The Methodological Questions Being Addressed

How will healthy young Japanese subjects respond to experimental pain and can the response be reversed by oxycodone?

Introduction

Pain is the most common health problem in human. However, because of lack of the reliability of the animal models and the psychological, pathophysiological and cultural nature of pain itself, it is often a challenge to assess the efficacy of pain medicine in the drug developments. In addition, it is important to assess the drug efficacy at the early stage of the pain medicine developments using experimental pain model in health subjects before the drug is tested in target patients because the pain can often be biased by many other aspects in clinical pain. Since it is well known that the pain is perceived, assessed, and treated differently depending on people's sex, age and ethnocultural groups, many studies have been conducted and shown different sensitivities to the experimental pain in different ethnicities. However, most studies have been conducted in western countries, and nearly no literature is found to demonstrate the validity of using experimental pain model in healthy Japanese subjects in clinical trial settings.

Ethnic concerns of experimental pain models in health subjects were thought to be one of the reasons in Japan, and finding the optimal pain models to produce right amount of experimental pain to evaluate the efficacy of pain medicine without the concerns has drawn the attention.

In this study, we planned and performed a clinical research on the purpose of establishing a pain evaluation method for assessment of drug efficacy using the cold pressor test (CPT) in healthy young Japanese subjects. Also, Oxycodone was used to investigate if the pain produced by the CPT is responsive to opioids.

Methods

- A randomized, double-blind, placebo-controlled, 2-group 2-period cross-over study in healthy young Japanese male volunteers was planned and conducted at SOUSEIKAI global clinical research center in Japan.
- The CPT was used as an experimental pain model.
- The water temperature was maintained at 4°C using a low-temperature thermostatic water bath (Thomas Kagawa, Japan).
- The CPTs were performed at pre-, and 1, 2, 5, and 8 hours after the Oxycodone or placebo administration.
- Oxycodone or placebo were administered orally once on the 1st day of the 1st and 2nd period.
- Pain latency and Pain tolerance were measured by the investigators during the tests based on the subject's response to the pain.
- Pain intensity was recorded by each subject by rating it via Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), and the Japanese version of Short Form McGill Pain Questionnaire (SF-MPQ-2) after each CPT.
- The clinical research was reviewed and approved by SOUSEIKAI Hakata Clinic IRB.

Results

- We were able to produce both consistent and safe experimental pain in healthy Japanese volunteers by using the CPT (4°C) and confirmed that it is possible to evaluate the pain using VAS and NRS.

* Pain Latency and Tolerance

<table>
<thead>
<tr>
<th>Hazard Ratio (Oxy/Plc)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.47</td>
<td>0.36, 0.65</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Tolerance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.47</td>
<td>0.33, 0.66</td>
<td>p = 0.001</td>
</tr>
</tbody>
</table>

- Both on the VAS and NRS, the Cumulative Odds Ratio (Oxy/Plc) were below 1 for all the time points from 1 hr to 8 hrs, which indicated that the Oxycodone suppressed the cold pressor-induced pain in healthy Japanese volunteers.

* Pain Intensity (VAS/NRS)

<table>
<thead>
<tr>
<th>VAS</th>
<th>1hr</th>
<th>2hr</th>
<th>3hr</th>
<th>6hr</th>
<th>8hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>7.0</td>
<td>7.1</td>
<td>7.1</td>
<td>7.1</td>
<td>7.1</td>
</tr>
<tr>
<td>NRS</td>
<td>6.6</td>
<td>6.7</td>
<td>6.7</td>
<td>6.7</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Results-2

- We were also able to evaluate the psychological aspects of the cold pressor pain using the Japanese version of the short-form McGill Pain Questionnaire.

The Oxycodone suppressed the cold pressor pain, shown by the Cumulative Odds Ratio (Oxy/Plc) being below 1 for 11 items out of 13 items in the SF-MPQ-2.

Conclusion

It is possible to produce and evaluate experimental pain in healthy volunteers using the CPT in healthy Japanese male volunteers.

Analogic effects were shown for the experimental pain induced by CPT in correlation with the plasma concentration of the Oxycodone.

The CPT can be useful to measure the analogic properties of new drug candidates for pain in early phase clinical studies without compound effects in Japanese subjects.

Additional research to determine the validity of other types of analogic medicines will be followed in Japanese subjects.