VITAMIN D IN THE TREATMENT OF INFECTIOUS ARTHRITIS *

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IN 1935 Dreyer and Reed [1] reported clinical improvement among patients who had infectious (rheumatoid, atrophic) arthritis when treated with large doses of vitamin D. Reports which have appeared in the literature are summarized in table 1. Livingston [2] reported that his best results were

TABLE I

Summary of Findings in the Literature Concerning Treatment with Vitamin D in Cases of Infectious Arthritis

Investigators	Patients Treated with Vitamin D	Percentage with Clinical Improvement
Dreyer and Reed[1]	34	73.5
Vrtiak and Lang[4]	20	60
Holbrook and Hill[6]	25	20
Livingston[2]	14	86
Wyatt, Hicks and Thompson[7]	40	20
Farley[8]	27	100
Steck[9]	Not stated	75 to 80
Steinberg[10]	29	34
Abrams and Bauer[3]	18	44
Snyder and Squires[11]	13	69

from the combination of vitamin D therapy and fever therapy. Abrams and Bauer [3] seldom saw objective evidence of improvement accompany clinical improvement in their patients and observed that the beneficial effects of vitamin D were only transitory.

PROCEDURE

Fourteen patients with chronic infectious (rheumatoid, atrophic) arthritis were chosen for study. Their ages were from 17 to 59 years. The infectious arthritis had been present from seven months to seven years. For each patient conservative treatment had been tried, but it was inadequate in controlling the arthritis. Preparations of vitamin D used were "Viosterol —Experimental" (1,000,000 units per gram), a special solution of activated ergosterol, and a crystalline vitamin D in propylene glycol (40,000 U.S.P. units per gram). These were furnished, respectively, by Parke, Davis and Company, Mead Johnson and Company, and the Winthrop Chemical Company. The daily dosage varied from 52,500 units to 386,000 units. The administration of vitamin D was continued from twelve days to fifteen and a half months. If no clinical improvement occurred, its administration was continued for at least one and a half months. Each patient was studied during the administration of vitamin D in regard to subjective and objective

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changes, clinical and laboratory evidence of toxicity, and the duration of improvement following discontinuance of the medication.

Because of the marked variation of symptoms in infectious arthritis, several courses of treatment were given to some of the patients, to be as certain as possible that such improvement as was obtained was due to the vitamin D and not to spontaneous remissions. The 14 patients were given 25 periods of treatment with vitamin D. These patients have been followed for at least one year since the administration of vitamin D was discontinued.

Clinical improvement was evaluated on the basis of the information obtained from the patient in regard to pain, subjective stiffness, fatigue, limbering up, and the amount of aspirin required. Objective improvement was determined on the basis of swelling and tenderness of the joints.

Results

Clinical improvement to the extent of disappearance of 25 to 75 per cent of symptoms occurred in seven patients (50 per cent); four (28.6 per cent) obtained no relief of symptoms; three (21.4 per cent) had partial relief of symptoms during one or more periods of treatment but did not improve during a subsequent trial of treatment with vitamin D.

The 14 patients were given a total of 25 periods of treatment. Eight treatments (32 per cent) resulted in no symptomatic relief; three treatments (12 per cent) resulted in subjective improvement to a degree of 25 per cent; twelve treatments (48 per cent) resulted in improvement to the extent of 50 per cent; and two (8 per cent) resulted in improvement to the extent of 75 per cent (table 2). Objective improvement was not noticed after 11

Table II

Effects of 25 Courses of Therapy with Vitamin D in 14 Cases of Infectious Arthritis

Treatment	Symptomatic Improvement		Vitamin D, units	
	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
25 courses	17	0	386,000	52,500
	0	8	315,000	80,000

treatments (44 per cent); objective improvement to the extent of 25 per cent was noticed after 12 treatments (48 per cent); and improvement to the extent of 50 per cent was noticed after two treatments (8 per cent). There was considerable variation in the readings of the sedimentation rate of erythrocytes and in the concentration of hemoglobin; improvement in these was very inconstant and frequently did not parallel the clinical and objective improvement.

There was no correlation between the amount of improvement and either the daily dose or the total dosage. When improvement occurred it was first

noticed from five days to three weeks after starting the administration of vitamin D.

After the administration of vitamin D was discontinued, one patient maintained the improvement for one and a half years and another for two and a half years, before having a return of the active infectious arthritis. The other patients had a return of symptoms within eight days to two and a half months after administration of the vitamin D was discontinued. In most cases, the symptoms returned and were as severe as they were before vitamin D was given. Three of the patients had transitory exacerbations of the infectious arthritis while taking vitamin D, and in one case the infectious arthritis was more active after the administration of vitamin D was discontinued than when it was started.

The most frequent symptoms of toxicity from vitamin D were loss of appetite, the presence of a sweet taste in the mouth, nausea, vomiting, headache, polydipsia and polyuria. Twelve of the 14 patients had toxic symptoms in at least one period of treatment. Toxic symptoms occurred in 17 of the 25 periods of treatment (table 3).

TABLE III

Relation of Symptoms of Toxicity to Symptomatic Improvement and Daily Dosage during 25 Courses of Vitamin D in 14 Cases of Infectious Arthritis

Treatment	Symptoms of Toxicity		Symptomatic Improvement		Vitamin D. Units	
	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
25 courses	17	0	12	5	386,000	52,500
	0	8	5	3	315,000	70,000

There was a higher percentage of improvement among those who had toxic symptoms than among those who did not, but it is obvious that toxic symptoms are not necessary to produce improvement, nor will doses of vitamin D sufficient to produce toxicity necessarily produce improvement in a case of infectious arthritis. Some patients tolerate very large doses of vitamin D and others react to small doses. It did appear that patients who had had toxic symptoms from vitamin D usually did not tolerate as much on subsequent trials without producing toxic symptoms.

Studies of the serum calcium were made during 15 of the 25 courses of treatment (table 4). Symptomatic improvement was experienced by all of the patients who had an elevation of serum calcium, but of four patients with a serum calcium of less than 11 mg. per 100 c.c. two experienced improvement and two did not. It is not necessary to produce a high serum calcium in order to obtain improvement of the patient's condition, but such an elevation frequently occurs. Toxic symptoms may occur with or without an elevation of serum calcium and this elevation is no gauge of the toxicity of the vitamin D for the patient.

The blood urea was studied because of the known toxic effects of large

TABLE IV

Relation of Serum Calcium to Symptoms of Toxicity, Symptomatic Improvement and Daily Dosage during 15 Courses of Vitamin D in 11 of 14 Cases of Infectious Arthritis

Treatment	Serum Calcium		Symptoms of Toxicity		Symptomatic Improvement		Vitamin D, Units	
	More than 11 mg. per 100 c.c.	Less than 11 mg. per 100 c.c.	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
15 courses	11	0	8	3	11	0	386,000	52,500
	0	4	4	0	2	2	210,500	140,000

TABLE V

Relation of Blood Urea to Serum Calcium, Symptoms of Toxicity, Symptomatic Improvement and Daily Dosage during 16 Courses of Vitamin D in 12 of 14 Cases of Infectious Arthritis

Treatment	Blood Urea		Serum Calcium		Symptoms of Toxicity		Symptomatic Improvement		Vitamin D, Units	
	More than 40 mg. per 100 c.c.	Less than 40 mg. per 100 c.c.	More than 11 mg. per 100 c.c.	Less than 11 mg. per 100 c.c.	Present	Absent	Present	Absent	Maximal Daily Dose	Minimal Daily Dose
16 courses	6	0	4	0	5	1	6	0	386,000	105,000
	0	10	6	4	8	2	7	3	280,000	52,500

doses of vitamin D on the kidneys (table 5).[4] The level of blood urea was followed during 16 of the 25 periods of treatment with vitamin D. Readings of more than 40 mg. per 100 c.c. were found in six of the 16 periods of treatment. All six of the patients with an elevated urea obtained some relief of symptoms and five had toxic symptoms to warn the patient to stop taking vitamin D. However, one patient with a blood urea of 46 mg. per 100 c.c. had no symptoms to warn him of the toxicity of the vitamin D for the kidneys. By the time the concentration of urea was elevated, that of the serum calcium was also elevated. A normal concentration of blood urea was not an indication that the patients would experience symptomatic improvement or symptoms of toxicity. It is apparent that an elevated level of blood calcium is much more readily produced than is demonstrable damage to the kidneys. Large doses of vitamin D may produce damage to the kidneys sufficient to elevate the blood urea. In each case the concentration of urea returned to normal after administration of the vitamin D was discontinued.

SUMMARY

Large doses of vitamin D have been of help in partially controlling the symptoms of infectious arthritis in seven of 14 patients and in 68 per cent of 25 courses of treatment. Very little effect was seen on the objective

findings in the patients so treated. Vitamin D is not a specific agent for the control of infectious arthritis. Exacerbations may occur while the patient is taking large doses of vitamin D. The beneficial effects are only transitory, as a return of symptoms usually occurs after discontinuing its use. There is some risk of renal damage, which is apparently temporary if the administration of vitamin D is discontinued promptly after evidence of toxicity appears, but serious damage may occur. It is not necessary to produce toxic symptoms or renal damage to obtain clinical improvement.

There is no good correlation between clinical improvement and toxic symptoms or renal damage as evidenced by retention of urea. However, 11 patients who had an elevated concentration of blood calcium had clinical improvement and of four who had normal calcium, two experienced improvement and two did not.

Gastrointestinal upset was the most frequent sign of toxicity and usually gave adequate warning of the toxicity of the vitamin D; however, in one case the concentration of urea became elevated without the occurrence of any gastrointestinal upset. Patients receiving vitamin D should be watched carefully for symptoms of toxicity. Vitamin D therapy should be considered as one of many types of treatment which is sometimes of help in the temporary and partial control of symptoms of infectious arthritis. It is of very little, if any, use when lasting improvement is sought for the patient who has infectious arthritis.

The frequency of toxicity in this series is higher than has been reported in other series of patients treated with vitamin D. This may in part be due to other preparations being used by some of the other investigators.

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