Increasing access to oxytocin for the prevention of postpartum haemorrhage: Inhaled Oxytocin A Phase I Study

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The following clinical trial (NCT02542813) was funded entirely by the pharmaceutical company GSK and conducted at the GSK Clinical Trials unit in Addenbrooke’s Hospital, Cambridge, UK.

The speaker of this presentation Dr. Disala Fernando is an employee and a shareholder of GSK.
Background
Heat Stability

Unpublished studies: Monash University and GSK internal data
Results

Median oxytocin plasma concentration-time profile

- IM oxytocin 10 IU (17 μg)
- IH oxytocin 50 μg
- IH oxytocin 200 μg
- IH oxytocin 400 μg
- IH oxytocin 600 μg

LLQ = 2 pg/mL
Next Steps
Partnerships

Project Partners
- Monash University (Innovator and Development Partner)
- GlaxoSmithKline (Development Partner, Co-Funder)

Current Funding Partners
- McCall MacBain Foundation
- Saving Lives at Birth
- RHSC Innovation Fund

Previous Funding Partners
- Bill & Melinda Gates Foundation
- ANZ Partners
- UN Commission Innovation Working Group
- Grand Challenges Canada
- Planet Wheeler Foundation
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Abstract (on line supplement to BJOG) – JP238
Increasing access to oxytocin for the prevention of postpartum haemorrhage in resource-limited settings: Phase I data for a heat-stable, dry-powder formulation of inhaled oxytocin in healthy, non-pregnant volunteers

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Objective
Reducing maternal mortality is a key UN Sustainable Development Goal. However, over 300,000 women still die from complications of pregnancy and childbirth every year; the vast majority in developing countries.1 Postpartum Haemorrhage (PPH) accounts for 19.7% of these maternal deaths.2 Intramuscular (IM) oxytocin is the gold standard for prevention of PPH, but access in developing countries is limited by formulation stability and availability of trained professionals to administer injections. A heat-stable, inhaled (IH) formulation delivered via a simple inhaler (Modified Air Inlet ROTAHALERTM Dry Powder Inhaled Device [Figure 1]) provides an opportunity to offer women in resource poor settings access to this gold standard treatment. Here we report the first IH oxytocin clinical study which was conducted in healthy non-pregnant volunteers, and designed to assess the safety, tolerability and pharmacokinetics (PK) of IH oxytocin compared to IM oxytocin.

Study Design
• This was a single-blind, dose-escalation, fixed-sequence study in healthy, non-menopausal, non-pregnant, non-lactating women aged 18–45 years.
• In dosing session 1 (S1), subjects received IM oxytocin 10 IU on day 1, IH placebo on day 2 and IH oxytocin 50 µg on day 3. In dosing Session 2 (S2) to Session 4 (S4), subjects were randomized to receive either IH placebo or ascending doses of IH oxytocin (200, 400, 600 µg). [Figure 2]
• Plasma PK profiles were compared for each IH dose vs IM oxytocin focusing on rate and extent of systemic exposure, specifically quantified concentration at 10 and 30 min (Cp10 and Cp30) post dose and area under concentration-time curve over 3h post dose (AUC0-3).
• Adverse events (AEs), laboratory tests, vital signs, electrocardiograms, physical exams, telemetry and spirometry were assessed.

Results
15 of 16 randomised females completed the study. In general, the shape of the observed PK concentration-time profile for IM oxytocin was consistent with the IM profile [Figure 3] with slightly reduced absorption of oxytocin into plasma following both IM and IH administration. Median Tmax (0.17 h) after IM administration, 0.14-0.33h following IH oxytocin over the dose range of 50-600 µg. Thereafter, plasma concentration fell with estimates of the apparent terminal elimination half-life consistent across routes (IM vs IH) and adjusted mean ratios for PK parameters were >1.0 for Cp10, Cp30 and AUC(0-3) following 400 and 600 µg IH oxytocin and were lower for the lower doses [Table 1]. No serious AEs were reported. No clinically significant findings were observed for any safety parameter.

*One subject was withdrawn at the investigator’s discretion.

Table 1 - Summary of Statistical Analysis of oxytocin PK Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Comparison</th>
<th>Adj. geometric mean (test/ref)</th>
<th>Adj. geometric mean ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cp10 (pg/mL)</td>
<td>50 µg IH vs 10 IU IM</td>
<td>12.0/171.2</td>
<td>0.07 (0.05, 0.09)</td>
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<tr>
<td></td>
<td>200 µg IH vs 10 IU IM</td>
<td>72.7/171.2</td>
<td>0.42 (0.33, 0.55)</td>
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<td>400 µg IH vs 10 IU IM</td>
<td>188.1/171.2</td>
<td>0.10 (0.85, 1.43)</td>
</tr>
<tr>
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<td>600 µg IH vs 10 IU IM</td>
<td>258.3/171.2</td>
<td>1.51 (1.16, 1.96)</td>
</tr>
<tr>
<td>Cp30 (pg/mL)</td>
<td>50 µg IH vs 10 IU IM</td>
<td>9.6/82.2</td>
<td>0.12 (0.09, 0.15)</td>
</tr>
<tr>
<td></td>
<td>200 µg IH vs 10 IU IM</td>
<td>58.6/82.1</td>
<td>0.71 (0.56, 0.91)</td>
</tr>
<tr>
<td></td>
<td>400 µg IH vs 10 IU IM</td>
<td>135.6/82.2</td>
<td>1.65 (1.30, 2.09)</td>
</tr>
<tr>
<td></td>
<td>600 µg IH vs 10 IU IM</td>
<td>191.0/82.2</td>
<td>2.32 (1.83, 2.95)</td>
</tr>
<tr>
<td>AUC0-3 (pg.h/mL)</td>
<td>50 µg IH vs 10 IU IM</td>
<td>14.8/272.6</td>
<td>0.12 (0.10, 0.14)</td>
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<tr>
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<td>200 µg IH vs 10 IU IM</td>
<td>69.8/272.6</td>
<td>0.55 (0.46, 0.65)</td>
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<td>400 µg IH vs 10 IU IM</td>
<td>161.8/272.6</td>
<td>1.27 (1.07, 1.50)</td>
</tr>
<tr>
<td></td>
<td>600 µg IH vs 10 IU IM</td>
<td>234.5/272.6</td>
<td>1.84 (1.56, 2.18)</td>
</tr>
</tbody>
</table>

Conclusion & Long-Term Goals
• Preliminary plasma PK data suggest that similar oxytocin systemic exposure can be achieved with IM and IH administration routes with no new safety concerns.
• A second study enrolling pregnant women is currently underway in Cambridge, UK evaluating the PK of IH oxytocin compared to IM oxytocin during the third stage of labour.
• Future studies will aim to confirm the final dose, and explore safety in sub-populations such as asthmatics and smokers.
• The inhalation route may offer the opportunity to deliver an effective oxytocin dose to women giving birth in resource poor settings.

REFERENCES
• GlaxoSmithKline Document Number 2016N286552_00. Study ID IIVF116828; 29-NOV-2016.

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