

# Nerve Formula Research

## **Effectiveness of Different Benfotiamine Dosage Regimens in the Treatment of Painful Diabetic Neuropathy**

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Arzneimittelforschung. 1999 Mar;49(3):220-4.

### **Abstract**

The therapeutic effectiveness of a benfotiamine vitamin B combination, administered in high (4 x 2 capsules/day, = 320 mg benfotiamine/day) and medium doses (3 x 1 capsules/day), was compared to a monotherapy with benfotiamine (3 x 1 tablets/day, = 150 mg benfotiamine/day) in diabetic patients suffering from painful peripheral diabetic neuropathy (DNP). In a 6-week open clinical trial, 36 patients (aged 40 to 70 yrs) having acceptable metabolic control (HbA1c < 8.0%) were randomly assigned to three groups, each of them comprising 12 participants. Neuropathy was assessed by five parameters: the pain sensation (evaluated by a modified analogue visual scale), the vibration sensation (measured with a tuning fork using the Riedel-Seyfert method) and the current perception threshold (CPT) on the peroneal nerve at 3 frequencies: 5, 250 and 2000 Hz). Parameters were registered at the beginning of the study and at the end of the 3rd and 6th week of therapy. An overall beneficial therapeutic effect on the neuropathy status was observed in all three groups during the study, and a significant improvement in most of the parameters studied appeared already at the 3rd week of therapy ( $p < 0.01$ ). The greatest change occurred in the group of patients receiving the high dose of benfotiamine ( $p < 0.01$  and  $0.05$ , resp., compared to the other groups). Metabolic control did not change over the study. It is concluded that benfotiamine is most effective in large doses, although even in smaller daily dosages, either in combination or in monotherapy, it is effective

### **Comparison of Benfotiamine to Thiamine**

#### **Pharmacokinetics of Thiamine Derivatives Especially of Benfotiamine**

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Wuppertal, Germany.  
Int J Clin Pharmacol Ther. 1996 Feb;34(2):47-50.

### **Abstract**

Pharmacokinetic data of orally administered lipid-soluble thiamine analogues like benfotiamine are reviewed and assessed. It is quite clear that benfotiamine is absorbed much better than water-soluble thiamine salts: maximum plasma levels of thiamine are about 5 times higher after benfotiamine, the bioavailability is at maximum about 3.6 times as high as that of thiamine hydrochloride and better than other lipophilic thiamine derivatives. The physiological activity (alphaETK) increased only after benfotiamine was given. Due to its excellent pharmacokinetic profile benfotiamine should be preferred in treatment of relevant indications.

### **Benfotiamine and Improvement in Nerve Conduction Velocity**

#### **A Benfotiamine-vitamin B Combination in Treatment of Diabetic Polyneuropathy**

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Exp Clin Endocrinol Diabetes. 1996;104(4):311-6.

### **Abstract**

In a double-blind, randomized, controlled study, the effectiveness of treatment with a combination of Benfotiamine (a lipid-soluble derivative of vitamin B1 with high bioavailability) plus vitamin B6, B12 on objective parameters of neuropathy was studied over a period of 12 weeks on 24 diabetic patients with diabetic polyneuropathy. The results showed a significant improvement ( $p = 0.006$ ) of nerve conduction velocity in the peroneal nerve and a statistical trend toward improvement of the vibration perception threshold. Long-term observation of 9 patients with verum over a period of 9 months support the results. Therapy-specific adverse effects were not seen. The results of this double-blind investigation, of the long-term observation and of the reports in the literature support the contention that the neurotropic benfotiamine-vitamin B combination represents a starting point in the treatment of diabetic polyneuropathy.

### **Benfotiamine Slowing the Process of Cellular Aging**

## **Benfotiamine Inhibits Intracellular Formation of Advanced Glycation End Products in vivo**

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### **Abstract**

We have demonstrated previously that intracellular formation of the advanced glycation end product (AGE) N-epsilon-(carboxymethyl)-lysine (CML) inversely correlates with diabetic vascular complications independently from glycemia (Diabetologia 42, 603, 1999). Here, we studied the effect of benfotiamine, a lipid-soluble thiamine derivative with known AGE-inhibiting properties in-vitro on the intracellular formation of (CML) and methylglyoxal-derived AGE in red blood cells. Blood was collected from 6 Type 1 diabetic patients (2 m, 4 f, age 31.8 ± 5.5 years; diabetes duration 15.3 ± 7.0 years) before and after treatment with 600 mg/day benfotiamine for 28 days. In addition to HbA1c (HULK), CML and methylglyoxal were measured using specific antibodies and a quantitative dot blot technique. While treatment with benfotiamine did not affect HbA1c levels (at entry: 7.18±0.86%; at conclusion 6.88±0.88%; p not significant), levels of CML decreased by 40 % (737 ± 51 arbitrary unit/mg protein (AU) vs. 470 ± 86 AU; p<0.001). The levels of intracellular methylglyoxal-derived AGE were reduced by almost 70% (1628 ± 1136 AU vs. 500 ± 343 AU; p < 0.01). The data indicate that thiamine derivatives are effective inhibitors of both intracellular glycoxidation and AGE formation.

### **Benfotiamine Slowing and Blocking Diabetic Complication and Retinopathy**

### **Benfotiamine Blocks Three Major Pathways of Hyperglycemic Damage and Prevents Experimental Diabetic Retinopathy**

Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D, Neumaier M, Bergfeld R, Giardino I, Brownlee M.

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Nat Med. 2003 Mar;9(3):294-9

## **Abstract**

Three of the major biochemical pathways implicated in the pathogenesis of hyperglycemia induced vascular damage (the hexosamine pathway, the advanced glycation end product (AGE) formation pathway and the diacylglycerol (DAG)-protein kinase C (PKC) pathway) are activated by increased availability of the glycolytic metabolites glyceraldehyde-3-phosphate and fructose-6-phosphate. We have discovered that the lipid-soluble thiamine derivative benfotiamine can inhibit these three pathways, as well as hyperglycemia-associated NF-kappaB activation, by activating the pentose phosphate pathway enzyme transketolase, which converts glyceraldehyde-3-phosphate and fructose-6-phosphate into pentose-5-phosphates and other sugars. In retinas of diabetic animals, benfotiamine treatment inhibited these three pathways and NF-kappaB activation by activating transketolase, and also prevented experimental diabetic retinopathy. The ability of benfotiamine to inhibit three major pathways simultaneously might be clinically useful in preventing the development and progression of diabetic complications.

## **Methylcobalamine and Diabetic Neuropathy**

Clinical usefulness of intrathecal injection of methylcobalamin in patients with diabetic neuropathy Ide H Fujiya S Asanuma Y Tsuji M Sakai H Agishi Y, Clin Ther (1987) 9(2):183-92

Seven men and four women with symptomatic diabetic neuropathy were treated with methylcobalamine (2,500 micrograms in 10 ml of saline) injected intrathecally. Treatment was begun when patients had good metabolic control, as determined by measurements of plasma glucose and hemoglobin, and was repeated several times with a one-month interval between injections. Three patients were re-treated one year after the last intrathecal injection. Symptoms in the legs, such as paresthesia, burning pains, and heaviness, dramatically improved. The effect appeared within a few hours to one week and lasted from several months to four years. The mean peroneal motor-nerve conduction velocity did not change significantly. The mean (+/- SD) concentration of methylcobalamin in spinal fluid was 114 +/- 32 pg/ml before intrathecal injection (n = 5) and 4,752 +/- 2,504 pg/ml one month after intrathecal methylcobalamin treatment (n = 11). Methylcobalamine caused no side effects with respect to subjective symptoms or characteristics of spinal fluid. These findings suggest that a high concentration of methylcobalamin in spinal fluid is highly effective and safe for treating the symptoms of diabetic neuropathy.

## **Nerve Regeneration with Methylcobalamine**

Ultra-high dose methylcobalamine promotes nerve regeneration in experimental acrylamide neuropathy. Watanabe T Kaji R Oka N Bara W Kimura J, J Neurol Sci (1994 Apr) 122(2):140-3

Despite intensive searches for therapeutic agents, few substances have been convincingly shown to enhance nerve regeneration in patients with peripheral neuropathies. Recent biochemical evidence suggests that an ultra-high dose of methylcobalamin (methyl-B12) may up-regulate gene transcription and thereby protein synthesis. We examined the effects of ultra-high dose of methyl-B12 on the rate of nerve regeneration in rats with acrylamide neuropathy, using the amplitudes of compound muscle action potentials (CMAPs) after tibial nerve stimulation as an index of the number of regenerating motor fibers. After intoxication with acrylamide, all the rats showed equally decreased CMAP amplitudes. The animals were then divided into 3 groups; rats treated with ultra-high (500 micrograms/kg body weight, intraperitoneally) and low (50 micrograms/kg) doses of methyl-B12, and saline-treated control rats. Those treated with ultra-high dose showed significantly faster CMAP recovery than saline-treated control rats, whereas the low-dose group showed no difference from the control. Morphometric analysis revealed a similar difference in fiber density between these groups. Ultra-high doses of methyl-B12 may be of clinical use for patients with peripheral neuropathies.

### **Regeneration of Motor Nerve Terminals with Methyl B12**

#### **Methylcobalamine (methyl-B12) Promotes Regeneration of Motor Nerve Terminals Degenerating in anterior gracile muscle of gracile axonal dystrophy (GAD) mutant mouse**

Yamazaki K Oda K Endo C Kikuchi T Wakabayashi T, Neurosci Lett (1994 Mar 28) 170(1):195-7

We examined the effects of methylcobalamin (methyl-B12, mecobalamin) on degeneration of motor nerve terminals in the anterior gracile muscle of gracile axonal dystrophy (GAD) mutant mice. GAD mice received orally methyl-B12 (1 mg/kg body wt/day) from the 40th day after birth for 25 days. In the distal endplate zone of the muscle, although most terminals were degenerated in both the untreated and methyl-B12-treated GAD mice, sprouts were more frequently observed in the latter. In the proximal endplate zone, where few degenerated terminals were seen in both groups of the mice, the perimeter of the terminals was increased and the area of the terminals was decreased significantly in the methyl-B12-treated GAD mice. These findings indicate that methyl-B12 promotes regeneration of degenerating nerve terminals in GAD mice.

## **Protective Effects of Methyl B12 In Retinal Cells**

### **Protective Effects of Methylcobalamine, A Vitamin B12 Analogue, Against Glutamate-induced Neurotoxicity in Retinal Cell Culture**

Kikuchi M Kashii S Honda Y Tamura Y Kaneda K Akaike,  
Invest Ophthalmol Vis Sci (1997 Apr) 38(5):848-54

**Purpose:** To examine the effects of methylcobalamine on glutamate-induced neurotoxicity in the cultured retinal neurons. **Methods:** Primary cultures obtained from the fetal rat retina (gestation days 16 to 19) were used for the experiment. The neurotoxicity was assessed quantitatively using the trypan blue exclusion method. **Results:** Glutamate neurotoxicity was prevented by chronic exposure to methylcobalamine and S-adenosylmethionine (SAME), which is formed in the metabolic pathway of methylcobalamin. Chronic exposure to methylcobalamine and SAME also inhibited the neurotoxicity induced by sodium nitroprusside that release nitric oxide. By contrast, acute exposure to methylcobalamine did not protect retinal neurons against glutamate neurotoxicity. **Conclusions:** Chronic administration of methylcobalamine protects cultured retinal neurons against N-methyl-D-aspartate-receptor-mediated glutamate neurotoxicity, probably by altering the membrane properties through SAME-mediated methylation.

#### **Protection via Methylcobalamine**

Life Extension magazine republishes abstracts on health and longevity topics in each issue, drawn from research papers originally published in science and medical journals throughout the world.

Protective effects of a vitamin B12 analogue, methylcobalamin, against glutamate cytotoxicity in cultured cortical neurons Akaike A Tamura Y Sato Y Yokota T, Eur J Pharmacol (1993 Sep 7) 241(1):1-6 The effects of methylcobalamin, a vitamin B12 analogue, on glutamate-induced neurotoxicity were examined using cultured rat cortical neurons. Cell viability was markedly reduced by a brief exposure to glutamate followed by incubation with glutamate-free medium for 1 h. Glutamate cytotoxicity was prevented when the cultures were maintained in methylcobalamin-containing medium. Glutamate cytotoxicity was also prevented by chronic exposure to S-adenosylmethionine, which is formed in the metabolic pathway of methylcobalamin. Chronic exposure to methylcobalamin and S-adenosylmethionine also inhibited the cytotoxicity induced by methyl-D-aspartate or sodium nitroprusside that releases nitric oxide. In cultures maintained in a standard medium, glutamate cytotoxicity was not affected by adding methylcobalamin to the glutamate-containing medium. In contrast, acute exposure to MK-801, a NMDA receptor antagonist,

prevented glutamate cytotoxicity. These results indicate that chronic exposure to methylcobalamin protects cortical neurons against NMDA receptor-mediated glutamate cytotoxicity.