Ohlsson, B and Truedsson, M and Bengtsson, M and Torstenson, R and Sjölund, K and Björnsson, E S and Simrèn, M

"Effects of long-term treatment with oxytocin in chronic constipation; a double blind, placebo-controlled pilot trial."

Neurogastroenterol Motil. 2005 Oct;17(5):697-704.

Publisher: Blackwell-Synergy

Alternative location: http://dx.doi.org/10.1111/j.1365-2982.2005.00679.x

Short title; Oxytocin and constipation

Effects of long-term treatment with oxytocin in chronic constipation; a double-blind, placebo-controlled pilot trial R1

Bodil Ohlsson[1], Mikael Truedsson[1], Mariette Bengtsson[1], Richard Torstenson[2], Kristina Sjölund[3], Einar S Björnsson[4] & Magnus Simrén[4]

Department of Medicine[1] and Hospital Pharmacy[2], Malmö University Hospital, Sweden,
Department of Medicine, Lund University Hospital[3], Sweden,
Department of Internal Medicine, Division of Gastroenterology and Hepatology, Sahlgrenska University Hospital[4], Gothenburg,

Correspondence to; Bodil Ohlsson
Entrance 35
Malmö University Hospital
S-205 02 Malmö
Sweden
Phone +46 +40 33 10 00
Fax +46 +40 33 62 08
E-mail bodil.ohlsson@kir.lu.se

Abstract

Background: Oxytocin and its receptor have been found throughout the gastrointestinal (GI) tract, where it affects gut function. Clinically, we have noticed an improvement of bowel habits during lactation in constipated women. The aim of this study was to examine whether oxytocin has an effect on bowel symptoms and psychological well-being in women with refractory constipation.

Methods: Fifty-nine women with refractory constipation were included in a double-blind, multicentre study. After a 2 week run-in period, they were randomly allocated to nasal inhalation of either placebo or oxytocin treatment twice daily for 13 weeks, followed by a 2-week, post-treatment period. The patients completed a questionnaire every day concerning bowel habits, abdominal pain and discomfort, and Gastrointestinal Symptoms Rating Scale (GSRS) and Psychological General Well-being (PGWB) twice during the study; namely, during the baseline period and at the end of the treatment period.

Results: Both oxytocin and placebo led to improvement of the constipation according to the GSRS and led to improvement in the sensation of incomplete evacuation and anorectal obstruction, without significant differences between the groups. Abdominal pain and discomfort responded weakly to oxytocin, with no effect of the placebo. In a subgroup of patients with IBS and concomitant depression, a weak improvement in depressed mood was observed after oxytocin administartion.

Conclusion: Nasal administration of oxytocin had no significant advantage over placebo concerning an effect on constipation. However, it seems to have a positive effect on abdominal pain and discomfort and depressed mood. These findings should be further explored.

Introduction

Oxytocin has important effects on the myoepithelial cells and uterine smooth muscles in the responses associated with the milk ejection reflex and parturition, respectively. Nasal inhalation of oxytocin is an established pharmacological treatment in the obstetrics (1, 2). Recently, it has been hypothesized that oxytocin also contributes to the control of gastrointestinal (GI) motility. Oxytocin is secreted into the blood in response to stimulation of endogenous cholecystokinin (CCK), released after a fatty meal, and exogenous CCK in women (3). Intravenous infusion of oxytocin stimulated colonic peristalsis and accelerated gastric emptying in healthy women (4, 5). In contrast, gastric motility was inhibited in animals (6-8). Oxytocin relaxed the ileum and the caecum, while it had a contracting effect on the colon, both in vitro (9, 10) and in vivo (6, 7, 11). These effects may be explained by the fact that oxytocin and its receptor have been found throughout the GI tract, predominately on the myenteric plexus and interstitial cells of Cajal (ICCs) (12, Ohlsson et al., unpublished observation). Furthermore, oxytocin has been shown to elevate the threshold for peripheral pain in rats (13, 14) and visceral pain in patients suffering from irritable bowel syndrome (IBS) (15).

Chronic constipation and abdominal pain are problems that are often difficult to handle in clinical praxis and lead to an impaired quality of life (QoL) (16). We have noticed clinically that women with constipation have been improved during lactation, a state in which the levels of oxytocin in plasma are high (17). In an open-based pilot trial, we found that nasal inhalation of oxytocin increased stool frequency in constipated women (18). The primary aim of the present pilote study was to examine whether oxytocin affects bowel habits as compared to placebo in patients suffering from severe constipation refractory to other medical treatments. The secondary aims were to evaluate the effect on other GI symptoms related to constipation, and psychological well-being.

Methods

This study was performed as a randomised, double-blind, placebo-controlled, multi-centre study. It was approved by the Ethics Committees of Lund and Gothenburg University and the Swedish Medical Agency. The study was performed in accordance to the declaration of Helsinki, and all subjects gave their written, informed consent before being included in the study.

Inclusion- and exclusion criteria

Subjects considered for participation in the study were women with severe constipation over several years, refractory to medical treatments such as fibre supplement and/or laxatives. The definition of constipation used was that according to the Rome II-criteria (19). At the same time, it was noted if the subject also fulfilled the Rome II-criteria for IBS (19).

The exclusion criteria were;

1) Age <20 and >70 years
2) Pregnancy
3) Lactation
4) Allergy to preservatives
5) Heart disease or prolonged p-q time
6) Mental illness
7) Other severe disorders such as malignancy, kidney-, liver- and pulmonary diseases

Subjects

The subjects were recruited from the Departments of Medicine and Surgery at Malmö University Hospital and Trelleborg Hospital, and from the Departments of Medicine at Lund University Hospital and Sahlgrenska University Hospital, Gothenburg. Before entry, all women were investigated with colonoscopy or barium contrast of the colon and rigid sigmoidoscopy. Colonic transit time was calculated according to Abrahamsson et al. (20). An

oroanal transit time >5 days was defined as slow transit constipation (STC). A physical examination and routine laboratory tests were performed.

Drugs

Oxytocin was purchased from Novartis (Syntocinon©, Novartis, Täby, Sweden) and Apoteksbolaget, Kungens Kurva, Sweden produced the corresponding placebo, a randomization protocol and code envelopes. The active study drug constists of oxytocin, sodium phosphate, citric acid, sodium chloride, sorbitol, glycerol and preservatives in a concentration of 68 µg oxytocin/ml (40 IE/ml), which gives a dose of 4 IE oxytocin/dose. In the placebo drug oxytocin was excluded. The drug was transferred to blinded 5 ml flasks and was kept in the refrigerator until use. The patients were randomised at the Pharmacy of Malmö University Hospital in a consecutive order.

Study design

After a baseline period of two weeks the patients were randomly assigned to 13 weeks of twice-daily treatment with 5 nasal inhalations in each nostril of either placebo or oxytocin after meals. This gave a dose of 40 IE oxytocin twice daily. After the end of the treatment period, the patients were followed for two more weeks. Altogether, the study lasted for 4 months. The patients visited the enrolling physicians at the start, at week 6±1 week of the treatment period, and at the end of the study. The patients completed a questionnaire concerning bowel habits and abdominal complaints every day throughout the study. Moreover, questionnaires assessing bowel symptoms and psychological well-being were completed at the end of the baseline and the treatment period. In order to check compliance, the patients returned the medication not used at the end of the treatment period. The primary endpoint in this trial was to examine the effect of oxytocin on bowel habits. The secondary endpoints were to study the effects of oxytocin on other constipation-related GI symptoms and psychological well-being.

Outcome Meausures

The Daily Questionnaire. This protocol consisted of questions about stool frequency and consistency according to the Bristol stool form scale (21). Sensation of anal obstruction, incomplete evacuation or need for manual maneuvers were answered with yes or no, and the need to strain on a 3-point scale (1=none, 2=moderate, 3=severe). In the same way, the subjects graded abdominal pain and discomfort, bloating and gas on a 5-point scale (0=none, 1=mild, 2=moderate, 3=intense, 4=severe). They were allowed to continue to take their usual laxatives during the study, and the consumption of laxatives and enemas was registered. No new laxatives were allowed to be introduced during the study. During the first 2 weeks the consumption of coffee, tea, alcohol and cigarette smoking were reported, in order to evaluate differences between the groups. The subjects also reported possible side effects and disturbances of their menstrual cycle.

The Psychological questionnaire. Psychological General Well-Being (PGWB) Index. This index has been developed for the purpose of providing a self-reporting instrument that can be used to measure subjective well-being or distress (22). It can be viewed as a QoL instrument with its focus on psychological, general well-being. The PGWB index includes 22 items that, in addition to combining into a global overall score, are divided into six dimensions: Anxiety (5 items), Depressed mood (3 items), Positive well-being (4 items), Self-control (3 items), General health (3 items), and Vitality (4 items). The subscales used to measure these states use a 6-grade Likert scale which gives a maximum value of 132, indicating optimal well-being, and a minimum value of 22, which corresponds to a very poor level of psychological well-being.

The Gastrointestinal questionnaire. Gastrointestinal Symptoms Rating Scale (GSRS). The GSRS was originally constructed as an interview-based rating scale designed to evaluate a wide range of GI symptoms (23) and was later modified to become a self-

administered questionnaire (24). The questionnaire includes 15 items and uses a 7-grade Likert scale. The higher the scores, the more pronounced are the symptoms. The items are divided into five dimensions: Abdominal pain syndrome (3 items), Reflux syndrome (2 items), Indigestion syndrome (4 items), Diarrhoea syndrome (3 items) and Constipation syndrome (3 items). The GSRS data are presented in syndrome scores and a total score.

Physician´s assessment. The enrolling physicians completed a separate case record form (CRF) assessing effects of the study drug, dose adjustments, disturbances in the menstrual cycle and need for other laxatives. An open question about side effects was also included. The patients had to grade their bowel habits and abdominal symptoms during the last weeks on a 5-point scale (0=none, 1=mild, 2=moderate, 3=intense, 4=severe) at the time of the consultations.

Statistical analysis

Mean values were calculated weekly for each parameter for each patient. Thereafter, the difference between the mean for the current treatment week and the baseline was calculated. In questions answered by yes or no, the number of affirmative answers per week was used in the calculations. Values are expressed as median and interquartile ranges (IQR) or mean ±standard deviation (SD). The area under the curve (AUC) was calculated for the treatment period for each parameter and patient. The Mann-Whitney U test was used to calculate differences between placebo and oxytocin according to the AUC, and the difference in the scores of the GSRS and PGWB between baseline and after 3 months of treatment. Due to multiple comparisons within each hypothesis, a cut off value for significance was set at $p < 0.01$ to avoid mass significance. Wilcoxon signed rank test was used to examine the effects before and after treatment in subgroup analyses.

Results

Patients. Fifty-nine women still fulfilling the criteria for constipation when pharmacologically treated, 29 randomized to oxytocin and 30 to placebo, were included in the study. Of these, 46 (78 %) completed the study. Ten patients dropped out during the first 3 weeks and these data were not included in the analyses. Of the drop-outs, two patients in the oxytocin group and one in the placebo group suffered from severe vertigo already during the first day. The other seven early drop-outs (4 oxytocin and 3 placebo) withdrew from the study without any special reason and no adverse events were reported. One in the oxytocin group withdrew from the study after 7 weeks because of pregnancy, one in the oxytocin group after 9 weeks due to relapse of a previously known depressive disorder, and one in the placebo group after 8 weeks because of no effect of the drug. These three subjects were included in the analyses. Thus, totally 49 patients were enrolled in the statistical calculations, 23 from the oxytocin group and 26 from the placebo group. For patient characteristics, see Table 1. There were no differences between the groups regarding the consumption of coffee, tea, alcohol and smoking (data not shown).

Treatment effects. None of the treatments had any effect on stool frequency and consistency, straining, gas or bloating according to the daily questionnaire (data not shown). The average stool frequency during the run-in period was 0.9±0.6/day and 0.9±0.5/day in the placebo and oxytocin group, respectively. Both treatment groups responded by a reduction in the sensation of incomplete evacuation, with no significant difference between the groups (Fig 1). There was a reduction of the sensation of anorectal obstruction in both the oxytocin and the placebo group, and comparisons between the groups showed no significant difference ($p=0.06$). The placebo group showed a reduction in the need for manual manipulation to evacuate stools during the first week of treatment, with a tendency towards a difference between the groups ($p=0.03$).

Oxytocin showed a tendency to decrease pain as compared to placebo. Extrapolation of standard deviations indicates that a participation of 60-120 patients per group is recommended in order to get a difference between placebo and oxytocin during most of the treatment period, at a p value of <0.05 with 80% power. Abdominal discomfort decreased in the oxytocin group, but not in the placebo group, with no statistical significant difference of the AUC (Fig 2). Subgroup analyses including only patients with IBS did not give any further information (data not shown).

Four of the patients in the oxytocin group and one in the placebo group did not complete the GSRS and PGWB questionnaires after the treatment. Therefore only 19 and 25 subjects, respectively, were included in the analyses. These questionnaires indicated no differences between the groups at baseline (data not shown). When comparing the change in each group before and after treatment according to PGWB, there was no statistical difference between the two groups (Table 2). Subgroup analyses revealed that when only patients with depression were included (8 in the oxytocin and 6 in the placebo group), scores for depressed mood were increased in the oxytocin group (p=0.03) but not in the placebo group (p=0.92) (Wilcoxon signed rank test). There was no statistical significant difference in the change in scores between the groups (p=0.34).

Both groups showed an improvement in GSRS of constipation, with no difference between groups (Table 3). However, subgroup analyses including only patients with IBS revealed a tendency to reduced abdominal pain in the oxytocin group (p=0.05), but not in the placebo group (p=0.78) (Wilcoxon signed rank test). The difference between the groups was not statistically significant (p=0.31)

At the consultations with the physicians, about half of the patients in every group answered that they experienced an effect on their constipation by the drug, whereas one-third experienced an effect on abdominal pain. The physician´s protocol was in agreement with the patient´s protocol, and therefore only the patient´s protocol is shown. With

a few exceptions, the same dose of the inhalations was used throughout the study. The need for other laxatives and enemas was unchanged in the majority of patients, whereas it was slightly reduced to the same extent in both groups over the whole study (data not shown).

Side effects. No effects on blood pressure or electrolyte concentrations were seen in either group (data not shown). On the second consultation, two subjects in each group reported disturbances in their menstrual cycle. At the third visit, one patient in the oxytocin group and three in the control group reported menstrual disturbances. Eleven in the oxytocin group (48%) and twelve in the control group (47%) reported side effects in the form of headache (11), nausea (6), abdominal pain (6), weight gain (4) and local irritation in the nasal mucosa (8). The distribution of side effects was equal in the two groups.

Discussion

Although oxytocin has been shown to stimulate colonic motility in healthy women (5), it failed to improve gut function in constipated subjects in the present study which included subjects with a comparable, advanced constipation. One pathological mechanism in constipation might be the lack of a proper reaction to physiological stimulus. There might be disturbances at the receptor level or in intracellular signal cascade pathways. Even if a substance has an effect on normal cells, it is not certain that it has any effect on pathological cells with an abnormal function. In our previous study we saw an effect of oxytocin on bowel habits (18). However, that study was not randomized, double-blind placebo-controlled. The pathogenesis of constipation is unknown. In idiopathic, slow-transit constipation (STC) an impaired gastrocolonic (enterocolonic) reflex (25) and abnormalities in the concentrations of neuropeptides and peptide hormones have been described (26, 27). In normal-transit constipation (NTC), the aetiology is even more uncertain.

Other studies showing an effect of oxytocin on intestinal motility have used continuous or repeated intravenous infusions of the hormone (5-7, 11). The method of administration may be important for the effect. This may be similar to the case of sumatriptan (Imigran®), which induced a relaxation of the gastric fundus with reduced perception of discomfort after subcutaneous injections in healthy subjects (28), but not when nasally administered (29).

Oxytocin, a polypeptide not possible to administer orally, has a very short half-time in plasma after nasal inhalation and infusion, 3-17 min (30). The oxytocin concentration in the blood was not measured in this study, but 40 IE has in an earlier study been shown to elevate plasma levels from 10 pg/ml to 36-85 pg/ml (31). Nasal inhalation of oxytocin is a well-established treatment in obstetrics, where a dose of 4-5 IE increases uterine activity and make the establishment of breast-feeding easier (1, 2). Repeated administration of up to 15 IE

maintains the response for 30 min (1). This along with the recommendations from drug companies of a maximal nasal dose of 40 IE oxytocin, suggest that our dose of 40 IE twice daily after a meal was high enough to exert a systemic effect. Further, this nasal dose corresponds to the intravenous dose earlier shown to stimulate colonic peristalsis in human (1, 5). However, the short half-time of oxytocin, in combination with only two administrations daily, might explain the absence of effects on constipation in our study. Oxytocin is released in response to a meal (3), and therefore there are probably many spikes of release during a day. Furthermore, the endogenous oxytocin release measured after CCK-stimulation, persisted for the entire study duration of 2 hours (3). Thus, although no effect was found in the present study, with two administrations per day, oxytocin may play a role under physiological conditions for GI motility. Particularly as the recently identified oxytocin receptors in the GI tract are localized on the enteric nerve tissue and ICCs (Ohlsson et al., unpublished observation).

Oxytocin had a tendency for a positive effect on abdominal pain and discomfort. This is in accordance with previous studies performed in IBS patients by Louvel et al. (15). In rats, oxytocin has been shown in several studies to increase the threshold for peripheral pain (13, 14). Children suffering from recurrent abdominal pain exhibited lower plasma levels of oxytocin than healthy controls (32). Oxytocin receptors have been found on dorsal roots ganglia, an important area for joint pain processing (33), and on enteric nerve plexa and nerve fibres in the bowel wall (Ohlsson et al, unpublished observations). Oxytocin may thus act on peripheral afferent neurons. Furthermore, 1-2 ‰ of circulating oxytocin crosses the blood-brain barrier (34). Inhaled oxytocin may therefore exert its effects also directly on central neurons. Under physiological conditions, oxytocin is released into the circulation in response to physical contact and massage (35) and a fatty meal (3). Oxytocin is at the same time released centrally via neuronal projections emanating from the paraventricular nuclei of the

hypothalamus (36). The oxytocin and serotonin and dopaminergic systems are interconnected by these pathways (37, 38).

Of our 23 patients in the oxytocin group, 9 had a history of depression. Oxytocin has antidepressive effects on rats (38), and the administration of selective serotonin re-uptake inhibitors (SSRIs) to rats was associated with an elevation of the plasma concentration of oxytocin (39). In rats, the administration of oxytocin produces antistress and anti-nociceptive effects that persist for several weeks after the administration. This suggests that secondary, centrally mechanisms have been activated, especially as oxytocin receptor antagonists are unable to reverse the effects, while the opioid receptor antagonist naloxone does, and that they are exerted by i.c.v. injection, and by peripheral administration in 1 000-fold doses (14, 40). The weak effect of a reduction in depressed mood, observed in our study with a low number of patients, may also be a central effect in the same way, activating secondary mechanisms.

Lower values of plasma oxytocin have been reported in patients suffering from dyspepsia and IBS (41). However, this has not been confirmed when focusing on patients with constipation (3). Patients suffering from fibromyalgia and depression have also been reported to have lower oxytocin levels (37, 42). There are clear overlaps between fibromyalgi, IBS and depression (43, 44). These conditions are characterized by hyperalgesia, fatigue and depressed mood, symptoms that might be reversed by oxytocin. The role of oxytocin in these disease entities therefore needs further evaluation. Notwithstanding the moderate effects on pain and mood in the present study, we must keep in mind that the goal of this study was another symptom, namely, constipation, and the calculations are performed with a low amount of patients.

When patients were asked to participate in this study, they were informed about its primary aim, which was the only expected effect, to examine whether oxytocin had any effect on constipation. The only dimension in the GSRS, PGWB and the patient´s protocol that was improved by placebo was constipation. This suggests that the psychological

expectation and attitude determines the effect of the placebo observed. We chose to examine patients with refractory constipation. In this way, it was more difficult to achieve an improvement of the drug. We chose this approach as ethical considerations can be raised against treating mild constipation, responding to fibre and/or osmotic laxatives, with a hormonal treatment. Nevertheless, they responded to placebo. A decrease of sensation of incomplete evacuation was the parameter most affected by both placebo and oxytocin. This is a subjective feeling. The more objective parameter such as stool frequency was not affected. This suggests that objective parameters are not affected by placebo to the same extent as subjective parameters, further underlining that psychological mechanisms are involved and determine the outcome in this patient population, as well as in several other disorders.

In conclusion, nasal administration of oxytocin twice daily had no significant advantage on constipation compared to placebo in a patient group with refractory constipation. However, oxytocin seems to have a positive effect on depressed mood, and abdominal pain and discomfort, and must be further evaluated as an antidepressant and analgetic drug, especially in diseases associated with decreased levels of oxytocin.

Acknowledgements: We wish to thank Birgitte Bimenoir, St Gobain Desjonqueres, for providing glass flasks and Karl Juul, Dansk glaskontor, for providing pumps and nasal adaptors. We also want to thank the staff at the Pharmacy of Malmö University Hospital and of the Apoteksbolaget, also Simon Antov, RN, Department of Radiology, Sahlgrenska University Hospital for recruiting the patients, Lena Rubin for secretarial work and Jan-Åke Nilsson and Per Nyberg for assistance with the statistics. The Federation of County Councils (Landstingsförbundet) and the local pharmaceutical committee (lokala läkemedelskommittén) and the Åke Wiberg Founding provided funding for this study, which was performed without involvement of the pharmaceutical industry. Bodil Ohlsson was supported by the drug

company Novo Nordic with a personal, unrestricted grant and by the Development

Foundation of Region Skåne.

References

1. Hendricks CH, Pose SV. Intranasal oxytocin in obstetrics. JAMA 1961;175:384-387.

2. Huntingford PJ. Intranasal use of synthetic oxytocin in management of breast-feeding. BMJ 1961;11:709-711.

3. Ohlsson B, Forsling ML, Rehfeld JF, Sjölund K. Cholecystokinin stimulation leads to increased oxytocin secretion in women. Eur J Surgery 2002;168:114-118.

4. Petring OU. The effect of oxytocin on basal and pethidine-induced delayed gastric emptying. Br J Clin Pharmacol 1989;28:329-332.

5. Ohlsson B, Ringström G, Abrahamsson H, Simrén M, Björnsson ES. Oxytocin stimulates colonic motor activity in healthy women. Neurogastroenterol Mot 2004;16:33-40.

6. Milenov K, Kasakov L. Effect of synthetic oxytocin on the motor and bioelectrical activity of the stomach and small intestines (in vivo). Acta Physiol et Pharmacol Bulg 1975;3-4:31-39.

7. Milenov K, Barth T, Jost K, Kasakov L. Effect of deamino-dicarba-oxytocin and oxytocin on myoelectrical and mechanical activity of uterus, stomach and small intestine in dog. Endocrinol Experiment 1979;13:177-183.

8. Flanagan LM, Olson BR, Sved AF, Verbalis JG, Stricker EM. Gastric motility in conscious rats given oxytocin and an oxytocin antagonist centrally. Brain Res 1992;578:256-260.

9. Bisset GW, Lewis GP. A spectrum of pharmacological activity in some biologically active peptides. Brit J Pharmacol 1962;19:168-182.

10. Botting JH. An isolated preparation with a selective sensitivity to vasopressin. Brit J Pharmacol 1965;24:156-162.

11. Levy B. The intestinal inhibitory response to oxytocin, vasopressin and bradykinin. J Pharmacol Exp Therap 1963;140:356-366.

12. Monstein H-J, Grahn N, Truedsson M, Ohlsson B. Oxytocin and oxytocin receptor mRNA expression in the human gastrointestinal tract: A polymerase chain reaction study. Regul Pept 2004;119:39-44.

13. Uvnäs-Moberg K, Bruzelius G, Alster P, Bileviciute I, Lundeberg T. Oxytocin increases and a specific oxytocin antagonist decreases pain threshold in male rats. Acta Physiol Scand 1992;144:487-488.

14. Petersson M, Alster P, Lundeberg T, Uvnäs-Moberg K. Oxytocin increases nociceptive thresholds in a long-term perspective in female and male rats. Neurosci Lett 1996;212:87-90.

15. Louvel D, Delvaux M, Felez A, Fiormonti J, Bueno L, Lazorthes Y, Frexinos J. Oxytocin increases thresholds of colonic visceral perception in patients with irritable bowel syndrome. Gut 1996;39:741-747.

16. Glia A, Lindberg G. Quality of life in patients with different types of functional constipation. Scand J Gastroenterol 1997;32:1083-1089.

17. Chiodera P, Salvarani C, Bacchi-Modena A, Spallanzani R, Cigarini Alboni A, Gardini E, Coiro V. Relationship between plasma profiles of oxytocin and adrenocorticotropic hormone during suckling or breast stimulation in women. Horm Res 1991;35:119-123.

18. Ohlsson B, Sjölund K. Oxytocin increased stool frequency in patients with chronic constipation. A preliminary report. Int J of Surg Investig 2001;3:287-292.

19. Thompson W, Longstreth G, Drossman D, Heaton K, Irvine E, Muller-Lissner S. Functional bowel disorders and functional abdominal pain. Gut 1999;45:1143-1147.

20. Abrahamsson H, Antov, S, Bosaeus I. Gastrointestinal and colonic segmental transit time evaluated by a single abdominal X-ray in healthy subjects and constipated patients. Scand J Gastroenterol 1988;23:72-80.

21. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol 1997;32:920-924.

22. Dupuy HJ. The psychological General Well-Being (PGWB) index. In: Wenger NKL, Mattson ME, Furberg CF, Elinson J, editors. Assessment of quality of life in clinical trials of cardiovascular therapies. USA: Le Jacq Publishing Inc; 1984.p.170-183.

23. Svedlund J, Sjödin I, Dotevall G. GSRS-a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988;33:129-134.

24. Dimenäs E, Glise H, Hallerbäck B, Hernqvist H, Svedlund J, Wiklund I. Quality of life in patients with upper gastrointestinal symptoms. An improved evaluation of treatment regimens? Scand J Gastroenterol 1993;28:681-687.

25. Björnsson ES, Chey WD, Hooper F, Woods M, Owyang, Hasler WL. Impaired gastrocolonic response and peristaltic reflex in slow-transit constipation: Role of 5-HT_3 pathways. Am J Physiol 2002;283:G400-G407.

26. Sjölund K, Ekman R, Akre F, Lindner P. Motilin in chronic idiopathic constipation. Scand J Gastroenterol 1986;21:914-918.

27. Sjölund K, Fasth S, Ekman R, Hultén L, Jiborn H, Nordgren S, Sundler F. Neuropeptides in idiopathic chronic constipation (slow transit constipation). Neurogastroenterol Mot 1997;9:143-150.

28. Tack J, Coulie B, Wilmer A, Andrioloi A, Janssens J. Influence of sumatriptan on gastric fundus tone and on the perception of gastric distension in man. Gut 2000;46:468-473.

29. Sarnelli G, Janssens J, Tack J. Effect of intranasal sumatriptan on gastric tone and sensitivity distension. Dig Dis Sci 2001;46:1591-1595.

30. Forsling ML, Chard T, Boyd NHR. The dissociation of the immunological and biological activity of oxytocin: in vivo studies in Radioimmunoassay Methods (European Workshop), Ed KE and Hunter WM pp 549-558, Churchill Livingstone (1971).

31. Landgraf R. Plasma oxytocin concentrations in man after different routes of administration of synthetic oxytocin. Exp Clin Endocrinol 1985;85:245-248.

32. Alfven G. Plasma oxytocin in children with recurrent abdominal pain. J Pediatr Gastroenterol Nutr 2004;38:513-517.

33. Yang Q, Wu ZZ, Li X, Li ZW, Wei JB, Hu QS. Modulation by oxytocin of ATP-activated currents in rat dorsal root ganglion neurons. Neuropharmacology 2002;43:910-916.

34. Ermrich A, Barth T, Ruhle HJ, Skopkova J, Hrbas P, Landgraf R. On the blood-brain barrier to peptides: accumulation of labelled vasopressin, DesGlyNH_2 vasopressin and oxytocin by brain regions. Endocrinol Exp 1985;19:29-37.

35. Matthiesen A-S, Ransjö-Arvidson A-B, Nissen E, Uvnäs-Moberg K. Postpartum maternal oxytocin release by newborns: effects of infant hand massage and suckling. Birth 2001;28:5-12.

36. Sawchenko PE, Swanson LE. Immunohistochemical neurons that project to the medulla or the spinal cord in the rat. J Comp Neurol 1982;205:260-272.

37. Anderberg UM, Uvnäs-Moberg K. Plasma oxytocin levels in female fibromyalgia syndrome patients. Z Rheumatol 2000;59:373-379.

38. Arletti R, Benelli A, Poggioloi R, Luppi P, Menozzi B, Bertolini A. Aged rats are still responsive to the antidepressant and memory improving effects of oxytocin. Neuropeptides 1995;29:177-182.

39. Uvnäs-Moberg K, Bjorkstrand E, Hillegaart V, Ahlenius S. Oxytocin as a possible mediator of SSRI-induced antidepressant effects. Psychopharmacology 1999;142:95-101.

40. Uvnäs-Moberg K. Oxytocin linked antistress effects-the relaxation and growth response. Acta Physiol Scand Suppl 1997;640:38-42.

41. Uvnäs-Moberg K, Arn I, Theorell I, Jonson C-O. Gastrin, somatostatin and oxytocin levels in the patients with functional disorders of the gastrointestinal tract and their response to feeding and interaction. J Psychosom Res 1991;35:525-533.

42. Frasch A, Zetzsche T, Steiger A, Jirikowski GF. Reduction of plasma oxytocin levels in patients suffering from major depression. Adv Exp Med Biol 1995;395:257-258.

43. Lydiard RB, Fossey MD, Marsh W, Ballenger JC. Prevalence of psychiatric disorders in patients with irritable bowel syndrome. Psychosomatics 1993;34:229-234.

44. Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakrah M, Fich A, Buskila D. Fibromyalgia in the irritable bowel syndrome: Studies of prevalence and clinical implications. Am J Gastroenterol 1999;3541-3546.

Table 1. Patient characteristics

	Oxytocin (n=23)	Placebo (n=26)
Mean age (range)	47 (24-63)	49 (28-68)
Slow transit constipation (STC)	13	12
Normal transit constipation (NTC)	10	14
Irritable bowel syndrome (IBS)	16	19
Outlet obstruction	1 (16 not examined)	2 (15 not examined)
History of abdominal surgery	16	20
Anamnesis of depression	9	6
Examined after menopause	10	13

(n)=number of patients in each group.

Table 2. The difference in Psychological General Well-Being (PGWB) Index before compared to after 3 months of treatment with placebo respective oxytocin

PGWB	The difference in scores, placebo group n=25		The difference in scores, oxytocin group n=19		P-value
	median	interquartile range	median	interquartile range	
Anxiety (range 5-30)	-0.5	4.25	-1	5	0.53
Depressed mood (range 3-18)	-1.5	4.25	-1	4	0.74
Positive well-being (range 4-24)	-1	6.25	-2	3	0.74
Self-control (range 3-18)	-1	4	-1	2.5	0.87
General health (range 3-18)	-1	4.25	-1	5	0.79
Vitality (range 4-24)	0	4.5	-1	5	0.74
TOTAL (range 22-132)	-4.5	21.5	-10	18.5	0.39

No statistical significant differences were seen between the groups; Mann-Whitney U test. An increas in PGWB index after 3 months means better quality of life.

Table 3. The difference in Gastrointestinal Symptoms Rating Scale (GSRS) before compared to after 3 months of treatment with placebo respective oxytocin

GSRS	The difference in scores, placebo group n=25		The difference in scores, oxytocin group n=19		P-value
	median	interquartile range	median	interquartile range	
Reflux (range 2-14)	0	1.5	0	0	0.42
Abdominal pain (range 3-21)	0	2	1	2	0.31
Constipation (range 3-21)	2.5	7.25	2	5	0.49
Indigestion (range 4-28)	1	3	0	7	0.66
Diarrhoea (range 3-21)	0	2	0	3	0.82
TOTAL (range 15-105)	4	12	6	10.5	0.76

No statistical significant differences were seen between the groups; Mann-Whitney U test.

A decrease in GSRS index after 3 months means better quality of life.

Legends to figures

1. The median value of the difference in the number of affirmative answers per week between the run-in period (set to 1.0) and each week of treatment concerning the sensation of incomplete evacuation. The last value is the follow-up period, week 14-15. There was no statistical significant difference between the placebo and oxytocin according to the AUC, Mann-Whitney U test.
2. The median value of the difference between the run-in period (set to 1.0) and each week of treatment concerning abdominal discomfort. The last value is the follow-up period, week 14-15. There was no statistiacl significant difference between placebo and oxytocin according to the AUC, Mann-Whitney U test.