PHARMACOKINETICS OF INTRAVENOUSLY AND ORALLY ADMINISTERED MEMANTINE IN SWINE

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Abstract
A pharmacokinetic study of intravenously and orally administered memantine was run on 12 pigs. The blood samples were collected up to 12 hours after drug administration. The memantine plasma levels were determined using a validated method of liquid chromatography coupled with mass spectrometry detection. Six pharmacokinetic models were screened and the best one describing the absorption and disposition of memantine was chosen. The pharmacokinetics of memantine in pigs is best described by a monocompartmental pharmacokinetic model and 1st order kinetics for both absorption and elimination processes. The memantine has an absolute bioavailability of about 34% and is rapidly cleared from the body, with an elimination rate constant from the central compartment of 0.34±0.06 hr⁻¹ and a mean half-life of 2 hours.

Keywords: memantine, pharmacokinetics, swine

Introduction
The process of neuronal degradation in cases of deprived oxygen supply (ischemia), as in cardiac arrest is closely connected with the activity of the N-methyl-D-aspartate (NMDA) receptors [5]. Despite recent data
regarding neuronal vulnerability to hypoxia, at the moment the only clinically available mean of neuroprotection is the therapeutic hypothermia [6]. However, this method has limited applicability. The NMDA receptors are also responsible for the neurodegeneration in Alzheimer [5]. The normal NMDA receptor activity can be reestablished by using substances called NMDA receptor antagonists. Out of this class, memantine proved to be the best tolerated, and ended up being used in therapy as an orally administered drug. Orally administered memantine’s neuroprotective effect was intensely studied and demonstrated in patients with vascular dementia, Alzheimer disease, hemorrhagic stroke and neuropathic pain [8,16]. The similar mechanisms of neuronal injury in Alzheimer disease and in cerebral ischemia suggested the idea of potential neuroprotective effects of intravenous (i.v.) memantine administered during global cerebral ischemia due to experimentally induced cardiac arrest in pigs.

In literature there is limited information regarding pharmacokinetics (PK) of memantine in humans or on animal models. A few studies regarding the PK of memantine after oral administration on humans [3,9,10] or animals [14] were carried out, but there is no information about its PK after i.v. administration.

The experimental model in pigs was selected due to the major similarities in the cerebral and cardiovascular anatomy, physiology and hemodynamics in humans and pigs; moreover, many of the cardiopulmonary resuscitation studies in literature use the same experimental swine model [4,7,15]. The determination of pharmacokinetics of i.v. and orally administered memantine in pigs is a first step required in the evaluation process of memantine’s neuroprotective effect in global cerebral ischemia following cardiac arrest on animal model.

**Materials and methods**

**Animal model**

The study was performed on 12 pigs (hybrid pigs PIC) (30.6±3.8 Kg). The clinical protocol was reviewed and approved by the Internal Committee for animal protection of the University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca.

**Study design**

The study consisted of 2 phases: Phase 1, when each pig received a single i.v. dose of 100 mg memantine and Phase 2, when each pig received a single oral dose of 200 mg memantine. The pharmaceutical product used
was an injectable solution of memantine hydrochloride with a concentration of 10 mg/mL. This pharmaceutical product was an experimental preparation, a sterile and isotonic solution (sodium chloride isotonic agent). The oral dose of memantine was administered directly in the stomach using a gastro-esophageal dye. The wash-out between the two periods was one week. All the drugs were administered in the morning, in fasted state. Venous blood (1 mL) was drawn into heparinized tubes, in the study periods, before drug administration as well as at 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after drug administration and the separated plasma was stored frozen (-20° C) until analysis.

Analysis of plasma samples

The plasma samples containing memantine were analyzed by a validated LC/MS analytical method, using an ion trap mass spectrometer. The HPLC system was an Agilent 1100 series (binary pump, autosampler, thermostat) (Agilent Technologies, USA) and was coupled with a Brucker Ion Trap SL (Brucker Daltonics GmbH, Germany). A Zorbax SB-C18 chromatographic column (100 mm x 3.0 mm i.d., 3.5 µm) (Agilent Technologies) was used. The mobile phase consisted of 45:55 (V/V) 0.1%(V/V) formic acid in water: methanol. The flow rate was 1 mL/min and the thermostat temperature set at 45°C. The mass spectrometry detection was in multiple reaction monitoring mode (MRM), positive ions, using an electrospray ionization source. The ion transitions monitored were m/z 180→m/z 163. The calibration curve of memantine was linear in a concentration range of 4.85-485 ng/mL plasma, with a correlation coefficient $r> 0.994$.

Pharmacokinetic analysis

The compartmental pharmacokinetic analysis method was employed to determine the pharmacokinetic parameters of memantine administered i.v. and orally in pigs, by using six user-defined mathematical models [2,11-13]. Each pharmacokinetic model is simultaneously fitting the plasma levels of memantine after i.v. and oral administration, for each subject. The difference between models consisted in absorption kinetics (1st order or zero order), in the presence or absence of a lag time before absorption and in the number of compartments in which memantine is distributed. The models used for pharmacokinetic analysis are presented in Table I. After fitting the data to all the considered pharmacokinetic models, the best model was chosen based on Akaike goodness-of-fit indicator [1].
The best model describing the pharmacokinetics of memantine in pigs after i.v. and oral administration was used for calculating the corresponding parameters. The half-life, \( t_{1/2} \) was calculated as \( 0.693/K_{10} \) (where \( K_{10} \) represents the elimination constant).

### Table I

The mathematical models created for the study of pharmacokinetics of memantine

<table>
<thead>
<tr>
<th>Model no.</th>
<th>Absorption kinetics</th>
<th>lag time</th>
<th>No. of compartments</th>
<th>Model parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model1</td>
<td>1st order</td>
<td>NO</td>
<td>1</td>
<td>( K_{01}, K_{10}, F, V_d )</td>
</tr>
<tr>
<td>Model2</td>
<td>1st order</td>
<td>YES</td>
<td>1</td>
<td>( T_{lag}, K_{01}, K_{10}, F, V_d )</td>
</tr>
<tr>
<td>Model3</td>
<td>0 order</td>
<td>NO</td>
<td>1</td>
<td>( K_0, K_{10}, F, V_d )</td>
</tr>
<tr>
<td>Model4</td>
<td>0 order</td>
<td>YES</td>
<td>1</td>
<td>( T_{lag}, K_0, K_{10}, F, V_d )</td>
</tr>
<tr>
<td>Model5</td>
<td>1st order</td>
<td>NO</td>
<td>2</td>
<td>( K_{01}, K_{10}, K_{12}, K_{21}, F, V_d )</td>
</tr>
<tr>
<td>Model6</td>
<td>1st order</td>
<td>YES</td>
<td>2</td>
<td>( K_{01}, K_{10}, K_{12}, K_{21}, F, V_d )</td>
</tr>
</tbody>
</table>

where \( K_{01} \) is the absorption rate constant (1st order kinetics), \( K_{0} \) is the elimination rate constant from the central compartment (1st order kinetics), \( K_{0} \) is the absorption rate constant (zero order kinetics), \( K_{12} \) and \( K_{21} \) are the distribution rate constants, \( F \) is the absolute bioavailability and \( V_d \) is the distribution volume of the central compartment.

For example, the equations used in Model 1 are presented below:

\[
\begin{align*}
\frac{dQ_{IV}}{dt} &= -K_{10} \cdot Q_{IV} \quad (\text{Eq1}) \\
\frac{dQ_{O,A}}{dt} &= -K_{01} \cdot Q_{O,A} \quad (\text{Eq2}) \\
\frac{dQ_{O,C}}{dt} &= K_{01} \cdot Q_{O,A} - K_{10} \cdot Q_{O,C} \quad (\text{Eq3}) \\
C_{IV} &= \frac{Q_{IV}}{V_d} \quad (\text{Eq4}) \\
C_{O,C} &= \frac{F \cdot Q_{O,C}}{V_d} \quad (\text{Eq5})
\end{align*}
\]

where \( Q_{IV} \) is the amount of drug in the central compartment after i.v. administration, \( Q_{O,A} \) is the amount of drug in gut in case of oral administration, \( Q_{O,C} \) is the amount of drug in the central compartment after oral administration, all the other terms are defined in Table I.

The pharmacokinetic analysis was performed using WinNonlin 6 software (Pharsight, USA).

### Results and discussion

The mean plasma concentrations of memantine administered intravenously or orally in pigs are shown in Figure 1.
Figure 1
Mean (±SD) plasma levels of memantine administered i.v. (100 mg) or orally (200 mg) in 12 pigs

The values of Akaike index for the solutions of the tested pharmacokinetic models are presented in Fig. 2.

Figure 2
The Akaike index values for the models describing the pharmacokinetics of memantine in pigs.

Analyzing the Akaike index values obtained for the studied models, one can observe that the minimal value (the best model) is the Model 2 (first
order absorption kinetics with lag-time for memantine and mono-compartmental distribution). A typical fitting of the model 2 to subjects data are presented in Figure 3.

![Figure 3](image)

Typical fitting of the pharmacokinetic model to subject data. A: a case when $K_{01} > K_{10}$. B: a case when $K_{01} < K_{10}$ (flip-flop).

The experimental data was analyzed using the chosen pharmacokinetic model. The individual and mean values of the obtained pharmacokinetic parameters of memantine are presented in Table II.
The individual and mean pharmacokinetic parameters of memantine administered in pigs as a single i.v. dose (100 mg) and a single oral dose (200 mg), respectively

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>$F$</th>
<th>$K_{01}$</th>
<th>$K_{10}$</th>
<th>$T_{lag}$</th>
<th>$V_d$</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units</td>
<td>1/hr</td>
<td>1/hr</td>
<td>hr</td>
<td>L</td>
<td>hr</td>
<td></td>
</tr>
<tr>
<td><strong>Subject</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.28</td>
<td>2.33</td>
<td>0.33</td>
<td>0</td>
<td>379.2</td>
<td>2.10</td>
</tr>
<tr>
<td>2</td>
<td>0.56</td>
<td>1.74</td>
<td>0.29</td>
<td>0</td>
<td>286.3</td>
<td>2.39</td>
</tr>
<tr>
<td>3</td>
<td>0.37</td>
<td>1.21</td>
<td>0.28</td>
<td>0</td>
<td>242.8</td>
<td>2.48</td>
</tr>
<tr>
<td>4</td>
<td>0.28</td>
<td>4.36</td>
<td>0.35</td>
<td>0</td>
<td>220.4</td>
<td>1.98</td>
</tr>
<tr>
<td>5</td>
<td>0.16</td>
<td>0.56</td>
<td>0.34</td>
<td>0.27</td>
<td>142.0</td>
<td>2.04</td>
</tr>
<tr>
<td>6</td>
<td>0.29</td>
<td>0.31</td>
<td>0.32</td>
<td>0.08</td>
<td>294.4</td>
<td>2.17</td>
</tr>
<tr>
<td>7</td>
<td>0.35</td>
<td>9.96</td>
<td>0.31</td>
<td>0.32</td>
<td>354.0</td>
<td>2.24</td>
</tr>
<tr>
<td>8</td>
<td>0.35</td>
<td>1.43</td>
<td>0.31</td>
<td>0.28</td>
<td>227.9</td>
<td>2.24</td>
</tr>
<tr>
<td>9</td>
<td>0.07</td>
<td>0.26</td>
<td>0.51</td>
<td>0.31</td>
<td>96.0</td>
<td>1.36</td>
</tr>
<tr>
<td>10</td>
<td>0.73</td>
<td>0.21</td>
<td>0.43</td>
<td>0.17</td>
<td>174.6</td>
<td>1.61</td>
</tr>
<tr>
<td>11</td>
<td>0.26</td>
<td>0.94</td>
<td>0.33</td>
<td>0</td>
<td>198.6</td>
<td>2.10</td>
</tr>
<tr>
<td>12</td>
<td>0.38</td>
<td>1.80</td>
<td>0.32</td>
<td>0.23</td>
<td>215.8</td>
<td>2.17</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>0.34</td>
<td>2.09</td>
<td>0.34</td>
<td>0.14</td>
<td>235.99</td>
<td>2.07</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>0.17</td>
<td>2.73</td>
<td>0.06</td>
<td>0.14</td>
<td>82.42</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Min</strong></td>
<td>0.07</td>
<td>0.21</td>
<td>0.28</td>
<td>0.00</td>
<td>95.99</td>
<td>1.36</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>0.32</td>
<td>1.32</td>
<td>0.33</td>
<td>0.13</td>
<td>224.13</td>
<td>2.13</td>
</tr>
<tr>
<td><strong>Max</strong></td>
<td>0.73</td>
<td>9.96</td>
<td>0.51</td>
<td>0.32</td>
<td>379.16</td>
<td>2.48</td>
</tr>
<tr>
<td><strong>Geo Mean</strong></td>
<td>0.30</td>
<td>1.14</td>
<td>0.34</td>
<td>N/C*</td>
<td>221.66</td>
<td>2.05</td>
</tr>
</tbody>
</table>

* N/C – not computed

The absorption of orally administered memantine in pigs is best described by a 1st order kinetic process with a rate constant of $2.09 \pm 2.7$ hr$^{-1}$, and, as expected, has a high variability. In some cases (subjects 6, 9, 10) the absorption rate constant has a lower value than the elimination rate constant (flip-flop phenomena) and in their corresponding log-fittings graphs the slopes of the terminal elimination phases are different (Fig. 3.B). The absorption lag-time varies among subjects ($0.14 \pm 0.14$ hr). The elimination rate constant of memantine is $0.34 \pm 0.06$ hr$^{-1}$ and its mean half-life about 2 hr. The distribution volume of memantine is about 236 L (7.8 L/Kg). The absolute bioavailability of orally administered memantine is about 34%. Our results show an important difference in the PK of memantine in pigs versus humans regarding the drug half-life (2 hours in pigs versus 64 hours in humans), this requiring a higher dose in pigs in order to have the same drug plasma levels as in humans [9].
Conclusions

The pharmacokinetics of memantine in pigs is best described by a 1st order absorption kinetic process with lag-time (in case of oral administration), monocompartmental distribution and a 1st order kinetics elimination process. The flip-flop phenomena may sometimes occur due to the high variability of the absorption process. The oral absolute bioavailability of memantine is about 34% and its systemic half-life about 2 hours. These pharmacokinetic data are essential information that will be used to determine the optimum therapeutic study design/dosage in order to study the neuroprotective effect of memantine.

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References


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