Peripherally-Restricted Dual-Acting Kappa/Delta Opioid Agonist (CAV1001) Prevents Formalin-Induced Hyperalgesia

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**Background**

In the periphery, kappa (KOR) and delta-opioid (DOR) receptors are constitutively present. In an uninjured state peripheral mu-opioid receptors (MOR) play a minor role in the pain pathway; however, the MOR are responsible for opioid-induced constipation. The DOR become active following the induction of the inflammatory response. The relative contribution of DOR agonism following the induction of inflammation was examined comparing a novel dual-acting peripherally-restricted DOR/KOR agonist (CAV1001) to a pure KOR peripherally-restricted agonist (ICI204448) in the formalin model.

**Objective**

The plantar injection of formalin causes a biphasic nocifensive behavioral response; the early phase (phase 1: acute injury) is followed by an interphase without discernible nociceptive reactions, after which the late phase ensues (phase 2: inflammatory response); Phase 2 is used as a pharmacodynamic surrogate of central sensitization.

**Methods**

Following IACUC approval, mice were randomly pretreated with inert vehicle, ICI204448 1 mg/kg, ICI204448 10 mg/kg, CAV1001 1 mg/kg, or CAV1001 10 mg/kg. Spontaneous nocifensive behaviors were blindly assessed (video recording).

**Results**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group Treatment</th>
<th>Dose Level (mg/kg)</th>
<th>Route</th>
<th>Dose Vol. (mL/kg)</th>
<th>Pre-Treatment Time</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle (1:1:8 Ethanol: Tween 80: 0.9% Saline)</td>
<td>0</td>
<td>IP</td>
<td>20</td>
<td>30 min</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>ICI204448 – Low Dose</td>
<td>1</td>
<td>IP</td>
<td>20</td>
<td>30 min</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>ICI204448 – High Dose</td>
<td>10</td>
<td>IP</td>
<td>20</td>
<td>30 min</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>CAV1001 – Low Dose</td>
<td>1</td>
<td>IP</td>
<td>20</td>
<td>30 min</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>CAV1001 – High Dose</td>
<td>10</td>
<td>IP</td>
<td>20</td>
<td>30 min</td>
<td>8</td>
</tr>
</tbody>
</table>

**Comparison to Peripherally-Restricted KOR Agonist**

- Neither agent was effective in reducing the acute (0-5 minutes) response to formalin injection (phase 1);
- CAV1001 1 mg/kg was as effective as ICI204448 10 mg/kg in reducing formalin-induced responses at 20-35 minutes;
- CAV1001 10 mg/kg was significantly more effective than ICI204448 10 mg/kg (phase 2; p<0.01);
- Moreover, CAV1001 10 mg/kg effectively prevented the development of the phase 2 hyperalgesic response (p<0.003).

**Conclusion**

The apparent synergistic effect of simultaneous kappa and delta opioid agonism in the presence of inflammation suggests potential advantage over pure peripherally-restricted kappa agonists in inflammatory pain settings and further supports a preemptive effect that can eliminate the hyperalgesic response in painful inflammatory states.

**Reference**