

ANAPHYLACTOID REACTION FOLLOWING THE ORAL ADMINISTRATION OF IODIDE-CONTAINING CHOLECYSTOGRAPHIC MEDIA

SHELDON G. COHEN, M.D.,* ROBERT N. ARMEN, M.D.,** AND
MILTON KANTOR, M.D., WILKES-BARRE, PA.

INTRODUCTION

THE etiological role of iodine in hypersensitivity reactions has been repeatedly demonstrated so that it is not unusual to see allergic symptoms develop following the administration of iodide-containing radiographic contrast media to a patient later proved to be sensitive to this radical. The literature pertaining to this subject has been recently summarized in a comprehensive review by Alexander.¹ Dermatologic eruptions and minor allergic symptoms such as pruritus, flushing, sneezing, and urticaria are the usual clinical manifestations noted in iodide sensitivity^{1, 2} reactions following intravenously administered contrast media for pyelography and the intratracheal introduction of iodized oil for bronchography. However, fatal reactions of the delayed type, attributed to renal damage³ and those of an acute anaphylactic type characterized by the sudden onset of flushing, sneezing, urticaria, cough, dyspnea, syncope, and shock and occasionally progressing to a fatal termination,^{1, 3-5} have been reported with these diagnostic procedures.

A review of the literature pertaining to oral cholecystography revealed that side reactions such as burning sensations of the throat, dysuria, diarrhea, abdominal cramps, headache, nausea, and dizziness, are occasionally seen and that only minor allergic phenomena, such as urticaria, have rarely occurred.⁶⁻⁸ However, to the best of our knowledge, there have been no instances reported of the immediate severe allergic- or anaphylactic-type reactions following the oral ingestion of iodide containing cholecystographic media. Recent experience with a patient experiencing a near-fatal, acute reaction following the oral administration of iodoalphonic acid, preparatory to cholecystography, was considered noteworthy and therefore prompted the reporting of this case in order to point out this apparently rare but potentially serious manifestation of hypersensitivity in a procedure hitherto considered innocuous.

CASE REPORT

K. S., a 43-year-old clerk, was admitted to this hospital on Oct. 24, 1955. For the past eleven years he had complained of recurrent attacks of postprandial epigastric discomfort, accompanied by nausea and occasional vomiting. Investigation of these complaints in the

From the Medical Service, Veterans Administration Hospital, Wilkes-Barre, Pennsylvania.
Received for publication April 3, 1956.

*Attending physician (Allergy).

**Chief of Medical Service.

past had included diagnostic x-ray procedures, including a gastrointestinal x-ray series, cholecystogram three years previously, and an intravenous pyelogram seven years previously, with normal roentgenographic findings. He could recall no untoward reactions to any of these procedures. Because of a recent exacerbation of symptoms, his physician decided to repeat the gall bladder studies. As directed, on Oct. 24, 1955, at 6:00 P.M. he took two tablets of iodoalphonic acid and continued to take two tablets every five minutes until he had ingested a total of twelve tablets. Two hours later, at approximately 8:00 P.M., he began to complain of generalized pruritus soon accompanied by the appearance of giant urticarial wheals which rapidly progressed until almost the entire skin was involved. At 9:30 P.M., he reported to the hospital complaining of the skin lesions and associated marked pruritus. Shortly after his arrival at the hospital, while being examined, the patient suddenly collapsed and became comatose. The blood pressure was unobtainable and marked respiratory distress with inspiratory stridor developed. Emergency treatment was instituted, which included adrenalin 1-1,000, 0.5 ml. subcutaneously; diphenhydramine hydrochloride, 10 mg. intramuscularly; and hydrocortisone, 100 mg. in 500 ml. of 5 per cent glucose, intravenously. With this therapy, the blood pressure gradually returned to normal levels and the respiratory difficulty subsided. The urticaria disappeared during the next twelve hours. Treatment with hydrocortisone intramuscularly and later orally was continued for the next two days, during which time there was no recurrence of symptoms. A gall bladder x-ray on the day after admission revealed a normally functioning organ thus indicating absorption and concentration of the media.

A complete physical examination later revealed no abnormal physical findings and all laboratory tests, chest x-rays, and electrocardiographic tracings were within normal limits.

A review of the past history referable to allergic manifestations revealed that three years previously he had experienced a penicillin reaction manifested by symptoms of urticaria that persisted for only three or four days. Subsequently, he had taken courses of penicillin orally without the appearance of similar symptoms or other untoward effects. An allergy survey failed to reveal any evidence of associated atopic manifestations. There was no history of symptoms of asthma, allergic rhinitis, atopic dermatitis, migraine, urticaria, or angioedema other than that associated with the transient drug reactions, food intolerances, or other associated allergic symptoms.

A routine survey of intracutaneous tests to common perennial inhalant, food, mold, and pollen allergens was negative. An attempt was made to detect circulating reagins against suspected iodide containing antigens by means of the Prausnitz-Küstner serum passive transfer technique. The patient's serum was transferred intracutaneously to multiple skin sites of normal recipients. After the suitable time period these recipient sites were challenged by the following methods: (1) scratch test with sodium iodide; (2) scratch test with iodoalphonic acid powder and N/10 sodium hydroxide; (3) oral administration of iodoalphonic acid; and (4) intracutaneous tests with serum of normal patients who had taken tablets of iodoalphonic acid orally three hours previously. Negative reactions were obtained following the first three testing procedures and, in the last instance, equally positive whealing reactions were obtained in both the passively transferred and normal control sites apparently due to the nonspecific whealing effects of the serum, even when diluted 1-100 in physiologic saline.

Continued observation and follow-up examinations of this patient have shown him to remain asymptomatic since the initial episode, taking no medication and avoiding all iodide-containing drugs and foods.

COMMENT

Iodide sensitivity through allergic mechanisms is a well-documented phenomenon and a discussion of this need not be entered into here. Though fortunately rare, anaphylactoid reactions of the type suffered by this patient have been reported in iodide-sensitive patients receiving contrast media by the intravenous route,^{2, 4} apparently as a result of being immediately presented

with a high blood level of the offending antigen. It is therefore considered a highly unusual situation when this clinical picture presents itself in an otherwise nonatopic individual following the oral ingestion of an organic iodide compound with which only minor allergic reactions have been reported⁶⁻⁸ after extensive use. The only other severe allergic reaction to iodoalphonic acid described has been that of a near-fatal attack of severe asthma in an iodide-sensitive patient reported by Sheldon and Lovell.⁹

Since this material is rapidly absorbed from the gastrointestinal tract into the blood stream, an anaphylactoid reaction of this type is entirely possible if the blood concentration should reach a critical level in a highly sensitive patient. This is in contrast to the analogous situation in penicillin sensitivity where the oral administration of penicillin, potentially capable of producing anaphylactic reactions, is considered a relatively safe procedure¹⁰ even in sensitive individuals because of its slower rate of absorption. In this regard, it is also of interest to note that the relative infrequency of severe reactions following the intrabronchial installation of iodized oil in bronchography has been attributed to the stability of the chemical combination of the iodine and unsaturated fats resulting in little decomposition of the oil in the lung.¹¹

It is of interest to point out that this patient had previous exposure to iodide-containing contrast media without any untoward reactions noted. An intravenous pyelogram had been done seven years before and a cholecystogram three years previous to this exposure and reaction to iodoalphonic acid. In all probability these previous exposures, though without reactions themselves, served as the sensitizing mechanisms, although one might suspect that the development of this high a degree of hypersensitivity would be preceded by some lesser allergic manifestations on previous exposures. It is entirely possible that the hypersensitivity existed specifically to iodoalphonic acid or some other radical of this compound rather than to the iodide portion since this could be neither proved nor disproved by available diagnostic procedures, skin tests, or other confirmatory data. The etiology of hypersensitivity to iodoalphonic acid in the production of this patient's anaphylactoid reaction can only be suspected and the diagnosis made only on the grounds of clinical association. The only other ingredients contained in these tablets were cornstarch and magnesium stearate⁷ and allergy to these were excluded in this patient. The failure to demonstrate circulating reagins in the patient's serum does not imply that they did not exist since there is no definite knowledge of the exact offending antigen. One can only suspect that this may be iodine and/or iodoalphonic acid but the failure to demonstrate positive whealing reactions to these only demonstrates once again the failure of skin tests when dealing with suspected simple chemical antigens.¹²

Suspecting that the antigen might be iodine in haptenic combination with a serum protein, a test antigen of serum from a normal individual who had absorbed iodoalphonic acid into his blood stream from his gastrointestinal tract was used as a test antigen. However, the nonspecific irritating effects of the serum itself prevented its usefulness in the detection of reagins. In addition

to the limitations of all simple chemicals as skin test antigens,¹² iodoalphonic acid presents its own particular problems in this regard. This material, a crystalline powder, is insoluble in water or saline. It is partially soluble in benzene and chloroform; soluble in alcohol, ether, and in alkali carbonate, or hydroxide solutions.⁷ These resulting solutions are unsuitable for intracutaneous injection or conjunctival instillation because of their nonspecific irritating properties, or high pH. The solubility of iodoalphonic acid in hydroxide may be taken advantage of by applying a paste of the powder in N/10 sodium hydroxide in scratch test procedures. Though the scratch test is generally a less sensitive technique than the intracutaneous test in eliciting sensitivity, it may be reliably employed even in Prausnitz-Küstner passive transfer tests.¹³ Thus, the scratch test, though limited in sensitivity and of undetermined accuracy in this situation, may be the only method available for any future studies or attempts in screening patients potentially sensitive to the orally administered cholecystographic contrast media currently available.

SUMMARY

1. A case report is presented in which a nonatopic patient with no previous history of iodide sensitivity developed an anaphylactoid reaction characterized by urticaria, angioedema, dyspnea, loss of consciousness, and cardiovascular collapse following the oral administration of iodoalphonic acid, a cholecystographic contrast media.

2. Prompt treatment with adrenalin, parenteral antihistaminics, and adrenal corticosteroids resulted in complete recovery.

3. Attempts to demonstrate circulating reagins against iodide and iodoalphonic acid were unsuccessful.

Iodoalphonic acid (Priodax) in crystalline form was supplied by Dr. G. K. Hawkins of the Schering Corporation. His assistance in this study and case report is gratefully acknowledged.

REFERENCES

1. Alexander, H. L.: *Reactions With Drug Therapy*, Philadelphia, 1955, W. B. Saunders Company, pp. 185-192.
2. Crepea, S. B., Allanson, J. C., and DeLambre, L.: The Failure of Antihistamine Drugs to Inhibit Diodrast Reactions, *New York State J. Med.* **49**: 2556, 1949.
3. Pendergrass, E. P., Chamberlin, G. W., Godfrey, E. W., and Burdick, E. D.: A Survey of Deaths and Unfortunate Sequellae Following the Administration of Contrast Media, *Am. J. Roentgenol.* **48**: 741, 1942.
4. Simon, S.: Sudden Death Following Intravenous Administration of Contrast Media, *J. A. M. A.* **138**: 127, 1948.
5. Mahon, G. S.: Reaction Following Bronchoscopy With Iodized Oil, *J. A. M. A.* **130**: 194, 1946.
6. Seedorf, E. E., Powell, W. N., and Dysart, D. N.: A Comparison of Five Gallbladder Media, *South. M. J.* **47**: 809, 1954.
7. Hawkins, G. K. (Schering Corporation): Personal Communication.
8. Scribner, A. (Winthrop Laboratories): Personal Communication.
9. Sheldon, J. M., and Lovell, R. G.: Asthma Due to Halogens, *Am. Pract.* **4**: 443, 1949.
10. Siegal, S., Steinhardt, R. W., and Gerber, R.: Fatal and Near-Fatal Penicillin Anaphylaxis, *J. ALLERGY* **24**: 1, 1953.
11. Theodos, P. A.: Bronchography in Iodine Sensitivity, *J. A. M. A.* **148**: 1419, 1952.
12. Sherman, W. B.: Drug Allergy, *Am. J. Med.* **3**: 586, 1947.
13. Coca, A. F., Walzer, M., and Thommen, A. A.: *Asthma and Hay Fever in Theory and Practice*, Springfield, Ill., 1931, Charles C Thomas, publisher, p. 361.