Pharmacokinetic Modeling of Fentanyl Citrate and Norfentanyl in Calves Using a Nonlinear Mixed-Effects Approach

Jonathan Mochel, DVM, M.S, Ph.D, DECVPT
Joe Smith, DVM, MPH, DACVIM
Iowa State University College of Veterinary Medicine
Motivation

Background and Objectives

**Limited options** for pain management in cattle (no drug labelled for surgical analgesia in the U.S)

A promising drug candidate (rapid onset of action, pharmacological efficacy ~ Morphine, potency 100 x Morphine)

Characterize the safety and disposition kinetics of fentanyl citrate and its primary metabolite in Holstein calves

Determine whether I.V bolus doing with fentanyl reaches therapeutic systemic concentrations in calves
Methods

Procedure, Data Analysis and Pharmacokinetics

• Experimental Design
  – 8 Female Calves (58.6 +/- 2.2 kg), 3-4 weeks
  – Fentanyl citrate I.V bolus single dose (5 µg/kg)
  – Pre-dose, +2, 5, 10, 30, 45, 60 min and 1.5, 2, 2.5, 3, 4, 6, 10, 16, 24h
  – Heart and respiratory rates were measured at each timepoint

• Bioanalytics
  – Plasma Fentanyl and Norfentanyl
  – LC-MS (Agilent 1100 HPLC coupled to Thermo LTQ ion trap MS)
  – LLOQ: 0.03 ng/mL (F) and 0.05 ng/mL (NF)

• Model Development
  – Nonlinear mixed-effects
  – Stochastic Approximation Expectation Method (SAEM 2.0)
Methods

Model Diagram
## Results

### Parameter Estimates

#### Facts & Figures

- Low **extraction ratio** (7%)
- Relatively high distribution volume
- What about eta-**shrinkage**?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>RSE (%)</th>
<th>IIV (CV%)</th>
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</thead>
<tbody>
<tr>
<td>CL</td>
<td>0.34 (L/h/kg)</td>
<td>36</td>
<td>47</td>
</tr>
<tr>
<td>V1</td>
<td>2.88 (L/kg)</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>Q2</td>
<td>2.63 (L/h/kg)</td>
<td>11</td>
<td>30</td>
</tr>
<tr>
<td>V2</td>
<td>29.9 (L/kg)</td>
<td>17</td>
<td>39</td>
</tr>
<tr>
<td>Q3</td>
<td>2.2 (L/h/kg)</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>V3</td>
<td>1.53 (L/kg)</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>kt</td>
<td>0.42 (h⁻¹)</td>
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<td>26</td>
</tr>
<tr>
<td>km</td>
<td>0.36 (h⁻¹)</td>
<td>7</td>
<td>-</td>
</tr>
</tbody>
</table>
Results

Model Predictions: fentanyl
Results

Model Predictions: norfentanyl
Results

Model Validation
Results

Model Simulations

Clinical efficacy window
(cats, dogs, humans)
Results

Model Simulations
Conclusions

‘Take-home’

• Fentanyl citrate is safe in calves
  – No adverse effects throughout the study period
  – No noticeable change in temperature, heart and respiratory rate
  – Reaches systemic levels associated with analgesia in other species

• M&S can be used for dosing optimization
  – Model building/evaluation/validation followed by Simulations
  – Establish dosing schedules (dose/frequency) leading to therapeutic efficacy
  – Account for between-subject variability in pharmacokinetics (and response)

• NLMEs allow information sharing to make the best use of the data
  – Leveraging high signal:noise ratio from Fentanyl data to model Norfentanyl PK
  – Using data from ‘informative’ individuals to estimate model parameters of more ‘noisy’ subjects
Conclusions

‘Simplicity is the ultimate sophistication’