The Safe Use of Bumetanide in Children with Autism

Practical Tips for Parents and Professionals

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Bumetanide is a prescription diuretic drug usually used to treat heart diseases or hypertension in adults. It also affects neuronal chloride regulation and was found to improve the quality of life of autistic children targeting core autism symptoms in clinical trials in Europe. Bumetanide has been used off-label in children and adults across the autism spectrum for several years, mostly in France. It is a safe drug with a long history of use in medicine and well-known precautions ensure side effects are avoided.

Details of bumetanide's mechanism of action and its beneficial effects in autism were discussed elsewhere – see the references below. According to the most recent review of bumetanide clinical trials in autism:

"***Current evidence suggests bumetanide, with close monitoring, may be useful in patients with moderate to severe ASD when traditional behavioral therapies are not available or an irritability-modifying pharmacological agent is not required***" [James et al. 2019].

Bumetanide treatment should be supervised by a physician. Multinational phase 3 trial of bumetanide for children with autism aged 2-17 years of age started in Europe in 2018. If you live elsewhere and consider bumetanide, this article can be used as a practical companion to ensure safe treatment. It is written for parents and physicians who are not experienced with diuretic use in children or bumetanide itself. While bumetanide's safety precautions can be summarized in short as "drinking more water, eating bananas and if required, use potassium supplementation", this document aims to explain those in detail and provide practical tips for a variety of clinical scenarios.

> ***#1 Myth: Bumetanide is an experimental drug.***
>
> No. Bumetanide has been used in medicine for years. It's safety profile and recommended precautions are well known and understood. Bumetanide has been studied in both adults and children and found to be well tolerated.

Who can use bumetanide? What should you do before starting bumetanide?

If you are considering using bumetanide, make sure to check with your doctor if there are any contraindications in your child. Bumetanide is a sulfonamide drug. Children with allergy to sulfonamides should not take bumetanide. Another sulfonamide drug commonly used in children is an antibiotic called trimethoprim/ sulfamethoxazole (TMP/SMX), also known as co-trimoxazole. In many European countries co-trimoxazole's brand name is Bactrim. If your child is allergic to co-trimoxazole (Bactrim) or any other sulfonamide drug, then bumetanide should not be used.

It is important to make a distinction between sulfonamide drugs and other sulfur-containing medications and additives, such as sulfates and sulfites, which are chemically unrelated to the sulfonamide group. Allergic reactions associated with sulfonamides are not associated with sulfur, sulfates or sulfites intolerance.

The full list of bumetanide interactions with other drugs is long, but most of the drugs included are not usually used in children.

Children with liver or kidney diseases as well as those with abnormal ECG (electrocardiogram) findings were excluded from the French bumetanide trials. If your child suffers from one of these conditions you need to discuss bumetanide safety with the relevant specialist. **Epilepsy does not preclude bumetanide use**. In fact, preliminary research showed bumetanide has a positive impact on seizures in temporal lobe epilepsy in adults.

What laboratory tests are needed before and during bumetanide treatment in children

Bumetanide is a safe drug, provided basic precautions related to its diuretic mechanism of action are taken. One of the most important safety considerations associated with bumetanide use is electrolyte balance. Bumetanide can affect electrolyte blood level and increase potassium loss. Extremely low potassium levels are dangerous, but this is preventable with simple measures in a person using bumetanide.

#2 Myth: Bumetanide use in children with autism is associated with significant risk of dangerous adverse effects.

No. Clinical trials and off-label prescribing experience proved that bumetanide adverse effects can be easily prevented in children. No dangerous symptoms were related to bumetanide in studies on its use in children with autism.

No serious symptoms associated with low potassium levels or electrolyte imbalance were seen in children included into bumetanide trials and case reports so far. However, they might affect a child's well-being and possibly reduce bumetanide's positive behavioral or sensory effect. You may not see the expected results of bumetanide treatment if an adequate potassium level and hydration are not ensured in your child.

That is why it is necessary to test electrolytes levels (potassium, sodium, chloride, magnesium and calcium) before bumetanide introduction and repeat them, especially potassium blood concentration, after the treatment is started.

In the French bumetanide trials several other blood tests were offered to children i.e. g-glutamyltransferase, transaminases, alkaline phosphatases, glucose, uric acid and creatinine. While it is not required to order all of them in a similar way as in the research clinical studies, they are basic and cheap tests, available in most laboratories and it is prudent to check these parameters at least once during early phase of the bumetanide treatment. In clinical trials children were examined by a physician on a regular basis and had their heart rate, blood pressure and weight checked. Such approach also improves safety of bumetanide use. In turn, all these simple steps increase the chance of experiencing positive effects of bumetanide treatment. Bumetanide proved to be a safe treatment in the trials. Blood pressure and results of the routine tests did not differ between the bumetanide and placebo groups. Kidney ultrasound did not reveal any abnormalities during treatment. Children in the trials had also ECG (electrocardiogram) done as a precaution. It is prudent to offer a child such test as they are non-invasive and can be done in a stress-free manner.

As bumetanide is a diuretic drug, it is highly recommended to explain its effects prior to treatment and with the use of the communication means used by that child. Social stories, visuals and AAC tools can be helpful for some children. This approach can reduce psychological stress potentially related to the diuretic treatment in children prone to anxiety in new situations.

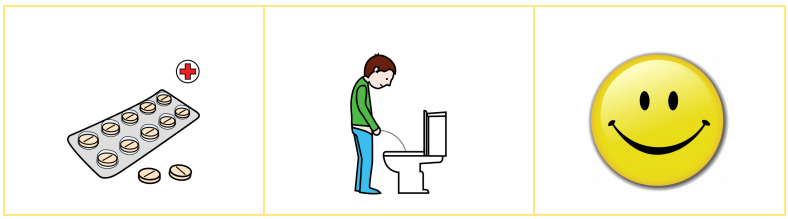

Fig. 1. Visuals can help a child anticipate and accept bumetanide diuretic effect prior to start of treatment.

The diuretic effect of bumetanide is strongest within the first 2 hours of taking the drug. Bumetanide given early in the morning (straight after waking up) lets the child avoid unnecessary toilet visits at school or kindergarten. Giving bumetanide once a day may be much more convenient depending on the person's particular circumstances.

Starting bumetanide - what dose should be used and what to expect?

In the first randomized clinical trial in France the dose of 0.5 mg bumetanide was given twice daily to children 3-11 years old and was found effective in many of them. However, for some people this dose may not be sufficient as actually only about 1% of bumetanide can cross the blood brain barrier and act on neurons. In the 2017 bumetanide study doses up to 2 mg twice daily were trialed. While using higher doses may increase the amount of bumetanide that would reach the brain and so enhance the positive effects of the treatment, it also was found that drug-related adverse event risk is dose dependent and 0.5 mg b.i.d (twice daily) dose was found to be the best tolerated. It is a matter of a careful, individual trial to find an optimal dose for each person.

The benefits of bumetanide treatment can sometimes be seen as early as after 2 weeks, but it is not uncommon to have to wait longer. It is recommended to continue up to 3 months to assess the full impact of bumetanide use. Minor effects may indicate that the child is indeed a bumetanide responder, but the dose needs to be increased.

The beneficial effects seen in a child taking bumetanide are highly variable and individual. In general, this drug targets core autism symptoms and improvements in communication, social skills, including eye contact, speech and sensory issues were reported on bumetanide, as well as stereotyped behaviors decrease, better mood or increased cognition. Many parents can notice more awareness in their children and describe it as if "the fog has lifted". Behavioral improvements were also reported on bumetanide e.g. reduction in aggressive behaviors.

The only known indicator of which people with autism respond to bumetanide, is a previous unexpected negative reaction to Valium (diazepam), or other benzodiazepine drug. These drugs should be calming, but in some people with the GABA neurotransmitter dysfunction targeted by bumetanide, the effect can be agitation and aggression.

How to control hydration in children using bumetanide?

Bumetanide belongs to the "loop diuretics" class of drugs which can lower blood potassium level and increase the body fluid loss. You need to monitor hydration in a child treated with bumetanide. If fluid consumption is increased to compensate for the diuresis, there will be no significant blood pressure lowering effect from bumetanide, nor will there be dehydration. The daily amount of fluid required varies, but it usually needs to be significantly higher than the volume drank by a child before bumetanide treatment.

Some children drink up to 3 liters (3 US quarts) per day while on bumetanide, others need less. It is safer to err on the side of too much fluid intake rather than too little. Drinking 3 liters of fluids a day in a teenager on bumetanide is not unusual.

In children who still wear diapers/nappies the amount of diuresis may cause a problem with leakage.

Monitoring hydration and potassium control are two key safety precautions in bumetanide use in children with autism.

No severe adverse clinical symptoms related to dehydration were found during the bumetanide pediatric trials. However, a child who develops dehydration issues on bumetanide may feel unwell, so it is highly recommended to prevent it.

An easy way to check hydration status in a child is an assessment of mouth mucosa. You can ask your child to present her or his tongue and compare the tongue look with another member of the family. It can be made a good fun for younger children. If the tongue mucosa looks drier in a child on bumetanide, then you need to help the child drink more. Most children automatically drink more fluids, but some refuse to cooperate and drink more. Finding out beverages attractive for your child (e.g. drinking water from a dispenser, juice with ice-cubes etc.) may be useful in such a situation.

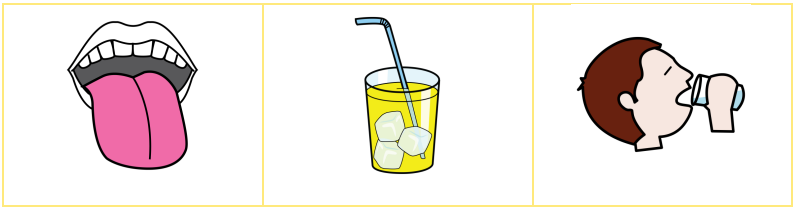

Fig. 2. Monitoring hydration may be done in a funny way to make the treatment stress-free.

Monitoring hydration with weight checks or measuring urine volume, while used in other situations, are impractical in a person on bumetanide.

You can read more on child dehydration symptoms here. It is useful to learn about those symptoms as a parent even if you do not plan to use bumetanide.

How to ensure enough potassium intake in a child on bumetanide?

Simple dietary modifications can provide necessary additional potassium and are recommended for every child on bumetanide. Use potassium salt and increase other dietary potassium in your kitchen. Bananas, kiwis, dried fruit, tomatoes are all examples of foods rich in potassium. The daily recommended intake of potassium is 3 to 4 g depending on age. A medium sized banana contains about 0.5g. Most people do not achieve the RDA for potassium but exceed the maximum limit for sodium, which is about 2g. More on potassium food content can be found here.

#3 Myth: Potassium supplements can cause serious heart rhythm issues in children on bumetanide.

No. Recommended potassium daily intake is well above the supplement doses usually used with bumetanide. Provided normal kidney function, there is no significant risk of dietary/oral supplement potassium overdose when typically recommended doses are considered.

Apart from dietary modifications, low dose potassium supplementation can be used in addition to bumetanide from the beginning of the treatment. In the first weeks of bumetanide use it is also necessary to test potassium blood level. In the French trial blood potassium levels were checked before bumetanide introduction and then at 7, 30, 60 and 90 days after the treatment started. You may consider potassium blood level test sooner than after 30 days: it can be scheduled 2-3 weeks after bumetanide introduction to detect low potassium level early. The normal blood level range of potassium is 3,5 - 5,0 mmol/l. In case of abnormally low blood potassium level (which is called “hypokalemia”) you need to consult your doctor and add or adjust the dose of potassium supplement for your child. The target is to keep the potassium level well within the normal range. In the first bumetanide randomized clinical trial 22% of children taking bumetanide 0.5 mg b.i.d. (twice daily) experienced benign hypokalemia (low potassium), which was resolved by giving potassium gluconate syrup. In the next French trial the potassium level fell below normal range in 30% of children on that dose, but no serious potassium-related adverse event was seen. A potassium supplement was given to all these children to correct the low blood level.

The potassium dose should be adjusted individually according to blood level and repeat tests may be helpful. As some autistic children seem not to tolerate even minor drops in potassium level, you and your doctor may consider increasing potassium supplementation to keep its level in the upper normal range in those cases.

The optimal dose of potassium varies and is highly individual: few children need dietary modifications only, some use as low as 100 mg potassium daily, while some require 500 mg t.i.d. (three times a day) to maintain normal potassium level on bumetanide. Potassium supplements come in different forms e.g. syrup, effervescent tablets, slow-release capsules. Liquid supplements, including effervescent drinks, seem free from the risk of GI distress associated with tablets, which may be especially important in a child who is not able to communicate the pain. It is very hard to do harm by eating too much dietary potassium, because it is absorbed very slowly. Many potassium supplements are absorbed quickly and so giving more than 500mg at once is unwise. Note that in America most potassium supplement tablets do not contain more than 100mg.

Side effects of bumetanide and how to manage them:

- "Accidents" caused by diuresis: need to plan ahead. Don't give bumetanide before starting a long car journey or before sleep.

- Dehydration has many effects that you may not notice. Make sure your child carries a water bottle and so has easy access to fluids.

- Low potassium has many effects and so add potassium to diet as a precaution. Most people are nowhere near the recommended intake of potassium, so add potassium-rich food to diet.

It is necessary to actively prevent dehydration and potassium loss while on bumetanide treatment. The good news is that it is easy to achieve with simple steps described above. These precautions become even more important in children who struggle to report thirst and distress due to communication difficulties as well as in situations which make a child prone to dehydration regardless of diuretic use e.g. diarrhea, vomiting, fever or very hot summer temperatures, especially during physical exercise. If such issues occur, you need to be vigilant, consider a doctor's appointment and potassium blood level check with additional supplementation as needed.

In case of persistent low blood potassium concentration it is recommended to check blood levels of magnesium as well. Magnesium deficiency may contribute to hypokalemia (low potassium). If this is the case, supplementing magnesium along with potassium is a solution. Low potassium levels can also be made worse by high sodium levels.

Is long term bumetanide use safe and practical?

Over time, on a proper diet and potassium supplementation, a child treated with bumetanide usually achieves a stable electrolyte balance, so control blood tests are rarely required on long term bumetanide treatment. In fact long term bumetanide use is very practical, and the simple safety precautions required are nothing compared to coping with untreated symptoms common in severe autism e.g. sensory suffering, which may significantly improve on bumetanide.

#4 Myth: While on bumetanide every child is required to have often blood draws to check potassium.

No. Repeated blood draws are required at the beginning of bumetanide treatment to assess individual supplemental potassium needs. Later there is no need to test potassium on regular basis.

If a blood draw is an issue in a child with anxiety or sensory disorders, this is what might help:

- Visuals to reduce anxiety in a child e.g. picture social stories explaining blood draw procedure
- AAC used for communication in a non-verbal or minimally verbal children

- Video modeling or blood draw play at home before the procedure
- Skilled nurse and friendly environment, which can be arranged in advance
- At home blood draw service.

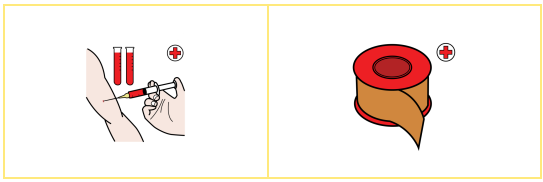

Fig. 3. Visuals can help with reducing the blood draw related anxiety.

It needs to be stressed that in general, presumed behavioral difficulties should not be a barrier to necessary medical examinations or procedures needed for health in autistic children, as avoiding them can result in increasing the medical risks in a population already prone to co-morbidities and poor health outcomes. It is the responsibility of the health provider and the parent to find the most convenient and effective way to perform the examinations needed. It is not unusual that all medical procedures get easier over the time in a child who uses bumetanide and develops communications skills and improves their cognitive function and awareness.

How to deal with the "bumetanide has stopped working" problem?

After some months or even years some parents may feel that "bumetanide has stopped working", this may well not be their imagination and it can be very disconcerting. A little science is required to explain what may be happening. It appears that bumetanide responders have too many NKCC1 transporters in their neurons and too few KCC2. Only about 1% of bumetanide can cross the blood brain barrier where it blocks the NKCC1 transporter. An inflammatory response elsewhere in the body sends inflammatory signals throughout the body and some reach the brain where this causes an increase in NKCC1 and a reduction in KCC2 expression. This effect can wipe out the beneficial effect of that tiny 1% of bumetanide that is present. You can increase the dose of bumetanide and try and reduce the source of inflammation, which might be as simple as an allergy, or the cause might be harder to identify. There will be many other biological reasons why a shift in NKCC1/KCC2 might occur, so some detective work will be needed. The beneficial effect of bumetanide will then be restored.

Conclusions

Almost all parents whose children were included into the first bumetanide randomized clinical trial in France asked for treatment continuation after the study finished. Safe use of bumetanide for up to 2 years later were reported in this group. According to personal communication, bumetanide has been successfully subsequently used off label for at least 8 years in children and youth with autism, and no long-term issues emerged on long-term treatment. **While this treatment does not offer an "autism cure", it could significantly increase the quality of life of autistic persons thanks its potential to bring about improvements in sensory processing and hypersensitivity, cognition and acquiring communication skills** (see published studies, linked below, for details on potential positive effects of bumetanide).

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References:

1. Lemonnier et al.: A randomised controlled trial of bumetanide in the treatment of autism in children. Transl Psychiatry 2012 2:e202. https://www.ncbi.nlm.nih.gov/pubmed/23233021
2. Lemonnier et al.: Treating Fragile X syndrome with the diuretic bumetanide: a case report. Acta Paediatr. 2013, 102(6):e288-90 http://www.ncbi.nlm.nih.gov/pubmed/23647528
3. Grandgeorge et al.: The effect of bumetanide treatment on the sensory behaviours of a young girl with Asperger syndrome. BMJ Case Rep 2014 pii: bcr2013202092. http://www.ncbi.nlm.nih.gov/pubmed/24488662
4. Bruining et al.: Paradoxical Benzodiazepine Response: A Rationale for Bumetanide in Neurodevelopmental Disorders? Pediatrics 2015 136(2): e539-43 http://www.ncbi.nlm.nih.gov/pubmed/26216321
5. Lemonnier et al.: Effects of bumetanide on neurobehavioral function in children and adolescents with autism spectrum disorders. Transl Psychiatry 2017, 7(3):e1056 https://www.ncbi.nlm.nih.gov/pubmed/28291262
6. James et al.: Bumetanide for Autism Spectrum Disorder in Children: A Review of Randomized Controlled Trials. Ann Pharmacother. 2019, 53(5):537-544 https://www.ncbi.nlm.nih.gov/pubmed/30501497
7. Gharaylou et al.: A Preliminary Study Evaluating the Safety and Efficacy of Bumetanide, an NKCC1 Inhibitor, in Patients with Drug-Resistant Epilepsy. CNS Drugs. 2019, 33(3):283-291 https://www.ncbi.nlm.nih.gov/pubmed/30784026

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