The approval of Protopam Chloride for use in pediatric patients

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Pralidoxime chloride (2-formyl-1-methylpyridinium chloride oxime; 2-PAM)
2-PAM

- For the treatment of poisoning due to organophosphate pesticides and nerve agents having anticholinesterase activity
- Always given with atropine
Organophosphate nerve agents with anticholinesterase activity

- Acetylcholine is the neurotransmitter at the neuromuscular junction (nicotinic receptors), secretory glands and smooth muscle (muscarinic receptors), and at respiratory centers in the central nervous system.

- Acetylcholinesterase is the enzyme responsible for the inactivation of acetylcholine.
Organophosphate nerve agents with anticholinesterase activity

- Organophosphate nerve agents irreversibly bind to acetylcholinesterase, prolonging the activity of acetylcholine at these various sites, resulting in symptoms that can result in, among other things, respiratory failure and death.
- Pyridostigmine, a reversible inhibitor of acetylcholinesterase, is approved as a pre-treatment for nerve agent poisoning (in conjunction with atropine and 2-PAM).
Organophosphate nerve agents with anticholinesterase activity

- 2-PAM reactivates acetylcholinesterase (outside the CNS), allowing accumulated acetylcholine to be inactivated
- 2-PAM also slows the process known as “aging” of phosphorylated acetylcholinesterase
- It presumably also can detoxify some organophosphates by direct chemical reaction
- Atropine blocks the effects of acetylcholine at nicotinic and central receptors
Regulatory history of 2-PAM

- NDA approved in 1964, for use in adult and pediatric patients
- Approval probably based on animal studies and anecdotal reports in people exposed to organophosphate pesticides
- Although not approved until recently, 2-PAM has been used extensively in pediatric patients; dosing recommendations have been provided by numerous professional organizations
Regulatory history of 2-PAM

- The current supplement contained reports of animal studies as well as clinical data.
- The intravenous recommendations borrow much from adult data (presumably cholinesterase levels and the PK of 2-PAM are similar in both populations) and are also based on pediatric and animal data.
Regulatory history of 2-PAM

- It occurred to us that intramuscular dosing recommendations would be extremely important in the pediatric population.
- As a treatment for nerve agent poisoning, IM dosing would be critical for use by first responders in the field.
- This was achieved by modeling.
Dosing recommendations in adults

- Pralidoxime: For use in nerve agent and insecticide poisoning only
- Intramuscular dosing guidelines for Pralidoxime in adults
  - 600 mg into mid-lateral thigh. Subsequent doses based on severity of symptoms. If a patient has severe symptoms, administer 2 additional injections in rapid succession.
  - Based on achieving a target concentration of 4 ug/mL.
- Intravenous dosing guidelines for Pralidoxime in adults
  - Inject an initial dose of 1000 to 2000 mg, preferably as an infusion in 100 mL of normal saline, over a 15- to 30-minute period. A second dose of 1000 to 2000 mg may be indicated after about one hour if muscle weakness has not been relieved. Additional doses may be given every 10-12 hours if muscle weakness persists.
Intravenous dosing recommendations in pediatric patients

Intravenous dosing guidelines in pediatrics (based on pediatric and animal data)

• **Loading Dose Followed By Continuous Infusion**
  Administer a loading dose of 20-50 mg/kg (not to exceed 2000 mg/dose) over 15-30 minutes followed by a continuous infusion of 10-20 mg/kg/hour.

• **Intermittent Infusion Dosing**
  Administer an initial intermittent infusion of 20-50 mg/kg (not to exceed 2000 mg/dose) over 15-30 minutes. A second dose of 20-50 mg/kg may be indicated after about one hour if muscle weakness has not been relieved. Repeat dosing is permissible every 10-12 hours as needed.
Approach to determining IM recommendations in pediatric patients

- To define intramuscular dosing guidelines in pediatrics it is important to know
  - If Pralidoxime will be absorbed rapidly and completely in pediatrics (Birth onwards) after intramuscular administration.

- To bridge intramuscular PK data in adults to pediatrics
  - Published data for 12 drugs administered via intravenous and intramuscular routes were analyzed.
  - Physicochemical differences, such as molecular weight, water solubility, between drugs were considered
  - Tmax and bioavailability in pediatrics and adults were compared
Pharmacokinetics of Pralidoxime
Rapid and Complete Absorption* of Pralidoxime (600 mg) in Adults

- $C_{\text{max}}$: 6 ug/mL
- $T_{\text{max}}$: 28 min

* Based on urinary excretion data
Maturation of renal function was incorporated into simulations

\[ y = 1.3846x^{0.7867} \]

\[ CL = 39.16 \cdot (\text{Weight} / 70)^{0.78} \cdot \frac{PMA^{3.4}}{47.7^{3.4} + PMA^{3.4}} \]
Simulated Pralidoxime concentrations in a neonate (3 d)
Pharmacokinetics of drugs administered intramuscularly
Tmax, Bioavailability (F) in adults and pediatrics across drugs administered intramuscularly

Based on molecular weight, solubility it is expected that Pralidoxime will have absorption characteristics similar to adults.
Recommended intramuscular dosing guidelines in pediatrics and adults

<table>
<thead>
<tr>
<th>Weight in kg</th>
<th>Dose Per Injection</th>
<th>Total Dose per Three-Injection Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 kg</td>
<td>15 mg/kg</td>
<td>45 mg/kg</td>
</tr>
<tr>
<td>≥ 40 kg⁴</td>
<td>Use Adult Dosing Recommendations</td>
<td>Use Adult Dosing Recommendations</td>
</tr>
</tbody>
</table>

¹ Dosing is based on an approximate 300 mg/mL solution.

² During the treatment for mild symptoms, if at any time after the first dose, the patient develops severe symptoms, administer two additional weight-appropriate intramuscular doses of PROTOPAM in rapid succession.

³ Additional courses of PROTOPAM may be administered beginning one hour after the last injection. A single course consists of three separate, weight-appropriate injections, administered either with 15 minute inter-injection observation periods for patients with mild symptoms, or all in rapid succession for patients with severe symptoms.

⁴ Weight of 40 kg corresponds to approximately the 50th percentile for a 12 year old child per the weight-for-age percentile growth charts published by the Centers for Disease Control and Prevention in 2000.

⁵ Adult Dose Per Injection is 600 mg; Total Adult Dose per Three-Injection Course is 1800 mg.
Lessons to be learned

• We believe under certain circumstances clinical data in pediatric patients may not be necessary in order to grant a specific claim and/or write dosing recommendations.

• When clinical data are necessary, they don’t necessarily have to come from randomized, controlled trials.

• Multiple and varied regulatory pathways exist and can be used in unusual circumstances.