On the Intravenous Administration of Cyanocobalamin

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THERE IS general acceptance of the therapeutic effectiveness of intramuscular injections of crystalline cyanocobalamin (vitamin B_{12}) in a number of diverse pathologic states. The complete absence of side reactions (toxic or allergic) following this mode of therapy is very striking. The peroral administration of this drug, however, has caused a controversy based upon conflicting evidence as to its complete or effective absorption from the gastrointestinal tract.

The intravenous administration of cyanocobalamin has rarely been utilized, although it has, in my experience, advantages over the intramuscular injection, in certain circumstances. If the safety of intravenous administration can be shown to be as complete as that established for the intramuscular route, a technique of therapy becomes available to the clinician in which the rate and amount of absorption of the vitamin need not be taken into consideration.

Folkers[1] administered vitamin B_{12} intravenously to mice in doses as high as 1600 mg./Kg. without death or toxic manifestations. Such doses correspond to 112 million times the generally accepted daily human requirement of 1 μg. of cyanocobalamin. Ogasawara, Ata, and Hisada[2] reported that mice sustained the intravenous administration of cyanocobalamin in 15 μg. doses and rabbits in from 5 to 30 μg. amounts without toxic effect.

The first investigator who administered vitamin B_{12} intravenously to the human subject appears to have been Spies.[3] He gave cyanocobalamin intravenously to a group of patients with lateral sclerosis resulting from pernicious anemia, and concluded that the intravenous administration of this substance was both effective and non-toxic.[3a] His report was followed by that of Klima and Wengraf,[4] who gave daily intravenous doses of 15 μg. of vitamin B_{12} to 34 patients with pernicious anemia. They reported no hypersensitivity or toxic reactions. Chow[5] gave vitamin B_{12} intravenously in doses varying from 50 to 1000 μg. while studying the urinary excretion of this agent. No untoward results were noted. Similarly, Conley, Green, Hartmann, and Krevens[6] utilized 1000 μg. doses without undesirable side effect. Meyer, McInerny, and Ritz[7] also gave this material by vein in doses varying from 1 μg. daily to 7 μg. weekly, with satisfactory clinical response and without untoward reactions. In the treatment of three patients with pernicious anemia, Jännes[8] gave 75 μg. of vitamin B_{12} intravenously as single doses, without side effects. Goldeck and Weis[9] investigated the vitamin B_{12} activity in blood serum following the intravenous injection of 90 μg. of this material on nine successive days in three normal subjects, and in six with various diseases. All these individuals sustained the injections without side effect. In 1954, Morrison[10] utilized daily intravenous doses of 20 μg. of the vitamin as a lipotropic agent.

In 1950, I administered vitamin B_{12} intravenously in doses of from 15 to 30 μg. to determine the effect of this drug upon levels of vibratory perception in a group of normal subjects and in patients with various diseases. No side reactions were observed.

During an extensive investigation of the use of the intramuscular cyanocobalamin in the treatment of lupus erythematosus,[11,12,13] it appeared that perhaps even better results

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might be obtained by the use of this material intravenously in large daily doses.

Originally, crystalline cyanocobalamin (without preservative) in concentrations of 1000 μg. per ml.* was administered intravenously in daily doses of from 15 to 3000 μg. to a small group of patients. The complete lack of toxic or allergic reaction following the intravenous injection of this single-dose material suggested that the drug as found in multiple dose vials, containing 1.5% solution of benzyl alcohol as a bacteriostatic agent,† might be utilized. With this material also, no toxicity was noted, and, to date, 150 patients have been treated by the intravenous administration of 1000 μg. or more daily for varying periods of time, without toxic reaction. In some cases, the intravenous cyanocobalamin constituted only part of the treatment used.

The study includes 96 white and 7 colored females, and 43 white and 4 colored males, with an age range of from 4 to 78 years. Successive daily injections of 1000 μg. were given to a girl, age 10 years, for a period of over 270 days, without reaction. The largest single dose was 3000 μg., (white female, age 46, with uncontrollable pain after cervical laminectomy), given daily for a period of 2 weeks, interrupted for 1 week, and then repeated in similar courses for a total of 6 courses (86 intravenous injections of 3000 μg. each), without reaction.

Table I indicates the types of diseases treated, the variation in size of the individual dose, the number of doses given, and the total number of injections given to the patients in each group.

Case 47, B. H., white female, age 48, who was seen with an obscure condition previously mistakenly diagnosed as acute disseminated lupus erythematosus, described the occurrence of burning tongue, headache, and a post-nasal "drip" beginning ten minutes after injection of 1000 μg. of vitamin B_{12}, after having received numerous injections of this material previously without reaction. Observation of this patient for one hour immediately following the injection in which she described the burning of the tongue revealed no redness or swelling of the tongue or increased lachrymation, photophobia, or other signs of allergic reaction. Moreover, she has since then re-

TABLE I

Dosage of Intravenous Cyanocobalamin

Diagnosis	No. cases	No. of 1000 μg. inj.	No. of 2000 μg. inj.	No. of 3000 μg. inj.	Total no. inj.
Lupus erythematosus					
Acute disseminated	4	180	23		203
Subacute disseminated	3	95			95
Chronic disseminated	1	66			66
Chronic discoid	8	441			441
Photosensitivity	1	25			25
Psoriasis	11	222	4		226
Local neurodermatitis	10	111			111
Generalized neurodermatitis	2	31			31
Seborrheic dermatitis	5	116	6		122
Pyogenic infections	2	8			8
Viral infections	6	63	5		68
Fungus infections	5	94	5		99
Allergic manifestations	6	45	2		47
Contact dermatitis	13	140			140
Vesicular dermatoses	4	50	1		51
Acneform eruption	21	152			152
Alopecia areata	4	50	1		51
Vitiligo	3	51			51
Scleroderma	3	59			59
Endocrine disorders	18	278	3		281
Migraine	4	60	4		64
Severe neurologic diseases*	8	707	3	86	796
Malignancies	3	79			79
Miscellaneous†	5	31			31
Total	150	3154	57	86	3297

* In one case of juvenile syringomyelia the first 29 doses were of 500 μg. each.

† Miscellaneous cases include the following: pruritus ani (3); hyperhidrosis (1); pityriasis rosea (1).

* Crystalline vitamin B_{12} in 1000 μg./ml. without preservative, supplied through the kindness of Dr. Nathaniel Ritter of Merck and Co., Rahway, N. J.

† Crystalline vitamin B_{12} made by Durr Products, Inc., Dayton, Ohio.

ceived numerous injections of this vitamin without any complaints, so that it is probable that the administration of the drug was not responsible for the symptoms.

Aside from this very questionable reaction, none of the patients revealed subjective complaints or objective findings which might be construed to be allergenic or toxic effects from the 3297 intravenous injections of cyanocobalamin.

No attempt will be made here to evaluate the therapeutic effect of this mode of therapy as contrasted with that obtained by the administration of this agent orally or intramuscularly. The clinical results will be described elsewhere.

Summary

This report is presented to indicate that the intravenous administration of vitamin B_{12}, with or without bacteriostatic preservative (benzyl alcohol), is painless, non-toxic, and without allergenic side reactions. No reactions were noted in the course of 3297 intravenous injections among 150 patients with various diseases. The dosage ranged from 15 to 3000 μg. The clinician may, in my opinion, safely utilize this route of administration.

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