A pilot study of vitamin B_{12} in the treatment of tiredness

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1. Twenty-eight subjects complaining of tiredness completed a double-blind cross-over trial of injections of hydroxocobalamin (5 mg twice weekly for 2 weeks) followed by a rest period of 2 weeks and then a similar course of matching placebo injections. Symptoms were assessed by a daily self-rating method and included appetite, mood, energy, sleep and general feeling of well-being.

2. Those subjects who received the placebo in the first 2-week period showed a favourable response to hydroxocobalamin in the second period in all measurements made. The response achieved statistical significance ($P = 0{\cdot}006$) in respect of general well-being; 'happiness' achieved a value of $P = 0{\cdot}032$. Subjects who received hydroxocobalamin in the first period showed no difference between responses to active and placebo treatments, which suggests that the effects of the vitamin may persist for a period of at least 4 weeks.

There are a number of instances in the literature where it is claimed that vitamin B_{12} has improved the well-being of patients not suffering from a deficiency of the vitamin (Morwood, 1952; O'Brien, 1954; Wilkinson, 1968). In none of these instances does the assertion have the backing of a properly controlled trial. Nevertheless the belief that vitamin B_{12} has this capacity is widely held (Ellis, Nasser & Wrighton, 1970). A small controlled trial was carried out to investigate the validity of this belief.

EXPERIMENTAL

Subjects were obtained from two sources. One source was local general practitioners, who were asked by letter to refer any patients complaining of fatigue or tiredness for which no cause could be found; the other was hospital staff, from whom volunteers were sought who professed to be suffering from tiredness for no apparent reason.

All subjects were given a thorough physical medical examination, including chest X-ray and electrocardiograph. Blood samples were obtained for the following investigations: haemoglobin, packed cell volume and white cell count were determined on a Coulter Model 'S' (Coulter Electronics, Luton, Beds.), the erythrocyte sedimentation rate by the method of Westergren (1921), serum folate concentration by the method of Chanarin (Chanarin & Berry, 1964), and serum vitamin B_{12} concentration with *Lactobacillus leichmannii* (Spray, 1955); the serum concentrations of urea, cholesterol, calcium, phosphate and proteins were determined by standard automated techniques.

The tests were repeated on most subjects every 2 weeks throughout the period of study. Some of the subjects were submitted to a psychiatric interview. The smoking habits of the subjects were noted.

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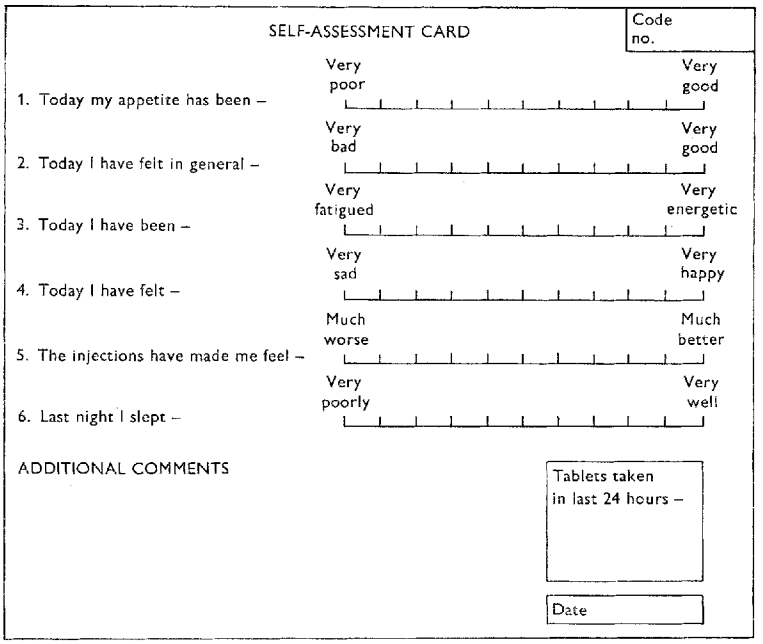

Fig. 1. Self-assessment card used by subjects to show response to treatment with hydroxocobalamin injections.

Treatment with intramuscular injections of 5 mg hydroxocobalamin or solutions of phenol red of matching colour was given in double blind manner. Both solutions were packed in amber glass ampoules to mask any small differences in the quality of the colour between the two solutions.

A cross-over within-subject design was used with random allocation of the two alternative regimens. The first regimen consisted of hydroxocobalamin, 5 mg by intramuscular injection on Tuesday and Friday for 2 consecutive weeks, then 2 weeks without injections, followed by intramuscular injections of placebo on Tuesday and Friday for 2 further weeks. The second regimen was exactly the same as the first except that the placebo was administered over the first 2 weeks and hydroxocobalamin over the last 2 weeks.

Response to treatment was determined by the use of self-assessment cards for each subject. Each card (Fig. 1), by means of six questions, inquired about appetite, general feeling of well-being, mood, fatigue, sleep, and the effect of injections. Each answer was shown by the subject's making a mark along a graduated line representing the difference between the extremes experienced by that patient. The line was 100 mm long and marked off at 10 mm intervals. Every subject was asked to complete a card on each of the 42 d of the trial and to post it immediately to the clinic.

Forty-eight subjects entered the trial, of whom thirty-one were volunteers and seventeen were patients referred by their general practitioner. Nineteen failed to complete the course of treatment or were excluded because their records were incomplete.

Table 1. *Mean serum concentrations and ranges of vitamin B_{12}, folate and haemoglobin in human subjects receiving an injection of 5 mg hydroxocobalamin twice weekly for 2 weeks, before or after a similar course of placebo injections, with a 2-week rest period between (numbers of estimations in parentheses)*

Subjects		Concentration: Initial	After 2 weeks	After 4 weeks	After 6 weeks
Vitamin B_{12} (pg/ml)					
Given hydroxocobalamin first:					
	Mean	363·2 (15)	> 2000 (7)	(13)	(15)
	Range	200–625	> 2000	850–> 2000	450–> 2000
Given placebo first:					
	Mean	353·9 (13)	384·5 (12)	376·0 (11)	> 2000 (12)
	Range	220–625	196–600	175–625	
Folate (ng/ml)					
Given hydroxocobalamin first:					
	Mean	5·5 (14)	8·5 (8)	5·4 (13)	6·2 (14)
	Range	2·2–10·8	2·2–18	2–25	1·0–25
Given placebo first:					
	Mean	7·6 (13)	6·2 (13)	5·7 (10)	6·1 (11)
	Range	1·8–25	1·0–21·8	1·5–25	1·3–25
Haemoglobin (g)					
Given hydroxocobalamin first:					
Females	Mean	132 (12)	128 (11)	129 (11)	127 (12)
	Range	124–140	117–146	116–161	116–135
Males	Mean	156 (3)	157 (3)	153 (2)	157 (3)
	Range	150–162	146–163	150–155	146–165
Given placebo first:					
Females	Mean	134 (11)	128 (11)	133 (10)	130 (10)
	Range	120–150	120–142	110–152	115–146
Males	Mean	151 (3)	149 (3)	153 (2)	150 (3)
	Range	139–169	140–165	150–156	142–158

RESULTS

Of the twenty-nine subjects providing a complete set of results seven were male and twenty-two female; the mean age was 41·5 years (range 22–71 years). Fifteen received hydroxocobalamin first and fourteen received placebo first.

The initial mean serum vitamin B_{12} concentration was 358·4 pg/ml (range 200–625 pg/ml) and the initial serum folate concentration was 7·3 ng/ml (range 1·8–25 ng/ml) respectively. Table 1 shows initial values of serum vitamin B_{12}, serum folate and haemoglobin concentrations according to which treatment group the subjects were allocated and the three subsequent estimations at 2-week intervals. No subject was included in the trial whose initial blood values were not in the normal range. It was noted that at the end of treatment with hydroxocobalamin the serum concentrations of vitamin B_{12} had risen to more than 2000 pg/ml in all subjects in whom it was estimated. This high concentration was sustained in all but three subjects for the rest

Table 2. *Preference with respect to order of treatment shown by tests on human subjects treated with hydroxocobalamin injections before or after a similar course of placebo injections*

	Order of treatment	
	Placebo first	Hydroxocobalamin first
No. in favour of hydroxocobalamin		
Total	56	36
Patients*	36	16
Hospital staff†	20	20
No. showing no difference		
Total	8	16
Patients*	4	12
Hospital staff†	4	4
No. in favour of placebo		
Total	20	38
Patients*	8	26
Hospital staff†	12	12

* Referred by their general practitioners. † Volunteers.

of the trial. These three subjects had concentrations of 450, 475 and 1750 pg/ml at the end of the period. No other blood value altered significantly during the trial.

Sixteen subjects were assessed psychiatrically; thirteen of them were included in the final analysis, five were from the hospital staff group and eight were patients. Of the five hospital staff, two were considered to be under stress, one was aged and infirm, one was pregnant and one was considered to have an anxiety neurosis. Of the eight patients, one was under stress, four were psychiatrically unstable and three were considered normal.

Self-assessment ratings were analysed as follows. The position of each mark was scored 1–5 by measuring its distance from the midline. If the mark was to the left of the midline it was given a negative value and if to the right a positive value. All scores during the two treatment periods were summed algebraically for each question.

If the score attained during hydroxocobalamin therapy was greater than that attained during the period of placebo injections then the response to that subject was regarded as in favour of hydroxocobalamin. If the reverse was true, this was regarded as being in favour of placebo. No quantitative assessment was made of the difference in the scores because of their subjective origin.

It can be seen from Table 2 that when hydroxocobalamin injections were given at the first treatment, thirty-six assessments were in favour of placebo, thirty-eight in favour of placebo, with sixteen showing no difference. However, in the group who received placebo first a larger proportion of assessments (fifty-six) were in favour of hydroxocobalamin. These results seem to indicate that the response to hydroxocobalamin was long-lasting and continued in the placebo period. Certainly the serum concentrations in all but three instances were still more than 2000 pg/ml. For this reason only the information from the fourteen subjects receiving the placebo first were subjected to further analysis.

The numbers of subjects in favour of hydroxocobalamin and of placebo were assessed separately for each of the six criteria, and the difference was analysed statisti-

Table 3. *Table of binomial distribution of criteria among human subjects treated with hydroxocobalamin injections before or after a similar course of placebo injections*

Question no.	Criteria	Subjects in favour of hydroxocobalamin (patients* + hospital staff†)	Subjects in favour of placebo (patients* + hospital staff†)	Binomial probability (single tail)
1	Appetite	9 (5+4)	3 (2+1)	0·073
2	General well-being	12 (8+4)	2 (0+2)	0·006
3	Fatigue	10 (7+3)	4 (1+3)	0·090
4	Happiness	9 (6+3)	2 (0+2)	0·032
5	Injection effect	7 (5+2)	5 (2+3)	0·387
6	Sleep	9 (5+4)	4 (3+1)	0·133

* Referred by their general practitioners.
† Volunteers.

cally to see whether the result would support the null hypothesis that B_{12} has no effect on patients without deficiency of the vitamin. No preference between the placebo and hydroxocobalamin periods was found for questions no. 1, no. 4, no. 5 and no. 6 in two, three, one and one subjects respectively. The remaining subjects and the other criteria showed preferences as shown in Table 3. It can be seen that the response of the subjects' well-being (question 2) reached significance at the 1% level ($P = 0{\cdot}006$). For this criterion all fourteen subjects indicated a preference for one or the other treatment. Only one of the other criteria ('happiness', question 4) reached significance at the 5% level ($P = 0{\cdot}03$): nine subjects favoured hydroxocobalamin, two favoured placebo and three showed no difference between the regimens. All the remaining criteria showed a trend in favour of hydroxocobalamin. Division of results between patients and hospital staff showed that preference for hydroxocobalamin occurred more frequently in the former.

DISCUSSION

Only three of the patients (18%) failed to complete the 42 d of the study; the other sixteen subjects excluded from the analysis comprised 53% hospital staff. This suggests that the two groups of subjects differed, at least in their motivation to complete the treatment course. This also raises the possibility that the hospital staff completing the course may have been self-selected to a group experiencing beneficial results from the second course. However, this is unlikely as the favourable response to hydroxocobalamin when given as the second course of injections was commoner among the patients than among the hospital staff.

Estimations of 'injection effect' (question 3) and general well-being (question 2)

probably measured the sum of many different symptoms, including those also assessed individually as appetite, mood, fatigue and quality of sleep. The greater degree of statistical significance in favour of hydroxocobalamin over placebo found in answer to question 2 compared with other questions suggests that question 2 does indeed represent the sum of some of the other symptoms. However, other symptoms, not assessed individually, may also partly contribute to the response to question 2.

Future studies should explore this possibility by examining other symptoms. These results seem to offer support for the widely held belief that vitamin B_{12} has a definite 'tonic' effect (Ellis *et al.* 1970).

The mode of action of vitamin B_{12} is open to speculation. There was no direct correlation between serum vitamin B_{12} concentration and improvement; the subject with the lowest concentration of 450 pg/ml at the final estimation 4 weeks after the last injection of active hydroxocobalamin, showed marked improvement in symptoms. However, most concentrations were 2000 pg/ml at this stage of the study. Response may have been related to pharmacological factors such as the ability of the vitamin to penetrate into brain or neurones or to an influence of vitamin B_{12} on neural metabolism, or penetration of other substances such as folate. From investigation in neurological disorders it seems that vitamin B_{12} has a role in the physiology of nervous tissue, but its exact function remains unknown so far. Spinal-cord lesions, optic atrophy and psychiatric disturbances are well known in vitamin B_{12} deficiency. The lack of homogeneity among the diverse patients may also explain differences in degree of response experienced.

Hydroxocobalamin seems to have a specific role in the treatment of tobacco amblyopia (Foulds, Chisholm, Bronte Stewart & Wilson, 1969); this is considered to be due to its avidity for cyanide ions, which are present in excess owing to over-indulgence in smoking tobacco, especially by pipe. Heavy smokers of more than forty cigarettes/d were not included in this series of subjects; in fact a large proportion (52%) of the subjects were non-smokers. Favourable response to hydroxocobalamin was as common in non-smokers as in smokers. It is unlikely therefore that the benefit from hydroxocobalamin in this study was related to the reversal of tobacco intoxication.

Whatever the mechanism, the improvement after hydroxocobalamin may be sustained for at least 4 weeks after stopping the drug. Hence, the improvement after hydroxocobalamin was not able to be compared to the placebo response when the former was given as first treatment. Future similar trials should be designed to take account of this prolonged effect, both to assess its length and to make greatest use of all available subjects.

It would be interesting to compare the response to orally administered hydroxocobalamin with that to a placebo in a double-blind manner with a similar group of subjects when the rest period could be avoided and the duration extended.

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