Medical Memoranda

Anaphylactic Reaction after Injection of Vitamin B_{12}

Brit. med. J., 1968, **3**, 102

This report concerns a 67-year-old man with pernicious anaemia who developed a severe anaphylactic reaction after receiving an intramuscular injection of vitamin B_{12}, and who showed positive reaction to cyanocobalamin and hydroxocobalamin by intradermal tests.

Case Report

The patient had no history of allergic diseases, and had not previously shown allergic or adverse reactions to drugs. He had been treated for pernicious anaemia since 1949, initially with intramuscular injections of liver extract and cyanocobalamin 0.2 mg. at intervals of two to eight weeks. Cyanocobalamin was given from 1965 to November 1966, when the treatment was changed to hydroxocobalamin. The proprietary preparations of cyanocobalamin and hydroxocobalamin used contained benzyl alcohol 1.5% as preservative, and were distributed in multiple-dose phials.

Until the third and last injection of hydroxocobalamin in April 1967 he had never shown any adverse reaction either to the liver extract or to the different preparations of vitamin B_{12}. Within a couple of minutes after receiving the last injection of hydroxocobalamin he developed symptoms of anaphylactic shock, with peripheral circulatory collapse, unrest, shiverings, and general itching. He had a feeling of swelling of the whole body and was on the point of unconsciousness. After receiving 0.75 ml. of adrenaline subcutaneously he slowly recovered, but had nausea, vomiting, diarrhoea, shiverings, and itching during the following three to four hours, and also developed an evanescent exanthema. During the next couple of weeks he felt unwell and had periods of itching and transitory exanthema.

Results of Intradermal Tests (by Injection)

Test Substance	Test Concentration	Test Dose	Reaction
Cyanocobalamin with 1·5% benzyl alcohol, commercial brand	100 μg./ml.	0·05 ml.	Weal with pseudopodia
Hydroxocobalamin, commercial brand	100 μg./ml.	0·05 ml.	,, ,,
Hydroxocobalamin, very highly purified	100 μg./ml.	0·05 ml.	,, ,,
Cyanocobalamin prepared from very highly purified hydroxocobalamin ..	100 μg./ml.	0·05 ml.	,, ,,
Coenzyme B_{12}	100 μg./ml.	0·05 ml.	,, ,,
Methylcobalamin	100 μg./ml.	0·05 ml.	,, ,,
Benzyl alcohol	1·5%	0·05 ml.	No reaction
Cobalt chloride	10^{-6}	0·05 ml.	No reaction

The results of intradermal tests are shown in the Table. The reactions developed within 10 to 15 minutes. The weals disappeared within four to five hours, while the surrounding flare persisted for about 20 hours. There was no general reaction to the tests. By further dilution of the test substances he gave reactions with weals and pseudopodia even to test concentrations of 1 μg./ml. of all the vitamin B_{12} preparations listed in the Table. He also gave positive reactions to intradermal tests with commercial cyanocobalamin from two other producers of vitamin B_{12}. Intradermal tests with identical technique and test substances were negative in three healthy controls.

The treatment has been changed to a vitamin B_{12} preparation intended for peroral use. So far he has shown no adverse reaction to this medication. It is, however, too early to state if he can utilize the vitamin B_{12} by this route of administration.

Discussion

Reports on anaphylactic shock after injection of vitamin B_{12} preparations have been published by Young *et al.* (1950), Borodulin (1961), Roy (1961), and Marinkovic (1962). In the case described by Roy the anaphylactic reaction resulted in death. Less severe allergic reactions have been reported by Bedford (1952), Gillhespy (1955), and Ungley (1955).

Allergic reactions to proprietary preparations of vitamin B_{12} might be due to substances added to the solutions as preservatives or for other reasons, to impurities from the production, or to the vitamin B_{12} itself. Lagerholm *et al.* (1958) reported a case of hypersensitivity to benzyl alcohol added as preservative, resulting in urticaria after injection.

Vitamin B_{12} is produced by biosynthesis, and the proprietary preparations probably always contain carry-over impurities. Bedford (1952) suggested that these impurities are responsible for the antigenic properties of vitamin B_{12} preparations, and further that there is an antigenic relation between these impurities and antibiotics, and vice versa. A similar explanation is conceivable regarding the case described by Young *et al.* (1950). Their patient developed anaphylactic shock after receiving an injection of vitamin B_{12} concentrate made from streptomyces broth, and gave a positive reaction to intradermal test with this preparation. On the other hand, he neither reacted to intradermal test nor showed evidence of sensitivity to treatment with crystalline vitamin B_{12} made from streptomyces broth.

Animal experiments concerning the sensitizing properties of vitamin B_{12} are controversial. Traina (1950) reported the inability to produce anaphylactic shock in guinea-pigs by multiple injections of small doses of crystalline vitamin B_{12}. On the other hand, Lipton and Steigman (1963), by artificial means, succeeded in sensitizing guinea-pigs to crystalline vitamin B_{12} by intradermal injections of cyanocobalamin emulsified in Freund's adjuvants. They used crystalline cyanocobalamin derived from streptomyces fermentation liquor for sensitization, and the skin reactions were elicited by the use of cyanocobalamin derived from liver. This fact was claimed to ascertain the specificity of sensitization to vitamin B_{12} itself rather than to contaminants in its preparation. Delayed reaction of tuberculin type of crystalline vitamin B_{12} was reported by Rostenberg, jun., and Perkins (1951) in a patient with allergic contact dermatitis from cobalt. They claimed this to be the first report of sensitivity to vitamin B_{12}, and connected the reaction with the cobalt in the vitamin molecule.

The preparations of cyanocobalamin and hydroxocobalamin used in the present patient are highly purified. Though used for years, no reports of untoward reactions have been published. The patient's reactions both to the specially prepared, highly purified hydroxocobalamin and other cobalamins might suggest that he has been sensitized to the cobalamin molecule itself. This should imply that vitamin B_{12} constitutes a complete antigen, an assumption which is not very likely. Further research must decide whether a polypeptide bound to the vitamin, or a carry-over polypeptide, was the antigen in the present case.

My thanks are due to Nycgaard & Co. A/S for the supplies of vitamin B_{12} preparation.

Gunnar Høvding, M.D.,
Department of Dermatology, University of Bergen, Bergen, Norway.

References

Bedford, P. D. (1952). *Brit. med. J.*, **1**, 690.
Borodulin, Yu. D. (1961). *Klin. Med. (Mosk.)*, **39**, No. 8, p. 139.
Gillhespy, R. O. (1955). *Lancet*, **1**, 1076.
Lagerholm, B., Lodin, A., and Gentele, H. (1958). *Acta allerg. (Kbh.)*, **12**, 295.
Lipton, M. M., and Steigman, A. J. (1963). *J. Allergy*, **34**, 362.
Marinkovic, V. (1962). *Srpski, Arkh. tselok. Lek.*, **90**, 547.
Rostenberg, A., jun., and Perkins, A. J. (1951). *J. Allergy*, **22**, 466.
Roy, A. N. (1961). *J. Indian med. Ass.*, **36**, 262.
Traina, V. (1950). *Arch. Path.*, **49**, 278. Cited by Lipton and Steigman (1963).
Ungley, C. C. (1955). *Vitam. and Horm.*, **13**, 137.
Young, W. C., Ulrich, C. W. and Fouts, P. J. (1950). *J. Amer. med. Ass.*, **143**, 893.