Effect of megavitamin treatment on mental performance and plasma vitamin B_6 concentrations in mentally retarded young adults[1-4]

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ABSTRACT Other workers have reported preliminary results suggesting that vitamin and mineral supplements might improve the mental performance of mentally retarded children. The current study examined the effect of 20 wk of the suggested supplement on Stanford Binet scores in mentally retarded adults with nonspecific diagnoses, Down's syndrome, and subjects receiving anticonvulsant medication. No improvement in Stanford Binet scores was observed. However, serum pyridoxal phosphate concentrations were significantly ($p < 0.05$) increased in subjects with Down's syndrome receiving the supplement compared with subjects with nonspecific diagnoses receiving the same treatment thus providing further evidence of abnormal vitamin B_6 metabolism in Down's syndrome. *Am J Clin Nutr* 1983;38:352–355.

KEY WORDS Megavitamins, Down's syndrome, vitamin B_6

Introduction

Harrell et al (1) reported preliminary results suggesting that chronic intake of megadoses of a mixture of most vitamins and some minerals significantly improved the intellectual performance of mentally retarded children. Several limitations of this study have been discussed (2, 3). Perhaps one of the most important was the fact that the only psychologist who tested all of the participants was aware of the treatments for the last half of the experiment. If the scores from this person are eliminated, the apparent improvement drops considerably. In addition to its main purpose of attempting to reproduce the work of Harrell et al (1), the present study was designed to help identify the cause of any beneficial effects on mental performance as well as to provide information relevant to our work with vitamin B_6 regardless of the outcome of the intellectual tests. Therefore, we added a group receiving supplements providing only the Recommended Dietary Allowance of the various vitamins in order to determine whether any beneficial effects might be due to correcting subclinical deficiencies rather than megadose effects. Since several of the B vitamins are known to have dramatic effects on the nervous system, we included a group receiving megadoses of only B vitamins to help determine which of the many factors in the Harrell treatment might be most directly involved with any beneficial effects. Subjects with Down's syndrome and others receiving anticonvulsant medication were included because of evidence that these conditions are associated with altered metabolism of vitamin B_6 (4–6).

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Methods

All subjects were residents of the Fort Wayne State Hospital and Training Center. The subjects used by Harrell et al (1) could not all be tested with the same instruments. Our subjects were chosen from those able to take the Stanford Binet test. The subjects were chosen from three categories: nonspecific etiology; Down's syndrome; and persons receiving anticonvulsant medication. The protocol was approved by our human subjects committee. Parental permission was obtained and one subject who objected to participating was allowed to drop out. In addition to the placebo and megavitamin groups used by Harrell et al (1), we included one group receiving minimal supplements and one group receiving megadoses of only the B vitamins (**Table 1**). The placebo (group I) and Harrell treatment supplements (group II) were identical in appearance and were administered at 12 tablets/day. The tablets for groups III and IV differed in appearance and were administered at 6 tablets/day. However, all supplements were prescribed by coded names and cottage staff and psychometrists were unaware of the identity of the treatments. Due to the obvious differences in blood composition, the laboratory staff could determine which subjects were receiving megavitamins. However, care was taken not to communicate this information to other staff. The Stanford Binet test was administered at 0, 10, and 20 wk. Blood samples were obtained at the same times. Vitamin A (7) and vitamin B_6 (8) were determined by high performance liquid chromatography. Copper and zinc were determined by atomic absorption spectros-

TABLE 1
Daily supplements*

Supplement	Form	Units	Group			
			I	II	III	IV
Vitamin						
A	Palmitate	IU		15,000	7,500	
Biotin		ug		300	300	2,400
C	Ascorbic acid	mg		1,500	250	
Choline	Bitartrate	mg			250	
Cyanocobalamin		ug		1,000	9	600
D	Cholecalciferol	IU		300	400	
E	*d*-α tocopherol succinate	IU		600	40	
Folic acid		ug		400	400	2,400
Nicotinamide		mg		750	20	1,800
Pantothenic acid	Calcium salt	mg		450	15	600
Pyridoxine	Hydrochloride	mg		350	3	300
Riboflavin		mg		200	2	300
Thiamin	Mononitrate	mg		300	2	300
Minerals						
Calcium	Carbonate	mg		400	250†	
Chromium	Chromic sulfate	mg			1	
Copper	Gluconate	mg		1.75	2‡	
Iodine	Potassium iodide	ug		144	150§	
Iron	Ferrous fumarate	mg		7.5	15	
Magnesium	Oxide	mg		300	200‖	
Manganese	Gluconate	mg		3	5	
Molybdenum	Sodium molybdate	ug			100	
Phosphorous	Calcium phosphate	mg			250	
Selenium	Dioxide	ug			20	
Zinc	Oxide	mg		30	15¶	
Other						
p-aminobenzoic acid		mg			30	
Inositol		mg			250	
Rutin		mg			200	

* All supplements were obtained from Bronson Pharmaceuticals, LaCanada, CA. I was the placebo (12 tablets/day), II was the GTC 3 formula used by Harrel et al (1) (12 tablets/day), III was Bronson's chewable vitamin and mineral insurance formula (6 wafers/day), and IV was Bronson's super B formula (6 tablets/day).
† Calcium phosphate.
‡ Copper sulfate.
§ Kelp.
‖ Magnesium carbonate.
¶ Zinc gluconate.

copy. Free thyroxin was determined using a commercial assay (Amersham Corp, Arlington Heights, IL).

The data were analyzed by analysis of variance. In view of limited number of Down's syndrome subjects and the large variance in their pyridoxal phosphate concentrations after 20 wk, the 20-wk comparison with the nonspecific subjects in group II was made with the Wilcoxon two sample test which makes no assumptions about the distribution and parameters of the population (9).

Results and discussion

None of the treatments had any significant effect on the performance of subjects on the Stanford Binet test (**Table 2**). Since these subjects were older than those of Harrell et al (1), it appears that any benefits of megavitamin treatment on intellectual activity may be limited to younger subjects. The treatments did not have any significant effect on body weight or serum concentrations of vitamin A, copper, or zinc suggesting that the supplements did not noticeably improve the general nutritional status of the subjects.

Using morning axial temperatures Harrell et al (1) concluded that all but one of their subjects required thyroid supplementation. Based on clinical impression and free thyroxin concentrations, none of our subjects was deemed to require thyroid supplements. Therefore, none was given. Free thyroxin concentrations were not significantly altered by any of the treatments.

The only forms of vitamin B_6 consistently detected in serum were pyridoxal, pyridoxal phosphate, and pyridoxic acid (**Table 3**). Pyridoxamine, pyridoxamine phosphate, and pyridoxine were detected only sporadically even in subjects receiving 350 mg pyridoxine hydrochloride per day. We have no explanation for the rise in pyridoxal and pyridoxal phosphate concentrations in groups I and III during the study. Vitamin A concentrations also increased. The experiment ran from February through June. It may be that by spring and summer more fresh fruits and vegetables were included in the diet.

In a series of studies, McCoy et al (4) found changes in the urinary excretion of xanthurenic acid, 3-hydroxykynurenine, taurine, and 4-pyridoxic acid suggesting abnormal vitamin B_6 metabolism in Down's syndrome. Mahuren and Coburn (5) observed significantly reduced concentrations of pyridoxal phosphate in platelets from subjects with Down's syndrome. In the current study the concentration of pyridoxal phosphate in the plasma of subjects with Down's syndrome who received the Harrell treatment was significantly ($p < 0.05$) increased at both 10 and 20 wk compared with subjects with nonspecific diagnoses receiving the same treatment. This increase does not appear to be solely due to the slightly lower

TABLE 2
Effect of vitamin and mineral supplementation on intellectual performance

		Treatment						
		I Placebo			II Harrell		III RDA	IV B
Diagnosis	NS*	AC	DS	NS	AC	DS	NS	NS
No subjects								
Male	6	3	4	7	4	4	8	8
Female	3	2	0	2	2	1	2	2
Total	9	5	4	9	6	5	10	10
Age (yr)	24 ± 4	20 ± 4	25 ± 4	23 ± 4	26 ± 3	25 ± 4	25 ± 5	23 ± 5
Range	18–30	16–25	21–29	17–30	21–28	20–30	17–30	14–29
Wt (kg)								
0 wk	66 ± 10	58 ± 5	57 ± 5	65 ± 9	58 ± 11	55 ± 8	66 ± 6	68 ± 15
10 wk	66 ± 10	58 ± 5	59 ± 6	63 ± 8	59 ± 11	56 ± 7	66 ± 6	68 ± 15
20 wk	64 ± 9	59 ± 7	59 ± 7	62 ± 8	58 ± 11	55 ± 6	65 ± 5	67 ± 16
Stanford Binet								
0 wk	31 ± 10	29 ± 11	16 ± 5	33 ± 9	35 ± 9	20 ± 12	30 ± 9	35 ± 14
Range	10–40	17–45	10–22	22–49	18–42	10–36	17–45	19–46
10 wk	33 ± 8	29 ± 11	15 ± 5	34 ± 10	34 ± 7	18 ± 10	30 ± 9	35 ± 12
Range	16–39	16–46	10–19	24–53	21–40	8–32	17–42	18–50
20 wk	31 ± 9	28 ± 11	17 ± 6	35 ± 10	35 ± 8	17 ± 11	31 ± 12	32 ± 13
Range	8–38	13–42	10–20	26–54	22–43	8–34	17–49	16–48

* NS, nonspecific diagnosis; AC, anticonvulsant medication; DS, Down's syndrome.

TABLE 3
Serum concentrations of major forms of vitamin B_6 (n*M*)

Vitamer	Week	Treatment									
		I Placebo			II Harrell			III RDA	IV B		
		NS	AC	DS	NS	AC	DS	NS	NS		
Pyridoxal	0	21 ± 01	21 ± 7	19 ± 4	23 ± 8	30 ± 20	24 ± 4	20 ± 10	28 ± 11		
	10	56 ± 19	44 ± 22	41 ± 12	4691 ± 1943	3228 ± 1590	3209 ± 2328	64 ± 36	1362 ± 868		
	20	41 ± 24	27 ± 11	34 ± 20	5087 ± 3038	4651 ± 2891	4124 ± 1333	51 ± 29	1885 ± 1592		
Pyridoxal phosphate	0	61 ± 27	32 ± 7	60 ± 27	58 ± 27	47 ± 23	64 ± 13	51 ± 20	58 ± 33		
	10	121 ± 102	82 ± 27	116 ± 69	690 ± 228	581 ± 184	1261 ± 339	229 ± 130	784 ± 206		
	20	112 ± 88	68 ± 31	106 ± 45	739 ± 317	725 ± 173	1308 ± 686	127 ± 54	640 ± 153		
Pyridoxic acid	0	50 ± 18	49 ± 16	35 ± 30	43 ± 16	55 ± 10	47 ± 19	51 ± 19	53 ± 24		
	10	48 ± 24	43 ± 13	53 ± 24	2662 ± 1186	2636 ± 1350	3084 ± 1479	68 ± 23	793 ± 232		
	20	51 ± 12	58 ± 12	64 ± 13	2451 ± 1306	3149 ± 1687	3865 ± 1055	75 ± 27	904 ± 474		

weights of the subjects with Down's syndrome (Table 2) since the subjects receiving anticonvulsant medication had weights comparable to the Down's syndrome group but showed no tendency toward increased pyridoxal phosphate concentrations. Therefore, these data provide additional evidence of abnormal vitamin B_6 metabolism in Down's syndrome. Further studies will be needed to elucidate the mechanisms underlying these observations.

Increasing the daily vitamin B_6 supplement of subjects with nonspecific diagnoses from 300 mg in group IV to 350 mg in group II had no significant effect on serum pyridoxal phosphate concentrations but increased the concentrations of pyridoxal and pyridoxic acid almost 3-fold suggesting that some parts of the vitamin B_6 pathway become saturated at an intake of about 300 mg/day or less.

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