Compatibility of Oxytocin and Tranexamic Acid Injection Products

Pete Lambert - Director, Monash Quality of Medicines Initiative, Monash University
Maternal Health Supplies Caucus
19 October 2023
E-MOTIVE Protocol
Early Response for Treatment of PPH

- Comprises four key elements:
  - Uterine massage
  - Administration of:
    - Oxytocin (OXY) injection
    - Tranexamic acid (TXA) injection
    - Intravenous fluids

- Assessed in large scale clinical trial
  - ~210,132 vaginal births in Nigeria, Tanzania, Kenya and South Africa
  - 60% reduction in sPPH, laparotomy or maternal death from bleeding

- Quality assessment of OXY and TXA products conducted prior to/during early stages of study
E-MOTIVE Protocol
Quality of PPH Products Used in the Study

**OXY Quality Results**
- 17 products assessed
- **Drug content**
  - 10/17 products passed drug content specification (90-110% of labelled content)
  - 7/17 products failed drug content specification (69.3% and 89.2%)
- **Related Substances/Impurities**
  - 10/17 products passed related substances/impurity specification
  - 7/17 products failed related substances/impurity specification (nmt one impurity >2%, no impurity >5%)

**TXA Quality Results**
- 18 products assessed
- **Drug content**
  - 17/18 products passed drug content specification (95-105% of labelled content)
  - One product showed minor out-of-specification result in 3 of 4 ampoules tested (93.6-94.6%)
  - 11/18 products passed the related substances /impurities specification (no impurity >0.2%)
  - 6/18 products failed specification with related substances/impurity content between 0.2-2%
  - One product exhibited gross failure with related substances/ impurities of as high as 250%

➢ Clinical sites were notified to exclude poor quality products from the E-MOTIVE study
E-MOTIVE Protocol
Quality of PPH Products Used in the Study

Summary

• Both OXY and TXA products showed quality issues

• First study indicating quality issues with TXA injection products

• Oxytocin products demonstrated issues of drug content and impurities
  • Oxytocin impurities included known degradation products and other impurities indicating issues of both storage and manufacturing quality

• TXA quality issues largely limited to related substances/impurities most likely associated with manufacturing
E-MOTIVE Protocol
Can OXY and TXA be mixed for administration with IV fluids

• Question from clinical sites:
  “To simplify administration, can OXY and TXA be mixed and co-administered with the IV fluids?”

• No studies previously conducted to investigate this question

• Screen conducted of 18 TXA products combined with a good quality (not SRA-approved or quality assured) OXY product.
  • Small volume study (~1mL) due to limited availability of supplies
  • Concentrations matched those that would be used with a 200mL IV infusion
  • 0.9%w/v saline used as diluent
  • Compatibility assessed over 1 hour
E-MOTIVE Protocol
Can OXY and TXA be mixed for administration with IV fluids

Follow up Investigations:

• OXY and TXA drug substances (i.e. when not formulated as injection products) do not interact with each other therefore....

• ... the loss of oxytocin is likely due to an interaction with a non-drug component/impurity within these TXA formulations.

• Both TXA formulations contain significant impurities not present in the SRA-approved innovator product (Cyklokapron®) however:
  • Not all of these impurities can be detected using the pharmacopoeial methods
  • A number of the other TXA products contain high levels of impurities and do not interact with OXY
  • It is not yet clear which impurity is responsible for the interaction with OXY (investigations ongoing)

➢ OXY and TXA injection products should NOT be mixed for co-administration
Acknowledgements

Lester Chinery
Anne Ammerdorfer
Alessandra Fleurent
Alessandra Tomazzini

Phil Wright
Claire McEvoy
David Rudd
Matt Parsons