



Heat-Stable Carbetocin for the prevention of postpartum hemorrhage

The Problem

The United Nations estimated that 303,000 women died from complications associated with pregnancy and childbirth in 2015ⁱ. 99% of these deaths occurred in the developing world.

A price too high to bear: The costs of maternal mortality to families and communities documents the extraordinarily severe financial, economic and social impact of maternal death in Kenya. Of the 59 maternal deaths in the study, only 15 babies survived the first 60 daysⁱⁱ. In another study that reviewed the impact of maternal mortality over 25 years in Ethiopia, it was found that children whose mother dies within 42 days of their birth faced 46 times greater risk of dying within one month when compared to babies whose mothers survivedⁱⁱⁱ. It is imperative that we continue to seek to reduce maternal mortality.

Postpartum hemorrhage (PPH) is responsible for approximately 10.8% of global maternal mortality (with prevalence across Africa averaging 25.7% and as high as 39.7% in one African region ⁽²⁰¹²⁾^{iv}). The leading cause of PPH is uterine atony^v.

Administration of an effective uterotonic immediately following the delivery of the baby is recommended by the WHO to prevent PPH resulting from uterine atony (failure of the uterus to contract).^{vi}

Oxytocin, the WHO-recommended standard medicine administered for the prevention of PPH in women^{vii}, is temperature-sensitive and requires sustained cold chain distribution and storage to ensure its quality.^{viii}

The quality, and therefore effectiveness, of uterotonics available in low income countries is often poor resulting in failure to prevent hemorrhage. The principle causes of poor quality in oxytocin are:

- sub-standard manufacturing and
- susceptibility to degradation due to heat exposure.

There is an unmet need for a low-cost, quality assured, heat-stable uterotonic to prevent postpartum hemorrhage in low income countries.

Heat-Stable Carbetocin Project

MSD for Mothers, the World Health Organization (WHO) and Ferring Pharmaceuticals are collaborating to provide access to a heat-stable formulation of the uterotonic carbetocin, a medicine used to prevent postpartum hemorrhage in women after childbirth.

The availability of a medicine that does not require refrigeration during transportation and storage, and can be kept at elevated temperatures for at least three years, has the potential to significantly improve the prevention and management of bleeding following childbirth in the many areas of the world where cold storage is difficult to achieve and maintain. This will help reduce maternal deaths in those areas.

Children who experienced a maternal death within 42 days of their birth faced 46 times greater risk of dying within one month when compared to babies whose mothers survived.

A WHO-led multi-centre Phase III clinical study is comparing the effectiveness of Heat-Stable Carbetocin (HSC) and oxytocin (both delivered intramuscularly) in the prevention of postpartum hemorrhage and severe postpartum hemorrhage after vaginal births. The study, which will include approximately 30,000 women, is taking place in 10 countries: Argentina, Egypt, India, Kenya, Nigeria, Singapore, South Africa, Thailand, Uganda, and the United Kingdom^x. Enrolment of subjects has passed 23,000 with the trial expected to be completed in Q3 2017.

If the results of the study are positive, the aim of the collaborating organizations is to provide access to Heat-Stable Carbetocin in the public sector of low income countries that have a high burden of maternal mortality, at an affordable and sustainable price.

Concept Foundation is contributing expertise in maternal health supplies for low income countries to the project.



A young girl holds her new-born infant sibling while their mother rests in the Emergency Obstetric Care unit in Upazila Health Complex, Ajmeriganj, Bangladesh. © 2006 Salma Siddique, Courtesy of Photoshare

Heat-Stable Carbetocin

Heat-Stable Carbetocin is a uterotonic medicine used for the prevention of postpartum hemorrhage.

A single 100µg dose of Heat-Stable Carbetocin is effective in preventing postpartum hemorrhage after caesarean section^x.

Heat-Stable Carbetocin remains stable (retains potency) for at least 36 months (3 years) in hot and humid climatic conditions^{xi}. It does not require cold-chain transport or storage.

Carbetocin, developed and manufactured by Ferring Pharmaceuticals since 1997, has been used for the prevention of PPH in over 8.5 million women in over 80 countries worldwide, primarily after caesarean section deliveries (7 countries have also approved it for use following vaginal deliveries).

The heat stable formulation, Heat-Stable Carbetocin, has recently been introduced into 27 countries, including Australia, Mexico and across Europe.^{xii}

Comparison with Oxytocin

Heat Stable Carbetocin	Oxytocin
Heat-stable for at least 3 years at 30°C (ICH Zone IV Stable – Hot/Humid Tropical Zone). Retains potency even when exposed to heat for extended periods of time ^{xiii} .	Rapidly degrades when exposed to heat. ^{xivxxvi}
Does not require refrigeration ^{xvii} .	Requires sustained cold-chain transport and storage ^{xviii} .
The half-life of carbetocin is 40 minutes ^{xix} .	The half-life of oxytocin is 3-5 minutes ^{xx} .
Carbetocin produces rhythmic contractions lasting for up to 120 minutes ^{xxi} .	The duration of effect of oxytocin is approximately 30 minutes ^{xxii} .

Global Engagement

Broad engagement across a wide variety of stakeholders is needed to ensure that women in low income countries have access to Heat-Stable Carbetocin. Normally, the introduction of a medicine into a market would entail large, expensive marketing campaigns. In this case, on successful completion of the WHO trial, low cost advocacy and community engagement will be necessary in order to ensure that HSC is available to the public sector in low income countries at an affordable price. Some of the changes that will be necessary in order for women to receive HSC to prevent postpartum hemorrhage include:

- Updating global guidelines on the recommended prevention and treatment of PPH
- Updating country and facility level guidelines on the prevention and treatment of PPH
- Including HSC in country formularies, essential medicines lists and registered drugs lists
- Country level registration and marketing approval for HSC
- Updating pre-service and in-service training programs for healthcare professionals including midwives, physicians and obstetricians on the correct use of HSC for PPH
- Including HSC in medicines procurement decisions
- Development of job aids and tools to ensure correct usage of HSC

Members of the global maternal health community can assist the project partners in achieving the goal of ensuring access to quality assured Heat-Stable Carbetocin in all low-income countries through engagement in advocacy, collaboration on community awareness activities and expert contributions.

Contacts

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