The Effect of Orally Administered Folinic Acid in the Treatment of Tropical Sprue

By Ramón M. Suárez, Sr., M.D., D.Sc. (Hon.), Ramón M. Suárez, Jr., M.D., Roberto Busó, M.D., and Juan Sabater, M.D.

It has been accepted as an undisputed fact that the parenteral administration of antianemic factors is generally more effective in the treatment of sprue than their oral administration because of poor intestinal absorption. The flat oral glucose tolerance curve, the low serum proteins, the apparent diminished absorption of vitamin A and of certain fats, the loss of weight, and the diarrhea seem to be corroborative evidences of poor absorption. The assertion concerning the route of administration holds true for most liver extracts and for vitamin B₁₂. Folic acid seems to be an exception. This substance appears to be equally or nearly as effective when given orally as when administered parenterally.

Spies and his collaborators have shown that orally administered vitamin B₁₂ with or without the addition of the intrinsic factor seems to be ineffective in patients with sprue in doses that had proved effective in the treatment of pernicious anemia. On the other hand massive oral doses of vitamin B₁₂ and probably the use of more potent preparations of the intrinsic factor might prove effective in some cases.

In 1931 Suárez showed that patients with sprue who failed to respond to adequate doses of Ventriculin given orally, exhibited maximal reticulocytic and clinical responses following the oral administration of aqueous liver extract (Valentine). It was also observed by the senior author that during the early days of liver therapy a few patients responded better to the aqueous preparation than to the powdered liver extracts although both were given orally. It seems that some factor other than malabsorption must have been involved.

That citrovorum factor (folinic acid) is effective in the control of the hematologic manifestations of sprue has been confirmed by several investigators. Spies et al., Suárez et al., and Romero et al. were among the first to report their observations. They used the parenteral route of administration. Suárez and his collaborators found that a daily intramuscular dose of 3 mg. (2 million units) seemed adequate in most cases, and a small number of cases have been maintained in good clinical and hematologic remission for over one year with an intramuscular dose of only 3 mg. given once or twice weekly.

When folic acid in tablet form for oral use became available, we employed it in five case of acute sprue in relapse.
EFFECT OF FOLINIC ACID UPON TROPICAL SPRUE

CASE 1

A. C., a 64 year old white man, suffering from sprue in relapse complicated by severe pyorrhea alveolaris and chronic gastritis. His initial erythrocyte count was 2.18 millions, hemoglobin 7 Gm. (48.6 per cent), leukocytes 3400, and reticulocytes 0. Megaloblasts were present in bone marrow aspirations to the extent of 13.3 per cent. Gastric analysis using alcohol test meal and histamine stimulation revealed a very low titer of free hydrochloric acid and of total acidity, the figures being 5, 10, 0, 0, and 0 degrees for the former and 42, 25, 19, 21, and 22 degrees for the latter.

Calcium leucovorin was given orally in daily doses of 5 mg. The highest reticulocyte count was 4 per cent observed on the eighth day of treatment. On the tenth day the erythrocytes were 2.25 millions, hemoglobin 7.9 Gm. (55.3 per cent), leukocytes 9000 per cu. mm., and reticulocytes 1.6 per cent. Calcium leucovorin was raised to 15 mg. daily. There was no further increase in the reticulocytes, which ranged between 1.4 and 2.6 per cent. Ten days later folic acid in the same dose, 5 mg, three times a day, was substituted for folinic acid. It also failed to induce a definite reticulocytosis, but the patient was kept on this vitamin and when discharged two months later the hemogram was as follows: red blood cells 4.19 millions per cu. mm., hemoglobin 8.9 Gm. (62.4 per cent) and leukocytes 6200 per cu. mm.

Comments

This case gave a poor response to all medication. His sprue was complicated by chronic gastritis apparently due to infection and poor mastication. Gastric
analysis revealed marked hypochlorhydria. He finally recovered under prolonged oral folic acid therapy.

Case 2

R. H., a 61 year old white man suffering from acute sprue in relapse. Gastric aspiration showed a histamine fast achlorhydria and a total acidity of only 19, 26, 23, 24, and 26 degrees.

When calcium leucovorin in 5 mg. daily oral doses was started, his red blood cells were 1.39 million, hemoglobin 6.0 Gm. (62.1 per cent), white blood cells 4500 per cu. mm., and reticulocytes 0.6 per cent. There were 19.6 per cent megaloblasts in the aspirated marrow removed from the iliac crest. Despite a reticulocyte peak of only 10 per cent obtained on the fourth day of treatment, the blood picture on the tenth day had shown marked improvement: red blood cells were 2.51 millions, hemoglobin 7.9 (55.3 per cent) and leukocytes 8300 per cu. mm. The dose of folic acid was then increased to 15 mg. daily and there was a slight secondary response. Reticulocytes increased to 4 per cent four days later. The subsequent use of folic acid when the patient’s peripheral blood showed 3.28 million red blood cells led to no further response. After one month of folic acid therapy the patient was discharged from the hospital. At this time his erythrocytes were 4.11 million per cu. mm., hemoglobin 11.6 Gm. (80.1 per cent) and leukocytes 3900 per cu. mm.

Comments

A sprue patient showing histamine fast achlorhydria and severe megaloblastic anemia responded submaximally to oral folic acid in 5 mg. daily doses (reticulocytosis of only 10 per cent with an initial red blood cell count of 1.39 million). A slight secondary reticulocyte peak was obtained when the dose was increased to 15 mg. daily (5 mg. three times a day). There was no secondary response to the subsequent use of oral folic acid. Despite the relatively poor reticulocytic response, the clinical and hematologic improvement was excellent.

Case 3

A. M., a 65 year old white man suffering from acute sprue in relapse. Gastric analysis could not be performed because he refused intubation. His anemia was very severe: red blood cells 1.01 million per cu. mm., hemoglobin 4 Gm. (28.0 per cent), leukocytes 2450
EFFECT OF FOLINIC ACID UPON TROPICAL SPRUE

CASE 3. A. M. — AGE 65 — WHITE — SPRUE IN RELAPSE

Fig. 3.—The apparent secondary response to folic acid after initial treatment with leucovorin.

per cu. mm., and no reticulocytes. Calcium leucovorin 5 mg. three times a day was given orally. He showed an excellent but not optimal reticulocyte response of 18.2 per cent on the eighth day of treatment. On the tenth day erythrocytes had increased to 1.89 million, hemoglobin to 5.5 Gm. (38.0 per cent), and leukocytes to 4200 per cu. mm.

The subsequent oral administration of folic acid in the same dose as calcium leucovorin (5 mg. three times daily) induced a secondary reticulocyte peak of 8 per cent. With a maintenance dose of 5 mg. folic acid daily the patient was discharged in complete clinical and hematologic remission one and a half months later.

Comments

Leucovorin in oral doses of 5 mg. three times a day induced an excellent reticulocyte response, but not a maximal one. With an initial erythrocyte count of 1.01 million per cu. mm. the reticulocytes increased only to 18.2 per cent. The subsequent oral use of folic acid in the same dose induced a secondary response.

Case 4

J. T., a 46 year old white man suffering from severe sprue with profound anemia also received leucovorin orally in doses of 5 mg. three times daily.

Gastric analysis revealed histamine fast achlorhydria and total acidity of 10, 14, 10, 20, and 8 degrees in the five aspirated specimens. His bone marrow showed 26.8 per cent megaloblasts and his initial hemogram, 980,000 red blood cells per cu. mm., 3.0 Gm. (20.6 per cent) hemoglobin, 2600 leukocytes per cu. mm., and 0.4 per cent reticulocytes. The highest reticulocyte response obtained was only 16.2 per cent on the tenth day of treatment. The subsequent administration of folic acid in doses of 5 mg. three times a day was followed by another, although less marked, reticulocyte peak of 6.4 per cent on the fifth day. On discharge after one month on folic acid, his red blood cells had increased to 4 million and hemoglobin to 85 per cent.

Comments

A sprue patient showing profound macrocytic anemia, megaloblastic bone marrow, and histamine resistant achlorhydria responded submaximally to
leucovorin given orally in doses of 5 mg. thrice daily. Although he gave a good response to calcium leucovorin there was a definite secondary response to orally administered folic acid.

Case 5

J. R., a 50 year old white man suffering from sprue in relapse received calcium leucovorin in oral doses of 5 mg. three times a day.

His gastric secretion using alcohol test meal and histamine stimulation showed marked hypochlorhydria. The four specimens recovered gave 5, 0, 5, and 8 degrees of free hydrochloric acid and 20, 15, 20, and 20 degrees total acidity.
This patient's diet was not restricted as was that of the other four patients. He was allowed a regular diet, high in animal proteins and low in carbohydrates and fats.

The initial red blood cell count was 2.38 millions per cu. mm., hemoglobin 10.0 Gm. (69.8 per cent), leukocytes 5700 per cu. mm., reticulocytes 1 per cent. His anemia was macrocytic with a mean cell volume of 132 cu. μ and the bone marrow aspiration showed 18 per cent megaloblasts in the differential count. A reticulocyte response of 12.0 per cent was observed on the fifth day of treatment. The subsequent intramuscular administration of folinic acid in doses of only 3 mg. daily produced a low but persistent reticulocytosis which varied between 2 and 4 per cent. In less than a month the patient had shown marked clinical and hematologic improvement. His red blood cells were near 4 million per cu. mm. and hemoglobin 12.5 Gm.

Comments

This case proves again the well known fact that sprue patients respond better to antianemic factors when they are given an adequate diet, rich in animal proteins and low in fats and carbohydrates.

Discussion

Folinic acid appears to be at least one metabolically active form of folic acid and it is highly probable that dietary folic acid is converted to folinic acid, and that the latter active principle is the naturally occurring factor. It has been found also that the methods employed in the isolation of folic acid from natural sources will convert folinic acid to folic acid.6

On the basis of microbiologic assay it has been reported7 that naturally occurring folinic acid (citrovorum factor) appears to be 15 times as effective as folic acid in reducing the toxicity of x-methyl folic acid for Lactobacillus casei.

The metabolism of folic acid is complex and poorly understood. By microbiologic methods using the Leuconostoc citrovorum, Girdwood8 has recently shown that in cases with histamine fast achlorhydria, orally administered citrovorum factor appears in the serum and urine largely as citrovorum factor. In the presence of free hydrochloric acid it is supposed that citrovorum factor is converted into folic acid or some related substance and it is absorbed as such. When citrovorum factor is given parenterally, it appears in the urine largely unchanged. Based on the fact that he found 10 times as much citrovorum factor (probably in a conjugated form), as folic acid in the liver of normal persons, this author states that storage normally occurs as citrovorum factor.

Sprue patients of the older age group, as in the case of those we are now reporting, show either a marked hypochlorhydria or a histamine resistant achlorhydria in their gastric secretion. They all respond to orally administered folic acid in the usual dosage of 15 to 20 mg. daily.

In the present group of five cases, there were two cases with histamine resistant achlorhydria and two cases showing marked hypochlorhydria. The remaining case refused to have gastric intubation performed. The results obtained did not seem to differ between patients with total absence of free hydrochloric acid and those in whom it was present in small amounts in the gastric secretion.

Case 1 showed poor response to all medication. The other four cases gave either good or excellent clinical and hematologic responses to the oral administration of leucovorin in doses of 15 mg. daily, but the reticulocyte responses were not ...
imal. Doses of 5 mg. daily proved definitely inadequate. Two cases showed significant secondary responses to the oral administration of folic acid in doses of 15 mg. daily and another case gave slight secondary response to the parenteral administration of leucovorin in doses of 3 mg. daily.

**CONCLUSION**

Folinic acid (calcium leucovorin) administered orally in 15 mg. daily doses gave good or excellent clinical and hematologic responses in uncomplicated sprue patients independent of the absence of free hydrochloric acid or its presence in low titers in their gastric secretion.

A maximal reticulocyte response was not obtained.

Despite the fact that on the basis of microbiologic assay folic acid appears to be 15 times more effective than folic acid in reducing the toxicity of x-methyl folic acid for *Lactobacillus casei*, in the treatment of acute tropical sprue, at the same dosage level, and when administered orally, we consider folic acid to be more effective than folic acid in the form of calcium leucovorin.

**SUMMARIO IN INTERLINGUA**

In cinque casos de patientes con sprue non-complicate bon o excellentes responsas clinic e hematologic esseva obtenite per le administration oral de acido folinic. (Previe reportos esseva concernite con terapias a administration parenteral.) Le acido folinic esseva administrate in le forma de tablettes de calcic leucovorina in dosages de 15 mg per die. Le responsas non esseva afficite per le absentia de libere acido hydrochloric o de su presentia in basse titros in le secretion gastric del del patientes.

Un obtenite responsa reticulocytic non esseva maximal.

In despecto del facto que in essayos microbiologic acido folinic pare esser 15 vice plus efficace que acido folic in reducer le toxicitate de acido folic a x-methylo pro *Lactobacillus casei*, nos considera que in le tractamento de sprue tropic, acido folic, si administrate oralmente, es plus efficace que acido folinic in le forma de calcic leucovorina.

**REFERENCES**

The Effect of Orally Administered Folinic Acid in the Treatment of Tropical Sprue

RAMÓN M. SUÁREZ, SR., RAMÓN M. SUÁREZ, JR., ROBERTO BUSÓ and JUAN SABATER