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Effects of methylcobalamin on diabetic neuropathy

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Summary

We studied the clinical and neurophysiological effects of methylcobalamin on patients with diabetic neuropathy. In a double-blind study, the active group showed statistical improvement in the somatic and autonomic symptoms with regression of signs of diabetic neuropathy. Motor and sensory nerve conduction studies showed no statistical improvement after 4 months. The drug was easily tolerated by the patients and no side effects were encountered.

Introduction

The aetiopathogenesis of diabetic neuropathy is controversial. Metabolic insult to the peripheral nerves is thought to be the main factor [1,2], however, a vascular aetiology cannot be excluded [3,4].

Although a meticulous diabetic control delays the development, or slows the progression of neuropathy, treatment is difficult [5–8]. Symptomatic relief may be obtained from chinese medicine [9], imipramine [10], amityphilene with fluphenazine [11], intravenous lignocaine [12,13] or oral mexiletine [14].

Prostaglandin E_1 is reported to improve perfusion of ischaemic microcirculation leading to improvement of diabetic neuropathy [15].

Aldose reductase inhibitor sorbinil, prevents the increase in nerve sorbitol and restores *myo*-inositol levels to normal. This prevents defects of axonal transport and improves conduction velocity without interferring with the hypoglycaemia, its efficacy in treatment of diabetic neuropathy has been reported [16–25].

Other agents are reported to be effective in treatment of neuropathy without improving the ischaemic performance or interferring with metabolic changes or hyperglycaemia like gangliosides [26] and cobalamin [27]. Gangliosides enhance axonal regenerations and compensate for the derangement of axonal transport which occurs in diabetic neuropathy [26].

Cobalamin facilitates myelinogenesis and nerve regeneration, so it can actively improve diabetic neuropathy [27]. Cobalamin has 4 analogues: cyanacobalamin (CN-12), hydroxycobalamin (OH-B_{12}) 5-deoxyadenoxyl cobalamin (DBCC) and methylcobalamin (CH_3-B_{12}). In CSF, methylcobalamine accounts for 90% of total cobalamin, suggesting its close relationship with the nervous system, so it will be more appropriate to use it in neuropathy rather than other analogues [28].

The aim of our study is to analyze the effect of methylcobalamin on the symptomatology and electrodiagnostic studies in patients with established diabetic neuropathy.

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Patients and methods

Fifty patients with definite diabetic neuropathy were identified. All have clinical symptoms, signs and/or neurophysiological abnormalities compatible with diabetic neuropathy and conform with recent recommendations of diagnosis of diabetic neuropathy [29]. The symptoms were parasthesias, burning sensations, numbness, loss of sensation and muscle cramps. The signs were absent ankle jerks and/or other tendon reflexes, impairment of vibration sense, decreased sensation to pain and/or lower motor neuron weakness. Patients were classified as having good control of diabetes with HbA_1 value of 5.5–8% in the 6 months prior to the trial. All patients were kept on the same regimen of hypoglycaemic medication throughout the period of the trial. Type of diabetes or duration of diabetes was not a criteria for entry of the trial. Thirty-nine patients were non-insulin dependent and 11 were insulin dependent. The duration of diabetes ranged from 5 to 20 years with a mean of 9 years. Patients were treated with either insulin or hypoglycaemic agents. Patients on other medications of chronic use or with other diseases that may play part in neuropathy such as renal failure, hereditary motorsensory polyneuropathy, lymphoma or others were excluded from the study.

The patients were divided randomly into two groups and given similar medication with different codes for placebo and active drug. Seven patients did not continue the study but only one had a side effect. The remaining patients were 21 in the active group, 14 men and 7 women with a mean age of 55.1, and 22 from the placebo group, 14 men and 8 women with a mean age of 51.3. Each was given 2 capsules 3 times daily for 4 months. The effective dose of methylcobalamin in each capsule was 250 mg. Clinical and neurophysiological evaluations were done by the same investigator and technician at the entry of the trials and 4 months later. The investigators did not know whether the patient was on placebo or active drug.

Nerve conduction studies were done in an air-conditioned room at a temperature of 20°C. The nerves sampled were median (sensory and motor), common peroneal and sural nerves. The technique of electrical studies is that recommended by Kimura [30], for motor conduction studies, the nerve was stimulated at two points along its course, compound muscle action potentials were recorded using a pair of surface electrodes. In the upper limbs, orthodromic sensory conduction studies were done by stimulating the nerve and recording sensory potentials by surface electrode from a proximal site of the nerve, in the lower limbs, antidromic sensory potentials were recorded by placing surface electrodes on the sural nerve as it passes around the lateral malleolus, and stimulating the nerve in the calf. If the sensory action potential was not obtained by surface electrode, needle electrodes were used. All results were obtained from a computerized printout of the EMG machine (Mystro).

Scoring

A special scoring system was adopted for clinical and neurophysiological evaluation, Peripheral Neurology Score (PNS) (Tables 1 and 2). This scoring system is a modification from that used by Wormolts et al. [5]. A score of 140 was given to somatic symptoms, 35 to autonomic symptoms and 320 to clinical signs. Evaluation of each score was done independently without evaluating the grand total score.

In somatic evaluations, 5 symptoms were included: dull pain or tightness, numbness, cramps, fatigue and weakness (Table 1a). In autonomic evaluations there were 5 symptoms: recurrent diarrhea, episodic vomiting, urinary disturbances, and diminished sexual potency (Table 1b). Patients were given a score of either 0 or 5 according to the presence or absence of the symptoms evaluated. Signs score included sensations, power, deep tendon reflexes and blood pressure changes in the supine and upright position. Neurophysiological evaluation included 2 motor (median and common peroneal) and 2 sensory (median and sural) nerves. A score of 8 was given to each motor or sensory nerve. A score of minus 1 was given to abnormality less than 2 SD in amplitude or area, and a score of minus 3 was given to abnormality less than 2 SD in velocity or more than 2 SD in distal latency.

Results

Seven subjects dropped out, 6 did not show up at the neurological follow-up evaluation, 1 neurological follow-up developed side effects of gastric irritation, and the drug was discontinued, he was on placebo.

Table 4 summarizes the scores and P value for both groups at the start of the study (R_0) and 4 months later (R_4).

The results show a significant improvement in somatic and autonomic symptoms in the active groups (P=0.003 for somatic, and P=0.01 for autonomic).

There is also improvement of the signs in the active group with P value 0.05.

TABLE 1

PERIPHERAL NEUROPATHY (PNS) SYMPTOM[a] SCORE

(a) Somatic symptom[a]	Right upper limb	Left upper limb	Right lower limb	Left lower limb	Total
Dull pain tightness	5	5	5	5	20
Numbness	10	10	10	10	40
Cramps	5	5	5	5	20
Fatigue	5	5	5	5	20
Weakness	10	10	10	10	40
Total					140
(b) Autonomic[a]					
Recurrent diarrhea with or without nocturnal attacks	(5)				
Episodic vomiting	(5)				
Gastric severity	(5)				
Urinary retention and incontinence	(10)				
Diminished sexual potency	(10)				
Total	(35)				

[a]Each was given either whole score or 0 accordingly.

Neurophysiological studies showed no change in the motor scores. The sensory score improved in the active group, however, this was not statistically significant.

Discussion

Diagnosis of diabetic neuropathy needs careful history-taking, clinical examination and detailed neurophysiological studies. More than one indice should be used in the diagnosis as recommended by the San Antonio Conference on diabetic neuropathy [29]. In this study we used special scoring system (PNS) which includes clinical and neurophysiological parameters. This scoring system will be more objective in evaluating therapy or drug trials, also it will be useful in the follow-up of diabetic patients.

Treatment of diabetic neuropathy is a frustrating experience for the physicians and the patients. The failure of the treatment reflects the undetermined aetiopathogenesis of this disease [1–4], which seems to be multifactorial. A reasonable strategy would be to try the symptomatic drugs [9–14] as a transitionary method until the active therapy has an effect (if at all). This includes: strict control of hyperglycaemia, agents which improve the nerves microcirculation, drugs which inhibit the increase in nerve sorbitol and/or some agents which help in nerve regeneration and repair [15–28].

Cobalamin is closely associated to the nervous system; its deficiency leads to different neurological disorders such as tobacco amblyopia of the optic nerve, spastic ataxia due to subacute combined degeneration of the cord and peripheral neuropathy [27]. In diabetes there is no evidence of cobalamin deficiency, however, there is conflicting data suggesting improvement of the peripheral neuropathy regardless of the mechanism or the

TABLE 2

PERIPHERAL NEUROPATHY SIGNS SCORE

(a) Sensations (T. score = 80)

Test	RT upper limb (5)	LT upper limb (5)	RT lower limb (5)	LT lower limb (5)	Total (20)
Vibration					
Position					
Pain					
Touch					

(b) Motor power[2] (T. score = 120)

Groups	RT (5)	LT (5)	Total (10)
Wrist extensors			
Wrist flexors			
Finger extensors			
Finger flexor			
Elbow flex			
Shoulder abductor			
Hip flexors			
Knee flexor			
Ankle dorsiflexion			
Ankle eversion			
Toe plantiflex			
Ankle plantiflex			

(c) Deep tendon reflexes[3] (T. score = 100)

Test	RT (10)	LT (10)	Total (100)
Biceps			
Supinator			
Triceps			
Knee			
Ankle			

(d) Autonomic (T. score = 20)

Test	RT (10)	LT (10)	Total (20)
Blood pressure drop.			

Total signs score	(320)

(1) Sensation: (1) sensory loss above knee or elbow; (2) sensory loss ascending to but not above knee or elbow; (3) sensory loss ascending to but not above foot or hand; (4) sensory loss confined to toes or fingers; (5) normal. (2) Motor: (0) no contraction; (1) flicker of contraction; (2) active movement with gravity eliminated; (3) active movement against gravity but not resistance; (4) active movement against gravity but not full resistance; (5) normal strength. (3) Tendon reflexes: (0) absent; (4) present with reinforcement only; (8) depressed but obtainable without reinforcement; (10) normal. (4) Blood pressure: blood pressure checked in supine and standing up position. (2) drop in pressure of 30 mm Hg or more; (4) drop in pressure of 20–29 mm Hg; (8) drop in pressure of 11–19 mm Hg; (10) drop in pressure of 10 mm Hg or less.

TABLE 3

PERIPHERAL NEUROPATHY SCORE (NEUROPHYSIOLOGY)

	Motor results		Total score motor (16)	Sensory results		Total score sensory (16)
	Median nerve (8)	Common peroneal (8)		Median n. sensory (8)	Sural nerve (8)	
Distal latency (3)						
Amp (1)						
Area (1)						
Velocity (3)						

[a]For scoring see text.

cause of the neuropathy [27]. Cobalamin is an important cofactor for methyltetrahydrofolate methyltransferase in the transmethylation process where by homocysteine is converted to methionine which is associated with the biosyntheses of myelin protein DNA in peripheral nerves. It is also concerned with the biosynthesis of lecithin which is indispensable to myelination and nerve regeneration, so it has an effect on nerve repair in diabetic neuropathy [27].

Methylcobalamin was easily tolerated by the patients and no side effects were encountered. The study was a double-blind study where a placebo was used; no other agent has shown proven efficacy. In M-cobal patients the clinical improvement was not accompanied by statistical improvement in neurophysiological studies. Ide et al. [28] reported the same results after intrathecal injection of methylcobalamin. This may indicate that neurophysiological changes need a longer time to become apparent. As the number of our patients was small and duration of treatment short, conclusive results need further studies of longer duration and on larger populations.

In conclusion methylcobalamin showed efficacy in the treatment of diabetic neuropathy and may be used as one of many to improve the symptomatology in a disease which is still resistant to treatment.

TABLE 4

EFFECTS OF METHYLCOBAL ON PATIENTS AND PLACEBO

	Active			Placebo		
	R_0	R_4	P value	R_0	R_4	P value
Symptoms						
(a) somatic	72.2 ± 32.2	106.6 ± 20.4	0.003	95.5 ± 25.4	94.8 ± 27.9	–
(b) automomic	15.1 ± 11.9	23.7 ± 7.6	0.01	22.8 ± 10.3	24.2 ± 9.0	–
Signs	203.6 ± 49.6	229.6 ± 43.0	0.05	224.1 ± 46.2	221.8 ± 50.9	–
Neurophysiology						
(a) motor	9.0 ± 3.9	8.9 ± 3.7	–	9.95 ± 4.1	9.71 ± 3.7	–
(b) sensory	5.7 ± 3.3	7.3 ± 4.1	0.09	7.6 ± 5.2	7.7 ± 4	–

R_0: score at the start of the trial;
R_4: score after 4 months of treatment

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