The compatibility of oxytocin and tranexamic acid injection products when mixed for co-administration by infusion for the treatment of postpartum haemorrhage: an in vitro investigation

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Abstract

Objective: To investigate the compatibility of oxytocin and tranexamic acid injection products when mixed for the purpose of co-administration by intravenous infusion. Population or Sample: Oxytocin and tranexamic acid were collected from hospitals taking part in a multicentre postpartum haemorrhage treatment (E-MOTIVE) trial in Kenya, Nigeria, Tanzania, and South Africa. Methods: The compatibility of two sentinel products of oxytocin injection and tranexamic acid injection in 200mL infusion bags of both 0.9%w/v saline and Ringer's Lactate was assessed. We analysed all tranexamic acid -oxytocin combinations, and each evaluation was conducted for up to 6hrs. Subsequently, the compatibility of multiple tranexamic acid products with reference oxytocins products when mixed in 0.9%w/v saline over a period of 1 hour was investigated. Results: We found a significant interaction between certain oxytocin and tranexamic acid products after mixing them in vitro and observing for 1 hour. The interaction substantially impacted oxytocin content leading to reduction in concentration (14.8% - 29.0%) immediately on mixing (t=0 minutes). In some combinations, the concentration continued to decline throughout the stability assessment period. Oxytocin loss was observed in 7 out of 22 (32%) combinations tested. Conclusions: In a clinical setting, mixing oxytocin and tranexamic acid may result in an underdosing of oxytocin, compromising care in an emergency life-threatening situation. The mixing of oxytocin and tranexamic acid injection products for co-administration with IV infusion fluids should be avoided until the exact nature of the interaction and its implications are understood.

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Running title Oxytocin and tranexamic acid products mixed for co-administration

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Conclusions: In a clinical setting, mixing oxytocin and tranexamic acid may result in an underdosing of oxytocin, compromising care in an emergency life-threatening situation. The mixing of oxytocin and tranexamic acid injection products for co-administration with IV infusion fluids should be avoided until the exact nature of the interaction and its implications are understood.

Keywords

Oxytocin, tranexamic acid, intravenous infusion, co-administration, drug interaction, postpartum haemorrhage

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Background

The WHO has defined a postpartum haemorrhage (PPH) 'first-response' treatment bundle based on evidence, current recommendations, and international consensus [1]. The bundle comprises the four key elements of uterotonic drugs, tranexamic acid (TXA), intravenous (IV) fluids, and uterine massage. This treatment bundle has been further developed with the creation of the E-MOTIVE intervention to improve the detection and first response management of PPH, which consists of: (1) **E** arly PPH detection using a calibrated drape; (2) **M** assage of uterus; (3) **O** xytocic drugs; (4)**T** XA; (5) **IV** fluids; and (6) **E** xamination of the genital tract and escalation when necessary [2]. The E-MOTIVE intervention is currently being evaluated in Kenya, Nigeria, Pakistan, South Africa, and Tanzania.

A key implementation approach that we explored for the use of the E-MOTIVE bundle is the co-administration (infusion) of the oxytocin (OXY) and TXA components with the IV fluids. This approach could simplify administration, which may be particularly important in resource-constrained settings with limited numbers of healthcare practitioners to attend a PPH emergency. Following an extensive literature review, no reports were identified providing evidence of the compatibility of OXY and TXA when mixed for intravenous administration. Therefore, the aim of this study was to conduct a preliminary investigation of the compatibility of OXY and TXA injection products when mixed for the purpose of co-administration by IV infusion as part of the treatment bundle for PPH. We used products collected from clinical sites supporting the E-MOTIVE implementation research project. We previously reported on the quality of individual oxytocin and TXA injection products, sampled from E-MOTIVE sites in Kenya, Nigeria, South Africa and

Tanzania[3]. The results indicated samples of both products that did not meet pharmacopoeial standards of quality in terms of drug content and/or related substances and impurities.

Methods

The study was conducted in two stages. Firstly, we developed the analytical methodology to assess the compatibility of the two sentinel products of OXY injection (10IU/mL) and TXA injection (100mg/mL) in 200mL infusion bags of both 0.9%w/v saline and Ringer's Lactate. We analysed all TXA-OXY combinations, and each evaluation was conducted for up to 6hrs. Based on the results from these investigations, the second stage comprised a screen of the compatibility of multiple TXA products with reference OXY products (5 IU/mL and 10 IU/mL) when mixed in 0.9%w/v saline in glass vials over a period of 1 hour.

Analytical Methodology

OXY Analysis

Analysis of OXY was conducted using a validated reversed phase LC-MSMS method. Reversed phase chromatography was performed using a Waters XSelect CSH C18 column (2.1 x 50 mm, 2.5 µm particle size) and a 0.1% formic acid / acetonitrile gradient at 0.5 mL/min flow rate. The injection volume was 8 µL and the total run time was 6 minutes. Quantitation was performed on a Shimadzu LCMS-8060 instrument in positive ESI mode using multiple reaction monitoring (MRM). Parent/daughter transitions acquired for quantitation were 1007.4>723.3 (single charge) and 504.3>285.2 (double charge). The validated range was 20 – 100 ng/mL OXY using external standard quantitation. It should be noted that a LC-MSMS method was used in preference to pharmacopoeial methods to provide the necessary sensitivity to quantify the low concentrations of OXY present when ampoules are further diluted in preparations for infusion use.

TXA Analysis

Analysis of TXA was conducted using an HPLC assay based on the British Pharmacopoeia (2019) method. Briefly, chromatography was performed on a Shimadzu Nexera UHPLC system using an Agilent Zorbax Eclipse Plus C18 column (4.6 x 250 mm, 5 µm particle size). The mobile phase comprised 0.1 M anhydrous sodium dihydrogen phosphate dissolved in 60:40 water:methanol and adjusted to pH 2.5 with phosphoric acid. Sodium dodecyl sulphate (SDS, 5 mM) was added as an ion pairing reagent and separation was performed in isocratic mode at a flow rate of 0.9 mL/min using a 20 µL injection volume. TXA for injection samples (100 mg/mL) were diluted 1:20 to bring them within the validated range of the method (2.5 – 6.0 mg/mL).

Method Verification

Prior to commencing the study, both methods were evaluated to verify that the presence of each active substance did not interfere with the quantitation of the other in both 0.9%w/v saline and Ringer's Lactate solutions (selectivity). Additional method verification was undertaken to demonstrate that the validated parameters, accuracy, precision, linearity, carryover and matrix effect, were not affected by the mixing of TXA and oxytocin.

Study Methods (Part 1)

Materials

Two batches of each OXY injection 10IU/mL and TXA injection 100mg/mL were used in Part 1 of the study as shown in Tables 1 and 2. These batches were collected from sites in Kenya and Nigeria supporting the E-MOTIVE Trial. Prior analysis of these batches of product had shown that all batches were within their expiry date and met BP specifications for these products in terms of assay and related substances. However, neither the OXY nor TXA products were quality-assured, under the definition of having been assessed and listed by WHO under the prequalification of medicines programme or, approved by a Stringent Regulatory Authority (SRA).

Methods

In each experiment, duplicate glass volumetric flasks containing 200mL of either 0.9%w/v saline solution or Ringer's Lactate were accurately prepared. A 200mL volume was selected as this was reported to be the smallest volume of IV fluids used at the E-MOTIVE implementation sites. Therefore, this volume likely represents the greatest risk if compatibility issues exist, as it will lead to the highest concentration of active compounds once added to the IV solution.

Into each flask, one 1mL ampoule of OXY (10IU, ˜17ug) and two 5mL ampoules of TXA injection (1000mg) were added and the bulk solution mixed vigorously. On completion of mixing, 1 mL of solution was immediately removed for analysis from the duplicate solutions and the remaining bulk solutions were transferred to an empty IV infusion bag. The bag was stored under ambient conditions and further duplicate samples taken over a period of 6 hours.

The following two combinations of products were evaluated in these experiments, OXY A with TXA A and OXY B with TXA B.

Based on the results of these experiments, the compatibility of the reverse combinations of products was then evaluated, specifically OXY A with TXA B and OXY B with TXA A. However, in these experiments, the bulk solutions, once mixed, were not transferred into IV infusion bags, but stored under ambient conditions in the glass volumetric flasks in which they were prepared. This change was made to eliminate the possibility of surface effects (e.g. adhesion, adsorption etc.) within the bags. In addition, the stability of the solutions in terms of the OXY concentration only was evaluated for a reduced period of approximately 30 minutes, reflecting the results observed in the first experimental series.

Study Methods (Part 2)

The second part of the study involved a comprehensive screening of a wider range of TXA injection products collected from the E-MOTIVE implementation sites in Kenya, Nigeria, South Africa and Tanzania. Compatibility was assessed against two OXY injection products used at the trial sites.

Materials

Individual batches of two OXY products and 18 TXA products of 100mg/mL were used in Part 2 of the study as shown in Tables 2. All batches were tested for quality against the BP specifications for assay and related substances prior to study start. Both OXY products passed quality testing against the BP specification in terms of assay and related substances but neither was quality assured through listing under the WHO prequalification programme or approval by a SRA. TXA products marked with a single asterisk failed quality testing in terms of TXA content, while those marked with two asterisks failed total impurity specifications. One TXA product (TXA 8) was quality-assured product manufactured by the innovator company.

Methods

In Part 2 of the study, the following adaptations were made to the study methodology:

- Mixing was conducted in a deactivated glass HPLC vial to minimise the possibility of surface interactions and accommodate limited sample quantities.
- Test mixtures were prepared in 0.9%w/v saline only as no differences between saline and Ringer's Lactate were observed in the first part of the study.
- Only OXY concentration was assayed as Part 1 results had provided no indication that TXA concentration is compromised by co-mixing.

1.0 mL of 0.9%w/v saline solution was accurately pipetted into a deactivated glass HPLC vial. An accurately pipetted aliquot of OXY injection solution was added to the saline solution in the HPLC vial and the solution vortex mixed. The volume of OXY injection solution added was 20µL for experiments using OXY 1 (5 IU/mL) and 10µL for OXY 2 (10 IU/mL) to accommodate the different concentration strengths of the two products. Following the addition of OXY, a 100µL aliquot of TXA injection solution was accurately measured into the HPLC vial and the solution vortex mixed. This provides solution concentrations for both active compounds comparable to those used in Part 1 of the study. On completion of mixing, the HPLC vial was placed

immediately into the LC-MS equipment and the assay process started with samples analysed at t=0 minutes and every 10 minutes thereafter over a 1-hour period.

In total, 19 combinations of OXY and TXA in saline solution were evaluated. All 18 TXA products were assessed in combination with the OXY 1 product, while a combination of TXA 8 and OXY 2 was assessed to evaluate a specific combination of interest to the E-MOTIVE Trial.

Results (Part 1)

The results derived from the initial combinations evaluated (OXY A/TXA A and OXY B/TXA B) were inconsistent in terms of OXY concentration over the time evaluated. In the OXY A/TXA A combination solutions, using both diluents, OXY concentration was observed to decline rapidly, becoming undetectable by the assay method within one hour (Figure 1A). The experiment was stopped on observation of this phenomenon and did not continue to 6 hours as originally planned. No significant change in TXA concentration was observed across the duration of the study.

It is noted that the OXY concentrations at t=0 showed significant variation between experiments. This warrants further investigation, however, it should be noted that while t=0 samples are taken immediately on completion of mixing, there is necessarily a time period to prepare and transfer the sample for LC-MSMS analysis, where any interaction will continue to occur and may vary between samples.

The second combination evaluated (OXY B/TXA B) showed a modest drop in OXY concentration immediately after addition of the mixed solution to the IV infusion bag; however, unlike the first combination, the OXY concentration remained stable thereafter (Figure 1B). The TXA concentration across samples in this second experiment remained stable throughout.

The compatibility of the reverse combinations (OXY A/TXA B and OXY B/TXA A) was evaluated in terms of OXY concentration when mixed in glass vials over a period of 30 minutes. The results show that the OXY B/TXA A combination showed a similar rapid decline in oxytocin concentration to that observed with OXY A/TXA A, while oxytocin concentration remained stable in OXY A/TXA B (Figure 1C).

The HPLC chromatograms of TXA A and TXA B were reviewed to look for differences that might correlate with these observations. These chromatograms are shown in Figure 1D and Figure 1E. While both TXA products met British Pharmacopoeia assay and related substances specifications, it is clear that TXA A contains significantly more impurities than TXA B. In particular, a pair of early eluting peaks observed at ˜5.5 min and ˜ 7.5 min (circled in Figure 1D) were several times larger than the main TXA peak by area. This offers one possible line of enquiry to explain the results observed, specifically that these impurities in TXA A, and possibly other impurities not detected by the HPLC method, interact with OXY on mixing to reduce its solution concentration.

Results (Part 2)

The results for the 19 combinations of OXY and TXA injection products evaluated over a period of one hour are shown in Table 3. Five of the 19 combinations of products showed a significant decrease in OXY concentration immediately on mixing such that the OXY concentration at the start of the stability assessment (t=0 minutes) was greater than 10% (14.8% - 29.0%) below the nominal concentration of the solution (i.e. outside the BP assay limits for the oxytocin injection product). In two of these combinations (OXY 1/TXA 4 and OXY 1/TXA 18) the OXY concentration continued to decline during the stability period resulting in solutions at t=60 minutes post-mixing containing 1.9% and 29.5% of the nominal initial OXY concentration respectively. The three remaining combinations, where losses were observed immediately on mixing (OXY 1/TXA 11, OXY 1/TXA 16 and OXY 2/TXA 8), showed no further significant change in OXY concentration during the period of stability assessment. All other combinations showed no significant losses on mixing and remained stable throughout the study.

Discussion

*Main findings*We found an unexpected interaction between certain OXY and TXA products after mixing them in vitro and observing for up to 60 minutes. The interaction significantly impacted OXY content leading to reduction in concentration within a short period of time.

The results of the two experiments indicate that mixing some combinations of OXY and TXA injection in 0.9%w/v saline solution or Ringer's Lactate results in an immediate and significant (14.8% - 29.0%) loss of OXY as measured against the target concentration. In a subset of the combinations where losses are observed, the concentration continues to decline after mixing and throughout the stability assessment period (up to 3 hours). These results were observed across both infusion fluids.

The initial exploratory investigation (Part 1) suggested some indications as to possible causes for this phenomenon. Specifically, the presence of impurities in the TXA product that, when combined with each of two OXY products, may have led to loss of OXY on mixing and throughout the stability period. Also, the possibility of surface adhesion of OXY within the infusion bag cannot be ruled out as contributing to the observations upon mixing. However, the subsequent screen of multiple OXY-TXA injection combinations in 0.9%w/v saline (Part 2) indicates that other factors may be contributing to the effects observed. Firstly, these experiments were conducted in deactivated amber glass HPLC vials, selected to minimise surface effects, yet a similar phenomenon was observed. Secondly, the combinations where OXY losses were observed did not correlate completely with TXA products where significant impurity content was observed on the HPLC chromatograms. We have previously reported quality issues with samples of TXA collected from the clinical sites involved in the E-MOTIVE Trial[3] in terms of excessive impurity content. While seven of the 18 TXA products used in this study showed similar deficiencies, only four of five affected combinations in Part 2 of the study contained TXA products with significant impurity profiles. Finally, one quality assured TXA product (TXA 8) was evaluated with two OXY products (OXY 1 and OXY 2) and loss of OXY on mixing was observed only in combination with one OXY product (OXY 2). This may indicate that some characteristic of the oxytocin product contributes to these effects.

It is worth noting that the ratio of the OXY injection product (10IU, 17µg/mL) concentration to the TXA injection product (500mg/5mL) is very small. Consequently, reactive species present at a proportionally low level within the TXA product, while meeting all quality specifications for the TXA product, might be present at concentrations in the same order as the OXY and could feasibly lead to a substantial loss of OXY, if an interaction were to occur.

*Strengths and Limitations*The strength of this study is that it is the first to examine the compatibility of these two life-saving medications in the context of PPH treatment. In addition, the samples analysed were collected from the point of use in clinical sites in lower and middle-income countries and therefore, represent commodities that would be available for combination if sites were to adopt a co-administration approach in implementing the E-MOTIVE protocol. The main limitation of the study is the small numbers of samples analysed due to constraints on the availability of products for testing. In Part 1 of the study, samples were prepared in duplicate, while in Part 2, only single evaluations of the compatibility of each combination were conducted.

Clinical implications

Administration of IV fluids, OXY (IV or IM) and TXA (IV) is recommended as standard of care by the WHO for the treatment of PPH[1]. Since both IV TXA and therapeutic OXY are administered in IV bags, intuitively there will be inclination to put the two drugs together. In the WOMAN trial (WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial) 99% of all women in TXA group received therapeutic OXY although it is not clear whether they were mixed in the infusion bags or not [4].

Key elements of the PPH first response bundle are the administration of uterotonic drugs (with OXY injection preferred where quality can be assured), TXA injection and IV fluids. The co-administration of these three elements by IV infusion offers the potential to simplify administration in situations where resource constraints

exist.

However, the results of this preliminary study indicate that the potential exists for the mixing of OXY and TXA injection products in IV fluids to result in a significant loss of OXY in the mixed solution. OXY loss was observed in approximately 25% of combinations tested and if these results are replicated in a clinical setting, this practice may result in an underdosing of OXY, compromising care in an emergency life-threatening situation.

Conclusion

The mixing of OXY injection and TXA products for co-administration with IV infusion fluids should be avoided until the exact nature of the interaction and its implications for quality-assured and non-quality-assured products are understood. Further investigation is urgently needed to characterise the underlying mechanisms leading to the observed phenomena and, as appropriate, determine mitigation strategies.

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Contribution to Authorship

IDG, AC and AMG conceptualized and initiated the study. PW and CM were responsible for method development and analysis. All authors contributed to interpretation of the findings. PL and PW wrote the draft manuscript. All authors approved the final version.

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