ECRONICON OPEN ACCESS

EC CLINICAL AND MEDICAL CASE REPORTS
Research Article

Adjunctive Applications with Exogenous Riboflavin Supplementation in the Rare Riboflavin Transporter Deficiency (RTD) Disorder

Christopher C Ukpong[1,2] and Nicholas A Kerna[3]*

[1]*University of Science, Arts and Technology, BWI*

[2]*University of Health and Humanities, BVI*

[3]*SMC-Medical Research, Thailand*

***Corresponding Author**: Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand. Contact: medpublab+drkerna@gmail.com

Received: November 29, 2019; **Published:** November 29, 2019

DOI: 10.31080/eccmc.2019.2.00128

Abstract

Riboflavin transporter deficiency (RTD) is a progressive neurodegenerative disease. As a genetic condition, there is currently no known cure; exogenous riboflavin supplementation is indicated. The effective results of riboflavin supplementation are based on early diagnosis and a short time interval between diagnosis and initiation of treatment. With a small RTD-subgroup exception, the exogenous supplementation of riboflavin is effective in managing early symptoms of RTD. However, other adjuncts, such as probenecid, CoQ10, glutathione, acylcarnitine, and antacids, might be considered not only to address exogenous riboflavin-supplemented responders but also to enhance outcomes in the RTD subgroups that respond favorably to exogenous riboflavin supplementation.

Keywords: *Antacids; Child Onset; Genetic; Neurodegenerative; Probenecid; Riboflavin; Vitamin B2*

Abbreviations

ACAD: Acyl-Coenzyme A Dehydrogenase; CAM: Complementary and Alternative Medicine; CoQ10: Coenzyme Q10; EGRAC: Erythrocyte Glutathione Reductase Activity Coefficient; OAT: Organic Anion Transporters; ROS: Reactive Oxidative Species; RTD: Riboflavin Transporter Deficiency; SLC52A2: Solute Carrier 52A2; SLC52A3: Solute Carrier 52A3

Introduction

Riboflavin transporter deficiency (RTD) is a rare genetic disorder. According to Manole and Houldren (2015): "Riboflavin transporter deficiency is a progressive neurodegenerative disease characterized by paralysis of the cranial nerves, sensorineural deafness, and signs of damage to other nerves. Symptoms may begin from infancy to early adulthood and worsen over time" [1]. Although there is currently no cure for RTD, supplementation with riboflavin is considered by many healthcare practitioners a life-saver, particularly for children with RTD.

A small percentage of RTD-patients do not respond favorably to oral riboflavin supplementation. This variation in response to riboflavin supplementation can be explained partly by the time therapy begins relative to the time a definitive diagnosis is made. The earlier the diagnosis-and the sooner therapy begins following the diagnosis-the better the prognosis. However, a small percentage of RTD-positive patients do not respond favorably even with a proximal diagnosis-treatment interval; thus, other factors must be at play and need further investigation.

With this unique subgroup of riboflavin-nonresponders in mind, acyl-L-carnitine, coenzyme Q10 (CoQ10), and glutathione are being considered as adjuncts with riboflavin supplementation in the treatment of RTD. Antacids and probenecid, with their effect on the riboflavin absorption, are also being considered.

Discussion

RTD is a rare, neurodegenerative disease [2,3]. Generally, it presents in childhood in an autosomal recessive pattern. Thus, for a child to display the phenotypic symptoms of RTD, each parent must be a carrier of the mutated gene—the child has two mutated genes, one from each parent. RTD was largely undiagnosed or missed diagnosed until 2010 when the first documented case was published.

Currently, there are three types of RTD: riboflavin transporter deficiency type 1, riboflavin transporter deficiency type 2, and riboflavin transporter deficiency type 3. RTD type 2 and RTD type 3 are due to mutations of solute carrier 52A2 (SLC52A2) gene and solute carrier 52A3 (SLC52A3) gene, respectively [2,3]. These two mutated genes lead to the malfunctioning of RFVT2 and RFVT3 protein transporters. Exome sequencing has identified a mutation of SLC52A1, which affects the functioning of RFVT1 [3]. However, RFVT1 deficiency (and therefore RTD type 1) is not implicated in the pathology of RTD. It is the deficiency of RFVT2 and RFVT3 transporters that leads to pathology in RTD [2].

Riboflavin is a water-soluble vitamin (B2) that is not synthesized in the body. It is generally supplied exogenously from diet and, to a lesser extent, from the intestinal microflora [3]. In RTD, riboflavin entry into the cell is impeded, resulting in the decreased availability of FAD and FMN in the cell. RTD is a neuropathy that can destabilize the homeostatic cellular environment, leaving it susceptible to reactive oxidative species (ROS). Excess ROS, such as hydrogen peroxide and superoxide, are free radicals that can negatively impact the metabolic efficiency of the mitochondria, compounding the challenges of managing this disorder [4].

Studies have shown that flavin vitamins (e.g., vitamins B2 and B6)—acting as enzyme cofactors—play significant roles in redox processes that neutralize the reactive ability of specific free radicals. The collective roles of these coenzymes have demonstrated therapeutic effects in the management of many neurodegenerative diseases, both as coenzymes and antioxidants. Thus, it seems clinically-prudent to examine the potential of glutathione, CoQ10, and acyl-L-carnitine as adjuncts to riboflavin supplementation in the management of RTD.

Riboflavin supplementation: a current treatment approach

Riboflavin supplementation is the standard treatment for RTD [11,13]. It has been effective in ameliorating the symptoms of RTD in most patients. However, there remains a small percentage of patients with RTD whose symptoms are not relieved by riboflavin supplementation. Thus, the variability in the effectiveness of riboflavin supplementation may depend on several factors not yet fully understood. Given what is known to date about RTD and riboflavin supplementation, the effectiveness of this supplementation may depend on bioavailability and intracellular dynamics between riboflavin (FAD and FMN) and flavoenzymes. This effectiveness (or lack thereof) might be impacted by the degree of damage to transporters (RFVT2 and RFVT3), the variability of intestinal factors, and the quality of the supplements, among others.

The stage of the disorder and the time between diagnosis and treatment are well-documented and significant elements in treatment outcome. Studies have shown that if a person receives the treatment weeks or even months after the initial symptoms, those symptoms usually diminish or, in some cases, vanish altogether. Thus, the earlier treatment is implemented, the higher the likelihood of a better treatment outcome. However, as stipulated previously, there is currently no cure for RTD; any successful symptom reduction is palliative, not curative.

CoQ10 as an adjunct therapy for RTD

Coenzyme Q10 (CoQ10), also referred to as ubiquinone, plays a role of cofactor as well as antioxidant in cellular metabolism. Its role as an electron carrier in the mitochondrial respiratory change results in a reduced form, thereby allowing it to function as an antioxidant as well [5,6]. CoQ10's functional ability as an electron carrier depends on flavin-linked dehydrogenase enzymes [6]. It is at this functional

crossroads between dehydrogenase dependency on flavin and CoQ10 dependency on flavin-linked dehydrogenase that a case can be made for its suitability as an adjunct treatment for a flavin-related neurodegenerative disorder, such as RTD.

Glutathione as an adjunct therapy for RTD

Glutathione is a cofactor of the flavin enzyme (glutathione reductase), which participates with ROS, such as hydrogen peroxide [7]. Research has shown that RTD predisposes the body to oxidative stress, resulting in free radicals. In an optimal physiologic environment, free radicals are neutralized by endogenous antioxidants. However, in the pathologic state of RTD, endogenous antioxidants are insufficient and ineffective. Thus, the dependency of glutathione reductase on FAD could affect its function in RTD.

Glutathione supplementation could reinvigorate the antioxidant machinery and mitigate damage by free radicals [7,8]. Whether or not oral supplementation is useful in this regard remains under consideration. Erythrocyte glutathione reductase activity coefficient (EGRAC) is a sensitive and stable means of determining riboflavin deficiency in vitro. However, the reliability of this method has come under scrutiny.

Acyl-L-carnitine as an adjunct therapy for RTD

L-carnitine (3-hydroxy-4-N-trimethylaminobutyrate) is a fatty acid transporter that occurs naturally and is present in all mammals. Acyl-L-carnitine is an L-carnitine supplemented exogenously [9]. In the cell, fatty acid is converted into acyl-CoA, carried into the inner mitochondria by acyl-L-carnitine, and catabolized by acyl-coenzyme A dehydrogenase (ACAD) [5]. ACAD has tightly bound FAD as a prosthetic group, which enables it to play a role in the fatty acid oxidative cycle. A deficiency of this dehydrogenase enzyme in the beta-oxidative pathway leads to the accumulation of an acyl-L-carnitine substrate in the cell [8-10]. This outcome presents a complicated clinical picture in the management of the RTD symptoms.

Thus, it is conceivable that RTD—which typically leads to reduced cellular FAD—could affect the functionality of ACAD that depends on FAD as its coenzyme. This rationale justifies a theoretical case in favor of acyl-L-carnitine as a viable supplement in the adjunct treatment of RTD. Further research and clinical studies on this specific topic are necessary.

Biochemical precautions in the management of RTD

The molecular hallmark of RTD is the deficiency of protein transporters and active riboflavin metabolites (FAD and FMN). Supplementation with riboflavin yields an effective therapeutic outcome in most RTD patients, which suggests a bioavailability issue. RTD as a neurodegenerative disorder is a relatively novel discovery, and much about this neuropathy remains unknown. Thus, clinical prudence is indicated when treating children with suspected RTD. When RTD is suspected, it is advised that riboflavin supplementation be implemented while awaiting genetic testing results.

An infant with a suspected or confirmed vitamin B2 deficiency should not be exposed to prolonged phototherapy or extended periods in sunlight. Research has shown that light rapidly destroys vitamin B2.

Also, it is crucial to recognize the adverse effect of certain antibiotics. Aminoglycosides, such as gentamicin, tobramycin, neomycin, streptomycin, amikacin, and plazomicin, may exacerbate or even precipitate the development of hearing loss [2,3]. One of the major symptoms of RTD is sensorineural deafness. The implied clinical warning is to manage RTD patients who are receiving aminoglycosides with due observation and caution.

The possible role of antacids in RTD

Another class of drug that must be used with caution in patients with RTD is the antacids. There are three classes of antacids: calcium-based, aluminum-based, and magnesium-based.

Calcium carbonate antacids carry a high risk of drug toxicity due to their ability to alkalinize the urine, slowing its excretion and increasing the retention time of the drug metabolite in the body. The release of carbonate during its reaction with stomach hydrochloric acid is responsible for this complication [6,7]. Also, calcium slows GI motility, delaying the passage of the drug through the GI tract.

Similarly, aluminum-based antacids decrease stomach motility, leading to prolonged absorption. In theory, both calcium-based and aluminum-based antacids have the potential to aid in the enhanced rate of absorption of riboflavin. However, since the principal problem with RTD does not necessarily concern riboflavin bioavailability—instead, transporter functionality—this possible pathway needs further investigation.

Conversely, magnesium-based antacids facilitate rapid stomach motility and pose a risk of decreased drug absorption due to the accelerated transition time [6]. Vitamin B2 requires stomach acid for optimal absorption; rapid transition through the stomach can theoretically affect its rate of absorption. This transition-factor also holds true for medications that require prolonged intestinal contact for absorption.

The role of probenecid in RTD

Probenecid is a class of medications generally referred to as uricosurics. As the body breaks down purines (amino acids), uric acid is formed as the final product of that process, and the kidneys filter it for excretion. However, there is reuptake of about 90% of the uric acid by organic anion transporters (OAT). Probenecid plays a role in renal tubular excretion and secretion of uric acid and antibiotics, respectively [11].

It is probenecid's action as an inhibitor of renal tubular secretion of antibiotics that warrants its inclusion in this review. Although the mechanism of action is not clearly stated, it is believed that its action increases efficacy of the drugs and decreases their volumes of distribution. Thus, it can be hypothesized that if probenecid is coadministered with riboflavin, kidney excretion of riboflavin might be reduced, thereby increasing its plasma concentration.

According to pharmaceutical research, a 40–60 ug/ml concentration of probenecid in the plasma can cause inhibition of kidney penicillin excretion [11-13]. Conversely, a plasma concentration of 100–200ug/ml of probenecid will have a uricosuric-type effect. Thus, to have a synergistic effect for riboflavin, the plasma concentration of probenecid must be considerably small (Figure 1).

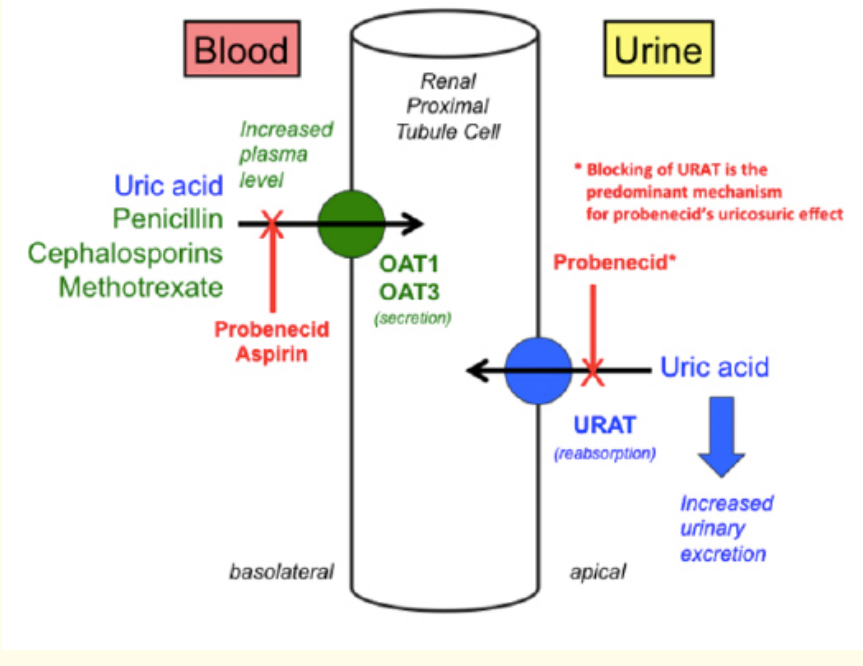

Figure 1: *A depiction of the inhibitory role of probenecid at the renal tubular. This action can potentially increase the plasma concentration of riboflavin. Note. TMedWeb. Medical Pharmacology, Tulane University School of Medicine [14].*

Conclusion

Riboflavin transporter deficiency is a rare, genetic, neurodegenerative disease, currently having no cure. The challenge to manage and treat neurodegenerative diseases, such as RTD, may help forge a clinical alliance among CAM and conventional medicine. RTD treatment is based primarily on exogenous riboflavin supplementation. However, supplements should be considered not only in the palliative treatment of RTD but also as conjunctive therapy. Probenecid, CoQ10, glutathione, acylcarnitine, and antacids might be considered as possible adjuncts in the treatment of riboflavin transporter deficiency. Further studies are needed to confirm the practical applications of these synergistic therapies.

Conflict of Interest

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

References

1. Manole A and H Houlden. "Riboflavin Transporter Deficiency Neuronopathy". *GeneReviews* (2015).
2. Nigam SK., *et al*. "The organic anion transporter (OAT) family: a systems biology perspective". *Physiological Reviews* 95.1 (2015): 83–123.
3. Rahman K. "Studies on free radicals, antioxidants, and co-factors". *Clinical Interventions in Aging*, 2.2 (2007): 219–236.
4. Singh P and Terrell JM. "Antacids". *In StatPearls* (2019).
5. Moriyama Y. "Riboflavin transporter is finally identified". *Journal of Biochemistry* 150.4 (2011): 341–343.
6. Spindler M., *et al*. "Coenzyme Q10 effects in neurodegenerative disease". *Neuropsychiatric Disease and Treatment* 5 (2009): 597–610.
7. Longo N., *et al*. "Carnitine transport and fatty acid oxidation". Biochimica et Biophysica Acta, 1863.10 (2016): 2422–2435.
8. Tsim, K., *et al*. "Application of Complementary and Alternative Medicine on Neurodegenerative Disorders: Current Status and Future Prospects". *Evidence-Based Complementary and Alternative Medicine* (2012).
9. Lobo V., *et al*. "Free radicals, antioxidants and functional foods: Impact on human health". *Pharmacognosy Reviews* 4.8 (2010): 118–126.
10. Knottnerus SJG., *et al*. "Disorders of mitochondrial long-chain fatty acid oxidation and the carnitine shuttle". *Reviews in Endocrine & Metabolic Disorders* 19.1 (2018): 93–106.
11. Greene TA., *et al*. "Probenecid Inhibits the Human Bitter Taste Receptor TAS2R16 and Suppresses Bitter Perception of Salicin". *PLoS ONE* 6.5 (2011).
12. Mancuso M., *et al*. "Coenzyme Q10 and Neurological Diseases". *Pharmaceuticals* 2.3 (2009): 134–149.
13. Powers HJ. "Riboflavin (vitamin B-2) and health". *The American Journal of Clinical Nutrition* 77.6 (2003): 1352–1360.
14. TMedWeb. Medical Pharmacology, Tulane University School of Medicine [15].

Volume 2 Issue 9 December 2019