Bumetanide reduces seizure frequency in patients with temporal lobe epilepsy

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SUMMARY

Alterations in the balance of K-Na-2Cl cotransporter (NKCC1) and Na-Cl cotransporter (KCC2) activity may cause depolarizing effect of γ-aminobutyric Acid (GABA), and contribute to epileptogenesis in human temporal lobe epilepsy. NKCC1 facilitates accumulation of chloride inside neurons and favors depolarizing responses to GABA. In the current pilot study we provide the first documented look at efficacy of bumetanide, a specific NKCC1 antagonist, on reduction of seizure frequency in adult patients with temporal lobe epilepsy. According to our results, seizure frequency was reduced considerably in these patients. Furthermore, epileptiform discharges decreased in two of our patients. If the efficacy of bumetanide is proven in large scale studies, it can be used as a supplemental therapy in temporal lobe epilepsy.

KEY WORDS: Bumetanide, Temporal lobe epilepsy, NKCC1, GABA.

It has been shown that changes in γ-aminobutyric acid (GABA)ergic signaling play an important role in temporal lobe epileptogenesis (Cohen et al., 2003). GABA, the main inhibitory transmitter in the adult central nervous system (CNS), at early developmental stages depolarizes target cells through an outwardly directed flux of chloride. In mature neurons, because of the low level of intracellular chloride ([Cl^-]), GABA triggers membrane hyperpolarization due to passive influx of chloride down its electrochemical gradient. In contrast, immature neurons have an elevated intracellular [Cl^-], so that GABA triggers chloride efflux and membrane depolarization (Ben-Ari, 2002). Two cation-chloride cotransporters may be especially important in controlling neuronal intracellular [Cl^-]: the Na-K-2Cl cotransporter (NKCC1) loads neurons with Cl^- and favors depolarizing responses to GABA, whereas the K-Cl cotransporter (KCC2) normally extrudes Cl^- ions, thereby promoting hyperpolarizing responses (Ben-Ari et al., 2007). In patients with epilepsy, changes in expression of NKCC1 and KCC2 may cause a depolarizing effect of GABA and contribute to epileptogenesis in the hippocampal formation (Ben-Ari & Holmes, 2005).

According to previous studies, patients with temporal lobe epilepsy (TLE) showed depolarizing GABAergic neurons in subicular pyramidal cells, and bumetanide suppressed this activity (Huberfeld et al., 2007). Muñoz et al. (2007), showed upregulation of the NKCC1 mRNA in the human epileptic hippocampus. Bumetanide is a specific NKCC1 antagonist that reduces [Cl^-], and switches GABA from excitation to inhibition (Delpire & Mount, 2002). This drug has been used in adults as a diuretic since 1975, with known pharmacokinetics and side effects (Sullivan et al., 1996). Suppression of seizure activity by bumetanide in a neonate was studied by Kahle et al. (2009).

In the current study, we provide the first documented data of bumetanide efficacy on reduction of seizure frequency in adult patients with temporal lobe epilepsy (TLE).

METHODS

We evaluated the effect of bumetanide in patients with drug-resistant TLE who were candidates for surgery. This study has been approved by the ethical committee of Tehran University of medical sciences, and all patients gave a written informed consent prior to start this study.