Dr Michelle McIntosh has assembled a world-class team of researchers to aid her in cutting incidence of postpartum haemorrhage in the developing world. Here, she talks about why their efforts are so crucial.

How did you become aware of the problem of postpartum haemorrhage (PPH) – uncontrolled loss of blood after delivery of a baby – in resource poor countries?

We had been contacted by a student from Botswana who had an AusAID scholarship to study a Master's degree in Australia and expressed an interest in learning more about pharmacokinetics, bioequivalence and analytical techniques. When I met with two colleagues at Monash University to discuss whether we had a suitable project, Dr Richard Prankerd mentioned that he was aware of the limitations associated with oxytocin injections in developing countries, and suggested that we could look at preparing an inhaled formulation. Dr David Morton had the expertise to create a dry powder for inhalation and I had experience in characterisation of drug pharmacokinetics, bioequivalence studies and the required analytical methods to conduct these studies. Six months after starting the project, we saw a call for proposals from the Bill & Melinda Gates Foundation's (BMGF) Grand Challenges Exploration (GCE) for innovative ideas capable of improving maternal and neonatal healthcare in developing countries. This was when we began to fully understand the need for a product such as inhaled oxytocin.

Why is an alternative solution to how PPH is already treated in developed countries needed?

Oxytocin is the gold standard drug for the management of PPH around the world, and can be given as an injection one to two minutes after childbirth. However, for injectable oxytocin to be effective it requires cold chain supply and storage to prevent degradation. In developing countries, many women give birth at home where it is not possible to receive an injection immediately after childbirth, and even for those who do give birth in a hospital setting oxytocin may not be available, or may be degraded. A further limitation in some countries is lack of access to the supplies required to give the injection, such as needles and syringes, and there is also a risk of needle stick injuries and blood borne virus transmission. Further, midwives or birth attendants may not always have enough time to give an injection immediately after childbirth.

Could you offer an overview of how you propose to treat PPH in developing countries?

Our intention is that an inhaled oxytocin product would negate the need for cold chain storage, remove the risk of needle stick injuries, allow medical intervention at more peripheral levels of the healthcare system and could potentially be self-administered at home births in the event that a woman is unable to reach a hospital for childbirth.

How has this project benefited from the support of the BMGF’s GCE initiative? What purpose does this initiative serve?

Both the phase I and phase II funding from the BMGF have been essential in providing the resources to move the project forward. We have also been funded through the Saving Lives at Birth programme, which is offered through a consortium of funding bodies (BMGF, USAID, UKAID, Norwegian Government and Grand Challenges Canada). These funding programmes have helped to raise the awareness of our programme and have led to the inclusion of inhaled oxytocin as potentially lifesaving innovation in the 2012 UN Commission report on Life Saving Commodities for Women and Children.

Who else is involved in this project? What range of expertise and backgrounds contribute to the research?

We are very fortunate to have a wide range of partners on this project. They include Dr Richard Prankerd, an expert in understanding the physicochemical properties of drugs and mechanisms of drug degradation from the Monash Institute of Pharmaceutical Sciences (MIPS); Associate Professor David Morton, also at MIPS, who has over 20 years of experience in spray drying and engineering of particles/aerosols; our project manager, Pete Lambert, research scientist at MIPS and a specialist in nasal and respiratory drug delivery; Dr Eddie French from TEKH Consulting, who has expertise in delivery of therapeutically active biological and inhalation devices; and Dr Rob Bischof from the Department of Physiology at Monash University, an expert in airway physiology and disease. In addition to these people we also have five postdocs with experience in formulation science (Dr Felix Meisser and Dr Tomas Sou), pharmacokinetic studies and analysis (Dr Tri-Hung Nguyen and Dr Tori Oliver) and a pharmacometrician (Dr Kashyap Patel). There are also three PhD students working on a variety of aspects related to the inhaled delivery of oxytocin.
Developing novel drug formulations

Ongoing studies at Monash University, Australia, are making great strides in reformulating oxytocin for delivery via a dry powder, with the aim of making the drug more reliably available in developing countries.

POSTPARTUM HAEMORRHAGE (PPH) – the loss of more than 500 ml of blood from the genital tract following vaginal delivery – is the most common form of obstetric haemorrhage and the single largest contributing factor to maternal morbidity worldwide. Occurring during the third stage of labour, the period comprising the expulsion of the placenta, PPH is estimated to cause up to 150,000 fatalities in the developing world every year. Promisingly, the complication is almost entirely preventable via the administration of an oxytocin drug, but intramuscular (IM) injection of the drug requires levels of expertise and equipment which often preclude its reliable availability in resource poor areas.

In response, groundbreaking studies at the Monash Institute of Pharmaceutical Sciences in Melbourne, Australia, are pioneering a novel method for delivery of oxytocin, recommended by the World Health Organization as the first-line therapy for the prevention and treatment of PPH. Led by Dr Michelle McIntosh in close collaboration with her colleagues, there is much hope that the project will result in the wider and more consistent availability of effective preventative methods for PPH in developing countries, potentially saving tens of thousands of lives every year.

RESPIRATORY TRACT DELIVERY

Injecting oxytocin is not a reliable method in many developing countries and a recent study in Ghana showed that 74 per cent of oxytocin ampoules did not contain the specified concentration of the drug due to temperature induced degradation – a heat stable, non-injectable formulation is seen as the way forward. In a number of economically emerging and developed countries, drug delivery to the respiratory tract is a popular technique for a variety of airway conditions such as asthma and chronic obstructive airway disease. Although these examples are aimed at local activity within the airway, it is possible to use either the pulmonary or nasal respiratory tract as a means of accessing systemic circulation. Indeed, this has already been demonstrated in the delivery of peptide molecules such as calcitonin, desmopressin and insulin, which are not bioavailable following oral administration. Interestingly, oxytocin – a small peptide – is already available in several countries as a nasal spray to stimulate lactation and, taking this into account, McIntosh and her colleagues are confident that they can further expand the field of respiratory tract drug delivery to encompass PPH preventing oxytocin.

SPRAY-DRYING

In order to render oxytocin deliverable via inhalation, McIntosh and her fellow researchers have been working to employ a technique known as spray-drying, a method of turning a liquid into a dry powder by rapidly drying it with a hot gas. “Spray-drying can be used to carefully engineer the desired properties in powder particles, ensuring that they are aerodynamically designed to reach the location where the majority of drug absorption from the lung occurs: in the deep lung,” she expands. In order for the particles to reach this target, they need to measure between 1-3 microns in diameter. To their knowledge, the group is the first to have developed a dry powder containing oxytocin for inhalation, and they are confident that their success can herald a major breakthrough in making the drug more accessible in developing countries.

HUMAN TRIALS

Although the project is not yet at a stage where human trials are possible, a prototype formulation has already been developed which the researchers are seeking to use in phase I clinical trials. As with any similar drug development process, before such trials can commence the researchers are required to both establish good manufacturing practice (GMP) and obtain approval from a human ethics research committee. Due to the results they have already obtained, the researchers are confident they can achieve these targets, and are actively pursuing funding to assist them in performing the trials. “Encouragingly, the preclinical data indicate that the oxytocin plasma versus time profiles following inhaled delivery can match the profiles for IM injection, making inhalation an eminently workable alternative,” McIntosh enthuses.

LOGISTICS

One of the key advantages of the inhaled form of oxytocin is its demonstrated ability to retain its potency when stored at ambient conditions comparable to those in the resource poor settings where it is likely to be sent. “While further studies are required, a key development has been to show that the dry powder formulation confers greater stability of the product than the solution for injection which is currently available,” McIntosh elaborates. Another major factor in determining how widespread the formulation will be, and thus how significant its potential for reducing maternal morbidity, is its eventual cost. This, too, is an area about which McIntosh and her fellow researchers are
optimistic. Because it does not require storage and transportation within the cold chain, the inhaled formulation of oxytocin is expected to require significantly less logistical expenditure than its injectable counterpart.

The project members have also ascertained that it is possible to manufacture low cost, single use inhalers which can be employed to administer the dry powder. This could be pivotal for the success of the project, meaning that the overall price per dosage is expected to be roughly similar to that of the injected formulation. In addition, there are a number of options available for how these inhalers may be distributed. McIntosh elucidates: “In some cases, inclusion in clean birth kits may be an option, or distribution to pregnant women at antenatal visits; alternatively the product may be carried and administered by skilled birth attendants or by medical staff in labour and delivery wards”. Whatever the means, the inhalers are expected to be much more easily transported and dispensed than the conventional injectable solution.

CULTURAL CONSIDERATIONS
Despite the significant scientific, logistical and funding challenges they have encountered in devising and developing this novel form of oxytocin delivery, McIntosh and her fellow researchers maintain that the most momentous challenge they face will be in establishing a complementary education programme for the drug. Due to the geography of many of the developing countries for which the formulation has been developed, significant numbers of the women and birth attendants targeted live in remote and inaccessible locations, making it difficult to increase their awareness of the importance of appropriately managing the third stage of labour.

Further to this, there are also many cultural beliefs around the importance of bleeding after child birth as a way of cleansing the woman, and McIntosh is acutely aware of the importance of such beliefs: “In each region where we plan to introduce inhaled oxytocin, it will be essential for us to understand the community, the traditions and the culture around child birth, and to look for opportunities to introduce inhaled oxytocin in a complementary manner”. They have already visited a number of rural communities in Tanzania, Uganda and the Uttar Pradesh region of India to meet with mothers, birth attendants and clinicians. This has allowed the researchers to ensure that any product they design will meet the needs of end-users, thus reducing PPH-related fatalities worldwide without attempting to compromising historically, socially and culturally significant beliefs and practices.

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