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Oral β-Hydroxybutyrate Supplementation in Two Patients with Hyperinsulinemic Hypoglycemia: Monitoring of β-Hydroxybutyrate Levels in Blood and Cerebrospinal Fluid, and in the Brain by *In Vivo* Magnetic Resonance Spectroscopy

BARBARA PLECKO, SYLVIA STOECKLER-IPSIROGLU, EDITH SCHOBER, GEORG HARRER, VLADIMIR MLYNARIK, STEPHAN GRUBER, EWALD MOSER, DOROTHEA MOESLINGER, HEINZ SILGONER, AND OSMAN IPSIROGLU

Divisions of Metabolism [S.S.-I., D.M.] and Endocrinology and Diabetes [E.S.], Department of Pediatrics; Department of Neonatology [H.S., O.I.]; and Department of Anesthesiology [G.H.], Institute of Medical Physics [V.M., S.G., E.M.], University Hospital of Vienna, Waehringerguertel 18-20, A-1090 Vienna, Austria; and Division of Metabolism and Pediatric Neurology, Department of Pediatrics, University Hospital of Graz, A-8036 Graz, Austria [B.P.]

ABSTRACT

In persistent hyperinsulinemic hypoglycemia of infancy, ketone body concentrations are abnormally low at times of hypoglycemia, depriving the brain of its most important alternative fuel. The neuroprotective effect of endogenous ketone bodies is evidenced by animal and human studies, but knowledge about exogenous supply is limited. Assuming that exogenous ketone body compounds as a dietetic food might replace this alternative energy source for the brain, we have monitored the fate of orally supplemented DL sodium β-hydroxybutyrate (β-OHB) in two 6-mo-old infants with persistent hyperinsulinemic hypoglycemia for 5 and 7 mo, while on frequent tube-feedings and treatment with octreotide. Near total (95%) pancreatectomy had been ineffective in one patient and was refused in the other. In blood, concentrations of β-OHB increased to levels comparable to a 16- to 24-h fast while on DL sodium β-OHB 880 to 1000 mg/kg per day. In cerebrospinal fluid, concentrations of β-OHB increased to levels comparable to a 24- to 40-h fast, after single dosages of 4 and 8 g, respectively. High ratios of β-OHB to acetoacetate indicated exogenous origin of β-OHB. An increase of intracerebral concentrations of β-OHB could be demonstrated by repetitive single-voxel proton magnetic resonance spectroscopy by a clear doublet at 1.25 ppm. Oral DL sodium β-OHB was tolerated without side effects. This first report on oral supplementation of DL sodium β-OHB in two patients with persistent hyperinsulinemic hypoglycemia demonstrates effective uptake across the blood–brain barrier and could provide the basis for further evaluation of the neuroprotective effect of β-OHB in conditions with hypoketotic hypoglycemia. **(*Pediatr Res* 52: 301–306, 2002)**

Abbreviations

PHHI, persistent hyperinsulinemic hypoglycemia of infancy
MRS, magnetic resonance spectroscopy
CSF, cerebrospinal fluid
β-OHB, β-hydroxybutyrate
AA, acetoacetate

PHHI is the most common cause of recurrent hypoglycemia in infancy (1). PHHI is characterized by inappropriately high blood insulin levels in the presence of symptomatic hypoglycemia (2) and by a prompt responsiveness to glucagon (3). Pathogenetically, PHHI may result from different molecular defects in the regulation of β-cell–mediated insulin release with diffuse or focal β-cell hyperplasia (4, 5).

Treatment with diazoxide, a potassium-channel opener at the pancreatic β-cell and inhibitor of insulin secretion, and octreotide, a long-acting somatostatin analog, is often hampered by poor effect or severe side effects (3, 6–9), and pancreatectomy, at least in cases with diffuse hyperplasia, bears the risk of postoperative diabetes (10).

In most hypoglycemic states, ketone bodies (β-OHB and AA) are released from counterregulatory lipolysis, serving as an alternative, neuroprotective, energetic fuel for the brain (3,

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Correspondence and reprint requests: Sylvia Stoeckler-Ipsiroglu, M.D., Department of Pediatrics, University Hospital Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria; e-mail: stoeckler@metabolic-screening.at
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11–13). Healthy neonates have high ketone body concentrations when blood glucose levels fall into the hypoglycemic range (14). In PHHI, however, owing to insulin-mediated suppression of lipolysis, the ketotic response to hypoglycemia is absent, increasing the risk of early, irreversible brain damage (6, 15, 16).

The neuroprotective role of ketone bodies is evidenced by animal and human studies. Intraperitoneal application of β-OHB was found to reverse insulin-induced hypoglycemic coma in suckling-weanling mice despite low blood and brain glucose levels (17), and adults were shown to become resistant to insulin-induced hypoglycemic reactions after fasting owing to augmented cerebral ketone uptake (18). Studies of ketone body metabolism in neonates and infants have been limited up to now.

Assuming that supplementation of β-OHB as a dietetic food provides an exogenous, alternative energy source for the brain during states of hypoglycemia and inadequate ketone body production, we investigated levels of β-OHB in blood, CSF, and brain tissue after oral supplementation of DL sodium β-OHB in two patients with PHHI, who despite vigorous treatment suffered from recurrent hypoglycemia.

METHODS

Patients. Both patients are the products of uncomplicated pregnancies from healthy unrelated parents. Birth weight was 4460 and 4680 g (>97th percentile), length was 54 and 53 cm (>90th percentile), head circumference was 36 and 36.5 cm (90th percentile). Because of symptomatic hypoglycemia on the second day of life in one and macrosomia in the other, the diagnosis of PHHI was established by high insulin levels in the presence of hypoglycemia (insulin-to-glucose ratio > 0.5) and a clear increase of blood glucose levels (Δ2.2, Δ 5.7 mM) after the i.v. administration of 0.5 mg of glucagon.

In patient 1, pharmacologic treatment with diazoxide (up to 20 mg/kg per day) and octreotide (up to 30 μg/kg per day) failed to restore euglycemia. Near total pancreatectomy (95%) was performed at the age of 2.5 mo of life. Histology revealed diffuse β-cell hyperplasia. Postoperatively hypoglycemia persisted but parents refused a second pancreatectomy.

In patient 2, pharmacologic treatment with diazoxide (up to 20 mg/kg per day) and nifedipine (0.7 mg/kg per day) failed to restore euglycemia. Under s.c. application of octreotide (30 μg/kg per day) continuous i.v. glucose supply could be withdrawn, but blood glucose levels still occasionally dropped to levels below 2.6 mM. Subtotal pancreatectomy was refused by the parents.

Oral supplementation of DL sodium β-OHB and monitoring of biochemical variables. Oral administration of DL sodium β-OHB up to 8 g/d has been described previously in a 12-mo-old child with hypoketotic hypoglycemia caused by a fatty acid oxidation disorder without any side effects (19).

DL Sodium β-OHB was obtained from Fluka Chemicals (product number 54965; Buchs, Switzerland). On administration, 1g of DL sodium β-OHB was dissolved in 100 mL of an oral formula feeding, providing a 1% solution, pH 7.2.

Both patients received DL sodium β-OHB from the age of 6 mo onward, while on frequent tube feedings and treatment with octreotide. In both patients, 1 g of DL sodium β-OHB was added to every tube feeding, 8 times a day (880–1000 mg/kg per day) and later increased to 2 g and 4 g, 8 times a day in patient 1. Because of good tolerance of DL sodium β-OHB, the observational period was extended to 5 and 7 mo, respectively. Intervals of tube feeding and octreotide dosage remained unchanged in both patients for the whole observational period.

Ketone bodies may potentially influence blood glucose levels, either by their glucose-sparing effect (20) or, at higher concentrations contrary, by enhancing insulin release (13). We therefore have paid special attention to changes in mean blood glucose levels and frequency of hypoglycemic episodes before and during treatment with DL sodium β-OHB.

Blood glucose levels were checked 6 to 8 times daily by the parents, using a Glucocard Memory (A. Menarini, Diagnostics, Firenze, Italy). For monitoring of possible side effects, acid base balance, electrolytes, transaminases, creatinine, and urea were checked in daily to weekly intervals. ECGs were performed in patient 1 after 2 and 4 mo and in patient 2 after 4 mo of treatment. EEGs in patient 2 were performed before and after 2, 3, and 4 wk of treatment and 1 mo after treatment with DL sodium β-OHB had been stopped.

For determination of FFA, β-OHB and AA venous blood samples were taken 30 min to 3.0 h after oral intake of the DL sodium β-OHB. Lumbar puncture was performed under sedation with midazolam, 0.1mg/kg. Concentrations of β-OHB in CSF were measured in both patients after a single dose of DL sodium β-OHB, 8 g in patient 1 and 4 g in patient 2.

EDTA blood and CSF was immediately deproteinized with 1 N perchlorate. FFA, β-OHB, and AA were subsequently measured by gas chromatography–mass spectrometry (21). Brain levels of β-OHB in response to oral supplementation of DL sodium β-OHB were determined by *in vivo* proton MRS of the brain in patient 1. Spectroscopy of the brain was performed as described (22). Sedation was performed with propofol i.v. under spontaneous breathing and continuous pulse oximetry. Euglycemia was maintained throughout the procedure by providing adequate amounts of glucose and octreotide via a Broviac catheter. For technical details see legend to Figure 1.

Parental consent and Institutional Review Board. Written informed consent had been given by both parents of our two patients for oral supplementation of DL sodium β-OHB, blood sampling, and spinal tap and for cerebral MRS in patient 1. This observation study on the oral application of DL sodium β-OHB to two patients with PHHI and recurrent hypoglycemia despite vigorous treatment was acknowledged by the local ethical committee of the Medical Faculty of Vienna. MRS on a 3.0-T whole-body imager was approved by the same local ethical committee (approval 291/98).

Calculations and statistical methods. Student's *t* test was used for statistical intraindividual comparison of mean ± SD 1-mo blood glucose levels before and during supplementation with DL sodium β-OHB. χ^2 test was used for intraindividual comparison of hypoglycemic episodes (blood glucose < 2.6 mM) before and during supplementation with DL sodium β-OHB; $p < 0.05$ was considered significant.

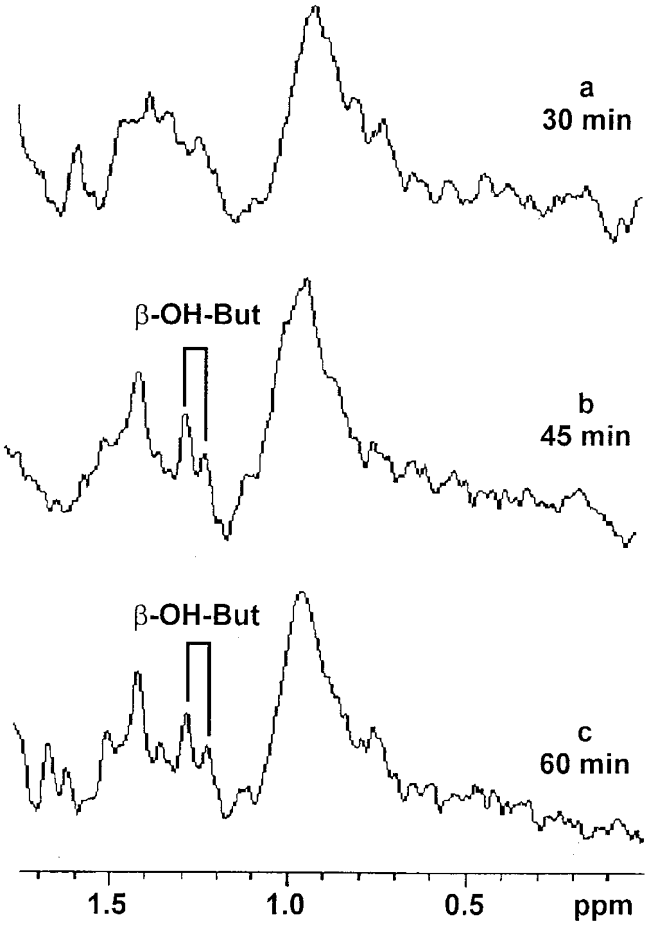

Figure 1. STEAM spectra from basal ganglia after oral administration of DL sodium β-OHB. In patient 1, MR spectra were measured 30, 45, and 60 min after oral administration of a single dose of 8 g of DL sodium β-OHB. Localized proton MRS was performed on a 3.0-T whole-body imager (Bruker Medspec S30/80, Ettlingen, Germany) using a standard head resonator and repetitive single-voxel measurement. A STEAM (TE/TM/TR = 20/30/6000 ms) protocol with 64 averages was used (22). Water suppression was performed by chemical shift selective sequence (CHESS) consisting of three 24-ms hermite radiofrequency pulses. The $2 \times 2 \times 2$ cm^3 volume of interest was positioned in basal ganglia. The methyl protons of DL β-OHB were visible as a doublet at 1.25 ppm. The first spectrum taken 30 min after oral administration of DL sodium β-OHB showed a very low intensity of DL β-OHB signal within the noise level. In the spectrum taken 45 min after oral administration, a clear doublet (J = 7 Hz) appeared at 1.25 ppm. The same doublet with slightly lower intensity was observed 60 min after oral administration.

RESULTS

FFA and ketone bodies in blood, CSF, and brain tissue. Blood ketone bodies measured at various times before initiation of β-OHB treatment were within or slightly above concentrations referenced for children in the fed state (23). Compared with these basal pretreatment values, there was an almost 10-fold increase of β-OHB concentrations in blood at 0.5- to 3-h intervals after last meal and oral intake of DL sodium β-OHB. Values of FFA, β-OHB, and AA in blood and ratios of β-OHB to AA and of FFA to β-OHB before and during treatment with DL sodium β-OHB are given in Table 1. In patient 2, presupplemental blood concentrations of FFA and ketone bodies were variable, mostly depending on different feeding intervals and different insulin concentrations.

In CSF, concentrations of β-OHB, measured at 1.5- and 2-h intervals to their last meal and oral β-OHB administration, were 5- to 15-fold higher than in a nonfasted 14-y-old control individual. Values of β-OHB and AA in CSF during treatment with DL sodium β-OHB are given in Table 2.

In vivo *proton MRS of the brain.* In the brain MRS, the methyl protons of DL β-OHB were visible as a doublet at 1.25 ppm. Figure 1 shows relevant regions of the spectra (0–1.7 ppm) measured at different times after oral supplementation of DL sodium β-OHB.

Blood glucose levels. Mean 1-mo glucose levels before supplementation were not significantly different from levels during supplementation with DL sodium β-OHB (patient 1: 4. 4 ± 1. 6 mM, $n = 241$, and 4. 5 ± 1. 7 mM, $n = 225$; patient 2: 3. 3 ± 1. 2 mM, $n = 243$, and 3. 2 ± 1. 2 mM, $n = 311$), as was frequency of hypoglycemic episodes (blood glucose < 2. 6 mM; patient 1: $p = 0.938$, patient 2: $p = 0.077$).

Further investigations and clinical course. ECG showed normal QTc intervals (390/420 and 420 ms) in both patients.

Patient 1 had no seizures during episodes of hypoglycemia while receiving DL sodium β-OHB but had had repeated hypoglycemia with generalized convulsions before and 1 mo after supplementation had been stopped.

At the age of now 16 mo, his head circumference is 48.5 cm (50th percentile) and his psychomotor development corresponds to that of a 10-mo-old child.

In patient 2, EEG records showed improvement of background activity, which persisted after cessation of treatment with DL sodium β-OHB (results not shown). At the age of now 16 mo, her head circumference is 48 cm (75th percentile) with normal psychomotor development.

DISCUSSION

Based on the well-known neuroprotective role of ketone bodies (12, 13), we have performed an observational study to monitor the fate of exogenous β-OHB in two patients with PHHI and to evaluate its uptake into the brain by single-voxel proton MRS.

β-OHB is water soluble, absorbed in the gastrointestinal tract, and able to cross the blood–CSF–brain barrier (23). The D- form of β-OHB is believed to be the physiologically more important isomer (12, 13), but isoenzymes for the utilization of both the D- and L- isomers of β-OHB are expressed from early gestational age in various tissues (24). Because of preliminary data on one patient with a fatty acid oxidation defect treated with DL sodium β-OHB (19) and the easier access to the DL-racemate, we have decided to administer the DL- form of sodium β-OHB to our patients. Gas chromatography–mass spectrometry as well as MRS detected the D- as well as the L-form of β-OHB.

Blood ketone bodies, measured in both patients at various times before initiation of β-OHB treatment, were within or slightly above concentrations compared with control values of children in the fed state (23). In the presence of hypoglycemia these concentrations would be considered hypoketotic. Interpretation of these retrospectively evaluated data were limited by the fact that exact assignment to last meals and blood insulin

Table 1. *Blood levels of β-OHB, AA, FFA, and their ratios in two patients with PHHI compared with reference values**

Patient No.	β-OHB doses/meal	Interval to last meal/adm.	Glucose (mM)	Insulin (pM)	FFA (mM)	β-OHB (mM)	AA (mM)	β-OHB/AA	FFA/β-OHB
1	–	–	1.05	14	1.210	0.486	0.264	1.81	2.48
	1 g	1 h	4.05	11	0.82	1.466	0.165	8.88	0.55
	1 g	2.5 h	3.77	n.d.	0.85	1.230	0.258	4.8	0.69
	1 g	3.0 h	3.05	n.d.	0.63	1.558	0.189	8.24	0.4
	2 g	0.5 h	6.55	n.d.	0.925	1.931	0.341	5.7	0.47
	2 g	1.5 h	7.27	n.d.	0.796	1.449	0.352	4.1	0.54
	2 g	2.5 h	7.05	n.d.	0.83	1.736	0.177	9.8	0.47
	4 g	0.5 h	4.61	n.d.	1.085	2.122	0.463	4.6	0.51
	4 g	1.5 h	4.27	n.d.	1.024	2.570	0.363	7.1	0.39
2	–	–	1.22	n.d.	0.192	0.093	0.080	1.1	2.4
	–	3 h	2.55	11.4	n.d.	0.340	0.103	3.3	–
	–	–	2.77	n.d.	n.d.	0.273	0.145	1.88	–
	–	–	3.72	n.d.	1.244	0.294	0.243	1.2	4.2
	1 g	0.5 h	4.94	18.1	1.610	2.13	0.278	7.66	0.7
	1 g	1 h	4.27	18.6	1.46	2.0	0.293	6.98	0.75
	1 g	1.5 h	3.11	n.d.	0.8	2.75	0.503	5.48	0.72
	1 g	3 h	2.50	21	1.3	1.71	0.211	8.1	0.29
1-h postprandial					0.4 ± 0.28	0.21 ± 0.13	0.05 ± 0.03		
16-h fast					1.6 (mean)	1.22 ± 1.15	0.28 ± 0.22		
24-h fast					2.46 ± 0.69	2.8 ± 1.3	0.3 ± 0.12		

* Blood concentrations of β-OHB, AA, FFA, and ratios of FFA/β-OHB and β-OHB/AA, as well as corresponding glucose and insulin levels in two patients with PHHI before and during oral supplementation of DL sodium β-OHB. Samples were collected on different days before treatment with DL sodium β-OHB and different time intervals to oral administration of different dosages, as indicated. Reference values (mean ± SD) in fed and fasted children are shown for comparison 23.

Abbreviation used: nd, not done.

Table 2. *Concentrations of ketone bodies during treatment with DL sodium β-OHB**

Patient No.	β-OHB doses/meal	Interval to last meal/adm.	β-OHB (mM)	AA (mM)	β-OHB/AA	β-OHB CSF/blood	AA CSF/blood
1	8 g	2 h	0.229	0.036	6.3	0.24	0.11
2	4 g	1.5 h	0.654	0.045	14.5	0.23	0.15
†	–	Fed state	0.043	0.033	1.3	0.13	0.15
24-h fast	–	24-h fast	0.250	0.130	1.9	0.10	0.20
40-h fast	–	40-h fast	0.595	0.266	2.2	0.16	0.34

* Concentrations of β-OHB, AA, and ratio of β-OHB/AA in CSF from two patients with PHHI during oral supplementation of DL sodium β-OHB. Samples were collected during treatment with DL sodium β-OHB and different time intervals to meals and oral administration of different doses, as indicated.

† Values of a 14-y-old control patient in the fed state, measured in our laboratory, are shown. Normal (median) values as reported in the literature from 11 healthy, 24-h fasted boys aged 3–5 y and from 58 40-h fasted boys, aged 6–15 y, are shown for comparison 28.

levels was not possible for all values. However, compared with these basal pretreatment values, there was an almost 10-fold increase of β-OHB concentrations in blood at 0.5- to 3-h intervals after last meal and oral intake of DL sodium β-OHB. Still, these values were not beyond physiologic limits as comparably high values were found in healthy children after a 16- to 24-h fast (23, 25, 26). However, whereas in fasted healthy subjects, as a result of enhanced lipolysis, high β-OHB concentrations are most consistently associated with high AA and FFA levels, in our patients, an isolated elevation of β-OHB was present. Therefore, the disproportionally high ratio of β-OHB to AA and the low ratio of FFA to β-OHB are highly indicative of the exogenous origin of β-OHB measured in the patients' blood. Interestingly, patient 1 needed 4-fold the dosage to reach equal blood levels as patient 2. We cannot explain this otherwise than by recurrent small vomiting in patient 1, which had been preexistent to the supplementation of DL sodium β-OHB. Another reason might be accelerated enteral passage with minor absorption after subtotal pancreatectomy in patient 1.

In CSF, no presupplemental β-OHB values were available. However, concentrations of β-OHB, measured at 1.5- and 2-h intervals to their last meal and oral β-OHB administration, were 5- to 15-fold higher than in a nonfasted 14-y-old control individual. As in the blood, these high postsupplementation values were not beyond physiologic limits as comparably high values were found in healthy, 24- to 40-h fasted boys (27). Again, in CSF the high β-OHB to AA ratio is highly indicative of the exogenous origin of high ketone bodies.

The ratio between CSF and blood β-OHB was rather high, reaching levels approximately twice those reported in fasted children older than 3 y of age (27). This increased ratio observed in our patients may be explained by the physiologically higher cerebral uptake of β-OHB in younger children (28–30).

Orally administered DL sodium β-OHB crosses the blood–brain barrier and accumulates in brain tissue. This could be clearly demonstrated by an increase of tissue concentration in basal ganglia on sequential MRS analysis at 1.25 ppm. Proton MR spectra measured at 3 T allow a higher signal to noise ratio

and better discrimination of peaks than spectra measured at 1.5 T, making analysis of our spectra most reliable. The slight decrease of the β-OHB signal at 60 min may be interpreted as short half-life of DL sodium β-OHB. Considering the persistence of high β-OHB concentrations in blood up to 3.5 h after oral administration, the early decrease of β-OHB levels in the brain could rather document a rapid clearance by cerebral utilization.

With regard to side effects, possible further stimulation of insulin secretion by accumulating β-OHB (13, 31) could be excluded in our two patients, as comparison of mean 1-mo blood glucose levels and frequency of hypoglycemic episodes revealed no significant differences between the periods before and during DL sodium β-OHB supplementation. Loss of appetite, as reported in rats (32) and in obese adults with high blood concentrations of β-OHB (33), could not be evaluated in our patients as both were on continuous tube feeding.

Ketogenic diet as applied in children with intractable epilepsy results in β-OHB levels in the blood that are usually much higher (>4 mM) (34) than those observed in our patients. Recently, in three patients receiving ketogenic diet, prolonged QT intervals were reported as the first adverse effect possibly directly associated with high blood concentrations of β-OHB, but simultaneously low bicarbonate levels were also observed (35). In our two patients, repeated ECGs showed normal QT intervals during the 5- and 7-mo period of supplementation.

It has been shown that children with symptomatic hypoglycemia have significantly lower ketone bodies than those who remain clinically asymptomatic (36–38). Evidence about the clinical benefit of orally supplemented DL sodium β-OHB in our two patients is limited by the short-term application of the substance. Patient 1 experienced recurrent symptomatic hypoglycemic episodes with generalized seizures before DL sodium β-OHB supplementation and 1 mo after supplementation had been stopped. During supplementation no seizures were observed despite similar frequency and severity of hypoglycemic episodes. In patient 2 repeated EEG records showed improvement of slow background activity, which persisted even after cessation of the add-on therapy with DL sodium β-OHB (results not shown). The neurologic outcome in patients with PHHI is of potential interest. Therefore neurologic variables should be end points in any future trial.

Achievement and maintenance of euglycemia remains the main goal in the treatment of PHHI. However, taking into account that a considerable proportion of patients suffer from recurrent hypoglycemic episodes despite vigorous treatment, add-on therapy with DL sodium β-OHB would complement a new therapeutic approach, by providing an alternative fuel for the brain during these attacks of hypoketotic hypoglycemia. In this observational study performed in two patients with PHHI, the fate of orally supplemented DL sodium β-OHB has been documented by increased concentrations of β-OHB in blood, CSF, and brain, as shown by cerebral *in vivo* proton MRS. At least in our two patients, DL sodium β-OHB did not seem to alter insulin secretion and was tolerated without side effects. This knowledge could provide the basis for further studies aimed at documenting the neuroprotective effect of orally supplemented β-OHB in conditions with hypoketotic hypoglycemia.

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