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Research Paper

Safety, Tolerability and Pharmacokinetics of Single Doses of Oxytocin Administered via an Inhaled Route in Healthy Females: Randomized, Single-blind, Phase 1 Study☆

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ABSTRACT

Background: The utility of intramuscular (IM) oxytocin for the prevention of postpartum hemorrhage in resource-poor settings is limited by the requirement for temperature-controlled storage and skilled staff to administer the injection. We evaluated the safety, tolerability and pharmacokinetics (PK) of a heat-stable, inhaled (IH) oxytocin formulation.

Methods: This phase 1, randomized, single-center, single-blind, dose-escalation, fixed-sequence study (NCT02542813) was conducted in healthy, premenopausal, non-pregnant, non-lactating women aged 18–45 years. Subjects initially received IM oxytocin 10 international units (IU) on day 1, IH placebo on day 2, and IH oxytocin 50 μg on day 3. Subjects were then randomized 4:1 using validated GSK internal software to IH placebo or ascending doses of IH oxytocin (200, 400, 600 μg). PK was assessed by comparing systemic exposure (maximum observed plasma concentration, area under the concentration-time curve, and plasma concentrations at 10 and 30 min post dose) for IH versus IM oxytocin. Adverse events (AEs), spirometry, laboratory tests, vital signs, electrocardiograms, physical examinations, and cardiac telemetry were assessed.

Findings: Subjects were recruited between September 14, 2015 and October 12, 2015. Of the 16 subjects randomized following initial dosing, 15 (IH placebo $n = 3$; IH oxytocin $n = 12$) completed the study. IH (all doses) and IM oxytocin PK profiles were comparable in shape. However, systemic exposure with IH oxytocin 400 μg most closely matched IM oxytocin 10 IU. Systemic exposure was approximately dose proportional for IH oxytocin. No serious AEs were reported. No clinically significant findings were observed for any safety parameters.

Interpretation: These data suggest that similar oxytocin systemic exposure can be achieved with IM and IH administration routes, and no safety concerns were identified with either route. The inhalation route may offer the opportunity to increase access to oxytocin for women giving birth in resource-poor settings.

1. Introduction

Oxytocin is a neuropeptide involved in the onset and progression of labor (Arrowsmith and Wray, 2014; Blanks and Thornton, 2003). Oxytocin acts as a potent endogenous uterotonic (Arrowsmith and Wray, 2014), causing an increase in uterine contraction intensity and frequency, which facilitates labor and delivery (Blanks and Thornton, 2003). Following delivery, the mother is, however, at risk of postpartum hemorrhage (PPH), defined as blood loss of ≥500 mL within 24 h after birth (World Health Organization, 2012), most commonly due to uterine atony (Weeks, 2015). In the 25 years between 1990 and 2015, an estimated 10.7 million women worldwide died in pregnancy and childbirth (World Health Organization, 2015a). Of the estimated 303,000 women who died during and following pregnancy and childbirth in 2015, 99% were from low-income countries, with approximately two-thirds of deaths occurring in sub-Saharan Africa and one-third in Asia (World Health Organization, 2015a). PPH is estimated as the single largest contributor to maternal mortality, responsible for 19.7% of maternal deaths

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worldwide (Say et al., 2014). Many of these deaths could be prevented by effective access to treatments to reduce PPH (World Health Organization, 2012). Active management of the third stage of labor, including prophylactic administration of injectable oxytocin immediately after delivery, has been shown to significantly reduce primary blood loss ≥ 500 mL compared with expectant management (Begley et al., 2015).

Intramuscular (IM) oxytocin (10 international units [IU]) was identified as one of 13 life-saving commodities for women and children in a 2012 United Nations (UN) Commission Report (United Nations, 2012), and was included in the World Health Organization (WHO) model list of essential medicines (World Health Organization, 2015b). Oxytocin is supplied as an aqueous solution in an ampoule and requires cold-chain storage, sterile needles with sharps disposal, and trained healthcare professionals for administration. This significantly limits access in resource-poor settings, where many women cannot attend medical facilities, their birth attendants are not allowed to administer injections, or the oxytocin cannot be refrigerated, leading to use of material of degraded quality. A review of studies assessing the quality of oxytocin ampoules for injection in low- and middle-income countries found that 58% and 22% of ampoules collected in Africa and Asia, respectively, contained less than the specified content of oxytocin, according to pharmacopoeial limits (Torloni et al., 2016).

Inhaled (IH) delivery of heat-stable oxytocin could offer a practical means to deliver this medicine without the need for cold-chain storage and provide access in those resource-poor settings of greatest unmet need. The Innovation Countdown 2030 Initiative has estimated that the introduction of non-injectable, heat-stable formulations of oxytocin could prevent 146,000 maternal deaths over a period of 8 years (Innovation Countdown 2030, 2015).

We have developed a heat-stable dry powder formulation of oxytocin for inhalation and sought to evaluate the safety, tolerability and pharmacokinetics (PK) in this study. Subjects also received IM oxytocin 10 IU for PK comparison.

2. Materials and Methods

2.1. Study Design

This phase 1, randomized, single-center, single-blind, ascending dose-escalation, fixed-sequence study with IH oxytocin (NCT02542813) was conducted at the GSK Clinical Unit Cambridge, Addenbrooke's Centre for Clinical Investigation (Addenbrooke's Hospital, UK). Ethical approval for the study was obtained from the Office for Research Ethics Committees Northern Ireland. The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, all applicable subject privacy requirements, and the ethical principles outlined in the Declaration of Helsinki 2013. The full protocol can be accessed at https://gsk-clinicalstudyregister.com/search/ps/1/?study_ids=201558.

2.2. Subjects

Subjects eligible for inclusion in the study were healthy, premenopausal, non-pregnant, non-lactating women aged 18–45 years inclusive, with a body mass index of 18–30 kg/m^2, who were taking an estrogen-containing oral contraceptive pill both prior to and for the duration of the study. Key exclusion criteria included a history of chronic lung conditions, respiratory tract infection within 4 weeks of screening, and history of smoking within 1 year of screening. A full list of exclusion criteria are included in Supplementary Appendix A. Potential subjects were identified from the volunteer panel of the GSK Unit and by advertising. Written informed consent was obtained prior to the performance of any study-specific procedures.

2.3. Randomization and Masking

Suitable subjects were enrolled for the study by the principal investigator or designee based on the inclusion and exclusion criteria. Subjects were randomized 1:4 to receive either IH placebo or ascending doses of IH oxytocin (50, 200, 400, 600 μg). Subjects were assigned to study treatment in accordance with the randomization schedule generated by GSK prior to the start of the study using validated internal software. Dosing with IH placebo and IH oxytocin was single blind (blinded to subjects only) for all subjects throughout the study. The excipients in the placebo formulation had not, to our knowledge, previously been included in an inhaled product in this combination. Although the respiratory risk was deemed to be low, the investigator remained unblinded to allow differentiation of adverse events related to inhaled placebo from inhaled oxytocin in order to monitor the tolerability of the study medication and the safety of the subjects. Blinding for subjects was maintained by the use of a matched inhaler device and capsule presentation for both IH placebo and IH oxytocin. The timings of all procedures after IH placebo and IH oxytocin were identical.

2.4. Procedures

2.4.1. Interventions

In dosing session one, all subjects received oxytocin 10 IU (17 μg) (EVER Neuro Pharma GmbH, Unterach, Austria) by IM injection in the thigh on day 1. The excipients in the dry powder IH formulation capsules have been used previously in other IH products, but not in the combination used in this study. Therefore, the safety and tolerability of the excipients alone (IH placebo) were tested in all subjects on day 2. IH oxytocin was then administered to all subjects at a dose of 50 μg on day 3. All IH treatment capsules were administered by oral inhalation using a Modified Air Inlet ROTAHALER™ Dry Powder Inhaler. Study investigators were trained to use the inhaler, and trained subjects prior to use. The first dosing session employed a sentinel cohort approach, in which a pilot group of three subjects was evaluated first, before the remaining 12 subjects were dosed in a staggered fashion, with no more than four subjects dosed per day.

The doses of IH oxytocin selected for investigation were expected to encompass the likely IH therapeutic dose (ie, with a similar systemic exposure to IM oxytocin 10 IU). Dose selection considerations encompassed the predicted amount of drug delivered to the lungs (% nominal) for the current dry powder formulation delivered via the ROTAHALER™ inhaler device, and assumptions around the likely range of relative bioavailability values of IH oxytocin compared with recently reported exposure values following IM administration of oxytocin 10 IU to healthy subjects. Lung bioavailability was assumed to be between 10% and 150% of IM availability, with the upper bound of the range reflecting lung bioavailability reported for other low molecular weight proteins, such as leuprolide (Adjei and Garren, 1990) and insulin (Patton et al., 2004).

In dosing sessions two, three, and four, subjects randomized to placebo received IH placebo (excipients only), while subjects randomized to IH oxytocin received escalating doses of IH oxytocin: 200 μg, 400 μg, and 600 μg (administered as 200 μg and 400 μg capsules using one ROTAHALER™ inhaler device per capsule). The decision to proceed to the next increased dose level was made by the dose-escalation committee based on the available safety and tolerability data from not less than nine subjects receiving oxytocin at the prior dose level, as well as any available PK data from the previous dose levels. A follow-up visit was conducted 7–21 days after the last IH oxytocin or IH placebo administration. An overview of the study design is shown in Fig. 1.

2.4.2. Assessments and Analyses

2.4.2.1. Safety Assessments. Adverse events (AEs) and serious AEs (SAEs) were monitored throughout the study. Spirometry, clinical laboratory

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