Simultaneous quantification of vortioxetine, carvedilol and its active metabolite 4-hydroxyphenyl carvedilol in rat plasma by UPLC–MS/MS: Application to their pharmacokinetic interaction study

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A B S T R A C T

To establish a rapid and sensitive ultra performance liquid chromatography tandem mass spectrometry (UPLC–MS/MS) method for the determination of vortioxetine, carvedilol and its metabolite 4-hydroxyphenyl carvedilol in rat plasma. The analytes and the internal standard (diazepam) were separated on an Acquity UPLC BEH C18 chromatography column (2.1 mm × 50 mm, 1.7 μm) using gradient elution with a mobile phase of acetonitrile and 0.1% formic acid in water at a flow rate of 0.4 mL/min. The detection was performed on a triple quadrupole tandem mass spectrometer by multiple reaction monitoring (MRM) mode to monitor the precursor-to-product ion transitions of m/z 299.2 → 150.1 for vortioxetine, m/z 407.2 → 100.3 for carvedilol, m/z 423.2 → 100.1 for 4-hydroxyphenyl carvedilol and m/z 285.2 → 193.1 for diazepam (IS) using a positive electrospray ionization interface. The method was validated over a concentration range of 0.5–100 ng/mL for vortioxetine, 0.5–1000 ng/mL for carvedilol and 0.1–50 ng/mL for 4-hydroxyphenyl carvedilol. Total time for each chromatograph was 3.0 min. The intra- and inter-day precision and accuracy of the quality control samples at low, medium, and high concentrations exhibited relative standard deviations (RSD) < 11.6% and the accuracy values ranged from −12.2% to 11.3%. The analytical method was successfully applied to a pharmacokinetic interaction study of vortioxetine and carvedilol after oral administration vortioxetine and carvedilol in rats. Results suggested that the co-administration of vortioxetine and carvedilol results in a significant drug interaction in rats.

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1. Introduction

Vortioxetine (Fig. 1A) is a novel antidepressant approved in the USA and EU for the treatment of major depressive disorder [1]. In clinical studies, the commonly reported adverse effects were nausea, dry mouth, diarrhea, headache, dizziness, somnolence and nasopharyngitis [2–4]. Vortioxetine has been shown to be a substrate for several of the CYP450 isozymes in clinical studies, although no effect with CYP2C19 was observed [5]. No inducing or inhibitory effect on CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 has been seen [6]. No pharmacodynamic interactions with aspirin or oral contraceptives were observed [7,8]. However, clinical drug–drug interaction studies in healthy individuals have shown that co-administration of bupropion (CYP2D6 inhibitor) increased the exposure of vortioxetine approximately 2-fold [9].

Carvedilol (Fig. 1B) is an antihypertensive and antianginal compound which combines nonselective β-adrenoceptor blocking and vasodilator properties with intrinsic sympathomimetic activity [10]. The oxidation pathway of carvedilol is mainly catalyzed by CYP2C9 and CYP2D6 enzymes in human being, and then CYP2D6 is responsible for the formation of its metabolite 4-hydroxyphenyl carvedilol [11]. CYP2D6 polymorphisms have been shown to cause variation in carvedilol pharmacokinetics [12–14]. CYP450 pathway is important for the oxidative metabolism of various drugs and therefore implicated in drug–drug interactions [15,16]. Such interactions are a major cause of adverse events
with pharmacotherapy [17]. Therefore, the identification and quantification of these interactions in vivo is important for avoiding or minimizing the interaction-induced adverse events associated with specific drug combinations. When vortioxetine and carvedilol are used in combination in clinic, they may have many potential drug interactions as they are all CYP2D6 substrates. It is therefore necessary to perform a study to compare the pharmacokinetics of vortioxetine and carvedilol in rats when being administered orally alone or being co-administered. To best of our knowledge, there is only one LC–MS/MS method reported for the quantification of vortioxetine in plasma [18]. Many methods for the determination of carvedilol and its active metabolite 4-hydroxyphenyl carvedilol in biological fluids by LC–MS/MS have been reported [19–21]. However, reports describing an LC–MS/MS-based method for simultaneous determination of vortioxetine, carvedilol and its active metabolite in plasma are not available.

In this paper, an ultra performance liquid chromatography-tandem mass spectrometry (UPLC–MS/MS) method was developed to determine the concentrations of vortioxetine, carvedilol and its active metabolite 4-hydroxyphenyl carvedilol in rat plasma and pharmacokinetic interaction between them was studied to provide some suggestion for clinical practice.

2. Materials and methods

2.1. Chemicals materials

Vortioxetine (purity > 98.0%), carvedilol (purity > 98.0%), 4-hydroxyphenyl carvedilol (purity > 98.0%) and diazepam (internal standard, IS, purity > 98.0%) were obtained from Sigma (St. Louis, MO, USA). Acetonitrile and methanol were HPLC grade and purchased from Merck Company (Darmstadt, Germany). HPLC grade water was obtained using a Milli Q system (Millipore, Bedford, USA).

2.2. UPLC–MS/MS conditions

Liquid chromatography was performed on an Acquity ultra performance liquid chromatography (UPLC) unit (Waters Corp., Milford, MA, USA) with an Acquity BEH C18 column (2.1 mm × 50 mm, 1.7 μm) and inline 0.2 μm stainless steel frit filter (Waters Corp., Milford, MA, USA). A gradient elution program was conducted for chromatographic separation with mobile phase A (acetonitrile), and mobile phase B (0.1% formic acid) as follows: 0–1.0 min (10–95% A), 1.0–1.9 min (95–95% A), 1.9–2.0 min (95–10% A), 2.0–3.0 min (10–10% A). The flow rate was 0.40 mL/min. The overall run time was 3.0 min. A XEVO TQD triple quadrupole mass spectrometer equipped with an electrospray ionization (ESI) source (Waters Corp., Milford, MA, USA) was used for mass spectrometric detection. The detection was operated in the multiple reaction monitoring (MRM) mode under unit mass resolution in the mass analyzers. The MRM transitions were m/z 299.2 → 150.1 for vortioxetine, m/z 407.2 → 100.3 for carvedilol, m/z 423.2 → 100.1 for 4-hydroxyphenyl carvedilol and m/z 285.2 → 193.1 for IS, respectively. Mass spectrometry was operated with the capillary voltage set at 2.50 kV, the cone and source offset set at 35 and 50 V, respectively. The desolvation temperature and desolvation gas flow rate set at 500 °C and 600 L/h, respectively. And argon flow rate and collision set at 150 L/h and 7.0 bar, respectively. The Masslynx 4.1 software (Waters Corp., Milford, MA, USA) was used for data acquisition and instrument control.

2.3. Standard solutions, calibration standards and quality control (QC) sample

Stock solutions of vortioxetine, carvedilol, 4-hydroxyphenyl carvedilol and IS were prepared in methanol at 1 mg/mL and stored at 4 °C. The working solutions for the calibration standards containing vortioxetine, carvedilol and 4-hydroxyphenyl carvedilol were prepared by dilution of the stock solution with methanol. Calibration standards in rat plasma were prepared by diluting the corresponding working solutions with blank plasma samples at the following concentrations: 0.5, 1.0, 2.5, 5.0, 10, 25, 50, 100 ng/mL for vortioxetine, 0.5, 1.0, 5.0, 10, 50, 100, 500, 1000 ng/mL for carvedilol, and 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 10, 50 ng/mL for 4-hydroxyphenyl carvedilol, respectively. The working solutions for the quality control (QC) samples were prepared at the following concentrations: 1.0, 8.0, 80 ng/mL for vortioxetine, 1.0, 80, 800 ng/mL for carvedilol, and 0.2, 2.0, 40 ng/mL for 4-hydroxyphenyl carvedilol, respectively. All stock solutions,
working solutions, calibration standards and QCs were immediately stored at −20 °C.

2.4. Sample preparation

Before analysis, frozen plasma sample was thawed to room temperature. In a 1.5 mL centrifuge tube, an aliquot of 200 μL of the internal standard working solution (100 ng/mL) was added to 0.1 mL of plasma sample. The tubes were vortex mixed for 1.0 min. After centrifugation at 13,000g for 10 min, the supernatant (2 μL) was injected into the UPLC–MS/MS system for analysis.

2.5. Method validation

Method validation was performed to evaluate the specificity, linearity, sensitivity, accuracy and precision and matrix effect according to the “Guidance for Industry–Bioanalytical Method Validation,” recommended by the US Food and Drug Administration [22].
Table 1
Intra- and Inter-day accuracies and precisions of vortioxetine, carvedilol and 4-hydroxyphenyl carvedilol in rat plasma (n=6).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Concentration (ng/mL)</th>
<th>Intra-day</th>
<th>Inter-day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RSD%</td>
<td>RE%</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>1.0</td>
<td>8.3</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>5.9</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>2.6</td>
<td>3.3</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>0.1</td>
<td>6.0</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>6.1</td>
<td>−6.4</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>3.0</td>
<td>3.7</td>
</tr>
<tr>
<td>4-hydroxyphenyl carvedilol</td>
<td>0.2</td>
<td>8.7</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>5.5</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>3.2</td>
<td>−3.0</td>
</tr>
</tbody>
</table>

2.5.1. Selectivity
Selectivity was evaluated using six independent blank rat plasma. Chromatograms of these blank samples were compared with the corresponding spiked plasma for the test of endogenous interferences.

2.5.2. Linearity of calibration curve and lower limit of quantification
Calibration curves were constructed at 0.5–100 ng/mL for vortioxetine, 0.5–1000 ng/mL for carvedilol, and 0.1–50 ng/mL for 4-hydroxyphenyl carvedilol, pretreated in duplicate and analyzed in three consecutive runs. The calibration curves were fitted using a weighted (1/x^2) least-squares linear regression method by measuring the peak-area ratio of the analytes to the IS. Concentrations of QC samples and study samples were calculated in accordance with the calibration curves. The acceptance criterion for each back-calculated standard concentration was ± 15% deviation from the nominal value, except for the lower limit of quantification (LLOQ), for which a deviation of ± 20% was permitted.

2.5.3. Precision and accuracy
The precision and accuracy of the assay were determined by analysis of the QC samples. The intra-day precision and accuracy were evaluated by analysis of six replicates QC samples at low, medium, and high concentration levels within one day. The inter-day precision and accuracy were assessed by repeating the analysis.
of three concentration levels of QC samples on six consecutive days. The accuracy was required to be within ±15% and the intra- and inter-day precision values were not to exceed 15%.

2.5.4. Extraction recovery and matrix effect

The recoveries of vortioxetine, carvedilol and 4-hydroxyphenyl carvedilol from plasma were calculated by comparing the peak area of extracted three levels QC samples to that of the analytes spiked to the blank sample extracts at the same concentration. The recoveries of the compounds in rat plasma were examined at least six times. The matrix effects were evaluated through comparison of the peak areas obtained from samples where the extracted matrix was spiked with standard solutions to those obtained from the pure reference standard solution at equivalent concentrations.

2.5.5. Stability

The stability of the analytes in rat plasma were assessed by analyzing replicates (n = 5) of QC samples at the low, medium, and high concentrations. The samples were exposed to different conditions (time and temperature). The spiked plasma samples were analyzed after storage at room temperature for 2 h, in an autosampler for 24 h at ambient temperature after protein precipitation, at −20 °C for 35 days and after three freeze-thaw cycles from −20 °C to room temperature. The analytes were considered to be stable in plasma when 85–115% of the initial concentrations were found.

2.6. Pharmacokinetic study

Male Sprague-Dawley rats (180–220 g) were obtained from Laboratory Animal Center of Wenzhou Medical University (Wenzhou, China) used to study the pharmacokinetic interaction of vortioxetine and carvedilol. All experimental procedures and protocols were reviewed and approved by the Animal Care and Use Committee of Wenzhou Medical University and were in accordance with the Guide for the Care and Use of Laboratory Animals. Diet was prohibited for 12 h before the experiment but water was freely available. Rats were randomly divided into three groups (n = 6/group). Rats in Group 1 were orally administered vortioxetine (4.0 mg/kg); rats in Group 2 were given carvedilol (6.0 mg/kg) and rats in Group 3 were given vortioxetine (4.0 mg/kg) plus carvedilol (6.0 mg/kg). Blood samples (0.3 mL) were collected from the tail vein into heparinized 1.5 mL polyethylene tubes at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h after oral administration, respectively. The samples were immediately centrifuged at 4000 g for 8 min. The plasma obtained (100 µL) was stored at −20 °C until analysis.

Plasma concentration versus time data for each rat was analyzed by DAS (Drug and statistics) software (Version 2.0, Shanghai University of Traditional Chinese Medicine, China). Statistical analysis was computed using SPSS 13.0 software. Data were expressed as mean ± SD. Statistically significant differences of data from two sets were compared using one-way analysis of variance. In all statistical analyses, P < 0.05 or P < 0.01 was considered to indicate a statistically significant result.

3. Results and discussion

3.1. Method development and optimization

Liquid-liquid, solid phase extraction (SPE) and protein precipitation (PPT) are the most commonly used sample preparation techniques. With the emergence of UPLC technology combined

### Table 2
Stability results of vortioxetine, carvedilol and 4-hydroxyphenyl carvedilol in rat plasma in different conditions (n = 5).

<table>
<thead>
<tr>
<th>Analytes</th>
<th>Concentration (ng/mL)</th>
<th>Remaining (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Room temperature, 2 h</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>1.0</td>
<td>105.6</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
<td>95.7</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>98.9</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>108.1</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>80</td>
<td>103.2</td>
</tr>
<tr>
<td></td>
<td>800</td>
<td>107.8</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>94.4</td>
</tr>
<tr>
<td>4-hydroxyphenyl carvedilol</td>
<td>40</td>
<td>101.7</td>
</tr>
</tbody>
</table>

** Significantly different from control, P < 0.01.

### Table 3
The pharmacokinetic parameters of vortioxetine in rat plasma after oral administration of 4.0 mg/kg vortioxetine alone or in combination with 6.0 mg/kg carvedilol (n = 6, Mean ± SD).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Vortioxetine</th>
<th>Vortioxetine + Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2 (h)</td>
<td>1.99 ± 0.24</td>
<td>1.86 ± 0.27</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.20 ± 0.45</td>
<td>0.95 ± 0.11</td>
</tr>
<tr>
<td>CL/F (L/h/kg)</td>
<td>36.56 ± 6.69</td>
<td>20.08 ± 4.33*</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>26.91 ± 4.28</td>
<td>55.72 ± 8.26*</td>
</tr>
<tr>
<td>AUC0-24h (ng/mL*H)</td>
<td>122.1 ± 48.4</td>
<td>223.61 ± 73.4*</td>
</tr>
<tr>
<td>AUC0-∞ (ng/mL*H)</td>
<td>125.7 ± 50.4</td>
<td>225.90 ± 74.9*</td>
</tr>
</tbody>
</table>

** Significantly different from control, P < 0.01.

### Table 4
The pharmacokinetic parameters of carvedilol and 4-hydroxyphenyl carvedilol in rat plasma after oral administration of 6.0 mg/kg carvedilol alone or in combination with 4.0 mg/kg vortioxetine (n = 6, Mean ± SD).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Carvedilol</th>
<th>Vortioxetine + Carvedilol</th>
<th>4-hydroxyphenyl carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2 (h)</td>
<td>1.99 ± 0.11</td>
<td>3.86 ± 0.14*</td>
<td>2.45 ± 0.45</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.60 ± 0.22</td>
<td>0.75 ± 0.18*</td>
<td>0.50 ± 0.10</td>
</tr>
<tr>
<td>CL/F (L/h/kg)</td>
<td>3.76 ± 0.43</td>
<td>2.81 ± 0.13*</td>
<td>93.49 ± 7.82</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>433.40 ± 33.04</td>
<td>829.84 ± 73.80*</td>
<td>20.17 ± 3.05</td>
</tr>
<tr>
<td>AUC0-24h (ng/mL*H)</td>
<td>1607.2 ± 173.4</td>
<td>2326.0 ± 215.4</td>
<td>64.0 ± 4.5</td>
</tr>
<tr>
<td>AUC0-∞ (ng/mL*H)</td>
<td>1611.1 ± 177.5</td>
<td>2352.0 ± 239.7*</td>
<td>64.5 ± 5.1</td>
</tr>
</tbody>
</table>

* Significantly different from control, P < 0.05.

** Significantly different from control, P < 0.01.
with high sensitive tandem mass spectroscopy, it is possible to quantify analytes at a low concentration without having a high extraction recovery, provided that the recovery remains constant over time and concentration. With time-saving advantage and simplicity, PPT was used for sample preparation because it is a simple, easy, and rapid sample clean-up procedure. Extraction of analytes and IS from various tissues was achieved using different organic solvents such as methanol, methanol/water, acetonitrile, and acetonitrile/water. The test results showed that acetonitrile yielded higher analytes recovery than other solvents. High extraction efficiency was obtained using acetonitrile, so it was selected as the extraction solvent.

To obtain chromatograms with optimal resolution and symmetrical peaks, we investigated the use of different solutions of acetonitrile in water and methanol in water as mobile phases, with or without 0.1% formic acid, for binary isocratic and gradient elutions. A gradient mobile phase consisting of 0.1% formic acid in water and acetonitrile achieved good separation and symmetrical peaks. No interference was observed at the retention times for the analytes and IS. Typical chromatograms of blank plasma, plasma spiked with the analytes and IS, and plasma with the IS are shown in Fig. 2.

3.2. Method validation

3.2.1. Selectivity

As shown in Fig. 2, there are no significant interference from rat plasma observed at the retention times of the analytes and IS. The retention time of vortioxetine, carvedilol, 4-hydroxyphenyl carvedilol and IS was 1.61, 1.51, 1.41, and 1.78 min, respectively.

3.2.2. Linearity of calibration curve and LLOQ

The calibration curve was linear over the concentration range of 0.5–100 ng/mL for vortioxetine, 0.5–1000 ng/mL for carvedilol, and 0.1–50 ng/mL for 4-hydroxyphenyl carvedilol, respectively. The regression equations obtained by least square regression were 

\[ Y = (2.4784 \pm 0.1131) \times X + (0.6382 \pm 0.0144) \]  
\[ r^2 = 0.998 \]

for vortioxetine, 

\[ Y = (4.6760 \pm 0.2876) \times X + (2.0233 \pm 0.0830) \]  
\[ r^2 = 0.999 \]

for carvedilol and 

\[ Y = (0.1188 \pm 0.0051) \times X + (0.0169 \pm 0.0008) \]  
\[ r^2 = 0.996 \]

for 4-hydroxyphenyl carvedilol, where \( Y \) represents the peak-area ratio of an analytic to IS and \( X \) represents the plasma concentration of the analytic. The observed deviations were within ±15% for all calibration concentrations. The lower limit of quantification (LLOQ) was established as 0.5 ng/mL for both vortioxetine and carvedilol, 0.10 ng/mL for 4-hydroxyphenyl carvedilol. In the present study, the precision and accuracy of LLOQ were acceptable, with RSD values < 6.3% and RE values within 7.5% for the analytes.

3.2.3. Precision and accuracy

The accuracies and intra- and inter-day precisions were expressed in Table 1. The accuracies (RE%) of low, medium, and high QC levels of the analytes were within ±12.2%. The intra- and inter-day precisions (RSD%) of the analytes ranged from 2.6 to 11.6%, which were within the acceptable limits. The results indicated that the present method was reliable and reproducible for the simultaneous quantitative analysis of vortioxetine, carvedilol and 4-hydroxyphenyl carvedilol in rat plasma samples.

3.2.4. Recovery and matrix effect

The mean recoveries of all the analytes ranged from 94.6% to 91.1% across the concentration range. In addition, the mean recovery of the IS was 87.9%. The average matrix effects of all analytes ranged from 90.2% to 110.6% over their corresponding concentration ranges. Moreover, the matrix effects of the IS was 103.3%. These data indicated that ion suppression or enhancement from the rat plasma was negligible under the current conditions.

3.2.5. Stability

The stability of the analytes was investigated at three concentrations under a variety of storage and process conditions. All established stability for the analytes were summarized in Table 2. The data showed that the stability of QC samples at room temperature for 2 h, 24 h in the auto-sampler (4 °C), three freeze-thaw cycles (at −20 to 20 °C) and long-term storage in freezer (35 days at −20 °C) was acceptable.

3.3. Pharmacokinetic interaction between vortioxetine and carvedilol study

A rapid and efficient UPLC–MS/MS method has been widely used in biological and medical research, biological analysis, food safety, environmental monitoring and forensic examination [23–25]. This experiment is first time to use UPLC–MS/MS method to determine the concentration of vortioxetine, carvedilol and 4-hydroxyphenyl carvedilol in rat plasma and its application to a pharmacokinetic interaction study.

The mean plasma concentration-time profiles of vortioxetine were shown in Fig. 3, and the main relevant pharmacokinetic parameters from non-compartment model analysis were listed in Table 3. After co-administration of vortioxetine and carvedilol in Group 3, \( C_{\text{max}} \) and AUC\(_{0\rightarrow\infty}\) of vortioxetine were significantly increased by 107.1% and 79.7%, respectively, when compared with that in Group 1; whereas CL/F was significantly decreased by 45.1% compared with that in Group 1. On the other hand, there were no significant differences in \( t_{1/2} \) and \( T_{\text{max}} \) of vortioxetine between Group 1 and Group 3.

In addition, the mean plasma concentration-time curves of carvedilol and its metabolite 4-hydroxyphenyl were illustrated in Fig. 4, and the main relevant pharmacokinetic parameters were listed in Table 4. Plasma carvedilol and 4-hydroxyphenyl carvedilol concentration in Group 3 were significantly higher than those in Group 2. Moreover, parameters \( C_{\text{max}} \) and AUC\(_{0\rightarrow\infty}\) of carvedilol and 4-hydroxyphenyl carvedilol were significantly increased in Group 3 compared with that in Group 2, indicating that vortioxetine could promote the absorption of carvedilol and 4-hydroxyphenyl carvedilol. These results showed that the pharmacokinetics of vortioxetine and carvedilol changed when being co-administered.

4. Conclusions

A sensitive and simple UPLC–MS/MS method for simultaneous measurement of vortioxetine, carvedilol and its metabolite 4-hydroxyphenyl carvedilol in rat plasma has been developed and validated. The method was found to be accurate, precise and specific, and was successfully applied to the pharmacokinetic interaction investigation of vortioxetine and carvedilol in rats. Results indicate that co-administration of vortioxetine and carvedilol might result in a significant change in vortioxetine and carvedilol plasma levels.

References


