Paradoxical Benzodiazepine Response: A Rationale for Bumetanide in Neurodevelopmental Disorders?

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The diuretic agent bumetanide has recently been put forward as a novel, promising treatment of behavioral symptoms in autism spectrum disorder (ASD) and related conditions. Bumetanide can decrease neuronal chloride concentrations and may thereby reinstate γ-aminobutyric acid (GABA)-ergic inhibition in patients with neurodevelopmental disorders. However, strategies to select appropriate candidates for bumetanide treatment are lacking. We hypothesized that a paradoxical response to GABA-enforcing agents such as benzodiazepines may predict the efficacy of bumetanide treatment in neurodevelopmental disorders. We describe a case of a 10-year-old girl with ASD, epilepsy, cortical dysplasia, and a 15q11.2 duplication who had exhibited marked behavioral arousal after previous treatment with clobazam, a benzodiazepine. We hypothesized that this response indicated the presence of depolarizing excitatory GABA and started bumetanide treatment with monitoring of behavior, cognition, and EEG. The treatment resulted in a marked clinical improvement in sensory behaviors, rigidity, and memory performance, which was substantiated by questionnaires and cognitive assessments. At baseline, the girl’s EEG showed a depression in absolute α power, an electrographic sign previously related to ASD, which was normalized with bumetanide treatment. The effects of bumetanide on cognition and EEG seemed to mirror the “nonparadoxical” responses to benzodiazepines in healthy subjects. In addition, temporal lobe epilepsy and cortical dysplasia have both been linked to disturbed chloride homeostasis and seem to support our assumption that the observed paradoxical response was due to GABA-mediated excitation. This case highlights that a paradoxical behavioral response to GABA-enforcing drugs may constitute a framework for targeted treatment with bumetanide.

abstract

Dr Bruining was responsible for the clinical diagnosis of autism spectrum disorder, performed the overall clinical treatment and monitoring, initiated and drafted the first version of the manuscript, and critically reviewed the manuscript; Drs Passtoors and de Jonge developed the cognition and behavioral assessment battery, performed the cognitive studies, and critically reviewed the manuscript; Dr Jansen was responsible for the diagnosis and treatment of the patient’s epilepsy, initiated and drafted the first version of the manuscript, and reviewed the manuscript; Dr Hakvoort collected the EEG data of the control children and reviewed the manuscript, and Drs Poil and Gourionova developed and analyzed the EEG recordings and critically reviewed the manuscript. All authors approved the final manuscript as submitted.

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 PATIENT PRESENTATION

The patient, a 10-year-old girl, was the fourth child of nonconsanguineous healthy parents. The family history was unremarkable, and the pregnancy and birth were uneventful. The child displayed an apparently normal development up to 4 years of age, when she began experiencing epileptic seizures. She was diagnosed with focal epilepsy with right temporoparietal localization, with focal seizures occurring in clusters.

An MRI revealed a focal cortical dysplasia of the right temporal lobe. Coinciding with the onset of epilepsy, learning difficulty and behavioral rigidity emerged but were not evaluated at that time by a child psychiatrist. At the age of 8 years, she was referred to our clinic for diagnostic evaluation of increasing learning disability, behavioral inflexibility, and emotional disturbance. We observed a delay in language development, rigidity, and repetitive behaviors with peculiar

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Pages 1-5
interests. She also displayed evident deficits in long-term memory performance. A diagnosis of autism spectrum disorder (ASD) was confirmed by using a diagnostic evaluation and the Autism Diagnostic Observation Schedule criteria. The Autism Diagnostic Interview–Revised revealed ASD at current age but subclinical scores for the “ever” algorithm. Her full scale IQ was 71 (Wechsler Intelligence Scale for Children–III), with significantly better performance skills (performance IQ: 86) than verbal skills (verbal IQ: 63). Genetic testing was conducted by using array comparative genomic hybridization, and we found a duplication of ~630 kb on chromosome 15q11.2 (15: 20.220.216–20.851.879) containing 5 genes: TUBGCP5, CYFIP1, NIPA 1, NIPA 2, and WHAMML1. This copy number variant is commonly found in neurodevelopmental problems, including ASD, but it is also observed in healthy subjects. Carrier analysis among the parents revealed that the father had the same duplication but no clinical symptoms.

The patient’s treatment history revealed that several antiepileptic drugs had been attempted, including valproic acid, lamotrigine, and oxcarbazepine (without seizure reduction), and some led to adverse effects such as fatigue or diplopia. When the child was aged 6.3 years, prophylactic antiepileptic drugs were stopped, and the benzodiazepine clobazam (5–10 mg) was commenced daily during the clustering of seizures only, with the goal of attaining rapid control. Although clobazam was partly successful in controlling the seizures, it also led to an immediate aberrant behavioral reaction, characterized by profound restlessness, arousal, and talkativeness lasting for days (she had normally displayed reserved and shy social demeanor). This response to benzodiazepine treatment was striking and seemed to counteract an expected sedative effect through the positive allosteric action of GABA$_A$ receptors of this drug. These so-called paradoxical responses have been described previously in the literature and have also been specifically reported in children with ASD. The group of Yehezkel Ben-Ari in Marseille has previously suggested that such a response may indicate depolarizing (instead of hyperpolarizing) GABA activity due to elevated levels of intraneuronal chloride, which in turn may be treated with bumetanide, a selective chloride importer (NKCC1) antagonist.

Based on these considerations, we obtained approval from the local ethics committee and parental consent to start a 6-month trial of bumetanide 0.5 mg twice daily with monitoring of behavior, cognition, and EEG findings. The treatment did not cause adverse effects or discomfort with its diuretic effects. While the child previously had initiated limited social activities and struggled with remembering places and interactions, parents noted that she now could recall events in chronological order, with more insight in social context. This improvement was reflected in the parental questionnaires showing that aberrant response to sensory stimuli (Sensory Profile) and behavioral rigidity (Repetitive Behavior Scale–Revised) had declined from clinical to normal levels. The notion of cognitive improvement was further substantiated in a prominent improvement on neuropsychological testing. Assessment before the start of the intervention (T1 baseline) revealed average performance (z scores greater than –1) on baseline attention, visual working memory, visual learning, and cognitive flexibility to visual stimuli. In contrast, she exhibited significant impairments (z scores less than –2) on auditory learning and short-term memory, cognitive flexibility to auditory stimuli, and impulse inhibition.

After 6 months of treatment, the child’s memory skills improved remarkably. Auditory learning and memory skill improved from markedly impaired to within normal ranges (z score = –2.4 at T1; z = –1.3 at T2 after 3 months; and z = –0.7 at T3 after 6 months of treatments) (Fig 1A). This outcome was unlikely to be due to multiple testing because 3 different word lists of the Rey Auditory Verbal Learning Test were used on 3 occasions. The child’s improvements in memory were also clinically significant according to her parents (absolute increase in working memory z score was 1.3 on the Behavior Rating Inventory of Executive Function [BRIEF]). The parents reported significant improvement in flexibility in daily life according to the BRIEF. Inhibitory control on a task that required visuospatial processing improved significantly (absolute increase in z score of 0.9 at T2 and 1.9 at T3, from abnormal to normal range). Performance in other tasks of response inhibition and attentional flexibility in response to auditory information remained unchanged throughout treatment. Seizure frequency or severity had not changed, although her postictal symptoms were less severe, which enabled her to attend school during her clustering of seizures.

To substantiate an effect on brain activity, EEG spectral power was compared with 15 age-matched healthy subjects. A localized (Pz and neighboring channels) progressive increase in the power of $\alpha$ frequency oscillations (6–12 Hz) with treatment was found (Fig 1 B–D).

**METHODS**

Cognitive and EEG tests were performed in seizure-free episodes during morning hours in quiet, dedicated testing facilities to avoid distraction.

**Questionnaires**

The Sensory Profile, a caregiver questionnaire, was used to measure the child’s sensory processing abilities and their impact on daily functioning. Repetitive behavior in daily situations at home were assessed by using the
Repetitive Behavior Scale–Revised. The BRIEF is a daily functioning questionnaire completed by parents. Cognitive Tests

Memory tests included the digit span of the Wechsler Intelligence Scale for Children–III and the spatial span of the Wechsler Nonverbal Scale of Ability. The Rey Auditory Verbal Learning Test, Dutch edition, and the Rey Visual Design Learning Test, Dutch edition, were used to examine verbal and visual learning and memory. The Amsterdam Neuropsychological Tasks battery was used to assess inhibitory control and attentional flexibility (shifting attentional set visual [SSV] and shifting attentional set auditory [SSA]).

EEG Measurements

Routine EEG recordings were performed according to the International 10–20 System (SystemPlus Evolution, Micromed SpA, Mogliano Veneto, Italy) against G2 as a reference electrode (placed between Cz and Fz) and referenced to an average montage for further analysis. Impedance of each electrode was kept at <5 kΩ. Data were high- and low-pass, filtered at 0.008 and 45 Hz, respectively. Sampling frequency was 512 Hz. All EEG recordings contained 21 scalp electrodes (F8, F4, Fz, F3, F7, T8, C4, Cz, Pz).

FIGURE 1
Effects of bumetanide treatment on memory and resting state brain activity. A, Change (z score based on age-matched Dutch population norm scores). B, Example EEG trace in the Pz channel (black arrow in D) before and after 6 months of treatment. C, Power spectrum density plot of the Pz channel showing the increase in power in the α frequency band during bumetanide treatment compared with healthy control children (n = 15; age range: 10–11 years). Control data shown as mean power (black) with SEM (gray). D, Power of the α frequency band (6–12 Hz) in 23 EEG channels of the patient before and during treatment; the difference in power after 6 months of treatment is shown on the right. Median power in the 6- to 12-Hz range went from 3.9 ± (3.5–4.8) μV² (median ± [95% confidence interval of power density estimate]) before treatment, to 4.2 ± (3.7–4.8) μV² after 3 months, to 6.1 ± (5.4–7.0) μV² after 6 months. Control subjects had a median power (6–12 Hz) of 4.2 ± (2.1–13.4) μV² (median ± (95th bias corrected and accelerated bootstrap confidence interval)). Peak power increased from 6.9 ± (6.1–7.9) μV² before treatment, to 8.4 ± (7.5–9.7) μV² after 3 months, to 13.8 ± (12.1–15.8) μV² after 6 months. The peak power was 7.7 ± (4.9–11.1) μV². Peak frequency was 7.9 Hz before treatment, 8.3 Hz after 3 months, and 7.8 Hz after 6 months. Control peak frequency was 9.4 ± (8.4–9.9).
C3, T7, P8, P4, Pz, P3, P7, O1, O2, Fp1, Fp2, A1, and A2). Changes in power were analyzed by using the Neurophysiological Biomarker Toolbox15 and compared with 5-minute EEG recordings of 15 age-matched (9–11 years old) healthy subjects with normal development. These data were collected as part of the Dutch Dyslexia Programme (DDP).16 These EEG values were used to revert GABA polarity14 and lowering diuretic bumetanide may be depolarizing; second, the chloride-paradoxical reactions when GABA is enforced GABA synapses may cause consequences. First, agents that mediated by GABA has recently been shown in cognition and behavior.

DISCUSSION

Persistence of depolarizing excitation mediated by GABA has recently been offered as a treatment target for behavioral symptoms in ASD and other neurodevelopmental disorders.5,17 This finding has important consequences. First, agents that enforce GABA synapses may cause paradoxical reactions when GABA is depolarizing; second, the chloride-lowering diuretic bumetanide may be used to revert GABA polarity14 and perhaps safely ameliorate behavioral autistic symptoms.6 The present article provides the first case example in which a behavioral disinhibition to a benzodiazepine was noted and used as a rationale to initiate bumetanide treatment. Indeed, adverse effects to GABA-enforcing agents have been experimentally linked to disturbed chloride homeostasis,1,10,19 and behavioral disinhibition after benzodiazepine treatment is a common phenomenon2,3,20–24 also noted in patients with ASD.4 Bumetanide led to a remarkable improvement in sensory behaviors, rigidity, memory, and learning in our patient, which suggested that the diuretic had improved neural functioning. This notion could be supported by changes on resting state EEG. The baseline decreased resting state power was consistent with other EEG studies in ASD.25,26 Moreover, a role for α frequency band oscillations has been shown in specific cognitive mechanisms.27 The increase in the α frequency power after treatment may be an underlying mechanism of patient’s improvement in cognition and behavior.

In healthy individuals, it is established that resting state power is reduced with benzodiazepine treatment,28,29 and it is well known that these agents affect different aspects of memory functioning.30–32 Our findings in a patient with a paradoxical benzodiazepine response seem to mirror this picture. Before treatment, the patient exhibited reduced α power and impaired short- and long-term memory functions. Both these traits normalized with treatment, thus producing the opposite profile of changes in healthy individuals with benzodiazepine treatment. In addition, this case had other clinical features that may point to aberrant GABAergic transmission. Temporal lobe epilepsy has been linked to elevated expression of the chloride importer NKCC1, the specific target of bumetanide.33,34 In addition, increased NKCC1 expression was found in cortical dysplasia specimens of humans with focal epilepsy.35,36 These additional clinical features may support our hypothesis that the observed paradoxical response indicated depolarizing GABA activity. Clearly, these first observations are preliminary, and other cases with paradoxical responses need to be studied.

CONCLUSIONS

We highlight that a paradoxical response to GABA-enforcing drugs may offer a rationale for administration of bumetanide in individual cases.

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ABBREVIATIONS

ASD: autism spectrum disorder
BRIEF: Behavior Rating Inventory of Executive Function
GABA: γ-aminobutyric acid

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