Case Report

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UCD Case Report: Glycerol Phenylbutyrate in the Management of Female Patients with Ornithine Transcarbamylase Deficiency

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Abstract

Context: Urea Cycle Disorders (UCDs) are rare inborn errors of metabolism resulting from a defect in one of the urea cycle enzymes. Patients with UCDs are unable to detoxify ammonia and convert it into urea properly, which can result in toxic levels of ammonia building up in the blood. Ornithine Transcarbamylase (OTC) deficiency is the most common UCD. If OTC deficiency is not adequately treated, it can lead to hyperammonemic crises which can be life-threatening, regardless of the age or overall health of the patient.

Case report: This case report outlines clinical and biochemical observations of four unrelated Canadian females with OTC deficiency, with a focus on observations 12 months before, and 12 months after their ammonia-scavenging therapy was switched to glycerol phenylbutyrate. Following the switch to glycerol phenylbutyrate, each patient in the study experienced a mild reduction in mean ammonia levels, fewer hospitalizations, and improved quality of life and adherence to ammonia-scavenging therapy.

Conclusion: More patients would need to be included in the study and for longer period of time, in order to make a more meaningful outcomes statement. As clinical experience in the management of OTC-deficient female patients continues, these cases suggest the importance of early and effective ammonia control using glycerol phenylbutyrate.

Keywords: Hyperammonemia; Ornithine Transcarbamylase (OTC); OTC deficiency, Phenylbutyrate, Urea cycle disorder

Abbreviations: CSF: Cerebrospinal Fluid; OTC: Ornithine Transcarbamylase; UCD: Urea Cycle Disorder

Introduction

Urea Cycle Disorders (UCDs) are rare inborn errors of metabolism resulting from a defect in one of the urea cycle enzymes [1-3]. Patients with UCDs are unable to detoxify ammonia and convert it into urea properly, which can result in toxic levels of ammonia building up in the blood. Most UCDs are autosomal recessive inherited conditions–with the exception of Ornithine Transcarbamylase (OTC) deficiency, which is a X-linked condition–and are a result of inherited genetic variants. However, some pathogenic variants can arise spontaneously in a child . It is estimated that 1 in 35,000 infants are born with some form of UCD [4].

UCDs are characterized by hyperammonemia and life-threatening hyperammonemic crises [5]. If untreated, high levels of ammonia can travel to the brain and cause health problems such as memory loss, behaviour changes, and even coma or seizures [4,6]. Long-term UCD management usually involves a combination of a low-protein diet, supplementation of essential amino acids (e.g., arginine, citrulline), vitamins and minerals, and ammonia scavengers such as sodium benzoate, sodium phenylbutyrate, or glycerol phenylbutyrate [1,7,8].

X-linked Ornithine Transcarbamylase (OTC) deficiency is the most common form of UCD, representing approximately 62% of all cases [9]. It is caused by pathogenic variants in the OTC gene. OTC-deficient females typically present in the post-neonatal period, ranging from infancy to later childhood, adolescence, or adulthood [10]. Prognosis is better for those with an onset later in life. Patients with OTC deficiency often experience neuropsychological complications such as learning disabilities, intellectual disability, attention deficit disorder, and executive function deficits; however, morbidity from brain damage does not appear to be linked to the number of hyperammonemic crises that have occurred [6,11]. Although most OTC-deficient females inherit the heterozygous variant from an unaffected mother, and typically are clinically asymptomatic, many still experience mild-to-severe signs and symptoms of a UCD,

including hyperammonemic crises–and may need to be treated. Untreated hyperammonemic crises can be life-threatening events to any individual with an OTC deficiency, regardless of their age or overall health.

In this report, we describe the clinical and biochemical observations of four unrelated Canadian females with OTC deficiencies, with a focus on observations 12 months before and after their ammonia scavenger was converted to glycerol phenylbutyrate. Data collection was done through retrospective chart reviews.

We present new information for patient 2, who has been previously reported [12], but the other three represent some of the first OTC-deficiency Canadian female cases to be published. Based on institutional differences, the upper limit of normal for ammonia was established as >35 µmol/L for patients 1 and 2 similar to previous studies [3,5]–and >50 µmol/L for patients 3 and 4. We defined ammonia levels of >80 µmol/L–in combination with additional clinical factors such as metabolic decompensation, clinical encephalopathy, and changing neurological behavior–as a hyperammonemic crisis.

Case Study

Patient 1

Patient 1, a 20-year-old female, was diagnosed with OTC deficiency at 10 years of age, initially presenting with vomiting, drowsiness, irritability, confusion, and vision loss. Laboratory investigations at diagnosis showed: Ammonia 90 µmol/L, plasma glutamine 1259 µmol/L, and low levels of citrulline of 13 µmol/L and arginine of 35 µmol/L. CSF glutamine was elevated at 1407 µmol/L. Treatment with sodium phenylbutyrate (250 mg/kg/day) was initiated following diagnosis. Mean ammonia levels increased progressively with age: 12.2 µmol/L at 10 years of age, 14.8 µmol/L from 11 years-15 years of age, and 25 µmol/L from 16 years-18 years of age. An MRI completed at age 10 years showed focal area of subcortical white matter T2 hyperintensity in her left frontal lobe and mild high T2 signal intensity within the cortical spinal tracts. She was admitted to the hospital at 16 years of age due to elevated ammonia levels (69 µmol/L). The patient has mild developmental delay.

At 18 years of age, the patient was converted from sodium phenylbutyrate to glycerol phenylbutyrate, on the basis that she and her caregivers were experiencing challenges determining the appropriate dose of sodium phenylbutyrate. Daily protein intake was approximately 29 g/day (20 g-25 g from diet and the remainder from formula) and total calories remained unchanged. In the 12 months prior to converting ammonia scavenger therapy, her mean ammonia level was 29.2 µmol/L on sodium phenylbutyrate. Her mean 12-month ammonia decreased to 20.5 µmol/L following conversion to glycerol phenylbutyrate. Mean 12-month glutamine levels increased from 1027.2 µmol/L to 1137 µmol/L following conversion from sodium phenylbutyrate to glycerol phenylbutyrate. She was transitioned to adult metabolic care, and due to this stressful social circumstance, she became non-compliant with her bloodwork and diet, although she found glycerol phenylbutyrate easier to measure. In the 12 months following conversion to glycerol phenylbutyrate, this patient had not been hospitalized or experienced a hyperammonemic crisis (Table 1).

	Patient 1	Patient 2	Patient 3	Patient 4
At diagnosis				
Age	10 years	12 years	12 months	2 years
Ammonia pre-initiation of ammonia-scavenging therapy (µmol/L)	90	242	251	339
Mean glutamine (µmol/L)	1259	2000	1205	No data available
12 months prior to conversion to glycerol phenylbutyrate				
Number of hyperammonemic crisis	0	0	0	0
Mean ammonia (µmol/L)	29.2	39.4	66.57	56
Mean glutamine (µmol/L)	1027.2	917.8	1066	1036
12 months after conversion to glycerol phenylbutyrate				
Number of hyperammonemic crisis	0	0	0	0
Mean ammonia (µmol/L)	20.5	30	14.67	50
Mean glutamine (µmol/L)	1137	1113.4	682	802

Table 1: Summary of patient characteristics and outcomes.

Patient 2

Patient 2 is a 28-year-old female who was diagnosed with OTC deficiency at 12 years of age. She initially presented with delirium, emesis, weakness, and weight loss. Laboratory investigations at diagnosis showed: Ammonia 242 µmol/L (normal: 5 µmol/L-35 µmol/L), glutamine 2000 µmol/L (normal: 450 µmol/L-750 µmol/L), citrulline 25 µmol/L (normal: 1 µmol/L-40 µmol/L), and ornithine 103 µmol/L (normal: 50 µmol/L-100 µmol/L). Orotic acid was not elevated. Past medical history revealed developmental delay at 8 months-12 months of age. She had a tendency towards recurrent vomiting, headaches, lethargy, and abnormal behaviour, which improved with avoidance of meat and dairy products. She also had mild congenital optic nerve hypoplasia. At 12 years of age, she was functioning at the level of a 3-4-year-old. MRI of her brain showed cortical atrophy in the left frontal region. Since diagnosis, treatment has consisted of dietary protein restriction supplemented with Cyclinex®-1 amino acid formula, sodium phenylbutyrate, and L-citrulline. At 24 years of age, she demonstrated cognitive delays, lack of executive functioning, and inability to live independently. Her highest ammonia level since diagnosis was 406 µmol/L, but glutamine never exceeded 2000 µmol/L. She had multiple hospital admissions due to hyperammonemic encephalopathy but no other medical complications. In general, she has been very stable in her adult years.

She was converted to glycerol phenylbutyrate at 27 years of age due to non-specific abdominal symptoms with sodium phenylbutyrate and decreasing compliance due to poor palatability of the tablets and difficulty in taking the powder. In the 12 months prior to the conversion, her mean ammonia levels with sodium phenylbutyrate were 39.4 µmol/L. Ammonia decreased to a mean level of 30 µmol/L in the 12 months after converting to glycerol phenylbutyrate. Mean glutamine levels increased from 917.8 µmol/L in the final 12 months on sodium phenylbutyrate to 1113.4 µmol/L in the first 12 months on glycerol phenylbutyrate. This patient was hospitalized once after converting to ammonia scavenger therapy; she was admitted with encephalopathy. Her ammonia levels were within the normal range, but her glutamine levels were significantly elevated (1700 µmol/L) and had been for approximately one week. She had symptoms of aggression, emotional lability, memory loss, and severe headaches. She was started on an emergency protocol, improved from a neurological perspective, and diet therapy was reinstituted. There was concern regarding non-compliance and her healthcare team took this opportunity to optimize her management, including increasing the dose of glycerol phenylbutyrate. In the 12 months following conversion to glycerol phenylbutyrate, the patient had not experienced a hyperammonemic crisis (Table 1).

Patient 3

Patient 3 is a 4-year-old female who was diagnosed with OTC deficiency at 12 months of age. She experienced recurrent vomiting and lethargy since birth. Prior to diagnosis, she was hospitalized four times due to unexplained vomiting. The patient experienced a seizure at 12 months of age, with subsequent decreased tone and regression of developmental milestones. Her initial ammonia level was 123 µmol/L, which reached a peak of 251 µmol/L upon admission to the hospital. A next generation sequencing panel confirmed a pathogenic variant in the OTC gene. During admission, she was treated with intravenous sodium benzoate and sodium phenylacetate, intravenous dextrose/sodium chloride at 1.5 times the maintenance rate, and intravenous intralipids. Upon discharge from the hospital, she was treated with oral sodium benzoate (255 mg/kg/day), essential amino acid formula, and oral citrulline. Protein intake was restricted to 1.2 g/kg/day. At 14 months of age, she was converted from oral sodium benzoate to oral sodium phenylbutyrate. She then experienced challenges with medication compliance and undissolved sodium phenylbutyrate granules appeared in her stool. For this reason, she was converted to glycerol phenylbutyrate.

From the time of diagnosis to discharge from the hospital while being treated with IV sodium benzoate and sodium phenylacetate, her mean ammonia levels were 66.57 µmol/L (n=28; normal 21 µmol/L-50 µmol/L). The mean ammonia level following discharge from hospital while taking sodium benzoate was 23.86 µmol/L (n=14). Upon conversion to glycerol phenylbutyrate, the mean ammonia level decreased to 14.67 µmol/L (n=6). The mean glutamine level followed a similar trend with values of 1205 µmol/L at time of diagnosis, 1066 µmol/L during treatment with sodium benzoate, and 682 µmol/L following conversion to glycerol phenylbutyrate. Parents of the patient communicated that glycerol phenylbutyrate was easier to administer and compliance was improved. Daily protein intake remained unchanged at 1.2 g/kg/day when converting from sodium phenylbutyrate to glycerol phenylbutyrate.

This patient presented to the emergency room twice while being treated with sodium phenylbutyrate–once due to recurrent vomiting (ammonia level of 33 µmol/L) and once due to fever (ammonia level of 23 µmol/L); intervention was not required in both instances. She was hospitalized once while taking glycerol phenylbutyrate due to recurrent vomiting and lethargy. Her ammonia level was determined to be 33 µmol/L and no intervention was required. In the 12 months following conversion to glycerol phenylbutyrate, no hyperammonemic crises had been reported (Table 1).

Patient 4

Patient 4 is a 7-year-old female who was diagnosed with OTC deficiency at 2 years of age. The patient experienced recurrent vomiting since she was 12 months of age. Outpatient investigation prior to diagnosis revealed elevated liver enzymes

and hyperammonemia. Ammonia peaked at 339 µmol/L during the first admission. A next generation urea cycle sequencing panel confirmed OTC deficiency with a pathogenic mutation. She required treatment with intravenous sodium benzoate and sodium phenylacetate during her first hospitalization, as well as intravenous dextrose/sodium chloride at 1.5 times the maintenance rate. Following diagnosis, she was initiated on a treatment regimen consisting of oral sodium benzoate (250 mg/kg/day), citrulline, a low-protein diet (restricted to 1.2 g/kg/day), and an essential amino acid formula. The patient was speaking in short sentences at 2 years of age, and normal cognitive development was reported prior to her diagnosis. However, language regression was noted after her first hyperammonemic episode. She then developed echolalia and had further regression in language skills, decrease in eye contact, and increase in hyperactivity. She was subsequently diagnosed with autism spectrum disorder at 3 years of age. Oral texture aversions have made the low-protein diet and medication administration challenging.

This patient was hospitalized or assessed in the emergency room on 13 separate occasions prior to converting to glycerol phenylbutyrate–8 of these hospitalizations occurred in the 12 months prior to treatment modification. The primary issues that necessitated medical care included recurrent vomiting, fever, and hyperammonemia. Treatment primarily involved intravenous dextrose/sodium chloride and/or intravenous sodium benzoate and sodium phenylacetate. Between hospitalizations the patient was converted from oral sodium benzoate to oral sodium phenylbutyrate, although the latter was not tolerated due to taste and texture. Consequently, the patient was converted back to sodium benzoate, but at an increased dose of 350 mg/kg/day divided into 4 doses/day. Seven hyperammonemic crises were reported while the patient was treated with sodium benzoate. Two crises required intervention with intravenous ammonia scavengers and five were responsive to intravenous dextrose/sodium chloride alone. Six months later, the patient was converted to glycerol phenylbutyrate, while daily protein intake remained unchanged at 1.2 g/kg/day. The patient was admitted to the hospital on two occasions following conversion, which necessitated a dose increase of glycerol phenylbutyrate. No further hospital admissions were reported in the 1 year following this dose increase. In the 12 months prior to conversion to glycerol phenylbutyrate the mean ammonia level was 56 µmol/L and the mean glutamine level was 1036 µmol/L. In the 12 months following conversion to glycerol phenylbutyrate the mean ammonia level was 50 µmol/L and the mean glutamine level was 802 µmol/L. In the 12 months following conversion to glycerol phenylbutyrate, the patient had not experienced a hyperammonemic crisis. Her quality of life greatly improved following conversion, due to reduced hospitalizations and ease of medication administration (Table 1).

Results and Discussion

Each patient experienced a mild reduction in ammonia levels after converting to glycerol phenylbutyrate, lowering their risk of hyperammonemic crises and life-threatening complications. In addition, mean ammonia levels for patient 2 dropped below the upper limit of normal of 35 µmol/L, respectively, suggesting an improvement in ammonia control. This is consistent with what has been reported for glycerol phenylbutyrate in the literature. Diaz G and colleagues observed significantly lower 24-hour blood ammonia concentration with glycerol phenylbutyrate versus sodium phenylbutyrate [5]. Glycerol phenylbutyrate also controlled adult and pediatric mean ammonia levels below the 35 µmol/L upper limit of normal over a 12-month period [1]. Berry and colleagues also observed lower ammonia levels in pediatric patients treated with glycerol phenylbutyrate versus sodium phenylbutyrate [13].

At this time, we cannot explain the mild increase of glutamine in patients 1 and 2, but it may be explained by the short length of the follow up after switching to glycerol phenylbutyrate and possibly fewer measurements of plasma amino acids, which could all be considered limitations in the current case study.

Patients 1, 2 and 3 were fortunate to experience minimal hospitalizations and did not experience any hyperammonemic crises in the 12 months before or after converting to glycerol phenylbutyrate. Patient 4 did not experience any hyperammonemic crises–she only experienced two hospitalizations in the 12 months after converting to glycerol phenylbutyrate, which led to dose adjustments, versus eight hospitalizations in the prior 12 months. These improvements may be attributed to optimization of the glycerol phenylbutyrate dose [13].

None of the patients required any dietary changes, and Patients 1, 3 and 4 each cited the liquid formulation of glycerol phenylbutyrate as easier to dose and administer, which contributed to an improvement in their quality of life and may have also improved their adherence to therapy. Glycerol phenylbutyrate is currently the only oral liquid therapy available for UCD management in Canada, as sodium phenylbutyrate is only available in granules.

Conclusion

In conclusion, we observed a mild reduction in mean ammonia levels, fewer hospitalizations, and improved quality of life and adherence in four Canadian OTC-deficient females following a conversion in treatment to glycerol phenylbutyrate. However, more patients will need to be included and for longer period of time, in order to make a more meaningful statement in outcomes, especially in the light of the monitoring of glutamine levels. As clinical experience in the management of OTC-deficient female patients continues, these cases suggest the importance of early and effective ammonia control using glycerol phenylbutyrate.

Limitations of the Study

Bias in the mean ammonia levels has the potential to be introduced from a variety of mechanisms. This first notable mechanism is that some patients may only have ammonia levels checked at times of illness/decompensation, while others may have had ammonia levels checked frequently as part of their routine surveillance. In addition, the measurement of ammonia

levels may vary in reliability depending on the laboratory's experience with this test (*i.e.*, sampling and/or processing errors), which may lead to falsely elevated levels.

Disclosures

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