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ORIGINAL ARTICLE

Inhibitory effects of SR 49059 on oxytocin- and vasopressin-induced uterine contractions in non-pregnant women

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Background. Compounds that block uterine oxytocin and vasopressin V_{1a} receptors have a therapeutic potential in preterm labor and primary dysmenorrhoea. The orally active vasopressin V_{1a} receptor antagonist, SR49059, inhibits the effect of vasopressin on human uterine activity *in vivo*, but the influence on the response to oxytocin is unknown.
Methods. In a placebo-controlled, double-blind, parallel-group, four-dose comparison, the inhibitory effect of SR 49059 on oxytocin- and vasopressin-induced uterine contractions in humans was investigated. Sixteen healthy female subjects, who had previously undergone sterilization with tubal ligation, participated in intrauterine pressure recordings at one of the first 3 days of bleeding of two menstrual cycles. Intravenous bolus injections of 10 pmol/kg body weight of vasopressin (Period 1) and of 50 pmol/kg body weight of oxytocin (Period 2) were given 1 h before and 1 , 2 and 4 h after oral administration of 0 (placebo), 25 , 75 or 200 mg of SR 49059. The area between the recording curve and zero level of intrauterine pressure (AUC) was calculated. Vital signs as well as urine and plasma safety parameters were measured. The plasma concentrations of oxytocin, vasopressin and the study drug were also estimated.
Results. The plasma concentrations of SR 49059 appeared to be dose related, with mean maximal values of 62.0, 163.7 and 468.0 ng/ml in the 25, 75 and 200 mg dose groups, respectively, in Period 1 with vasopressin and 34.4, 116.7 and 418.0 ng/mL, respectively, in Period 2 with oxytocin. T_{max} was observed at about 1 h. The cumulative AUC over 50 min after vasopressin injection *per se* was significantly higher than that after oxytocin in spite of a five times lower dose and lower plasma concentrations. Pretreatment by SR 49059 caused a dose-related reduction in AUCs for vasopressin, whereas no such effect was seen for oxytocin. With vasopressin as an agonist, a lower diastolic blood pressure was observed in all SR 49059 treatment groups, but not with oxytocin.
Conclusions. The much higher potency of vasopressin compared with oxytocin on uterine activity in non-pregnant women at menstruation was confirmed. SR 49059 dose-dependently inhibits vasopressin-induced contractions, whereas such an effect was not seen with the present doses of SR 49059 and oxytocin. A marked reduction by SR 49059 of diastolic blood pressure after vasopressin injection was observed, indicating an inhibition by this compound of vascular vasopressin receptors.

Key words: non-pregnant women; oxytocin; SR49059; uterine contractions; vasopressin

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The initiation of uterine contractions in pregnant women, both preterm and at term pregnancy, may involve oxytocin, which is circulating (1) and/or locally released in the uterus (2,3). An upregulation of uterine oxytocin receptors, on which this hormone has its predominant action, may also be a mechanism of importance for the onset of labor contractions (4,5). The

oxytocin-related, posterior pituitary hormone vasopressin has a powerful effect on the uterus via vasopressin V_{1a} receptors (6,7). This hormone possibly also contributes to the induction of labor, as it is released during stressful situations such as labor (8), and the vasopressin V_{1a} receptors are upregulated at the onset of labor contractions (4,5). Oxytocin also binds to the vasopressin V_{1a} receptor to some extent, as does vasopressin to the uterine oxytocin receptor of pregnant women (7,9).

In women with primary dysmenorrhoea, myometrial hyperactivity and reduced uterine blood flow have been demonstrated to be related to the pain (10). Increased vasopressin secretion is apparently an important pathophysiological factor for these changes (11–13).

Compounds that block the oxytocin and the vasopressin V_{1a} receptors of the uterus are of potential therapeutic interest for inhibiting the uterine hyperactivity of preterm labor (14,15) and primary dysmenorrhoea (16,17). Animal experiments are of little value for the prediction of such effects with these compounds in the human in relation to these two conditions (18). Furthermore, results from experiments with isolated human myometrium only give limited guidance (18). However, in the development of the peptide oxytocin and vasopressin V_{1a} antagonist, 1-deamino-2-D-Tyr-(OEt)-4-Thr-8-Orn-oxytocin, which was recently approved in Europe for the inhibition of preterm labor contractions (14,15), results in non-pregnant volunteers *in vivo* gave important leads for the further clinical development of the drug in this condition (19,20). Studies with oxytocin and vasopressin V_{1a} antagonists *in vivo* in the human may also assist in the delineation of the effects of oxytocin and vasopressin *per se* on uterine contractions (9,21,22). In the present investigation, we examined the effect of SR49059, a preferential vasopressin V_{1a}-receptor antagonist compared with its effect on oxytocin (7), on oxytocin- and vasopressin-induced uterine contractions in healthy, sterilized, non-pregnant women.

Materials and methods

Material

Sixteen healthy women, permanently sterilized by tubal division during laparoscopy, participated in this study. Their mean age was 40.4 years (range 33–44 years), and they had a body mass index with a mean of 24.6 kg/m^2 (range 21–30 kg/m^2). The women menstruated regularly, had no menstrual pain and also had no history of gynecologic health problems. The Ethics committee of the University of Lund, Sweden approved the study protocol. The nature and purpose of the investigation was described to each woman verbally and in writing, and they all gave their written consent to participation. Before inclusion, all subjects were found medically healthy at a screening visit with general and gynecologic examinations, measurements of plasma and urine safety parameters, and serology for hepatitis-B and human immunodeficiency virus 1 and 2 antibodies.

Recordings of myometrial contractility were obtained on days 1, 2 or 3 of two usually consecutive menstruations and usually on the corresponding cycle days in each woman. Before each recording, an electrocardiogram was obtained. Blood pressure and pulse rate were noted repeatedly during the experiment and any adverse events recorded. At a follow-up visit, 7 days after the second recording, electrocardiogram, vital signs and adverse events were again recorded and routine safety plasma and urine parameters obtained.

Myometrial contractile activity was measured by recording intrauterine pressure via a microtransducer catheter as previously described (22). The intrauterine pressure signals were analyzed using a computer (Polygraaf and Software from Synetics AB, Stockholm, Sweden). The area between the pressure curve and zero level of pressure over 10-min periods was calculated. Before each recording, an indwelling venous catheter was also inserted in each arm, one for injections and one for blood sampling.

In a randomized order with four subjects in each group, SR 49059 was given in a single, oral dose of 0 (placebo), 25, 75 or 200 mg. Each subject received the same treatment during both recording sessions. The drug was administered in soft gelatine capsules containing 25 mg each. At the first recording session, each woman received intravenous bolus injections over 1 min of arginine vasopressin (Pitressin®, Parke Davis, Berlin, Germany) at a dose of 10 pmol/kg body weight. At the second session, the subject received intravenous bolus injections over 1 min of oxytocin (Syntocinon®, Sandoz, Basel, Switzerland) at a dose of 50 pmol/kg body weight. The agonist was injected four times at each recording, 1 h before administration of the study drug (T-1 h) and 1 (T1 h), 2 (T2 h) and 4 (T4 h) hours thereafter.

During the experiments, blood samples for the estimation of plasma concentrations of oxytocin and vasopressin were taken 5 min before and after the first (T-1 h) and the second (T1 h) injection of the agonists. The samples were taken in

chilled tubes, immediately centrifuged for 10 min at 4 °C and at 2000 *g*, the plasma was then stored deep-frozen at − 20 °C until assay (kindly performed by Dr D. G. Bichet, Department of Clinical Chemistry, Hôpital de Sacre Coeur, Montreal, Canada).

The plasma concentrations of SR 49059 were measured in samples obtained before and at 0.5, 1, 1.5, 2, 3, 4 and 5 h after intake of the study drug. SR 49059 was determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method under the responsibility of the Clinical Metabolism and Pharmacokinetics Department of Sanofi-Synthelabo Pharmaceuticals Inc. Malvern, Pennsylvania, USA. The limit of quantification (LOQ) was 0.5 ng/ml.

At each recording session, the plasma and urine parameters as during the screening visit, except serology, were measured. Electrocardiograms were obtained 1 h before the first injection of arginine vasopressin and after each experiment. Blood pressure recordings were obtained at 60-min intervals throughout the experiments, the pressure being measured immediately before each agonist injection.

The purpose of this study was to determine potency of the compound against two challenge criteria (AVP-induced uterine contractions and OT-induced uterine contractions) using dose-dependent parameters such as inhibition concentration and/or inhibition dose. Therefore, the number of volunteers recruited was not essentially based on any formal power calculation. The area under the recording curve (AUC) of intrauterine pressure was calculated for 10-min periods from 0 to 50 min after each agonist injection. The 10 min before the next bolus was taken as baseline for the subsequent agonist challenge. Results were analyzed using an ANOVA test following the model: treatment sequence + period + treatment, sequence × period + subject representing the effect of treatment. Differences between the two treatments were assessed using a Fischer–Snedecor test. The statistical package used for analysis was SAS version 6.9 (SAS Institute Inc., Cary, North Carolina, USA). A two-sided *t*-test of statistical significance was applied at the 5% level.

Results

Sixteen subjects participated in the first recording and 11 in the second. One subject discontinued because of an adverse event (on placebo) and four, one in each treatment group, because the study was stopped as requested by the Sponsor for a potential safety reason.

The plasma levels of oxytocin and vasopressin before and after the first and second injections with the different concentrations of SR 49059 and placebo are shown in Table I. The differences between dose groups were small, although oxytocin at a fivefold higher dose caused a larger increase in plasma levels than the corresponding vasopressin injections. The maximum plasma concentration of the study drug appeared to be dose related, with mean maximal values (SD) 62.0 (46.8), 163.7 (107.9) and 468.0 (116.6) ng/ml in the 25, 75 and 200 mg dose groups, respectively, in the Period 1 with vasopressin and 34.4 (23.9), 116.7 (140.8) and 418.0 (320.0) ng/ml, respectively, in the Period 2 with oxytocin. T_{max} was observed at approximately 1 h.

Table I. Vasopressin (AVP) and oxytocin (OT) concentrations (pmol/l) before and after injections in the different treatment groups

Dose	Challenge	Sample	Mean concentrations
Placebo	AVP T-1h test no. 1	AVP − 5 min	0.79
		OT − 5 min	1.45
		AVP + 5 min	45.59
	AVP T+ 1h-test no. 2	AVP − 5 min	0.61
		AVP + 5 min	56.11
	OT T-1h test no. 1	AVP − 5 min	1.71
		OT − 5 min	0.50
		OT + 5 min	67.59
	OT T + 1h test no. 2	OT − 5 min	2.30
		OT + 5 min	62.15
SR49059 25 mg	AVP T-1h test no. 1	AVP − 5 min	1.26
		OT − 5 min	1.11
		AVP + 5 min	51.64
	AVP T + 1h test no. 2	AVP − 5 min	0.55
		AVP + 5 min	42.97
	OT T-1h test no. 1	AVP − 5 min	1.35
		OT − 5 min	0.55
		OT + 5 min	82.43
	OT T + 1h test no. 2	OT − 5 min	2.39
		OT + 5 min	93.72
SR49059 75 mg	AVP T-1h test no. 1	AVP − 5 min	1.12
		OT − 5 min	1.81
		AVP + 5 min	61.72
	AVP T + 1h test no. 2	AVP − 5 min	0.71
		AVP + 5 min	58.26
	OT T-1h test no. 1	AVP − 5 min	1.64
		OT − 5 min	1.57
		OT + 5 min	66.88
	OT T + 1h test no. 2	OT − 5 min	12.32
		OT + 5 min	85.97
SR49059 200 mg	AVP T-1h test no. 1	AVP − 5 min	0.57
		OT − 5 min	1.35
		AVP + 5 min	48.95
	AVP T + 1h test no. 2	AVP − 5 min	1.30
		AVP + 5 min	60.25
	OT T-1h test no. 1	AVP − 5 min	1.32
		OT − 5 min	0.50
		OT + 5 min	80.35
	OT T + 1h test no. 2	OT − 5 min	2.09
		OT + 5 min	71.48

A representative recording of the effect of oxytocin and vasopressin injections in a subject receiving 25 mg of SR 49059 and of vasopressin in a subject who received placebo is shown in Fig. 1. The results in AUCs of each 10-min period up to 50 min after injection of both agonists and with all study drug doses are shown in Fig. 2. Finally, a summary of the difference in baseline corrected cumulative AUCs (0–50 min) for each dose of SR49059 versus placebo by challenge is shown in Table II. There was a statistical difference between challenges, cumulative AUCs being higher with vasopressin than with oxytocin ($p = 0.001$), in spite of a fivefold higher intravenous dose of oxytocin (Figs 1 and 2). Difference estimates in baseline-corrected cumulative AUC (0–50 min) between challenges for each SR 49059 dose indicated that the cumulative AUCs for vasopressin were higher on average compared with oxytocin (Table II). SR 49059 caused a dose-dependent inhibition in cumulative AUCs for vasopressin, whereas no such effect was observed for oxytocin (Figs 1 and 2, Table II).

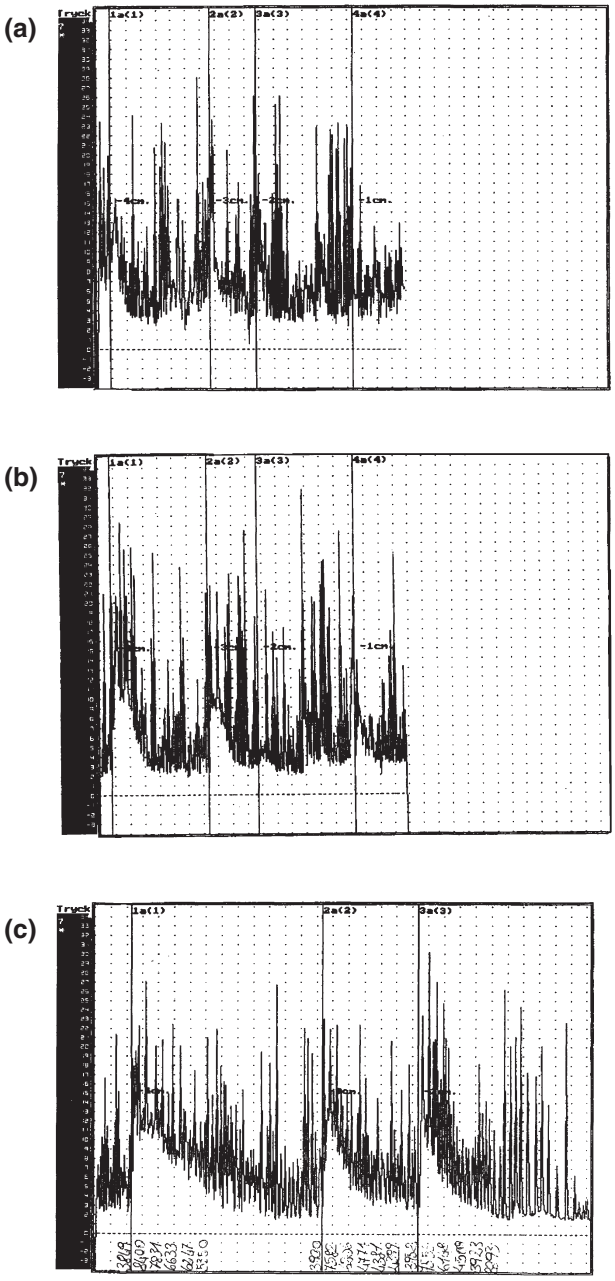

Fig. 1. Representative recording of the effect of oxytocin (a) and vasopressin (b) injections in a subject receiving 25 mg of SR 49059 and of vasopressin in another subject receiving placebo (c).

A summary of the difference in baseline-corrected supine systolic and diastolic blood pressures for each SR 49059 dose versus placebo by challenge is shown in Table III. In subjects receiving vasopressin, diastolic blood pressures were significantly lower with each of the SR 49059 doses compared with that in the placebo group (Table III).

A total of four subjects experienced adverse events. These were headaches (six episodes in two subjects in the 25 mg SR group with one of the two subjects noting hot flushes and chest pain), nausea (one subject in the Placebo group) and tachycardia (one subject in the 200 mg SR group). None of the events were considered related to SR 49059, but to vasopressin- or oxytocin-concomitant administration. There were no abnormalities reported in laboratory parameters.

Discussion

As the study was stopped, the information obtained is somewhat limited. However, the present results confirmed the high potency of vasopressin on uterine activity in non-pregnant women (19–22). In spite of a five times lower dose than that of oxytocin, the uterine effects were higher in the vasopressin group. This is also in agreement with the five times higher myometrial content of vasopressin V_{1a} receptors than of oxytocin receptors in the non-pregnant condition (21). Furthermore, the vasopressin V_{1a} receptor concentration and the uterine potency of this hormone increase premenstrually (21). In pregnancy, oxytocin appears to be more important as a uterine stimulant and, in fact, is centrally involved in mechanisms of labor (for review, see 23). It is known, however, that oxytocin may influence not only the oxytocin but also the vasopressin V_{1a} receptor, both in the pregnant and in the non-pregnant uterus, and that vasopressin has an effect on both receptors as well (5,7,21). The potency of vasopressin on the pregnant human uterus appears to be slightly higher than that of oxytocin but the number of binding sites for oxytocin and vasopressin seems

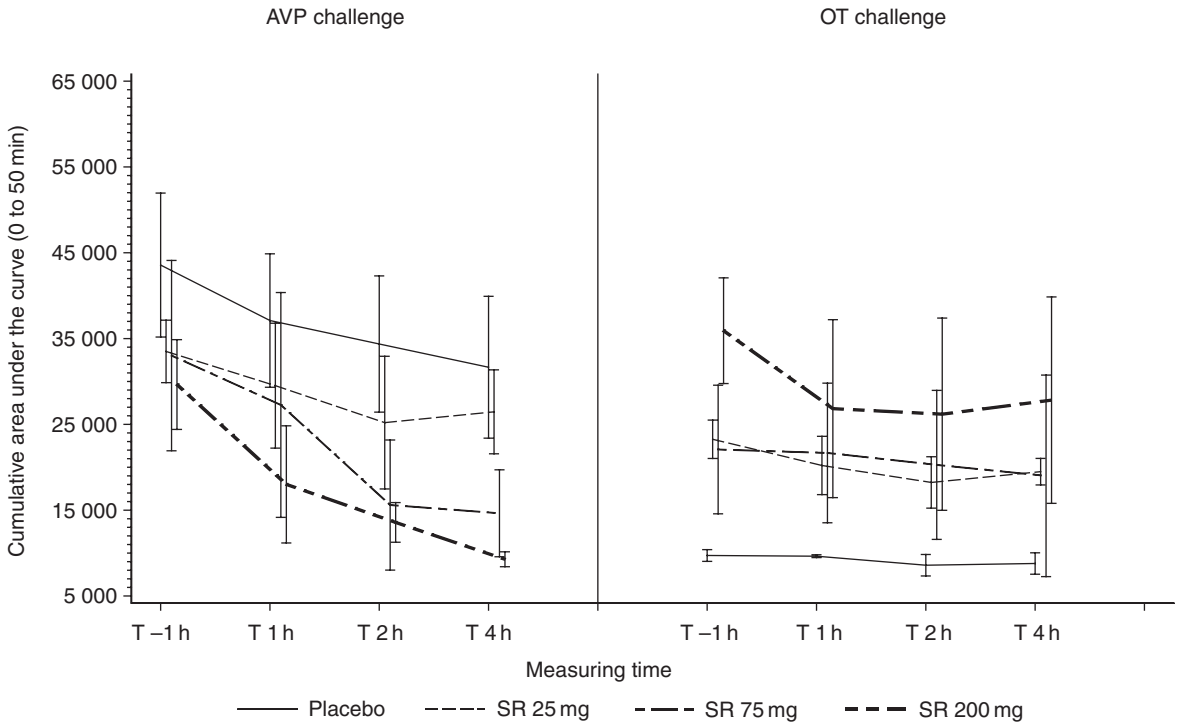

Fig. 2. Cumulative area under the curve (0–50 min) after vasopressin (AVP) and oxytocin (OT) challenges in women during intrauterine pressure recordings receiving placebo, 25 mg, 75 mg or 200 mg SR 49059.

Table II. Summary of the difference in baseline-corrected cumulative AUC (0–50 min) for each SR 49059 dose versus placebo by vasopressin (AVP) and oxytocin (OT) challenge

Challenge	Comparison	Difference estimate	95% CI	*p*-Value
AVP	SR 25 mg versus placebo	2747.6	(−6060.6, 11555.7)	0.535
	SR 75 mg versus placebo	901.8	(−8749.7, 10553.3)	0.852
	SR 200 mg versus placebo	−6829.2	(−15637.3, 1979.0)	0.126
OT	SR 25 mg versus placebo	−5045.2	(−15415.7, 5325.2)	0.334
	SR 75 mg versus placebo	−166.1	(−10571.6, 10239.3)	0.975
	SR 200 mg versus placebo	−7418.6	(−17789.0, 2951.9)	0.157

Table III. Summary of the difference in baseline-corrected supine systolic and diastolic blood pressures for each SR 49059 dose versus placebo by vasopressin (AVP) and oxytocin (OT) challenge

Parameter	Challenge	Comparison	estimate	95% CI	*p*-Value
SBP	AVP	SR 25 mg versus Placebo	−4.9	(−14.7, 5.0)	0.329
		SR 75 mg versus Placebo	−1.8	(−11.6, 8.0)	0.714
		SR 200 mg versus Placebo	−1.8	(−11.6, 8.0)	0.718
	OT	SR 25 mg versus Placebo	−0.5	(−11.6, 10.5)	0.926
		SR 75 mg versus Placebo	−6.1	(−17.1, 4.9)	0.275
		SR 200 mg versus Placebo	−4.3	(−15.4, 6.8)	0.441
DBP	AVP	SR 25 mg versus Placebo	−14.0	(−19.8, −8.2)	<0.001
		SR 75 mg versus Placebo	−6.6	(−12.4, –0.9)	0.025
		SR 200 mg versus Placebo	−7.6	(−13.4, −1.8)	0.010
	OT	SR 25 mg versus Placebo	−2.8	(−9.9, 4.2)	0.430
		SR 75 mg versus Placebo	2.0	(−5.1, 9.0)	0.582
		SR 200 mg versus Placebo	3.8	(−3.3, 10.9)	0.290

to be approximately the same (5). There is a tendency for an increase in density of oxytocin and vasopressin V_{1a} receptors at the onset of labor preterm and at term. The importance of both the oxytocin and the vasopressin V_{1a} receptor in uterine activation is supported by the studies of gene expression for these receptors (24).

Although the present study was not completed as planned, we observed a dose-dependent inhibition by SR 49059 of vasopressin-induced contractions, whereas no such effect was observed against oxytocin. This finding is in agreement with the previously observed sevenfold higher binding affinity of SR 49059 to vasopressin V_{1a} receptors compared with oxytocin receptors (23). It can be concluded that SR 49059 is a powerful vasopressin V_{1a} receptor inhibitor, whereas the effect on the oxytocin receptor is weak or inexistent.

Diastolic supine blood pressure was significantly lower after pretreatment with SR 49059. This finding emphasizes the particular importance of vascular effects of vasopressin. Some indications in fact exist that there are slight differences in the myometrial and vascular vasopressin V_{1a} receptors (25) and SR 49059 appears to be more effective on the latter ones. Such an effect may be of particular interest in conditions with disturbed uterine circulation, i.e. primary dysmenorrhoea.

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