

ADEQUATE DOSAGE OF ORAL CYANOCOBALAMIN IN VITAMIN B12 DEFICIENCY AND HOMOCYSTEINE LOWERING



Mats Nilsson¹ and Bo Norberg²,

Departments of Family Medicine¹ and Internal Medicine², University Hospital of Northern Sweden, SE-901 85 Umeå, Sweden

Summary

Background. In case homocysteine lowering should be initiated for large patient populations, it is essential to evaluate the documentation for a safe and reliable dose of cobalamin in treating elderly people over decades. The reason is that many elderly patients develop severe B12 malabsorption due to atrophic gastritis.

Aim. To review the historical documentation of oral cyanocobalamin, 0.5 mg daily, and 1 mg daily, in deficiency treatment (1,2).

Patients. In the first report of the Berlin group (1), nearly all patients (n=64) were treated with oral cyanocobalamin, 0.5 mg daily (n=52-59). In the second report (2), 47 patients out of 64 were treated with oral cyanocobalamin, 1 mg daily.

Results. In the first report (1), the median value of serum cobalamin was 205 pmol/L, interquartile range 170-280, and range 95-395. In the second report (2), the median value of serum cobalamin was 470 pmol/L, interquartile range 280-580, and range 130-675.

Conclusion. Oral cyanocobalamin, 1 mg daily, is documented as a safe and reliable long-term prophylaxis and treatment of vitamin B12 deficiency (1-4). Hitherto, lower cobalamin doses are not proven safe (1). Thus, it is suggested that cyanocobalamin, 1 mg daily, is chosen as folate adjunct in future trials of homocysteine lowering.

Introduction

In general practice, homocysteine serves as a sensitive but non-specific marker of cobalamin deficiency or folate deficiency, or a combined cobalamin/folate deficiency. From a statistical point of view, homocysteine has been singled out as an independent risk factor for vascular disease. However, the biological significance of homocysteine in vascular disease is still obscure – causal or casual (cf. Fig 1). There has been much discussion about the optimal dosage of oral cyanocobalamin (1-5) Thus, it is desirable to review the documentation of oral cyanocobalamin dosage for prophylaxis and treatment of vitamin B12 deficiency (1, 2).

Material and methods

The Berlin group (1, 2) studied 64 patients with proven B12 malabsorption and 10 healthy controls during the period 1955-1967.

Results

The study started about 1955 in Falköping and Eskilstuna (1). All 64 patients had been recruited by 1964; their B12 uptake had been studied with 0.5 mg radioactive cyanocobalamin, and 60 patients were treated for more than one year at that time (1). Then oral cyanocobalamin, 1 mg (Behepan), was registered; during the following three years, all patients were treated with oral cyanocobalamin, 1 mg daily (2).

Comparison of serum cobalamin levels at registration of Behepan 1964 (1) and at end of the study (2) is illustrative. Only 5-12 patients had been treated with oral cyanocobalamin, 1 mg daily prior to Behepan registration (Fig 2). This interpretation is supported by comparison between serum concentrations at registration (1) and serum concentrations at end of study – half the dose, half the serum concentration (Table 1). It is reasonable to assume that the 17 patients with the lowest serum B12 concentrations in the final report had left the trial prior to the introduction of the 1 milligram dose (Fig 2).

Table 1. Median and 25th and 75th percentiles for serum cobalamin (in pmol/L) in the two reports by Berlin et al. 1965 and 1968.

Study	P ₂₅	Median	P ₇₅
Berlin 1965	170	205	280
Berlin 1968	280	470	580

Discussion

The study of the Berlin group 1955-1967 (1, 2) is considered to provide the largest and best-controlled study on oral cyanocobalamin therapy (cf. 5). The study started with 0.5 mg cyanocobalamin daily, which was considered a giant dose at that time (cf. 1, 2, 5). However, the uptake studies under ideal conditions and on empty stomach suggested that a considerable proportion of patients would turn out treatment failures with such a dose. Thus, the dose was doubled, 1 mg daily, prior to Behepan registration 1964 (1, 2). This dosage has gained the confidence of Swedish physicians and stood the test of time; in the period 1990-2000, the prescriptions in Sweden corresponded to one million patient years.

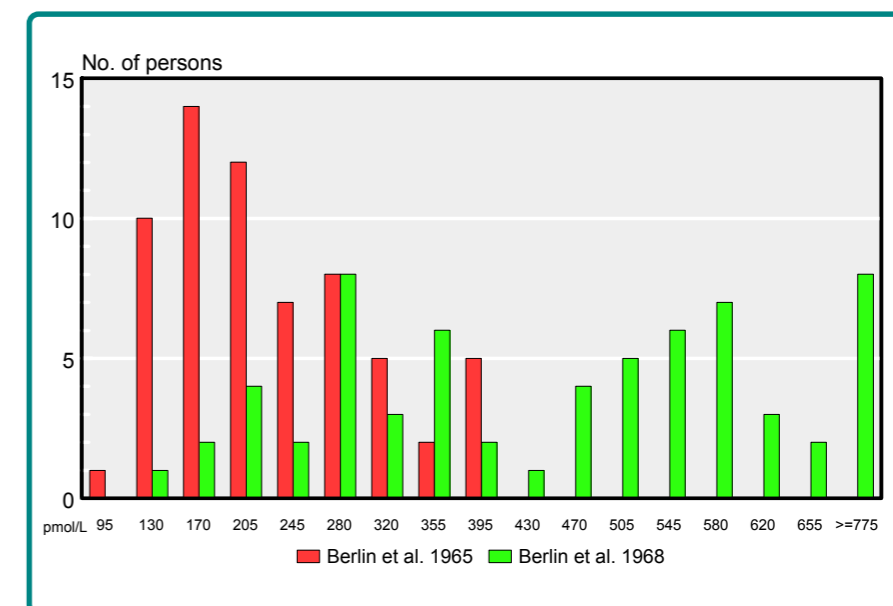


Figure 2. Distribution of serum cobalamin concentrations in the Berlin reports (1,2). 1 pg/mL = 0.75 pmol/L.

Conclusion

Oral cyanocobalamin, 1 mg daily, is documented as a safe and reliable long-term prophylaxis and treatment of vitamin B12 deficiency (1-4). Many elderly persons will proceed to severe B12 malabsorption during their last decade of life. Thus, it is suggested that cyanocobalamin, 1 mg daily, is chosen as folate adjunct in future trials of homocysteine lowering in persons at risk of vascular events.

References

- Berlin et al. *Läkartidningen* (Swe.) 1965; 62:773-81.
- Berlin et al. *Acta Med Scand* 1968; 184-258.
- Norberg B. Treatment of vitamin B12 deficiency – documentation of oral cyanocobalamin [editorial]. *Rondel* 2005; 22. URL: <http://www.rondellen.net>
- Nilsson M. Cobalamin communication in Sweden 1990-2000. Views, knowledge and practice among Swedish physicians. Dissertation. Umeå University, Sweden 2005. <http://urn.kb.se/resolve?urn=urn:nbn:se:umu:diva-416>
- Kuzminski A M, Del Giacco E J, Allen R H, Stabler S P, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. *Blood* 1998; 92:1191-8.

How we wish to be cited:

Brattström L. Homocysteine, vitamin B12, and folate in Parkinson's disease treated by levodopa [evaluation]. *Rondel* 2005; 22. URL: <http://www.rondellen.net>

Homocysteine, vitamin B12, and folate in Parkinson's disease treated by levodopa



Many studies have shown that levodopa treatment in Parkinson's disease patients is associated with increased plasma levels of total homocysteine (tHcy), an indicator of vitamin B12 and folate deficiency. In fact, in competition with several essential cerebral transmethylation reactions, levodopa consumes large amounts of methyl groups for its methylation to 3-O-methyldopa, methyl groups that have to be synthesised by vitamin B12- and folate-dependent metabolism. The increase in tHcy can be interpreted as a marker of insufficient methyl group synthesis for covering both the methylation of levodopa and endogenous compounds. By this competitive mechanism, levodopa may be toxic leading to hypomethylation of myeline, receptor proteins, DNA, membrane phospholipids, and catecholamines. This may explain why cerebral symptoms of vitamin B12 and folate deficiency as depressed mood and cognitive decline are common in Parkinson's disease. Moreover, homocysteine itself may be toxic by contribution in processes causing vascular disease and neural damage. More research on this topic is warranted.

Figure 1. Homocysteine - causal or casual?

Poster P 025 at Homocysteine Metabolism,
5th International Conference, Milano June 26 - 30, 2005

Further information: mats.nilsson@fammed.umu.se, bo.norberg@vll.se