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# ONO-8815Ly, an EP2 agonist that markedly inhibits uterine contractions in women

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**Objective** To determine the effect of ONO-8815Ly on uterine contractions.

**Design** A randomised, double-blind, placebo-controlled, dose-ascending, cross-over study.

**Setting** Department of Obstetrics and Gynaecology, University Hospital of Lund, Sweden.

**Population** Seventeen, healthy, parous and permanently sterilised women.

**Methods** Intrauterine pressure was recorded on days 1–3 of bleeding of two menstruations. Subjects were intravenously treated with 4 or 8 μg/minute of ONO-8815Ly or placebo for 130 minutes. Intravenous bolus injections of oxytocin, 50 pmol/kg body weight, were given 10 minutes before, during infusion after 60 and 120 minutes and 60 minutes after completion of infusion. The plasma concentrations of ONO-8815Ly were measured in samples obtained immediately before each oxytocin injection.

**Main outcome measure** Area under pressure recording curve (AUC) 10 minutes before and after each oxytocin injection.

**Results** Twelve women, six in each dose group, completed both recordings. Of these, two women of each group were not included in efficacy analysis due to non-responsiveness to oxytocin or missing baseline value. The AUC over 10 minutes before oxytocin injection after 60 minutes of infusion of ONO-8815Ly at 4 and 8 μg/minute was reduced to 21% and 37% of that before infusion, respectively. The AUC after oxytocin at that time amounted to 21% and 19%, respectively, of that before infusion. The activity and responsiveness remained low after 120 minutes but started to return to baseline 60 minutes after stopping infusion. Placebo had no effect.

**Conclusions** ONO-8815Ly is a potent inhibitor of spontaneous uterine contractility in non-pregnant women and it reduces the uterine response to oxytocin injections.

## INTRODUCTION

Prostanoids represent an alternative and potentially attractive approach to the treatment of preterm labour and primary dysmenorrhoea. Endoperoxins (EP) are directly involved in normal and pathological uterine activity in human parturition; agonists of the EP1 and EP3 receptors (found in uterine tissue) are responsible for uterine contraction, whereas EP2 and EP4 agonists are responsible for uterine relaxation.[1] A substantial body of evidence suggests that prostanoids are also involved in the physiology of cervical ripening and dilatation during labour.[1] The specific involvement of EP2 and EP4 agonists in uterine physiology in the non-pregnant state or in mechanisms of primary dysmenorrhoea has, to our knowledge, not been studied previously.

An EP2 agonist, ONO-8815Ly, was recently synthesised and tested *in vitro* and a marked inhibition of contractions of isolated myometrial strips from pregnant women was observed.[2] In the present study, this compound was for the first time studied in healthy, non-pregnant volunteers as to the effect on spontaneous and oxytocin-induced uterine contractility.

## METHODS

Eligible women had to be healthy, regularly menstruating, not pregnant and sterilised. Exclusion criteria were presence of any serious disease process or abnormal screening laboratory or physical examination suggesting a disease process that could interfere with the interpretation of the results of the study. All women were well informed about the purpose and procedure of the study and gave their written consent to participation. The study was conducted according to ICH guidelines, and approval of a total of 12 patients that completed the study was given by the local ethics committee.

The study comprised three phases: a screening phase (visit 1), a treatment phase (visits 2 and 4) and a follow up phase (visits 3 and 5). Each woman received one dose of ONO-8815Ly and one dose of placebo. Infusion solutions were prepared by the hospital pharmacy according to a

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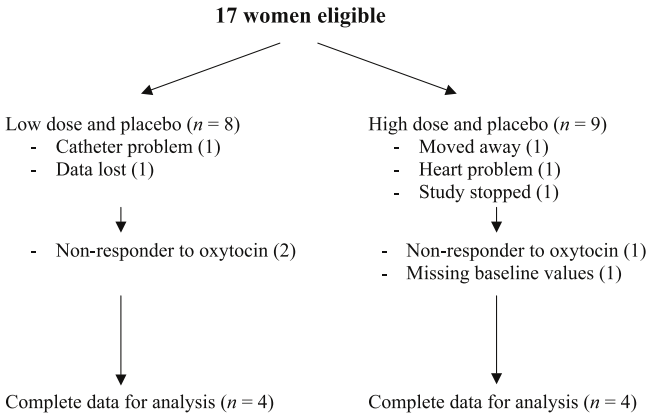


**Fig. 1.** Flow chart of disposition of women of the study.

randomisation schedule and were supplied blinded to the investigator. Women were randomised for assignment to treatment groups (i.e. for order of treatments and dosing groups) following initial contact but prior to screening. Once a potential subject had been randomised, the investigator was non-blinded to the dosing group assignment, but blind to the treatment assignment (i.e. active or placebo group). Subjects who failed or were withdrawn before treatment were replaced with the same randomisation assignment, but with a prefix to uniquely identify these women as different from the replaced ones. The women in the low dose group were intravenously treated with 4 μg ONO-8815Ly/minute or placebo (physiological saline) for 130 minutes on two separate occasions. Women in the high dose group received ONO-8815Ly 8 μg/minute for 130 minutes or placebo. The two dose groups were studied in ascending dose order. Progression from the low to the high dose was permitted after satisfactory review of safety data of the low dose group, all these experiments being completed before the high dose experiments were performed. All doses of ONO-8815Ly are expressed as the dose of the base molecule.

The first recording of uterine contractility was done on one of the first three days of a menstruation. A second recording of intrauterine pressure was performed during subsequent menstruation. Follow up visits were planned one week after each recording session.

Intrauterine pressure was recorded by a microtransducer catheter (Millar Instruments, Houston, Texas) as was previously described.[3] After sterilising the vagina, the catheter was inserted through the cervix to the bottom of the fundus. Thereafter, it was withdrawn 1–2 mm. The catheter was kept in place by a sterile gorge surrounding it in the vagina. Subjects were lying on the backs throughout the recording sessions. The pressure signals of the catheter were stored in a computer (software from Synectics, Stockholm) connected via an A/D signal converter (Polygraaf 12 Bit, Synetics).[4] The women were also fitted with two indwelling venous catheters, one in each arm. One of these catheters was used for administration of the study drugs, the other for blood sampling.

The infusion was started 40 minutes after insertion of the uterine catheter and lasted for 130 minutes, with intrauterine pressure recording continuing for another 70 minutes. Thus, intrauterine pressure was recorded for a total of 240 minutes. During each recording, the women received four intravenous bolus injections over 1 minute of 50 pmol/kg body weight of oxytocin (Syntocinon, Sandoz, Basel). The injections were given at 30, 100, 160 and 230 minutes after insertion of the uterine catheter. Plasma samples for estimation of the concentration of ONO-8815Ly were taken immediately before each oxytocin injection. After centrifugation, plasma was stored at −20°C until assay in one batch, which was performed by LC/MS/MS at Sumika Chemical Analysis Service, Japan.

Before the start of each recording, a physical examination was performed and blood and urine samples were taken for laboratory safety assessments. Electrocardiographic recording was done continuously throughout each

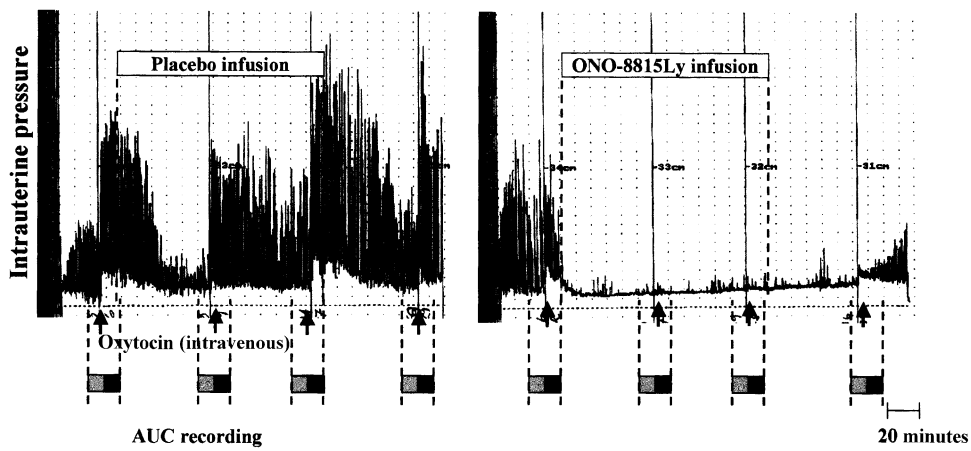


**Fig. 2.** Representative recordings of the effect of placebo (left) and ONO-8815Ly at an infusion rate of 8 μg/minute (right) on intrauterine pressure in a healthy woman at menstruation. Intravenous bolus injections of oxytocin in a dose of 50 pmol/kg body weight were given on four occasions each time (indicated). The AUC was calculated for 10 minute periods before and after each oxytocin injection (also indicated).

**Table 1.** Summary of pharmacodynamic area under intrauterine pressure curves before oxytocin injections (− 10 minutes). Values are given as mean (SD).

| Time-point (minutes) | ONO-8815Ly | | Placebo | | *P* value (Student's paired *t* test) |
|---|---|---|---|---|---|
| | Low dose ($n = 4$) | High dose ($n = 4$) | Low dose ($n = 4$) | High dose ($n = 4$) | |
| 30[a] minutes | 3964 (1313) | 2745 (1311) | 3121 (1743) | 2760 (1257) | 0.1422 (L), 0.9876 (H), 0.4219 (T) |
| 100[b] minutes | 815 (427) | 1028 (333) | 3274 (2391) | 2957 (2551) | 0.1724 (L), 0.2451 (H), 0.0440 (T) |
| 160[b] minutes | 928 (348) | 1340 (715) | 4886 (3367) | 2501 (2441) | 0.1131 (L), 0.4467 (H), 0.0627 (T) |
| 230[c] minutes | 1418 (521) | 1201 (403) | 3901 (2245) | 2608 (2637) | 0.1532 (L), 0.3665 (H), 0.0639 (T) |

L = low dose group; H = high dose group, T = total (= L + H).
[a] Before administration of study drug.
[b] During administration of study drug.
[c] After administration of study drug.

experimental session and oral temperature and vital signs were measured at 20–40 minute intervals. At two follow up visits, a physical examination was again conducted, and routine blood and urine safety tests and electrocardiographic recording were performed.

The area under the intrauterine pressure curves (AUC) was calculated for the 10 minute periods before and after each oxytocin injection during the two recordings for each subject, and numerical changes in AUC were estimated.

The statistical package used for the analyses was SAS (SAS Institute, Cary, North Carolina). A *P* value less than 0.05 was considered significant. The selection of the sample size was based on the experience gained from exploratory studies with intrauterine pressure measurements previously conducted at the centre. No formal power calculations were performed.

## RESULTS

The disposition of the subjects of the study is shown in the flow chart of Fig. 1. Of the 17 women that were eligible for the study, eight were assigned for the low dose group and nine for the high dose group. One woman in the low dose group was withdrawn before administration of study treatment due to inability to insert the intrauterine pressure catheter. Another woman in the low dose group was withdrawn after one treatment since AUC data were lost due to an accidental disconnection of the PC. In the high dose group, three subjects were withdrawn after randomisation. One woman moved to another city, another subject was excluded when her electrocardiogram revealed AV block I and one woman was withdrawn in order to be able to keep the study time schedule. The remaining 12 women completed the study.

Three women were excluded from the per protocol analyses, since they were classified as non-responders to oxytocin during the placebo treatment. A fourth woman was excluded due to missing baseline values for the placebo treatment. This left eight women for efficacy analyses, four in the low dose and four in the high dose administration groups.

A representative recording of the effect of ONO-8815Ly is shown in Fig. 2 and a summary of AUC values 10 minutes prior to each oxytocin injection in Table 1. The uterine activity after administration of ONO-8815Ly at both infusion doses was markedly inhibited. After 60 minutes of infusion before oxytocin injection, the mean AUC in the low dose group was 21% of that before start of infusion, and in the high dose, the corresponding figure was 37%. At 120 minutes, the AUCs remained low, 23% and 49%, respectively, of that before start of drug administration. When infusion of ONO-8815Ly had been stopped for 60 minutes, the spontaneous contractile activity started to return to baseline (Table 1). During placebo infusion, the uterine activity in both groups remained constant throughout the recordings (Table 1). This resulted in a statistically significant difference

**Table 2.** Summary of pharmacodynamic area under pressure curves after oxytocin injection (+ 10 minutes). Values are given as mean (SD).

| Time-point (minutes) | ONO-8815Ly | | Placebo | | *P* value (Student's paired *t* test) |
|---|---|---|---|---|---|
| | Low dose ($n = 4$) | High dose ($n = 4$) | Low dose ($n = 4$) | High dose ($n = 4$) | |
| 30[a] | 5560 (2155) | 4805 (1832) | 4499 (2298) | 4300 (2052) | 0.2950 (L), 0.7188 (H), 0.3094 (T) |
| 100[b] | 1170 (161) | 926 (446) | 4481 (2411) | 3424 (2904) | 0.0696 (L), 0.2148 (H), 0.0171 (T) |
| 160[b] | 1019 (413) | 1256 (611) | 5627 (2336) | 2987 (2551) | 0.0374 (L), 0.3024 (H), 0.0181 (T) |
| 230[c] | 2901 (1100) | 2691 (1959) | 4647 (2083) | 3271 (2591) | 0.3282 (L), 0.4862 (H), 0.1908 (T) |

L = low dose group; H = high dose group; T = total (= L + H).
[a] Before administration of study drug.
[b] During administration of study drug.
[c] After administration of study drug.

**Table 3.** Number of adverse events by relation to the study drug.

| Adverse events | ONO-8815Ly | | Placebo ($n = 13$) |
|---|---|---|---|
| | Low dose ($n = 6$) | High dose ($n = 6$) | |
| Tachycardia | 1 | 3 | 1 |
| Headache | 2 | 1 | 2 |
| Flushing | | 2 | 2 |

in AUC for the total population after 60 minutes of infusion (Table 1).

A summary of pharmacodynamic AUC 10 minutes after oxytocin injections is shown in Table 2. Administration of oxytocin before infusion of the test drug resulted in a pronounced increase in uterine activity (Fig. 1, Table 2). In contrast, administration of oxytocin during infusion of ONO-8815Ly resulted in only marginal changes in the uterine activity (Fig. 1, Table 2). Thus, the AUC after 60 minutes in the low dose group amounted to 21% of that before start of infusion and in the high dose group to 19%. After 120 minutes, the AUCs in the corresponding groups amounted to 18% and 26%. The response in the placebo groups remained constant, which resulted in a statistically significant difference between the EP2 agonist and placebo in the low dose group after 120 minutes (Table 2). For the total groups, the differences at both 60 and 120 minutes were statistically significant (Table 2).

The change in AUC values 10 minutes after oxytocin injection *versus* plasma concentrations of ONO-8815Ly (not shown) showed a negative correlation (Pearson's correlation coefficient $-0.49$, $P = 0.015$) (i.e. the increase in AUC induced by oxytocin was more suppressed by higher plasma concentrations of ONO-8815Ly).

No significant changes in vital signs, electrocardiogram or clinical laboratory safety assessments were observed in connection with administration of ONO-8815Ly. Of a total of 13 women, 10 reported a total of 25 adverse events. Seventeen adverse events were reported by the women receiving ONO-8815Ly, 12 of these occurred in the high dose group. In the placebo phase, eight adverse events were reported. The most common adverse events are summarised in Table 3. The adverse events were evenly distributed between ONO-8815Ly and placebo treatments except tachycardia, which was reported on four and one occasions, respectively. All events of tachycardia were reported within 2 minutes of oxytocin injection.

## DISCUSSION

The mean values (AUCs) for uterine activity during the 10 minute periods before oxytocin injections were markedly decreased during treatment with ONO-8815Ly, but not during placebo infusion. The latter finding is in agreement with previous experiences of this technique indicating the stability of intrauterine pressure recordings in non-pregnant women.[4–6] The inhibition of uterine activity was also obvious at visual inspection of the individual graphs. No difference between the two doses of ONO-8815Ly was observed, indicating that a maximal effect was already obtained with the low dose. This marked effect of the compound suggests an involvement of EP2 agonist in the regulation of uterine activity in non-pregnant women. ONO-8815Ly is a highly selective agonist for the EP2 subtype of the PGE receptor (ONO data on file). This receptor stimulates adenylyl cyclase and is coupled to $G\alpha_s$, when causing uterine relaxation.[7]

In women receiving ONO-8815Ly, the effect of oxytocin injections on uterine activity was reduced. However, with the limited number of women in the present study, the change in response compared with placebo was not statistically significant throughout. This was probably due to the fact that the effect of oxytocin on uterine activity was small and also to the low basal uterine activity. The baseline at the intrauterine pressure recordings was set at 0 kPa, but periods when the uterus was non-contracting still generated a curve above the baseline, contributing to the AUC value. This observation is in agreement with the results of a previous study with comparison of three peptide oxytocin antagonists in non-pregnant women.[5] In that study, although a complete inhibition of vasopressin-induced contractions was obtained with one of the analogues (atosiban), a large part of the AUC remained due to the influence of the basal tone. This basal tone may vary between individuals and within them due to the hormonal state.[6]

The uterine contractions started to reappear at the fourth injection of oxytocin 1 hour after administration of ONO-8815Ly, when the plasma concentration was low. A relation between the plasma concentrations of this drug and the inhibitory effect is also suggested by the negative correlation of changes in AUC values 10 minutes after oxytocin injection *versus* plasma concentration.

During this study, headache, flushing and tachycardia were the most commonly reported adverse events. Headache and flushing are known to appear after administration of oxytocin and were observed in about the same number of subjects during placebo and ONO-8815Ly treatment. Tachycardia was however reported by more subjects during ONO-8815Ly treatment than during placebo, but this event appeared to be related to the oxytocin injections.

The tolerability of EP2 agonist, ONO-8815Ly, appears to be good. The drug may have a therapeutic potential in preterm labour and primary dysmenorrhoea. ONO-8815Ly may also be a useful tool in studies of the physiological and pathophysiological role of endoperoxins in myometrial activity of the non-pregnant women.

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## References

1. Gibb W. The role of prostaglandins in human parturition. *Ann Med* 1998;**30**:235–241.
2. Ono Pharmaceutical Co., Ltd. *ONO-8815Ly Investigator's Brochure, 3rd edition,* 2000-07-11.
3. Åkerlund M, Bengtsson LPH, Ulmsten U. Recording of myometrial activity in the non-pregnant uterus by a microtransducer catheter. *Acta Obstet Gynecol Scand* 1978;**57**:429–433.
4. Bossmar T, Brouard R, Döberl A, Åkerlund M. Effects of SR 49059, an orally active V1a vasopressin and oxytocin antagonist, on vasopressin-induced uterine contractions. *Br J Obstet Gynaecol* 1997; **104**:471–477.
5. Åkerlund M, Hauksson A, Lundin S, Melin P, Trojnar J. Oxytocin analogues which competitively inhibit vasopressin stimulated uterine activity in healthy women. *Br J Obstet Gynaecol* 1986;**93**:22–27.
6. Bossmar T, Åkerlund M, Szamatowicz J, Laudanski T, Fantoni G, Maggi M. Receptor-mediated uterine effects of vasopressin and oxytocin in nonpregnant women. *Br J Obstet Gynaecol* 1995;**102**: 907–912.
7. Coleman RA, Smith WL, Narumiyz S. International union of pharmacology. Classification of prostanoid receptors: properties, distribution, and structure of the receptors and their subtypes. *Pharmacol Res* 1994;**46**:205–229.

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