

REGULAR ARTICLE

Bumetanide for autism: Open-label trial in six children

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Abstract

Aim: Bumetanide, a diuretic agent, that reduces intracellular chloride—thereby reinforcing GABAergic inhibition—has been reported to improve core symptoms of autism in children. Given the positive results reported from French trials of bumetanide in children with autism, we decided to evaluate its effects in a small-scale pilot study, in advance of a larger randomised controlled study (RCT).

Methods: This was an open-label three-month trial of bumetanide on six children (five boys), aged 3–14 years with autism. Ratings according to the Parental Satisfaction Survey (PASS) were used after four and twelve weeks to assess symptom change. Blood electrolyte status was monitored.

Results: Improvement in the PASS domain “Communicative and cognitive abilities” was marked or very marked in four children, and two had some improvements. Few negative side effects were reported.

Conclusion: Our small cohort responded well to bumetanide, particularly with regard to “Communicative and cognitive abilities”. Taken with the evidence from larger-scale RCTs, we suggest that bumetanide should be considered for inclusion in ethically approved treatment/management trials for children with autism, subject to rigorous follow-up in large-scale RCTs.

KEYWORDS

autism, bumetanide, gamma-amino-butyric acid, GABA, parental satisfaction survey

1 | INTRODUCTION

The aetiological heterogeneity in autism spectrum disorder (ASD) is considerable.¹ At the molecular level, there has been increasing interest in the role played by the excitatory neurotransmitter glutamate, and several genetic studies support the involvement of the glutamate system in autism.^{2,3} There is a complex balance between glutamate and the inhibitory transmitter gamma-amino-butyric acid (GABA) in the brain, and some evidence supports GABA dysfunction in children with autism.^{4,5} In immature neurons (particularly during

foetal life), with high intracellular chloride concentration, GABA operates mainly as an excitatory transmitter. During maturation, the chloride concentration decreases which results in GABA switching from being excitatory in the embryo to inhibitory after birth.^{6,7} The intracellular level of chloride is primarily controlled by two chloride co-transporters—the chloride importer NKCC1 and the chloride exporter KCC2. The diuretic bumetanide is a specific NKCC1 antagonist that reduces intracellular chloride.⁷⁻⁹ It appears that bumetanide can restore GABAergic inhibition in patients with neurodevelopmental disorders by decreasing neuronal chloride concentration.⁸

Abbreviations: ASD, autism spectrum disorder; CARS, childhood autism rating scale; CGI-S, clinical global impression-severity; CGI-I, clinical global impression-improvement; GABA, gamma-amino-butyric acid; ID, intellectual disability; PASS, parental satisfaction survey.

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Elevated levels of intracellular chloride, which shift the polarity of GABA from inhibition to excitation, have been observed for example in neurons in epilepsy.¹⁰

The first study that reported that bumetanide treatment of children with autism was associated with decreased autistic behaviour, without serious adverse effects, was published in 2010.¹¹ Follow-up double-blind placebo-controlled trials in 60 and 88 children with autism, respectively, showed significant improvements when children were treated with bumetanide.^{8,12} Positive results of bumetanide in children with autism have also been reported in two studies from China,^{13,14} referring to the effect of the NaKCC1 blocker bumetanide reducing the excitatory action of GABA and from Tunisia.¹⁵ In a study from the Netherlands, children with tuberous sclerosis and autism, aged between 8 and 21 years, were treated with bumetanide and improvements with regard to irritable, explosive and social behaviour were reported.¹⁶ Experimental studies and off-label use of bumetanide—to modulate neuronal transmembrane Cl⁻gradients by blocking NKCC1 in the CNS—were presented in the comprehensive overview by Kharod and collaborators.⁹ The authors demonstrated positive outcomes attributed to bumetanide in studies evaluating its off-label use in autism and in some other conditions.⁹ A recent review of RCTs in 2019 suggested that bumetanide might be tried in autism particularly "when behavioral therapies are not available".¹⁷

Given the positive results reported from the French trials of bumetanide in children with autism, and requests to our centre from parents of children with autism who wanted their child to try bumetanide, we decided to evaluate the effect of Burinex® in a small-scale Swedish open trial while awaiting the start of a larger randomised controlled study. Burinex®—containing bumetanide—is a registered and approved diuretic agent in Sweden.

2 | METHOD

2.1 | Patients

Six children, five boys and one girl, age 3–14 years (Table 1), participated in the study. All six had been comprehensively, clinically assessed by an experienced child psychiatrist and a child neuropsychologist prior to being included in the study, and all met both the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and Fifth Edition criteria for autistic disorder and autism spectrum disorder (ASD). According to clinical and to the Childhood Autism Rating Scale (CARS),¹¹ all six children had severe autism with a CARS score above 37 (see below). Their intellectual levels varied from average to severe intellectual disability. Language ability also varied in the study group, from children who were non-verbal to those who could form complex sentences (Table 1). None of the children had a specific underlying aetiology, medical syndrome or epilepsy. Height and weight were within ± 2 standard deviations for five of the children and for the oldest child at +3 and +4 standard deviations, respectively.

Key notes

- Bumetanide, a diuretic agent, that reduces intracellular chloride and thereby reinforcing GABAergic inhibition, has been found to improve core autism symptoms in children.
- Six children with autism, aged 3–14 years, were treated with bumetanide in an open-label three-month trial.
- Bumetanide showed positive results in the five boys and one girl according to the Parental Satisfaction Survey (PASS)—measuring symptom change—particularly with regard to "Communicative and cognitive abilities".

2.2 | Treatment

Bumetanide (Burinex®) is available in Sweden in the form of 1 mg tablets that can easily be split in half. Our aim was to use a dose of 0.5 mg twice a day in younger children, in accordance with Lemonnier and Ben-Ari⁹ and Lemonnier et al.¹² If the children had a body weight of less than 25 kg, the bumetanide dose was 0.02 mg/kg body weight or 0.5 mg twice a day. If the body weight was 25 kilogram or above the bumetanide was given at 0.5 mg twice daily. One child with a body weight of 80 kg was started on two doses of 1 mg per day.

All the children had their serum electrolytes checked (sodium, potassium and chloride) and underwent an electrocardiogram (ECG) before they started treatment. Electrolytes were then monitored during the course of their treatment.

Due to the risk of potassium deficit during treatment with a diuretic, all children received extra potassium as a prophylactic, that is 0.5–1 ml per kilogram of a potassium mixture of 33 mg (0,85 mmol) K⁺/ml.

3 | MEASURES

3.1 | The childhood autism rating scale

The Childhood Autism Rating Scale (CARS)¹⁸ was used to quantify the severity of autism.

A CARS score above 30 indicates mild to moderate autism and a score of 37 and above severe autism.

3.2 | Clinical global impression-severity and clinical global impression-improvement

The Clinical Global Impression-Severity (CGI-S) scale¹⁹ rates the global symptom severity from 1 to 7 (1= not at all ill, 2= borderline, 3= mildly, 4 =moderately, 5= markedly, 6= severely and 7=extremely ill). The Clinical Global Impression-Improvement (CGI-I) scale¹³ rates the global improvement or worsening of the patient's condition compared to a previous time point, for instance at

Patient	Age (y:m)	Sex	Intellectual level	CARS	Language level	CGI-S
1	6:10	Male	Average IQ	39.0	Sentences	4
2	8:2	Male	Low average IQ	42.5	Sentences	4
3	4:8	Male	Low average IQ	41.5	Single words	5
4	4:0	Male	Moderate ID	51.0	No words	6
5	14:0	Male	Severe ID	42.5	No words	6
6	3:4	Female	Severe ID	43.0	No words	6

ID, intellectual disability; y, years, m, months.

baseline before a treatment. This measure gives an indication of how clinically meaningful an improvement is. The scale is scored from 1 to 7 (1=very much improved, 2= much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse and 7=means very much worse). Clinical response was defined as CGI-I ratings of 1-2.¹⁹

CGI ratings were performed independently by two of the three physicians (EF and CG). Agreement was reached in all patients.

3.3 | Parental satisfaction survey

During the treatment period, the parents rated the children's behaviour and function using the Parental Satisfaction Survey (PASS).²⁰ PASS consists of a 30-item questionnaire, grouped into six domains, with each domain comprising five symptoms, that correspond to behaviours associated with autism (Table 2). Ratings are given according to a nine-point scale to estimate the parents' perceived changes in child behaviour over the course of the study. Each symptom change can be rated as follows: substantial (-4), clear (-3), slight (-2) or marginal worsening (-1), no change (0), or as marginal (+1), slight (+2), clear (+3) or substantial improvement (+4). Thus, symptom scores range from -4 to -1, 0, and from +1 to +4 for each item. A possible total symptom score will vary from -120 (6×5×4), indicating maximum worsening of all five symptoms in the six domains to +120, indicating maximum improvement. The parents were asked to rate their child's behaviour

TABLE 2 The six main PASS domains and the specific items included in each domain.

I) <i>Sensory motor behaviours</i> : 1) coordination, 2) sound tolerance, 3) stereotyped behaviours, 4) activity level, 5) touch responsivity
II) <i>Expressions of motivation</i> : 1) appetite, 2) thirst, 3) sleep habits, 4) desire to interact, 5) curiosity/interest
III) <i>Emotions and moods</i> : 1) anger/aggression, 2) happiness, 3) anxiety/crying, 4) patience, 5) number of good days;
IV) <i>Social responsiveness</i> : 1) smiling, 2) eye contact, 3) play behaviour, 4) imitative behaviour, 5) cooperation
V) <i>Communicative and cognitive abilities</i> : 1) interest in the world, 2) attempts to communicate, 3) number of words/sounds used, 4) clarity of communication, 5) initiation of interactions
VI) <i>Life habits</i> : 1) ability to dress and care for oneself, 2) concern with the welfare of others, 3) appropriateness of public behaviour, 4) coping with new situations, 5) tendency to be self-centred

TABLE 1 Patients, ages and developmental data at treatment start.

after four weeks and 12 weeks of treatment with Burinex and to compare with the child's behaviour before treatment start.

All scores rated from -120 to zero were regarded as "negative". All scores from +1 to +120 were regarded as "positive".

The study was carried out as a pilot study, initiated after approval by the ethics committee at Gothenburg University of a randomised controlled treatment study of bumetanide (Burinex®) in groups of children with autism (Dnr: 899-14). The substance (Burinex®) is a registered approved diuretic agent in Sweden. All parents of the children included provided informed consent.

4 | RESULTS

CARS ratings before start of treatment with Burinex ranged from 39.0 to 51.0, which indicated that all six children had "severe autism" at the start of treatment.

Four of the children, numbers two, four, five and six, had side effects within a few days after starting treatment (mainly severe hyperactivity, depressive mood, aggressiveness and large urinary volumes at night) which caused the dose to be reduced to 0.25 mg twice a day for one to two weeks. Thereafter a dose of 0.5 mg twice a day was well tolerated.

CGI-Severity at start of treatment varied between 4 and 6, that is between "moderately" and "severely ill" (Table 1).

The CGI-I scores after treatment varied between 1 and 3, that is between "very much" and "minimally improved".

Results from the PASS, which are presented in Tables 3 and 4, show the total positive and negative ratings of the six domains in each patient. The individual scores for each domain could range from zero to -20 and zero to +20 with total scores ranging from -120 and +120 for the individual's six domains.

The highest total score for most children at four and twelve weeks related to domain number five. This domain covered the items: interest in the world, attempts to communicate, number of words/sounds used, clarity of communication and initiation of interactions.

After the three-month treatment period, all the parents wanted their children to continue the bumetanide treatment, 0.5 mg twice a day and in the oldest child 1 mg twice a day. At the time of writing up this paper (7 - 21 months after onset of treatment), no child has stopped the treatment.

TABLE 3 Four weeks after treatment start (PASS data). Sums of possible negative and positive scores of the six domains, range 0–20 for each domain, and a total domain score with a range of 0–120.

Patient no	1	2	3	4	5	6
Domains						
1) Sensory motor behaviour	+5	+7	+2	+4	+1/-2	+1
2) Expressions of motivations	+6/-1	+8/-2	+6	+11	+3/-2	+4/-3
3) Emotions and moods	+6	+5	+1	+8	+4/-1	+1
4) Social responsiveness	+6	+9	+8	+15	+1	+8
5) Communicative and cognitive abilities	+5	+15	+11	+12	+3	+5
6) Life habits	+5	+6	+8	+6	0	+1
Total domain score	+33/-1	+50/-2	+36	+56	+12/-5	+20/-3

TABLE 4 Twelve weeks after treatment start (PASS data). Sums of the possible negative and positive scores of the six domains, range 0–20 for each domain, and a total domain score with a range of 0–120.

Patient no	1	2	3	4	5	6
Domains						
1) Sensory motor behaviour	+8	+2	+7	+5	+3	+2
2) Expressions of motivations	+10	+6	+5	+11/-3	+3	+6
3) Emotions and moods	+13	+9	+3	+12	+3/-2	+2/-1
4) Social responsiveness	+12	+2	+8	+13	+6	+8
5) Communicative and cognitive abilities	+15	+13	+11	+10	+3	+9
6) Life habits	+15	+4	+7	0	+1	+2
Total domain score	+73	+36	+41	+51/-3	+19/-2	+29/-1

The parents of all the children who participated reported some developmental progress in their child after starting treatment with Burinex®. Although the children differed in terms of developmental progress during the treatment, all of them displayed some improvements in the area of communication and social interest, better eye contact, more interest in participating in activities with other children and more interest in being with their family.

5 | DISCUSSION

This three-month open-label clinical study of bumetanide (Burinex®) in six children with autism was inspired by previous studies that had demonstrated the positive effects that the drug has had on core symptoms of autism.^{8,11,12}

One of the reasons we performed the study, on clinical grounds, was that a number of parents who were aware of the results of the French studies wanted their child to try the medication.

Our clinical findings were in accordance with the French studies that reported that the children who were treated with bumetanide were more “present” and interacted more with their environment.^{8,11,12} Also, the parents in our study reported

improvements in many aspects of their children's social functioning, including a more affectionate behaviour and increased interest in contact with other children.

Four children had side effects within a week of treatment start but these negative effects disappeared after the dose was reduced and did not return when the full dose was reinstated. To avoid low potassium, all children were supplemented from the start of treatment with oral potassium. However, one child discontinued potassium supplementation and continued with adequate potassium levels. Slightly increased urine volumes were common. One young child had increased night-time urine volume but this was temporary and the child's treatment was not discontinued. No other side effects of bumetanide were reported in our study group at the three-month and during later follow-ups, including up to one year.

Pharmacological treatments for autism have been used in clinical settings and in research in order to treat core symptoms or specific associated problems. However, no existing pharmacological intervention has been found to alleviate core autism symptoms. Because autism is such a heterogeneous condition, which includes multiple disease entities the failure to develop medical treatments is understandable.¹

The French studies that have explored bumetanide treatment for children with autism, have pointed to a novel and promising approach in autism treatment based on the paradoxical effect of GABA. This experimental research showed that GABA can be excitatory and that this state is possible to reverse to an inhibitory state using bumetanide to reduce intracellular chloride. A paradoxical response to GABA-enforcing agents, such as by benzodiazepines, may predict the efficacy of bumetanide treatment in neurodevelopmental disorders. It also showed that this paradoxical response to GABA-acting drugs may offer a rationale for administering bumetanide in individual cases.²¹

Another study showed that constraining eye contact led to an exaggerated increase in amygdala activation. Treating patients with bumetanide to restore GABAergic inhibition normalised the level of amygdala activation during forced eye contact. Such findings support the notion that bumetanide might be a beneficial pharmacological agent in treating autism.²²

Further double-blind placebo-controlled studies with larger cohorts of participants will help to clarify the usefulness of bumetanide in autism and its role in clinical practice. In our study, the trend was that children without severe intellectual disability showed greater improvements on the PASS scale. Future studies should investigate which subgroups of children with autism could benefit the most. These studies could investigate the influence of age, specific developmental profiles, associated neurodevelopmental disorders and associated medical disorders. Other aspects that could be studied include the optimal dose and length of treatment.

The limitations of this study included the very small cohort and the open study design. A strength of the study was that the participating children had been assessed and were followed by the same clinicians in child neuropsychiatry and neuropaediatrics.

6 | CONCLUSION

The results of this pilot, open-label treatment study of bumetanide in six children with autism showed positive results, particularly with regard to "Communicative and cognitive abilities". Very few side effects were reported. All the parents wanted their child to continue the treatment after they had received the medication for the three-month study period. The evidence from our study and the larger French randomised controlled studies suggest that bumetanide should be considered for inclusion in ethically approved treatment/management trials for children with autism, subject to rigorous follow-up in large scale RCTs.

DISCLOSURE

The authors report no conflicts of interest in this work.

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