Beating the heat: the development and implementation of heat-stable carbetocin to prevent postpartum hemorrhage in low-income countries

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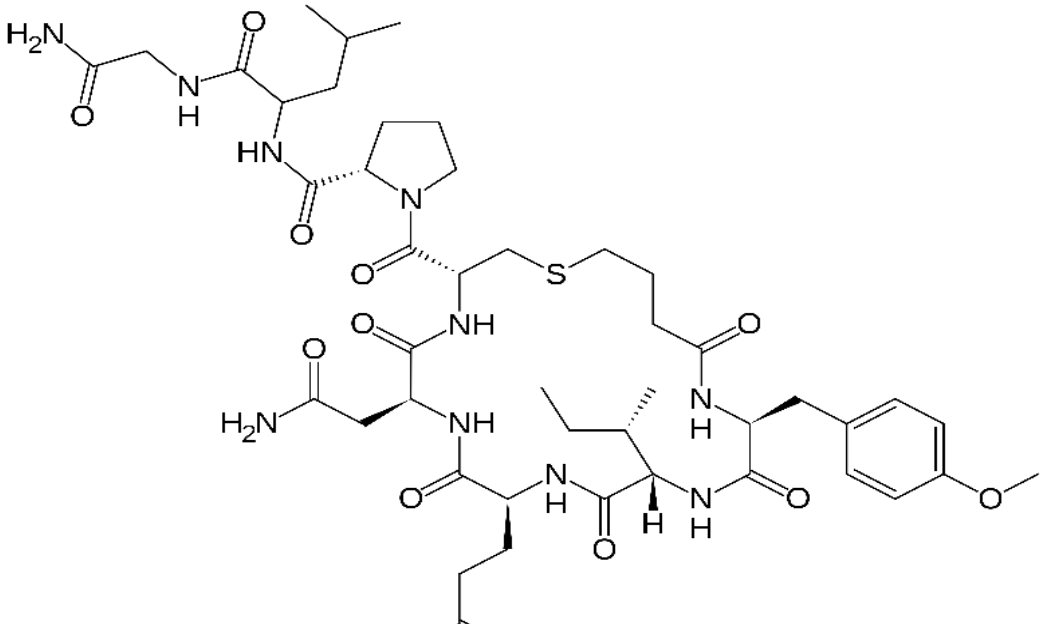

Introduction

A leading threat to maternal health is complications related to pregnancy and childbirth. Though the number of annual maternal deaths declined from 532,000 in 1990 to 303,000 in 2015 (1), the global maternal mortality rate (MMR) is still quite high, and a mother dies every two minutes due to complications of childbirth (2). Postpartum haemorrhage (PPH), accounting for one quarter of maternal deaths globally, is the greatest contributor to MMR (2). PPH is classified by the World Health Organization (WHO) as blood loss of exceeding 500 ml within the first 24 hours following birth. The most common cause of PPH, accounting for nearly 80% of the cases, is uterine atony (3). Under normal physiological conditions,

oxytocin released from the pituitary gland leads to uterine contractions that prevent blood loss (4). At term, approximately 500 millimeters of blood flows to the uterus per minute, and inadequate contractions can lead to substantial blood loss (5). The use of uterotonic agents that promote contraction of the uterus, therefore, presents a mainstay treatment for PPH caused by uterine atony (3).

Injectable oxytocin is the current uterotonic recommended by the WHO for PPH (6). The drug, however, has to be injected under the administration of a medical professional, presenting a limitation to its use. In addition, oxytocin must be stored in the dark and at temperatures requiring refrigeration (2°C to 8°C), or at controlled room temperature (25°C or lower) for a restricted amount of time in order to maintain its potency (7, 8). As such, a cold chain system for storing and transporting oxytocin is required. Due to the thermal instability of the product, there are limitations to oxytocin's efficacy in field conditions, particularly in hot climates where PPH-related maternal mortality is the greatest (8, 9).

Intervention: the heat-stable carbetocin

Carbetocin is a synthetic oxytocin analogue manufactured by Ferring Pharmaceutical that has similar pharmacodynamic properties to oxytocin (10). The therapy has been used in over 8.5 million women for the prevention of PPH. This alternative uterotonic agent, delivered through intramuscular or intravenous injection, has been shown in multiple studies to have fewer side effects than oxytocin (10). Owing to its longer half-life, carbetocin induces stronger and more frequent contractions than oxytocin when administered postpartum (11). Its high bioavailability paired with its long half-life allow for a single administration instead of multiple injections thus reducing the invasiveness of the treatment.

Recently, a heat-stable version of carbetocin (HSC) has been developed that does not require refrigeration and can be kept at high temperatures without losing potency for at least three years. The new version of the drug contains the same active ingredients as the original therapy, but differs in its excipients in order to increase stability. This new intervention presents a promising treatment for PPH in low- and middle-income countries, where maintenance of a cold chain can be challenging and, as a result, the quality of oxytocin variable. In an effort to prevent PPH, the WHO, Ferring Pharmaceuticals, and Merck for Mothers (MFM)—an offshoot of pharmaceutical company Merck—joined together in 2011 in a project called Project CHAMPION, which aims to develop and make HSC accessible to women in low- and middle-income countries (12).

With the benefits of being heat-stable and administered in a single dose, this new

HSC drug has promising applications in settings where cold storage is infeasible and intensive monitoring of women after birth is difficult. As of the time of writing, CHAMPION trials are expected to conclude in 2018. If trial results prove positive, the collaborating organizations intend to work together to make HSC available in the public health sector of countries facing a high burden of PPH. Collaboration on the parts of many players in global health will be needed in order to guarantee that HSC will be accessible to women in low-income countries. A number of challenges exist when introducing a new drug into market and necessary changes to a number public policies will be required. These may include, among others: updating global recommendations on the prevention and management of PPH, revising national and facility level guidelines on the prevention and management of PPH, registering and marketing approval for HSC at the national level, and providing training programs for healthcare professionals on the proper administration of HSC for PPH (13).

Efficacy

While carbetocin is known to be a safe and efficacious drug, the heat-stable version of the treatment must still undergo clinical trials to determine its effectiveness and safety following vaginal delivery. As part of the collaboration between MFM, the WHO, and Ferring Pharmaceuticals, the WHO is in the process of conducting a phase III clinical trial to evaluate the efficacy of HSC versus oxytocin in the prevention of PPH and severe PPH after vaginal birth (8). In addition to assessing efficacy, the safety of the drug in question will also be examined. Adverse effects will be reported whether they were described by the participant or detected by the investigator (8). The clinical trial has two primary endpoints: 1) to evaluate non-inferiority of HSC compared to oxytocin following vaginal delivery in the prevention of PPH, and 2) to assess non-inferiority of HSC compared to oxytocin in the prevention of severe PPH (defined as blood loss exceeding 1,000 millimeters or more at one hour) (8). To quantify these clinical endpoints, the WHO is assessing blood loss as measured by a calibrated drape placed under a woman's buttocks after the administration of the drug and the severance of the umbilical cord but prior to the delivery of the placenta. Blood loss will be measured for a period of one hour postpartum; if bleeding exceeds beyond the hour, measurements will be extended to two hours (8).

The key metrics for impact evaluation of the project as a whole include the quantification of maternal mortality averted, maternal morbidity averted, and the 'ripple effect' averted. As the intervention is currently in clinical trials and has not yet been scaled up, an impact evaluation has not been completed. However, as

previously mentioned, early results of the clinical trials do indicate that carbetocin may be more effective than oxytocin on a number of metrics (14). Based solely on its performance in clinical settings, it is reasonable to assume that if HSC were made available and affordable in health care settings in low- and middle-income countries, the intervention would have a significant impact in reducing PPH if only by providing a more reliable and effective treatment option. As well, this intervention could have a significant impact in terms of reducing the economic and social hardship of the 'ripple effect'—a term often used to describe the long-term impacts of a mother's death on families in developing countries. Studies in Malawi and Ethiopia have found that maternal death exacerbates children's vulnerabilities to long-term negative health outcomes and social impacts related to nutrition, education, employment, early partnership, pregnancy, and caretaking (15, 16). These impacts particularly affect female children in the family, who are often forced to take over the majority of the household and child-rearing responsibilities after the death of a mother (15). Although it is difficult to assess the impact of the ripple effect on all low-income countries, it is probable that if HSC is proven to be effective and made available, a large proportion of the negative economic, health, and social impacts on families would be averted.

Sustainability

A 2016 press release from Ferring Pharmaceuticals stated, "If the results of the study are positive, the collaborating organizations will work together to provide access to the treatment at an affordable and sustainable price, in countries with a high burden of maternal mortality—mainly in Africa and Asia" (19). It is not clear what a "sustainable and affordable" market price would look like for the HSC. Currently, in the U.K., Ferring sells its non-heat stable carbetocin for £10 per dose (20); otherwise, however, global prices are difficult to locate due to a lack of transparency on drug pricing worldwide. Moreover, no studies have been published to date that compare the cost-effectiveness of carbetocin versus that of oxytocin for the prevention of PPH following vaginal delivery, and without the completed WHO trial, it is not possible to determine with certainty the cost-effectiveness of the new HSC versus oxytocin. However, several studies have examined the cost-effectiveness of carbetocin versus oxytocin for the prevention of PPH following cesarean section.

The most recent and extensive cost analysis study of carbetocin was done as a prospective cohort study evaluating the cost of carbetocin compared to oxytocin when used for prevention of PPH following caesarean sections at a U.K. hospital.

This study showed that, when considering the costs associated with drugs, blood and blood products, midwifery, and time spent in recovery, the use of carbetocin translates to a total saving of £77, 201 (£68.93 per patient) per annum for the hospital unit (20). Studies in Canada, Mexico, and Poland showed that the use of carbetocin provided cost savings when compared to oxytocin. In Canada, a cost-minimization analysis of carbetocin (Duratocin label) for the prevention of PPH found that Duratocin was the cheapest treatment strategy for the prevention of PPH in elective caesarean section delivery (21). As well, the study conducted in Mexico found carbetocin to be more cost-effective than oxytocin at preventing uterine atony (22). The Polish study found that, when used following a cesarean section, carbetocin was more cost-effective than oxytocin in preventing PPH due to reduced drug costs, reduced blood product use, and faster discharge from hospital (23). Though, as mentioned earlier, none of these analyses examined cost savings associated with carbetocin use to prevent PPH following vaginal delivery, it is possible to make further extrapolations by looking at a 2017 study comparing the outcomes of high-risk patients treated with oxytocin versus carbetocin after vaginal delivery. Though not necessarily focused on cost analysis, this study found that there was no significant difference between study groups for the need of additional blood transfusions, but there was a significant difference in the use of additional uterotonics (23% vs. 37% in favor of carbetocin), and generally those in the carbetocin group fared better. For this reason, it is likely that the Merck project will also see cost-savings with respect to drug costs and length of hospital stay, but not for additional blood product use (13).

The final factor to be considered when evaluating the potential for cost-effectiveness of the MFM carbetocin project is the costs associated with cold-chain management. Oxytocin requires storage at between 2 to 8°C; this standard, however, is very hard to maintain in countries with average temperatures above 30°C and inadequate cold chain management infrastructure (24). The cold chain includes management of the personnel responsible for drug distribution, the equipment and packaging needed for storage and transport, as well as maintenance and monitoring of equipment, all presenting additional costs to patients and health care systems (25). Few studies show the exact costs of cold chain management; based on the WHO's Ebola vaccine implementation guidelines, however, they could potentially account for anywhere from 9% to 32% of vaccine costs (26). Moreover, there are also costs related to drugs rendered ineffective from poor cold chain management, translating to overuse of oxytocin in order to achieve desired effects (24). With the introduction of HSC, the cold chain management infrastructure will be unnecessary and there

could be significant savings at various points along the supply chain.

The possibility of scaling up

Although, contingent on the success of the clinical trial, the project has potential for scale-up. MFM and Ferring, however, have been unclear on how the drug will be made affordable in the target countries, and have only promised to make the drug available at an affordable price in the public sector. The latter limitation could lead to inaccessibility, as in many of the target countries a large percentage of the population relies on the private health sector; in India, for example, most people rely on private healthcare providers or private pharmacies for treatment and would not have access to the drug at the discounted rate (27). As well, in a number of African countries, small communities do not have access to public hospitals and instead rely on local community health care workers whose services are not always publicly-funded (28). Making the drug affordable in both public and private sectors would allow much greater access to the lifesaving medication and ameliorate both health systems. As improving health by bettering private healthcare is one of MFM's primary goals, making HSC available at an affordable cost in the private sector seems like a reasonable mandate.

Beyond price, the actual administration of the drug may also lead to its inaccessibility. As HSC must be given through intramuscular injection, its administration will require a skilled healthcare provider to perform this task. It has been estimated that more than half of all deliveries that occur in developing countries are home births that are attended by inadequately-skilled providers. Moreover, health facilities are vulnerable to understaffing and shortages of uterotonics (29). Therefore, it is possible that even if HSC was made affordable, it may still be inaccessible to over half of the women who need it most. A better solution then, perhaps, could be the development of a heat-stable, inhalable oxytocin (30). This new drug has shown much promise but has only just succeeded in phase I clinical trial, and it is unlikely that it will be on the market anytime soon. The question about the number of deaths averted following either of these interventions still remains, and will remain, until their respective clinical trials are completed and the projects are scaled up.

Finally, it is also important to put in perspective the $500 million contribution Merck has made for the 10-year MFM initiative. Since the commencement in 2011, Merck has netted over $33 billion in profit worldwide, translating to approximately $5.5 billion in profit for every year since the conception of MFM (31). The MFM initiative has provided $50 million on average a year to improving maternal health, approximately just 1% of the pharmaceutical's total

profit, begging the question of whether Merck is really contributing enough to fulfill MFM's mandate.

Conclusion

Although oxytocin is the suggested drug for the management and treatment of PPH, its thermal instability limits its effectiveness in settings where mortality caused by PPH is highest. The project to develop a heat-stable carbetocin, as such, is a promising solution to a problem that has long been neglected. Multiple studies have demonstrated the economic and pharmacological benefits of using carbetocin over oxytocin, although a formal impact evaluation of the project at hand has not yet been conducted. Still, the promise that the drug will be made affordable in the public sector, and Merck's expertise in navigating manufacturing, regulatory affairs, and supply/access, leads to optimism that the project will be effective in reducing maternal deaths caused by PPH.

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