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A New Old Treatment for Vitamin E Deficiency in Cholestasis

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Back in the 1980's, as infants and children with chronic cholestatic hepatobiliary disorders began to survive longer, it became evident that secondary nutritional deficiencies were causing major morbidity, and even mortality (e.g., intracranial hemorrhage from vitamin K deficiency). The observations of the neurologic effects of vitamin E deficiency first made in patients with abetalipoproteinemia were soon expanded to chronic cholestasis and cystic fibrosis liver disease (CFLD) patients (1). Malabsorption and subsequent deficiency of vitamin E (alpha tocopherol) was no longer a biochemical curiosity but rather a direct cause of a crippling progressive cerebellar ataxia, which had been described in non-human primates. This neurologic disease resembled many facets of Friedreich's ataxia, however was characterized by an axonal dystrophy, posterior column degeneration, and cerebellar and cranial nerve nuclei central nervous system lesions (1) with first symptoms of diminished deep tendon reflexes beginning in the first year of life and other signs of ataxia and peripheral neuropathy progressing over the first decade (2,3). Detecting vitamin E deficiency was hampered by the apparently normal serum levels of vitamin E in severely cholestatic patients with hyperlipoproteinemia (3). Because vitamin E is exclusively carried in serum lipoproteins, calculating ratios of serum alpha tocopherol to serum lipid levels to adjust for hyperlipidemia evolved as the preferred manner to detect deficiency during cholestasis (3).

Attempts at treating or preventing the vitamin E deficiency with huge doses of oral alpha tocopherol preparations (> 100 IU/kg/day) were limited by the highly hydrophobic nature of tocopherols and the severely diminished intraluminal bile acid concentrations in patients with biliary atresia, Alagille syndrome, progressive familial intrahepatic cholestasis (PFIC) and CFLD, among others. There simply were not adequate intraluminal concentrations of bile acids to form micelles and to solubilize alpha tocopherol (2). Consequently, intramuscular injections of investigational forms of alpha tocopherol were studied and shown to reverse or prevent progression of neurologic symptoms once the ataxic neuropathy was established, and to prevent neurologic abnormalities if begun early in life (4). However, the injections were painful, required frequent administration, and no parenteral form of vitamin E was ever approved for use in the United States. Therefore, exploration of new solubilized forms of vitamin E ensued. Alpha tocopheryl acetate was not found to be

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sufficiently water-soluble to overcome the intraluminal bile acid deficiency during cholestasis.

In the mid-1980's, Dr. Harry Greene, then at Vanderbilt University, mentioned to me that a polyethylene glycol (PEG) ester form of vitamin E in infant formulas might be sufficiently water-soluble to be absorbed in cholestasis. This substance, D-alpha tocopheryl PEG-1000 succinate (TPGS; tocophersolan), manufactured by Eastman Chemical Products (Kingsport TN) at the time, linked PEG-1000 to D-alpha tocopherol through a succinate ester bridge, allowing TPGS to form its own micelles at low concentrations owing to its amphipathic structure, and hence might not require the presence of bile acids. Clinical trials of TPGS in cholestatic infants and children were conducted first in Colorado (5), and then expanded to a larger trial involving 60 children at 8 sites in the United States (6). Remarkably, an oral solution of TPGS was shown to be absorbed in virtually all cholestatic children, to correct the biochemical deficiency of vitamin E, and to reverse (if not too advanced) and prevent the clinical signs of the axonal neuropathy and ataxia (5, 6). Co-administration of TPGS was also found to enhance intestinal absorption of other lipid soluble compounds (vitamin D and cyclosporine) in cholestasis, and has been used to enhance absorption of other lipid soluble drugs. Small amounts of the PEG in TPGS may be absorbed but have not been associated with any adverse effects; caution in renal failure has also been advised.

For the past 20 years TPGS has been available in United States in two health food company over-the-counter preparations, Liqui-E (25 IU/ml; Twinlab, Hauppauge, NY) and Aqua-E (20 IU/ml; formerly from Yasoo Health, Johnson City, TN, now from A.C. Grace, Big Sandy, TX). However, not infrequently shortages of these preparations, as well as corporate decisions about maintaining these product lines, have led to intermittent limited or non-availability of TPGS for patients who have no other effective means to prevent vitamin E deficiency. Unfortunately, there is no FDA approved TPGS preparation in the U.S. In contrast, European Medicines Agency recently approved an oral liquid preparation of TPGS that is marketed in multiple European countries as Vedrop (25 IU/ml of D-alpha tocopherol). In this issue of the Journal, Thebaut et al. (7) report on the results of a phase 4 European registry, and demonstrate the long-term effectiveness of 25 IU/kg/day of this oral preparation in correcting or preventing biochemical vitamin E insufficiency in 274 children from 7 centers in 4 countries with various causes of chronic cholestasis. No safety concerns were identified, confirming prior trials (6). Vitamin E sufficiency was restored in 89% of those with insufficient status at baseline, and all who had normal baseline vitamin E status maintained such at 6 months of treatment. There were several notable exceptions, however. In the 26 children with PFIC, sufficient vitamin E status was restored in only 69% at 3 months of treatment and 62% at 6 months. Moreover, only 11 of 16 patients with partial biliary diversions had restoration of normal vitamin E status, most of which probably had PFIC. Assuming that adherence to the Vedrops regimen was similar in these children compared to the other cholestatic subjects, this highlights that PFIC and Alagille syndrome patients following partial biliary diversion may be at *increased* risk of developing fat-soluble vitamin deficiency despite improvement in their cholestasis, as a large proportion of bile may be discarded from the stoma leading to low intraluminal concentrations. In addition, some of the PFIC patients received a bile acid binding resin which may also further diminish the capacity of bile acids to form micelles.

Thus, clinicians need to be vigilant in following serial serum parameters of vitamin E and other fat-soluble vitamin status in cholestatic patients following biliary diversion procedures and to adjust supplements with individual vitamins as needed. It has been well demonstrated that multiple vitamin preparations designed for patients with malabsorption (even those that contain TPGS!) do not contain adequate amounts of all fat soluble vitamins to prevent deficiency during persistent cholestasis (8). All fat soluble vitamin supplements are best administered in the morning (when bile flow may be maximal), with a meal and in the absence of bile acid binding drugs or pro-oxidants (such as iron sulfate).

The European Community now has an approved medicinal form of TPGS that should prevent vitamin E deficiency in the large majority of cholestatic children. In the United States we are beholden to the good nature of health food companies for the provision of TPGS for our patients. Should we not be pushing for approval of a medicinal form of TPGS by the FDA to ensure long-term availability of this critically important therapy for prevention and reversal of the devastating neurologic consequences of vitamin E deficiency in children with chronic cholestasis?

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References

1. Rosenblum JL, Keating JP, Prensley AL, Nelson JS. A progressive neurologic syndrome in children with chronic liver disease. *N Engl J Med*. 1981; 304:503–8. [PubMed: 7453784]
2. Sokol RJ, Heubi JE, Iannaccone ST, Bove KE, Balistreri WF. Mechanism causing vitamin E deficiency during chronic childhood cholestasis. *Gastroenterology*. 1983; 85:1172–1182. [PubMed: 6618108]
3. Sokol RJ, Heubi JE, Iannaccone ST, Bove KE, Balistreri WF. Vitamin E deficiency with normal serum vitamin E concentrations in children with chronic cholestasis. *N Engl J Med*. 1984; 310:1209–1212. [PubMed: 6709026]
4. Sokol RJ, Guggenheim MA, Iannaccone ST, Miller CA, Silverman A, Balistreri WF, Heubi JE. Improved neurologic function after long-term correction of vitamin E deficiency in children with chronic cholestasis. *N Engl J Med*. 1985; 313:1580–1585. [PubMed: 4069170]
5. Sokol RJ, Heubi JE, Butler-Simon N, McClung HJ, Lilly JR, Silverman A. Treatment of vitamin E deficiency during chronic childhood cholestasis with oral d- α -tocopheryl polyethylene glycol-1000 succinate. *Gastroenterology*. 1987; 93:975–985. [PubMed: 3653646]
6. Sokol RJ, Butler-Simon N, Conner C, Heubi JE, Sinatra F, Suchy F, Heyman MB, Perrault J, Rothbaum RJ, Levy J, Iannaccone ST, Shneider B, Rosenblum JL, Koch T, Narkewicz MR. Multicenter trial of D- α -tocopheryl polyethylene glycol-1000 succinate for treatment of vitamin E deficiency in children with chronic cholestatic liver disease. *Gastroenterology*. 1993; 104:1727–1735. [PubMed: 8500733]
7. Thebaut A, Nemeth A, Le Mouhaer J, Scheenstra R, Baumann U, Koot B, Gottrand R, Houwen R, Monard L, de Micheaux SL, Habes D, Jacquemin E. Oral Tocoferolan corrects or prevents vitamin E deficiency in children with chronic cholestasis. *J Pediatr Gastroenterol Nutr*. 2016 IN PRESS.
8. Shneider BL, Magee JC, Bezerra JA, Haber B, Karpen SJ, Raghunathan T, Rosenthal P, Schwarz K, Suchy FJ, Kerkar N, Turmelle Y, Whitingotn PF, Robuck PR, Sokol RJ. for the Childhood Liver Disease Research and Education Network (ChILDREN). Efficacy of fat soluble vitamin supplementation in infants with biliary atresia. *Pediatrics*. 2012; 130:e607–614. [PubMed: 22891232]