SICK: STIMULATORY ACTIVITIES STUDY OF INHALED ESKETAMINE AFTER A MULTIPLE Dose IN healthy VOLUNTEERS

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INTRODUCTION

Esketamine is a medicine used for over 50 years in human and veterinary anaesthesia and analgesia. Esketamine is a ketamine enantiomer showing 3- to 4-fold greater affinity to NMDA receptors than R-enantiomer. Several clinical studies with both single and multiple administrations have demonstrated the rapid antidepressant effect of esketamine in patients suffering from depression, mostly with treatment-resistant depression (TRD), as well as reducing the intensity of suicidal thoughts [1, 2, 3, 4]. In those studies ketamine was used as a racemic mixture in intravenous 40 min infusion or as an intranasal application of the S-enantiomer. Inhaled Esketamine represents a new approach. Recently we demonstrated the pharmacokinetic properties and safety of Esketamine delivered from dry powder inhaler (DPI) after a single dose in healthy volunteers [5]. The present study was intended to determine the pharmacokinetic properties and safety of esketamine after multiple administration via dry powder inhalation.

MATERIALS AND METHODS

Study population
- The study was a one-centre, randomized, double-blind, placebo-controlled, multiple ascending dose study in healthy volunteers.
- Participants underwent one cycle of treatment: 4 doses twice a week over 2 weeks period (Day 1, 4, 8 and 11). A single dose was defined as a dosing sequence consisting of 3 inhalation events spread over 30 minutes (2-12 inhalations in total) (Fig. 1). There were 4 cohorts (N = 8 cohort) with randomization 3:1.

Study design
- 33 healthy volunteers (18-55 years old), non-smokers, who met all the inclusion and none of the exclusion criteria were enrolled for the study.
- 10% of subjects of the total (i.e. due to the fact that, in cohort receiving NKRA, no subject withdrew from the study after two doses due to personal reasons or second subject was replaced to replace the first). The replacing subject also withdrew from the study after second dose due to personal reasons.

Investigational Medical Product (IMP)
- IMP contained esketamine hydrochloride as an active pharmaceutical ingredient, and was in the form of an inhalation powder delivered by dry powder inhaler (DPI).
- One inhalation of IMP contained 4.6 mg of esketamine hydrochloride (4 mg of esketamine free base) and excipients: lactose monohydrate and magnesium stearate.
- Placebo contained lactose monohydrate and magnesium stearate as an inhalation powder delivered by DPI.

Pharmacokinetics
- Blood samples for PK analysis were collected at the following time-points: predose (≤ 1 h before the IMP administration), 2, 4, 6, 10, 15, 20, 35, 30, 45, 60 min and 1, 2, 6, 12, 24 hours following the start of each dosing sequence.
- Esketamine and Esketamine concentration measurements were performed in human EDTA K. plasma samples using UPLC/MS/MS racemic method.

Safety evaluation
- Safety assessments included: adverse events (AE) reporting, clinical laboratory tests (haematology, blood chemistry, urinalysis), vital signs measurements, physical examination, electrocardiography (ECG). Questionnaire
- The questionnaire the participant answered to rate potential unusual feelings and impressions allowing for IMP psychostimulative side effects assessments were completed during the study.

Statistics
- Demographic data was analyzed descriptively.
- PK parameters were derived individually for each participant and computed using a non-compartmental modelling approach. PK parameters were analyzed with descriptive summary statistics (i.e. mean and standard deviation). Esketamine and Esketamine time-course plasma concentration profile of all participants and mean for each cohort were determined.
- Adverse events and symptoms reported through participant questionnaire were evaluated descriptively.

RESULTS

DEMOGRAPHICS

Table 1: Demographic data by sex

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>21.7 ± 3.1</td>
<td>21.1 ± 3.1</td>
<td>21.4 ± 3.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.6 ± 10.3</td>
<td>65.3 ± 9.3</td>
<td>69.5 ± 9.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181.6 ± 7.1</td>
<td>173.8 ± 7.1</td>
<td>177.7 ± 7.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 ± 3.1</td>
<td>25.1 ± 2.9</td>
<td>25.8 ± 3.0</td>
</tr>
</tbody>
</table>

ADVERSE EVENTS - TOTAL

Table 2: Total number of AEs by site, intensity and relationship to the study drug

<table>
<thead>
<tr>
<th>AE Category</th>
<th>Total</th>
<th>Number of Patients</th>
<th>Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza-like symptoms</td>
<td>14 (29.1%)</td>
<td>4 (24.2%)</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (87.2%)</td>
<td>13 (78.8%)</td>
<td>38</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (61.7%)</td>
<td>8 (47.1%)</td>
<td>21</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (38.3%)</td>
<td>6 (35.3%)</td>
<td>12</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (29.1%)</td>
<td>4 (24.2%)</td>
<td>10</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>16 (34.0%)</td>
<td>5 (29.4%)</td>
<td>11</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>16 (34.0%)</td>
<td>5 (29.4%)</td>
<td>11</td>
</tr>
</tbody>
</table>

SUMMARY AND CONCLUSIONS

- Inhaled Esketamine was well tolerated with no serious AEs.
- Most reported adverse events were classified as mild and few were classified as moderate.
- The dose-response relationship between IMP dose and AEs occurrence was observed for dizziness, feeling of relaxation and numbness of mouth and tongue.
- Symptoms reported through questionnaire may suggest possible psychostimulative (psychomimetic/dissociative) symptoms after administered doses of Esketamine, in some participants.
- The safety profile of Esketamine during the study did not differ from literature data.
- Pharmacokinetic profile of inhaled Esketamine supports dry powder inhalation as a delivery route.
- The obtained results suggest how susceptible variability.
- The study results justify further development of inhaled esketamine in patients suffering from treatment-resistant depression (TRD).

REFERENCES