REVIEW

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Does Long-Term Furosemide Therapy Cause Thiamine Deficiency in Patients with Heart Failure? A Focused Review

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ABSTRACT

Diuretic therapy is a cornerstone in the management of heart failure. Most studies assessing body thiamine status have reported variable degrees of thiamine deficiency in patients with heart failure, particularly those treated chronically with high doses of furosemide. Thiamine deficiency in patients with heart failure seems predominantly to be due to increased urine volume and urinary flow rate. There is also evidence that furosemide may directly inhibit thiamine uptake at the cellular level. Limited data suggest that thiamine supplementation is capable of increasing left ventricular ejection fraction and improving functional capacity in patients with heart failure and a reduced left ventricular ejection fraction who were treated with diuretics (predominantly furosemide). Therefore, it may be reasonable to provide such patients with thiamine supplementation during heart failure exacerbations.

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KEYWORDS: Furosemide; Heart failure; Thiamine; Thiamine deficiency

Heart failure is an important public health problem affecting more than 5 million persons in the United States and 23 million individuals worldwide.[1] The prevalence of this condition in the United States is steadily increasing with approximately 650,000 new cases diagnosed each year.[1,2] Heart failure hospitalizations in the United States also continue to increase and now exceed more than 1 million per year.[1,3] Diuretics commonly are used to reduce dyspnea and peripheral edema in both acute and chronic heart failure. Furosemide is the most frequently prescribed loop diuretic. Common side effects of furosemide therapy include hypovolemia and electrolyte depletion. Multiple studies have suggested that long-term furosemide therapy also may cause thiamine (vitamin B1) deficiency, although the exact mechanism remains unclear.[4-8] Thiamine deficiency has been known to cause a clinical cardiac syndrome known as "wet beriberi." Wet beriberi is a high cardiac output form of heart failure characterized by tachycardia, dyspnea, and peripheral edema.[3,9] In its severe form, thiamine deficiency can cause fulminant heart failure termed "shoshin beriberi," with signs of cardiovascular collapse, metabolic acidosis, and severe hemodynamic instability.[3,10] In the absence of urgent treatment with intravenous thiamine, death may ensue.[3,10] It is important for physicians to be aware that furosemide may cause thiamine deficiency and potentially cause worsening of preexistent heart failure.

The major dietary sources of thiamine are unprocessed rice, wheat germ, cereal grains, nuts, seeds, liver, beef, pork, poultry, fish, orange juice, and tomato juice.[3,11,12] In contrast, dairy products, fruits, and most vegetables are low in thiamine content.[3,11,12] Animals are prone to thiamine deficiency because they do not synthesize or store a sufficient amount of thiamine and therefore are dependent on regular dietary intake.[3,12] According to the 1980 Committee on Dietary Allowance, Food, and Nutrition Board, the recommended daily allowance of thiamine for adults aged $\geq$19 years is 1.2 mg per day for men and 1.0 mg per day for women.[13]

Thiamine deficiency clearly is an important health care problem in underdeveloped countries. However, it is not uncommon to encounter thiamine deficiency in developed

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countries. According to the Boston Nutritional States Survey, 15% of an elderly population who did not receive thiamine supplements had low thiamine levels.[14] Institutionalization and poverty have been associated with poor thiamine intake in the elderly.[15,16] Other independent risk factors for thiamine deficiency include excessive alcohol intake, malabsorption and eating disorders, various catabolic diseases, trauma, surgery, prolonged nausea and vomiting, and frequent use of processed foods.[3,11,15,16] A variety of drugs have been associated with thiamine deficiency, including antibiotics (penicillins, cephalosporins, fluoroquinolones, tetracyclines, sulfa-containing drugs, aminoglycoside) and phenytoin.[3] As a water-soluble vitamin, thiamine is excreted in the urine. Thus, it is not surprising that multiple studies have suggested that diuretics may facilitate thiamine deficiency.[3,5-8,12] Because diuretics, and in particular the loop diuretic furosemide, represent the cornerstone of pharmacotherapy of heart failure, it has been postulated that their long-term use may cause thiamine deficiency, thereby reducing ventricular function with a subsequent worsening of heart failure symptoms and signs. Indeed, various studies have reported the prevalence of thiamine deficiency in patients with heart failure to range from 0% to 98%.[3] The wide variation in prevalence values may reflect variability in age, risk factors, dietary intake, and severity of heart failure.

This is a focused review of the interrelationship of furosemide use, thiamine deficiency, and heart failure. We discuss the pathophysiology and biochemistry of thiamine deficiency as they relate to heart failure in patients receiving furosemide therapy, describe the results of clinical and experimental studies that address the relation of furosemide therapy and thiamine deficiency, and provide recommendations concerning the role of thiamine in the prevention and management of heart failure in patients receiving furosemide therapy. This focused review used a MEDLINE search using the terms "thiamine deficiency," "furosemide," and "heart failure" to identify relevant articles from the past 25 years. A total of 24 articles were identified that met the search criteria.

BIOCHEMICAL CONSIDERATIONS

Thiamine is a water-soluble vitamin that is present in the body in an unphosphorylated form and as a monophosphate, diphosphate, and triphosphate. Thiamine plays a vital role in numerous cellular functions. The most important of those related to the heart involve thiamine diphosphate, also known as "thiamine pyrophosphate." In the pentose phosphate pathway, thiamine pyrophosphate serves as a coenzyme to transketolase, facilitating the conversion of glucose-6-phosphate to ribose-5-phosphate, which in turn contributes to nucleic acid synthesis. In the citric acid (Kreb's) cycle, thiamine pyrophosphate serves as a coenzyme to the pyruvate dehydrogenase complex in the conversion of pyruvate to acetyl coenzyme A and then to alpha-ketoglutarate. Thiamine pyrophosphate also serves as a coenzyme to alpha-ketoglutarate dehydrogenase in the conversion of alpha-ketoglutarate to succinate, which facilitates adenosine triphosphate production.

CLINICAL SIGNIFICANCE

- Thiamine deficiency has been demonstrated to contribute to the development of heart failure.
- Loop diuretics commonly are used to treat heart failure.
- Furosemide therapy has been shown to produce thiamine deficiency.
- Thiamine supplementation may increase left ventricular ejection fraction and improve function capacity in patients with systolic heart failure.

QUANTIFYING BODY THIAMINE STATUS

Various laboratory tests are available to quantify body thiamine status. These include tests that directly measure thiamine levels in the serum, plasma, and urine, as well as high-performance liquid chromatography.[3] Other laboratory tests provide an indirect estimation of thiamine status, including the thiamine pyrophosphate effect. The thiamine pyrophosphate effect measures erythrocyte ketolase activity when thiamine diphosphate is added to serum in vitro.[3,17] This is an actual representation of tissue thiamine level. Measurement of thiamine pyrophosphate effect is widely available.[3,18] Thiamine pyrophosphate effect $>15\%$ suggests that thiamine deficiency is present, and thiamine pyrophosphate effect $>25\%$ suggests that severe thiamine deficiency is present.[19] The urine thiamine level provides information about the adequacy of thiamine intake, but does not quantify tissue thiamine stores.[19] The plasma or serum thiamine level does not accurately represent body thiamine status because it contains only a fraction of total body thiamine.[19]

EFFECT OF FUROSEMIDE ON BODY THIAMINE STATUS

In 1980, Yui et al[7] reported that thiamine deficiency may result from a long-term decrease in transketolase activity and serum thiamine levels, and a surge in thiamine pyrophosphate effect in rats treated with intraperitoneal administration of furosemide for 4 weeks.

A study reported by Seligmann et al[6] in 1991 suggested that urinary loss of thiamine may be the main cause for thiamine deficiency related to chronic diuretic therapy in patients with heart failure. Twenty-three patients with heart failure who were treated with furosemide (80-240 mg per day) for 3 to 14 months were found to have thiamine deficiency compared with 16 individuals who did not have heart failure and did not receive furosemide. There was a significantly higher mean thiamine pyrophosphate effect in the furosemide-treated group compared with a control group