



## Benfotiamine

### Introduction

Neurological disorders, particularly diabetic neuropathy, have been treated with vitamin B1 (thiamine) for decades; however, the bioavailability of orally administered, water-soluble thiamine salts is low compared to fat-soluble analogs. For treatment to be successful, high levels of thiamine are needed in both blood and tissues. In 1954, Fujiwara discovered a group of lipid-soluble thiamine derivatives, subsequently named allithiamines because they occur naturally in Allium family vegetables – roasted, crushed garlic, onions, leeks, shallots, etc. Of these, benfotiamine is the most effective and has an excellent safety profile. Oral administration of benfotiamine raises thiamine levels in blood and tissues to a much higher degree than the water-soluble salts. Benfotiamine also inhibits three major biochemical pathways implicated in diabetes-induced vascular damage and neuropathy. In addition to diabetic neuropathy, benfotiamine appears to be of value in treating diabetic retinopathy and nephropathy. It has also been shown to have beneficial effects in patients with end-stage renal disease and alcoholic neuropathy.

### Biochemistry and Pharmacokinetics

Unlike thiamine, benfotiamine's structure contains an open thiazole ring that closes once it is absorbed, producing biologically active thiamine. Several clinical trials in healthy adults have demonstrated the superior absorption of lipid-soluble thiamine analogues, such as benfotiamine, compared to water-soluble thiamine salts. Higher plasma thiamine levels are achieved with oral benfotiamine administration, and blood and tissue concentrations are maintained longer. Oral benfotiamine dosages in these studies ranged from 40-250 mg daily.<sup>1-3</sup>

Benfotiamine is absorbed via passive diffusion through the intestinal mucosa and is rapidly converted to biologically active thiamine. Peak plasma concentrations of thiamine after oral benfotiamine administration are at least five times greater than those observed after oral administration of water-soluble thiamine salts. Half-life of benfotiamine is similar to thiamine salts, but bioavailability of benfotiamine eight days after administration is roughly 25 percent of the original dose, about 3.6 times greater than after an oral dose of a thiamine salt.<sup>4</sup>

### Mechanisms of Action

Benfotiamine exerts its beneficial effects via a number of mechanisms. In the case of diabetes, benfotiamine increases transketolase activity, an important enzyme in glucose metabolism, and as a result, blocks three of the major molecular pathways leading to hyperglycemic damage. It prevents the increase in UDP-N-acetylglucosamine (UDP-GlcNAc) and enhances hexosamine pathway activity that decreases the buildup of detrimental glucose metabolites that can lead to advanced glycation end products (AGE). Benfotiamine also normalizes protein kinase

C (PKC) activity and prevents nuclear factor-kappaB (NF- $\kappa$ B) activation in the retina of diabetics.<sup>5</sup> In addition, benfotiamine corrects imbalances in the polyol pathway by decreasing aldose reductase activity, sorbitol concentrations, and intracellular glucose, thereby protecting endothelial cells from glucose-induced damage.<sup>6</sup> Benfotiamine also corrects glucose-induced endothelial cell damage by normalizing cell replication rates<sup>7</sup> and decreasing apoptosis.<sup>8</sup> Animal models of diabetic limb ischemia demonstrated these mechanisms are responsible for improved post-ischemic healing.<sup>9</sup> Research has also shown benfotiamine's enhancement of transketolase activity in erythrocytes and renal glomeruli protects the kidneys from glucose-induced damage and prevents the development of diabetic nephropathy.<sup>10,11</sup> In alcoholics<sup>12</sup> and patients with chronic renal disease,<sup>10</sup> benfotiamine corrects thiamine deficiency and can decrease the incidence of neuropathies.<sup>12</sup>

### Thiamine Deficiency States

Thiamine levels are significantly lower than normal in about 20 percent of alcoholics for several reasons: (1) the diet of an alcoholic tends to be heavy in carbohydrates, resulting in decreased thiamine intake; (2) absorption of thiamine and other nutrients is impaired due to the effects of chronic alcohol intake on the gut's absorptive mechanisms; (3) chronic alcohol consumption reduces the liver's ability to store thiamine; and (4) acetaldehyde, an ethanol metabolite, interferes with thiamine utilization.<sup>13</sup> These factors result in thiamine deficiency, which in many alcoholics does not respond to supplementation with oral water-soluble thiamine salts. Thiamine deficiency is also frequently observed in patients with diabetic neuropathy<sup>14</sup> and in patients who have undergone gastrectomy<sup>15</sup> or bariatric surgery<sup>16</sup> who subsequently develop neuropathies due to malabsorption.

### Clinical Indications

#### *Diabetic Neuropathy*

In a double-blind, randomized, placebo-controlled pilot study, 20 subjects with diabetic polyneuropathy were given two 50-mg tablets benfotiamine four times daily (400 mg total daily dose), and 20 subjects received placebo. Study duration was three

weeks, and assessment was via neuropathy symptoms and vibration sensation scores from both physician and patient. In the treatment group a statistically significant improvement in the neuropathy score was reported compared to placebo. The most significant improvement reported was decrease in pain, whereas, there was no significant improvement in the tuning fork test – a measure of vibration perception.<sup>17</sup>

Several studies have investigated the effect of benfotiamine in combination with other B vitamins in the treatment of diabetic neuropathy. One study included 45 patients with painful peripheral polyneuropathy. Thirty patients received Milgamma® (50 mg benfotiamine and 250  $\mu$ g B12 as cyanocobalamin per tablet) at a dose of two tablets four times daily for three weeks (total daily dose: 400 mg benfotiamine and 2,000  $\mu$ g cyanocobalamin), followed by one tablet three times daily for nine weeks. The second group of 15 patients received a conventional B-vitamin supplement at a dose of two tablets three times daily for the entire 12-week period. Changes in pain severity and vibration perception thresholds were measured at baseline and at the end of three months. All Milgamma-treated patients experienced significant relief in neuropathic pain and a dramatic improvement in vibration perception thresholds. In patients receiving the conventional B-vitamin treatment, slight, non-statistically significant improvement was noted.<sup>18</sup>

In a second trial lasting six weeks, 36 subjects with painful diabetic neuropathy were divided into three groups of 12 each. The first group received Milgamma-N® (40 mg benfotiamine, 90 mg pyridoxine, and 250  $\mu$ g cyanocobalamin per capsule) at a dose of two capsules four times daily (320 mg benfotiamine, 720 mg pyridoxine, and 2,000  $\mu$ g cyanocobalamin daily). The second group received Milgamma-N at a lower dose of one capsule three times daily (120 mg benfotiamine, 270 mg pyridoxine, and 750  $\mu$ g cyanocobalamin daily), while the third group received one capsule three times daily of straight benfotiamine (150 mg benfotiamine daily). Neuropathy was assessed via pain and vibration sensation at baseline and after three and six weeks. Patients in all three groups reported beneficial therapeutic effects, even at three weeks, although the most significant improvement was reported by patients receiving the highest-dose benfotiamine.<sup>19</sup>

A double-blind, randomized, placebo-controlled 12-week study examined the effectiveness of another benfotiamine combination containing both vitamins B6 and B12 in 24 diabetic patients with polyneuropathy. A statistically significant improvement in nerve conduction velocity in the peroneal nerve was observed in the treatment group compared to placebo. A trend toward improvement in vibration sensation was also reported in the treatment group; long-term observation of nine patients over a nine-month period supported the results.<sup>20</sup>

### Alcoholic Neuropathy

Chronic alcoholics commonly develop polyneuropathy as a result of dietary deficiency and poor absorption of thiamine. Benfotiamine's effect on neuropathy in alcoholics was investigated and compared to thiamine in a randomized, multicenter, placebo-controlled, double-blind study of 84 subjects over an eight-week period.<sup>12</sup> Benfotiamine was given orally at 320 mg daily during weeks 1-4, followed by 120 mg daily during weeks 5-8. A second group received Milgamma-N (providing a total daily dose of 320 mg benfotiamine, 720 mg pyridoxine, and 2,000  $\mu$ g cyanocobalamin) during weeks 1-4 and a total daily dose of 120 mg benfotiamine, 270 mg pyridoxine, and 750  $\mu$ g cyanocobalamin during weeks 5-8; a third group received placebo.

Parameters measured included vibration perception in the great toe, ankle, and tibia; neural pain intensity; motor function and paralysis; sensory function; and overall neuropathy score and clinical assessment. Neuropathy was scored from 0 (maximum clinical expression of neuropathy symptoms) to 16 (free of symptoms) with scores of  $\geq 10$  representing a mild clinical picture. Although benfotiamine therapy was superior to Milgamma-N and placebo for all parameters, results reached statistical significance only for motor function and paralysis and overall neuropathy score. Patients taking benfotiamine had a significantly lower degree of paralysis (90%) than those in the placebo group (60.7%) or the Milgamma-N group (53.9%). Overall neuropathy scores in the benfotiamine group were  $\geq 10$  in 93.3 percent of patients, compared to 67.9 percent in the placebo group and 76.9 percent in the Milgamma-N group.

Why the benfotiamine-alone group had better results than the Milgamma-N group, despite the fact that the benfotiamine dosage was equivalent, is not completely understood. The authors hypothesize the B6 and B12 might compete with the effects of B1 in the Milgamma-N group. On the other hand, in the case of diabetic neuropathy, the positive effects of the combination may be due to the fact that deficiencies of B1, B6, and B12 are implicated in its possible pathogenesis; whereas, alcoholic neuropathy is associated with primarily a B1 deficiency.

### Diabetic Vascular Complications

#### Diabetic Retinopathy

In diabetics, the development of microvascular disease is a leading cause of retinopathy and blindness.<sup>21</sup> In a study with both animal and *in vitro* arms, researchers in Germany discovered benfotiamine administration prevented experimental diabetic retinopathy in rats. Diabetic retinopathy is associated with increased AGE (a sign of oxidative stress) and elevations in retinal PKC activity. *In vitro*, a 50  $\mu$ M concentration of benfotiamine completely prevented increases in AGE and PKC activity.<sup>5</sup>

These same researchers also examined the *in vivo* effect of benfotiamine on retinas of diabetic rats; non-diabetic rats and untreated diabetic rats served as controls. Diabetic rats receiving benfotiamine for 36 weeks demonstrated a 2.5-fold increase in transketolase activity compared to untreated diabetic rats. Hexosamine pathway activity, PKC activity, AGE formation, and NF- $\kappa$ B activation in retinas of all three groups were analyzed. In diabetic rats, benfotiamine administration for 36 weeks reduced UDP-GlcNAc to levels lower than those observed in non-diabetic rats, normalized AGE levels and PKC activity, and inhibited activation of NF- $\kappa$ B in diabetic rat retinas. The results of this study indicate lipid-soluble benfotiamine may be of therapeutic benefit in patients with diabetic retinopathy by preventing or delaying the onset and progression of microvascular changes in the retina.<sup>5</sup>

#### Peripheral Vascular Disease

In two separate studies, a group of Italian researchers from the University of Turin examined the effect of benfotiamine on endothelial defects and

apoptosis in human umbilical vein endothelial cells cultured in the presence of high glucose.<sup>7,8</sup> Either thiamine or benfotiamine prevented AGE production<sup>7</sup> and apoptosis<sup>8</sup> in these cell cultures.

Aldose reductase activity and sorbitol levels are increased in human endothelial cells cultured in glucose, providing one mechanism for endothelial dysfunction in diabetes. Researchers found the addition of either thiamine or benfotiamine resulted in normalized intracellular glucose levels, decreased sorbitol concentrations, and reduction in aldose reductase activity.<sup>6</sup>

Using an animal model of hind limb ischemia in diabetic mice, researchers in England investigated whether benfotiamine administration was of benefit in reparative neovascularization. Mice were randomly assigned to receive 80 mg/kg/day benfotiamine or placebo in drinking water. Two weeks after benfotiamine initiation, ischemia was surgically induced in the left hind limb, and limb recovery was determined at two weeks post-surgery. Parameters of limb recovery were analyzed via Doppler flowmetry and histological analysis of adductor muscles in the affected limb. It was demonstrated that benfotiamine improves healing and neovascularization in ischemic limbs of diabetic animals, probably via protein kinase B potentiation of angiogenesis, manifesting in increased perfusion and oxygenation of ischemic tissue and improved blood flow to the limb. Benfotiamine also stimulated capillarization and reduced apoptosis in ischemic muscle tissue.<sup>9</sup>

### Cerebrovascular and Cardiovascular Oxidative Stress

Animal studies in diabetic male mice demonstrate high-dose benfotiamine (100 mg/kg/day) given via intraperitoneal injection for 14 days alleviates oxidative stress in both cerebral cortex tissue<sup>22</sup> and left ventricular myocytes. In cardiomyocytes, benfotiamine improved contractile function.<sup>23</sup>

### Diabetic Nephropathy

High glucose concentrations in diabetes can cause an accumulation of triosephosphates, which subsequently trigger biochemical changes that result in the development of diabetic nephropathy, a complication often associated with cardiovascular disease

and higher mortality rates. The effects of high-dose thiamine and benfotiamine (70 mg/kg daily) on triosephosphate accumulation were investigated in diabetic rats over a 24-week period. Both therapies inhibited the accumulation of triosephosphates, increased transketolase expression in renal glomeruli, decreased PKC activation, decreased oxidative stress and protein glycation, and inhibited the development of microalbuminuria. These results indicate both thiamine and benfotiamine might be of therapeutic benefit in renal complications of diabetes. Due to superior pharmacokinetics, benfotiamine appears to be the better choice.<sup>11</sup>

### End-Stage Renal Disease

The thiamine pool in the body exists mainly as thiamine diphosphate (TDP), 80 percent of which is found in the erythrocytes. Many patients with chronic renal insufficiency demonstrate decreased erythrocyte transketolase activity (a sign of thiamine deficiency) compared to healthy subjects. Consequently, many of these patients also develop neuropathies secondary to kidney disease.<sup>10,24</sup> In a clinical trial of 20 patients with end-stage renal disease, the effect of benfotiamine or thiamine nitrate on TDP blood levels and erythrocyte transketolase activity was evaluated. Patients were given single oral doses of 100 mg thiamine nitrate or benfotiamine and blood levels analyzed via high-performance liquid chromatography over a 24-hour period. Compared to patients in the thiamine nitrate group, patients receiving benfotiamine experienced higher TDP concentrations in erythrocytes as well as significantly improved erythrocyte transketolase activity. Benfotiamine may be of clinical benefit in thiamine-deficient patients with chronic renal insufficiency.<sup>25</sup>

### Drug/Nutrient Interactions

There are no reports of benfotiamine-drug interactions.

### Safety and Toxicity

Benfotiamine administration appears to be safe with no reports of toxicity in the scientific literature.

## Dosage and Administration

Based on clinical studies to date, daily doses of oral benfotiamine range from 300-450 mg daily in divided doses.

## References

- Greb A, Bitsch R. Comparative bioavailability of various thiamine derivatives after oral administration. *Int J Clin Pharmacol Ther* 1998;36:216-221.
- Ziems M, Netzel M, Bitsch I. Biokinetic parameters and metabolism of S-benzoylthiamine-O-monophosphate. *BioFactors* 2000;11:109-110.
- Bitsch R, Wolf M, Moller J, et al. Bioavailability assessment of the lipophilic benfotiamine as compared to a water-soluble thiamin derivative. *Ann Nutr Metab* 1991;35:292-296.
- Loew D. Pharmacokinetics of thiamine derivatives especially of benfotiamine. *Int J Clin Pharmacol Ther* 1996;34:47-50.
- Hammes HP, Du X, Edelstein D, et al. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. *Nat Med* 2003;9:294-299.
- Berrone E, Beltramo E, Solimine C, et al. Regulation of intracellular glucose and polyol pathway by thiamine and benfotiamine in vascular cells cultured in high glucose. *J Biol Chem* 2006;281:9307-9313.
- Pomero F, Molinar Min A, La Selva M, et al. Benfotiamine is similar to thiamine in correcting endothelial cell defects induced by high glucose. *Acta Diabetol* 2001;38:135-138.
- Beltramo E, Berrone E, Buttiglieri S, Porta M. Thiamine and benfotiamine prevent increased apoptosis in endothelial cells and pericytes cultured in high glucose. *Diabetes Metab Res Rev* 2004;20:330-336.
- Gadua S, Emanuelli C, Van Linthout S, et al. Benfotiamine accelerates the healing of ischaemic diabetic limbs in mice through protein kinase B/AKT mediated potentiation of angiogenesis and inhibition of apoptosis. *Diabetologia* 2006;49:405-420.
- Mestyán I, Jobst K, Hazafi K, Green A. Erythrocyte transketolase activity in patients with chronic renal disease. *Acta Med Hung* 1986;43:315-319.
- Babaei-Jadidi R, Karachalias N, Ahmed N, et al. Prevention of incipient diabetic nephropathy by high-dose thiamine and benfotiamine. *Diabetes* 2003;52:2110-2120.
- Woelk H, Lehl S, Bitsch R, Kopcke W. Benfotiamine in treatment of alcoholic polyneuropathy: an 8-week randomized controlled study (BAPI Study). *Alcohol Alcohol* 1998;33:631-638.
- Thomson AD. Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of the Wernicke-Korsakoff syndrome. *Alcohol Alcohol Suppl* 2000;35:2-7.
- Abbas ZG, Swai AB. Evaluation of the efficacy of thiamine and pyridoxine in the treatment of symptomatic diabetic peripheral neuropathy. *East Afr Med J* 1997;74:803-808.
- Koike H, Misu K, Hattori N, et al. Postgastrectomy polyneuropathy with thiamine deficiency. *J Neurol Neurosurg Psychiatry* 2001;71:357-362.
- Malinowski SS. Nutritional and metabolic complications of bariatric surgery. *Am J Med Sci* 2006;331:219-225.
- Haupt E, Ledermann H, Kopcke W. Benfotiamine in the treatment of diabetic polyneuropathy – a three-week randomized, controlled pilot study (BEDIP Study). *Int J Clin Pharmacol Ther* 2005;43:71-77.
- Simeonov S, Pavlova M, Mitkov M, et al. Therapeutic efficacy of “Milgamma” in patients with painful diabetic neuropathy. *Folia Med (Plovdiv)* 1997;39:5-10.
- Winkler G, Pal B, Nagybeganyi E, et al. Effectiveness of different benfotiamine dosage regimens in the treatment of painful diabetic neuropathy. *Arzneimittelforschung* 1999;49:220-224.
- Stracke H, Lindemann A, Federlin K. A benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy. *Exp Clin Endocrinol Diabetes* 1996;104:311-316.
- No authors listed. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977-986.
- Wu S, Ren J. Benfotiamine alleviates diabetes-induced cerebral oxidative damage independent of advanced glycation end-product, tissue factor and TNF-alpha. *Neurosci Lett* 2006;394:158-162.
- Ceylan-Isik AF, Wu S, Li Q, et al. High-dose benfotiamine rescues cardiomyocyte contractile dysfunction in streptozotocin-induced diabetes mellitus. *J Appl Physiol* 2006;100:150-156.
- Lange K, Lonergan ET, Semar M, Sterzel RB. Transketolase inhibition as a mechanism in uremic neuropathy. *Trans Assoc Am Physicians* 1971;84:172-181.
- Frank T, Bitsch R, Maiwald J, Stein G. High thiamine diphosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. *Eur J Clin Pharmacol* 2000;56:251-257.