

Adverse reactions associated with the administration of a tricarboyanine dye (Cardio-Green) to uremic patients

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The administration of a tricarboyanine dye (Cardio-Green) for evaluation of cardiac output in three clinically uremic patients produced untoward symptoms (diaphoresis, pruritus, and headache) in two and a severe anaphylactoid reaction in a third. A fourth patient, on concomitant steroid treatment, had no reaction to the dye. Skin tests in all patients were negative, and gel diffusion studies failed to show precipitating antibodies in the serum of the patient with the anaphylactoid reaction. It is proposed that these reactions were more likely due to a nonimmunologic histamine releasing effect than to an antigen-antibody reaction.

A major advance in the choice of indicator substances for the measurement of cardiac output by the Stewart-Hamilton technique came in 1956 with the introduction of a nontoxic dye, Cardio-Green, by Fox and associates.¹ This is a low-molecular weight (MW, 775) sodium salt of dibenzoindotricarboyanine hydroxide.

Cardio-Green has been administered in massive doses to nonuremic experimental animals and human beings without reported side effects.^{2, 3} Similarly, Hampers and associates⁴ and Goss and associates⁵ have used this drug to evaluate cardiac output in patients with chronic renal failure without adverse reactions. It was the original intent of the authors to evaluate hemodynamic functions in uremic patients undergoing hemodialysis. Because of the severity of the reactions encountered in the initial group of patients, further studies were not performed.

CASE REPORTS

All 4 patients included in this report were adult men on a chronic hemodialysis program. They had been entered into a study evaluating the effects of hemodialysis on hemodynamic function. None of the patients reported in this series had any known drug sensitivity and none had been exposed to Cardio-Green prior to this study.

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Case 1

M. D., a 53-year-old Caucasian man with chronic glomerulonephritis, had been treated with biweekly hemodialysis for 5 months. His usual predialysis blood urea nitrogen (BUN) averaged 126 mg. per cent. He occasionally took an antihistamine for relief of mild pruritus but had taken none the day of the study. Within 20 seconds of the injection of Cardio-Green the patient complained of severe generalized pruritus and weakness, and he began to perspire. To complete the study, his blood was reinfused, and another injection of the dye was made. The patient's pruritus increased, he became agitated, and then developed syncope. He was given 25 mg. of diphenhydramine intramuscularly. His symptoms gradually subsided, and he was returned to his room.

Case 2

U. L., a 51-year-old Negro man with chronic glomerulonephritis, had been dialyzed twice weekly for 22 months. Predialysis BUN values averaged 114 mg. per cent. He also took an antihistamine intermittently for mild pruritus but had taken none the day of the study. Within 15 seconds of injection of the dye, he became apprehensive and complained of generalized pruritus, which rapidly became intense, and he developed a headache. He was given diphenhydramine (25 mg.) intramuscularly, and the symptoms were promptly relieved.

Case 3

G. D., a 25-year-old American Indian man with chronic renal failure secondary to glomerulonephritis, had been on twice-weekly dialysis for 6 months. His predialysis BUN values averaged 110 mg. per cent. He was not on other medication. He underwent hemodynamic studies twice. During the first study, 30 seconds after injection of Cardio-Green he complained of severe itching of the right forearm where several wheals developed around the Scribner arteriovenous shunt. He became agitated and complained of a headache. Diphenhydramine, 25 mg. intravenously, relieved these symptoms. He returned 6 days later for repeat studies. Within 20 seconds of injection of Cardio-Green he became hypotensive (blood pressure 95/70 mm. Hg), extremely agitated, perspired profusely, and developed a headache. No indicator dilution curve was inscribed. The patient's blood was reinfused, and immediately following a second injection of dye he developed nausea, diaphoresis, and severe hypotension (blood pressure 30/5 mm. Hg). He vomited and passed flatus. Again, there was no inscription of an indicator dilution curve. Epinephrine (0.5 mg.) was administered via the intracardiac catheter. He remained hypotensive, and an additional 1.0 mg. of epinephrine was given, followed by 100 mg. of hydrocortisone. An intravenous infusion of 100 mg. hydrocortisone in 500 ml. of sodium chloride solution was started. He recovered and returned to the ward.

Case 4

L. I., a 51-year-old Caucasian man, had systemic lupus erythematosus with severe nephritis. For this he was receiving 30 mg. of prednisone daily. He was studied prior to his first hemodialysis. Two injections of Cardio-Green were made and satisfactory indicator dilution curves were obtained. No reaction to the dye was manifest. Two days later, following hemodialysis, the studies were repeated without complication.

METHODS**Hemodynamic studies**

For measurement of cardiac output, Cardio-Green (5 mg. dissolved in 1 ml. of distilled water supplied by the manufacturer) was injected in a bolus into the right atrium through a cardiac catheter. Blood was withdrawn from the opposite arm through a Gilford cuvette densitometer from the arterial

side of a Scribner arteriovenous shunt and reinfused into the venous limb of the shunt after each curve had been inscribed.

Gel diffusion studies

An Ouchterlony⁶ gel diffusion test was performed by standard methods using the patient's serum in the center well and varying concentrations of the tricarboyanine dye in the outer wells of the agar plate.

Skin tests

Skin sensitivity tests using two concentrations (0.05 mg. per milliliter and 5 mg. per milliliter) of Cardio-Green were performed, first doing scratch tests and then intradermal injection of 0.03 ml. of dye. In each instance the dilute solution was used for testing before employing the concentrated dye. Fifteen minutes after each procedure the results were read and recorded on a 0 to 4+ scale according to standard techniques.⁷ Three normal individuals served as control subjects.

Evaluation of Cardio-Green (Lot No. 438)

The interaction of the blood of Patient G. D. and Cardio-Green was tested *in vitro*. Various concentrations of the dye were mixed with the blood and withdrawn through the Gilford densitometer.

An aliquot of the dye was subjected to bacterial culture. Other vials from this same lot were used in routine cardiac output studies in nonuremic patients.

RESULTS

Hemodynamic studies

The cardiac output curves inscribed by these patients are not pertinent to this paper and will be reported elsewhere.

Gel diffusion studies

No precipitating antibodies were found in the serum of the patient (G. D.) with the anaphylactoid reaction.

Skin tests

All individuals were skin tested by both scratch and intradermal tests within a month of their clinical reactions to Cardio-Green. No wheal formation was noted in either patients or control subjects.

Evaluation of Cardio-Green

In vitro mixing of differing concentrations of the blood of Patient G. D. with Cardio-Green failed to demonstrate any reaction that would prevent the chemical detection of the dye in blood, since the classic stair-step curves were inscribed as blood was withdrawn through the densitometer.

The bacterial culture tests showed no growth after 4 days of incubation.

No other patient (none was uremic) studied by the Cardiac Catheterization Laboratories with the use of Lot No. 438 of Cardio-Green developed reactions from the dye.

DISCUSSION

The symptoms experienced by 3 of the 4 uremic patients (M. D., U. L., and G. D.) to the injection of Cardio-Green might be explained either as an antigen-antibody reaction or through the release of histamine or other mediators by nonimmunologic means. Although it is conceivable that Cardio-Green could have combined with a protein forming a hapten-protein complex and in this form become antigenic, there are several factors which make this unlikely. Uremic patients have an over-all decreased immunologic responsiveness,⁸ and they have decreased ability to manifest immediate cutaneous hypersensitivity reactions to antigenic stimuli⁹ as exemplified by negative skin tests (scratch and intradermal). Also, 2 patients (M. D. and U. L.) manifested reactions on their single, initial exposure to the drug, and another (G. D.) had a mild reaction on his first exposure and a severe reaction with the second exposure only 6 days later. The Ouchterlony gel diffusion test failed to show precipitating antibodies.

Nonimmunologic release of histamine from the mast cells could explain these reactions. Such responses may be produced by the injection of many, diverse histamine-releasing agents including compound 48/80, morphine, D-tubocurarine, polymyxin, chlortetracycline, atropine, and others.¹⁰ These compounds have very diverse chemical structures, but none is very similar to Cardio-Green. The one uremic patient (L. I.) who did not have a reaction to the dye had been on glucocorticoid therapy, which could have caused a diminution in the number of mast cells,¹¹ the principal storage site for histamine, but more likely may have suppressed the reaction by other mechanisms.¹² The patients (M. D. and U. L.) who were on intermittent antihistamine therapy manifested only moderate reactions of generalized pruritus and headaches following the injection of the dye, but since they had not taken this type of medication on the day of their reactions, it is questionable whether antihistamines affected their clinical course. The most intense anaphylactoid reaction was observed in the patient (G. D.) not on steroid or antihistamine therapy.

It was not possible to detect the presence of Cardio-Green in the arterial blood following injection into the right atrium of the patient (G. D.) with the anaphylactoid reaction. The fate of this material is undetermined; however, several possibilities exist. First, the dye might have been altered chemically in the patient's blood. This possibility was disproved by mixing the patient's blood with Cardio-Green *in vitro* and inscribing calibration curves. Second, the dye could have become entrapped within the pulmonary circulation. This would be unlikely in view of the small molecular weight of the dye alone and absence of data indicating protein binding. Third, Cardio-Green could have become concentrated within the mast cells of the lungs. This property has been demonstrated for another histamine liberator, 4:4'-diamidino stilbene, by Hawking and Smiles.¹³ No *in vitro* measurements of the histamine-releasing properties¹⁴ of Cardio-Green were performed, but in other clinical situations in which *in vivo* histamine release by drugs has been implicated, the *in vitro* studies have been negative.¹⁵ The release of other mediators is an additional possibility.

Although the mechanism of the adverse reactions is not clear and it is un-

known why uremic individuals seem to be particularly affected, it is recommended that caution be used when administering Cardio-Green to uremic patients for evaluation of cardiac or hepatic functions.

REFERENCES

- 1 Fox, I. J., Brooker, L. G. S., Heseltine, D. W., and Wood, E. H.: A new dye for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation, *Circulation* 14: 937, 1956.
- 2 Opdyke, D. F., and Sniffen, R. E.: Estimation of cardiac output by rapidly repeated dye-dilution technic, *Proc. Soc. Exp. Biol. Med.* 102: 725, 1959.
- 3 Cherrick, G. R., Stein, S. W., Leevy, C., M., and Davidson, C. S.: Indocyanine green: Observation on its physical properties, plasma decay, and hepatic extraction, *J. Clin. Invest.* 39: 592, 1960.
- 4 Hampers, C. L., Skilman, J. L., Lyons, J. H., Olsen, J. E., and Merrill, J. P.: A hemodynamic evaluation of bilateral nephrectomy and hemodialysis in hypertensive man, *Circulation* 35: 272, 1967.
- 5 Goss, J. E., Alfrey, A. C., Vogel, J. H. K., and Holmes, J. H.: Hemodynamic changes during hemodialysis, *Trans. Am. Soc. Artif. Intern. Organs* 13: 68, 1967.
- 6 Ouchterlony, O.: Antigen-antibody reactions in gels, *Acta Pathol. Microbiol. Scand.* 26: 507, 1949.
- 7 Sherman, W. B., and Kessler, W.: Allergy in pediatric practice, St. Louis, 1957, The C. V. Mosby Company.
- 8 Merrill, J. P.: The immunologic capability of uremic patients, *Cancer Res.* 28: 1449, 1968.
- 9 Wilson, W. E. C., Kirkpatrick, C. H., and Talmage, D. W.: Suppression of immunologic responsiveness in uremia, *Ann. Intern. Med.* 62: 1, 1965.
- 10 Paton, W. D. M.: Histamine release by compounds of simple chemical structure, *Pharmacolog. Rev.* 9: 269, 1957.
- 11 Salvato, D.: Mast cells in bronchial connective tissue of man. Importance of such cells in allergic tissue injury, *Experientia* 15: 308, 1959.
- 12 Fischil, E. E.: Effect of adrenocorticosteroids on various types of antigen-antibody reactions, in Mills, L. C., and Moyer, J. H., editors: *Inflammation and disease of connective tissue*, Philadelphia, 1961, W. B. Saunders Company.
- 13 Hawking, F., and Smiles, J.: The distribution of 4:4'-diamidino stilbene in trypanosomes and mice as shown by fluorescence, *Ann. Trop. Med. Parasitol.* 35: 45, 1941.
- 14 Lichtenstein, L., and Osler, A.: Studies on the mechanisms of hypersensitivity phenomena, *J. Exp. Med.* 120: 507, 1964.
- 15 Kohen, M., Mattikow, M., Middleton, E., Jr., and Butsch, D. W.: A study of three untoward reactions to dextran. *J. ALLERGY* 46: 309, 1970.