Bumetanide as an Effective Adjunct Therapy in Intractable Epilepsy

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Abstract

Introduction: Reduced KCC2 expression and increased NKCC1 expression can shift Gamma-aminobutyric acid (GABA) responses toward excitation and generate seizures. Previous studies suggested that bumetanide, an inhibitor of NKCC1, might have antiepileptic effects. Here, for the first time, we assessed NKCC1 and KCC2 dysregulation and possible modifying role of bumetanide in living human subjects with drug-resistant TLE. Materials and Methods: Eligible patients with drug-resistant TLE were included. Peripheral blood mononuclear cells (PBMCs) were isolated from collected blood samples and used for polymerase chain reaction (PCR) and western blot analyses. Bumetanide treatment was initiated with the dose of 0.5 mg/day and then was weakly increased by 0.5 mg until a target dose of 2mg/day was achieved. Then, seizure frequency and drug safety were assessed at each monthly visit. Results: A total of 39 patients were evaluated and 27 patients were included. Overall, 70.4% were responders. The median seizure frequency reduced significantly from 9 (7-15) at baseline to 4 (2-11.67) at first three months (P<0.001), 2.67 (1-5.33) at last three months (P<0.001), and 3.33 (1.33-7.17) during the six months of treatment (P<0.001). The forward logistic regression showed eGFR (OR: 0.953, 95% CI: 0.912-0.996, P=0.033) as the only significant predictor of drug response. The level of NKCC1 and KCC2 gene transcripts and KCC2 protein did not significantly alter following treatment (P>0.05). However, we observed a significant reduction in NKCC1 protein levels after bumetanide treatment (P=0.0156). Conclusion: Altogether, it seems that bumetanide is an effective and relatively tolerable drug in patients with drug-resistant TLE. We confirm that KCC2 is significantly downregulated while NKCC1 is markedly upregulated in TLE patients. Bumetanide treatment led to a significant reduction of NKCC1 protein expression which we believe is the underlying reason for its antiepileptic efficiency.

Keywords: Adjunct Therapy, Epilepsy, Expression.

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