The objective of this study was to assess the relative bioavailability of 2.0 mg naloxone HCl administered intramuscularly (IM), intranasally (IN) as monotherapy, and IN following IN administration of a vasoconstrictor (V+IN) in volunteers with chronic rhinitis.

Methods and Materials

This was a randomized, open-label, single-dose, 3-period crossover pharmacokinetic (PK) study.

Key eligibility criteria:
- Men and women 18-55 years of age.
- Diagnosed with chronic rhinitis (confirmed by an olfactory psychologist on Day -1) but with no clinically significant nasal abnormalities, surgery, polyos, or trauma.
- No other clinically significant abnormal findings that would jeopardize the safety of the participants or impact the validity of the study results.

Three study treatments:
- IN administration of 2.0 mg naloxone HCl (1 mg/ml in each flush) using a standard syringe and needle (IM).
- IN administration of 2.0 mg naloxone HCl (1 mg/ml, in each nostril) using the LMA MAD Nasal™ atomizer (IN).
- In administration of a vasoconstrictor (Oxymetazoline) per package labeling 30 minutes prior to IN administration of 2.0 mg naloxone HCl (V+IN).

Commercially available naloxone IN injection USP 2 mg/mL (IN, International Medications Systems) and Oxymetazoline HCl 0.05% nasal solution USP (Oxymet).

A washout period of at least 48 hours was considered sufficient to prevent carryover effects of previous test and reference products.

Results—Pharmacokinetic and Bioavailability

Thirty-six (36) volunteers completed the study (21 male/15 female; mean age: 33.7 years; mean body mass index 25.8 kg/m²).

Cmax and total naloxone exposure was greater after IM compared to IN and V+IN (Table 1 and Figure 2).

The geometric mean (GMR) for IN was 1.27 for Cmax and 1.28 for AUC∞ for both AUC∞ and AUC0-t, respectively.

The V+IN Cmax was approximately half the IN Cmax (GMR of 0.56) and the GMR for V+IN/AUC∞ and V+IN/V+IN was 1.70 for both AUC∞ and AUC0-t, respectively.

The early critical period of absorption (AUC0-0.5h) the GMR for V+IN/AUC∞ and V+IN/V+IN was 0.38, also indicating a lower naloxone exposure following IN in the presence of the vasoconstrictor.

Median Tmax was 15 minutes for IN and 10 minutes for V+IN (Table 1).

Results—Safety

In volunteers with chronic rhinitis, overall naloxone absorption was less for IN and V+IN than IM.

Naloxone absorption was slower in V+IN than IN, resulting in markedly lower Cmax and naloxone exposure in the early critical phase.

It is reasonable to expect that IN vasoconstricting agents (e.g., phenylephrine, oxymet) are likely to have similar effects on IN naloxone absorption.

The impact of common medical conditions and medications should be considered when selecting the route of naloxone administration to use in treatment of OIRD.

References

2. Barton E et al, JAMA 2010;303:1556-1566.

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Figure 2. Mean (±SD) Naloxone Plasma Concentration in Volunteers with Chronic Rhinitis

Figure 3. Mean (±SD) Naloxone Plasma Concentration During the Early Phase of Absorption after IN and V+IN Administration in Volunteers with Chronic Rhinitis

Table 1. Summary of PK Parameters for 2.0 mg Naloxone in Volunteers with Chronic Rhinitis (N=16)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax (pg/mL)</th>
<th>Tmax%(h)%</th>
<th>Min, Max</th>
<th>Median</th>
<th>Mean (SD)</th>
<th>GMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN (2.0 mg naloxone)</td>
<td>4539 (2089)</td>
<td>1.50 (0.34)</td>
<td>1000</td>
<td>2157</td>
<td>1288 (622)</td>
<td>1.00 (0.91-1.10)</td>
</tr>
<tr>
<td>IN (2.0 mg naloxone)</td>
<td>3950 (1479)</td>
<td>4.00 (1.90)</td>
<td>2500</td>
<td>2125</td>
<td>1547 (672)</td>
<td>0.95 (0.86-1.06)</td>
</tr>
<tr>
<td>V+IN (Afrin®+2.0mg naloxone)</td>
<td>4870 (1757)</td>
<td>1.75 (0.88)</td>
<td>6000</td>
<td>2200</td>
<td>3360 (1360)</td>
<td>1.00 (0.91-1.10)</td>
</tr>
<tr>
<td>V+IN (Afrin®+2.0mg naloxone)</td>
<td>3460 (1240)</td>
<td>4.00 (1.90)</td>
<td>3000</td>
<td>2200</td>
<td>1881 (744)</td>
<td>1.00 (0.91-1.10)</td>
</tr>
</tbody>
</table>

Pi et al. Pharmacokinetics of 2.0 mg Intranasal and Intramuscular Naloxone HCl Administration to the Vasconstrictor Use of the Bioavailability of Intranasal Naloxone HCl. Presented at the American Society of Clinical Pharmacology and Therapeutics Annual Meeting, March 1-4, 2013. New Orleans, LA.