Introduction

Previous study

- **Oxytocin** is secreted into the blood in response to endogenous stimulation with a **fatty meal**, and exogenous stimulation with **cholecystokinin (CCK)**
  - (Ohlsson B, et. al., 2002)

- Both mRNA for oxytocin and its receptor have been found throughout the **human GI tract**
  - (Monstein H-J, et. al., 2004)

Oxytocin may play a critical role in GI motility
The aim of this study

was to further examine the effect of oxytocin on gastric emptying in healthy individuals, by examining the gastric emptying rate (GER) during continuous infusion of either oxytocin or the oxytocin receptor antagonist (atosiban).

Methods

The study was performed according to the Helsinki declaration and approved by the Ethics Committee at Lund University.

All subjects gave written, informed consent before the experiments.

Material and methods

Subject
Test meal
Drugs
Ultrasonography
Experimental design

Subjects

Inclusion criteria

10 healthy volunteers (5 women)
A mean age of 40 ± 16 years (range, 25 - 62 years)
BMI 23.3 ± 1.7 kg/m² (range, 20.8- 26.7 kg/m²)
Without symptoms or a prior history of GI disease, abdominal surgery or diabetes mellitus
None of the subjects were using any pharmaceutical drugs affecting gut motility.
A basal physical examination before study.
**Methods**

**Test Meal**

- Subject was given 300 g of rice pudding.

- The total energy value for the rice pudding was 1386 kJ, (10% protein, 58% carbohydrate, and 32% fat).

- The nutrient composition per 100 g rice pudding was 3 g protein, 16 g carbohydrate and 4 g fat.

**Drugs**

- Subjects were randomly examined at 3 different occasions given either infusion of:
  - **Oxytocin** (Syntocinon® dose 40 mU/min.)
  - An oxytocin receptor antagonist (Tractocile® (atosiban), dose 300 µg atosiban/min.)
  - **Saline** (0.9% saline)

- The infusions continued for 90 min.

- At the rate of 2 ml/min

**Real-time ultrasonography**

- Provide method for assess gastric emptying indirectly.

- Using single scan to measure the changes in volume of gastric antrum.

- Ultrasonographic gastric emptying was monitored indirectly by determining the longitudinal and anteroposterior diameters of a single section of the gastric antrum.

- Use of the mean values of the longitudinal (d1) and the anteroposterior (d2) diameters to calculate the cross sectional area of the gastric antrum using the following formula:

\[ \text{Antrum area} = \pi \times \frac{d1}{2} \times \frac{d2}{2} = \pi \times \frac{d1 \times d2}{4} \]
Gastric emptying rate (GER) was assessed and expressed as the percentage reduction in antral cross-sectional area from 15 to 90 min after meal ingestion using the following formula:

\[
\text{GER} = [1 - \left( \frac{\text{Antrum area 90 min}}{\text{Antrum area 15 min}} \right)] \times 100
\]

This method has been evaluated in comparison to scintigraphic measurements of gastric emptying, and ultrasonographic gastric emptying rate has been shown to strongly correlate to scintigraphic half-time values.

(Darwiche G, et. al., 2003)

Methods

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Experimental design

After an 8 h fast

The sequence of experiments was randomly selected by the radiologist

300 g of rice pudding

Oxytocin (Syntocinon® dose 40 mU/min.)

An oxytocin receptor antagonist (Tractocile® (atosiban), dose 300 µg atosiban/min)

Saline (0.9% saline)

The infusions continued for 90 min., at the rate of 2 ml/min

Statistical analyses

Median

Interquartile ranges (IQR)

Areas under the curves (AUCs)

Wilcoxon signed rank test

P < 0.05 was considered statistically significant

Results
Results

Table 1: The gastric antral area

<table>
<thead>
<tr>
<th></th>
<th>Saline</th>
<th>Oxytocin #</th>
<th>Atosiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antrum area</td>
<td>704(606-796)</td>
<td>622(420-872)</td>
<td>512(389-478)*</td>
</tr>
<tr>
<td>15 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 min</td>
<td>293(222-505)</td>
<td>349(141-522)</td>
<td>315(230-520)</td>
</tr>
</tbody>
</table>

The area between saline and atosiban differed at 15 min, * = p < 0.05 Median, q1-q3, n = 10. Wilcoxon signed rank test.

# oxytocin high dose (pharmacologic dose)
Discussion

- **Atosiban** is an analogue of oxytocin and has been rationally designed to **compete** with endogenous oxytocin at myometrial and decidual oxytocin receptors.

- Atosiban is an effective and safe **tocolytic agent**. (prevent labor) (Goodwin TM, et. al., 1995)

- Atosiban has an equal, if not a greater, affinity for vasopressin receptors compared with oxytocin receptors due to their close chemical homology. (Ryden G, et. al., 1990 and Maggi M, et. al., 1994)

- An additional intracellular process may be attributed as atosiban has been shown to **dose-dependently** inhibit oxytocin-induced second messengers. (Lopez Bernal, et. al., 1989 and Thornton S, et. al., 1993)

- This intracellular inhibition was stronger against oxytocin than against vasopressin. (Phaneuf S, et. al., 1994)

- **No pure oxytocin receptor antagonist** is available for clinical use, and may be very difficult to develop.

In this study, it is not known whether the inhibitory effect of atosiban on the gastric emptying is mediated exclusively through oxytocin receptors.

- The effects observed due to inhibition of endogenous oxytocin to oxytocin/vasopressin receptors by atosiban .... may theoretically be due to inhibition of endogenous vasopressin as well.

- The expression of vasopressin receptors in the human GI tract has never been studied, although studies have shown the expression of vasopressin in gastric and duodenal cells in the rat. (Friedmann AS, et. al., 1993)

- The effect of vasopressin on the GI tract is only rudimentary examined.
Vasopressin has been shown to influence gastric motility in women. *(Caras SD, et. al., 1997)*

Vasopressin increases the colonic peristalsis in a way similar to oxytocin. *(Ohlsson B, et. al., 2004)*

The precise mechanism for the action of atosiban in the GI tract has thus to be further evaluated.

In the obstetrics, where atosiban has been developed as a tocolytic drug, this is not a problem as an increased expression of oxytocin receptors but not vasopressin receptors is found in the uterus during labour *(Wathes DC, et. al., 1999)*

It remains to be settled to what extent oxytocin, and to what extent vasopressin is involved in the regulation of GI motility.

Oxytocin in present study failed to improve the emptying rate.

This may depend on the dosage of the peptide.

The reason for choosing this dosage was that this was the highest dosage recommended by the drug company.

This dosage has, in an earlier dose-response study, been shown to stimulate colonic peristalsis. *(Ohlsson B, et. al., 2004)*

Earlier studies in man have shown that oxytocin improves gastric emptying. *(Petring OU, et. al., 1989 and Hasmonai M, et. al., 1979)*

Oxytocin may be of importance for the gastric emptying during physiological conditions, although not actual pharmacological dosage was.

The test meal *per se* may have given a high enough endogenous oxytocin secretion.
Stimulation by modest pharmacological dosage of oxytocin during these circumstances may be of no further benefit.

The oxytocin receptor mRNA found may be involved in regulation of slow waves, mixing movements and liquid emptying.

The actual method measured the gastric volume at two different time points, and thereby could the gastric emptying rate be calculated but the gastric emptying process is not studied in detail.

Oxytocin has an effect on dysmotility, in these dosages, on an empty stomach, it is not clear that it might have any effects with the same dosages in healthy volunteers after a meal.

In contrast to the above findings in human, the motility in the rat stomach was inhibited by oxytocin.

This might explain why the effects evoked by oxytocin on gastric and intestinal motility in rat are mediated by release of cholecystokinin (CCK) and CCK receptors, and differ from oxytocin effects evoked in human.

(Li C-Y, et. al., 2002 and Wu C-L, et. al., 2003)

This study has some limitations.

- Only one dosage of oxytocin was examined.
- This was a pilot trial, and it is difficult to examine the same subjects more than three times.
- Before planning next study, the optimal dosage of oxytocin for gastric motility must be titrated.

The interest for vasopressin has been modest, but after the present results also vasopressin will be further evaluated.

Before examining the effect of vasopressin on human GI tract, This study have to examine if the receptors are present, and if there is a postprandial vasopressin response.

Blockage of oxytocin and vasopressin receptors in man inhibited the gastric emptying. It remains to determine whether it is oxytocin or vasopressin, or both, that is most important for gastric motility.

One or both of these peptides seem to be regulators of gastrointestinal physiology in healthy subjects.

The level of action needs to be determined.

The role of these peptides in the pathophysiology of gastroparesis remains to be settled.
Oxytocin

- Peptide hormone or neuropeptide
- Effect on uterine smooth muscles and myoepithelial cells of the mammary gland

Oxytocin - ADH structure

Function

Associated with the milk ejection reflex and parturition,

- stimulates contraction of uterine smooth muscle
- stimulates contraction of smooth muscle in the mammary glands
- causes milk ejection, which is necessary for adequate lactation, but not milk production
The neurophyseal hormones vasopressin and oxytocin are cyclic nonapeptides whose actions are mediated by stimulation of specific G protein-coupled receptors.

\[ V_1 \text{ – vascular receptor, } V_2 \text{ – renal receptor,} \]

\[ V_3 \text{ – pituitary vasopressin receptors and oxytocin receptors.} \]

- Vasopressin is the ligand having the highest affinity for the human V receptors.
- Oxytocin is the ligand with the highest affinity for the oxytocin receptor.
- However, there is cross reactivity of the ligands to the receptors.

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