BACKGROUND

Naloxone, an opioid antagonist used in treatment of overdose, can be dosed for this indication at 0.4 to 2 mg IV push. This dose may be repeated every 2-3 minutes as needed based on patient response. Depending on the clinical situation and overdose amount, patients may require frequent dosing. This presents problems including frequent medication administration, the need for close patient supervision, extra nursing time, and potentiating drug interactions. A naloxone continuous infusion is advantageous to overcome these problems.

Naloxone for continuous infusion currently may be prepared in standard concentrations of 0.004 mg/mL (4 Naloxone for continuous infusion currently may be prepared in from commercially available injections available at infusions so that smaller volumes may be administered. This advantage is advantageous to increase the concentration of naloxone in heart failure, volume overload, kidney disease). It would be possible pitfall in patients who might need fluid restriction (eg.

OBJECTIVES

The purpose of this study is to determine if naloxone is soluble and stable as a highly concentrated version: naloxone hydrochloride (naloxone HCl) 400 µg/mL in NS or D5W.

METHODS

Solubility and Stability of Concentrated Naloxone Hydrochloride Intravenous Infusion

Solubility study:
- Shake-flask method was utilized to determine solubility of naloxone in normal saline (NS) and dextrose 5% in water (D5W) at room temperature. Large amounts of fluids would be administered to patients requiring high naloxone doses, a potential pitfall in patients who might need fluid restriction (eg. heart failure, volume overload, kidney disease). It would be advantageous to increase the concentration of naloxone in infusions so that smaller volumes may be administered.

Stability study (Figure 1):  
- High-performance liquid chromatography with diode array detection (HPLC-UV) (Agilent 1200 UHPLC, Santa Clara, CA) was utilized.
- HPLC method was adapted from the United States Pharmacopeia (USP) and validated.

RESULTS

No significant change in naloxone HCl concentrations in any of the four stability samples was observed at 24 hours (Table 1). The changes, if any, in the peak areas of the naloxone HCl concentrated solutions were within the range we observed for the stability studies of the 8 µg/mL standard infusions (0.4 to 3.3%) and thus may be attributable to sample preparation. At 24 hours, no additional peaks were seen in the chromatograms of any of the four stability samples.

Stability study results:  
- No change in appearance (eg. discoloration) or presence of particulate matter was observed over 24 hours in any of the four stability samples.
- The peak area of the naloxone HCl standard solution was observed at 24 hours (Table 2).

Table 1: Average results from the two stability runs that were completed.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Protected or Unprotected from Light</th>
<th>Initial Concentration [µg/mL]</th>
<th>% of Initial Concentration [% remaining +/- SD] at 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>Unprotected</td>
<td>400 µg/mL</td>
<td>99.56 +/- 1.05</td>
</tr>
<tr>
<td>NS</td>
<td>Protected</td>
<td>400 µg/mL</td>
<td>99.33 +/- 0.1</td>
</tr>
<tr>
<td>DSW</td>
<td>Unprotected</td>
<td>400 µg/mL</td>
<td>100.32 +/- 0.38</td>
</tr>
<tr>
<td>DSW</td>
<td>Protected</td>
<td>400 µg/mL</td>
<td>98.27 +/- 0.98</td>
</tr>
</tbody>
</table>

Figure 2: Chromatogram of a standard solution of naloxone HCl

CONCLUSIONS

- Solutions are stable regardless of protection from light.
- Solutions are stable regardless of being in NS or D5W.
- Naloxone is physically stable at the studied concentration of 400 µg/mL.
- IV infusions compounded with higher concentrations may be advantageous in patient specific scenarios.
- Solubility and stability past 24 hours remains to be determined.
- Injection site reactions at this concentration were not explored.

REFERENCES


DISCLOSURE

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
- Meredith Howard: Nothing to disclose
- Carolyn Honigford: Nothing to disclose
- Sarah Nisly: Nothing to disclose
- Hala Fadda: Nothing to disclose

Solubility study results:  
- Normal saline: Solubility 136 mg/mL  
  Average pH 5.12
- Dextrose 5% water Solubility 174 mg/mL  
  Average pH 5.13

- pH of the saturated solutions is higher than that of the 1 mg/mL injection from which it was prepared (pH 3.5 ± 0.5). Naloxone is a weakly basic drug and despite this rise in pH as well as the common ion effect in NS, naloxone HCl is soluble in NS and D5W at the desired concentration of 400 µg/mL.