Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl) butoxy]-3,4-dihydro-2(1H)-quinolinone) is an antiplatelet vasodilator agent that has been used for more than a decade in Japan for the treatment of chronic peripheral arterial occlusive disease (1). Cilostazol was also approved by the US Food and Drug Administration (FDA) in 1998 for the treatment of symptoms related to intermittent claudication (2). Cilostazol exerts its pharmacologic effects through selective inhibition of phosphodiesterase-3, which is abundant in platelets and vascular smooth muscle cells. These inhibitory effects mediate the antiplatelet properties of cilostazol and suppress vascular smooth muscle cell proliferation (3). Cilostazol is extensively metabolized primarily by the CYP3A4 enzymes into the active metabolites 3,4-dehydrocilostazol and 4’-trans-hydroxy-cilostazol (4-5). However, the effect of cilostazol on P-gp activity has not been reported. Therefore, we attempted to evaluate P-gp activity using the rhodamine-123 retention assay in P-gp-overexpressed MCF-7/ADR cells. Furthermore, we evaluated the effect of cilostazol on CYP2C9 activity.

EFFECTS OF CILOSTAZOL ON THE PHARMACOKINETICS OF CARVEDILOL AFTER ORAL AND INTRAVENOUS ADMINISTRATION IN RATS

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This study was designed to investigate the effects of cilostazol on the pharmacokinetics of carvedilol following oral or intravenous administration of carvedilol in rats. Clinically carvedilol and cilostazol can be prescribed for treatment of cardiovascular diseases. Carvedilol and cilostazol are all substrates of CYP2C9 enzymes. Carvedilol was administered orally or intravenously without or with oral administration of cilostazol to rats. The effects of cilostazol on cytochrome P450 (CYP) 2C9 activity and P-gp activity were also evaluated. Cilostazol inhibited CYP2C9 activity in a concentration-dependent manner with 50% inhibitory concentration (IC50) of 8.7 µM. Compared with the control group, the area under the plasma concentration-time curve (AUC) of carvedilol was significantly (P < 0.05) increased by 38.0%. The peak concentration (Cmax) was significantly (P < 0.05) increased by 49.2% in the presence of cilostazol after oral administration of carvedilol. Consequently, the relative bioavailability (R.B.) of carvedilol was increased by 1.15 – 1.38-fold, and the absolute bioavailability (A.B.) of carvedilol in the presence of cilostazol was significantly (P < 0.05) higher than that of the control. After intravenous administration, the AUC of carvedilol was significantly (P < 0.05) increased by 19.2% compared to that in the control by cilostazol. These results suggest that cilostazol effectively inhibited the metabolism of carvedilol. The increased oral bioavailability of carvedilol might be due to the inhibition of CYP2C9-mediated metabolism of carvedilol in the liver by cilostazol.

Key words: carvedilol, cilostazol, P-gp, pharmacokinetics, cytochrome P450 2C9, beta-adrenergic inhibitors

INTRODUCTION

Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl) butoxy]-3,4-dihydro-2(1H)-quinolinone) is an antiplatelet vasodilator agent that has been used for more than a decade in Japan for the treatment of chronic peripheral arterial occlusive disease (1). Cilostazol was also approved by the US Food and Drug Administration (FDA) in 1998 for the treatment of symptoms related to intermittent claudication (2). Cilostazol exerts its pharmacologic effects through selective inhibition of phosphodiesterase-3, which is abundant in platelets and vascular smooth muscle cells. These inhibitory effects mediate the antiplatelet properties of cilostazol and suppress vascular smooth muscle cell proliferation (3). Cilostazol is extensively metabolized primarily by the CYP3A4 enzymes into the active metabolites 3,4-dehydrocilostazol and 4’-trans-hydroxy-cilostazol (4-5). However, the effect of cilostazol on P-gp activity has not been reported. Therefore, we attempted to evaluate P-gp activity using the rhodamine-123 retention assay in P-gp-overexpressed MCF-7/ADR cells. Furthermore, we evaluated the effect of cilostazol on CYP2C9 activity.

Carvedilol is well absorbed from the gastrointestinal tract, but carvedilol is subject to considerable first-pass metabolism in the intestinal and/or liver (6-7). Carvedilol is more than 98% bound to plasma proteins. Carvedilol is metabolized by both oxidation and conjugation pathways in the liver into some metabolites (8-9). The oxidation pathways are mainly catalyzed by CYP2C9 enzymes in human (6, 7, 10) and then CYP2D6 is responsible for the formation of 4’-hydroxy carvedilol and 5’-hydroxy carvedilol, and both metabolites are excreted into urine (9).

Carvedilol is an arylethanolamine and has nonspecific β- and α1-adrenergic blocking effects (11). Carvedilol also reduces the release of endothelin and directly scavenges free radicals of oxygen (12). It is used to treat systemic arterial hypertension (13-16) and congestive heart failure (17-18) and is purported to improve exercise capacity (19-20) and longevity in humans (21). Since carvedilol is a substrate of both CYP2C9 enzymes and P-gp (22), the modulation of CYP enzyme activities may cause the significant changes in the pharmacokinetic profile of carvedilol.

Drug-drug interaction between carvedilol and cilostazol, antiplatelet vasodilator agent, is possibility, since they could be concomitantly prescribed for the prevention or treatment of cardiovascular diseases as a combination therapy. However, the effect of cilostazol on the pharmacokinetics of carvedilol in vivo has not been reported. Therefore, the present study aims to investigate the effect of cilostazol on the CYP2C9 activity and
P-gp activity. In addition, we investigated the effect of bioavailability and pharmacokinetics of carvedilol following oral and intravenous administration in rats.

MATERIAL AND METHODS

Chemicals and reagents

Carvedilol, cilostazol and nimodipine (an internal standard for high-performance liquid chromatograph (HPLC) analysis for carvedilol) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). HPLC grade acetonitrile was acquired from Merck Co. (Darmstadt, Germany). Rhodamine was obtained from Calbiochem (USA), and the CYP inhibition assay kit was obtained from Gentest Corp. (Woburn, MA, USA). Other chemicals used were of reagent or HPLC grade.

The apparatuses used in this study were a HPLC system equipped with a Waters 1515 isocratic HPLC Pump, a Waters 717 plus autosampler, a Waters® 474 scanning fluorescence detector (Waters Co., Milford, MA, USA), a HPLC column temperature controller (Phenomenex Inc., CA, USA), a Branson® Ultrasonic Cleaner (Branson Ultrasonic Co., Danbury, CT, USA), a vortex-mixer (Scientific Industries Co., NY, USA) and a high-speed micro centrifuge (Hitachi Co., Tokyo, Japan).

Animal experiments

Male Sprague-Dawley rats of 7 – 8 weeks of age (weighing 270 – 300 g) were purchased from the Dae Han Laboratory Animal Research Co. (Choongbuk, Republic of Korea). Animals allowed free access to a commercial rat chow diet (No. 322-7; Superfeed Co., Gangwon, Republic of Korea) and tap water ad libitum. The animals were housed (two rats per cage) in a clean room maintained at a temperature of 22 ± 2°C and relative humidity of 50 – 60%, with 12 h light and dark cycles. The rats were acclimated under these conditions for at least one week. All animal studies were performed in accordance with the “Guiding Principles in the Use of Animals in Toxicology” adopted by the Society of Toxicology (USA) and the Animal Care Committee of Chosun University (Gwangju, Republic of Korea) approved the protocol of this animal study. The rats were fasted for at least 24 hours prior to beginning the experiments and had free access to tap water. Each animal was anesthetized lightly with ether. The left femoral artery and vein were cannulated using polyethylene tubing (SP45, I.D. 0.58 mm, O.D. 0.96 mm; Natsume Seisakusho Co. LTD., Tokyo, Japan) for blood sampling and i.v. injection, respectively.

Oral and intravenous administration of carvedilol

The rats were divided into six groups (n = 6) as follows: oral groups administered 3 mg/kg of carvedilol dissolved in water (homogenized at 36°C for 30 min; 3.0 ml/kg) without (control) or with 1.5 or 6.0 mg/kg of oral cilostazol, and an i.v. group administered 1 mg/kg of carvedilol, dissolved in 0.9% NaCl solution (homogenized at 36°C for 30 min; 1.5 ml/kg) without (control) or with 0.1 or 0.4 mg/kg of oral cilostazol. Cilostazol was orally administered 30 min prior to oral or intravenous administration of carvedilol. Oral carvedilol was administered through a feeding tube, and carvedilol for i.v. administration was injected through the femoral vein within 0.5 min. Blood samples (0.5 ml) were collected into heparinized tubes from the femoral artery at 0, 0.1, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h after intravenous infusion and at 0, 0.1, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h after oral administration. Whole blood (approximately 1.2 ml) collected from untreated rats was infused via the femoral artery at 0.75, 4 and 8 h, respectively, to replace blood loss due to blood sampling. The blood samples were centrifuged (13,000 rpm, 5 min), and the plasma samples (0.2 ml) were stored at –40°C until HPLC analysis of carvedilol.

High-performance liquid chromatography assay

The plasma concentrations of carvedilol was determined by the HPLC assay method reported by Zarghi et al. (23). Briefly, 50 µl of dihydroergostine (20 µg/ml dissolved in methanol; an internal standard) and 0.5 ml of acetonitrile were added to a 0.2 ml aliquot of the plasma in a 2.0 ml polypropylene microtube. The mixture was then stirred for 10 min and centrifuged (13,000 rpm, 10 min). A 0.5 ml aliquot of the organic layer was transferred to a clean test tube and evaporated under a gentle stream of nitrogen gas at 35°C. The residue was reconstituted in a 150 µl of the mobile phase and centrifuged (13,000 rpm, 5 min). The resulting mixture was then vigorously vortex-mixed for 5 min and centrifuged at 13,000 rpm for 5 min. A 50-µl aliquot of the supernatant was injected into the HPLC system. Chromatographic separations were achieved using a Chromolith Performance (RP-18e, 100 mm × 4.6 mm) column from Merck (Darmstadt, Germany). The mobile phase consisted of 0.01 M disodium hydrogen phosphate (pH 3.5, adjusted with phosphoric acid)-acetonitrile (75:24.3: 0.7, v/v). The flow rate of the mobile phase was maintained at 2.0 ml/min. Chromatography was performed at 25°C, which was regulated by an HPLC column temperature controller. The fluorescence detector was operated at an excitation wavelength of 240 nm with an emission wavelength of 340 nm. The retention times at a flow rate of 2 ml/min were as follows: carvedilol at 8.076 min and internal standard at 9.305 min. The lower limit of quantification for carvedilol in rat plasma was 9 ng/ml. The coefficient of the variation of carvedilol was less than 11.3%.

CYP 2C9 inhibition assay

The inhibition assay on the human CYP2C9 enzyme activity was performed in a multwell plate using CYP inhibition assay kit (GENTEST, Woburn, MA) as described previously by Crespi (24). Briefly, human CYP enzyme was obtained from baculovirus-infect host cells. The CYP substrate (7-methoxytrifluoromethyl coumarin (MFC) for CYP2C9) was incubated with or without the test compounds in the enzyme/substrate buffer with 1.0 pmol of P450 enzyme and an NADPH-generating system (1.3 mM NADP, 3.54 mM glucose 6-phosphate, 0.4 U ml⁻¹ glucose 6-phosphate dehydrogenase and 3.3 mM MgCl₂) in potassium phosphate buffer (pH 7.4). Reactions were terminated by adding 75 µl stop solution after incubation for 45 min. Metabolite concentrations were measured by spectrophotometer (Molecular Device, Sunnyvale, CA) at an excitation wavelength of 409 nm and an emission wavelength of 530 nm. The positive control (1 µM sulfaphenazole for CYP2C9) was run on the same plate and produced 99% inhibition. All experiments were done in duplicate, and the results were expressed as a percentage inhibition.

Rhodamine-123 retention assay

The procedures used for the rhodamine-123 retention assay were similar to previously reported methods (25). The MCF-7/ADR cells were seeded in 24-well plates. At 80% confluence, the cells were incubated in fetal bovine serum (FBS)-free Dulbeccos modified eagles medium (DMEM) for 18 h. The culture medium was changed to Hanks’ balanced salt solution (HBSS) and the cells were incubated at 37°C for 30 min. After
incubation of the cells with 20 µM rhodamine-123 in the presence or absence of cilostazol (10, 30 and 100 µM) and verapamil (positive control) for 90 min, the medium was completely removed. The cells were then washed three times with ice-cold phosphate buffer (pH 7.0) and lysed in EBC lysis buffer. Rhodamine-123 fluorescence in the cell lysates was measured using excitation and emission wavelengths of 480 and 540 nm, respectively. Fluorescence values were normalized to the total protein content of each sample and were presented as a ratio to control.

Pharmacokinetic analysis

The plasma concentration data were analyzed by the noncompartmental method using WinNonlin software version 4.1 (Pharsight Co., Mountain View, CA, USA). The elimination rate constant (Kel) was calculated by log-linear regression of carvedilol concentration data during the elimination phase, and the terminal half-life (t1/2) was calculated by 0.693/Kel. The peak concentration (Cmax) and the time to reach peak concentration (Tmax) of carvedilol were obtained by visual inspection of the concentration-time curve. The area under the plasma concentration-time curve (AUC0–t) from time zero to the time of last measured concentration (Clast) was calculated by the linear trapezoidal rule. The AUC zero to infinity (AUC0–∞) was obtained by the addition of AUC0–t and the extrapolated area determined by Clast/Kel. Total body clearance (CL/F) was calculated by Dose/AUC. The absolute bioavailability (A.B.) of carvedilol was calculated by AUC0–∞,oral/AUC0–∞,iv×Doseiv/Doseoral×100, and the relative bioavailability (R.B.) of carvedilol was estimated by AUC0–∞,with cilostazol/AUC0–∞,control×100.

Statistical analysis

The data are presented as the mean ± standard deviation (S.D.). The pharmacokinetic parameters were compared using a one-way analysis of variance (ANOVA), followed by a posteriori test with the Dunnett correction. A P value of < 0.05 was considered statistically significant.

RESULTS

Effect of cilostazol on the CYP2C9 activity

The inhibitory effect of cilostazol on CYP2C9 activity is shown in Fig. 1. Cilostazol inhibited CYP2C9 activity in a concentration-dependent manner, and the 50% inhibition concentration (IC50) values of cilostazol on CYP2C9 activity was 8.7 µM. Sulfaphenazole inhibited CYP2C9 activity with IC50 of 0.78 µM.

Effect of cilostazol on the P-gp activity

As shown in Fig. 2, the accumulation of rhodamine-123, a P-gp substrate, was not raised in MCF-7/ADR cells overexpressing P-gp compared to that in MCF-7 cells lacking P-gp. The concurrent use of cilostazol did not enhance the cellular uptake of rhodamine-123 in a concentration-dependent manner ranging from 3 – 30 µM. This result suggested that cilostazol could not inhibit P-gp activity.

Effects of cilostazol on the pharmacokinetics of oral carvedilol

The mean plasma concentration-time profiles of oral carvedilol in the presence or absence of cilostazol are also summarized in Table 1. The AUC of carvedilol was significantly (6 mg/kg, P < 0.05) increased by 38.0%, and the Cmax was significantly (6 mg/kg, P < 0.05) increased by 49.2% in the presence of cilostazol after oral administration of carvedilol. Consequently, the relative bioavailability of carvedilol was increased by 1.15 – 1.38-fold, and the absolute bioavailability of carvedilol in the presence of cilostazol was significantly (6 mg/kg, P < 0.05) higher (16.5%) than that of the control. However, there was no significant changes in the half-life (t1/2) and Tmax of carvedilol in the presence of cilostazol.

Effects of cilostazol on the pharmacokinetics of intravenous carvedilol

The mean plasma concentration-time profiles of i.v. carvedilol in the presence or absence of cilostazol are illustrated in Fig. 4. The mean pharmacokinetic parameters of carvedilol are also summarized in Table 2. The AUC of carvedilol was significantly (6
mg/kg, \( P < 0.05 \)) increased by 19.2% in the presence of cilostazol, this result suggested that cilostazol might inhibit metabolism of carvedilol in the intestine and/or in the liver. The increased bioavailability of carvedilol might be mainly due to inhibition of CYP2C9-mediated metabolism of carvedilol in the liver rather than inhibition of P-gp-mediated efflux by cilostazol.

**DISCUSSION**

CYPs enzymes contribute significantly to the first-pass metabolism and oral bioavailability of many drugs. Moreover, inhibition or induction of intestinal CYPs may be responsible for significant drug interactions which one agent decreases or
increases the bioavailability and absorption of a concurrently administered drug (26).

Therefore, inhibitors of CYP2C9 activity should have a great impact on the bioavailability of many drugs which is substrate of CYP2C9. Since carvedilol is a substrate of CYP2C9 enzymes (25), the modulation of CYP enzyme activities may cause the significant changes in the pharmacokinetic profile of carvedilol.

Clinically carvedilol and cilostazol can be prescribed for treatment of cardiovascular diseases. However, pharmacokinetic interaction between cilostazol and carvedilol has not been reported in vivo. Therefore, the present study aims to investigate the effect of cilostazol on the CYP2C9 activity and pharmacokinetics of carvedilol after oral and intravenous administration in rats.

The inhibitory effect of cilostazol on CYP2C9-mediated metabolism was confirmed by the employment of recombinant CYP2C9 enzyme. As shown in Fig. 1, cilostazol exhibited inhibitory effect on CYP2C9 activity with IC$_{50}$ of 8.7 µM.

**Table 1.** Mean (± S.D.) pharmacokinetic parameters of carvedilol after oral administration of carvedilol (3 mg/kg) in the presence or absence of cilostazol to rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (1.5 mg/kg)</th>
<th>Carvedilol + cilostazol (6 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng·h/ml)</td>
<td>1.590 ± 284</td>
<td>1.831 ± 342</td>
</tr>
<tr>
<td>C$_{max}$ (ng/ml)</td>
<td>130 ± 22</td>
<td>145 ± 27</td>
</tr>
<tr>
<td>T$_{max}$ (h)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>t$_{1/2}$ (h)</td>
<td>10.3 ± 2.0</td>
<td>10.6 ± 2.2</td>
</tr>
<tr>
<td>A.B. (%)</td>
<td>27.5 ± 3.8</td>
<td>28.8 ± 3.9</td>
</tr>
<tr>
<td>R.B. (%)</td>
<td>100</td>
<td>115</td>
</tr>
</tbody>
</table>

Mean ± S.D. (n = 6), * P < 0.05, significant difference compared to the control.

AUC: area under the plasma concentration-time curve from 0 h to infinity; C$_{max}$: peak plasma concentration; T$_{max}$: time to reach peak concentration; t$_{1/2}$: terminal half-life; A.B.: absolute bioavailability; R.B.: relative bioavailability compared to the control group.

**Table 2.** Mean (± S.D.) pharmacokinetic parameters of carvedilol after intravenous administration of carvedilol (1 mg/kg) in the presence or absence of cilostazol to rats.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control (1.5 mg/kg)</th>
<th>Carvedilol + cilostazol (6 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng·h/ml)</td>
<td>1.920 ± 215</td>
<td>2.131 ± 228</td>
</tr>
<tr>
<td>CL$_t$ (ml/min/kg)</td>
<td>523 ± 130</td>
<td>492 ± 125</td>
</tr>
<tr>
<td>t$_{1/2}$ (h)</td>
<td>7.9 ± 1.6</td>
<td>8.0 ± 1.7</td>
</tr>
<tr>
<td>R.B. (%)</td>
<td>100</td>
<td>111</td>
</tr>
</tbody>
</table>

Mean ± S.D. (n = 6), * P < 0.05, significant difference compared to the control.

AUC: area under the plasma concentration-time curve from 0 h to infinity; t$_{1/2}$: terminal half-life, R.B. (%): relative bioavailability compared to the control group.
Sulfaphenazole inhibited CYP2C9 activity with IC\(_{50}\) of 0.78 µM. The inhibitory effect of cilostazol (IC\(_{50}\) = 8.7 µM) on CYP2C9 is weaker than that of sulfaphenazole (IC\(_{50}\) = 0.78 µM) externally. In general, when inhibitory effect (IC\(_{50}\)) of CYP2C9 is below 25 µM, bioavailability (AUC) of a CYP2C9 substrate is weaker than that of sulfaphenazole (IC\(_{50}\) = 0.78 µM).

Therefore, the pharmacokinetic characteristics of carvedilol were evaluated in the absence and presence of cilostazol in rats. There are some papers that the results obtained in vivo in rats could be extrapolated on human from results obtained in vitro with human CYP3A4 and CYP3A4 and P-gp. Human CYP2C9 and 3A4 and rat CYP2C11 and 3A4 have 77 and 73% protein homology, respectively (31-33). As CYP3A9 expressed in rat corresponds to the ortholog of CYP3A4 in human (34-35), and rat CYP3A2 is similar to human CYP3A4 (36).

As shown in Fig. 2, accumulation of rhodamine-123, a P-gp substrate, was not raised in MCF-7/ADR cells overexpressing P-gp compared to that in MCF-7 cells lacking P-gp. The concurrent use of cilostazol did not enhance the cellular uptake of rhodamine-123 in a concentration-dependent manner ranging from 3 – 30 µM. This result suggested that cilostazol could not inhibit P-gp activity. When it comes to review the inhibition of P-gp activity, inhibitors of P-gp was performed generally to compare with verapamil 100 µmol/L, standard index of P-gp activity, inhibition of P-gp compared to that in MCF-7 cells lacking P-gp. These results were consistent with previous report (27-28) showing that ticlopidine and glipizide significantly increased the AUC and C\(_{\text{max}}\) of carvedilol, a substrate for CYP2C9.

Rats were selected as an animal model in this study to evaluate the potential pharmacokinetic interactions mediated by CYP2C9, although there may be some difference in enzyme activity between rat and human (37). The AUC was significantly increased by 38.0%, and the C\(_{\text{max}}\) was significantly increased by 49.2% in the presence of cilostazol after oral administration of carvedilol. Consequently, the relative bioavailability (R.B.) of carvedilol was increased by 1.15 – 1.38-fold, and the absolute bioavailability (A.B.) of carvedilol was significantly increased. These results were consistent with previous report (27-28) showing that ticlopidine and glipizide significantly increased the AUC and C\(_{\text{max}}\) of carvedilol, a substrate for CYP2C9.

Studies on drug interactions with grapefruit juice have provided much understanding of the role of intestinal CYP450 in the absorption of orally administered drugs. CYP2C9 is the predominant P450 present in the small intestine (38). After intravenous administration of carvedilole, the AUC of carvedilol was significantly (6 mg/kg, P \(<\) 0.05) increased by 19.2% in the presence of cilostazol, which suggested that cilostazol may inhibit metabolism of carvedilol in the liver. These results were not consistent with previous report (27-29) showing that ticlopidine, glipizide and licochalcone A did not significantly change the pharmacokinetic parameters of intravenous administration of carvedilol and nifedipine.

The increased bioavailability of carvedilol might be mainly due to inhibition of CYP2C9-mediated metabolism of carvedilol in the liver by cilostazol. Therefore, concomitant use of cilostazol with carvedilol will require close monitoring for potential adverse interactions such as hepatotoxicity or puritus by carvedilol (39) and hyper-sensitivity reaction or photosensitivity by cilostazol (40) in the therapy of cardiovascular diseases. The increased bioavailability of carvedilol might be mainly due to inhibition of CYP2C9-mediated metabolism of carvedilol in the liver by cilostazol.

Abbreviations: A.B. (%): absolute bioavailability; AUC: area under the plasma concentration-time curve from 0 h to infinity; C\(_{\text{max}}\): peak plasma concentration; CL\(_{\text{e}}\): total body clearance; HPLC: high-performance liquid chromatograph; IC\(_{50}\): 50% inhibitory concentration; R.B. (%): relative bioavailability compared to the control group; t\(_{1/2}\): terminal half-life; T\(_{\text{max}}\): time to reach peak concentration; R.B. (%): relative bioavailability compared to the control group.

Conflict of interests: Non declared.

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Received: January 13, 2015
Accepted: June 2, 2015

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