Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol16Issue1abst071P.pdf

Evaluation of a translational oxytocin challenge paradigm to assess contractility in the non-pregnant uterus

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Introduction

Despite advances in the treatment of infertility by assisted reproductive technologies, the rate of loss of transferred embryos remains high. To combat this, current practice is to transfer several embryos which may result in multiple pregnancies, increasing risk to both mother and child. Several factors influence successful implantation including the frequency of uterine contractions around the time of embryo transfer. To provide proof of pharmacology and evaluate the effect of potential drug candidates on uterine contractility we sought to develop an oxytocin challenge paradigm model in non-pregnant females prior to clinical studies in pregnant women. Preclinical rat studies showed a dose dependent increase in uterine contraction rate in response to oxytocin.

Methods

Following regulatory and IRB approval, healthy non-pregnant women aged 18-35, willing to use oral contraceptives (OCP), were enrolled across two sites. Normal ovarian/uterine anatomy was confirmed by transvaginal ultrasound before subjects underwent menstrual cycle synchronisation using OrthoCyclen®. Subjects received oxytocin or placebo challenges (10:3) at the time of ovulation (D0=17-21 days after stopping OCP) to reflect the time of implantation. Escalating IV oxytocin infusions were administered on D0 (5, 10, 20 mU/min), an IV bolus (5IU) on D1 post ovulation, and an IM injection (10 IU) D2 post ovulation. Uterine contractions were measured by transvaginal ultrasound pre-challenge and at 0.5, 1, 4 and 8 hours. Results were read by a single, blinded independent reader. Oxytocin PK was measured.

Inconsistent initial uterine contraction results led to a protocol amendment and three randomized IV bolus injections of 0.5, 2.5 and 5 IU tested in a new cohort of subjects. Systemic exposure to oxytocin was consistent with other published series.

Results

Summary of Log-Transformed Derived Plasma Oxytocin Pharmacokinetic Parameters

GeoMean (95% CI)

Cohort 1				**Cohort2**			
Oxytocin dose	**N**	**AUC(0-inf) h*pg/mL**	**Cmax pg/mL**	**Oxytocin dose**	**N**	**AUC(0-inf) h*pg/mL**	**Cmax pg/mL**
5 mU/min infusion	10	7 (6,8)	11 (9,12)	0.5 IU iv bolus	4	30 (17,53)	135 (80,228)
10 mU/min	10	12 (10,14)	18 (16,20)	2.5 IU iv bolus	5	97 (83,114)	436 (335,568)

infusion							
20 mU/min infusion	10	27 (23,31)	39 (34,45)	5 IU iv bolus	4	228 (174,299)	915 (552,1517)
5 IU iv bolus	10	240 (202,285)	1086 (941,1253)				
10 IU im	10	164 (125,217)	271 (218,337)				

Change from **Pre-challenge in Endometrial Contraction Rate (contractions/min) for iv oxytocin**							
Cohort 1							
		Placebo			Oxytocin infusion		
Time (day 0)	Dose mU /min	N	Mean	SD	N	Mean	SD
1 H	5	3	-0.64	0.36	9	0.08	0.58
4 H	10	3	-0.41	0.42	9	0.18	0.31
8.5 H	20	3	0.32	0.38	9	0.26	0.63

Cohort 2									
	Oxytocin IV Bolus; 0.5 IU			Oxytocin IV Bolus 2.5 IU			Oxytocin IV Bolus 5 IU		
Time (day 0)	N	Mean	SD	N	Mean	SD	N	Mean	SD
5 M	4	-0.08	0.53	5	0.01	0.35	4	0.33	0.50
15 M	4	-0.28	0.59	5	-0.01	0.07	4	-0.37	0.43
0.5 H	4	-0.23	0.29	5	-0.09	0.27	4	-0.41	0.62
0.75 H	4	-0.29	0.81	5	0.18	0.12	4	-0.10	0.43
1 H	4	-0.50	0.77	5	-0.05	0.20	4	-0.39	0.65
2 H	4	-0.26	0.82	5	-0.01	0.41	4	-0.19	0.53
4 H	4	0.27	0.59	5	0.19	0.32	4	-0.02	0.64

Unexpectedly, oxytocin was not associated with a dose dependent increase in the frequency of uterine contractions. Post-hoc exploratory analyses examining myometrium vs. endometrium and area under the curve of uterine contractions also failed to show a robust response despite the wide dose range.

Conclusion

Challenge paradigms are an important way to test early clinical drug candidates to provide proof of pharmacology information to inform subsequent efficacy studies in patients. Development of such a paradigm for drugs to reduce uterine contractility at the time of embryo transfer in IVF was attempted. Administration of oxytocin to women after withdrawal of OCP did not result in a consistent or robust dose-dependent, change in uterine contractility using transvaginal ultrasonography.Funded and sponsored by GlaxoSmithKline