Summary:

Bumetanide to Ameliorate Tuberous Sclerosis Complex Hyperexcitable Behaviors (BATSCH)

Background

Tuberous sclerosis complex (TSC) is an autosomal dominant disease that affects multiple organs including the brain. TSC is strongly associated with broad neurodevelopmental disorders, including autism spectrum disorder symptomatology. Preclinical TSC studies have indicated altered neuronal chloride homeostasis affecting the polarity of γ-aminobutyric acid (GABA)ergic transmission as a potential treatment target. Bumetanide, a selective NKCC1 chloride importer antagonist, may attenuate depolarizing GABA action, and in that way reduce disease burden. In this open-label pilot study we tested the effect of bumetanide on a variety of neurophysiological, cognitive and behavioral measures in children with TSC.

Methods

Participants were treated with bumetanide (2dd0.5-1.0mg) for 13 weeks in an open-label trial. The Aberrant Behavior Checklist-Irritability (ABC-I) subscale was chosen as the primary endpoint. Secondary endpoints included other behavioral questionnaires in addition to event related potentials (ERP) and neuropsychological tests if tolerated. Additionally, treatment effect on seizure frequency and quality of life was assessed. Endpoint data were collected at baseline, after 91 days treatment and after a 28-day wash-out period.

Results

Fifteen patients (8-21 years old) with TSC were included of which 13 patients completed the study. Treatment was well-tolerated with only expected adverse events due to the diuretic effects of bumetanide. Irritable behavior (ABC-I) showed significant improvement after treatment in 11 out of 13 patients ($t(12)=4.41$, $p=.001$, $d=.773$). A favorable effect was also found for social behavior (Social Responsiveness Scale) ($t(11)=4.01$, $p=.002$, $d=.549$) and hyperactive behavior (ABC-hyperactivity subscale) ($t(12)=3.65$, $p=.003$, $d=.686$). Moreover, patients rated their own health related quality of life higher after treatment. At baseline, TSC patients showed several atypical ERPs versus typically developing peers of which prepulse inhibition was significantly decreased in the TSC group. Neuropsychological measurements showed no change and bumetanide had no effect on seizure frequency.

Limitations

The sample size and open-label design of this pilot study warrants caution when interpreting outcome measures.

Conclusions

Bumetanide treatment is a potential treatment to alleviate the behavioral burden and quality of life associated with TSC. More elaborate trials are needed to determine the application and effect size of bumetanide for the TSC population.