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ORIGINAL ARTICLE

Pharmacokinetics and safety of inhaled oxytocin compared with intramuscular oxytocin in women in the third stage of labour: A randomized open-label study

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Abstract

Aims: To compare pharmacokinetics (PK) and safety of heat-stable inhaled (IH) oxytocin with intramuscular (IM) oxytocin in women in third stage of labour (TSL), the primary endpoint being PK profiles of oxytocin IH and secondary endpoint of safety.

Methods: A phase 1, randomized, cross-over study was undertaken in 2 UK and 1 Australian centres. Subjects were recruited into 2 groups: Group 1, women in TSL; Group 2, nonpregnant women of childbearing potential (Cohort A, combined oral contraception; Cohort B, nonhormonal contraception). Participants were randomized 1:1 to: Group 1, oxytocin 10 IU (17 μg) IM or oxytocin 240 IU (400 μg) IH immediately after delivery; Group 2, oxytocin 5 IU (8.5 μg) intravenously and oxytocin 240 IU (400 μg) IH at 2 separate dosing sessions.

Results: Participants were recruited between 23 November 2016 to 4 March 2019. In Group 1, 17 participants were randomized; received either IH ($n = 9$) or IM ($n = 8$) oxytocin. After IH and IM administration, most plasma oxytocin concentrations were below quantification limits (2 pg/mL). In Group 2 ($n = 14$), oxytocin IH concentrations remained quantifiable ≤3 h postdose. Adverse events were reported in both groups, with no deaths reported: Group 1, IH $n = 3$ (33%) and IM $n = 2$ (25%); Group 2, $n = 14$ (100%).

Conclusion: Safety profiles of oxytocin IH and IM were similar. However, PK profiles could not be established for oxytocin IH or IM in women in TSL, despite using a highly sensitive and specific assay.

The authors confirm that the principal investigators for this paper were Dr Katarzyna Gajewska-Knapik and Dr Kirsten Palmer and that they had direct clinical responsibility for patients. Dr Subramanya Kumar had direct responsibility for the nonpregnant patients.

KEYWORDS
obstetric haemorrhage, oxytocin, pharmacokinetics, randomized clinical trial

1 | INTRODUCTION

With approximately 295 000 maternal deaths per year globally, reducing maternal mortality has been adopted as a Sustainable Development Goal by the United Nations, with the aim of reducing the global maternal mortality ratio to <70 per 100 000 live births by the year 2030 (Goal 3).[1] Postpartum haemorrhage (PPH) is the leading cause of maternal mortality, accounting for nearly 20% of all maternal deaths globally.[2] In low- and middle-income regions such as northern Africa and eastern Asia, this proportion can be as high as ~30%.[2]

Oxytocin is included in the World Health Organization List of Essential Medicines as a preventive intervention for PPH, and is considered the gold standard of treatment by Cochrane review and the World Health Organization; 10 IU given via the intramuscular (IM) or intravenous (IV) route during the third stage of labour (TSL) is recommended for prevention.[3,4] However, the current aqueous formulation of oxytocin for injection requires cold-chain storage and injection by skilled birth attendants.[5,6] The degradation of oxytocin injection products, when stored without refrigeration,[7] is a widespread issue in resource-poor settings; a systematic review found that 57.5 and 22.3% of oxytocin ampoules tested in Africa and Asia, respectively, contained <90% of labelled oxytocin.[8] The availability of high-quality oxytocin in this setting is limited.[5,6]

Implementation of a simply administered, heat-stable, noninjectable, dry powder formulation of oxytocin would remove the need for refrigeration and consumables (i.e. syringes, needles) and allow task shifting to a wider range of birth attendants. This would increase access to oxytocin and could be effective in the prevention of PPH in resource-poor settings. A first-time-in-human (FTIH) study investigating the safety, tolerability and pharmacokinetics (PK) of 4 ascending doses of an inhaled (IH), heat-stable, dry powder formulation of oxytocin in nonpregnant women showed favourable results.[9] Oxytocin IH demonstrated rapid absorption into plasma with a similar PK profile to oxytocin administered by IM injection, and there were no significant safety findings.[9] Importantly, a dose of oxytocin 240 IU (400 μg) IH was found to result in similar systemic exposure to that of oxytocin 10 IU (17 μg) IM.[9]

The aim of the current study (NCT02999100) was to characterize the safety and PK of oxytocin 240 IU IH compared with oxytocin 10 IU IM in women in TSL, and oxytocin 240 IU IH compared with oxytocin 5 IU IV in nonpregnant women.

What is already known about this subject

- Oxytocin intravenous/intramuscular is standard of care for the prevention and treatment of postpartum haemorrhage.
- Access to high quality oxytocin injection products in resource constrained settings is significantly compromised due to inadequate cold-chain storage infrastructure.
- In nonpregnant subjects intramuscular and inhaled oxytocin formulations have shown similar pharmacokinetic profiles and exposures.

What this study adds

- The first study showing the pharmacokinetics of intramuscular and an inhaled oxytocin formulation in women in third stage of labour.
- Demonstrates that the systemic exposure of oxytocin in third stage of labour was too low to be accurately and reproducibly quantified in plasma despite the use of a selective and sensitive bioanalytical method (liquid chromatography–tandem mass spectrometry).

2 | METHODS

2.1 | Study design

This was a phase 1, randomized, open-label study conducted at 2 centres in the United Kingdom and 1 centre in Australia. The study design is shown in Figure S1. Group 1 was terminated following an interim analysis due to low/undetectable oxytocin concentrations (Supporting information); Group 2 was completed. The study protocol for NCT02999100 can be found online (https://clinicaltrials.gov/ProvidedDocs/00/NCT02999100/Prot_000.pdf).

2.2 | Participants

Two groups of healthy women aged 18–40 years were enrolled. Group 1 included women with an uncomplicated pregnancy and at low risk of PPH. Group 2 included nonpregnant, nonlactating women of childbearing potential. Women in Group 2 were divided into 2 cohorts; those taking combined oral contraception (COC; Cohort A) and those who were using a nonhormonal form of contraception (Cohort B). Inclusion and exclusion criteria are detailed in Table S1. Written informed consent was obtained from each participant prior to the performance of any study-specific procedures.

2.3 | Treatment

Participants were assigned (1:1) to drug administration regimens under the randomization schedule generated by GSK before the start of the study using validated internal software. This was an open-label study; therefore, no masking was necessary. Group 1 participants received active management of TSL via a single dose of either oxytocin 10 IU (17 μg) by IM injection into thigh (standard intervention) or oxytocin 240 IU (400 μg) IH powder according to local standard of care (usually within 5 min of birth; Figure S1). Oxytocin IH powder was delivered using a capsule-based inhaler (Modified Air Inlet ROTAHALER Dry Powder Inhaler device, hereafter referred to as ROTAHALER). Group 2 participants received oxytocin 5 IU (8.5 μg) by IV bolus over 30 s or slow infusion over 5 min and oxytocin 240 IU (400 μg) IH powder administered using a ROTAHALER. These were administered at 2 separate dosing sessions in a crossover design, with the order being randomly assigned (Figure S1).

2.4 | Endpoints and outcome assessments

The objectives of the study were to characterize PK and safety after single-dose administration of IH, IM or IV oxytocin. The primary endpoint in both Groups 1 and 2 was the plasma concentration–time profile for oxytocin over 4 h. Other PK endpoints included the maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$), the terminal-phase half-life ($T_{1/2}$), plasma clearance (CL) after IV dosing (Group 2 only) and the volume of distribution (V_D) after IV dosing (Group 2 only). In Group 2, primary endpoints included safety; these were secondary endpoints for Group 1. For Group 1, Safety/tolerability endpoints were temperature, systolic and diastolic blood pressure, heart rate and respiratory rate only. While for Group 2 included changes in general safety parameters, adverse events (AEs) including PPH, absolute values and changes in vital signs (blood pressure, heart rate, respiratory rate), forced expiratory volume at 1 s and 12-lead electrocardiogram (ECG) parameters (PR, QRS, QT, corrected QT interval [QTc] intervals) from predose values. Exploratory endpoints included evaluation of endogenous plasma oxytocin concentrations in nonpregnant women (i.e. Group 2) in the presence and absence of COC.

For PK analyses, blood samples were taken at prespecified time points (predose, and at 3, 5, 10, 15, 20 and 30 min postdose, then at 1, 2, 2.5, 3 and 4 h postdose). Plasma sample preparation and oxytocin measurements are described in the Supporting information. For safety assessments, AEs, serious AEs (SAEs) and medical device incidents were monitored and documented throughout the study (follow-up Days 14 and 21 postdose for Groups 1 and 2, respectively). Additional safety assessments were carried out for Group 1 (AEs of special interest, i.e. PPH, delivery of the placenta) and for Group 2 participants (including monitoring for pregnancies). For the exploratory endpoints, predose plasma concentrations of oxytocin were measured in Group 2 participants, and the PK of oxytocin IH and IV were compared in Cohort A (using COC) and Cohort B (using a nonhormonal form of contraception).

A core outcome set for studies investigating postpartum haemorrhage was published during the study[10]; however, as enrolment began in November 2016, we did not amend the study design to include these outcomes.

2.5 | Assay

Plasma samples were analysed using a validated liquid chromatography–tandem mass spectrometry method to determine the concentration of oxytocin. Following automated solid phase extraction, samples were mixed with internal standard (d5-oxytocin), extracted on Oasis MCX μElution plates (Waters, Milford, MA, USA) and injected onto an Acquity UPLC BEH C18 column (Waters, Milford, MA, USA). Oxytocin was detected in the column eluant by a XEVO-TQS mass spectrometer (Waters, Milford, MA, USA) operated in positive-ion mode. The quantitation range for oxytocin was linear ($R^2 \geq .9946$) across the concentration range of 2–500 pg/mL using a 350 μL aliquot of plasma. The mean internal standard recovery across all runs was 70.25%, with between and within run precision of 2.17–14.30% and 1.05–12.50% respectively.

2.6 | Ethical approval

The study protocol was reviewed and approved by the Office for Research Ethics Committees of Northern Ireland (UK;16/NI/0214; 27 October 2017) and the Monash Health Human Research Ethics Committee (Australia; HREC/18/MonH/72; 9 March 2018) in accordance with Good Clinical Practice guidelines.

2.7 | Statistical analyses

Sample size was based on feasibility; however, a precision calculation was also conducted to approximate the expected half width of the 90% confidence interval around the point estimate for the main comparison of interest (oxytocin IH *vs.* IM in women in TSL) using a *t*-test. While no statistical analysis was planned as this was a feasibility study, the dose chosen for the IH route was expected to achieve a similar T_{max} and C_{max} to IM but less than IV and an AUC similar to IM route. The safety population comprised participants who received at least 1 dose of study medication, and was used for study population and safety analyses based on the treatment participants actually received. The PK population included all participants in the safety population for whom a PK sample was obtained and analysed. Further details of statistical analyses are provided in the Supporting information.

2.8 | Role of the funding source

GSK Plc funded this study (NCT02999100) and was involved in all stages of study conduct, including analysis of the data. GSK Plc also

funded all costs associated with the development and publication of this manuscript. The corresponding author had full access to all the study data and had final responsibility for the decision to submit for publication.

3 | RESULTS

3.1 | Participants

Participants were recruited between 23 November 2016 and 1 March 2019, and the study was terminated on 4 March 2019. Of 36 participants enrolled to Group 1, 29 were randomized to either oxytocin IH ($n = 16$) or IM ($n = 13$), and 7 were not randomized due to study halt. Of the 29 randomized 17 participants, went on to receive oxytocin IH ($n = 9$) and IM ($n = 8$; Figure S2). In Group 2 Cohort A, 9 participants were enrolled, of whom 8 were randomized and 7 completed the study (Figure S2). Five participants received oxytocin IV as a 30-s bolus, while the remaining 2 participants received a slow infusion push over a 5-min duration. One participant was withdrawn at the investigator's discretion following an AE of headache after session 1 (oxytocin IH). One participant completed the IV bolus dosing session, but was excluded from IH group analyses because they did not receive any investigational product. Another participant received a partial oxytocin IV dose due to T-wave inversion identified at 2 min, resulting in slow infusion being stopped early. In Cohort B, 6 participants were enrolled and randomized, of whom 5 completed the study and 1 withdrew consent after session 1 (IV slow infusion; Figure S2). One participant received a partial oxytocin IV bolus dose due to cardiovascular (CV) AEs; another participant received IV bolus dosing and the remaining 5 participants received an IV slow infusion dose over a 5-min duration.

Participant characteristics were generally balanced between the various groups and cohorts (Table 1). In Group 1, mean age was 30.1 years; in Group 2, mean age was 6 years younger in Cohort A (26.5 years) than in Cohort B (32.5 years).

3.2 | PK

In Group 1, predose concentrations of oxytocin were unquantifiable in all but 1 individual. Postdose, the number of samples with quantifiable (>2 pg/mL) oxytocin plasma concentrations was limited. The majority of participants had no or a single quantifiable postdose concentration of oxytocin (Table S2). Individual concentration–time data from women in TSL following treatment with oxytocin IH or IM are shown in Figure S3. Moreover, a lack of measurable postdose oxytocin concentrations in participants in TSL limited the estimations and interpretation of PK parameters. No major differences in the median time of last observed quantifiable concentration (T_{last}) or T_{max} were observed between oxytocin IH ($n = 6$) and IM ($n = 3$) arms (Table 2).

Following both IV and IH dosing in Group 2, oxytocin was quantified in the plasma of all participants up to at least 1.5 h postdose. There were no quantifiable predose concentrations of oxytocin (−1 h, and −30 and −15 min) in either cohort. Median oxytocin plasma concentrations are shown in Figure S4. Geometric mean plasma oxytocin PK parameter estimates for both cohorts are summarized in Table 3. The estimated relative bioavailability of the IH dose was 1.96 and 3.33% for Cohorts A and B, respectively. C_{max} and $AUC_{0-\infty}$ were 37–48% lower in Cohort A than in Cohort B following administration of oxytocin 240 IU IH. There was no/negligible difference in T_{max}, $T_{1/2}$, CL or V_D between Cohorts A and B. Within Cohort A, participants receiving oxytocin 5 IU IV (bolus and slow infusion) had higher exposure than those receiving oxytocin 240 IU IH (C_{max} 838 and 698 pg/mL, respectively, *vs.* 224 pg/mL). $AUC_{0-\infty}$ was similar across arms (130, 147 and 167 h*pg/mL) for oxytocin 240 IU IH, 5 IU IV bolus and 5 IU IV slow infusion, respectively. Within Cohort B, participants receiving oxytocin 5 IU IV (bolus and slow infusion) also had higher exposure than those receiving oxytocin 240 IU IH (C_{max} 1313 and 722 pg/mL, respectively, *vs.* 357 pg/mL); $AUC_{0-\infty}$ was similar between treatment arms (210, 173 and 251 h*pg/mL).

TABLE 1 Participant characteristics.

	Group 1		Group 2	
	Oxytocin 240 IU IH ($N = 9$)	Oxytocin 10 IU IM ($N = 8$)	Cohort A ($N = 8$)	Cohort B ($N = 6$)
Mean (SD) age, years[a]	31.8 (3.5)	28.1 (5.8)	26.5 (4.9)	32.5 (6.8)
Female sex, *n* (%)	9 (100)	8 (100)	8 (100)	6 (100)
Mean (SD) BMI, kg/m^2	25.3 (4.5)	24.9 (3.03)	23.6 (3.68)	24.4 (3.79)
Mean (SD) height, cm	165.2 (4.5)	159.6 (5.15)	166.4 (6.93)	160.2 (6.65)
Mean (SD) weight, kg	69.2 (13.3)	63.8 (10.00)	65.4 (12.55)	63.1 (13.44)
Race, *n* (%)				
White/Caucasian/European	7 (78)	5 (63)	7 (88)	6 (100)
Asian	2 (22)	2 (25)	1 (13)	0
Mixed	0	1 (13)	0	0

Abbreviations: BMI, body mass index; IH, inhaled; IM, intramuscular; IU, international units; SD, standard deviation.
[a]Age was imputed when full date of birth was not provided.

TABLE 2 Summary of derived plasma oxytocin pharmacokinetic parameters for participants in TSL (PK population).

Parameter	240 IU oxytocin IH ($N = 9$)[a]	10 IU oxytocin IM ($N = 8$)[b]
AUC_{0-t}, h*pg/mL	NC (NC–8.10)	NC (NC–2.30)
C_{max}, pg/mL	2.46 (NC–36.00)	NC (NC–4.50)
T_{max}, h	0.15 (0.05–2.50)	0.25 (0.17–0.48)
T_{last}, h	0.50 (0.12–2.5)	0.48 (0.33–1.00)

Note: All values are median (range); untransformed data.

Abbreviations: AUC_{0-t}, area under the concentration–time curve to the last quantifiable concentration; C_{max}, maximum observed plasma concentration; IH, inhaled; IM, intramuscular; IU, international units; NC, noncalculable; PK, pharmacokinetics; T_{last}, time of last observed quantifiable concentration; T_{max}, time to C_{max}; TSL, third stage of labour.

[a]The number of evaluable participants with nonmissing observations (including NC values) was 9 for AUC_{0-t} and C_{max}, and 6 for T_{max} and T_{last}; the number of participants for whom parameters could not be derived because of nonquantifiable concentrations was 6 for AUC_{0-t}, and 3 for C_{max}, T_{max} and T_{last}.

[b]The number of evaluable participants with nonmissing observations (including NC values) was 8 for AUC_{0-t} and C_{max}, and 3 for T_{max} and T_{last}; the number of participants for whom parameters could not be derived because of nonquantifiable concentrations was 5 for AUC_{0-t}, C_{max}, T_{max} and T_{last}.

TABLE 3 Derived geometric mean plasma oxytocin pharmacokinetic parameters in Cohort A (COC) and Cohort B (nonhormonal contraceptive).

	Cohort A[a]			Cohort B[b]		
	Oxytocin IH ($N = 7$)	Oxytocin IV bolus ($N = 5$)	Oxytocin IV inf ($N = 2$)	Oxytocin IH ($N = 5$)	Oxytocin IV bolus ($N = 1$)	Oxytocin IV inf ($N = 5$)
Geometric mean (90% CI) [%CVb]						
C_{max}, pg/mL	224 (126, 400) [92.5]	838 (409, 1719) [67.2]	698 (697698) [0]	357 (225, 567) [51.4]	1313 (NC, NC) [NC]	722 (448, 1162) [42.2]
$AUC_{0-\infty}$, h*pg/mL	130 (88, 193) [57.5]	147 (70, 309) [46.3]	167 (82, 342) [16.1]	251 (204, 208) [21.8]	210 (NC, NC) [NC]	173 (131, 227) [23.6]
AUC_{0-t}, h*pg/mL	128 (86, 190) [58.6]	161 (98, 265) [44.1]	164 (82, 331) [15.8]	247 (200, 305) [22.3]	208 (NC, NC) [NC]	171 (130, 226) [23.9]
CL, L/h	–	57.9 (27.6, 122) [46.3]	50.9 (24.9, 104) [16.1]	–	40.4 (NC, NC) [NC]	49.2 (37.4, 64.8) [23.6]
V_D, L	–	31.2 (12.9, 75.8) [56.5]	25.5 (18.0, 36.1) [7.8]	–	20.9 (NC, NC) [NC]	23.5 (17.1, 32.2) [27.4]
Median (range)						
T_{max}, h	0.083 (0.05, 0.25)	0.04 (0.03, 0.18)	0.08 (0.08–0.08)	0.08 (0.05, 0.33)	0.05 (0.05, 0.05)	0.08 (0.08, 0.13)
$T_{1/2}$, h	0.55 (0.37, 0.88)	0.37 (0.34, 0.41)	0.35 (0.29–0.41)	0.61 (0.42, 0.72)	0.36 (0.36, 0.36)	0.34 (0.26, 0.40)

Abbreviations: %CVb, interparticipant variability; AUC_{0-t}, area under the concentration–time curve to last quantifiable concentration; $AUC_{0-\infty}$, area under the concentration–time curve to infinity; CI, confidence interval; CL, clearance; C_{max}, maximum observed plasma concentration; COC, combined oral contraceptive; IH, inhaled; inf, infusion; IU, international units; IV, intravenous; NC, noncalculable; $T_{1/2}$, terminal phase half-life; T_{max}, time to C_{max}; V_D, volume of distribution.

[a]The number of participants with nonmissing observations (including imputed NC values) was 7 for oxytocin 10 IU IH (all parameters except CL and V_D), 4 (C_{max}, T_{max}, AUC_{0-t}) or 3 ($T_{1/2}$, $AUC_{0-\infty}$, CL, V_D) for oxytocin 5 IU IV bolus and 2 for oxytocin 5 IU IV infusion (all parameters).

[b]The number of participants with nonmissing observations (including imputed NC values) for all parameters was 5, 1, 4 for oxytocin 10 IU IH, 5 IU IV bolus and 5 IU IV infusion, respectively.

3.3 | Safety

In Group 1, no AEs or SAEs were considered drug-related and the majority of AEs were moderate in intensity (Table 4). A total of 4 SAEs were reported in Group 1. Among these, 2 events of pyrexia were reported in the oxytocin 240 IU IH group: Grade 3 pyrexia (38.3°C) was noted 30 min after vaginal delivery, prompting blood cultures (negative) to be drawn and IV antibiotics to be administered; Grade 2 pyrexia (38.5°C) occurred 1.5 h after dosing in another participant, which resolved within 6.5 h of receiving IV antibiotics. The other 2 SAEs, both in the oxytocin 10 IU IM group, included Grade 3 anaemia (haemoglobin 63 g/dL) that was treated to resolution with blood

TABLE 4 Adverse events profile.

			Group 2					
	Group 1		Cohort A ($N = 8$)			Cohort B ($N = 6$)		
n (%)	Oxytocin IH ($N = 9$)	Oxytocin IM ($N = 8$)	Oxytocin IH ($N = 7$)	Oxytocin IV bolus ($N = 5$)	Oxytocin IV inf ($N = 2$)	Oxytocin IH ($N = 5$)	Oxytocin IV bolus ($N = 1$)	Oxytocin IV inf ($N = 5$)
Any AE	3 (33)	2 (25)	7 (100)	5 (100)	1 (50)	3 (60)	1 (100)	5 (100)
Common AEs[a]								
PPH	1 (11)	1 (13)	0	0	0		0	0
Pyrexia	2 (22)	1 (13)	0	0	0	0		0
Anaemia	1 (11)	2 (25)	0	0	0	0	0	0
Headache	0	0	4 (57)	4 (80)	0	2 (40)	0	4 (80)
Feeling hot	0	0	1 (14)	1 (20)	0	2 (40)	1 (100)	2 (40)
Flushing	0	0	0	2 (40)	0	0	0	1 (20)
Hot flush	0	0	2 (29)	0	1 (50)	1 (20)	0	2 (40)
Nasopharyngitis	0	0	2 (29)	0	0	0	0	0
Cough	0	0	2 (29)	1 (20)	0	1 (20)	0	0
ECG QT prolonged	0	0	0	2 (40)	0	0	0	1 (20)
Sinus tachycardia	0	0	0	2 (40)	0	0	0	0
Palpitations	0	0	0	0	0	0	0	2 (40)
Any SAE	2 (22)	2 (25)	0	0	0	0	0	0
Drug-related AE	0	0	6 (86)	5 (100)	1 (50)	3 (60)	1 (100)	5 (100)
AEs leading to withdrawal	0	1 (13)	0	0	0	0	0	0

Abbreviations: AE, adverse event; ECG, electrocardiogram; IH, inhaled; IM, intramuscular; inf, infusion; IV, intravenous; PPH, postpartum haemorrhage; SAE, serious adverse event.
[a]Reported in ≥2 participants.

transfusion and ferrous sulphate, and Grade 3 PPH (also considered severe) that developed as a result of uterine atony and started at the time of oxytocin dosing; study doses were permanently discontinued and the participant was treated by removal of clots caused by possible retained membranes, suturing of a second-degree tear and ergometrine/oxytocin, oxytocin, carboprost, tranexamic acid, fresh frozen plasma and packed red blood cells. Normal haemoglobin concentrations were confirmed 2 days later. This event led to the withdrawal of the participant from the study. One additional participant (in the oxytocin 240 IU IH group) had a nonserious AE of PPH. Further information on these PPH events is provided in the Supporting information. There was no notable difference in the nature of AEs reported with IH and IM dosing, and no difficulties with IM administration.

All participants in Group 2 experienced at least 1 AE, with at least half of participants experiencing AEs with both routes of administration of oxytocin (Table 4). No AEs or SAEs led to withdrawal; however, 1 participant (Cohort A) experienced an AE of severe headache 4 h after receiving oxytocin 240 IU IH, lasting 20 h. This participant did not receive their subsequent dose of oxytocin 5 IU IV, at the investigator's discretion (although it was not technically reported as a withdrawal for an AE). Drug-related AEs were mild in severity except for 1 migraine reported during oxytocin 5 IU IV bolus dosing, which was considered moderate. In Cohort A, the most frequently reported drug-related AEs were headache ($n = 5$), flushing, hot flush, feeling hot, ECG QT prolongation and sinus tachycardia (all $n = 2$). A higher proportion of participants in the IV bolus arm reported drug-related headache than those in the IV slow infusion or IH arms (80% [4/5], 0% and 29% [2/7], respectively). In Cohort B, the most frequently reported drug-related AEs were feeling hot ($n = 5$), headache ($n = 4$), hot flush ($n = 3$) and palpitations ($n = 2$). The frequency of most drug-related AEs was higher in the IV slow infusion arm than in the other arms.

In addition, clinically significant abnormal ECG findings were reported in one participant in each of Group 2 Cohorts A and B (Table S3). In Cohort A, based on 12-lead ECG tracings, one participant had a nonserious AE of transient T-wave inversion during oxytocin 240 IU IH dosing, as well as short-duration QT prolongation, sinus tachycardia and transient T-wave inversion during oxytocin 5 IU IV bolus dosing. These were judged by the investigator and a cardiologist as nonserious but related to the study drug, thus dosing was discontinued during the IV bolus dose (partial dose). Another participant had mild-intensity AEs of short-duration QT prolongation with tachycardia

and chest discomfort during oxytocin 5 IU IV bolus dosing. One additional clinically significant abnormal ECG finding in the IV infusion group was not reported as an AE. In Cohort B, there were 4 participants with abnormal ECG findings, 2 subjects with mild intensity palpitations and one participant had treatment-related, nonserious, mild AEs of short-duration QT prolongation and chest discomfort while receiving a partial dose of oxytocin 5 IU IV infusion. The other abnormal ECG finding was not reported as an AE.

There were no clinically important trends between the dosing arms for haematology or vital signs and significant abnormalities were reported as AEs (Supporting information). No changes in forced expiratory volume at 1 s were reported.

4 | DISCUSSION

4.1 | Main findings

This is, to our knowledge, the first study to assess PK parameters of IH oxytocin in women in TSL. In this study, the PK characteristics of oxytocin following IM or IH administration could not be accurately characterized in women in TSL due to a lack of quantifiable plasma concentrations. The current study used a highly sensitive and specific liquid chromatography–tandem mass spectrometry assay to detect plasma oxytocin concentrations (lower limit of quantitation 2 pg/mL), yet this was not sufficiently sensitive to quantify plasma oxytocin concentrations in these women; also ex vivo stability of plasma oxytocin was confirmed in vitro prior to study start (reported separately, see Oliver *et al.*[11]). Contrastingly, oxytocin remained quantifiable (>2 pg/mL) in the plasma of healthy, nonpregnant, nonlactating women of childbearing potential up to 3 h post-IH administration, with derived PK parameters similar to those observed in the FTIH study.[9] Data from the present and FTIH[9] studies indicate that oxytocin can be quantified in plasma following IH, IM and IV administration in nonpregnant women. In both Cohorts A and B, higher peak oxytocin systemic exposure (C_{max}) was observed following IV (either bolus or infusion) *vs.* IH administration. Interestingly, in this limited population, systemic exposure (C_{max} and AUC_{0-3h}) was generally lower following oxytocin 240 IU IH in participants receiving COC (Cohort A) than in those using nonhormonal contraception (Cohort B), but systemic CL and V_D after IV dosing were consistent between cohorts. This finding may be indicative of additional interactions between oxytocin and oestrogen, higher systemic concentrations of which are present in women taking COC and in pregnant women compared with women using nonhormonal forms of contraception[12]; however, small sample numbers in the current study preclude any clear conclusions.

Although oxytocin IH, IM and IV were considered well tolerated across all groups, several important CV effects were observed in nonpregnant women. Transient AEs were observed in nonpregnant women receiving oxytocin IH or IV, including flushing, chest tightness, palpitations and ECG abnormalities. Transient increases in heart rate and QTc were observed in Group 2 participants in both IH and IV arms, with numerically larger changes seen with the IV route of administration. No significant changes in blood pressure were noted with either route of administration. Although these CV findings were observed in nonpregnant women, they are of interest to the therapeutic use of oxytocin in pregnant women, and are particularly relevant to IV use during caesarean section.

4.2 | Strengths and limitations

This was the first study investigate oxytocin IH in women in TSL and define the PK of oxytocin IM using a specific and highly sensitive analytical method. The study was performed in the challenging context of TSL, with frequent PK sampling. Safety profiles of oxytocin IH and IM were comparable. The results presented here do not eliminate a potential therapeutic benefit, particularly in low- and middle-income countries, for oxytocin IH in TSL, as low or nonquantifiable oxytocin concentrations were also observed following IM administration, the current standard of care.

Limitations include study halt per the protocol-defined stopping criteria due to low or undetectable oxytocin concentrations (<2 pg/mL) in the majority of samples from Group 1, preventing interpretation. Alongside premature study termination, the number of participants in Group 1 was low due to difficulties recruiting patients during pregnancy who remain at low risk throughout, logistical difficulty in achieving 24-h coverage by a research team, and the unpredictability of the onset and length of labour. Additionally, data from the nonpregnant group should be interpreted in the context of low cohort numbers, which was optimized for assessment of PK. A core outcome set for studies evaluating interventions for preventing postpartum haemorrhage was published during our study.[10] Shock, additional use of uterotonics, transfer for higher level of care, women's sense of wellbeing, acceptability and satisfaction with the intervention and breastfeeding have not been reported in our study.

4.3 | Interpretation

Previously, plasma oxytocin has been detected up to 18 and 60 min postdose (IV and IM administration, respectively) in late-stage pregnancy; however, methods utilized were probably not as specific as current technologies and considerable variability was identified.[13] Therefore, the low concentrations of oxytocin observed during TSL were most likely to be attributable to increased metabolic clearance of oxytocin, which is observed during the late stages of pregnancy and postdelivery,[14,15] as discussed further in Oliver *et al.* 2021.[11] These results do not rule out a potential therapeutic role for oxytocin IH during TSL; however, this study highlights the challenges involved in designing effective clinical development pathways in this area. Future studies should include efficacy assessments for PPH prevention, in addition to PK analyses in nonpregnant women, to more fully evaluate the benefit of oxytocin IH in women in TSL.

CV effects of oxytocin, especially with IV administration, are well recognised[16,17] and may be due to higher oxytocin systemic exposure (C_{max}) following IV dosing, as seen in our study. CV effects may also be influenced by variables such as dose,[17,18] the physiological stress of childbirth, surgery, blood loss, use of anaesthetic and other vasoactive agents.[19] The exact mechanisms through which oxytocin exerts CV effects are unknown but may include effects on vascular tone[19] and/or direct actions on the heart.[20] To mitigate CV effects, we changed the oxytocin IV administration method from a 30-s bolus infusion to a 5-min slow injection (as recommended in the oxytocin Summary of Product Characteristics[21]). Optimal dose and device for IH administration are further areas in need of exploration. Future research into the differences in CV changes associated with oxytocin administration between pregnant women and nonpregnant women may be of interest.

5 | CONCLUSIONS

This study is the first to investigate oxytocin IH administration in women in TSL. Unexpectedly, it was not possible to define PK profiles for either oxytocin IH or IM in women in TSL: the systemic exposure of oxytocin was too low to be accurately and reproducibly quantified in plasma despite the use of a selective and sensitive analytical method and confirmation that the PK sampling procedures used substantially inhibited ex vivo sample degradation/metabolism. PK analysis in nonpregnant women showed that oxytocin was rapidly absorbed into plasma after IH administration and remained quantifiable up to 3 h postdose. Single-dose oxytocin was well tolerated, with no drug-related AEs observed in women in TSL. Drug-related AEs in healthy volunteers were all mild to moderate in intensity and CV effects were noted. More research is warranted in women in TSL to determine whether oxytocin IH will be able to address the currently unmet clinical need for preventing PPH in resource-limited settings.

AUTHOR CONTRIBUTIONS

Rachel A. Gibson, Anthony Cahn, Ian Schneider, Annie Stylianou, Kimberley Hacquoil, Pete Lambert and Sarah Siederer were involved in the study design and data analysis; Amy Sutton-Cole and Carl Kirkpatrick contributed to the acquisition of data and data analysis; Subramanya Kumar, Kirsten R. Palmer, Simon Parry, Marcy Powell and Melissa Ellis contributed to data analysis. Katarzyna Gajewska-Knapik and Michelle P. McIntosh were involved in study design, acquisition of data and data analysis. All authors were involved in the revision of the manuscript and approved the final version.

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CONFLICT OF INTEREST STATEMENT

K.R.P. declares having received consulting fees from Janssen Pharmaceuticals and funding to her institution from GSK. S.K., A.C., R.A.G., A.S., M.P., M.E. and S.S. are employees of and hold stocks in GSK. S.P., I.S. and K.H. were employed by GSK at the time of the study. S.P. and I.S. hold stocks in GSK. M.P.M. declares having received research support from Janssen Pharmaceuticals, and grants/contracts from the Department of Education and Training, Victoria State Government (Smart Manufacturing and Technology Hub), the Victorian Medical Research Acceleration Fund, Department Jobs, Precincts and Regions, Victoria State Government (Clinical proof of concept for the inhaled oxytocin project), and the Medical Research Future Fund, Australian Government (Stroke – Prevention of Reperfusion Injury and Neuroinflammation – a Therapeutic Strategy: Medical Research Future Fund, Australian Government; Novel inhibitors of SARS coronaviruses targeting ACE2). M.P.M. also declared speaker honorarium for International Society for Aerosol Medicines Congress 2021, and is inventor on the patent method and formulation for oxytocin inhalation: McIntosh, M., D. Morton, T. Sou, L. Olerile and R. Prankerd (2014). US20140294969A1 - WO2013/016754 A1 - PCT/AU2011001430. These authors declare no other financial or nonfinancial relationships and activities. K.G.-K., A.S.-C., C.K. and P.L. declare no financial or nonfinancial relationships and activities and no conflicts of interest.

DATA AVAILABILITY STATEMENT

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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