Can ziconotide as a N-type voltage-sensitive calcium channel blocker open a new mode for treatment of autism? *A hypothesis.*

Ahmad Ghanizadeh, *MD.*

Social interaction impairment, abnormalities in communication skills, stereotypic behaviors, restricted activities, and interests are the main symptoms of autism spectrum disorders. Its rate in boys is higher than that of girls in clinical samples.[1] The rate of 0.9% in children aged 8 years is reported. A study from Iran on 2000 school age children showed that 1.9% of the sample had the screening symptoms of an autistic disorder.[2] Autism is one of the pervasive developmental disorders, the pathophysiology of which is not exactly known. The GABAergic/glutamineric system is abnormal in autism. The GABAergic system is attenuated.[3] This suppression has an etiological role in autism. Moreover, there is no curative drug treatment for autism. It is reported that the hyperglutamatergic condition may have a role in autism pathophysiology,[4] and the antagonists of the N-methyl-D-aspartic acid (NMDA) glutamate receptor such as memantine, significantly improve some of the symptoms of individuals with autism. There is only one Food and Drug Administration (FDA) approved medication for the treatment of autism.[5] This medication is risperidone. Therefore, suggesting and exploring novel treatments is highly recommended for the treatment of autism. This article, according to the following evidence, introduces a hypothesis that N-type voltage-sensitive calcium-channel blockers such as ziconotide may open a new mode for the treatment of autism.

Presentation of hypothesis. Ziconotide, previously called SNX-111, is a synthetic peptide that selectively blocks N-type voltage-sensitive calcium-channels. It is approved by the FDA and the European Medicines Agency for patients with severe refractory chronic pain. The safety and effectiveness of ziconotide were discussed in a recently published article.[6] Calcium influx through these channels at presynaptic terminals of neurons is required for the release of the neurotransmitter.[7] The inhibition of the N-type calcium channels by ziconotide blocks calcium entering the neuron. So, the release of neurotransmitters such as glutamate into the synaptic space is reduced.[7] Considering the hyperglutaminergic state in autism,[4] the efficacy of the NMDA glutamate receptor antagonists for improving autism, and the effect of ziconotide in decreasing glutamate release into the synaptic space,[7] the possible effect of ziconotide, an N-type voltage-sensitive calcium-channel blocker, on autism symptoms, is hypothesized. This may open a window to a number of new treatment strategies to reduce autism symptoms.

Testing the hypothesis. There are some serious concerns regarding ziconotide's substantial CNS side-effects and safety, such as its slow passing into the CNS parenchyma, its relatively narrow therapeutic window, susceptibility to proteolytic cleavage by peptidases/proteases existing in many organs, and route of intrathecal administration (not intravenously).[8] Therefore, after providing enough evidence supporting its safety and the possible proposed effects, culture medium or preclinical animal model experimental studies are required to be conducted testing this hypothesis.

Disclosure. Author has no conflicting interests, and was not supported or funded by any drug company.

Received 17th August 2010. Accepted 7th November 2010.

From the Research Center for Psychiatry and Behavioral Sciences, Department of Psychiatry, Shiraz University of Medical Sciences, Hafez Hospital, Shiraz, Iran. Address correspondence and reprint requests to: Dr. Ahmad Ghanizadeh, Associate Professor of Child and Adolescent Psychiatry, Research Center for Psychiatry and Behavioral Sciences, Department of Psychiatry, Shiraz University of Medical Sciences, Hafez Hospital, Shiraz, Iran. Tel/Fax. +98 (711) 6279319. E-mail: ghanizad@sina.tums.ac.ir

References

1. Ghanizadeh A, Mohammadi MR, Sadeghiyeh T, Shooshtari AA, Akhondzadeh S. Symptoms of children with autism spectrum disorder, a clinical sample. ***Iran J Psychiatry*** 2009; 4: 165-169
2. Ghanizadeh A. A preliminary study on screening prevalence of pervasive developmental disorder in schoolchildren in Iran. ***J Autism Dev Disord*** 2008; 38: 759-763.
3. Blatt GJ. GABAergic cerebellar system in autism: a neuropathological and developmental perspective. ***Int Rev Neurobiol*** 2005; 71: 167-178.
4. Shinohe A, Hashimoto K, Nakamura K, Tsujii M, Iwata Y, Tsuchiya KJ, et al. Increased serum levels of glutamate in adult patients with autism. ***Prog Neuropsychopharmacol Biol Psychiatry*** 2006; 30: 1472-1477.
5. Rossignol DA. Novel and emerging treatments for autism spectrum disorders: a systematic review. ***Ann Clin Psychiatry*** 2009; 21: 213-236.
6. Wallace MS, Rauck RL, Deer T. Ziconotide combination intrathecal therapy: rationale and evidence. ***Clin J Pain*** 2010; 26: 635-644.
7. Schmidtko A, Lotsch J, Freynhagen R, Geisslinger G. Ziconotide for treatment of severe chronic pain. ***Lancet*** 2010; 375: 1569-1577.
8. Smith HS, Deer TR. Safety and efficacy of intrathecal ziconotide in the management of severe chronic pain. ***Ther Clin Risk Manag*** 2009; 5: 521-534.