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CASE REPORT

One Year Experience of Pheburane® (Sodium Phenylbutyrate) Treatment in a Patient with Argininosuccinate Lyase Deficiency

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Abstract Argininosuccinate lyase deficiency (ASLD) is a urea cycle disorder (UCD) treated with dietary adjustment and nitrogen scavenging agents. "Pheburane®" is a new tasteless and odour-free formulation of sodium phenylbutyrate, indicated in the treatment of UCD.

A male patient diagnosed with ASLD was put on treatment with the new formulation of sodium phenylbutyrate (granules) for a period of one year, at 500 mg/kg orally in 3 intakes/day. Plasma glutamine, arginine, citrulline, argininosuccinate, serum sodium, potassium, liver function tests and urine orotate all remained unchanged over this period. There was no difference in mean ammonia levels before and after treatment, and no hyperammonemia episode occurred during treatment with Pheburane®. An improvement in a measurement of quality of life (QOL) was noted after treatment with Pheburane®.

Conclusion: Good metabolic control and improved QOL were achieved throughout the treatment period.

Abbreviations

ASLD	Argininosuccinate lyase deficiency
NaPB	Sodium phenylbutyrate
QOL	Quality of life
UCD	Urea cycle disorder

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Argininosuccinate lyase deficiency (ASLD), caused by the deficiency of the enzyme argininosuccinate lyase, is the second most common urea cycle disorder. Dietary restriction and arginine supplementation combined with an ammonia scavenger such as sodium phenylbutyrate (NaPB) are the main therapeutic modalities used in the chronic treatment of ASLD (Erez 2013). The unpleasant taste and odour of the medicine is a significant burden adding to the stress of the families faced with the daily challenge of getting the children to take a medicine for a life-threatening disease (Brusilow and Maestri 1996). Pheburane® is a new, taste -masked and odour-free formulation of NaPB (developed by Lucane Pharma, France). Results following the use of Pheburane in patients with UCD under a French cohort temporary utilisation protocol have been recently published (Kibleur et al. 2014). NaPB is an established treatment for UCD, available for over three decades (Brusilow et al. 1980). NaPB, as a precursor of sodium phenylacetate, provides an alternative pathway of nitrogen excretion by conjugation with glutamine. The decrease in urea cycle flux and hence decrease in the production of argininosuccinate may also mitigate the hepatic injury described in ASLD (Smith et al. 2013). Pheburane® (granules) consists of small spherical sugar cores which are then coated with NaPB and ethylcellulose sequentially in two separate layers. Ethylcellulose is a well-known taste-masking agent for active substances (Guffon et al. 2012).

Here we report 1 year usage of Pheburane® in a case of late onset ASLD (asymptomatic until the first three months of life) prescribed because it is a tasteless and odour-free formulation. A male patient first presented at three months of age with symptoms of retarded development, strabismus and vomiting. He was the first offspring of parents both working as high school teachers. There was no

Table 1 Levels of plasma ammonia, glutamine, arginine, citrulline, argininosuccinate, serum sodium, potassium, liver function tests and urine orotate at diagnosis and during periods of different therapies

Parameters	Normal values	At diagnosis (mean ± SD)	Na-benzoate (mean ± SD)	Na-phenylbutyrate (mean ± SD)	Pheburane® (mean ± SD)
Ammonia (p) (μg/dL)	21–50	150	48 ± 10	49 ± 9	33 ± 5
Glutamine (p) (μmol/L)	333–809	760	570.8 ± 52	549.3 ± 51	540.6 ± 49
Arginine (p) (μmol/L)	12–112	10	102.6 ± 28	49.6 ± 18	46 ± 19
Citrulline(p) (μmol/L)	3–35	55	35.6 ± 10	33.2 ± 8	30.1 ± 5
Argininosuccinate(p) (μmol/L)	0.0	0.1	0.0	0.0	0.0
Potassium (s) (mEq/L)	3.5–5.0	4.1	3.8 ± 1.1	3.9 ± 0.9	3.8 ± 0.8
Sodium (s) (mEq/L)	136–145	140	138 ± 2.1	139 ± 1.8	138 ± 1.9
Aspartate aminotransferase (AST,SGOT) (s) (U/L)	15–55	22	25 ± 3	28 ± 5	26 ± 4
Alanine aminotransferase (ALT, SGPT) (s) (U/L)	5–45	51	28 ± 5	25 ± 7	26 ± 5
Orotic acid (u) (mmol/mol creatinine)	0.02–3.6	4.2	0.01	0.01	0.01

p plasma, *s* serum, *u* urine. Mean levels of parameters ±SD were presented

consanguinity between the parents. Born as a healthy baby (weight, 3,000 g (50th percentile); length, 50 cm (50th percentile); head circumference, 38 cm (50th percentile); Apgar, 10/10) after an uneventful pregnancy, the patient was found to have hyperammonemia during an attack of bronchiolitis. ASLD was diagnosed based on moderately elevated plasma citrulline (55 μmol/L, *N*: 3–35) and argininosuccinate (0.1 μmol/L, *N*: 0.0) levels and decreased argininosuccinate lyase activity measured in red blood cells (9.0 nmol/min/gHb, *N*: 50–140). Treatment was initiated with a diet containing 1.25–2 g/kg/day protein and supplementation of L-arginine (250 mg/kg/day) and Na-benzoate (500 mg/kg/day). Based on the recommendation to reduce the L-arginine dose at the age of four, this was decreased from 250 to 100 mg/kg/day (Nagamani et al. 2012). This was followed by an increase in ammonia levels, and Na-benzoate (500 mg/kg/day) was replaced with NaPB (500 mg/kg/day) to improve scavenging. At the age of six, weight was 18 kg (3–10th percentile range), height 103 cm (<3th percentile) and head circumference 48 cm (3th percentile). Clinical examination revealed mild mental retardation (IQ 69) (References: IQ 50–70 according to ICD10) and strabismus. The family reported refusal to eat or drink because of the taste and smell of the accompanying drugs, particularly NaPB. Attempts by the parents to mask the taste in food (particularly in yogurt) were unsuccessful. The consequences of the child not taking the medication added a significant burden to the stress already experienced by the parents caring for a child with a history of hyperammonemia (three episodes of hyperammonemia and hospitalisation (one in intensive care unit) during febrile infections in infancy). The quality of life (QOL) score was 23.9 (Uneri et al. 2008).

The new formulation of NaPB was started and continued at the same dose range (500 mg/kg/day orally) in 3 intakes/day as before. No hyperammonemia episode occurred over one year of treatment with Pheburane®. There was no significant difference in the mean ammonia level before and after treatment with Pheburane® (Table 1). Mean levels of plasma glutamine, arginine, citrulline, argininosuccinate, serum sodium, potassium, liver function tests and urine orotate remained unchanged (Table 1). During the first week of administration, the parents reported vomiting during administration. However, successful posology adjustment to ensure rapid swallowing, minimising the time with the medicine in the mouth, was achieved by the end of the first week. The patient became fully compliant with the prescribed doses of Pheburane® at the end of the first month. A decrease in family stress was observed during regular outpatient visits. A repeat of the QOL measurement indicated an improved quality of life; the QOL score increased from 23.9 to 57.6. Additionally, a detailed interview with the parents performed by a psychologist revealed decreased anxiety and improved compliance.

Considering that new aspects of NaPB usage are emerging which may indicate further therapeutic activity (enhancement of pyruvate dehydrogenase complex enzymatic activity in vitro and in vivo by increasing the proportion of unphosphorylated enzyme through inhibition of pyruvate dehydrogenase kinase), the development of a new NaPB formulation which is far more palatable is extremely important (Ferriero et al. 2013).

In conclusion, despite the limited observational time of one year in this single patient, we would like to share our experience of use of Pheburane® with the aim of informing

clinicians about this new option for treatment in UCD which may improve QOL for these patients.

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Compliance with Ethics Guidelines

Conflict of Interest

Sema Kalkan Uçar, Burcu Özbaran,Yasemin Atik Altinok, Melis Köse, Ebru Canda, Mehtap Kağnc, Mahmut Coker declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from the patient for being included in the study.

Authors' Contributions

SKU had primary responsibility for protocol development, patient enrollment, outcome assessment, data analysis and writing the manuscript. BO contributed to the psychological evaluation and report of the work. YAA participated in patient's nutritional management. MK, EC, MK participated in patient follow-up. MÇ supervised the design, performed the final data analyses and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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