The Effect of Sublingual Administration of Crystalline Vitamin B₁₂ in Tropical Sprue

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SPIES and his collaborators,¹−⁴ from Cuba and Puerto Rico, as well as several other investigators in various parts of the world, have proved definitely the efficacy of vitamin B₁₂ administered intramuscularly in the treatment of sprue. The usual clinical and hematologic signs and symptoms of acute sprue respond rapidly and dramatically to the parenteral administration of vitamin B₁₂. The neurologic complications which occasionally occur in sprue are also controlled or prevented by the intramuscular administration of small doses of the vitamin.

Oral administration of vitamin B₁₂ has, in our experience, failed to be of any value in the treatment of sprue when given in daily doses of 25 μg. and in single oral doses of 100, 500, and as much as 1000 μg. In common with Ungley et al.,⁵ we have nevertheless obtained good clinical and hematologic remissions with the oral administration of single doses of 3000 μg. and have even obtained maximal responses when 5000 μg. were given.

It is well known that certain drugs and hormones are readily absorbed when administered sublingually and that their action through this route is as rapid and practically as effective as when given parenterally. This fact led us to study the effect of crystalline vitamin B₁₂* administered sublingually to sprue patients.

Five patients showing all the criteria for a diagnosis of either acute sprue or sprue in relapse were studied. During the period of observation all cases were kept on an inadequate diet, low in animal proteins and its vitamins. This diet, which we have called in previous communications “preliminary sprue diet,” is made up almost entirely of polished rice and kidney beans with codfish and vegetables; one cup of coffee with milk was given daily, and there was a weekly allowance of one or two eggs.

A daily dose of 25 μg. was given to all 5 patients for a period of ten days. The administration of the vitamin was closely supervised by one or other of the authors to be sure that the tablet was not swallowed by the patient but allowed to dissolve slowly under the tongue.

Treatment was started when basal figures for red blood cells, hemoglobin and reticulocytes had been reached and all necessary clinical and laboratory investigations, including bone marrow studies, gastric analysis, gastrointestinal x-rays, glucose tolerance curve, etc., had been performed. This period of observation usually lasted from seven to ten days.

* The crystalline vitamin B₁₂ was generously supplied by Dr. Eaton MacKay of E. R. Squibb and Sons, Inc.
On September 7, 1951 the first two patients with tropical sprue were started on the sublingual administration of vitamin B₁₂.

Case 1. J. R. (age 65, white, sprue in relapse). This man was given 25 µg. crystalline vitamin B₁₂ sublingually for ten consecutive days. Figure 1 shows that when treatment was started his red cell count was only 1.225 million per cu. mm., hemoglobin 4.6 Gm. and reticulocytes were 0.5 per cent. This patient, in common with most cases of sprue, showed a leukopenia of 2,500 per cu. mm. There was no reticulocytic response during the administration of the vitamin. The highest counts were 1 per cent on the sixth day and 1.5 per cent on the tenth day of treatment. Most of the time, no reticulocytes could be demonstrated in the peripheral blood. On the tenth day, the red cell count had decreased to 1.06 million per cu. mm. and the hemoglobin to 3.7 Gm. The patient was in such poor physical condition that a transfusion of 500 cc. of blood was given together with a combination of liver extract amid vitamin B₁₂ known as Rulivan* in 1 cc. daily doses intramuscularly; this was begun on the twelfth day. When Rulivan was started, erythrocytes numbered 1.422 million, hemoglobin was 5.0 Gm. and reticulocytes were 0.5 per cent. There was a gradual increase in the number of the reticulocytes: 2 per cent on the second day, 4 per cent on the third day, 11.8 per cent on the fifth, 16.8 per cent on the seventh, and 19 per cent on the ninth day. This was the highest figure obtained and was then followed by a gradual decrease in the number of reticulocytes. On the tenth and last day of treatment with intramuscular Rulivan, red blood cells had increased to 2.005 millions per cu. mm., hemoglobin to 5.2 Gm. and leukocytes to 4700 per cu. mm. Folic acid given orally in doses of 5 mg. three times a day while the patient was still showing reticulocytic response induced by the previous treatment, failed to provoke a new reticulocytic peak, but served to maintain a prolonged moderate reticulocytosis. Ten days after folic acid treatment was started, the patient's erythrocytes had increased to 2.940 millions per cu. mm., hemoglobin to 8.5 Gm. and leukocytes to 6100 per cu. mm. An oral dose of 5 mg. of folic acid daily since discharge from the hospital has maintained the patient in excellent clinical and hematologic remission.

* Rulivan is a combination of liver extract, 15 units, and vitamin B₁₂ 30 µg. prepared by E. R. Squibb and Sons, Inc., New York City.
Case 2. I. R. (age 65, white, sprue in relapse). When this patient was started on sublingual crystalline B₁₂ in 25 μg. daily doses on September 8, 1951 (fig. 2), the red blood cell count was 1.920 million per cu. mm., hemoglobin 7.5 Gm. and reticulocytes 2 per cent. During the next ten days the reticulocytes were only 0.5, 2, 3, 1, 1, 4, 1.8, 2, 2 and 2 per cent, respectively. If anything, the patient was worse clinically on the tenth day and the erythrocytes had decreased to 1.445 million per cu. mm., hemoglobin to 5.2 Gm. A blood transfusion of 500 cc. was given and 1 cc. Rulivan was injected daily for the next ten days. The reticulocytes rose rapidly, reaching a peak of 26.1 per cent on the sixth day of treatment and gradually diminishing to 8.5 per cent on the tenth day. On this day erythrocytes had increased to 3.010 millions per cu. mm. and hemoglobin to 9.5 Gm. The subsequent use of folic acid in oral doses of 5 mg. three times a day failed to induce a new reticulocytosis, but maintained the patient's improvement so much so that ten days later erythrocytes were 3.600 millions per cu. mm. and hemoglobin was 11.6 Gm.

Comments: While we were obtaining negative results with the sublingual administration of crystalline vitamin B₁₂ in our first 2 cases, information was received to the effect that a few cases of pernicious anemia studied in New York and 3 in Philadelphia had responded to the sublingual administration of as little as 10 μg. of vitamin B₁₂. This information, together with the unexpectedness of our own results, compelled us to investigate the problem further. Three additional typical cases of sprue were then studied.

Case 3. A. C. de V. (age 70, white, sprue in relapse). This woman was started on sublingual vitamin B₁₂ (fig. 3) when the erythrocytes were 1.430 million per cu. mm., hemoglobin was 5.2 Gm. and reticulocytes were 0.5 per cent. A daily dose of 25 μg. was given for ten consecutive days. The administration of the vitamin and the diet were carefully supervised. No reticulocytic response was obtained, daily counts varying from 0.3 to 0.6
per cent. There was no clinical improvement, and on the tenth day of treatment erythrocytes had decreased to 1.3 million per cu. mm. while hemoglobin remained at the original level of 5.2 Gm. Parenteral administration of 1000 μg. of vitamin B₁₂ was followed by a high reticuloecytic response which reached its peak of 40.2 per cent on the sixth day. The clinical improvement, also, was striking. Ten days following the intramuscular administration of the vitamin, erythrocytes had increased to 2.59 millions per cu. mm., hemoglobin to 7.6 Gm. and the leukocytes (which originally were 2250 per cu. mm.) increased to 8300.

Case 4. F. M. C. (age 26, white, with acute sprue). During the preliminary period of observation the reticuloecytes remained at a level of about 4 per cent and leukocytes varied from 9,900 to 11,400 per cu. mm. When the sublingual administration of crystalline vitamin

Fig. 3.—Patient A. C. de V., age 70 years. Sprue in relapse.

Fig. 4.—Patient F. M. C., age 26 years. Acute sprue.
When vitamin B₁₂ was started, the reticulocytes in the peripheral blood were 5.7 per cent, erythrocytes 2.64 millions per cu. mm. and hemoglobin was 6.9 per cent (fig. 4). The reticulocytic counts for the ten successive days were 5.4, 6.0, 6.0, 4.0, 2.4, 2.0, 1.9, 3.1, 6.1 and 8.3 per cent, respectively. At the end of this period the erythrocytes had decreased to 2.0 millions per cu. mm. and hemoglobin to 5.3 Gm. Two days later, when vitamin B₁₂ was given orally in a single dose of 3000 μg., the patient's peripheral blood showed the following figures: erythrocytes, 2.79 millions per cu. mm.; hemoglobin, 7.2 Gm.; leukocytes, 5000 per cu. mm. and reticulocytes 9.3 per cent. The reticulocytes showed a gradual and progressive increase, reaching a peak of 16.8 per cent five days later. Ten days following the oral administration of 3000 μg. of vitamin B₁₂, the erythrocytes had increased to 3.15 millions per cu. mm., hemoglobin to 6.6 Gm. and leukocytes to 7100 per cu. mm. The reticulocytes were 10.1 per cent, and the platelets, which originally were only 150,000 per cu. mm., had increased to 300,000 per cu. mm.

**Comments:** The preceding case, although typical of acute sprue, probably had some other complicating factor such as an attenuated or subclinical infection to explain the original leukocytosis but it also shows, as well as do the other 3 cases, the lack of response to sublingual administration of the vitamin.

**Case 5.** B. O. (age 38, white, sprue in relapse). This man received crystalline vitamin B₁₂ in 25 μg. sublingual daily doses when his peripheral blood showed 1.90 million erythrocytes, 6.6 Gm. hemoglobin and 0.6 per cent reticulocytes (fig. 5). Reticulocytes did not increase, the highest figure being 0.8 per cent. There was no clinical improvement. On the tenth day the peripheral blood showed only 1.85 million erythrocytes and 7.2 Gm. hemoglobin. Oral administration of 3000 μg. of vitamin B₁₂ was followed by slight reticulocytosis with a peak of only 7.3 per cent on the seventh day, but the subsequent intramuscular administration of 1000 μg. of vitamin B₁₂ resulted in marked clinical and hematologic response.

**Comments:** We were intrigued with the idea that the response of patients with pernicious anemia to the sublingual administration of vitamin B₁₂ and the lack...
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of response of sprue patients to the same treatment might prove to be an important differential point between the two conditions, but since writing this report we have heard of patients with pernicious anemia in whom this route of administration has also failed to result in a remission.

SUMMARY

Sublingual administration of crystalline vitamin B₁₂ in daily doses of 25 μg for ten consecutive days failed to induce clinical or hematologic remissions in 5 patients with tropical sprue.

REFERENCES

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