Controlled trial of combinations of hydroxocobalamin-cystine and riboflavine-cystine, in Nigerian ataxic neuropathy¹

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SUMMARY Chronic cyanide intoxication of dietary origin and riboflavine deficiency are believed to be major aetiological factors in Nigerian tropical ataxic neuropathy. The results are presented of a double-blind controlled therapeutic trial of combinations of large doses of hydroxocobalamin and cystine as cyanide binding agents together with riboflavine or placebos in Nigerian patients suffering from the tropical ataxic neuropathy. No clinical benefit was demonstrable with any of the treatments.

A syndrome of insidious onset and comprising bilateral optic atrophy, bilateral perceptive deafness, myelopathy, and peripheral neuropathy has been described in many parts of the tropics. It is often referred to as tropical (ataxic) neuropathy.

Chronic cyanide intoxication of dietary origin has been suggested as a major factor in the aetiology of the neuropathy in Nigeria (Mone-kosso and Wilson, 1966; Osuntokun, 1968, 1969; Osuntokun *et al.*, 1969; Osuntokun, 1971) and in Tanzania (Makene and Wilson, 1972). Deficiency of riboflavine has also been demonstrated in the Nigerian patients (Osuntokun, 1968; Aladetoyinbo *et al.*, 1971). However, no benefit could be demonstrated in a controlled clinical trial from treatment with hydroxocobalamin (which has a strong affinity for cyanide *in vitro* and has a demonstrable protective effect in acute cyanide poisoning), while any effect of riboflavine was small and statistically insignificant (Osuntokun *et al.*, 1970).

Sulphur-containing amino acids (cystine and cysteine) are thiol donors which combine with cyanide to form thiocyanate, an important pathway in man for detoxicating cyanide. In addition, plasma concentrations of cysteine and cystine

have been found to be reduced in Nigerian ataxic neuropathy (Osuntokun *et al.*, 1968), and it therefore seemed worthwhile to examine the value of cystine in treatment. It was combined with hydroxocobalamin in five times the dose previously used as a second cyanide binding agent. A second group received cystine plus riboflavine injections, the latter being added to determine if the previous mildly beneficial effect attributable to this drug was a consistent finding. The riboflavine injections were dyed so as to be indistinguishable from the vitamin B₁₂ and the results in these test groups were compared with those obtained in a control group receiving placebo tablets and 1 µg only of cyanocobalamin by injection.

METHODS

The subjects were 51 patients who showed the clinical features of the ataxic neuropathy as previously described (Osuntokun, 1968, 1969). Of these 36 took part in the previous trial (Osuntokun *et al.*, 1970). In the nine month interval between the end of the first trial and the beginning of the second, they received non-specific treatment which did not include administration of vitamin B₁₂, riboflavine, or amino-acid supplements and they continued to subsist on cassava meals eaten usually three or more times a

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day. The rest of the subjects were newly diagnosed cases, and had not previously received any form of conventional treatment. Advanced cases were not included in the trial. The patients were seen weekly at the Neuropathic Research Clinic maintained by the Wellcome Trust at Epe, or in the Neurology Clinic at the University College Hospital, Ibadan. During the trial, the patients remained on their normal diet comprising usually cassava meals eaten three or more times a day. The procedure employed in the trial was as previously described (Osuntokun *et al.*, 1970). The three treatment groups, to which patients were randomly allocated, received (1) weekly injections of 5,000 μ g hydroxocobalamin plus cystine tablets 500 mg daily, (2) weekly injections of 5 mg riboflavine dyed with amaranth (to resemble hydroxocobalamin) plus cystine tablets 500 mg daily, and (3) weekly injections of 1 μ g cyanocobalamin plus a placebo tablet identical with the cystine tablet, and given daily. The allocation to treatment groups was determined by a prearranged schedule prepared by M.J.S.L. The patients themselves and their examiner (B.O.O.) were unaware of any difference of treatment. The duration of treatment was 48 weeks. Clinical assessment was completed before and after trial as previously described (Osuntokun *et al.*, 1970). Improvement or deterioration during the trial was represented by a reduction or an increase in the score respectively. Plasma thiocyanate concentrations were estimated as previously described (Osuntokun *et al.*, 1970).

RESULTS

Of the 51 patients who commenced the trial, seven failed to complete the full treatment period. Four of these were on hydroxocobalamin-cystine, two on riboflavine-cystine, and one on cyanocobalamin-placebo tablets.

Table 1 shows that three groups were comparable with regard to age, sex, and initial

TABLE 1
COMPARABILITY OF PATIENTS GIVEN THE THREE TREATMENTS

	Treatment groups		
	Hydroxocobalamin + cystine	Riboflavine + cystine	Cyanocobalamin + placebo tablets
Men	14	12	6
Women	4	5	10
Mean age (yr)	53.9	51.0	46.6
Mean initial neurological score	117.2	133.2	140.6

TABLE 2

OVERALL RESULTS OF NEUROLOGICAL ASSESSMENT SCORES

Treatment group	Mean percentage change in neurological scores
Hydroxocobalamin + cystine	+ 8.1
Riboflavine + cystine	- 4.0
Cyanocobalamin placebo + cystine placebo	- 4.2

The percentage change in neurological score for each patient was calculated—for example, initial score = 50, final score = 60, percentage change = 20% in deterioration or + 20%. The mean of these figures was calculated. Positive changes indicate deterioration. Negative changes represent improvement.

(1) v. (3) 0.1 > P > 0.05 } Mann Whitney U test.
(1) v. (2) 0.1 > P > 0.05 }

TABLE 3

SUBJECTIVE CHANGES AT END OF TRIAL

Treatment groups	Better	No change	Worse	Total
Hydroxocobalamin + cystine	4	5	5	14
Riboflavine + cystine	11	1	3	15
Cyanocobalamin + placebo	10	3	2	15

TABLE 4

MEAN THIOCYANATE CONCENTRATIONS BEFORE AND AFTER TRIAL IN THOSE INDIVIDUALS IN WHOM PAIRED MEASUREMENTS WERE MADE

Treatment groups	No.	Mean plasma concentration (μ mol/100 ml. $\pm$ SEM)	
		Before trial	At end of trial
Hydroxocobalamin + cystine	14	11.0 $\pm$ 1.2	8.2 $\pm$ 1.0
Riboflavine + cystine	15	8.7 $\pm$ 0.9	8.4 $\pm$ 0.9
Cyanocobalamin + cystine	14	10.4 $\pm$ 1.2	8.5 $\pm$ 1.3

neurological score, except that the cyanocobalamin-placebo tablets group contained a high proportion of women.

Table 2 shows that treatment with hydroxocobalamin-cystine and riboflavine-cystine did not have any beneficial effect compared with placebo (cyanocobalamin-placebo tablets). Although the group treated with cyanocobalamin-placebo tablets contained more women than the other two groups, this was unlikely to have affected the results of the final assessment, for there was no significant difference between the changes in percentage neurological scores in men

TABLE 5

DISTRIBUTION OF PATIENTS TREATED IN BOTH THE FIRST AND SECOND TRIALS

First trial	Second trial		
	Hydroxocobalamin + cystine	Riboflavin + cystine	Cyanocobalamin + placebo tablets
Hydroxocobalamin	6	3	7
Riboflavin	3	3	4
Cyanocobalamin	2	5	2
	11	12*	13
Mean change in neurological score between end of first and start of second trial	+6.4	+6.8	+1.5

* The treatment in the first trial for one patient in this treatment group is not known.

and women (-0.6 and $+1.4$ for the mean percentage changes in the 28 men and 16 women respectively who completed the trial).

At the end of the trial, patients were asked whether they considered that they had benefited from the treatment. Table 3 shows the results, which are comparable with those obtained with neurological scoring. Plasma thiocyanate levels tended to fall during the trial and the greatest change recorded was in patients taking hydroxocobalamin plus cystine. However, this fall was little greater than in patients given a very small (placebo) dose of cyanocobalamin plus placebo tablets (Table 4).

Re-randomization resulted in an even distribution of patients in the first trial (Table 5) to the groups in the second trial.

DISCUSSION

The results of this study have shown that treatment with hydroxocobalamin in combination with cystine or riboflavin in combination with cystine is not beneficial in established Nigerian ataxic neuropathy.

Although the results are similar to our pre-

vious therapeutic trial mentioned earlier, both studies contrast with the benefit said to occur after admission of the patients to hospital. Empirical treatment regimens in hospital usually comprise oral or parenteral administration of B complex vitamins coupled with a more varied diet than that ordinarily consumed by the patients.

The failure of treatment in the field may depend more on the severity of dietary cyanide or cyanogen exposure than upon the failure of detoxication mechanisms, although this remains a possibility.

Therapeutic trials in experimental animals are now in progress. The problems of altering entrenched dietary habits are too formidable to make dietary trials feasible at present.

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