Case Report

Long-term use of investigational β-Hydroxybutyrate salts in children with multiple acyl-CoA dehydrogenase or pyruvate dehydrogenase deficiency

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ABSTRACT

Several disorders of energy metabolism have been treated with exogenous ketone bodies. The benefit of this treatment is best documented in multiple acyl-CoA dehydrogenase deficiency (MADD) (MIM#231680). One might also expect ketone bodies to help in other disorders with impaired ketogenesis or in conditions that profit from a ketogenic diet. Here, we report the use of a novel preparation of dextro-β-hydroxybutyrate (D-βHB) salts in two cases of MADD and one case of pyruvate dehydrogenase (PDH) deficiency (MIM#312170). The two patients with MADD had previously been on a racemic mixture of D- and L-sodium hydroxybutyrate. Patient #1 found D-βHB more palatable, and the change in formulation corrected hypernatraemia in patient #2. The patient with PDH deficiency was on a ketogenic diet but had not previously been given hydroxybutyrate. In this case, the addition of D-βHB improved ketosis. We conclude that NHS101 is a good candidate for further clinical studies in this group of diseases of inborn errors of metabolism.

1. Introduction

Multiple acyl-CoA dehydrogenase deficiency (MADD) (MIM#231680), also known as glutaric aciduria type II, is a rare inborn error of metabolism (IEM) affecting fatty acid, choline, and amino acid oxidation [1]. MADD is an inherited autosomal recessive disorder, with an estimated prevalence of 1/200,000 live births, although ethnic variations are seen (Orphanet).

The clinical presentation of MADD is heterogeneous and is broadly defined into three phenotypes that present either in the neonatal period with (type I) or without (type II) congenital anomalies or, more commonly, as a later onset, usually milder type III [2]. Type I symptoms appear hours after birth with recurrent vomiting due to severe acidosis, leading to respiratory distress, often accompanied by hypoglycaemia and hyperammonemia [1]. Other symptoms may include hepatomegaly, hypotonia, cystic kidneys [3], facial dysmorphic features, genital malformations, and an odour of sweaty feet [2]. Type I is the most severe

form of the condition, and most newborns die within the first week of life. Type II also presents in the neonatal period with metabolic decompensation but without congenital anomalies. Many die in the neonatal period or infancy due to hypertrophic cardiomyopathy or metabolic decompensation [4]. Symptoms attributed to later onset type III MADD can appear at any age, with clinical and genetic heterogeneity [5]. Patients typically present with chronic muscle pain or weakness and exercise intolerance. Metabolic stressors such as fasting or infection can initiate symptoms such as recurrent vomiting, nonketotic hypoglycaemia, metabolic acidosis, and reversible liver dysfunction.

Most cases of MADD are caused by a deficiency of the electron transfer flavoprotein (ETF), the electron transfer-flavoprotein ubiquinone oxidoreductase (ETFQO), or in rare cases, due to defects of riboflavin metabolism. ETF is a heterodimeric mitochondrial matrix enzyme with α or β subunits encoded by the genes *ETFA* (MIM# 231680) and *ETFB* (MIM# 130410). ETF accepts electrons from various dehydrogenation reactions, particularly the acyl-CoA dehydrogenases of fatty acid

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oxidation. These are then transferred to ETFQO in the inner mitochondrial membrane and passed to the electron transfer chain. ETFQO is encoded by the *ETFDH* gene (MIM# 231675). Flavin adenine dinucleotide (FAD) is an essential cofactor for both ETF and ETFQO [6].

Treatment for MADD varies depending on the precise defect. Many later-onset patients (mostly with *ETFDH* mutations) respond to pharmacological doses of riboflavin, which may stabilise the mutated protein by increasing FAD binding. Other patients are usually managed with a low-fat, low-protein, high-carbohydrate diet and special precautions during episodes of illness. Catabolism can lead to decompensation, so during illnesses, patients require plenty of glucose intravenously or as regular drinks. Carnitine supplements are often given, although their therapeutic value has not been unequivocally established. Since a ketogenic diet cannot be used in these patients, the administration of exogenous ketone bodies (KBs) might be the best option to bypass the disturbed ketogenesis. Indeed, over the last 20 years, it has been shown that treatment with KBs, such as D,L-3-HB, can be effective and safe in patients with MADD [7]. Though KBs are particularly important for the brain, they are also used by many other tissues, such as cardiac and skeletal muscle, in preference to fatty acids [8]. KBs also decrease fatty acid oxidation by inhibiting lipolysis [9]. Treatment with sodium hydroxybutyrate has led to improvements in myopathy, cardiomyopathy, liver dysfunction and leukodystrophy in patients with MADD [7,10]. The improvement in leukodystrophy reflects the role of KBs in the synthesis of myelin cholesterol. KB treatment may also affect the regulation of gene expression and inflammation. KBs have also been used during acute decompensation in patients with other defects of fatty acid oxidation or ketogenesis [11] and other disorders where they may enhance or provide an alternative to a ketogenic diet. Pyruvate dehydrogenase (PDH) is an essential enzyme for the oxidation of glucose, but it is not needed for the oxidation of fats or KBs. Patients with PDH deficiency are, therefore, often treated with a ketogenic diet, and although they remain profoundly handicapped, families generally report benefit.

The currently available sodium hydroxybutyrate preparations are unpalatable and often associated with gastrointestinal side effects [12]. Moreover, treatment has generally been with a racemic mixture of the D- and L- isomers of sodium hydroxybutyrate. Only D-BHB can be efficiently used as an energy source. If high doses of sodium D,L-3-hydroxybutyrate (Na—D,L-βHB) are administered to deliver the active enantiomer, it can cause alkalosis and hypernatraemia [13]. Each serving of the investigational nutritional product NHS101 is composed of 12 g of dextro-β-hydroxybutyrate (D-βHB), sodium (1.03 g), calcium (1.13 g), magnesium (0.26 g), and nicotinamide riboside (NR) chloride (0.56 g), citric acid, flavouring and stevia. The NR constituent of NHS101, Niagen® (ChromaDex, Inc.), has been extensively studied and is generally recognised as safe (GRAS) [14]. NR is a precursor of nicotinamide adenine dinucleotide (NAD), a co-enzyme and substrate for several enzymes in glucose and fatty acid metabolism and mitochondrial function.

We have previously generated pharmacokinetic (PK) data using NHS101 in healthy volunteers (NCT03603782) [15]. NHS101 was compared to a commercially available D,L-βHB salt (KetoCaNa, Keto-Sports). NHS101 led to a rapid increase in blood ketones (Cmax of 1.2 ± 0.1 mM). When the same amount of D,L-βHB was consumed, around a 50% lower Cmax from baseline was observed compared to D-βHB (Cmax D,L-βHB 0.62 ± 0.05 mM; versus D-βHB; $p < 0.001$). Tmax was reached after approximately 1 h for both products, with ketone levels returning to baseline between 3 and 4 h. The iAUC for D-βHB was ~1.5 fold higher than for D,L-βHB. As expected, D-βHB levels were 1.5–2-fold higher with NHS101 compared to D,L-βHB. Of note, NHS101 only contains the physiological D-isomer. PK data for NHS101 has also been generated in adults ($n = 3$) with long-chain fatty acid oxidation disorders (LC-FAODs). Preliminary data indicate that similar exposure is observed in these patients compared to healthy volunteers (manuscript under review). More studies are required in individuals with MADD to characterise the PK profile of NHS101 and optimise the dosing regimen.

Here, we report the use of a mixture of sodium, calcium and magnesium D-β-hydroxybutyrate (D-βHB) salts in two cases of MADD and one case of PDH deficiency.

2. Materials and methods

2.1. Subjects

Two children with MADD were treated from the age of ten months and ten years, respectively, and one child with PDH deficiency was treated from the age of 2 months. (Table 1). Patients were selected due to the severity of their disease symptoms and lack of alternative treatments.

2.2. Procedures

Treating clinicians from specialised paediatric centres across the UK requested compassionate use of NHS101 on a named-patient basis for individual treatment trials. Individual requests were scrutinised by local paediatric medicine management committees. Parents received extensive counselling regarding the experimental nature of the treatment. A patient information leaflet was provided to the parents before they were invited to consent to treatment.

Table 1
Patient demographics and dosing schedules.

Patient # Diagnosis	Age At Starting D-βHB	Weight At Starting D-βHB	Daily Dose Of D-βHB	Duration Of Follow-Up On Treatment	Plasma βHB (mmol/l)
#1 MADD	10y 3 months	34 kg	470 mg/kg in 4 doses, increasing to 940 mg/kg in 4 doses after one week	2y 7 months	Pre-dose: 0.2–0.3 60 min post-dose: 0.5–1.0 On higher dose: Pre-dose: 0.2–0.3 60 min post-dose: 0.7–1.6
#2 MADD	10 months	7.5 kg	600 mg/kg in 6 doses. Increasing to 725 mg/kg in 6 doses	16 months	60 min post-dose: 0.37
#3 PDH	2 months	4.9 kg	100 mg/kg Increasing to 400 mg/kg	5 months	On 3:1 diet Pre-feed: 0.4–0.7 Post-feed: Highest peak 1.0 Addition of NHS101 (400 mg/kg) Pre-feed: 1.6–1.8 Post-feed: 2.2–2.5

3. Results

3.1. Case 1

This ten-year-old child was diagnosed prenatally with a homozygous c.1693G > C p.(Val565Leu) mutation in the ETFDH gene. Prenatal testing was conducted because an older sibling died in infancy from MADD. A protein- and fat-restricted diet was provided, partially via a gastrostomy, including a continuous overnight feed. L-carnitine and riboflavin were given, though there was no clear response. Increasing muscle weakness developed from the age of four years, which worsened during and after illnesses, when the patient typically became too weak to walk despite the use of a glucose polymer-based emergency regimen.

Parental written informed consent was obtained for treatment and subsequent publication of results. Treatment with Na—D,L-βHB was given from the age of five years, initially at a dose of 350 mg/kg daily in 4 doses, gradually increasing over a period of 9 months to 1000 mg/kg daily in 4 doses. This led to a moderate increase in muscle strength, although plasma D-βHB concentrations remained at 0.44 and 0.27 mmol/l at 45 and 90 min post-dose, respectively. The child experienced nausea after each dose. At ten years old, treatment with Na—D,L-βHB was changed to NHS101 at an initial dose of 470 mg/kg daily, increasing to 940 mg/kg daily in four divided doses after one week. The patient was monitored on Day 1 and Day 7 of treatment with supervised intake of the drug. Blood samples were taken for safety analysis, including a full blood count, electrolytes, magnesium, creatine kinase (CK), beta-hydroxybutyrate and alanine transaminase (ALT), and urinalysis. At the start of NHS101 therapy, the liver extended 5 cm below the costal margin. There was mild weakness in the pelvic girdle while walking. The 6-min walk test was normal at 450 m before switching to NHS 101, 459 m after the first week and 480 m after two weeks. The plasma D-βHB was measured on several occasions during the first two weeks of treatment at home using a point-of-care ketometer (see Table 1).

The child continues to have chronic weakness, worse after infections, with fluctuating CK levels and no cardiomyopathy. There have been some hospital admissions during infections, but fewer than previously. The bouts of nausea, which had previously led to hospital admissions due to vomiting, improved after switching from Na—D,L-βHB to NHS101. However, they continue to have occasional retching and periods of anorexia. Except for a temporary interruption in supplementation with NHS101 due to a delay in requesting resupply, adherence has been good, and the child prefers NHS101 to Na—D,L-βHB because it is more palatable and induces less nausea. The parents report an improved quality of life, and after 2.5 years of NHS101 treatment, the clinical state is stable.

3.2. Case 2

This infant was born by caesarean section at 34 weeks gestation, with a weight of 2.7 kg, on the 97th percentile. An anteriorly placed anus and perineal fistula were noted but no other malformations. At 12 days of age, they had mild hypoglycaemia (2.8 mmol/l), acidosis and 15% weight loss despite nasogastric feeding. The blood acylcarnitine profile and pattern of urinary organic acids suggested MADD and a homozygous c.786G > T p.(Leu262Phe) mutation was identified in the ETFDH gene.

The baby was given a modular feed, very low in fat and protein and high in carbohydrates. They were also given regular sodium bicarbonate, carnitine and riboflavin, though the latter conferred no clear benefit. At one month of age, they underwent anal dilation and colostomy. Anorectoplasty, percutaneous endoscopic gastrostomy and circumcision was undertaken at seven months of age. The baby deteriorated following surgery, requiring intubation, ventilation and haemofiltration. The latter was stopped after two weeks, but long-term ventilation was needed. Cranial MRI at eight months of age showed volume loss of the cerebral hemispheres, an abnormal signal in the periventricular and cerebellar white matter and the dorsal brainstem with diffusion restriction.

D,L-βHB was started at 600 mg/kg daily in six doses. The preparation was changed to NHS101 after an episode of hypernatraemia because NHS101 has a lower sodium content, hoping it would be more effective than the racemic mixture. From ten months onwards, the NHS101 dose was increased to 725 mg/kg daily. The plasma D-βHB concentration was assessed using the RANBUT D-3-Hydroxybutyrate kit (Randox), validated for use on the Alinity® analyser (Abbott). The plasma D-βHB concentration was 0.37 mmol/l 60 min after a dose.

Unfortunately, the weakness gradually worsened. Initially, this affected proximal muscles in the legs, but by two years of age, they could only move their eyes and fingers. Echocardiography was normal until 15 months but subsequently showed increasingly severe left ventricular hypertrophy. The patient was discharged home on long-term ventilation at 22 months of age but readmitted the following month, requiring increased ventilatory settings and fluid restriction. Cranial MRI at 26 months showed marked worsening of the volume loss in the cerebral hemispheres and the abnormal signal, which now also affected the subcortical white matter. The NHS101 dose was increased to 890 mg/kg daily, but the patient became hypercalcaemic (maximum 3.6 mmol/l) due to the calcium content and fluid restriction. The hypercalcaemia was resolved by increasing his fluids, giving a single dose of pamidronate and stopping the NHS101. The racemic mixture of sodium D- and L-3-hydroxybutyrate was restarted at 700 mg/kg daily. The child was discharged home on ventilation and palliative care aged 27 months. They remained stable for three months but then developed seizures, oedema, hyperglycaemia and renal impairment. The child died due to a chest infection aged two years eight months. Written informed consent for the use of NHS101 and subsequent publication of results was obtained from the parents.

3.3. Case 3

Born at term, this infant was hypotonic and apnoeic. An MRI scan revealed a thin corpus callosum and reduced myelination, with minimal abnormal white matter signal. Prior to starting a ketogenic diet, at one month of age, a follow-up MRI showed progression of the white matter abnormality, a widening extra ventricular space consistent with atrophy and poor brain growth, and an elevated magnetic resonance spectroscopy (MRS) lactate peak.

Aged two months, the infant developed epileptic encephalopathy, at which point they were transferred to a specialist paediatric unit. Rapid exome sequencing identified a single nucleotide variant c.483C > T, p.(Tyr161=) mutation in *PDHA1*, leading to a diagnosis of pyruvate dehydrogenase (PDH) deficiency. The genetic alteration is a known mutation that, according to published reports, predicts death in the first few months [16,17]. The mother is a germline carrier. The infant was started on a ketogenic diet, and a follow-up scan was conducted after one month of diet, showing a further progression of the white matter abnormality and increasing cerebral atrophy but a mild decrease in MRS lactate.

The ketogenic diet was increased from 2:1 to 3:1, but ketosis and clinical effects were suboptimal. Ongoing seizures and respiratory insufficiency required ventilation, with biotin, Keppra and phenobarbitone. An initial improvement allowed extubation, but apnoeic episodes returned, requiring bag/mask ventilation. At ten weeks of age, NHS101 was started at 100 mg/kg daily, increasing to 200 mg/kg on Day 6 and 300 mg/kg on Day 10. A ketogenic diet was maintained at a 3:1 ratio, with regular ketone monitoring. βHB was measured before and after feeds on whole blood using the Nova Stat strip, which had previously been validated in the hospital and found to be comparative to plasma βHB. On a 3:1 ratio diet, pre-feed levels ranged between 0.4 and 0.7 mmol/l, and the highest peak achieved post-feed was 1.0 mmol/l. The infant stabilised and was discharged at two months of age. After treatment on NHS101 for one month, a follow-up scan revealed a stable

appearance with no further deterioration and a further decrease in MRS lactate peak. At five months of age, the seizures returned. The dose of NHS101 was increased to 400 mg/kg daily, reducing the seizure incidence. At six months, the child became sleepier. The NHS101 dose had decreased to 350 mg/kg daily, with a gain in weight. A subsequent return to 400 mg/kg daily had a good effect. At this dose, pre-feed βHB levels in whole blood ranged between 1.6 and 1.8 mmol/l and post-feed levels 2.2–2.5 mmol/l.

The child caught parainfluenza at seven months of age, which caused vomiting with secretions, leading to the child choking and subsequent respiratory arrest requiring resuscitation. They were transferred to the paediatric intensive care unit (PICU), where an MRI confirmed metabolic decompensation with acute hypoxic-ischaemic injury. The child was extubated in the hospice and died on the same day. A final MRI scan post-arrest showed sequelae of hypoxic-ischaemic encephalopathy (HIE) but no further progression of previous changes. The parents were committed to adherence to the medication and regular checks for ketosis. Although subjective, the parents were convinced that NHS101 improved responsiveness and decreased seizures, with a recognised response to dose increases. Written informed consent for the use of NHS101 and subsequent publication of results was obtained from the parents.

4. Safety

No serious adverse events considered related to NHS101 were reported. One case reported a suppression of appetite and nausea if they ate within 30 min of supplementation. This patient, however, said the nausea was less than with Na—D,L,βHB. Hypercalcaemia occurred in one patient on 890 mg/kg daily of NHS101, partly due to the concentration of calcium in the product and partly because they were on strict fluid restriction, illustrating the need for calcium monitoring.

All physicians stated that they would use NHS101 in other patients. It can be challenging to motivate some families to monitor treatment effects. Future studies should implement practical measures to encourage families to complete patient diaries, maintain adherence and record outcomes.

5. Discussion

D,L-3-Hydroxybutyrate has been used successfully in the clinic by a number of investigators for the management of multiple IEMs. Results from these cases suggest that the use of a novel D-βHB salt mixture (NHS101), delivering only D-βHB, can be safe and effective in MADD patients. Tested doses ranged from 470 up to 940 mg/kg/d divided into 4 to 6 doses which is in line with D,L βHB doses reported in the study conducted by van Rijt and colleagues [7]. These are encouraging results as they reported treatment-related clinical improvement of cardiomyopathy, leukodystrophy, liver symptoms, muscle symptoms and respiratory failure in 70% of patients. D-βHB supplementation may trigger these clinical improvements by affecting multiple pathways. First, D-βHB may significantly improve cellular energetics, which is impaired in MADD patients. This is particularly relevant in tissues with high energy demand, such as the brain or the heart. KBs and fatty acids serve as alternative fuels for brain, heart, muscle, and liver metabolism.

Interestingly, numerous cardiac diseases are characterised by a loss of metabolic flexibility, resulting in metabolic reprogramming. The reduced capacity to use fatty acids sets the stage for myocardial energy starvation, a key driver in heart failure physiopathology. In this context, the failing heart appears to rely more on KBs as a fuel source [18]. The role of KB metabolism is not limited to its involvement in energy metabolism as they also function as lipogenic and sterol biosynthetic substrates in various tissues, including the brain, liver, and heart [19]. During the neonatal period, KBs are key precursors for lipid synthesis (especially cholesterol) and amino acids [19]. KBs are essential for myelination, and the inability to make KBs is responsible for the

leukodystrophy seen in patient #2 and others with severe MADD. Finally, ketones and, more specifically, D-βHB act as potent signalling molecules affecting numerous pathways, resulting in anti-inflammatory and antioxidant properties, which may contribute to the clinical improvements observed in BHB-supplemented MADD patients [20]. Further studies are required to elucidate fully the molecular mechanisms of action of D-BHB in MADD.

In addition to the two MADD cases, we report the use of NHS101 as exogenous ketone supplementation in one case of PDH deficiency. NHS101 was successfully introduced in this patient in addition to a suboptimal ketogenic diet, resulting in a reduction of seizures. Treatment of PDH deficiency using a ketogenic diet has been well described. Sofou and colleagues characterised a cohort of 19 patients who were on a ketogenic diet for three years. Patients with the most favourable treatment outcomes were those with infantile or childhood disease onset. These patients experienced positive clinical effects on epilepsy, ataxia, sleep disturbance, and motor and neurocognitive functioning [21]. In our reported case, NHS101 supplementation may have contributed to improved nutritional ketosis, leading to reduced seizures.

NHS101 has three advantages over sodium D,L-hydroxybutyrate. First, it only contains the physiological D-isomer. The fate of the L isomer is uncertain when patients are given the racemic mixture, but one might expect the pure D-isomer to be twice as beneficial. Anecdotal evidence from patients also suggests that it is more palatable. Patients #2 and #3 were unable to communicate, but patient #1 complained of nausea after taking sodium D,L-hydroxybutyrate and preferred NHS101. Finally, the sodium load associated with high doses of sodium D,L-hydroxybutyrate can cause complications, such as hypernatraemia, as seen in patient #2. This is less likely with NHS101 as it is a mixture of sodium, magnesium and calcium D-βHB salts and has lower sodium. It is, however, important to monitor the plasma concentrations of these cations as the high intake can cause complications. Patient #2 developed severe hypercalcaemia, though their fluid restriction also contributed to this.

Clarke and colleagues have developed a keto-ester which allows D-hydroxybutyrate to be given without any cations [22]. 3-hydroxybutyrate is chemically coupled to a second molecule (1,3-butanediol) via an ester linkage, giving rise to the compound (*R*)-3-hydroxybutyl-(*R*)-3-hydroxybutyrate. Upon oral administration, this keto-ester leads to a significant increase in plasma D-βHB levels [22]. The ketone ester does, however, have a bitter taste [23], and although a single dose was acceptable to VLCAD-deficient patients [24], repeated administrations led to mild to severe gastrointestinal symptoms in healthy volunteers [22], raising doubts about long-term treatment adherence. Early pharmacokinetic studies found that NHS101 was generally well-tolerated in doses up to 1 g/kg body weight in four divided doses over a period of up to three years [15], supported by the three case studies presented. We report on a small heterogenous population in terms of pathology, severity, age, and age at commencement of treatment. Thus, additional studies are warranted on a larger sample size to determine the long-term safety/tolerability of NHS101 in patients.

6. Conclusion

In conclusion, results from these three cases suggest that NHS101 is a good candidate for further clinical studies in this group of diseases of inborn errors of metabolism.

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Andrew A.M. Morris: Writing – review & editing, Resources, Investigation. **Bernard Cuenoud:** Writing – review & editing, Resources, Methodology, Conceptualization. **Philippe Delerive:** Writing – review & editing, Resources, Methodology, Conceptualization. **Helen Mundy:** Writing – review & editing, Resources, Investigation. **Bernd C. Schwahn:** Writing – review & editing, Resources, Investigation.

Declaration of competing interest

The above work has not been previously published and is not under consideration for publication elsewhere. All authors approve the publication. Each author was actively involved in acquiring and reporting the data and the subsequent review and revision of this manuscript. Each author has agreed to be personally accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

The data that has been used is confidential.

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