Effects of Chungsinoryungsan, a polyherbal complex, on the pharmacokinetic profiles of perindopril in rats

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Abstract. For sufficient antihypertension with less adverse effects, numerous clinical trials have recommended combination therapy using two or more hypertensive drugs. Chungsinoryungsan (CSORS) is a polyherbal complex based on oriental medicine, which has shown therapeutic potentials for antihypertension and additional renal improvement. Therefore, the affect of CSORS on the pharmacokinetic profiles of perindopril, an antihypertensive drug, was analyzed as a novel combination of hypertensive drugs. Rats received perindopril with CSORS as the combination or distilled water as the control. The co-administration of perindopril with CSORS or distilled water was performed by single dosing or repeated dosing for a week at a 2-h interval. The analyzed pharmacokinetic parameters included peak concentration (C_{max}), time to reach the C_{max} (T_{max}), area under the plasma concentration-time curve, terminal half-life ($t_{1/2}$) and mean residence time to infinity (MRT_{inf}). In the single oral co-administration within 5 min, the pharmacokinetics of perindopril demonstrated an increased T_{max} and MRT_{inf} but reduced $t_{1/2}$ in the combination compared to the control treatment, indicating drug-drug interactions between perindopril and CSORS. However, in the repeated co-administration for a week at a 2-h interval, which was more than perindopril MRT_{inf} in the control treatment (1.5±0.1 h), the initial co-administration showed no differences in the pharmacokinetics between the combination and control treatments. Furthermore, the repeated co-administration also showed no differences between the combination and control treatment. The results indicate that CSORS can be co-administered at a 2-h interval that was more than perindopril MRT_{inf} and further clinical studies may provide detailed information for developing a drug regimen that generates enhanced combination effects of CSORS with hypertensive drugs.

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Introduction

Hypertension is one of the most significant public issues with a high worldwide prevalence and its treatment can lead to reduced incidences of complications, such as stroke, myocardial infarction and renal disease (1). There are a number of antihypertensive drugs of various categories, including angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, β-blockers and angiotensin II receptor antagonists. Thus far, clinical trials have indicated that monotherapy, the use of a single drug, is insufficient for achieving the goal blood pressure in patients with hypertension and ongoing trials have provided guidance on the appropriate combination regimens using ≥2 antihypertensive drugs for increasing the synergic effects and reducing the unexpected adverse effects (2,3). Furthermore, the combination regimens targeting functional improvement, as well as antihypertension, enhance the therapeutic effects even when the monotherapy is not evident in patients with renal dysfunction (4).

Perindopril is a long-acting ACE inhibitor that results in preventing the generation of angiotensin II in the renin-angiotensin-aldosterone system and subsequently lowering blood pressure. Numerous studies have revealed that perindopril is useful for treatment of hypertension (5), chronic heart failure (6) and diabetic nephropathies (7). Perindopril has good preclinical profiles with an LD_{50} at relatively high doses in various experimental animals (8), and clinical introduction and post-marketing surveillance studies have shown that perindopril is well-tolerated in a wide range of patients with hypertension (9). However, perindopril has a risk of severe hypotension despite low incidences and possible fetal and neonatal morbidity and mortality when used during pregnancy (9), indicating that the use of perindopril requires caution to avoid the unexpected adverse effects.

Natural products have received increasing attention in the development of novel drug materials. There are a number of natural herbal products based on Korean medicine that have been adjusted from traditional Chinese medicine and the commercially available herbal drugs have been evaluated for novel combination regimens as an adjunctive medication (10). Wu Ling San (Oryungsan, ORS) known as a five-ingredient formula with poria, is the most famous nephroprotective Korean traditional polyherbal formula (11). The accumulated clinical trials have shown that ORS is useful for various diseases involved in hypertension, such as kidney diseases, cardiac edema, ascites, diabetes, liver cirrhosis and hydrocephalus. In addition, the therapeutic improvement has been revealed in experimental animal models of renal damage (12), nephrotic syndrome (13) and renal dysfunction (14). Chungsinoryungsan (CSORS) is based on the materials of ORS and 20 types of herb exhibiting nephroprotective effects are also added additionally (15). CSORS is indicated to possibly be useful in combination with antihypertensive drugs as an adjunctive medication. Therefore, the aim of the present study was to examine the drug-drug interactions between CSORS and perindopril via comprehensive pharmacokinetic analyses.

Materials and methods

Animals. Six-week-old male Sprague-Dawley rats (170-190 g) were obtained from Japan SLC, Inc. (Shizuoka, Japan). A total of 20 rats were separated randomly to five per polycarbonate cage and acclimatized in a room controlled at 20-25˚C and 40-45% humidity for 2 weeks. The rats were maintained on a 12-h light/dark cycle with free access to standard rodent chow and water. All the experimental procedures were approved by the Institutional Animal Care and Use Committee at Daegu Haany University (Gyeongsan, Korea).

Drugs and treatment. Perindopril was purchased from Panaaya Pharma Private, Ltd. (Hyderabad, India). CSORS was prepared at the Department of Herbology (College of Korean Medicine, Daegu Haany University). For producing CSORS, 25 types of herb were purchased from Jecheon Hanbang Yakcho (Jecheon, Korea) following confirmation of the complete morphology under microscopy (Table I). The herbs (1,420 g) were boiled in 2 l distilled water for 3 h, three times at 80˚C and subsequently filtered. The resultant filtrate was decompressed with a rotary vacuum evaporator (Rotavapor R-144; Buchi, Flawil, Switzerland) and lyophilized in a programmable freeze dryer (FreeZone 1 Liter Benchtop; Labconco Corporation, Kansas City, MO, USA). Eventually, the acquired CSORS extract volume was 173.24 g as a light brown powder (yield, 12.2%). The perindopril and CSORS drugs were stored as a powder at 4˚C in the dark until required.

One batch of 10 rats received single oral dosing of perindopril combination with CSORS (combination group) or perindopril with distilled water (control) and another batch of 10 rats received repeated oral dosing of combination and control once a day for a week. The co-administration with CSORS or distilled water was performed by the single dosing within 5 min after perindopril, or the repeated dosing at a 2-h interval after perindopril. The drug dosing was a volume of 5 ml/kg at 100 ml/kg CSORS and 50 mg/kg perindopril, based on its toxicity and clinical database (8). Body weights were measured prior to every administration using an automatic electronic balance (Precisa Instruments AG, Dietikon, Switzerland).

Collection of blood samples and sample preparation. The rats were fasted overnight a day before collection of the blood sample to avoid dietary effects. The blood sample via the retro-orbital route was collected in anticoagulant tubes, including 50 IU heparin, at 0.5 h prior to the administration and 0.5, 1, 2, 3, 4, 6, 8 and 24 h post-administration. The plasma sample was centrifuged at 11,400 x g for 10 min and the supernatant aliquot was stored at -70˚C until pharmacokinetic analyses.

Sample preparation and calibrations. For a calibration, 1.0 mg/ml perindopril (Sigma, St. Louis, MO, USA) diluted with 50% acetonitrile was used as a primary stock solution and 500 ng/ml carbamazepine (Sigma) in acetonitrile was used as an internal standard (IS) solution. The working standard solutions were prepared by dilution of the primary stock solution with acetonitrile and stored in the dark at -20˚C. The 100 μl working standard solutions were mixed with 100 μl blank plasma and IS solutions in 100 μl acetonitrile for the perindopril concentration standard curve. The 100-μl plasma sample was prepared as a mixture with 100-μl IS solution in 200 μl acetonitrile. The mixtures were centrifuged at 9,700 x g for 10 min at 4˚C and the supernatant was transferred to injection vials for liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS).

LC-MS/MS conditions. Chromatographic analysis was performed using an Agilent 1100 series HPLC (Agilent Technologies, Santa Clara, CA, USA) equipped with online degasser, binary pump, auto-sampler, column compartment and column oven at 30˚C. Separation of the analyte from potentially interfering material was achieved using Waters XTerra MS C18 columns (2.1x50 mm, 3.5 μm) (Waters Corporation, Milford, MA, USA). The mobile phase for chromatographic separation was composed of 5-95% acetonitrile, including 0.1% formic acid, and it was delivered isocratically at a flow rate of 0.3 ml/min. The column effluent was monitored using an API 2000 triple quadrupole mass-spectrometer detector (Applied Biosystems, Foster City, CA, USA). The instrument was equipped with an electrospray interface in positive-ion mode, which was controlled by the Analyst version 1.4.2 software (Applied Biosystems). The samples were introduced to the interface through turbo ionspray at 400˚C. A high positive voltage of 5.0 kV was applied to the ion spray. Nitrogen was used as nebulizer gas, curtain gas and collision gas with sets of 12, 6 and 8 PSI, respectively. The multiple reaction monitoring detection method was employed for the detection of perindopril; the transitions monitored were carbamazepine (IS): m/z 237>194 (retention time, 2.7 min); and perindopril: 369>172 (retention time, 2.5 min). Calibration curves of perindopril were linear over the ranges with r^2>0.999. The lower limit of quantification was 0.1 ng/ml.

Pharmacokinetic analyses. The perindopril concentration in plasma was analyzed using a non-compartmental method

Table I. Twenty five types of herb consisting of Chungsinoryungsan aqueous extracts.

Herbs	Scientific names/produce region	Amounts, g
Alismatis rhizoma	*Alisma orientale* (Sam.) Juz./Chunnam	100
Tokoro rhizoma	*Dioscorea tokoro* Makino/China	100
Alpiniae fructus	*Alpinia oxyphylla* Miquel/China	80
Polyporus	*Dendropolyporus umbellatus* (Pers.:Fr.) Jülich/China	80
Hoelen	*Poria cocos* Wolf//China	80
Dioscoreae rhizoma	*Dioscorea batatus* Decne./Kyungbuk	80
Astragali radix	*Astragalus membranaceus* Bunge/Chungbuk	60
Mantidis ootheca	*Paratenodera sinensis* De Saussure/China	60
Atractylodis rhizoma alba	*Atractylodes ovata* (Thunb.) DC./China	60
Nelumbinis semen	*Nelumbo nucifera* Gaertn./China	60
Acori Gramineri rhizoma	*Acorus gramineus* Soland./China	60
Artemisiae capillaris herba	*Artemisia capillaris* Thunberg/Kyungbuk	60
Plantaginis semen	*Plantago asiatica* L./China	60
Amomi fructus	*Amomum villosum* Loureiro var. *xanthioides* T.L.Wu et Senjen/China	60
Remotiflori radix	*Adenophora remotiflora* (Siebold and Zucc.) Miq. /China	60
Citri unshii pericarpium	*Citrus unshiu* S.Marcov./Cheju	40
Fossilia ossis mastodi	*Fossilia ossis mastodi*/China	40
Terminaliae fructus	*Terminalia chebula* Retz./China	40
Ginseng radix alba	*Panax ginseng* C.A.Meyer/Chungnam	40
Cimicifugae rhizoma	*Cimicifuga heracleifolia* Kom./China	40
Aurantii immaturus fructus	*Citrus aurantium* L./China	40
Myristicae semen	*Myristica fragrans* Houtt./China	40
Pulvis ostreae testa	*Crassostrea gigas* Thunberg/China	30
Cinnamomi cortex	*Cinnamomum cassia* J. Presl./China	30
Mume fructus	*Prunus mume* Siebold et Zuccarini/China	20

All the individual herbs were purchased from the Local Pharmacy of Oriental Medicine (Jecheon, Korea) at the indicated amounts.

on the commercial pharmacokinetics data analyzer program (PK Solutions 2.0; Summit Research Services, Montrose, CO, USA) (16). The elimination rate constant (K_{el}) was calculated by log-linear regression of perindopril concentration data during the elimination phase, and the terminal half-life ($t_{1/2}$) was calculated by $0.693/K_{el}$. The peak concentration (C_{max}) of plasma perindopril and time to reach the C_{max} (T_{max}) were obtained by visual inspection in the concentration-time curve. The area under the perindopril concentration-time curve (AUC_{0-t}) from time zero to the time of the measured concentration (C_{last}) was calculated using the linear trapezoidal rule (17). The AUC zero to infinity (AUC_{0-inf}) was obtained by adding AUC_{0-t} and the extrapolated area was determined by C_{last}/K_{el}. The mean residence time to infinity (MRT_{inf}) was calculated by dividing the first moment curve ($AUMC_{0-inf}$) by AUC_{0-inf}.

Statistical analyses. All the data are presented as average values ± standard error of the mean (SEM). Data for body weights and perindopril concentration were examined by testing the homogeneity of variance, followed by analysis of variance (ANOVA) with the group as a main effect. The day on which the body weights were measured or the time collected for plasma samples was treated as repeated measurements. When the data passed at the test of homogeneity of variance, they were compared by independent t-test for post hoc test, otherwise, the data were compared by Mann-Whitney U test. All the pharmacokinetic parameters were examined by Mann-Whitney U test as a non-parametric comparison due to the small sample sizes, which have difficulties reaching a normal distribution. For all analyses, $P<0.05$ was considered to indicate a statistically significant difference.

Results

Single oral administration of perindopril combination with CSORS within 5 min

Body weight changes. There were no differences in the body weights between the combination and control treatment ($F=0.02$, $P>0.10$). The weight changes were 26.0±1.5 and 27.6±1.0 g in the combination and control groups, respectively.

Perindopril concentration. Perindopril was detected until 8 h post-administration in the combination treatment, whereas it was detected until 4 h in the control treatment (Fig. 1). The kinetics of perindopril concentration were examined by ANOVA with the group as a main effect and the collected time was treated as a repeated measurement. Overall, there were significant main effects for time ($F=143.8$, $P<0.01$), indicating time-dependent perindopril concentration. Although no main effects for group were found ($F=0.3$, $P>0.10$), there

Table II. Body weight changes following repeated administration of perindopril combination with Chungsinoryungsan for a week at a 2-h interval.

	Body weight (g)	
Perindopril combination	Distilled water	CSORS
Initial co-administration [A]	227.4±2.8	227.8±6.0
Last co-administration [B]	248.2±3.6	248.0±4.6
Changes [B]-[A]	20.8±2.7	20.2±2.3

Data represent average values (g) ± SEM in combination group [perindopril with Chungsinoryungsan (CSORS)] and control (periondopril with distilled water) following the initial and last co-administration of a repeated dosing for a week at a 2-h interval.

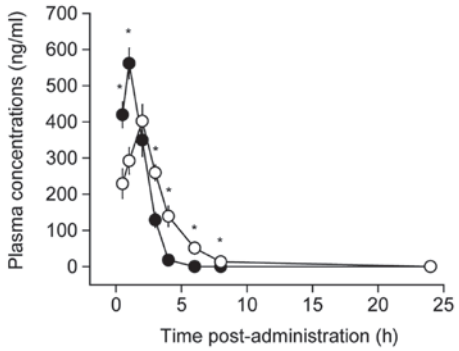

Figure 1. Plasma perindopril concentration in combination with Chungsinoryungsan (CSORS) within 5 min. The combination group of rats received oral co-administration of perindopril with CSORS within 5 min (open circles, n=5) and the corresponding control received perindopril with distilled water (closed circles, n=5). The plasma samples were assessed at 0.5, 1, 2, 3, 4, 6, 8 and 24 h post-administration. All the data represent average values (ng/ml) ± SEM. *P<0.01.

were significant interactions between time and group (F=24.0, P<0.01). Post hoc test revealed that the combination treatment reduced the perindopril concentration by 55% at 0.5 h post-administration and 52% at 1 h, and increased by 202, 771, 613 and 231% at 3, 4, 6 and 8 h, respectively, compared to the control (P<0.01) (Fig. 1). This indicates altered perindopril pharmacodynamics by CSORS.

Perindopril pharmacokinetics. Although it was not significant (P=0.06), for group analysis the C_{max} showed a 28% reduction in the combination (401.9±41.9 ng/ml) compared to the control treatment (561.5±46.0 ng/ml) (Fig. 2A). However, there were significant main effects for group for T_{max} (P<0.01) and $t_{1/2}$ (P<0.01) (Fig. 2B and C). T_{max} for the combination group was increased by 200% compared to the control and $t_{1/2}$ was reduced by 60%. T_{max} was 2.0±0.0 vs. 1.0±0.0 h in the combination versus the control treatment and $t_{1/2}$ was 0.59±0.03 h vs. 1.47±0.15 h, respectively. AUC_{0-t} of perindopril was not significantly increased in the combination (1,319.6±160.4 ng h/ml) compared to the control group (1,117.9±82.5 ng h/ml) (P>0.10) (Fig. 2D). No differences were detected in AUC_{0-inf} between the groups (P>0.10) (Fig. 2E). However, MRT_{inf} was significantly increased by 78% in the combination (2.7±0.1 h) compared to the control treatment (1.5±0.0 h) (P<0.01) (Fig. 2F). These results indicate delayed absorption and excretion of perindopril by combination with CSORS within 5 min.

Repeated oral administration of perindopril combination with CSORS for a week at a 2-h interval

Body weight changes. No evident differences were found in the gross aspects of behavior and weight changes (Table II). ANOVA revealed no main effects for the group (F=0.001, P>0.10) and no interactions between group and measured days (F=0.2, P>0.10).

Perindopril concentration. Following the initial and last co-administration, the perindopril was detected up until 4 h post-administration in the combination and control groups (Fig. 3). The time-concentration graph was similar between the combination and control groups. Following the initial co-administration (Fig. 3A), there were significant main effects for time (F=185.3, P<0.01), but no main effects for group (F=0.1, P>0.10) and no interaction between time and group (F=0.1, P>0.10). Following the last co-administration of the repeated administration (Fig. 3B), there were significant main effects for time (F=205.3, P<0.01), but no main effects for group (F=0.07, P>0.10) and no interaction between time and group (F=0.04, P>0.10). These indicate limited interaction between perindopril and CSORS by co-administration at a 2-h interval.

Perindopril pharmacokinetics. The perindopril combination with CSORS at a 2-h interval showed no differences in T_{max}, C_{max}, $t_{1/2}$, AUC_{0-t}, AUC_{0-inf} and MRT_{inf} compared to the control following the initial and last co-administration of the repeated administration for a week (Fig. 4). Mann-Whitney U test revealed no main effects for group for any of the parameters assessed (P>0.10).

Discussion

The effects of CSORS administration on pharmacokinetics of perindopril were examined in the present study. When perindopril was co-administered with CSORS within 5 min, the perindopril plasma concentration was different from the normal pharmacokinetics of the control (Fig. 1). The pharmacokinetic parameters showed reduced $t_{1/2}$ and increased T_{max} and MRT_{inf} in the combination compared to the control group. This indicates a drug-drug interaction between perindopril and CSORS (Fig. 2). Perindopril was hypothesized to possibly have a limited interaction with CSORS co-administration at an interval gap that was more than perindopril MRT_{inf} of the control treatment (1.51±0.09 h). When perindopril was co-administered with CSORS at a 2-h interval, the perindopril concentration and pharmacokinetic parameters were not different between the combination and control groups following the initial and last administration of a weekly repeated dosing (Figs. 3 and 4). These results provide detailed information for the drug regimen of perindopril combination with CSORS.

Perindopril has been shown to have various drug-drug interactions with diuretics (18,19), gentamicin (20) and lithium (21,22). However, there have been limited studies regarding the interactions between perindopril and natural

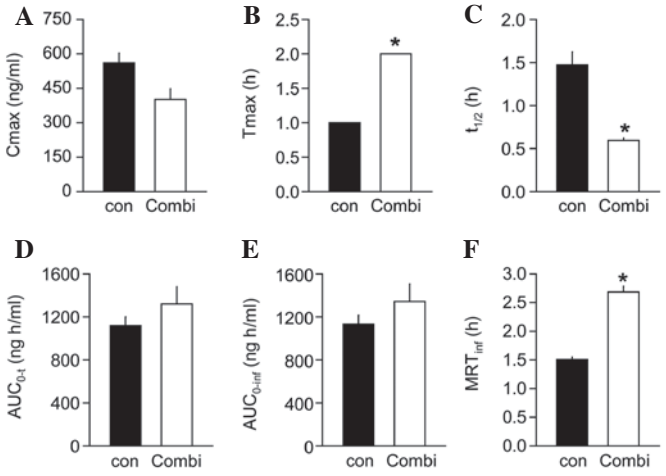

Figure 2. Pharmacokinetic profiles of perindopril in combination with Chungsinoryungsan within 5 min. The plasma samples used in Fig. 1 were subjected to analyses of pharmacokinetic parameters: (A) Peak concentration (C_{max}), (B) time to reach the C_{max} (T_{max}), (C) terminal half-life ($t_{1/2}$), (D) area under the perindopril concentration-time curve (AUC_{0-t}), (E) AUC zero to infinity (AUC_{0-inf}) and (F) mean residence time to infinity (MRT_{inf}). Each graph represents average values ± SEM in the combination (Combi, white bars) and control (con, black bars). *P<0.01.

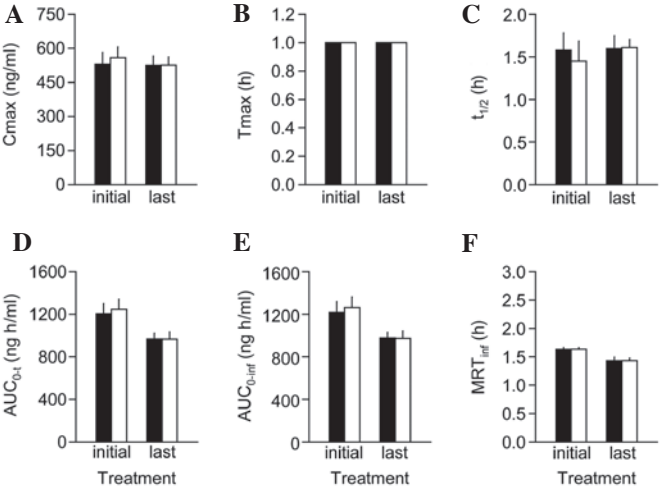

Figure 4. Pharmacokinetic profiles of perindopril in combination with Chungsinoryungsan at 2-h interval. The plasma samples used in Fig. 3 were subjected to analyses of pharmacokinetic parameters: (A) Peak concentration (C_{max}), (B) time to reach the C_{max} (T_{max}), (C) terminal half-life ($t_{1/2}$), (D) area under the perindopril concentration-time curve (AUC_{0-t}), (E) AUC zero to infinity (AUC_{0-inf}) and (F) mean residence time to infinity (MRT_{inf}). The corresponding data represent average values ± SEM in the combination group (white bars) and control (black bars) after the initial and last co-administration of repeated dosing for a week.

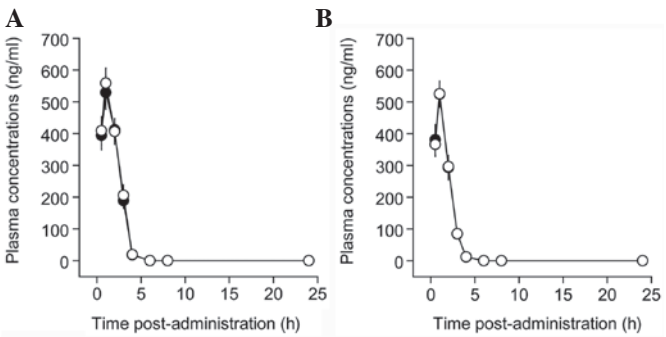

Figure 3. Plasma perindopril concentration in combination with Chungsinoryungsan (CSORS) at 2-h interval. The combination group received a repeated co-administration of perindopril in combination with CSORS for a week at 2-h interval (open circles, n=5) and the corresponding control received perindopril with distilled water (closed circles, n=5). The plasma samples were assessed at 0.5, 1, 2, 3, 4, 6, 8 and 24 h after (A) the initial and (B) last co-administration of the repeated dosing. All the data represent average values (ng/ml) ± SEM.

herbal products, except for digoxin (23,24). In the present study, single oral administration of perindopril combination with CSORS within 5 min markedly delayed the absorption of perindopril and its excretion, whereas the co-administration of the combination at a 2-h interval showed no interaction between perindopril and CSORS even by a weekly repeated dosing. Perindopril is well-absorbed in the gastrointestinal tract with a high bioavailability of 75% via the oral route (25), however, it is extensively metabolized to six metabolites, including perindoprilat, an active metabolite, in the liver (26,27). The maximal concentration of plasma perindoprilat is reached 2-6 h after oral administration of perindopril and 70% of perindoprilat is cleared by the kidneys. Food does not influence the rate or extent of perindopril absorption but reduces conversion to perindoprilat by ~35% (28). The present study results showed a T_{max} of 1 h in the control group, which had a similarity with that of humans (Figs 2B and 4B) (26). However, perindopril combination with CSORS within 5 min resulted in 2 h of T_{max}. Although the exact mechanism regarding how CSORS interacted with perindopril is unclear, it may be due to partial interruption of perindopril absorption by coexistence with CSORS or delayed conversion of perindopril to perindoprilat.

In the present study, CSORS had no interaction with perindopril in a weekly repeated co-administration at 2-h intervals, which indicates the suitable dosing regimen for the combination therapy. However, there are numerous clinical factors that alter perindopril pharmacokinetics. Since the active metabolites of perindopril are hydrolyzed in the liver and primarily excreted into the urine, the elimination kinetics can be altered in hepatic impairment (26,29), renal failure (30) or chronic heart failure (31). Ageing is also associated with the alteration in enhanced conversion to perindoprilat and the reduced renal clearance (32). Therefore, perindopril combination therapy requires further clinical studies for the pharmacokinetics in specific disease conditions. To the best of our knowledge, this is the first study to monitor the use of CSORS in combination with antihypertensive drugs. The results showed CSORS co-administration has limited interaction with perindopril at an interval that was more than mean residence time of perindopril. These results provide detailed information for a drug dosing regimen of perindopril with CSORS in human clinical studies of novel combination therapy.

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