

The Pernicious Anaemia Society Policy Statement on Cyanocobalamin Tablets

2008

Whilst the Pernicious Anaemia Society acknowledges that oral cobalamin tablets may be of some use to persons with Pernicious Anaemia, the society takes the view that before we can encourage our members to use oral cobalamin tablets and more particularly oral cyanocobalamin tablets in place of IM injections, there has to be more research conducted on the efficacy of oral B12 tablets and more particularly oral cyanocobalamin tablets.

The research must take into consideration the following:

- 1. The age of the participants and the length of the study. To obtain the best results, the studies must be long-term.*
- 2. The severity of PA.*
- 3. Cyanocobalamin versus Hydroxocobalamin. Cyanocobalamin is the least effective serum of all the B12 serums.*
- 4. Leber's Hereditary Optic Atrophy, tobacco amblyopia and retrobulbar neuritis in pernicious anaemia, and Tropical amblyopia are all associated with cyanide metabolism defects. Any person diagnosed with any of the above diseases and having PA should only be prescribed hydroxocobalamin and should never be prescribed cyanocobalamin in any form.*

1. The average age of participants involved in research studies into the efficacy of the oral cyanocobalamin is 60 years and older. The studies fail to take into consideration there are many people diagnosed with PA who are far younger than 60 years of age. In fact most of our members were diagnosed with PA in the age group of 20 to 35. We do not think it is inaccurate to state that the conclusion of studies conducted on persons over the age of 60 would not produce the same result if those studies were conducted on persons within the 20 to 35 age range. In a randomized open-label study involving newly diagnosed cobalamin deficient patients aged 60 and 64, Zahit Bolaman MD1, Gurhan Kadikoylu MD1, Vahit Yukselen MD2, Irfan Yavasoglu MD1, Sabri Barutca MD3 and Taskin Senturk MD state "However, because of the small sample size and the short term of this study, further long-term studies are needed to determine the efficacy of PO cobalamin treatment."¹

¹ *Oral versus intramuscular cobalamin treatment in megaloblastic anemia, Zahit Bolaman MD1, Gurhan Kadikoylu MD1, Vahit Yukselen MD2, Irfan Yavasoglu MD1, Sabri Barutca MD3 and Taskin Senturk MD4*

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2. Many of our members have neurological damage caused by a late diagnosis of PA. Most studies into the efficacy of oral cyanocobalamin tablets do not report if the participants have any neurological damage. In fact, according to L A Lane and C Rojas-Fernandez states the following: "Oral cyanocobalamin replacement may not be adequate for a patient presenting with severe neurologic manifestations that could have devastating consequences if the most rapid-acting therapy is not used immediately. Studies to date have not adequately addressed oral treatment in these patients; therefore, parenteral cobalamin is preferable in neurologically symptomatic patients until resolution of symptoms and hematologic indices".² Yoshio Mitsuyama and Hiroshi Kogoh also state that: "The vitamin B12 (VB12) parameter was studied in the serum and cerebrospinal fluid (CSF) of 14 demented patients. Eleven of these patients were in a state of dementia of the degenerative type such as Alzheimer's disease, Senile Dementia and Pick's disease. The serum VB12 concentration in all the patients was within normal limits, i.e. 500–1,300 pg/ml. There was no significant difference between the CSF-VB12 levels and the severity of dementia. The serum and CSF-VB12 levels of the demented patients did not show any significant elevation after the oral administration of CH₃-B12, 2 mg per day. On the other hand, there was a marked elevation of both the serum and CSF-VB12 after an oral medication (2 mg per day) plus intramuscular administrations (500 µg per day). These results confirm that **the intramuscular administration of CH₃-B12** is an effective way to get a higher value of the serum and CSF-VB12 levels."³ The Pernicious Anaemia Society agrees with the above studies that oral cobalamin should not be used in place of IM injections when neurological damage is present.

3. It is well known that hydroxocobalamin IM injections have a greater retention period than Cyanocobalamin IM injections. Herbert, Zalusky and Skeggs state: "It is demonstrated in normal subjects and in subjects with B12 deficiency maintained in remission by monthly injections of cyanocobalamin that the rise in serum cobalamin levels is more sustained after the intramuscular injection of 100 ug of hydroxocobalamin than

² Treatment of vitamin b(12)-deficiency anemia: oral versus parenteral therapy, LA Lane and C Rojas-Fernandez

³ Serum and Cerebrospinal Fluid Vitamin B12 Levels in Demented Patients with CH₃—B12 Treatment—Preliminary Study, Yoshio Mitsuyama M.D.11Department of Psychiatry, Miyazaki Medical Cdlege, Miyazaki,22Department of Psychiatry, Miyazaki Medical College, 5200 Kihara, Kiyotake, Miyazaki 889–16, Japan and Hiroshi Kogoh M.D.11Department of Psychiatry, Miyazaki Medical Cdlege, Miyazaki1Department of Psychiatry, Miyazaki Medical Cdlege, Miyazaki

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after the injection of 100 ug of cyanocobalamin.”⁴ The Society believes that the retention period of oral cyanocobalamin would be the same as injected cyanocobalamin therefore making it less effective as hydroxocobalamin.

4. Dr. A. G. Freeman, in a review titled, *Optic Neuropathy and Chronic Cyanide Intoxication* states the following: “Because confusion persists among doctors over the various commercial forms of vitamin B12 available for therapeutic use and about their possible adverse effects in neuro-ophthalmological disorders, we presented a case for withdrawal of Cyanocobalamin in favour of Hydroxocobalamin and submitted this in 1970 to the Committee on Safety of Medicines. As no action was taken by the manufacturers, we asked in 1978 ‘why has cyanocobalamin not been withdrawn? We laid particular emphasis on the fact that hydroxocobalamin, but not cyanocobalamin, was a powerful cyanide antagonist. Some patients with tobacco amblyopia fail to respond to treatment because, although hydroxocobalamin has been prescribed, cyanocobalamin has been administered instead. The diagnosis may then be questioned, treatment stopped and the patient condemned to a life of poor sight.⁵ Dr. Freeman further states: “Some patients with tobacco amblyopia fail to respond to treatment because they have received cyanocobalamin rather than the hydroxocobalamin prescribed. The retention of cyanocobalamin for therapeutic use and its selection places an incalculable number of patients with tropical and tobacco amblyopia and optic neuropathy in pernicious anaemia at risk of permanent blindness”.⁶

The Pernicious Anaemia Society holds firm in their view that at the present time it cannot promote the use of oral B12 tablets and particularly oral cyanocobalamin tablets to replace IM injections of serum B12 based on the lack of long-term studies involving people of a younger age. The PAS considers hydroxocobalamin to be a superior B12 serum over cyanocobalamin, firstly, for having a greater retention period in the body and secondly, unlike cyanocobalamin, hydroxocobalamin poses no threat to those of our members who smoke. The PAS does however agree that the use of oral B12 tablets and/or sublingual lozenges, in addition to IM injections, can be very beneficial to PA patients.

⁴ Retention of Injected Hydroxocobalamin versus Cyanocobalamin versus Liver Extract-Bound Cobalamin, Victor Herbert MD, Ralph Zalusky MD, and Helen R. Skeggs BS

⁵ Optic neuropathy and chronic cyanide intoxication: a review, A G Freeman MD FRCP Honorary Consultant Physician, Princess Margaret Hospital, Swindon

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