

Effective Treatment of Cobalamin Deficiency With Oral Cobalamin

By Antoinette M. Kuzminski, Eric J. Del Giacco, Robert H. Allen, Sally P. Stabler, and John Lindenbaum

Because cobalamin deficiency is routinely treated with parenteral cobalamin, we investigated the efficacy of oral therapy. We randomly assigned 38 newly diagnosed cobalamin deficient patients to receive cyanocobalamin as either 1 mg intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60, and 90 or 2 mg orally on a daily basis for 120 days. Therapeutic effectiveness was evaluated by measuring hematologic and neurologic improvement and changes in serum levels of cobalamin (normal, 200 to 900 pg/mL) methylmalonic acid (normal, 73 to 271 nmol/L), and homocysteine (normal, 5.1 to 13.9 μ mol/L). Five patients were subsequently found to have folate deficiency, which left 18 evaluable patients in the oral group and 15 in the parenteral group. Correction of hematologic and neurologic abnormalities was prompt and indistinguishable between the 2 groups. The mean pretreatment

values for serum cobalamin, methylmalonic acid, and homocysteine were, respectively, 93 pg/mL, 3,850 nmol/L, and 37.2 μ mol/L in the oral group and 95 pg/mL, 3,630 nmol/L, and 40.0 μ mol/L in the parenteral therapy group. After 4 months of therapy, the respective mean values were 1,005 pg/mL, 169 nmol/L, and 10.6 μ mol/L in the oral group and 325 pg/mL, 265 nmol/L, and 12.2 μ mol/L in the parenteral group. The higher serum cobalamin and lower serum methylmalonic acid levels at 4 months posttreatment in the oral group versus the parenteral group were significant, with $P < .0005$ and $P < .05$, respectively. In cobalamin deficiency, 2 mg of cyanocobalamin administered orally on a daily basis was as effective as 1 mg administered intramuscularly on a monthly basis and may be superior.

© 1998 by The American Society of Hematology.

THE DAILY REQUIREMENT for cobalamin (vitamin B₁₂) is 1 to 2 μ g. Such tiny doses of the vitamin are quite efficiently (~60%) absorbed bound to intrinsic factor via a specific ileal transport system.¹ Patients with pernicious anemia and other intestinal disorders develop cobalamin deficiency, because they cannot absorb the small amounts of cobalamin in food via this mechanism. It is stated in textbooks²⁻⁴ and widely believed by physicians that such patients cannot reliably absorb oral cobalamin and require frequent, usually monthly, intramuscular injections for life. Indeed, in a recent survey of 245 Minnesota internists, more than 90% believed that such patients cannot absorb sufficient quantities of vitamin B₁₂ when it is administered orally and 94% were unaware that any effective oral cobalamin preparations were available.⁵

However, in the 1950s and 1960s, several investigators⁶⁻¹¹ provided evidence for an additional pathway for cobalamin absorption that does not require intrinsic factor or the presence of an intact ileum.^{8,11-19} If very large doses of cyanocobalamin, in the range of 100 to 100,000 μ g, are administered to patients with pernicious anemia, approximately 1% of the dose is absorbed, so that enough can be administered by mouth to easily exceed the daily requirement. Excellent hematologic responses were also documented in 91 of 91 patients with pernicious anemia who had received 300 to 2,000 μ g or more of oral cyanocobalamin daily.^{8,11-19} Severe neurological involvement was also reported to respond to large oral doses.^{16,17,19} Finally, when patients with pernicious anemia were placed on daily oral maintenance doses of 1,000 μ g, no hematologic or neurologic relapses occurred and serum cobalamin concentrations remained normal.^{10-12,20}

However, oral treatment with the vitamin has never been the subject of a controlled study. Therefore, we conducted a randomized, controlled trial of oral versus parenteral cyanocobalamin therapy in patients with cobalamin deficiency. In addition to assessing hematologic and neurologic responses and changes in serum cobalamin levels, we measured changes in serum methylmalonic acid and total homocysteine levels, two metabolic indicators of cobalamin deficiency that are more sensitive than serum vitamin concentrations.²¹⁻²³

MATERIALS AND METHODS

Selection of patients. Patients were recruited from 4 ambulatory care centers that are part of the Bassett Healthcare network in central New York State. All patients who had serum cobalamin concentrations less than 160 pg/mL as measured in the Bassett Healthcare clinical laboratory between January 1993 and September 1996 were potential subjects. Of 138 such patients, 87 were excluded for one of the following reasons: location outside the immediate geographic area of Bassett Hospital; incapacity to give informed consent; refusal to participate; and associated life-threatening illness. Additional criteria for participation included confirmation of the low serum cobalamin level in another specimen and an elevation of serum methylmalonic acid, total homocysteine, or of both metabolites greater than 3 standard deviations (SD) above the mean in normal controls. As a result, another 13 patients were excluded (6 because of a normal repeat serum cobalamin and 7 in whom neither serum metabolite was elevated). The remaining 38 patients were randomized (Statistical Analysis System; SAS Institute, Cary, NC) to receive oral or parenteral therapy with cyanocobalamin. After completion of the trial, 5 were judged to have primary folate deficiency rather than of cobalamin (see Results) and were excluded from the final analysis. The remaining 33 patients, who were considered to be truly deficient in cobalamin, form the main subject of this report.

Study protocol. Patients were interviewed and examined by one of the investigators before and after the 4-month treatment period. Informed written consent was obtained. Before and after 1, 2, and 4 months of therapy, serum specimens were obtained before the daily oral dose or before the intramuscular treatment, with the exception of 3

From the Division of General Internal Medicine, Bassett Healthcare, Cooperstown, NY; the Division of Hematology, Department of Medicine, University of Colorado Health Sciences Center, Denver, CO; and the Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY.

Submitted February 26, 1998; accepted April 21, 1998.

Address correspondence to Robert H. Allen, MD, 4200 E 9th Ave, Box B-170, Denver, CO 80220.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1998 by The American Society of Hematology.

0006-4971/98/9204-0015\$3.00/0

patients early in the study in whom serum was taken (due to error) within minutes of an injection, on a total of 7 occasions (4 at 1 month, 2 at 2 months, and 1 at 4 months). These 7 specimens were excluded from analysis of serum cobalamin in the parenteral group, but were judged valid for serum metabolite concentrations. Serum was not available at the 2-month visit from 1 patient (no. 3). In patient no. 2, folic acid (400 µg/day by mouth) was administered in addition to oral cobalamin between the second and fourth month. The study was approved by the review boards of the Mary Imogene Bassett Hospital and Columbia-Presbyterian Medical Center.

Therapeutic regimens. Patients were randomized to receive 2,000 µg of oral cyanocobalamin (two 1,000 µg tablets; Nature's Bounty, Bohemia, NY) administered with breakfast daily for 4 months or 1,000 µg of cyanocobalamin intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60, and 90. A research nurse administered the injections and monitored compliance.

Laboratory methods. Serum cobalamin and folate concentrations were determined by radioassays using purified intrinsic factor and milk binder (Simultrac-S; Becton Dickinson Laboratories, Orangeburg, NY). Serum anti-intrinsic factor antibodies and unsaturated serum cobalamin-binding capacity were measured using a coated-charcoal assay.²⁴ Serum methylmalonic acid and total homocysteine were measured using capillary gas chromatography-mass spectrometry.²⁵ Serum pepsinogen I levels were determined by a double antibody radioimmunoassay (Sorin Biomedical Diagnostics, Incstar Corp, Steelwater, MN) as was serum gastrin (Becton Dickinson Laboratories).

Statistical analysis. Standard methods, including the Students' *t*-test and the χ^2 test with Yates' correction for continuity²⁶ were used.

RESULTS

Characteristics of patients. Eighteen cobalamin-deficient patients were randomized to oral cyanocobalamin (Tables 1 and 2) and 15 to intramuscular treatment (Tables 3 and 4). A majority in both groups were elderly women. All were white except for 1 Latina patient. All but 1 or 2 patients in each group were outpatients and most were not anemic. In 1 patient (no. 4), the serum creatinine was increased (1.7 mg/dL). In 2 anemic patients in the parenteral group (Table 3), iron deficiency appeared to contribute to the anemia. The erythrocyte mean cell volume (MCV) was elevated (>100 fL) in 7 and 8 patients, respectively, in the 2 groups. Four patients in each group had mild to moderate neurologic symptoms consistent with cobalamin deficiency.

All patients had a low serum cobalamin; 2 in each group had a decreased serum folate (Tables 2 and 4). Serum methylmalonic acid was greater than 3 SD above the mean in normal controls in all except no. 33 in the parenteral group. Serum total homocysteine was greater than 3 SD above the normal mean in 10 and 12 patients, respectively, in the oral and parenteral groups. The 2 groups did not differ significantly in mean age, pretreatment hematocrit, MCV, serum cobalamin, folate, methylmalonic acid, or total homocysteine.

Table 1. Pretreatment Clinical and Hematologic Findings and Responses to 4 Months of Therapy in Patients Randomized to Oral Cyanocobalamin

Patient No.	Age/Sex	Diagnosis*	Therapy	Hematocrit (%)		MCV (fL)		Neurologic Symptoms†	
				Pre†	4 mo†	Pre	4 mo	Pre	4 mo
1	70/F	AG	Oral	35	40	107	91		
2	76/F	PA, Diet	Oral	20	41	129	80	Memory loss	Improved
3	43/F	PA	Oral	25	38	118	83		
4	69/M	AG	Oral	41	40	90	89	Paresthesias	Improved
5	67/M	PA	Oral	34	43	107	79		
6	71/M	PA	Oral	36	41	87	81		
7	71/F	AG	Oral	41	39	99	99		
8	80/F	AG	Oral	42	42	89	90		
9	62/F	AG	Oral	41	41	112	88		
10	72/F	?AG, OMEP	Oral	40	40	82	81		
11	61/M	Diet	Oral	38	38	101	100		
12	81/F	PA	Oral	41	44	102	92		
13	84/F	AG	Oral	41	39	97	91	Paresthesias	Cleared
14	92/M	AG	Oral	43	46	100	100		
15	68/F	IR	Oral	42	40	92	91		
16	80/F	?AG	Oral	42	42	94	95	Paresthesias, ataxia	Cleared
17	75/F	Diet	Oral	35	36	87	81		
18	77/M	?AG, HIST	Oral	39	39	95	96		
Mean ± SD	72 ± 11		Oral	37.6 ± 6.2	40.5 ± 2.9	100 ± 12	90 ± 7		

*AG indicates evidence of chronic atrophic gastritis (low serum pepsinogen [<30 µg/L] in each instance with elevated serum gastrin [>100 pmol/L] in all except no. 8). In a series of 120 consecutive patients (J. Lindenbaum, unpublished data) with proven pernicious anemia (defined as the presence of antibodies to intrinsic factor and unequivocal evidence of cobalamin deficiency), serum pepsinogen concentrations were less than 30 µg/L in 110 (90.9%), in contrast to 2.5% of 120 normal controls. In the remaining 10 patients with pernicious anemia, serum pepsinogen levels varied from 30 to 70 µg/L, in the lower half of the normal range. Serum gastrin levels were greater than 100 pmol/L in 105 (87.5%) of the 120 patients with pernicious anemia, in contrast to none of the controls. PA indicates pernicious anemia (serum antibodies to intrinsic factor and low pepsinogen in each instance, with elevated serum gastrin in all except no. 6); ?AG indicates serum pepsinogen 47 to 67 µg/L, with elevated serum gastrin only in no. 18. OMEP indicates chronic omeprazole therapy for esophageal reflux; HIST indicates chronic H₂-blocker therapy. Diet indicates inadequate dietary protein intake. IR indicates prior ileal resection.

†Pre indicates pretreatment value; 4 mo indicates value after 4 months of oral cyanocobalamin at 2,000 µg/d.

‡Improved indicates dramatic improvement in neurologic symptoms and cleared indicates complete resolution of symptoms at 4 months.

Table 2. Serum Vitamin and Metabolite Concentrations Before and After 4 Months of Therapy in Patients Randomized to Oral Cyanocobalamin

Patient No.	Therapy	Serum Cobalamin (pg/mL)*		Serum Folate (ng/mL)*		Serum Methylmalonic Acid (nmol/L)*		Serum Total Homocysteine (μmol/L)	
		Pre†	4 mo†	Pre	4 mo	Pre	4 mo	Pre	4 mo
1	Oral	30	1,635	8.7	6.6	25,400	136	113.4	8.2
2	Oral	10	330	3.9	7.4‡	14,700	195	175.0	13.3‡
3	Oral	35	510	13.8	10.6	13,600	160	96.0	8.0
4	Oral	70	520	6.0	8.3	5,350	447	27.3	12.2
5	Oral	100	315	6.4	5.1	1,450	287	41.7	16.5
6	Oral	65	1,885	6.1	8.7	1,180	151	14.2	7.8
7	Oral	150	1,470	6.4	4.1	1,060	95	10.5	6.3
8	Oral	125	1,030	4.6	5.4	877	153	9.0	6.9
9	Oral	65	555	4.3	3.2	811	94	22.5	6.7
10	Oral	160	1,650	4.3	4.1	789	158	16.8	7.6
11	Oral	95	845	8.5	11.4	732	125	23.2	21.7
12	Oral	110	2,100	6.5	8.4	636	101	22.8	11.2
13	Oral	95	520	1.9	1.8	600	111	19.5	10.7
14	Oral	60	660	5.9	5.7	525	174	12.3	8.0
15	Oral	120	625	7.2	8.3	458	115	17.9	8.7
16	Oral	155	1,900	3.6	3.0	407	294	13.1	11.7
17	Oral	65	745	1.5	1.3	389	118	24.6	18.3
18	Oral	155	650	10.3	65.0	386	127	10.5	6.6
Mean	Oral	93 ± 46	1,005 ± 595	6.1 ± 3.0	9.4 ± 14.2	3,850 ± 6,930	169 ± 90	37.2 ± 44.9	10.6 ± 4.4

*Normal range for serum cobalamin, 200 to 900 pg/mL. Normal range for serum folate, 2.6 to 13.0 ng/mL. Normal range for serum methylmalonic acid, based on mean ± 3 SD after log normalization to correct for skewness of data toward higher values, 53 to 376 nmol/L, and based on mean ± 2 SD, 73 to 271 nmol/L; for serum total homocysteine, based on mean ± 3 SD, 4.0 to 17.9 μmol/L, and based on mean ± 2 SD, 5.1 to 13.9 μmol/L.

†Pre and 4 mo as in footnote to Table 1.

‡After 2 months of cobalamin treatment, the hematocrit was 41%, MCV was 90 fL, serum value for cobalamin was 315 pg/mL, for folate was 4.8 nmol/L (2.1 ng/mL), for methylmalonic acid was 231 nmol/L, and for homocysteine was 49.4 μmol/L. Folic acid at 400 μg daily by mouth was administered during the last 6 weeks before the 4-month specimen was obtained.

Etiology of cobalamin deficiency. Seven patients (Tables 1 and 3) had serum antibodies to intrinsic factor, establishing the diagnosis of pernicious anemia. In 4, there was a history of gastric or ileal surgery. Fourteen patients, 7 in each group, were felt to have severe chronic atrophic gastritis (which could cause either intrinsic factor deficiency or food-cobalamin malabsorption)^{27,28} using a combination of serum pepsinogen and gastrin concentrations²⁹⁻³¹ (see footnote to Table 1). Three had poor dietary animal protein intake and 3 were taking agents reported to cause food cobalamin malabsorption.^{32,33}

Hematologic and neurologic responses. Hematologic and neurologic responses to cyanocobalamin are shown in Tables 1 and 3 and are summarized in Table 5. They are similar to those observed in a larger study that used only parenteral cobalamin.³⁴ In approximately one half of the patients in each group, a major decrease in MCV occurred. The mean decrease after 4 months of treatment was highly significant in each group ($P < .005$). Substantial increments in hematocrit attributable to cobalamin therapy were seen in a minority of both groups, most strikingly in patients no. 2 and 3 on oral cyanocobalamin. Four patients on each treatment experienced dramatic improvement of neurologic complaints. Improvement in mental status, gait, or vibration sense was documented in 2 and 3 patients, respectively, after oral and parenteral therapy.

Serum cobalamin concentrations. The most striking difference between the two groups was in the behavior of the serum cobalamin level (Fig 1 and Tables 2 and 4). In patients receiving oral cyanocobalamin, serum cobalamin values continued to

increase throughout the 4-month treatment period. In contrast, following a substantial increase after 1 month of intramuscular therapy, the mean serum cobalamin in the parenteral group decreased at 2 months and remained essentially the same at 4 months. Serum cobalamin levels were significantly higher in the oral than the parenteral group at 2 months (643 ± 328 v 306 ± 118 pg/mL; $P < .001$). The difference was more than threefold at 4 months ($1,005 \pm 595$ v 325 ± 165 pg/mL; $P < .0005$). The 95% confidence intervals for the 4-month serum cobalamin concentrations were 708 to 1,300 pg/mL in the oral group and 230 to 420 pg/mL in the parenteral group.

In patients receiving oral therapy, all serum cobalamin concentrations were obtained more than 24 hours after the last oral dose. All of the cobalamin in serum was found to be bound to protein by coated-charcoal assay.

In the parenteral group, the serum specimen at 1 month was obtained 9 days after the last of a series of six 1,000 μg injections; the subsequent 2- and 4-month samples were collected 1 month after the most recent 1,000 μg maintenance injection. The serum cobalamin concentration was normal (>200 pg/mL) in all subjects in the oral group at 1, 2, and 4 months and in all in the parenteral group at 1 month. However, the serum cobalamin was again low at 2 and 4 months in 3 and 4 patients receiving intramuscular therapy, respectively. At 4 months, the serum value was greater than 300 pg/mL in only one half of the parenteral group compared with all of those receiving oral cyanocobalamin (Tables 2, 4, and 5; $P < .001$).

Table 3. Pretreatment Clinical and Hematologic Findings and Responses to 4 Months of Therapy in Patients Randomized to Parenteral Cyanocobalamin

Patient No.	Age/Sex	Diagnosis*	Therapy†	Hematocrit (%)		MCV (fL)		Neurologic Symptoms§	
				Pre‡	4 mo‡	Pre	4 mo	Pre	4 mo
19	70/M	AG	IM	45	45	103	82	Ataxia	Cleared
20	70/M	AG	IM	40	45	118	86	Paresthesias	Improved
21	41/F	AG	IM	30	43	91	83		
22	83/F	AG	IM	42	41	106	89	Memory loss	Improved
23	65/F	PA	IM	38¶	44¶	119	89		
24	60/F	PA	IM	39	41	112	94		
25	70/F	AG	IM	42	44	106	86		
26	85/F	IR	IM	38	34	99	90	Ataxia	Cleared
27	77/F	AG	IM	42	45	100	98		
28	73/F	Diet	IM	35	34	93	93		
29	79/F	Diet	IM	41	43	107	106		
30	37/F	GS	IM	30	37	129	86		
31	85/F	OMEPE	IM	39	41	84	86		
32	78/F	IR	IM	38	37	86	91		
33	85/F	AG	IM	35	34	100	97		
Mean ± SD	71 ± 15		IM	39.5 ± 2.9	40.6 ± 4.4	102 ± 11	91 ± 7		

*See footnotes to Table 1. GS indicates prior gastric stapling. All patients designated as AG or PA had low serum pepsinogen levels as well as elevated serum gastrin concentrations.

†IM indicates intramuscular cobalamin therapy.

‡Pre indicates pretreatment value. 4 mo indicates value after 4 months of intramuscular cyanocobalamin (total of nine 1,000 µg injections).

§See footnote to Table 1.

||Patient no. 21 received simultaneous iron therapy and patient no. 30 received simultaneous iron and folic acid treatment. Hematocrits on patients no. 21 and 30 are not included in the calculation of the mean values and the MCV of patient no. 30 was not included in the calculation of the mean values.

¶Also had atrophic glossitis before therapy, which had resolved completely at 4 months.

Serum metabolite levels. Elevated serum methylmalonic acid concentrations (Fig 2) decreased to less than 3 SD above the mean for normal controls during therapy in every patient except no. 4 (Table 2), in whom the serum creatinine was elevated. During oral treatment, the serum methylmalonic acid

decreased progressively over 4 months (Fig 2). In contrast, in the parenteral group, the nadir in the serum concentration was usually reached at 1 month, with a subsequent modest rebound (Fig 2), so that the levels were significantly higher at 2 and 4 months than at 1 month in those receiving intramuscular

Table 4. Serum Vitamin and Metabolite Concentrations Before and After 4 Months of Therapy in Patients Randomized to Parenteral Cyanocobalamin

Patient No.	Therapy*	Serum Cobalamin (pg/mL)†		Serum Folate (ng/mL)†		Serum Methylmalonic Acid (nmol/L)†		Serum Total Homocysteine (µmol/L)†	
		Pre‡	4 mo‡	Pre	4 mo	Pre	4 mo	Pre	4 mo
19	IM	90	170	9.0	4.9	22,200	339	45.0	14.5
20	IM	35	190	14.4	13.8	19,600	852	100.8	8.5
21	IM	70	350	2.6	2.7	2,510	238	70.9	9.1
22	IM	75	635	10.0	5.7	1,760	289	55.2	12.9
23	IM	45	175	5.4	5.7	1,170	370	23.9	10.0
24	IM	80	200	4.7	6.7	1,280	170	55.2	9.3
25	IM	30	230	8.3	8.5	1,070	444	71.8	11.4
26	IM	95	380	4.1	6.1	1,010	219	38.3	12.1
27	IM	170	390	3.4	3.9	665	120	14.4	19.0
28	IM	160	365	2.5	2.5	659	166	21.6	18.1
29	IM	110	295	3.4	3.7	502	172	26.0	17.3
30	IM	50	175	4.0§	13.7	421	177	21.3	8.4
31	IM	120	—	5.1	6.1	418	188	11.4	7.5
32	IM	155	690	25.6	50.2	396	136	10.4	7.5
33	IM	140	300	3.4	1.8	272	96	34.3	17.8
Mean ± SD	IM	95 ± 92	325 ± 165	7.1 ± 6.1	9.1 ± 11.9	3,630 ± 7,040	265 ± 190	40.0 ± 26.2	12.2 ± 4.1

*IM indicates intramuscular therapy.

†Normal ranges and conversion factors for serum vitamin concentrations as indicated in footnote to Table 2.

‡Pre and 4 mo as in footnote to Table 3.

§After 1 week of oral folic acid at 1 mg/d; previous serum folate level was less than 1.0 ng/mL.

||Value excluded from analysis due to error in sampling immediately after parenteral dose.

Table 5. Responses After 4 Months of Therapy With Oral or Parenteral Cyanocobalamin

	Oral	Parenteral
MCV decreased ≥ 5 fL	9/18	8/15
Hematocrit increased $\geq 5\%$	5/18	2/15
Marked improvement or clearing of paresthesias, ataxia, or memory loss	4/18	4/15
Serum methylmalonic acid decreased to < 3 SD above the mean in normal controls	17/18	12/14*
Serum total homocysteine decreased to < 3 SD above the mean in normal controls	16/18†	13/15
Serum cobalamin > 300 pg/mL at 4 mo	18/18	7/14§
Serum cobalamin > 200 pg/mL at 4 mo	18/18	10/14

*In 1 patient (no. 33), the pretreatment methylmalonic acid level was not increased.

†One responding patient (no. 2) required the addition of folic acid to normalize the serum homocysteine.

§Comparing oral versus parenteral treatment, $\chi^2 = 11.5$; $P < .001$.

||Comparing oral versus parenteral treatment, $\chi^2 = 5.9$; $P < .03$.

injections ($P < .001$ and $P < .05$, respectively). The methylmalonic acid value in patients no. 20 and 25, which had been less than 3 SD above the mean for normal controls at 30 days, was elevated by 4 months (Table 4); serum cobalamin concentrations had decreased to low to borderline values in these 2 patients. Mean concentrations of the metabolite (Fig 2) did not differ significantly between the 2 treatment groups except at 4

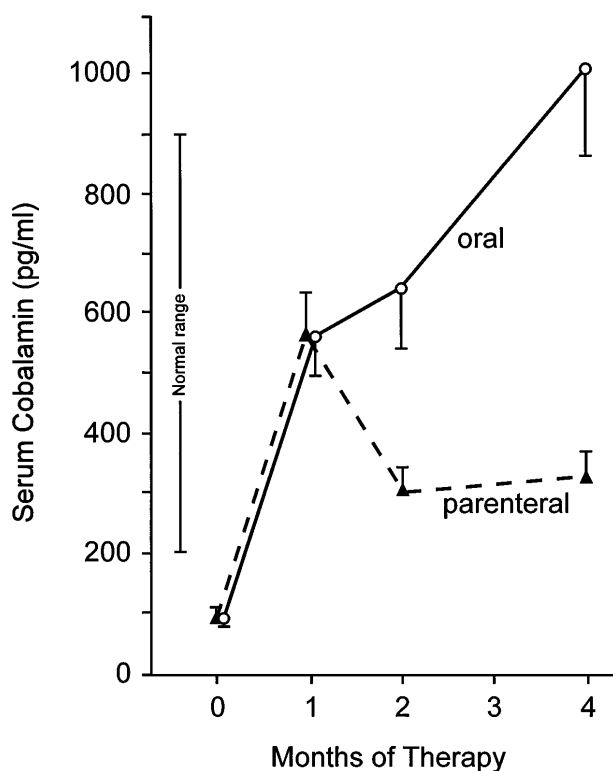


Fig 1. Mean serum cobalamin levels before and during 4 months of therapy with cyanocobalamin. Bars indicate ± 1 SEM. At 2 and 4 months, mean serum cobalamin concentrations were significantly higher with oral therapy ($P < .001$ and $P < .0005$, respectively).

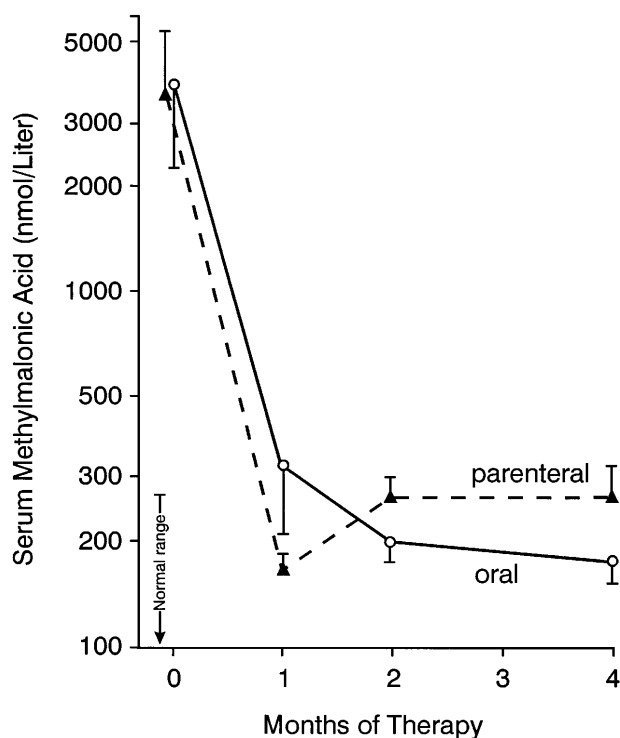


Fig 2. Mean serum methylmalonic acid concentrations before and during 4 months of therapy with oral or parenteral cyanocobalamin. Bars indicate \pm SEM. At 4 months, methylmalonic acid concentrations were significantly lower with oral therapy ($P < .05$).

months, when the value was higher in those receiving injections ($P < .05$).

Elevated serum total homocysteine concentrations decreased to normal in most patients in both groups (Tables 2 and 4), decreasing progressively over 4 months of oral therapy, in contrast to a more pronounced decrease during the first month of injections (Fig 3). However, in a minority of patients in both groups, the response of this metabolite was not optimal. At 4 months, serum homocysteine remained greater than 3 SD above the mean for normal controls in patients no. 11 and 17 of the oral group and in patients no. 27 and 28 receiving intramuscular therapy (Tables 2 and 4). All of these patients had achieved normal serum cobalamin and methylmalonic acid concentrations. Each gave a history consistent with markedly decreased dietary folate intake associated with depression, dementia, or alcoholism; in all except patient no. 11, the serum folate was low or low normal. It was not possible to undertake a subsequent trial of folic acid therapy in these patients. However, in a patient with pernicious anemia as well as severe anorexia and depression, a continued increase of serum homocysteine after 2 months of oral cobalamin therapy responded to folic acid (patient no. 2 in Table 2 as indicated in a footnote to Table 2).

Patients with primary folate deficiency. After completion of the trial, 5 patients were considered to have primary deficiency of folate rather than cobalamin and were excluded from the analysis. At entry, each of them had low levels of both cobalamin and folate; homocysteine values (but not those of methylmalonic acid) were greater than 3 SD above the normal mean. None had evidence of underlying atrophic gastritis. Four

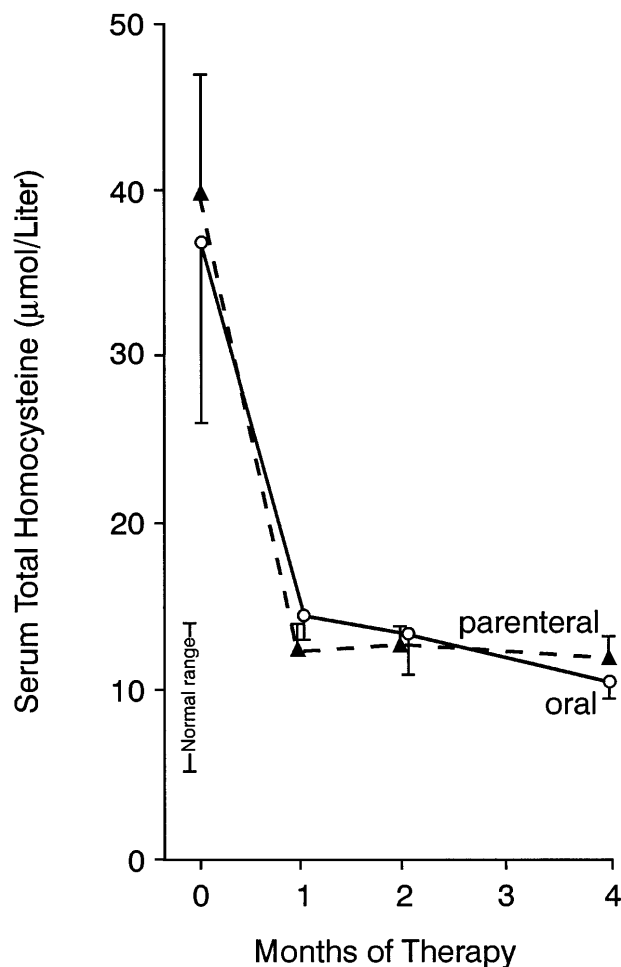


Fig 3. Mean serum total homocysteine concentrations before and during cyanocobalamin therapy administered by mouth (—) or by injection (---). Bars indicate 1 standard error above or below mean. The number of patients at each point is the same as in Fig 2. Normal range indicates 2 SD above and below the mean in normal controls. Mean values did not differ significantly between the 2 groups at any time point.

of the five gave a history of depression, alcoholism, or malnutrition. During parenteral or oral therapy, cobalamin levels became normal in all 5 patients, but there were no hematologic responses. Homocysteine concentrations did not normalize at 4 months (and actually increased during treatment in 4). In 1 of them who was available for subsequent study, the serum homocysteine had increased from 28.1 $\mu\text{mol/L}$ before therapy to 65.2 $\mu\text{mol/L}$ after parenteral cyanocobalamin, at which time the serum folate remained low at 1.8 ng/mL . After a 4-week course of 1 mg of daily oral folic acid, the serum homocysteine concentration decreased to 10.0 $\mu\text{mol/L}$ as the serum folate concentration increased to 27.4 ng/mL .

DISCUSSION

This randomized controlled trial of oral versus intramuscular cyanocobalamin in the treatment of well-documented cobalamin deficiency demonstrated that oral and parenteral therapy were equally effective in producing excellent hematologic and

neurologic remissions, as well as robust initial metabolic responses. Furthermore, an oral regimen of 2,000 μg per day resulted in serum cobalamin concentrations that were more than 3 times greater than those obtained with a standard parenteral schedule³⁵ of nine 1,000 μg injections administered over a 4-month period (Fig 1). Furthermore, the absorption of the oral preparation was good in every patient, so that at 4 months 18 of 18 receiving oral therapy versus only 7 of 14 receiving injections achieved serum cobalamin levels greater than 300 pg/mL , a value below which metabolic evidence of cobalamin deficiency is frequently demonstrated, especially in the elderly.^{23,36} Indeed, the lower vitamin concentrations in the parenteral group were associated with slightly but significantly higher values for methylmalonic acid, a metabolite that is frequently abnormal before serum cobalamin levels become subnormal as deficiency of the vitamin develops.²¹ The clinical importance of maintaining normal serum cobalamin and metabolite levels is unclear; however, it is reasonable to use a therapeutic preparation with the greatest overall bioavailability, particularly if it enjoys high patient acceptability.

Serum homocysteine levels may be elevated in either Cbl or folate deficiency.^{22,24} In the absence of an increased serum methylmalonic acid, an isolated increase in serum homocysteine is usually caused by folate deficiency.^{22,37} It is of interest that 5 patients entered into the trial were later considered to have primary folate deficiency. Although serum cobalamin levels were low, only serum homocysteine was increased and did not respond to 4 months of parenteral or oral cyanocobalamin (and even increased further in most of the subjects). Others have reported that serum cobalamin levels may often be low in patients with folate deficiency in the absence of defects in cobalamin intake, absorption, or body stores, and have noted increases in serum cobalamin after folate therapy alone.^{38,39} Our findings are consistent with previous reports that only specific therapy with the vitamin in which the patient is truly deficient will normalize increased metabolite levels.^{40,41}

In addition, among the 33 patients reported here who had clear-cut evidence of true cobalamin deficiency, despite impressive decreases in serum methylmalonic acid and the achievement of normal to increased serum cobalamin concentrations (Tables 2 and 4), 5 (3 on oral and 2 on parenteral therapy) showed only partial serum homocysteine responses. All gave a history consistent with folate deficiency, although 1 of them (patient no. 2) also had unequivocal underlying pernicious anemia. Thus, of 38 patients randomized into the study based on low serum cobalamin and increased metabolite levels, 10 (26%) were found to have folate deficiency as well, either primary or in association with lack of cobalamin.

In summary, in a randomized, controlled trial, large daily oral doses of cyanocobalamin were found equally effective in producing hematologic and neurologic responses as a standard parenteral regimen in patients with cobalamin deficiency and also resulted in clearly superior serum cobalamin levels after 4 months of treatment. Slightly better control of metabolic abnormalities was also achieved with the oral preparation. Our findings, taken together with the extensive and convincing, although uncontrolled, previous reports in the literature,^{8-19,42} strongly support the view that high doses of oral cyanocobalamin can replace intramuscular therapy in most situations in

which the latter is currently administered. Large doses of cyanocobalamin appear to be nontoxic.⁴³ The costs of either therapy are low, although the need for a health provider to administer monthly injections often adds considerable expense.^{5,44,45} It has been argued that patients are less likely to be compliant with oral treatment,⁴¹ although compliance has been reported to be very good.^{10,42} However, any maintenance therapy is likely to be associated with neglect, especially since today cobalamin injections are often administered outside the physician's office by the patient, a relative, or a friend. Of a large series of patients with pernicious anemia, 11% interrupted parenteral therapy and suffered a relapse.⁴⁶ Oral maintenance therapy has been widely used in Sweden for more than 25 years.^{5,10,44,47} In a series of 64 Swedish patients maintained for several years on 1,000 µg/d, none relapsed or had a low serum cobalamin level.¹⁰ The 2,000 µg dose used in our study might therefore be considered overly generous, although it may provide an element of safety in view of the wide range of serum cobalamin concentrations found after 4 months (Table 2). Because the various preparations of oral cyanocobalamin (as well as parenteral cobalamin) are not regulated by the FDA, bioavailability may be unpredictable. Use of oral preparations other than that used in this study may not yield similar results. Compliance and effectiveness of cobalamin therapy in individual patients can and should be checked occasionally by measuring the serum cobalamin level either alone or together with metabolite levels.

Undoubtedly, parenteral treatment will continue to play a role in the treatment of cobalamin deficiency, particularly in hospitalized patients; in those with diarrhea, vomiting, or otherwise unable to take medication by mouth; in the unreliable; and in patients with severe neurologic involvement. In the initial treatment of the average outpatient with mild to moderate deficiency or in patients who require maintenance therapy, oral cyanocobalamin with a preparation of proven bioavailability should be strongly considered, if not indeed viewed as the regimen of choice.

REFERENCES

- Chanarin I: *The Megaloblastic Anemias* (ed 2). Oxford, UK, Blackwell Scientific, 1979
- Babior BM, Bunn HF: Megaloblastic anemias, in Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL (eds): *Harrison's Principles of Internal Medicine* (ed 13). New York, NY McGraw-Hill, 1994, p 1731
- Lee GR: Megaloblastic and nonmegaloblastic macrocytic anemias, in Lee GR, Bithell TC, Foerster J, Athens JW, Lukens JN (eds): *Wintrobe's Clinical Hematology* (ed 9). Philadelphia, PA, Lea & Febiger, 1993, p 777
- Jeejeebhoy KN: Nutrient requirements and nutrient deficiencies in gastrointestinal diseases, in Sleisenger MH, Fordtran JS (eds): *Gastrointestinal Disease: Pathophysiology/Diagnosis/Management* (ed 5). Philadelphia, PA, Saunders, 1993, p 2039
- Lederle FA: Oral cobalamin for pernicious anemia: Medicine's best kept secret? *J Am Med Assoc* 265:94, 1991
- Doscherholmen A, Hagen PS, Liu M, Olin L: A dual mechanism of vitamin B₁₂ plasma absorption. *J Clin Invest* 36:1551, 1957
- Gaffney GW, Watkin DM, Chow BF: Vitamin B₁₂ absorption: Relationship between oral administration and urinary excretion of cobalt⁶⁰-labeled cyanocobalamin following a parenteral dose. *J Lab Clin Med* 53:525, 1959
- Ross GIM, Mollin DL, Cox EV, Ungley CC: Hematologic responses and concentration of vitamin B₁₂ in serum and urine following oral administration of vitamin B₁₂ without intrinsic factor. *Blood* 9:473, 1954
- Heinrich HC, Gabbe EE: Experimental basis of oral and parenteral therapy with cyano- and aquacobalamin, in Linnell JC, Bhatt HR (eds): *Biomedicine and Physiology of Vitamin B₁₂*. London, UK, The Children's Medical Charity, 1990, p 51
- Berlin H, Berlin R, Brante G: Oral treatment of pernicious anemia with high doses of vitamin B₁₂ without intrinsic factor. *Acta Med Scand* 184:247, 1968
- Waife SO, Jansen CJ, Crabtree RE, Grinnan EL, Fouts PJ: Oral vitamin B₁₂ without intrinsic factor in the treatment of pernicious anemia. *Ann Intern Med* 58:810, 1963
- McIntyre PA, Hahn R, Masters JM, Krevans JR: Treatment of pernicious anemia with orally administered cyanocobalamin (vitamin B₁₂). *Arch Intern Med* 106:280, 1960
- Spies TD, Stone RE, Lopez GG, Milanese F, Toca RL, Aramburu T: Vitamin B₁₂ by mouth in pernicious and nutritional macrocytic anemia and sprue. *Lancet* 2:454, 1949
- Chalmers JNM, Shinton NK: Absorption of orally administered vitamin B₁₂ in pernicious anemia. *Lancet* 2:1298, 1958
- Ungley CC: Absorption of vitamin B₁₂ in pernicious anaemia. I. Oral administration without a source of intrinsic factor. *Br Med J* 2:905, 1950
- Conley CL, Krevans JR, Chow BF, Barrows C, Lang CA: Observations on the absorption, utilization and excretion of vitamin B₁₂. *J Lab Clin Med* 38:84, 1951
- Conley CL, Green TW, Hartmann RC, Krevans JR: Prolonged treatment of pernicious anemia with vitamin B₁₂. *Am J Med* 13:284, 1952
- Conley LC, Krevans JR: Developments in the diagnosis and treatment of pernicious anemia. *Ann Intern Med* 43:758, 1955
- Unglaub WG, Goldsmith GA: Oral vitamin B₁₂ in the treatment of macrocytic anemias. *Southern Med J* 48:261, 1955
- Magnus EM: Cobalamin and unsaturated transcobalamin values in pernicious anaemia: Relation to treatment. *Scand J Haematol* 36:457, 1986
- Lindenbaum J, Savage DG, Stabler SP, Allen RH: Diagnosis of cobalamin deficiency: II. Relative sensitivities of serum cobalamin, methylmalonic acid, and total homocysteine concentrations. *Am J Hematol* 34:99, 1990
- Savage DG, Lindenbaum J, Stabler SP, Allen RH: Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. *Am J Med* 96:239, 1994
- Lindenbaum J, Rosenberg IH, Wilson PWF, Stabler SP, Allen RH: Prevalence of cobalamin deficiency in the Framingham elderly population. *Am J Clin Nutr* 60:2, 1994
- Gottlieb C, Lau KS, Wasserman LR, Herbert V: Rapid charcoal assay for intrinsic factor (IF), gastric juice unsaturated B₁₂ binding capacity, antibody to IF, and serum unsaturated B₁₂ binding capacity. *Blood* 25:875, 1965
- Allen RH, Stabler SP, Savage DG, Lindenbaum J: Metabolic abnormalities in cobalamin (vitamin B-12) and folate deficiency. *FASEB J* 7:1344, 1993
- Snedecor GW, Cochran WG: *Statistical Methods*. Ames, IA, Iowa University, 1973
- Doscherholmen A, Swaim WR: Impaired assimilation of egg ⁵⁷Co vitamin B₁₂ in patients with hypochlorhydria and achlorhydria and after gastric resection. *Gastroenterology* 64:913, 1973
- Carmel R: Subtle and atypical cobalamin deficiency states. *Am J Hematol* 34:108, 1990
- Westerveld BD, Pals G, Lamers CBHW, Defize J, Pronk JC, Frants RR, Ooms EC, Kreuning J, Kostense PJ, Eriksson AW: Clinical

significance of pepsinogen A isozymogens, serum pepsinogen A and C levels, and serum gastrin levels. *Cancer* 59:952, 1987

30. Carmel R: Pepsinogens and other serum markers in pernicious anemia. *Am J Clin Pathol* 90:442, 1988
31. Kekki M, Samloff IM, Varis K, Ihamaki T: Serum pepsinogen I and serum gastrin in the screening of severe atrophic corpus gastritis. *Scand J Gastroenterol* 26:109, 1991 (suppl 186)
32. Steinberg WM, King CE, Toskes PP: Malabsorption of protein-bound cobalamin but not unbound cobalamin during cimetidine administration. *Dig Dis Sci* 25:188, 1980
33. Schenk BE, Festen HPM, Kuipers EJ, Klinkenberg-Knol EC, Meuwissen SGM: Effect of short- and long-term treatment with omeprazole on the absorption and serum levels of cobalamin. *Aliment Pharmacol Ther* 10:541, 1996
34. Stabler SP, Allen RH, Savage DG, Lindenbaum J: Clinical spectrum and diagnosis of cobalamin deficiency. *Blood* 76:871, 1990
35. Schilling RG: Pernicious anemia. *J Am Med Assoc* 253:94, 1985
36. Pennypacker LC, Allen RH, Kelly JP, Matthews LM, Grigsby J, Kaye K, Lindenbaum J, Stabler SP: High prevalence of cobalamin deficiency in elderly outpatients. *J Am Geriatr Soc* 40:1197, 1992
37. Guttormsen AB, Ueland PG, Nesthus I, Nygard O, Schneede J, Vollset SE, Refsum H: Determinants and vitamin responsiveness of intermediate hyperhomocysteinemia (>40 $\mu\text{mol/liter}$). *J Clin Invest* 98:2174, 1996
38. Mollin DL, Waters AH, Harriss E: Clinical aspects of the metabolic interrelationships between folic acid and vitamin B₁₂, in Heinrich HC (ed): *Vitamin B₁₂ and Intrinsic Factor 2*. Europaisches Symposium. Stuttgart, Germany, Ferdinand Enke Verlag, 1962, p 737
39. Johnson S, Swaminathan SP, Baker SJ: Changes in serum vitamin B₁₂ levels in patients with megaloblastic anaemia treated with folic acid. *J Clin Pathol* 15:274, 1962
40. Allen RH, Stabler SP, Savage D, Lindenbaum J: Diagnosis of cobalamin deficiency. I. Usefulness of serum methylmalonic acid and total homocysteine concentrations. *Am J Hematol* 34:90, 1990
41. Landgren P, Israelsson B, Lindgren A, Hultberg B, Andersson A, Brattstrom L: Plasma homocysteine in acute myocardial infarction: Homocysteine-lowering effect of folic acid. *J Intern Med* 237:381, 1995
42. Reisner EH, Weiner L, Schittone MT, Henck EA: Oral treatment of pernicious anemia with vitamin B₁₂ without intrinsic factor. *N Engl J Med* 253:502, 1955
43. Hathcock JN, Troendle GJ: Oral cobalamin for treatment of pernicious anemia? *J Am Med Assoc* 265:96, 1991
44. Berlin R: Vitamin B₁₂ injections. *Br Med J* 291:56, 1985
45. Middleton J, Wells W: Vitamin B₁₂ injections: Considerable source of work for the district nurse. *Br Med J* 290:1254, 1985
46. Savage D, Lindenbaum J: Relapses after interruption of cyanocobalamin therapy in patients with pernicious anemia. *Am J Med* 74:765, 1983
47. Berlin R, Berlin H, Brante G, Pilbrant A: Vitamin B₁₂ body stores during oral and parenteral treatment of pernicious anemia. *Acta Med Scand* 204:81, 1978