Sterile Compounding for Acute Care: Papaverine Injectable Case Presentation

Northwest Pharmacy Convention
June 1, 2013

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Disclosure Statement

- Speaker: Megan McIntyre
- No relevant financial relationships
- Potential conflicts of interest: none
- Sponsorship: none
- Proprietary information or results of ongoing research that may be subject to different interpretations: none
- My goal is to be transparent with our processes
- Patient safety and quality come first
- I am not a 797 expert, and this is not the intent of the presentation

Learning Objectives

- Understand implications of changing sterile compounding landscape in light of safety concerns, drug shortages and regulatory changes
- Explain one system’s approach towards addressing a sterile compounding situation
Definitions

- High risk compounding includes a broad range of products for a variety of conditions and populations
- USP 797 criteria: contamination risk
- VM: Complex, coupled processes
  - E.g. TPN, intrathecal products, intraoperative vasodilators, ophthalmic injections, anesthesia etc.
- ASHP study guide resource

Situation

- Increased focus on compounding
- Lack of clear definitions
- Concurrent drug shortages
- Increasing regulatory activity and significant degree of practice variation
- Tension between meeting patient care needs and ensuring product integrity

VMMC Experience

- CDC One & Done campaign (multi-patient/dose vials)
- Pharmaceutical Compounding Quality and Accountability Act headed to Senate
- Verifying Authority and Legality In Drug (VALID) Compounding Act of 2013 introduced by House

Jan 2013
- Papaverine shortage/prohibited office use
- CDC One & Done campaign (multi-patient/dose vials)

Feb 2013
- VM high risk compounding

Mar 2013
- Capital request for powder hood
- Governor signed HB 1800

Apr 2013
- Powder hood installed

May 2013
- Site visit
- Validating internal sterility/batch testing
There are ...
- things we know that we know
  - known unknowns
- things we now know we don't know.
- unknown unknowns
  - things we don't know we don't know
- The absence of evidence is not evidence of absence
  - Simply because you do not have evidence
    that something exists does not mean that
    you have evidence that it doesn't exist.

VMMC Compounding Gap Analysis
- Overview:
  - Launched October 2012, continuous
  - Engaged clinic and section leadership to start discussions and
    inventory investigations
  - Goal: Capture internally and externally prepared products
  - Goal: Identify gaps in therapy and potential alternatives

Risk Assessment Tools
- Does not matter what tool, if any, is employed but...
- Be proactive, thorough, involve key stakeholders, simulate, fail forward, ask questions,
  over communicate, keep assessment dynamic, know what providers will see if they
  research, prepare for the worst, know what you don't know and look for the unknown
Case example: Papaverine injection
Situation: Papaverine sterile injectable is unavailable from manufacture

Papaverine Injection Strategies

**Intraoperative - Vasodilation**
- Immediate focus
- Understand intended pharmacological and operational application
- Vein bath, irrigation
- Injection
- Understand surgeons’ concerns
- Literature search on alternatives
- Complicated
- Engage the “experts”
- Be open to trial alternatives

**Office – Erectile Dysfunction**
- Long term focus
- Implications on clinic visits
- Requires additional equipment, training, infrastructure
- Alternatives
  - Prostaglandin or alprostadil for Duplex scan, Imaging
  - Counsel patients thoroughly about risks of Trimix, Bimix from compounding pharmacies

**Initial Trial**
- Nitroglycerin 4 mcg/ml in 50 ml NS syringes
- Not relaxing vein/vasospasm, syringe stability (?)

**Alternatives to Nitroglycerin**
- Yu et al 2011 survey
  - Top 2: papaverine and verapamil, mentions other (Rescor, verapamil, 42%; habit 21% and ‘it works’ 16%)
- Wei He et al 2008
  - Cocktail to address three classic vasoconstrictors: Membrane depolarizing + Thromboxane A2 + α-receptor

**Practice-based considerations**
- Mechanism of action, onset
  - Calcium channel blockers: membrane depolarization
  - Nitroglycerin (NO): α-receptors, thromboxane A, others (↑ cGMP)
  - Papaverine: phosphodiesterase (↑ cGMP)
- pH – Compatibility - Availability - Expense

**Intraoperative Papaverine Alternatives**

- **General Classifications**
  - Vasodilators
  - Calcium channel blockers
  - Nitric oxide donors
  - Prostaglandins

- **Specific Agents**
  - **Nitroglycerin**
    - pH: 3-6.5; heparin compatible; available
  - **Verapamil**
    - pH: 4-6.5; heparin compatible; available
  - **Diltiazem**
    - pH: 3.7-4.1; heparin variable compatibility; available
  - **Nicardipine**
    - pH: 3.5; likely not heparin compatible; available
  - **Prazosin**
    - pH: 6.6; heparin compatible; available
  - **Amitrapine**
    - pH: 6.6; heparin compatible; available
  - **Adenosine**
    - pH: 6.6; heparin compatible; available
  - **Lidocaine**
    - pH: 6.6; heparin compatible; available
  - **Verapamil**
    - pH: 6.6; heparin compatible; available

- **Notes**
  - Stability
  - Stability
  - Stability
  - Stability
  - Stability

6/1/2013
Nitroglycerin and Nicardipine Cocktail

- Wei He et al.
- Nicardipine 5mg
- Nitroglycerin 5mg (glyceryl trinitrate)
- 8.4% NaHCO3 0.3ml
- Normosol-R solution 300ml
- pH of 7.1

**VMMC**

- Nitroglycerin 5mg and nicardipine 5mg in 0.9% NaCl 250ml
- BBraun Excel bags (NTG adheres to PVC)
- Normal saline instead of Normosol-R
  - Buffered
  - pH of 7.1
  - pH of drugs and diluents vary batch to batch
- Surgery observation of vasodilation with cocktail
  - Report, instant feedback, clear picture of indication

**Summary**

- In the absence of commercial products designed to meet all needs, organizations need to
  - Assess current state of internal and external compounding
  - Identify and incorporate potential risk and mitigation strategies
  - Develop processes and policies to keep patients safe
  - Engage stakeholders early and understand their needs
  - “Go See”
  - Be ready to make the “right decision”

**References**