Observations on the Mechanism of Intranasal Absorption of Vitamin B₁₂ in Pernicious Anemia

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Recent experience has disclosed the efficacy of the control of pernicious anemia by the administration of vitamin B₁₂ via the respiratory route. Originally, it was postulated that absorption of the vitamin was possible by the capillary bed of the alveoli of the lungs; hence, initially, the B₁₂ was given by aerosol. It soon became evident that, with the aerosol apparatus employed, little, if any, of the material actually reached the alveoli. It was concluded that absorption was directly through the respiratory mucosa of the tracheo-bronchial tree. Recognizing the morphologic and physiologic similarity of the mucosal lining of the lung and of the nose, intranasal use of vitamin B₁₂ in pernicious anemia was undertaken. Previous reports have indicated satisfactory response from nasal instillation of B₁₂. This paper describes the mechanism of absorption of B₁₂ by the nasal mucosa without demonstrable participation of “intrinsic factor” in the process. Further attempts at the establishment of the smallest measurable amounts of vitamin B₁₂ therapeutically effective in pernicious anemia, made possible by this technic, are presented.

Methods and Materials

The patients studied had represented classic clinical and hematologic manifestations of pernicious anemia in relapse. Crystalline vitamin B₁₂ was used in these studies. The B₁₂ crystals were weighed in a gelatin capsule using a microbalance. The vitamin was then removed by a microspatula employing suitable magnification and placed under direct vision upon the mucosa of the inferior nasal turbinate bone.

The B₁₂-lactose powder was prepared by mixing 1 mg. vitamin B₁₂ in 120 mg. of lactose powder and placing into a number 4 gelatin capsule. Each end of the capsule was perforated by a small straight needle and then inserted into the Armour Inhalator (apparatus previously utilized for administration of powder posterior pituitary extract). The patient was instructed to hold his breath at the end of expiration during which period the apparatus was placed into the nares. A gentle but quick compression of the rubber bulb delivered a fine cloud of B₁₂-lactose powder in amount of approximately 100 μg. It was essential to release the bulb slowly to prevent reflux of the B₁₂ mixture.

Cases

Case 1. A 70 year old white female gave a history of increasing weakness associated with breathlessness of two months’ duration. More recently she complained of marked anorexia, faintness, and tingling of the extremities.

On examination the patient appeared pale with a lemon yellow tint to the skin. The tongue was atrophic. There was diminished vibratory sensation in both lower extremities.

The erythrocyte count was 1.58 million and the hemoglobin 5.7 Gm. The reticulocyte count was 1.1 per cent and the blood smear demonstrated a macrocytic anemia and morphologic changes of the polymorphonuclear leukocytes characteristic of that seen in pernicious anemia. A bone marrow aspiration was performed and 37.6 per cent of the nucleated cells were megaloblasts. The patient was achlorhydric after histamine stimulation.

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The patient was given a single insufflation of B12-lactose powder in an amount estimated to be 100 μg. On the fifth day following the single administration of the vitamin B12, the reticulocytes were noted to be 53.2 per cent. In an interval of one month after treatment the erythrocyte count was 2.99 million and hemoglobin 9.7 Gm. with the alleviation of all her complaints. The patient again was given insufflation of B12 at intervals indicated on chart 1 which shows the return of the hemoglobin and red blood cell count to normal.
Case II. A 56 year old white male complained of nausea and vomiting and a sore mouth of two months' duration. In the two-week period prior to initial contact he noted weakness, pain in the chest on exertion, numbness, and tingling of the extremities.

His blood count was as follows: erythrocytes 2.34 million, hemoglobin 7.4 Gm. Examination of the blood smear showed marked macrocytosis of the red cells as well as numerous hypersegmented polymorphonuclear leukocytes. Forty-five per cent of the nucleated marrow cells were megaloblasts. The reticulocyte count was 6.8 per cent and blood platelets 73,000. Gastric analysis failed to show hydrochloric acid after histamine stimulation.

Nasal washings obtained from a normal subject after instillation of 150 µg. of vitamin B₁₂ were introduced into the patient's stomach via a tube. In a ten-day period of observation there was no significant increase in the reticulocyte count.

Under direct vision, 150 vitamin B₁₂ crystals were placed upon the mucosa of the inferior turbinate bone. At the time of this procedure it was noted that the patient was suffering from chronic hypertrophy of the nasal mucous membranes, including a large number of nasal polyps. There was noted no irritant effect of the vitamin on the nasal membranes.

On the sixth day following treatment a maximal reticulocytosis of 43 per cent was obtained. In the two-months' period the erythrocyte count reached 5.30 million and the hemoglobin 16.4 Gm., chart 2. Three months after the single therapy, the patient again noted a return of mild glossitis. At this point further intranasal therapy was given.

Case III. A 57 year old white male complained of progressive weakness and anorexia of four months' duration. During this interim, he developed a sore tongue and chest pain on exertion. The initial erythrocyte count was 1.98 million and hemoglobin 6.2 grams. Examination of the blood smear revealed the typical findings of the macrocytic anemia seen in pernicious anemia.

In addition circulating megaloblasts were observed. A reticulocyte count was 2.8 per cent and the platelet count 119,000. A bone marrow examination demonstrated 38 per cent of the nucleated cells to be megaloblasts.

Two hundred µg. of crystalline B₁₂ crystals were placed under direct vision of the nasal mucosa. On the seventh day following therapy, a maximum reticulocytosis of 43.8 per cent
was obtained. Following this single treatment the patient’s clinical symptoms disappeared entirely, and there was gradual improvement in the blood count in a two-month period as seen in chart 3. In this patient urinary bioassay for vitamin B₁₂ activity utilizing the test organism, *Lactobacillus leichmannii*, showed 12 per cent of the administered dose excreted in the urine.

**Discussion**

In the past three years 32 patients with pernicious anemia in relapse have been treated successfully with vitamin B₁₂ administered via the respiratory route. Suboptimal reticulocyte response was noted following 15 µg. B₁₂ with maximum effect after application of 100 cu. µg. Fifty-five patients with pernicious anemia in remission have been satisfactorily maintained on therapy at intervals of three to four weeks. Dosage levels for maintenance averaged 100 µg. Equal response was found after treatment with either nasal instillation of B₁₂ solutions, B₁₂-lactose powder, or B₁₂ crystals.

The B₁₂ nasal drops were prepared by a mixture of 1 cc. commercially available B₁₂, 1,000 mg./cc., diluted with 9 cc. of physiologic saline. This mixture reduces the concentration of the preservative usually present and prevents the otherwise irritation effect. The patient is instructed to instill 0.5 cc. of this mixture, 50 mg. B₁₂, as nose drops. The B₁₂ solution should be refrigerated.

In addition to adequate hematologic response, improvement in gastrointestinal and neurologic manifestations occurred to a comparable degree noted after parenteral treatment.

Israels’ utilizing the B₁₂-lactose powder intranasally confirmed the effectiveness of this form of treatment, and the doses required were of the same order as those when given by the intramuscular route. He believed this method to be relatively inexpensive and a useful alternative to intramuscular injection.

The nasal washing experiment cited in Case II and urinary excretion studies suggest the direct absorption of the vitamin B₁₂ through the respiratory mucosa rather than “binding” or “combining” with a mucoprotein (intrinsic factor) of the nasal secretions.

**Summary and Conclusions**

Satisfactory clinical and hematologic response was obtained from the single application to the nasal mucosa of 200 and 150 micrograms of crystalline vitamin B₁₂ in two patients with pernicious anemia.

Thirty-two patients with pernicious anemia in relapse and 55 in remission have been controlled satisfactorily by intranasal B₁₂ either in saline solution, lactose powder, or as crystals. Absorption of the vitamin was probably direct and did not require binding with “intrinsic substance.” Chronic disease of the nose did not contraindicate this modality of therapy; local irritation of the mucous membranes by the crystalline B₁₂ or the vehicles employed has not been observed.

**Summario e Conclusiones in Interlingua**

In duo patientes con anemia pernicioso un satisfacente responsa clinic e hematologic esseva obtenite per un sol application de 200 e 150 µg de vitamin B₁₂ crystallin al mucosa nasal.
Un controlo satisfacente eseva attingite in 32 casos de anemia perniciose in recidiva e in 55 casos in remission per le administration intranasal de B₁₂ in solution salin, in pulvere de lactosa, o in forma crystallin. Le absorption del vitamina eseva probabilmente directe e non requireva ligation a “substantia intrinsec.” Chronic morbo del naso non eseva un contra-indication pro iste modo de therapia. Irritation local del membranas mucose per B₁₂ crystallin o le vehiculo usate non eseva observate.

REFERENCES

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