Heat-Stable Oxytocin

Technology Opportunity Assessment

Prepared for the Merck for Mothers Program
Heat-stable oxytocin

Summary

Oxytocin is a drug that can prevent and manage life-threatening blood loss after a woman gives birth, but current formulations must be given intravenously or by injection and are easily damaged by heat. In low-resource settings, it can be challenging to keep the drug at the right temperature and to administer it safely. To ease these barriers and increase access, several groups are researching oxytocin formulations that are heat stable, including an inhalable powder form that may be easier to administer.

Statement of need

Obstetric hemorrhage is estimated to cause 25% of all maternal deaths and is the leading direct cause of maternal mortality worldwide. Postpartum hemorrhage (PPH), defined as vaginal bleeding in excess of 500 mL after delivery, accounts for most cases of obstetric hemorrhage. It occurs in more than 10% of all births and is associated with a 1% case fatality rate. Although active management of the third stage of labor (AMTSL) can prevent up to 60% of PPH cases, PPH continues to have a devastating impact on women in low-resource settings where home births are common and health care facilities are often inaccessible. Obstetric hemorrhage accounts for 34% of maternal deaths in Africa, 31% in Asia, and 21% in Latin America and the Caribbean. Among women who do survive PPH, approximately 12% will have severe anemia. Also, women who survive severe PPH (greater than 1,000 mL of blood loss) are significantly more likely to die during the following year.

Injectable oxytocin has been recommended by the World Health Organization (WHO) for routine use during AMTSL and is the preferred drug for the prevention and management of blood loss after childbirth. Administering the injection, however, requires skill, sterilized equipment, and proper disposal of medical waste. In addition, in 1993 and 1994, WHO-supported studies demonstrated that oxytocin loses potency in field conditions, particularly tropical climates. Depending on the manufacturer and regulatory agency specification, all oxytocin products must be stored in either controlled room temperature (25°C or lower) or refrigerated storage (2°C to 8°C) to ensure quality.

Although oxytocin in liquid form is typically delivered with a needle and syringe, intranasal delivery of liquid oxytocin has been evaluated extensively in clinical trials and has been found to have side effects similar to those of placebos. For many years Syntocinon® from Novartis Pharmaceuticals, an oxytocin nasal spray in 2-mL or 5-mL liquid presentations, was available with a prescription for at-home use to promote lactation. In 1995 it was removed from the market in the United States due to concerns about its
safety and effectiveness. Other uterotonic\textsuperscript{*} have been investigated as candidates for safe, effective, thermostable, non-parenteral alternatives to oxytocin. Drugs for oral administration, such as ergometrine and methylergometrine tablets or formulations for buccal (dissolving) delivery of oxytocin or desamino-oxytocin, were investigated as possible solutions to replace parenteral (injectable) oxytocin. However, these tablets were found to be unstable in tropical climates.\textsuperscript{6,10} When oxytocin is not available, misoprostol tablets have been recommended for prevention of PPH, but the addition of misoprostol to the WHO Essential Medicines List for the treatment of PPH was not approved in March 2011.\textsuperscript{11} Misoprostol is reportedly less effective than oxytocin and has more adverse effects.\textsuperscript{12,13} These include a significant risk for fever and shivering as well as nausea, vomiting, and diarrhea.\textsuperscript{10}

Timely treatment with oxytocin is not always feasible because injectable oxytocin is only marginally stable in some field settings. There is a need for improved cold chain management and heat-stable forms of oxytocin for use where refrigeration is not available.

Technology solutions landscape

Oxytocin (chemical formula C\textsubscript{43}H\textsubscript{66}N\textsubscript{12}O\textsubscript{12}S\textsubscript{2}) is only marginally stable in an aqueous solution. However, unlike some other marginally stable drugs, it does not have to be formulated into a freeze-dried powder and then reconstituted with a diluent at the point of use.\textsuperscript{14} Oxytocin is sufficiently stable in a ready-to-use solution that requires refrigeration.\textsuperscript{15} Several research groups have developed formulation technologies that improve the temperature stability of oxytocin. A systematic review of these formulation approaches can be organized into three major groups, as discussed below and summarized in Table 1.

1. **Heat-stable parenteral formulations**

These formulations include the addition of metal ions and/or buffers to improve the stability of aqueous oxytocin by preventing the degradation pathways. Avanti et al. demonstrated that the stability of oxytocin in an aqueous solution can be improved with the addition of a combination of divalent metal salts and citrate buffer.\textsuperscript{16} This formulation, however, requires parenteral administration with a needle and syringe filled directly from an ampoule or vial or intravenous delivery. The use of a needle and syringe can be problematic in low-resource settings.

2. **Heat-stable non-parenteral formulations**

Spray-drying oxytocin into an ultrafine powder or particle form is another approach. It has the potential not only to achieve molecular stability but also to provide an alternative, non-parenteral delivery method. Such technology can allow for oxytocin to be inhaled and absorbed very rapidly upon delivery to the lungs, with potentially increased pharmacological action to generate uterine contractions. Research by Michelle McIntosh’s team at the McIntosh laboratory at Monash University (Australia)

\textsuperscript{*} Uterine stimulants (uterotonics or oxytocics) are medications given to cause a woman’s uterus to contract or to increase the frequency and intensity of the contractions.
demonstrated that the inhalation of pharmaceutically engineered particles of oxytocin could prevent and treat postpartum hemorrhage. This novel solution is promising for low-resource settings.

3. Chemical modification

Because oxytocin is a peptide hormone, it is susceptible to protein degradation pathways such as oxidation, disulfide (S-S) reduction, and hydrolysis. The decomposition of oxytocin is mainly caused by deamination, oxidation, hydrolysis, and dimerization. Chemical modification can increase the stability of oxytocin; this makes the peptide hormone less susceptible to degradation pathways. This approach delivers an analogue or derivative of oxytocin; additional research and clinical testing is required to ensure that the uterotonic properties or safety of the oxytocin has not been compromised.

Table 1. Summary of heat-stable oxytocin technologies.

<table>
<thead>
<tr>
<th>Common formulation approaches</th>
<th>Development stage</th>
<th>Delivery route (method)</th>
<th>Bundling considerations</th>
<th>Alignment with current WHO guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heat-stable parenteral</strong></td>
<td>Formulation development</td>
<td>Injection (needle and syringe)</td>
<td>None</td>
<td>Recommended</td>
</tr>
<tr>
<td>Addition of metal ions and or buffers. Lyophilized powder for reconstitution and injection.</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heat-stable non-parenteral</strong></td>
<td>Formulation development</td>
<td>Inhalation into the lungs or mucosa</td>
<td>Dry powder or aerosolized inhaler</td>
<td>Divergent</td>
</tr>
<tr>
<td>Spray dry oxytocin into an ultrafine powder.</td>
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<tr>
<td><strong>Oxytocin analogue</strong></td>
<td>Formulation development</td>
<td>Injection (needle and syringe)</td>
<td>None</td>
<td>Divergent</td>
</tr>
<tr>
<td>Modification of oxytocin chemical structure. Use of an oxytocin derivative.</td>
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Gap analysis

Two systematic reviews conducted by WHO, with data from more than 9,000 women, indicate that oxytocin should be offered to women in preference to other uterotonics. In addition, data from seven studies directly comparing oxytocin and misoprostol underscore the relative benefits of oxytocin in preventing blood loss with fewer adverse effects compared with misoprostol. Although injectable oxytocin is recommended by WHO to combat PPH, its use may not be feasible in some settings. In addition, stability studies indicate that these liquid oxytocin preparations rapidly degrade at temperatures greater than 30°C, and the results suggest that continued efforts are needed to develop temperature-stable oxytocin technologies.

Heat-stabilized oxytocin may offer a cost-effective resolution that could be easily administered for both prevention and treatment of PPH. As these technologies are further developed, one challenge will be to verify that the safety and effectiveness of oxytocin are not compromised by the presence of additives or...
when the drug is modified chemically or physically. It will also be necessary to develop packaging, a
delivery device, and a compound formulation that ensure proper delivery of dry-powder technologies into
the lungs.

Finally, inhalation technologies are required for heat-stable non-parenteral options. Therefore, dry-
powder inhalers (for example, Twincer®,† Puffhaler®,‡ and others) or aerosolized delivery technologies
will need to be evaluated for both clinical effectiveness and cost-effectiveness.

Two key groups are currently working toward heat-stable oxytocin. One is Michelle McIntosh’s group at
Monash University. This group has received funding from the US Agency for International
Development’s Saving Lives at Birth (SLAB) program and the SLAB Peer Choice Award, as well as a
Grand Challenges grant from the Bill & Melinda Gates Foundation, to develop a formulation for dry-
powder oxytocin and evaluate pharmacokinetics.17,19

In addition, TI Pharma, a nonprofit pharmaceutical development group based in the Netherlands, is also
pursuing work on heat-stable oxytocin.20

Investment opportunity

Further research and development are required for application of heat-stable oxytocin in the context of
PPH. Given the current development stage of heat-stable oxytocin technologies, a portfolio approach will
best guide future investments. This may include the following work for the three heat-stable oxytocin
approaches:

• **Formulation development**, including preclinical testing and confirmation of stability in field
  conditions.

• **Clinical studies** to confirm safety and efficacy.

• **Demonstrations and pilot studies**.

Other investments may be needed for the following activities:

• **Development of a regulatory strategy** for approval of successful formulation(s).

• **Economic and market analyses** to confirm the value proposition and sustainability of technological
  innovation.

• **Provider, community, and, where applicable, regulatory agency education and advocacy** to
  build understanding of the technology.

• **Technology transfer** to a suitable pharmaceutical manufacturer to allow for global access and use.

• **Scale-up** to meet market needs.

† Twincer is a registered trademark of the European Solutions Enterprise for Neglected Diseases (euSEND).
‡ Puffhaler is a registered trademark of Aktiv-Dry, LLC.
Development considerations specific to heat-stable non-parenteral technologies include:

- **Formulation development:** To establish moisture stability of dry, ultra-fine powder oxytocin.
- **Delivery:** To identify suitable delivery technologies and methods (dry-powder inhalers or other) given the timing of the delivery of dry-powder oxytocin and the recipient’s physical state.
- **Acceptability profile:** To evaluate human factors to confirm clinical usability of this technology approach.
References


