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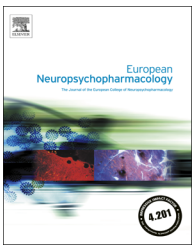

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Intranasal desmopressin as an adjunct to risperidone for negative symptoms of schizophrenia: A randomized, double-blind, placebo-controlled, clinical trial

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Abstract
Considering the role of neurohypophyseal peptides in normal development and function of higher cortical processes along with their proven abnormalities in schizophrenic patients, these pathways have recently attracted greater attention as treatment targets for schizophrenia. Desmopressin (DDAVP) is a synthetic analog of vasopressin. This study aimed to evaluate the efficacy and safety of DDAVP nasal spray as an adjunct to risperidone in improving negative symptoms of schizophrenia. In this randomized double-blind placebo-controlled clinical trial, forty patients aged 18–50 years with a DSM IV-TR diagnosis of chronic schizophrenia and a minimum score of 60 on positive and negative syndrome scale (PANSS) were equally randomized to receive DDAVP nasal spray (20 mcg/day) or placebo in addition to risperidone for 8 weeks. Patients were partially stabilized and treated with a stable dose of risperidone (5 or 6 mg/day) for at least four weeks prior to entry. Participants were rated by PANSS every two weeks and

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decrease in the PANSS negative subscale score was considered as our primary outcome. By the study endpoint, DDAVP-treated patients showed significantly greater improvement in the negative symptoms ($P=0.001$) as well as the PANSS total and general psychopathology subscale scores ($P=0.005$ and $P=0.003$; respectively) compared to the placebo group. Treatment group was the strongest predictor of changes in negative symptoms ($\beta=-0.48$, $t=-3.67$, $P=001$). No serious adverse event or fluid/electrolyte imbalance was reported in this trial. In conclusion, DDAVP nasal spray showed to be an effective and safe medication for improving negative symptoms in patients with chronic schizophrenia.

1. Introduction

Negative symptoms of schizophrenia lead to poor quality of life, profound functional impairment, and significant decline in schizophrenic patients' prognosis. In definition, negative symptoms consist of social aversion, apathy, bluntness of affect and catatonic features like mannerism and abnormal posturing (Fenton and McGlashan, 1991). It has been shown that negative symptoms of schizophrenia represent some distinct pathophysiological mechanisms and are not solely secondary to positive symptoms (Goff, 2013). There is inconsistency in the literature regarding the use of typical and atypical antipsychotics for improving negative symptoms of schizophrenia and these symptoms have still remained relatively resistant to current treatments (Kirkpatrick et al., 2006). Concerning the neurophysiological mechanisms responsible for negative symptoms of schizophrenia, recently described models explain complex networks of different overlapping and connected contributing mechanisms in this regard. Many studies are exploring novel therapeutic strategies aimed at negative symptoms based on these underlying defects (Murphy et al., 2006).

Neurohypophyseal peptides, particularly oxytocin (OT) and arginine vasopressin (AVP), have attracted much more attention in recent decades as contributing to the pathophysiology and thus potential targets in treatment of schizophrenic symptoms (Caceda et al., 2007; Holsboer, 2003; Lacrosse and Olive, 2013). Several studies indicate altered levels of these peptides in cerebrospinal fluid (CSF) of schizophrenic patients (Beckmann et al., 1985; Raskind et al., 1986; Sorensen et al., 1985). Besides their miscellaneous functions in human body, OT and AVP have been shown to influence higher cortical functions and to modulate memory, cognition, and complex social and emotional behaviors (de Wied and van Ree, 1989; Heinrichs et al., 2009; Winslow and Insel, 2004). Beneficial therapeutic effects of OT in improving neuropsychiatric disorders have been demonstrated in numerous clinical trials to date (Bakermans-Kranenburg and van Ijzendoorn, 2013; De Berardis et al., 2013; Macdonald and Feifel, 2012). Recently, we reported encouraging outcomes from OT administration to improve schizophrenic symptoms in a randomized clinical trial (Modabbernia et al., 2013).

Several human and animal studies have revealed important functions of AVP in memory, aggression, recognition, and social interaction (Caldwell et al., 2008; McCall and Singer, 2012). The key role of AVP in social memory has been illustrated in AVP receptor knockout mice as well (Bielsky et al., 2004, 2005). Interestingly, Brattleboro rats, which are unable to synthesize vasopressin due to a genetic mutation, display many abnormalities similar to negative and cognitive symptoms of schizophrenia (Engelmann and Landgraf, 1994; Laycock et al., 1983; Williams et al., 1983). These rats show diminished prepulse inhibition (PPI), a measure of central processing which is impaired in schizophrenia and has a negative correlation with severity of the disease (Cilia et al., 2010). Even more appealing, administration of vasopressin agonists can reverse the cognitive and behavioral abnormalities in Brattleboro rats (Bohus and de Wied, 1998; Engelmann and Landgraf, 1994). From another perspective, the AVP system has been shown to be in interplay with fundamental neurotransmitter deficits in schizophrenia including dopaminergic and glutamatergic systems. Some NMDA antagonists, such as phencyclidine and MK-801, reduce the density of vasopressin receptors in the brain and can impair the social interaction in rats which mimics negative symptoms of schizophrenia (Matsuoka et al., 2005; Sams-Dodd, 1995; Tanaka et al., 2003). Interestingly, some AVP analogs have the ability to reverse the social interaction deficits induced by NMDA antagonist (Matsuoka et al., 2005).

Based on the available data, it can be imagined that enhancing AVP levels and activity may improve at least some of the schizophrenia-related symptoms (Brambilla et al., 1986; Iager et al., 1986; Korsgaard et al., 1981), but no well-designed randomized clinical trial has been conducted to date to address this question. Desmopressin acetate, also known as Minirin or DDAVP (1-desamino-8-D-arginine vasopressin), is a synthetic analog of AVP which is widely used for the treatment of central diabetes insipidus and primary nocturnal enuresis. Compared to vasopressin, DDAVP has a longer duration of action and its intranasal preparation has an acceptable penetration to the central nervous system (CNS) (Ang and Jenkins, 1982; Vande Walle et al., 2007). Due to inadequate response seen with current medications, there is growing interest in adjunctive strategies with different agents for improving negative symptoms of schizophrenia. In the present study, we aimed to evaluate the efficacy and safety of DDAVP nasal spray as an add-on to risperidone in improving schizophrenic symptoms, particularly the negative ones.

2. Experimental procedures

2.1. Trial design

This was an 8-week, parallel-group, double-blind, placebo-controlled clinical trial in patients with chronic schizophrenia.