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CASE REPORT

INTRANASAL OXYTOCIN IN OBSESSIVE–COMPULSIVE DISORDER

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SUMMARY

A 55-year patient with obsessive–compulsive disorder showed clear improvement during 4 weeks of treatment with intranasal oxytocin compared to 4 weeks of intranasal placebo. This improvement was concurrent with the development of severe memory disturbances, supporting the amnestic properties of the peptide. However, the patient also developed psychotic symptoms and a marked decrease in plasma sodium and osmolality, which may have masked the obsessive symptomatology. This case highlights the need for careful monitoring in long-term oxytocin therapy.

INTRODUCTION

VASOPRESSIN and oxytocin are two neuropituitary nonapeptides of hypothalamic neurosecretory origin which affect consolidation and retrieval of memory in an opposite manner (Bohus *et al.*, 1978a; Bohus, 1980; Kovacs & Telegdy, 1982). Vasopressin facilitates these processes, while oxytocin appears to be an amnestic neuropeptide. In animals, oxytocin prevents the acquisition of conditioned behavior or facilitates its extinction in a way opposite to vasopressin (Kovacs & Telegdy, 1982). The opposite behavioral effects are in agreement with electrophysiological data which also argue for an opposite effect of the two peptides on neuronal activity: oxytocin desynchronises cortical EEG activity, while vasopressin synchronises EEG activity (Kovacs & Telegdy, 1982). The fact that oxytocin treatment facilitates the extinction of active avoidance behavior and attenuates passive avoidance behavior has led to the assumption that either learning or memory processes might be affected by this pituitary peptide.

Several animal experiments have shown that oxytocin has a dual effect on memory processes, attenuating both the consolidation and the retrieval of memory (Kovacs & Telegdy, 1982). Since vasopressin exerts opposite effects, it may be concluded that oxytocin is a neuropeptide with amnestic properties, whereas vasopressin exerts hypermnestic effects. The amnestic activity of oxytocin has been verified in controlled

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trials in normal volunteers (Ferrier *et al.*, 1980; Fehm-Wolfsdorf *et al.*, 1984). The oxytocin-induced attenuation of memory processes might be mediated by limbic-midbrain structures (e.g., hippocampus, dentate gyrus, dorsal raphe area) (Kovacs *et al.*, 1979). Since the same loci are involved in vasopressin-induced facilitation of memory processes, it seems possible that the two peptides affect the same neuronal target areas, but at different specific receptor sites, as shown by Mühlethaler *et al.* (1983) and Costantini & Pearlmutter (1984).

Among the psychiatric illnesses, obsessive – compulsive disorder is one of the most difficult to treat. Psychotherapy, behavior modification, and several pharmacologic treatments can provide substantial benefits, but a significant proportion of patients are refractory to the standard interventions and can be improved only by psychosurgery (Salzman & Thaler, 1981). According to learning theory, obsessions and compulsions are conditioned responses to anxiety-provoking events (Salzman & Thaler, 1981). Therefore, we tested in an obsessive – compulsive patient resistant to classical psychological and pharmacological interventions, the possible beneficial activity of intranasal oxytocin. Intranasal oxytocin has been shown to cross the blood – brain barrier in animals as well as in humans (Landgraf, 1985). This case-report sheds light on the biological and psychological tolerance of oxytocin when administered over a several week period.

CASE REPORT

Mr R., age 55, was hospitalized in October 1985 in the Biological Psychiatry and Psychopharmacology Unit of the University Hospital of Liège, Belgium, with a DSM-III diagnosis of obsessive – compulsive disorder. The patient, who was an insurance broker, has no family or personal psychiatric history. After 10 years of marriage, he was divorced in 1968 and remarried in 1974 for only 2 years. The initial symptomatology began in 1981 with obsessive thoughts and compulsive behavior: in stores, the patient felt the need to buy several non-useful items, and he had to keep samples of each type of food he ate, take note of any car plates he saw, and ask everybody he met his or her name, address, and phone number. This symptomatology had been increasing over a 5 year period despite various psychological interventions (analytical psychotherapy and behavior therapy), as well as treatments with high doses of anxiolytic benzodiazepines (lorazepam, bromazepam), tricyclic and monoamine oxidase inhibitor antidepressants (desipramine, clomipramine, melitracene, nialamide), and neuroleptics (haloperidol, loxapine, pimozide, levomepromazine, flupentixol).

The patient was asked to stop all pharmacologic therapy during the 3 weeks preceding admission. During the first 2 weeks of hospitalization, the patient had a complete medical, biological, and psychological evaluation. Medical examination, EKG, chest X-ray, EEG, and routine laboratory tests were normal. The patient had a lack of normal growth hormone release following i.v. clonidine (0.15 mg) but a normal growth hormone stimulation by subcutaneous apomorphine (0.5 mg). He exhibited normal cortisol suppression to dexamethasone (1 mg). Basal osmolality (290 mOsm/kg), and basal neurophysin (1.2 ng/ml) concentration and their responses to overhydration challenge were all in the normal range.

With his full informed consent, the patient was treated by intranasal oxytocin or

placebo (one squeeze in each nostril three times a day) in a double-blind, cross-over fashion. Each randomized period lasted for 4 weeks. The oxytocin solution contained 40 I.U./ml, and one squeeze delivered between 1.4 and 2.8 I.U.

After the study was completed, the code revealed that the patient had been initially treated by placebo and then by oxytocin. Clinical assessment was performed two times a week with the obsessive – compulsive subscale of the comprehensive psychopathological rating scale (CPRS-OC), which contains six items rated from 0 to 6 (Montgomery & Montgomery, 1980). The patient had a comprehensive assessment of psychologic symptoms before therapy and at the end of each treatment period by means of the system developed by the Association for Methodology and Documentation in Psychiatry (AMDP) (Guy & Ban, 1982). Factor analysis of the 115 items of the psychopathological AMDP scale has revealed 10 main factors (Bobon *et al.*, 1982).

Changes over time in CPRS-OC scores are displayed in Fig. 1, and changes in the AMDP factor scores are displayed in Fig. 2. While no significant changes in obsessive – compulsive symptoms were present during the placebo period, intranasal oxytocin induced a clear improvement in most items of the CPRS-OC: compulsive thoughts (from 6 to 4 points), indecision (from 5 to 4), worrying over trifles (from 6 to 4), rituals (from 6 to 2), and inner tension (from 6 to 3) (Fig. 1). This improvement was also clear on the AMDP factor scores related to obsessions and anxiety (Fig. 2). However, this syndromic profile also reflected the appearance of psychotic symptoms during oxytocin treatment: hallucinations and delusions of persecution (Fig. 2). The patient had the feeling that someone bore him a grudge but did not know who and why. He thought he was poisoned but added that this was perhaps only an idea. He heard people talk "in his head". Sometimes, he also heard knocking at the door when there was nobody. People could guess his thoughts by incomprehensible means in order to use them against him.

Moreover, with the oxytocin therapy, the patient complained of gross memory disturbances, which were specifically assessed. On the visual motor gestalt test (Bender, 1938), the patient obtained abnormally low results, showing maladaptation of motor control as well as unsatisfactory spatial interrelations. On the visual retention test (Benton, 1976), the results were dramatically low: Mr R. gave some responses unrelated to the models, which are only seen in severely demented or psychotic patients. The patient was unable to focus his attention to the tasks, was totally indifferent to the instructions, and did not exhibit any feeling of failure. Similar conclusions can be drawn from the complex figure test and the memory profile (Rey, 1959, 1966) On the 15 words test (Rey, 1958), initial acquisition level was rather satisfactory, but learning was nearly absent. The lack of a similar memory testing performed before the initiation of drug therapy prevents a comparison of results. However, the patient did not exhibit any complaint or evidence of memory disturbance during the placebo period, which suggests that the memory troubles were related to oxytocin intake.

The appearance and evolution of psychotic symptoms and memory disturbances were concurrent with the improvement in obsessive – compulsive symptomatology (Fig. 1).

The laboratory tests performed at the end of the oxytocin period revealed pathological alterations in plasma sodium level (126 mmol/1; normal: 135 – 145), and plasma osmolality (252 mOsm/kg; normal: 270 – 290) while plasma neurophysin was increased compared to pre-treatment (2.0 vs 1.2 ng/ml).

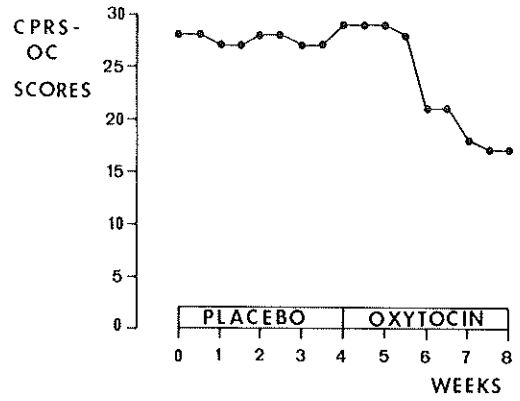

Fig. 1. Changes over time in the scores of the obsessive–compulsive subscale of the comprehensive psychopathological rating scale (CPRS-OC) in an obsessive–compulsive patient during 4 weeks of treatment by placebo followed by 4 weeks of treatment by intranasal oxytocin.

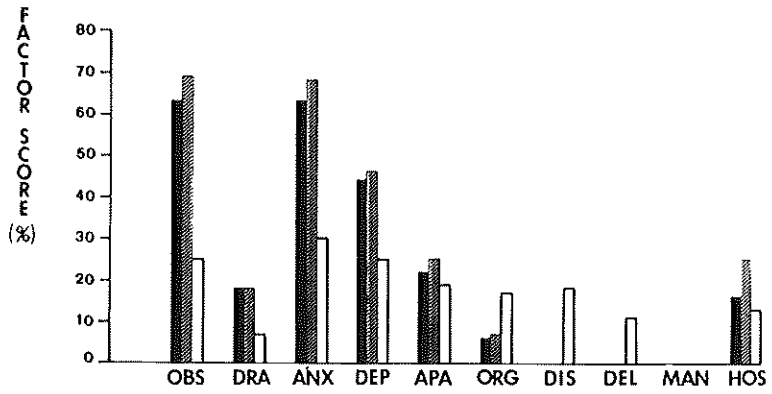

Fig. 2. Factor scores of the AMDP psychopathological scale in an obsessive–compulsive patient before therapy (black columns), after 4 weeks of placebo (hatched columns), and after 4 weeks of intranasal oxytocin (white columns). OBS, obsessions; DRA, dramatization; ANX, anxiety; DEP, depression; APA, apathy-retardation; ORG, psycho-organic syndrome; DIS, dissociation–depersonalisation; DEL, delusions; MAN, mania/agitation; HOS, hostility/irritability.

DISCUSSION

This case report suggests a beneficial activity of intranasal oxytocin in obsessive–compulsive disorder. This therapeutic property of oxytocin may be secondary to its amnestic activity. In animals, oxytocin facilitates the extinction of active and passive avoidance behavior in a way opposite to vasopressin (Schulz *et al.*, 1974, 1976; Kovacs *et al.*, 1978; Bohus *et al.*, 1978b). The amnestic properties of oxytocin may lead to a "deconditioning" effect which may be of therapeutic value in obsessive–compulsive disorder. Moreover, oxytocin may possess some anxiolytic properties: men and women following sexual intercourse as well as nursing mothers exhibit a decrease in anxiety scores associated with oxytocin increase (Newton, 1978).

However, in our patient, the apparent improvement in obsessive – compulsive symptoms could have been secondary to the development of psychotic symptoms, which may have distracted the patient from his usual rituals. This oxytocin-induced psychosis was unexpected, and its mechanism is unclear. It can correspond to a specific "psychodysleptic" effect of long-term oxytocin treatment. Favoring this interpretation, CSF oxytocin as well as oxytocin-associated neurophysin have been found to be increased in schizophrenic patients (Beckmann *et al.*, 1985; Linkowski *et al.*, 1984), while intranasal vasopressin may be of therapeutic value in the treatment of schizophrenic patients (Vranckx *et al.*, 1979). It also could be related to the metabolic changes secondary to oxytocin therapy, i.e. dramatic decreases in plasma osmolality and sodium levels. This unexpected side-effect of long-term oxytocin therapy can be explained by the fact that oxytocin is not totally devoid of antidiuretic activity, but has about 0.25% of the activity of vasopressin (Liggins, 1963; Pickering, 1970). Therefore, the relatively high amount of oxytocin received by the patient may have led to an iatrogenic inappropriate antidiuretic hormone secretion syndrome. However, the increase of neurophysin levels during oxytocin therapy may be difficult to reconcile with this hypothesis. Oxytocin has been described to induce its own release by a positive feedback mechanism (Moos *et al.*, 1984), which might explain the apparent contradiction between low sodium level and osmolality and elevated neurophysin.

In summary, this first trial of intranasal oxytocin in obsessive – compulsive disorder suggests a possible therapeutic activity. However, the possible utility of oxytocin in this disorder should be confirmed in a larger number of patients, in whom particular attention should be given to monitoring both the psychological and the biological tolerance of the peptide.

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