A NEW METHOD FOR DETERMINING THE DEGREE OF SEDATION IN BEAGLE DOGS; VALIDATION WITH PROPOFOL AND COMPARISON TO A NOVEL COMPOUND

G. M. Belfort¹, R. H. Hammond¹, W. W. Muir², Y. Ueyama², S. J. Kanes³, A. J. Robichaud¹, J. J. Doherty¹
¹Drug Discovery, Sage Therapeutics, ²Safety Pharmacology, QTest Labs, ³Clinical Development, Sage Therapeutics

Overview
A current challenge in developing novel drugs targeting specific levels of sedation (e.g., moderate sedation) is the lack of calibrated preclinical assays. Loss of righting reflex (LRR) in rodents and the induction of lateral recumbency in dogs are useful as gross measures of sedation, but not for ranking the degree of sedation (Fig. 1). The modified observer’s assessment of alertness and sedation (MOAA/S, Table 1) is a validated scoring system for determining the degree of sedation in humans. Here we report a novel method using similar auditory and somatosensory stimuli to measure depth of sedation in beagle dogs.

Methods
Male beagle dogs were administered an IV bolus of propofol (6 mg/kg, n=3) or SGE-746 (5 or 7.5 mg/kg, n=5) followed by a constant rate infusion (CRI) protocol to assess efficacy (Fig. 2A) or safety (Fig. 2B) with ≥45 min dose steps.

(A) Descending CRI protocol
- propofol CRI range: 105-400 μg/kg/min
- SGE-746 CRI range: 45-576 μg/kg/min

(B) Ascending CRI protocol
- propofol CRI range: 400-800 μg/kg/min
- SGE-746 CRI range: 412-891 μg/kg/min

Table 1. MOAA/S and a novel scoring system for categorizing depth of sedation in dogs.

<table>
<thead>
<tr>
<th>MOAA/S (human)</th>
<th>Sedation Score</th>
<th>General Anesthesia</th>
<th>Deep Sedation</th>
<th>Moderate Sedation</th>
<th>Awake/Alert</th>
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<tbody>
<tr>
<td></td>
<td>Stimulus</td>
<td>Response (Score)</td>
<td>Name (loud)</td>
<td>Name (normal tone)</td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>Lateral, unresponsive (≤2) to all</td>
<td>(0)</td>
<td>-</td>
<td>-</td>
<td>(1)</td>
</tr>
<tr>
<td></td>
<td>Lateral, responsive (≥2) to noxious only</td>
<td>(1)</td>
<td>-</td>
<td>-</td>
<td>(2)</td>
</tr>
<tr>
<td></td>
<td>Lateral despite stimuli, responsive (≥2) to all stimuli</td>
<td>(2)</td>
<td>-</td>
<td>-</td>
<td>(3)</td>
</tr>
<tr>
<td></td>
<td>Upright, responsive (≥2) to all</td>
<td>(3)</td>
<td>-</td>
<td>-</td>
<td>(4)</td>
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</tbody>
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Table 2. Overview of SGE-746 assays.

References

Figure 1. LRR (rat) and lateral recumbency (dog) endpoints are insensitive to different levels of sedation. Dotted lines demarcate the plasma concentration when the rat regained righting reflex (black) and the dog could stand without assistance (red).

Figure 2. Experimental designs. Behavioral assessments (BA) and plasma collection time points (PK) for bio-analysis. Continuous cardiovascular and respiratory monitoring was performed. Retesting was performed with at least a 3 day washout period.

Figure 3. Transition between sedation levels in dogs recapitulates clinical experience with propofol. SGE-746 exhibits a more gradual exposure-response relationship. Exposures were normalized by dividing individual values by the mean plasma concentration of the compound immediately after recovery, when the animal was awake.

Figure 4. Small increases in propofol CRI result in cardiorespiratory compromise. Fold changes in plasma concentration are calculated by dividing individual concentration values by the mean plasma concentration when the animal was in a state of moderate sedation. This normalization allows one to estimate the fold change index between a target level of sedation (e.g., moderate sedation) and cardiorespiratory compromise. Cardiorespiratory stopping criteria were not induced with SGE-746. Each line and color in the left panels and each color in the right panels corresponds to a single dog.

Conclusions
- Here we have described a new method for assessing degree of sedation in the dog.
- This method enables direct comparison of dose/response, exposure/response, and relative safety margins between sedative anesthetics.
- As observed clinically in humans, here in dogs small increases in propofol exposure result in a rapid transition through multiple depths of sedation and rapidly induce cardiorespiratory compromise.
- The synthetic neuroactive steroid SGE-746 exhibits a more gradual exposure-response relationship than propofol.