.2 (Q1) to *m/z* 179.1 (Q3) and valsartan-D3 (IS) *m/z* 437.2 (Q1) to *m/z* 179.1 (Q3) were detected by multiple reaction monitoring with electrospray interface in the negative ion mode. The stock solution of valsartan was prepared in acetonitrile and calibration curve was linear over range in a concentration of 5, 10, 50, 200, 1,000, and 5,000 ng/mL. Concentrations at 20, 500, and 4,000 ng/mL for valsartan was prepared as quality control samples. Internal standard solution of a concentration that 150 ng/mL was prepared in acetonitrile. Human plasma sample were thawed at room temperature, and 300 μL of internal standard solution was added to a 100 μL aliquot of plasma sample for precipitate proteins. One minute vortex mixing and 10 minutes at 14,000 rpm centrifuging were conducted, and the upper clear solution layer was collected and a 3 μL aliquot of solution was injected into the UPLC-MS/MS system.

BA-CALC 2008 program ver. 1.0.0 (Korea Food and Drug Administration, Cheongwon, Korea) that supplied by the KFDA was used to assessed individual pharmacokinetic parameters which include AUC_t, AUC_{inf}, C_{max}, and T_{max}.

4. Pharmacodynamic assessment

Twenty four hours blood pressure changes were monitored by ABPM. ABPM can provide a 24-hour blood pressure profile and blood pressure information over 24-hour as well as during specific periods, such as daytime, nighttime, and early morning.[7] The ABPM measurement was done according to "Guideline for blood pressure monitoring" established by Korean Society of Hypertension.[8] Total, daytime and nighttime systolic blood pressure (SBP), diastolic blood pressure, and heart rate of each participant were automatically measured every 20 minutes during the 24 hours (8 AM to next day 8 AM) with a validated device (TM 2430 ambulatory blood pressure monitor; A&D Medical, San Jose, CA, USA). Subjects were studied by ABPM under baseline conditions at 1st period when they were free of medication and assessed the effects of valsartan at 2nd period.

Table 1. The classification of blood pressure patterns

Group	Blood pressure pattern
Non-dipper	Blood pressure in night time is diminished below 10% than daytime
Dipper	Blood pressure in night time is diminished 10% to 20% than daytime
Extreme-dipper	Blood pressure in night time is diminished over 20% than daytime
Reverse-dipper	Blood pressure in night time is increased than daytime

Table 2. Groups according to response to valsartan

Group	Changes of blood pressure pattern from pre-dose to post-dose
Responder	Reverse-dipper to non-dipper/non-dipper to dipper
Non-responder	Blood pressure patters are same in pre- and post-dose.
Reverse-responder	Dipper to non-dipper/non-dipper to reverse-dipper

5. Group assignment

The blood pressure patterns were classified as non-dipper, dipper, extreme-dipper, and reverse-dipper (Table 1). Subjects that diurnal blood pressure pattern changed from reverse dipper to non-dipper or dipper and changed from non-dipper to dipper or extreme dipper were assigned to responder group; subjects that have no change in diurnal blood pressure pattern were assigned to non-responder group; subjects that diurnal blood pressure pattern changed from non-dipper to reverse dipper and changed from dipper to non-dipper were assigned to reverse-responder group (Table 2).

6. Tolerability

Adverse events (AEs) were monitored throughout the study based on spontaneous reports by volunteers, questioning by investigators, and clinical examinations. The investigators assessed all clinical adverse effects in terms of intensity (mild, moderate, or severe), duration, outcome, and relationship to the study drug.

7. Statistical analysis

Pre- and post-dose blood pressure changes matched to pharmacokinetic parameters were analyzed by Pearson correlation analysis using SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA). Pharmacokinetic parameters were analyzed between responder, non-responder and reverse-responder groups according to pre- and post-dose changes in ABPM pattern. SPSS ver. 20.0 was used to conduct the one-way analysis of variance to compare the differences of mean AUC_t, AUC_{inf}, and C_{max} between three groups. All analysis were performed at an α level of 0.05.

Results

1. Subjects

Twenty-one healthy Korean male volunteers were participated. The mean (standard deviation, SD) age, height, and weight of subjects were 25.3 ± 3.5 years, 175.0 ± 3.9 cm, and 68.5 ± 7.8 kg, respectively. Twenty-four hours blood pressure monitoring data was summarized in Table 3.

2. Pre- and post-dose changes in blood pressure and pharmacokinetics

The ABPM results and pharmacokinetic parameters of each individual were summarized in Table 3. Although all subjects were participated entire trial, ABPM data of

Table 3. Twenty-four hours ambulatory blood pressure monitoring (ABPM) data for 21 subjects

Subject no.	Pre-dose BP pattern						Pose-dose BP pattern						Changes in mSBP
	mSBP	mDBP	mdSBP	mdDBP	mnSBP	mnDBP	mSBP	mDBP	mdSBP	mdDBP	mnSBP	mnDBP	
1	131.8	87.3	130.2	87.6	139.1	86.1	110.3	68.0	111.8	69.2	105.4	63.7	21.5
11	141.4	79.4	145.3	81.7	127.1	70.7	121.5	65.9	124.3	67.6	112.8	60.4	19.9
8	141.8	86.3	141.3	87.6	143.5	82.0	123.9	78.2	125.3	80.9	118.7	68.7	17.9
15	146.6	93.4	146.5	92.4	148.0	103.5	130.7	84.4	131.6	84.4	127.4	84.5	15.9
21	139.3	84.9	137.8	85.0	143.7	84.8	123.8	69.0	124.3	69.5	122.1	66.8	15.5
6	118.7	75.4	119.9	76.8	114.5	70.4	110.0	66.6	111.6	67.2	104.0	64.2	8.7
3	115.8	62.3	116.6	63.5	112.8	58.0	107.3	54.8	108.2	56.8	103.6	46.5	8.5
18	125.8	75.7	125.4	75.6	127.8	76.1	118.5	72.4	114.3	70.1	136.8	82.1	7.3
12	130.1	84.9	130.6	86.7	127.8	75.8	123.4	74.6	125.0	74.6	112.2	74.2	6.7
4	114.3	67.3	115.5	68.2	109.8	64.3	110.6	70.3	111.2	71.0	108.4	68.3	3.7
5	117.5	74.8	121.3	77.1	104.5	66.8	114.9	69.9	116.2	70.0	110.1	69.6	2.6
9	119.6	65.5	120.1	67.2	118.0	59.6	118.4	68.8	119.7	80.2	114.3	64.3	1.2
20	146.6	92.3	148.0	94.3	142.1	85.8	145.5	89.5	143.6	88.5	156.4	95.4	1.1
10	124.0	75.1	126.6	77.9	111.5	62.0	123.0	77.0	125.0	80.1	116.3	66.3	1.0
13	123.4	83.6	126.4	86.6	112.8	73.4	122.4	80.1	124.5	82.8	114.2	69.6	1.0
17	104.5	66.5	105.9	68.2	99.7	60.5	110.1	64.8	110.9	66.6	104.2	51.7	-5.6
14	117.8	70.8	117.4	72.2	119.3	65.6	123.4	65.4	122.6	66.7	127.1	60.1	-5.6
19	111.0	64.4	111.5	65.6	109.5	60.0	125.9	66.9	125.7	67.4	126.5	65.1	-14.9
2	114.1	69.6	114.6	71.0	112.3	64.6	-	-	-	-	-	-	-
7	112.2	70.0	115.8	72.5	99.8	61.6	-	-	-	-	-	-	-
16	121.7	59.3	121.1	61.1	124.4	51.2	-	-	-	-	-	-	-

Blood pressure (BP) data of subjects 2, 7, and 16 were lossed during trial.
mSBP, mean systolic blood pressure; mDBP, mean diastolic blood pressure; mdSBP, mean daytime systolic blood pressure; mdDBP, mean daytime diastolic blood pressure; mnSBP, mean nighttime systolic blood pressure; mnDBP, mean nighttime diastolic blood pressure.

Table 4. Pearson correlation coefficient analysis of pre- and post-dose changes in blood pressure and pharmacokinetics

	Variable	AUC_t	AUC_{Inf}	C_{max}
Mean SBP	Pearson correlation coefficient	0.173	0.158	0.168
	p-value	0.491	0.532	0.505
Mean DBP	Pearson correlation coefficient	0.271	0.183	0.353
	p-value	0.276	0.468	0.151
Mean daytime SBP	Pearson correlation coefficient	0.160	0.129	0.149
	p-value	0.526	0.609	0.555
Mean daytime DBP	Pearson correlation coefficient	0.301	0.140	0.386
	p-value	0.224	0.579	0.114
Mean nighttime SBP	Pearson correlation coefficient	0.210	0.205	0.245
	p-value	0.404	0.414	0.327
Mean nighttime DBP	Pearson correlation coefficient	0.241	0.182	0.347
	p-value	0.335	0.469	0.158

AUC_t, area under the plasma concentration versus time curve from 0 hour to the last measurable concentration; AUC_{Inf}, area under the plasma concentration versus time curve extrapolated to infinity; C_{max}, maximum plasma concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 5. Pharmacokinetic and pharmacodynamic properties of three groups

Group	Subject no.	AUC_t (ng·hr/mL)	AUC_{inf} (ng·hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	Diurnal BP pattern_base	Diurnal BP pattern_after
Responder	1	13,844	14,420	1,800	2	4	1
	8	27,398	28,397	4,052	3	4	1
	12	28,393	28,945	4,786	3	1	2
	15	28,009	29,575	5,399	4	4	1
	21	31,396	32,213	5,532	4	4	1
	Mean ± SD	25,808 ± 6,863.0	26,710 ± 7,024.4	4,314 ± 1,522.6	3 ± 0.8		
Non-responder	3	12,765	13,231	1,710	4	1	1
	4	17,858	19,585	1,431	5	1	1
	6	28,107	29,137	2,939	4	1	1
	9	11,598	21,677	1,032	4	1	1
	13	13,335	13,969	2,518	4	1	1
	14	18,299	19,249	2,270	2.5	4	4
	17	28,087	28,747	4,366	4	1	1
	18	35,418	37,570	4,442	4	4	4
	Mean ± SD	20,683 ± 8,782.7	22,895 ± 8,344.0	2,588 ±1 273.9	4 ± 0.7		
Reverse-responder	5	15,844	16,233	2,972	4	2	1
	10	3,897	4,249	527	2.5	2	1
	11	10,862	11,421	1,513	2	2	1
	19	18,424	18,882	3,127	2	1	4
	20	13,481	13,925	2,144	5	1	4
	Mean ± SD	12,502 ± 5,566.6	12,942 ± 5,589.2	2,056 ± 1,075.5	3 ± 1.3		

Diurnal BP pattern, 1 = non dipper (with a BP drop at night time of less than 10%); 2 = dipper (with a BP drop at night time of 10% to 20%); 3 = extreme dipper (with a BP drop at night time of more than 20%); 4 = reverse dipper (with a BP increase at night time).
AUC_t, area under the plasma concentration versus time curve from 0 hour to the last measurable concentration; AUC_{inf}, area under the plasma concentration versus time curve extrapolated to infinity; C_{max}, maximum plasma concentration; T_{max}, time required to reach maximum plasma concentration; BP, blood pressure; SD, standard deviation.

post-dose from three subjects (R02, R07, and R16) was missed for various reasons. After finished 2nd period, 15 subjects showed decrease in mean SBP and 3 subjects showed increase in mean SBP. To associate pharmacokinetic parameters and changes in ABPM data, Pearson correlation analysis was conducted between ABPM data and pharmacokinetic parameters(C_{max}, AUC_t, and AUC_{inf}). There were no significant associations between changes of ABPM data and pharmacokinetic parameters (Table 4).

3. ABPM patterns and pharmacokinetics

The ABPM patterns and pharmacokinetic parameters of each individual were summarized in Table 5. Ten, four, and seven subjects showed dipper, non-dipper, and reverse dipper pattern in 1st period, respectively. After finished 2nd period, eleven, one, and four subjects showed dipper, non-dipper, and reverse dipper pattern in 1st period, respectively. The mean AUC_t (mean ± SD), total amount of absorbed valsartan was 25,808 ± 6,863.0 ng·hr/mL, 20,683 ± 8,782.7 ng·hr/mL, and 12,502 ± 5,566.6 ng·hr/mL in responder, non-responder, and reverse responder, respectively. There were significant differences between mean AUC_t of three groups (p = 0.041), and mean AUC_t of responder group was significant higher than reverse group (p = 0.035, Turkey honestly significant difference [HSD]). The mean AUC_{inf} (mean ± SD), total amount of absorbed valsartan was 26,710 ± 7,024.4 ng·hr/mL, 22,895 ± 8,344.0 ng·hr/mL, and

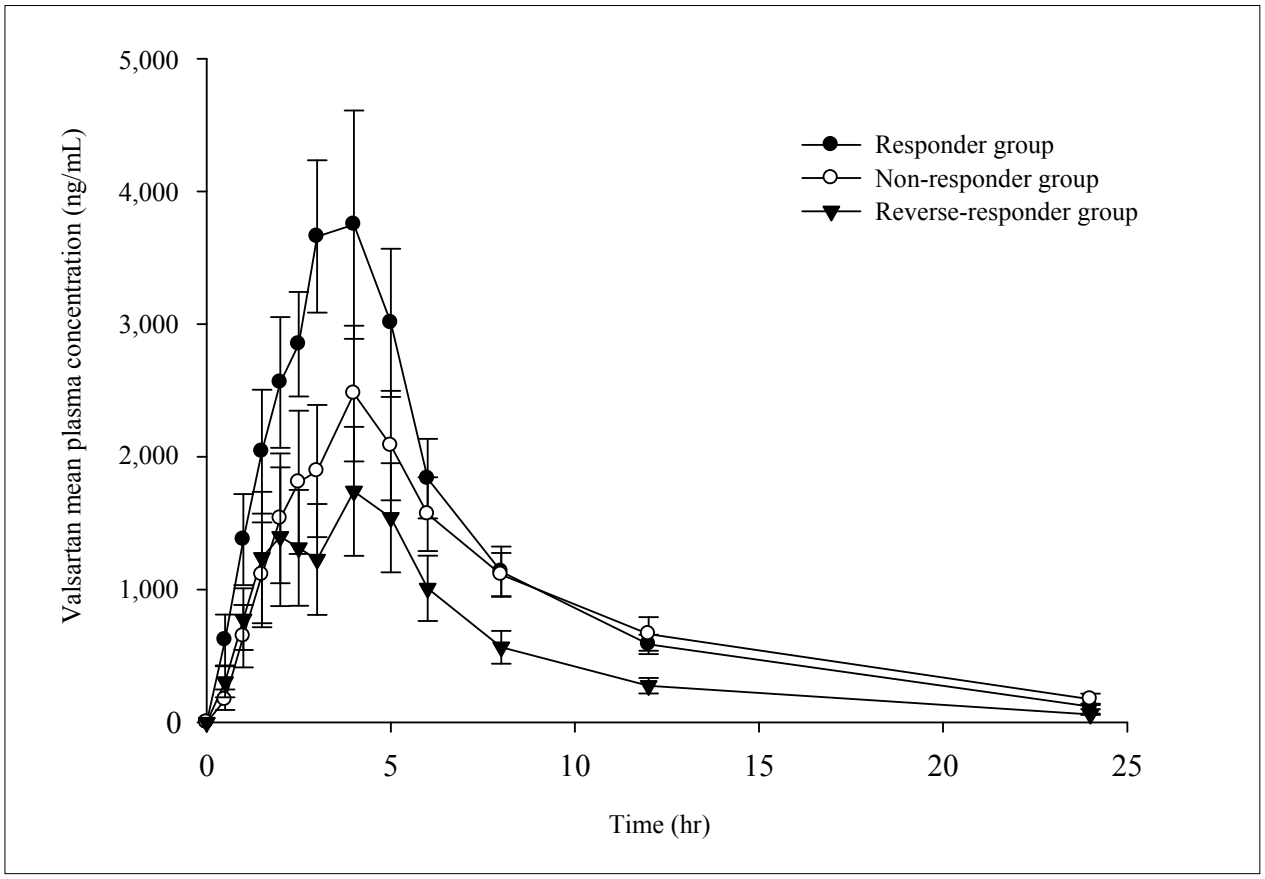

Fig. 1. Plasma concentration–time curves. Valsartan mean plasma concentration versus time profile of response group, non–response group and reverse response group. Values are presented as mean ± standard error of mean.

12,942 ± 5,589.2 ng·hr/mL in responder, non-responder, and reverse responder, respectively. There were significant differences between mean AUC_{inf} of three groups (p = 0.025), and mean AUC_t of responder group was significant higher than reverse group (p = 0.025, Turkey HSD). C_{max} was 4,314 ± 1,522.6 ng/mL, 2,588 ± 1,273.9 ng/mL, and 2,056 ± 1,075.5 ng/mL in responder, non-responder, and reverse responder, respectively. There were significant differences between mean C_{max} of three groups (p = 0.034), and mean C_{max} of responder group was significant higher than reverse group (p = 0.037, Turkey HSD). In Tmax, time required to reach maximum plasma concentration was 3 ± 0.8 hours, 4 ± 0.7 hours, and 3 ± 1.3 hours in responder, non-responder, and reverse responder, respectively. There were no significant differences between mean T_{max} of three group (p = 0.239). The mean plasma concentration versus time profiles of valsartan in responder, non-responder, and reverse-responder group were shown in Fig. 1.

4. Tolerability

No serious AEs were reported, and no subjects discontinued the study due to AEs. But three subjects were failure to obtain ABPM data at the second period, and total 18 subjects were enrolled the statistical analysis.

Discussion

In pharmacotherapy, response of drug mainly depends on the amount of drug absorbed. Other factors, such as

age, gender, genetic factor, and individual susceptibility affect the effect of drug.[9-13)]

In this study, we hypothesized that individual difference of valsartan effect mainly caused by amount of drug absorbed. So a single group, two-sequence, open label, pre- and post-comparison pharmacokinetic/pharmacodynamic (PK/PD) study was conducted. Total 21 subjects were enrolled and pre- and post-dose ABPM and pharmacokinetic data was used for PK/PD analysis.

We expected that blood pressure lowering effect of valsartan may be associated with amount of drug absorbed. However, there were no positive correlations between pharmacokinetic parameters of valsartan and blood pressure changes. These results showed that response to valsartan did not correlate with pharmacokinetic parameters of valsartan. Although there were no relations between response and pharmacokinetic parameters, this study has some limitations. Subjects were healthy volunteers and dose of valsartan was not sufficient to prove the effect of drugs in healthy volunteers. And other individual factors can affect the blood pressure status of two periods. So we analyzed pre- and post-dose changes in blood pressure patterns according to pharmacokinetic parameters.

Interestingly, three groups (responder, non-responder, and reverse responder) showed statistically different drug absorption pattern. In AUC_t which represents amount of drug absorbed, three groups showed statistically different valsartan absorption. Especially, difference between responder and reverse-responder was more than two fold (25,808 ± 6,863.0 ng·hr/mL and 12,502 ± 5,566.6 ng·hr/mL in responder and reverse responder, respectively). The maximum concentration of valsartan (C_{max}) also showed similar results.

These results showed that response to valsartan do not depend on amount of drug absorbed in this study. Because this study has some limitations, if subject factors (healthy volunteer) and clinical trial design had been changed, some significant results could be obtained. In conclusion, for tailored pharmacotherapy of valsartan, genetic and other factors which might affect the valsartan's effect should be studied.

Summary

연구배경: 발사탄은 안지오텐신 수용체 II의 억제제로 고혈압의 치료에 사용되고 있다. 발사탄의 혈압강하 효과는 개인별로 차이를 나타내지만 이러한 차이를 나타내는 약동학-약역학적 요인에 대한 연구는 없는 실정이다.

방법: 발사탄이 혈압의 변화에 미치는 영향을 알아보기 위하여 21명의 건강한 자원자를 대상으로 단일군, 공개, 비교 임상시험을 수행하였다. 모든 피험자는 1기에 약물을 투여하지 않은 상태에서 24시간 혈압 측정을 수행하였고 7일간의 휴약기를 가진 후에 2기에 발사탄 80 mg (Diovan HCT)을 투여하고 24시간 혈압을 측정하였다. 24시간 혈압의 측정은 ambulatory blood pressure monitoring에 의해 기록되었다. 약물농도 변화에 따른 24시간 혈압의 변화와 혈압 패턴의 변화는 연관분석에 의해 분석하였다. 피험자는 약물에 의한 반응에 따라 반응군, 비반응군, 역반응군으로 분류되었다. 약동학적인 분석을 위한 약물 농도는 초고성능 액체크로마토그래피-직렬질량분석법(ultra-performance liquid chromatography-tandem mass spectrometry)을 이용하여 측정하였다. 약동학적 파라미터는 최고혈중농도(C_{max}), 측정 가능한 마지막 채혈 시점까지의 혈중농도-시간 곡선하 면적(AUC_t)과 최고혈중농도도달시간(T_{max})을 분석하였다. 약동학적 파라미터의 분석은 식품의약품안전청에서 제공하는 프로그램인 BACALC 2008 program ver. 1.0.을 이용하여 비구획 방법을 가정하여 산출하였다.

결과: 발사탄의 약동학적 파라미터와 혈압의 변화는 유의한 연관성을 나타내지 않았다. 혈압의 패턴 변화는 약물농도와 관련이 있는 것으로 나타났다. 측정 가능한 마지막 채혈 시점까지의 혈중농도-시간 곡선하 면적은 반응군, 비반응군, 역반응군에서 각각 25,808 ± 6,863.0 ng·

hr/mL, 20,683 ± 8,782.7 ng·hr/mL, 12,502 ± 5,566.6 ng·hr/mL로 통계적으로 유의한 차이를 나타내었다(p = 0.041). 최고혈중농도는 반응군, 비반응군, 역반응군에서 각각 4,314 ± 1,522.6 ng/mL, 2,588 ± 1,273.9 ng/mL, and 2,056 ± 1,075.5 ng/mL로 유의한 차이를 나타내었다(p = 0.034).

결론: 건강한 자원자에서 발사탄의 약물 농도는 24시간 혈압측정 결과 발사탄에 의한 혈압저하 효과와 관련되지 않았으나 혈압의 패턴의 변화와는 관련이 있는 것으로 나타났다.

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