Sodium Oxybate Intolerance Associated with Familial Serum Acylcarnitine Elevation

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CASE REPORTS

Our case describes clinical features of two families defined by joint phenotypes: sodium oxybate intolerance and elevated serum acylcarnitines. Oxybate intolerance variably presents as either cervical dystonia or sleep-related eating disorder. Our objective is to identify biological markers which predict a poor response to sodium oxybate as a treatment for disturbed sleep. Familial inheritance pattern, genotype analysis, multiorgan system involvement, and response to treatment suggest the presence of a secondary cause of fatty oxidation defect,

i.e., mitochondrial disorder. Our case report supports the possible conclusion that variance in human mitochondrial metabolism may affect sodium oxybate tolerability.

Keywords: Mitochondria, pain, dystonia, sodium oxybate, gamma-hydroxybutyrate, narcolepsy, sleep-related sleeping disorder

Citation: Berner J. Sodium oxybate intolerance associated with familial serum acylcarnitine elevation. *J Clin Sleep Med* 2013;9(1):71-72.

Sodium oxybate is an approved treatment for narcolepsy and an off-label investigational treatment for refractory neurogenic pain disorders, e.g., fibromyalgia.¹ The clinical mechanism of action for sodium oxybate in pain patients is still unclear, but possibly relates to its activity as a GABA-B agonist.² Pain specialists commonly use the GABA-B agonist baclofen to treat spasticity associated with multiple sclerosis or low back pain.³

This simple model is not useful, however, in clinical practice where baclofen and oxybate are not interchangeable. Other mechanisms of sodium oxybate action may be involved, either its direct binding to γ -hydroxybutyric acid (GHB) receptors on the dendritic surfaces or indirectly by stoichiometric signaling in intracellular metabolic pathways.⁴

A full understanding of the side effect of sodium oxybate is underdeveloped. Although the package insert suggests against oxybate use in succinate semialdehyde dehydrogenase deficiency disorders (SSDH-), an enzyme in the pathway that oxidizes GABA in the mitochondria into succinic acid, this guideline is probably without practical clinical meaning, given that phenotypic diversity in this enzymatic defect is reportedly high. To expand that clinical database for relative contraindications for sodium oxybate use, we report two cases where oxybate intolerance may be related to a preexisting metabolic disorder.

REPORT OF CASES

Case 1: A 47-year-old female presented in 2003 with anxiety and fibromyalgia. She has been maintained for almost a decade on buspirone, methadone, and modafinil. Residual symptoms of broken sleep and excessive daytime sleepiness were addressed with an oxybate trial. Subjective response was excellent in terms of daytime cognitive clarity. This trial was subsequently terminated after weeks of progressively painful cervical dystonia.

Metabolic studies obtained one year following the trial given weakness in her daughter, revealed elevated medium acylcarnitines (C6-C10) in both mother and daughter. Clinical correlation and genetic testing for ACADM 985A > G and 199T > C variants suggested against a classical medium chain Acyl-CoA dehydrogenase deficiency. The mother also has additional mild elevations in other acylcarnitines (C4, C12, C14) and low free and total carnitine.

Case 2: A 10-year-old male presented with anxiety and narcolepsy with cataplexy in 2005. He was maintained with difficulty on both sertraline and sodium oxybate. Oxybate use for cataplexy was complicated by severe hyperphagic episodes. Twenty minutes after dosing, the patient would awaken from sleep with “giant pupils all happy,” and then eat until sleeping again. He often choked on the food in his mouth. If he was prevented access to food he would burst out crying. The family eventually switched out of necessity to sertraline for cataplexy, despite severe withdrawals if even one day’s dose was missed.

The patient presented again at age 15 for insidiously progressive chronic widespread pain requiring use of oxycodone and gabapentin. Given a maternal history of intermittent severe hypoglycemia, familial metabolic studies were performed. The son presented with elevated C6-C14 acylcarnitines. Glucose regulation was abnormal, with fasting glucose at low end of normal 76 incongruent with fasting insulin 11 at high end of normal. Post 4-h glucose challenge, glucose was 44. At this draw, family reported lethargy to the point where assistants were called to aid in standing and transferring for the car ride home. Mother’s studies revealed elevated C5-C16 acylcarnitines. Glucose regulation was less impaired but still marginally abnormal, with fasting blood sugar of 102 and 4-h subsequent to challenge of 67.

Further evaluation of the extended family at a tertiary metabolic center revealed narcolepsy with cataplexy in the mother and two siblings. The clinical impression was that the observed

fatty acid oxidation disorder was secondary to an underlying mitochondrial disorder given multiple features: (1) broad non-specific multiorgan involvement including fatigue, myopathic and gastrointestinal pain, poor exercise tolerance, tremors, nausea, and poor clearance of community infections; (2) maternal inheritance pattern; (3) absence of common associated urine organic acid abnormalities; and (4) broad symptomatic response in all family members to coenzyme Q10 and carnitine.

DISCUSSION

There is no direct proof that metabolic disturbance implied by the observed serological abnormalities directly causes oxybate/GHB intolerance. Clinical experience with known metabolic disorders, however, suggests a possible causal relationship. A major metabolite of sodium oxybate/GHB, D-2-hydroxyglutaric acid, acts as an endogenous uncoupling agent of mitochondrial respiration, reducing cell viability in rat cerebral cortex slices.⁵ Note that the peculiar side effect of Case 1, isolated change in cervical muscle tone, suggests a diagnosis of mitochondrial flavin and flavoprotein homeostasis.⁶ Acute changes in central feeding behavior in Case 2, described previously in another case report by other authors,⁷ do not clearly correspond closely to a known single metabolic syndrome. However, in a poly-genetic syndrome, insulin-resistance, consistent with an inappropriately high fasting insulin/glucose seen in Case 2, arcuate nucleus neurons driving central feeding behavior are known to have multiple intracellular metabolic abnormalities⁸: increased reactive oxygen species after low glucose load, a constitutive oxidized environment, and overexpression of several mitochondrial subunits of the respiratory chain.

The cases suggest further clinical efforts to characterize mild SSDH- phenotypes and/or elaborate on genetic polymorphisms related to oxybate metabolism. Preclinical research describing sodium oxybate effect in knockout animals with individ-

ual electron chain transport complex defects and/or control elements of mitochondrial biogenesis/mitophagy might more clearly illustrate the causality of the observed human sodium oxybate side intolerance.

REFERENCES

1. Russell IJ, Perkins AT, Michalek JE, et al. Sodium oxybate relieves pain and improves function in fibromyalgia syndrome. *Arthritis Rheum* 2009;60:299-309.
2. Vienne J, Bettler B, Franken P, Tafti M. Differential effects of GABA-B receptor subtypes, gamma hydroxybutyric acid, and baclofen on EEG activity and sleep regulation. *J Neurosci* 2010;30:14194-204.
3. Aisen ML, Dietz MA, Rossi P, et al. Clinical and pharmacokinetic aspects of high dose baclofen therapy. *J Am Paraplegia Soc* 1992;15:211-6.
4. Kemmel V, Miehe M, Roussel G, et al. Immunohistochemical localization of a GHB receptor-like protein isolated from rat brain. *J Comp Neurol* 2006;498:508-24.
5. Latini A, da Silva CG, Ferreira GC et al. Mitochondrial energy metabolism is markedly impaired by D-2 hydroxyglutaric acid in rat tissues. *Mol Genet Metab* 2005;86:188-99.
6. Olsen RKJ, Olpin SE, Andreson BS, et al. ETFH mutations as a major cause of riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency. *Brain* 2007;130:2045-54.
7. Wallace DM, Maze T, Shafazand S. Sodium oxybate induced sleep driving and sleep-related eating disorder. *J Clin Sleep Med* 2011;7:310-11.
8. Colombani A, Carneiro L, Benani A, et al. Enhanced hypothalamic glucose sensing in obesity: alteration of redox signaling. *Diabetes* 2009;58:2189-97

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February, 2012

Submitted in final revised form May, 2012

Accepted for publication May, 2012

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DISCLOSURE STATEMENT

Dr. Berner has indicated no financial conflicts of interest.