Comparative Pharmacokinetic Analysis of Community Use Naloxone formulations for Acute Treatment of Opioid Overdose

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Abstract

Recent increases in mortality from overdoses in the US have been primarily driven by deaths due to the more potent synthetic opioids. Naloxone is an effective countermeasure to treat opioid overdose. We compared the pharmacokinetics of the three available doses of naloxone used to treat prehospital opioid overdoses. Overall, the systemic exposures of 2 mg IM and 4 mg IM naloxone appear to be similar. By comparison, the exposure levels of the 5 mg dose intramuscular naloxone (ZIMHI) appears to be greater and more rapid. These results support the notion that higher doses of naloxone result in greater bioavailability which may be required for reversal due to the more potent synthetic opioids, such as fentanyl.

Key words: narcan; evzio; zimhi; naloxone; opioid; pharmacokinetics; overdose; fentanyl

Introduction:

The rapid rise of deaths in the current opioid epidemic has resulted in significant efforts by federal and local public health officials to develop countermeasures to effectively treat drug overdoses and to facilitate treatment programs for the problem of addiction [1]. Naloxone is an effective countermeasure to treat opioid overdoses and widespread use of naloxone is encouraged by public health experts, including the Surgeon General [2]. Naloxone is an opioid antagonist that competes for the mu receptors resulting in reversal of opioid toxicity. However, in spite of increased access to current formulations of naloxone, deaths due to the more potent synthetic opioids continue to increase [3]. One possible explanation for the increased mortality due to the synthetic opioids is the increased potency and rapid toxicity compared to other opioids [4]. Overdose deaths due to respiratory failure and brain hypoxia can occur within minutes of fentanyl exposure. Therefore, reaching adequate levels of naloxone in the CNS to antagonize the opioids may be a critical factor for successful reversal and survival.

ZIMHI is an investigational 5 mg intramuscular (IM) injection of naloxone hydrochloride utilizing a previously approved device [5]. Current doses for community and prehospital use of naloxone to treat opioid overdose are 2 mg IM (Evzio) or 4 mg intranasal (IN) (Narcan) [6]. Previously, we reported a pharmacokinetic study in healthy subjects comparing ZIMHI 5 mg IM dose to Evzio 2mg IM autoinjector dose. The results suggested higher Cmax and Area Under the Curve (AUC) exposures for ZIMHI compared to Evzio [7]. The purpose of this study was to compare the pharmacokinetics of the three available dose formulations of naloxone used to treat prehospital opioid overdoses. Overall, the systemic exposures of 2 mg IM and 4 mg IN were comparable. By comparison, the exposure levels of the 5 mg dose IM naloxone (ZIMHI) was observed to be significantly greater and more rapid.

Methods:

Data for comparison of the different formulations utilized two pharmacokinetics studies of naloxone that both enrolled healthy adults. APC 6000-03 was a Phase I, open-label, randomized, single-dose, 2-period, 2-treatment crossover bioavailability study comparing 5 mg/0.5 mL of IM naloxone HCl to 2 mg/2 mL IM naloxone HCl injection (1 mg/1 mL, International Medical Systems) in healthy subjects. Fourteen male and female subjects 18 to 55 years of age (inclusive) were enrolled in the study. APC 6000-03 was conducted in accordance with the United States (US) Code of Federal Regulations (CFR) governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), and Bioavailability and Bioequivalence Requirements (21 CFR 320), as appropriate. Informed consent and Institutional Review Board (IRB) approval was obtained prior to study initiation.

The primary Pharmacokinetic (PK) endpoints for APC 6000-03 were the area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinity (AUCinf) and the maximum observed plasma concentration (Cmax). This study consisted of a screening visit (up to 28 days before the first dosing period) and 2 study periods (each separated by a minimum of 48 hours). Subjects reported to the Clinical Research Unit (CRU) on Day -1 (Check-in) and remained at the CRU for 5 days (approximately 12 hours after Period 2, Day 4). Subjects were randomized to 1 of 2 treatment sequences on Day 1 of each study period which consisted of either ZIMHI (5 mg/0.5 mL naloxone hydrochloride) in a prefilled syringe device, or 2mg/2 mL of naloxone hydrochloride (1 mg/1 mL, International Medical Systems) in a prefilled syringe. Subjects then crossed-over to the alternative formulation. All subjects received a single intramuscular dose of naloxone hydrochloride in the anterolateral aspect of the thigh administered on Day 1 of each period (Study Days 1 and 3).
The second study was previously published and examined different doses of Narcan [8]. The details of this study can also be found in the Narcan label [9]. The data from this study was kindly provided by Dr. Phillip Krieter, NIDA, NIH. We utilized data from the 4 mg IN group in our comparison as it is the approved dose.

**Results:**

A comparison of the pharmacokinetic parameters is shown in Table 1 for 2mg IM, ZIMHI and Narcan.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4 mg IN (Narcan)</th>
<th>2 mg IM</th>
<th>5 mg IM (ZIMHI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>29</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>5.3 (44.6)</td>
<td>3.58 (58.1)</td>
<td>17.2 (44)</td>
</tr>
<tr>
<td>Tmax (hours)</td>
<td>0.5 (0.2, 1.0)</td>
<td>0.250 (0.05, 3)</td>
<td>0.250 (0.17, 0.52)</td>
</tr>
<tr>
<td>AUC 0-infinity (ng*h/ml)</td>
<td>8.5 (39.0)</td>
<td>9.97 (24.2)</td>
<td>26.6 (21.2)</td>
</tr>
<tr>
<td>T 1/2</td>
<td>2.2 (29.1)</td>
<td>1.81 (28.9)</td>
<td>1.5 (15.2)</td>
</tr>
<tr>
<td>AUC 2.5 min</td>
<td>ND</td>
<td>0.009 (164)</td>
<td>0.02 (208)</td>
</tr>
<tr>
<td>AUC 5 min</td>
<td>ND</td>
<td>0.04 (128)</td>
<td>0.147 (116)</td>
</tr>
</tbody>
</table>

Table 1: Pharmacokinetic parameters comparing 4 mg IN, 2 mg IM, and 5 mg IM. Mean (%CV) for all parameters except Tmax median (range) was used.

Figure 1a shows a comparison of the mean plasma concentration of all three different formulations of naloxone over 1 hour (a) and 12 hours (b). These data suggest the 4 mg IN (Narcan) and 2 mg IM doses have similar pharmacokinetics in terms of Cmax and AUC. In contrast, higher Cmax and AUC is observed for ZIMHI compared to the other two formulations. It is also demonstrated from figure 1a that there is a more rapid systemic exposure for ZIMHI compared to 2 mg IM and Narcan. Although not measured in the Narcan study, as noted in Table 1, the AUC’s for the first 2.5 and 5 minutes are significantly higher for ZIMHI compared to 2 mg IM dose of naloxone.

![Mean Plasma Concentration of Naloxone Over 1 Hour](image)

**Figure 1a:** Mean ± SD Plasma Concentration of Naloxone, 0-1h.
Discussion:

The purpose of this analysis was to compare the pharmacokinetics of three different dose formulations of naloxone approved for community and prehospital use. Naloxone can be administered in different forms including sublingual, buccal, subcutaneous, intranasal, intravenous and intramuscular. This study examined a comparison of two different doses of intramuscular naloxone with an approved nasal formulation. Results of this comparison suggest that the exposure levels of 2 mg IM and 4 mg IN are very similar. However, others have raised issues regarding factors that could affect absorption of nasal administration of naloxone in real life situations. For example, nasal absorption of naloxone could be impacted by nasally administered illicit drugs such as cocaine and nasal allergies [10]. However, in healthy normal subjects this comparison suggests the systemic levels of 2 mg IM and 4 mg IN are similar with the nasal product having about 45% bioavailability compared to IM administration [11]. Other factors involving the formulation of IN naloxone may be relevant to permeability and stability including preservatives, stabilizers, and the pH [12].

In comparison, the 5 mg IM naloxone (ZIMHI) was superior to both 4 mg IM and 2 mg IM in terms of PK exposure parameters. In addition, it is apparent that the 5 mg dose also resulted in a more rapid systemic exposure of naloxone. Because of the potency and rapid onset of the synthetic opioids, this characteristic may be critical in order to achieve a successful reversal. This notion agrees with a greater AUC during the first 2.5 and 5 minutes observed with the 5 mg naloxone dose (ZIMHI) compared to 2 mg IM. This pharmacokinetic comparison study between three different formulations of naloxone for community use suggest that the 2mg IM and 4 mg IN formulations of naloxone provide similar systemic exposure levels in healthy subjects. In contrast, the 5 mg dose of naloxone provides higher and more rapid exposure. Fentanyl can result in rapid respiratory failure with resulting brain hypoxia and ultimately, death. Rapid naloxone systemic exposure and egress to the mu receptors in CNS may mean the difference between life and death. The risks of underdosing with naloxone outweighs any risks particularly because of the more potent synthetic opioids that drive the current epidemic [13]. This pharmacokinetic comparison suggests that the 5 mg naloxone (ZIMHI) should result in more rapid and higher systemic levels of naloxone which may be needed to counter the more potent synthetic opioids such as fentanyl and its analogues.

References:

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7. Moss, RB (2019), “An Open-label, Randomized, Single-dose, 2-period, 2-treatment Crossover Bioavailability Study Comparing 5 mg/0.5 mL of Intramuscular Naloxone Hydrochloride to 2 mg/0.4 mL. Intramuscular Naloxone Hydrochloride Auto-injector in Healthy Subjects”, Institute of Human Virology Annual meeting, HIV-Opioid Session


