Adjunctive Intranasal Oxytocin Reduces Symptoms in Schizophrenia Patients

David Feifel, Kai Macdonald, Angel Nguyen, Patrice Cobb, Heather Warlan, Barbara Galangue, Arpi Minassian, Olga Becker, Jason Cooper, William Perry, Mischelle Lefebvre, James Gonzales, and Allison Hadley

Background: Both human and animal studies suggest oxytocin may have antipsychotic properties. Therefore, we conducted a clinical trial to directly test this notion.

Methods: Nineteen schizophrenia patients with residual symptoms despite being on a stable dose of at least one antipsychotic were enrolled in a randomized, double-blind, crossover study. They received 3 weeks of daily intranasal oxytocin (titrated to 40 IU twice a day) and placebo adjunctive to their antipsychotics. Order of intranasal treatment was randomly assigned and there was a 1-week washout between treatments.

Results: Analysis of the 15 subjects who completed all the study visits revealed that oxytocin significantly reduced scores on the Positive and Negative Symptom Scale ($p < .001$) and Clinical Global Impression-Improvement Scale ($p < .001$) compared with placebo at the 3-week end point. No benefit was seen at the early time points. Oxytocin was well tolerated and produced no adverse effects based upon patient reports or laboratory analysis.

Conclusions: The results support the hypothesis that oxytocin has antipsychotic properties and is well tolerated. Higher doses and longer duration of treatment may produce larger benefits and should be evaluated in future studies.

Key Words: Oxytocin, schizophrenia

Oxytocin and its receptors exist in areas of the brain implicated in the symptoms of schizophrenia such as the nucleus accumbens and the hippocampus (1). Previously, our laboratory demonstrated that peripherally administered oxytocin produces reversal of prepulse inhibition deficits induced in rats by amphetamine and the *N*-methyl-D-aspartate receptor antagonist, MK-801 (2), a finding consistent with the effects of atypical antipsychotics. Subsequently, other investigators have also reported preclinical findings supporting an antipsychotic role for oxytocin (3,4).

Human studies have provided further indirect support for the contention that oxytocin may have antipsychotic properties. Schizophrenia patients have been found to have altered oxytocinergic functions ([5–10] but see [11]). Recent studies found that intranasal oxytocin administered to normal human subjects increased perceived trustworthiness (12,13), suggesting paranoia may be ameliorated in schizophrenia patients. We conducted a proof-of-concept, pilot study of intranasal oxytocin in schizophrenia patients to test the hypothesis that oxytocin can reduce symptoms of this disease.

Methods and Materials

Participants

Subjects with a DSM-IV diagnosis of schizophrenia, confirmed by Structured Clinical Interview for DSM-IV interview, were enrolled in this double-blind, placebo-controlled, crossover study. Other main inclusion criteria were minimum 18 years of age, treatment with one or two approved antipsychotic medications with no dose changes in the previous 4 weeks, Positive and Negative Syndrome Scale (PANSS) score of at least 55, and a Clinical Global Impressions-Severity (CGI-S) scale score of at least 4 (moderately ill) at randomization. Because it was hypothesized that oxytocin may improve paranoia due to its protrust effect, subjects were also required to have a score of at least 4 (moderate) on item 6 (suspiciousness/persecution) of the PANSS. This study was approved by the University of California, San Diego Institutional Review Board and written informed consent was obtained from all subjects.

Study Drugs

Subjects were maintained on their prestudy antipsychotic medication regimen and doses were not changed during the study. Subjects received 3 weeks of daily intranasal oxytocin (Syntocinon, Novartis, Basel, Switzerland) and 3 weeks of daily intranasal placebo. Oxytocin was dosed at 20 IU (5 sprays) twice a day for the first week and 40 IU (10 sprays) twice a day thereafter. Order of treatment (placebo-oxytocin or oxytocin-placebo) was randomly assigned using a computer-generated random sequence.

Efficacy and Safety Assessments

Subjects, raters, and study staff enrolling patients were blinded to treatment condition. The total study duration for each individual subject was 7 weeks. Subjects were evaluated seven times. Visits 1 and 5 were baseline assessments and visits 2, 3, and 4 and 6, 7, and 8 were the weekly visits for the two treatment periods, respectively. Washout occurred in the week between visits 4 and 5. At each visit, raters assessed subjects using the PANSS (14), CGI-S, and Clinical Global Impressions-Improvement (CGI-I) (15). The PANSS total at the final visit of each treatment period was chosen a priori as the primary efficacy end point.

Safety was assessed at each visit by a medical examination and assessment of reported adverse events. In addition, urine was collected for osmolality testing and blood was drawn at each

From the Department of Psychiatry (DF, KM, AN, PC, HW, BG, AM, OB, JC, WP, AH), and Investigational Drug Service, Pharmacy Department (ML, JG), University of California, San Diego Medical Center, San Diego, California.

Address correspondence to David Feifel, M.D., Ph.D., University of California, San Diego Medical Center, Department of Psychiatry, 200 West Arbor Drive, San Diego, CA 92103-8218; E-mail: dfeifel@ucsd.edu.

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visit and analyzed at University of California, San Diego laboratories for basic chemistry analysis.

Statistical Methods

Data from all subjects who received at least one dose and one assessment in both treatment periods (intent-to-treat population) were subjected to analysis using SPSS version 11.0 (SPSS Inc., Chicago, Illinois). Baseline scores for both drug treatments were compared for similarity using paired t test. The change in baseline scores from period 1 to period 2 was compared among the placebo-oxytocin versus oxytocin-placebo groups using a two-sample t test to assess for period carryover effects (16). The PANNS and Clinical Global Impressions data were subjected to repeated measures analysis of variance with drug and treatment week as repeated measures factors. Treatment sequence was included as a between-subjects factor to evaluate possible period and carryover effects. Paired t tests, corrected for multiple comparisons using Bonferoni method, were used to compare placebo and oxytocin scores at end point and each of the other assessment visits. Cohen's d statistic was calculated for each measure at end point (17).

Results

Fifteen of 19 randomized subjects completed all study visits. Four randomized subjects were discontinued before completing the study, one due to nasal discomfort from the intranasal sprays and three due to insufficient compliance. None of the discontinued subjects reached the second treatment period; therefore, intent-to-treat population was identical to completer population. Eighty percent of completers were male, 53% black and 27% white, and average age and duration of disease were 48 (8.9) and 26 (14.6), respectively (Table S1 in Supplement 1). They were on a wide range of antipsychotics on entering the study (Table S2 in Supplement 1).

Table 1 lists efficacy results. Baseline scores at the start of each placebo and oxytocin treatment arm were highly similar for PANSS total (82.1 ± 11.06 and 81.4 ± 12.43) and CGI-S (4.60 ± .74 and 4.67 ± .74). Change in scores between first period and second period baselines did not significantly differ between groups, suggesting there was not significant carryover.

There was a significantly greater improvement in PANSS total scores across visits with oxytocin compared with placebo, as revealed by a significant drug by treatment week interaction [$F(2,26) = 6.493$, $p = .005$]. None of the other main or interaction effects were significant. Scores were significantly lower with oxytocin versus placebo at the end point (week 3) visit (difference = 5.46, $p < .001$, Cohen's d effect size = .43), whereas there was no significant difference at baseline (difference = .60), week 1 (difference = .60), or week 2 (difference = 1.20).

The CGI-I scores revealed a drug by treatment week interaction that approached significance ($p = .065$, Cohen's $d = .74$). No other main or interaction effect was significant. The CGI-I was significantly lower for oxytocin versus placebo at week 3 ($p < .001$) but not at baseline, week 1, or week 2.

Analysis of PANSS negative subscale scores did not reveal any significant main factor or interaction effects but were significantly lower for oxytocin versus placebo at week 3 only ($p = .023$, Cohen's $d = .50$).

A greater decrease in PANSS positive subscale scores under oxytocin was reflected in a nonsignificant trend toward a drug by treatment week interaction ($p = .089$). There was also a significant drug by treatment sequence effect [$F(1.13) = 11.57$, $p = .005$] reflected in the fact that PANSS positive scores were significantly lower with oxytocin treatment ($p = .01$) when it was the first treatment but not when it was the second treatment. There were no other significant main or interaction effects. Oxytocin scores were significantly lower than placebo scores at week 3 ($p = .006$, Cohen's $d = .4$) but not at baseline, week 1, or week 2.

A greater decrease in PANSS general psychopathology subscale scores under oxytocin was reflected in a nonsignificant trend toward a drug by visit interaction ($p = .069$, Cohen's $d = .24$). Oxytocin scores were not significantly different from placebo at any time point.

Overall, differences in the first period by itself (between-subjects analysis) did not reach statistical significance.

There were no serious adverse events reported during the

Table 1. Efficacy Scores (± Standard Deviation)

	Baseline	Week 1	Week 2	Week 3 [Cohen's *d*][a]
PANSS Total				
Placebo	82.1 (11.1)	76.9 (10.6)	75.7 (12.7)	79.1 (12.9)
Oxytocin	81.5 (12.4)	76.3 (11.3)	76.9 (13.2)	73.6 (13.6)[b] [.43]
PANSS Positive				
Placebo	22.8 (5.2)	21.2 (5.0)	20.0 (4.6)	21.9 (4.8)
Oxytocin	21.7 (4.1)	20.6 (4.5)	20.5 (4.6)	19.9 (5.2)[b] [.40]
PANSS Negative				
Placebo	21.8 (4.7)	20.5 (4.4)	20.2 (4.6)	20.7 (4.3)
Oxytocin	20.2 (4.7)	20.1 (4.8)	19.7 (4.3)	18.5 (4.5)[c] [.50]
PANSS General Psychopathology				
Placebo	37.5 (6.6)	35.2 (6.2)	35.4 (7.3)	36.4 (7.3)
Oxytocin	38.8 (7.6)	36.4 (8.1)	36.3 (8.2)	34.8 (6.9) [.24]
PANSS CGI-I				
Placebo	4.60 (.74)[d]	3.53 (.92)	3.53 (.92)	3.73 (1.03)
Oxytocin	4.67 (.61)[d]	3.33 (.62)	3.33 (1.20)	3.07 (.70)[b] [.74]

CGI-I, Clinical Global Impressions-Improvement; PANSS, Positive and Negative Syndrome Scale.
[a].2 small, .5 medium, .8 large (17).
[b]Significantly different versus placebo $p < .05$.
[c]Significantly different versus placebo $p < .01$.
[d]Clinical Global Impressions-Severity and not Clinical Global Impressions-Improvement noted for baseline.

Table 2. Reported Adverse Events

	Oxytocin (*n*)	Placebo (*n*)
Headache	26.7% (4)	20.0% (3)
Dyspepsia or Nausea	26.7% (4)	40.0% (6)
Sleep Impairment	33.3% (5)	26.7% (4)
Dizzy or Lightheaded	26.7% (4)	20.0% (3)
Nasal Irritation	26.7% (4)	13.3% (2)
Lethargy	.0% (0)	13.3% (2)

study and no significant differences in rates of reported adverse effects with oxytocin compared with placebo (Table 2). There were no significant differences between oxytocin and placebo in any of the measured blood chemistry or urine osmolality tests (Table S3 in Supplement 1).

Discussion

We found that 3 weeks of intranasal oxytocin, given adjunctive to standard antipsychotic medications, caused significantly greater reductions in schizophrenia symptoms at the study end point compared with placebo. This result supports our hypothesis that oxytocin exhibits antipsychotic properties and validates preclinical studies, case reports, and less well-controlled clinical studies suggesting oxytocin's ability to ameliorate symptoms of schizophrenia (18,19).

Oxytocin's effect appeared to manifest broadly across symptom clusters including positive and negative symptoms, although the improvement in positive symptoms appeared statistically more robust. Though the numerical effect of oxytocin is modest (7.9 point reduction on the PANSS total compared with 3.0 points for placebo), three points regarding its observed magnitude of benefit warrant consideration. First, subjects were already on stable therapeutic doses of at least one antipsychotic and oxytocin represented adjunctive treatment. Compared with a medication-free cohort, improvements in this already treated cohort are generally harder to come by. Notwithstanding this fact, the effect size of the improvements we observed were medium [(.43) PANSS scores] to large [(.74) CGI-I] (17). Second, this study had dosing and duration limitations that may have prevented the optimal magnitude of benefit from being observed: only one oxytocin dose was studied, and subjects were treated for only 3 weeks. Either higher doses or longer treatment duration may have yielded greater symptom improvements. Supporting this latter point, oxytocin's benefits emerged only at the week 3 assessment, a finding that suggests a delayed onset of action that may have grown with a longer treatment duration. Finally, while it is possible that a certain subpopulation of schizophrenia patients is particularly responsive to the benefits of oxytocin (based on oxytocin receptor variations or diagnostic subtype), our sample size was too small for a subanalysis along these lines. To fully characterize oxytocin's antipsychotic potential, future studies are warranted with larger sample sizes, different doses, and longer treatment durations, as well as pharmacogenetic and behavioral investigations.

Despite its therapeutic potential, there have been very few trials of oxytocin for psychiatric conditions. As such, our finding that oxytocin—given twice daily for 3 weeks—was well tolerated and did not appear to produce any subjective or objective adverse events is noteworthy.

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ClinicalTrials.gov: Oxytocin Treatment of Schizophrenia; http://clinicaltrials.gov/ct2/show/NCT00506909?termoxytocin&rank7; NCT00506909.

Supplementary material cited in this article is available online.

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