

Bumetanide for autism spectrum disorder: Current evidence

Otizm Spektrum Bozukluğunda Bumetanid: Güncel Deliller

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TO THE EDITOR

Autism spectrum disorder (ASD), a lifelong neurodevelopmental disability characterized by persistent defects at social interactions and restricted behaviors and interests, affects 1 in every 59 children while effective treatment options are yet to be identified (1). Novel treatment options including gluten-free diet, vitamin and mineral supplementation have been implemented along with pharmacotherapy with limited success. Bumetanide is a loop diuretic drug that works by inhibiting sodium-potassium-chloride (Na-K-Cl) cotransporters, namely NKCC1 and NKCC2, while NKCC1 is also present in brain in contrast to kidney-specific NKCC2 (2). Use of bumetanide in ASD patients was first proposed in 2010 in five infants treated with 1 mg/day bumetanide for 3 months (3). Effectiveness of bumetanide treatment has shown in a 3-month placebo-controlled double-blind randomized controlled trial (RCT) involving 60 children with ASD or Asperger syndrome in which autistic traits were evaluated by Childhood Autism Rating Scale (CARS), Clinical Global Impressions, Autism Diagnostic Observation Schedule and video films at day 0 and 90 (4). Further placebo-controlled RCTs revealed that administration of bumetanide treatment along with applied behavior analysis (ABA) is superior treatment option compared to ABA alone (5). Beneficial effects were also reported in few other RCTs involving 88 and 83 subjects with similar autistic behavior evaluation tools and case reports while most commonly observed adverse effects include hypokalemia, dehydration, loss of appetite and asthenia (6-8). Clinical trials investigating effectiveness of bumetanide in other neuropsychiatric disorders

including neonatal seizures, schizophrenia and Parkinson diseases have been conducted (9, 10).

Accumulation of chloride in neurons in early prenatal period has shown to regulate the levels of primary inhibitory neurotransmitter in humans, namely gamma-aminobutyric acid (GABA), which involves in many neurodevelopmental process through calcium-mediated cell signaling (11). Intracellular chloride accumulation is mediated via NKCC1 and KCC2 transporters which are influx and efflux pumps, respectively (11). Mechanism of action of bumetanide in ASD patients is believed to be the restoration of GABAergic system through decline in intracellular chloride levels. Over-activation of cortical regions involved in face processing and recognition including amygdala in ASD patients compared to controls has shown to be reversed with bumetanide treatment as shown in functional magnetic resonance imaging studies (12, 13). Even though bumetanide appears to be effective in the treatment of autistic behaviors with low adverse effect profile, further large-scale RCTs are necessary to recommend its' clinical implementation. However, it is important for clinicians to be aware of such possibly upcoming treatment option and its' pathophysiology.

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REFERENCES

1. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z, et al. Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2014. *MMWR Surveill Summ* 2018;67(6):1-23.
2. Brater DC. Pharmacology of diuretics. *Am J Med Sci* 2000;319(1):38-50.
3. Lemonnier E, Ben-Ari Y. The diuretic bumetanide decreases autistic behaviour in five infants treated during 3 months with no side effects. *Acta Paediatr* 2010;99(12):1885-8.
4. Lemonnier E, Degrez C, Phelep M, Tyzio R, Josse F, Grandgeorge M, et al. A randomised controlled trial of bumetanide in the treatment of autism in children. *Transl Psychiatry* 2012;2:e202.
5. Du L, Shan L, Wang B, Li H, Xu Z, Staal WG, et al. A Pilot Study on the Combination of Applied Behavior Analysis and Bumetanide Treatment for Children with Autism. *J Child Adolesc Psychopharmacol* 2015;25(7):585-8.
6. Lemonnier E, Villeneuve N, Sonie S, Serret S, Rosier A, Roue M, et al. Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders. *Transl Psychiatry* 2017;7(3):e1056.
7. Zhang L, Huang C-C, Dai Y, Luo Q, Ji Y, Wang K, et al. Symptom improvement in children with autism spectrum disorder following bumetanide administration is associated with decreased GABA/glutamate ratios. *Transl Psychiatry* 2020;10(1):9.
8. Grandgeorge M, Lemonnier E, Degrez C, Jallot N. The effect of bumetanide treatment on the sensory behaviours of a young girl with Asperger syndrome. *BMJ Case Rep* 2014;2014.
9. Damier P, Hammond C, Ben-Ari Y. Bumetanide to Treat Parkinson Disease: A Report of 4 Cases. *Clin Neuropharmacol* 2016;39(1):57-9.
10. Rahmazadeh R, Eftekhari S, Shahbazi A, Khodaei Ardakani MR, Rahmazade R, Mehrabi S, et al. Effect of bumetanide, a selective NKCC1 inhibitor, on hallucinations of schizophrenic patients; a double-blind randomized clinical trial. *Schizophr Res* 2017;184:145-6.
11. Cellot G, Cherubini E. GABAergic signaling as therapeutic target for autism spectrum disorders. *Front Pediatr* 2014;2:70-.
12. Hadjikhani N, Asberg Johnels J, Lassalle A, Zurcher NR, Hippolyte L, Gillberg C, et al. Bumetanide for autism: more eye contact, less amygdala activation. *Sci Rep* 2018;8(1):3602.
13. Hadjikhani N, Zurcher NR, Rogier O, Ruest T, Hippolyte L, Ben-Ari Y, et al. Improving emotional face perception in autism with diuretic bumetanide: a proof-of-concept behavioral and functional brain imaging pilot study. *Autism* 2015;19(2):149-57.