

BRIEF COMMUNICATION

A study of three untoward reactions to dextran

Michael Kohen, M.D., Michael Mattikow, M.D.,
Elliott Middleton, Jr., M.D., and David W. Butsch, M.D.,
New York, N. Y., Wayne, N. J., and Denver, Colo.

Three cases of clinical reactions to dextran have been reported. The 2 patients tested with intradermal dextran showed negative reactions. The serum of the 2 patients studied by gel diffusion analysis did not show precipitating antibody. Neither lymphocyte blast transformation (all 3 cases) nor histamine release (2 of the cases) could be demonstrated on incubation of cells with a wide range of dextran concentrations. It was also shown that dextran has no inhibitory effect on the lymphocyte blast transformation when stimulated by phytohemagglutinin. By conventional laboratory tests, we found no evidence of an allergic or immune reaction to dextran, even though the reactions appeared to be anaphylactic and allergic in nature.

Dextran came into clinical use as a plasma expander in the early 1940's.¹ In 1944, Thorsen,² and subsequently many others,³⁻⁵ reported adverse reactions secondary to the intravenous administration of dextran. Among the more commonly reported symptoms and signs are headache, chills, flushing, urticaria, angioneurotic edema, wheezing, nausea, chest pain, sneezing, rhinorrhea, joint pain (delayed onset), swelling of the extremities, hypotension, and syncope.³

Recently we have seen 3 cases of adverse reactions to dextran after intravenous administration. In an attempt to disclose or to exclude an immune type of response, the blood of these patients was studied for evidence of lymphocyte blast transformation, in vitro histamine release, and for the presence of antibody by gel diffusion. These reactions were studied from 3 months to 1 year after their occurrence. The patients received the same type of dextran (dextran 75, Abbott Laboratories) but with different control numbers.

CASE HISTORIES

Case No. 1

The patient was a 27-year-old Caucasian physician who sustained a blow to his right ileofemoral region 2 days prior to admission. One day prior to admission, he developed pain,

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tenderness, and possibly a red streak running up the medial upper thigh into the femoral area on the right. The clinical impression was thrombophlebitis, and an infusion of high-molecular weight dextran was started. After receiving 10 to 15 drops, he stated that he felt numbness and tightness in the chest and that breathing was difficult. The infusion was stopped, and concurrently the patient vomited and had an involuntary defecation. The conjunctivae became suffused, and his blood pressure was unobtainable at this time. He was given 0.3 ml. of 1:1,000 epinephrine subcutaneously and 50 mg. of diphenhydramine by vein. At this time his pulse was 160 and regular. He remained pale for a few minutes with persistent tachycardia, and at this time urticarial lesions appeared on his arms and legs. Approximately 15 minutes later his blood pressure was 90/70. An infusion of 5 per cent dextrose in water containing 100 mg. of hydrocortisone was started. Over the next 2 hours his symptoms slowly subsided, and his vital signs had returned to normal 3 hours later. This patient had never received dextran before, nor was there any history of allergy.

Case No. 2

A 64-year-old Caucasian man was admitted on October 25, 1967, for a peptic ulcer. A posterior gastrojejunostomy, gastrectomy, bilateral herniorrhaphy, and bilateral vagectomy were performed on October 30, 1967. Seven days later he developed a temperature of 101, hemoptysis, and pain at the right costal margin, and he was thought to have pneumonitis, thrombophlebitis, and pulmonary emboli. An infusion of high-molecular weight dextran was started, and within seconds he became dyspneic and diaphoretic. Vital signs, which had been within normal limits except for the elevated temperature, at this time showed blood pressure 90/40, pulse 120, and respiration 40. His lungs were clear to examination, and an electrocardiogram was normal. The dextran was discontinued, and 25 mg. of diphenhydramine were given intramuscularly. Vital signs returned to normal within a few minutes. A lung scan 2 days later was consistent with multiple pulmonary emboli. The possibility of an acute pulmonary embolus could not be ruled out, but the proximity of the reaction to the dextran infusion and its nature was interpreted as being allergic by the physician in charge. This patient had never received dextran in the past, and there was no history of previous allergic disease.

Case No. 3

A 30-year-old Caucasian physician developed thrombophlebitis of both legs for which he was treated with 500 c.c. of high-molecular weight dextran intravenously. The following day, within 5 minutes of starting a second dextran infusion, he became flushed and developed sneezing, rhinorrhea, and swelling of his eyelids. The infusion was stopped, and 100 mg. of diphenhydramine were administered by mouth. Within thirty minutes the nasal symptoms subsided, but the periorbital edema persisted for 24 hours. This patient had been troubled by bronchial asthma up to the age of 8, following which he had been completely free of any allergic symptoms.

MATERIALS AND METHODS

Skin tests

Intradermal skin tests were performed by injecting 0.05 ml. of various dextran solutions. The skin tests were read after 15 minutes and recorded on 0 to 4+ scale according to standard techniques.⁶ The actual amounts of dextran injected were 30, 300, and 3,000 μ g in each of the 2 patients studied. Case Nos. 1 and 3 were also skin tested with several common allergens including dust, feathers, dog, *Alternaria*, grasses, and ragweed.

Gel diffusion studies for antibody

Agar plates for double diffusion analyses were prepared according to a standard method.⁷ The patients' sera were placed in a center well and dextran solutions of various concentrations were put in the outer wells. The plates were kept at room temperature and examined daily for one week.

Lymphocyte blast transformation reaction

Fifty milliliters of blood were drawn in a heparinized syringe, and leukocyte suspensions were prepared according to a slight modification of the method described by Bain, Vas, and Lowenstein.⁸ A total of four million leukocytes were prepared in 4 ml. of the tissue culture medium (medium 199, Microbiological Associates, Inc.). To these suspensions dextran was added such that the final concentrations ranged from 15 μg per milliliter to 1,800 μg per milliliter. The dextran which was used in these experiments, as well as in the histamine release experiments described below, was the same as that which produced the clinical reactions (dextran 75, Abbott Laboratories). The cell cultures were incubated at 37° C. for 4 to 5 days, resuspended, and 2 μc of ³H-thymidine added to each tube. After 4 additional hours of incubation, the cells were immediately processed.⁸ Leukocyte cultures of each patient were also exposed to phytohemagglutinin.

Histamine release

Fifty to seventy-five milliliters of blood was drawn into a heparinized syringe and the leukocytes separated as described above for the lymphocyte blast transformation studies. Leukocyte suspensions containing 12.5×10^6 cells per milliliter were incubated for 60 minutes at 37° C. with dextran in concentrations ranging from 7.5 μg per milliliter to 1,500 μg per milliliter. Following incubation, the tubes were processed for the measurement of released histamine according to the technique of Lichtenstein and Osler.⁹ Control experiments revealed that dextran did not interfere with the spectrophotofluorometric technique for measuring histamine.

RESULTS

Skin tests

Neither Case No. 2 nor Case No. 3 developed positive wheal and erythema reactions on skin test with dextran. Refusal of Case No. 2 to return to the laboratory for skin tests with the common allergens makes it impossible to know if he had any common subclinical sensitivities despite a negative history. Case No.

Table 1. Uptake of ³H-thymidine by leukocyte cultures incubated with dextran

Stimulating substance	Uptake of ³ H-thymidine (c.p.m./culture)			
	Case No. 1*	Case No. 2	Case No. 3	Control†
Control (average)	3,253 (1475-4790)	449 (216-682)	509 (271-815)	456 (409-511)
Dextran (average) 15 $\mu\text{g}/\text{c.c.}$	1,977 (1273-2487)	—	—	—
Dextran (average) 60 $\mu\text{g}/\text{c.c.}$	5,050 (1502-7770)	390 (333-402)	698 (541-841)	414 (379-463)
Dextran (average) 180 $\mu\text{g}/\text{c.c.}$	5,865 (3887-8061)	458 (326-486)	437 (131-608)	403 (308-482)
Dextran (average) 1,800 $\mu\text{g}/\text{c.c.}$		401 (335-498)	598 (458-754)	443 (424-464)
Phytohemagglutinin‡ (average)	80,325 (79,827-80,822)	11,592 (8,252-14,933)	34,341 (31,605-36,851)	81,350 (70,842-92,303)

The figures represent the average counts per minute in duplicate or triplicate samples contained in tritiated thymidine.

*There is no explanation for the high culture control which does not differ significantly from the dextran containing tubes.

†A normal subject.

‡Phytohemagglutinin solution, 0.1 ml. (Burroughs Wellcome, MR10) prepared in accordance with recommendations of the manufacturer.

1 refused to be tested with dextran, but it was ascertained that he had negative skin tests with several common allergens 1½ year after his reaction. Case No. 2 was tested 5 months after his reaction, and Case No. 3 was tested 1½ years after his reaction. This individual had strong skin reactions to dust, feathers, *Alternaria*, and grasses.

Gel diffusion studies for antibody

Serum was available for these studies only from Cases Nos. 2 and 3. Precipitating antibody was not demonstrable by this technique in the serum of either of these patients.

Lymphocyte blast transformation reaction

The results displayed in Table I indicate that the cells of each of the patients failed to undergo blast transformation following incubation with dextran. Also, it is evident that the cells reacted normally to stimulation with phytohemagglutinin.

Using the cells of normal subjects, a second experiment indicated that dextran, either undiluted or diluted 1:10 and 1:100, did not enhance or inhibit the lymphocyte blast transformation induced by phytohemagglutinin.

Histamine release

In the 2 patients in whom this study could be completed (Case Nos. 1 and 3), there was no evidence of histamine release by dextran at concentrations of 35 per milliliter to 450 µg per milliliter (Case No. 1) and 7.5 to 1,500 µg per milliliter (Case No. 3).

DISCUSSION

Dextran is a high-molecular weight polysaccharide of molecular weight 10^7 to 10^8 made from *Leuconostoc mesenteroides* and *Leuconostoc dextranicum*.¹⁰ Most of the reported cases of adverse reactions to dextran have occurred in non-atopic individuals without previous exposure to dextran. Reactions have occurred with as little as 120 µg. Dextran has been found as a contaminant of commercial sugars,¹¹ and it can also be produced by gastrointestinal flora.¹² Cross-reactivity with the polysaccharides of the pneumococcus has also been demonstrated.¹³ Kabat and Bezer¹⁰ demonstrated the development of precipitating antibodies and positive skin tests (intradermal injection of 10 to 20 µg of dextran) in normal volunteers immunized with two subcutaneous doses of 0.5 mg. spaced one day apart. He also showed that the more complex branched-chain dextrans of molecular weight greater than 90,000 were more likely to be immunogenic. Most products in clinical use today have a molecular weight of $75,000 \pm 25,000$, are straight chains with an $\alpha_1, 6$ linkage, and are made from the naturally occurring dextrans by acid hydrolysis and ethanol fractionation. These products are associated with a lower incidence of reactions. Kabat and associates¹⁴ also indicated that people with a positive skin test prior to dextran injection were more likely to develop hypersensitivity reactions. Of the 2 of our 3 patients in whom we have skin test data, no positive reactions were obtainable.

The gel diffusion analyses also failed to demonstrate precipitating antibody. Using a clinical dextran with a molecular weight of 59,000, Kabat and associates¹⁴ infused 500 c.c. intravenously into 104 normal volunteers, 15 of whom had reactions of varying intensity. One month later the 15 reactors were tested for precipitins by quantitative precipitations. Fourteen of fifteen had levels of less than 1.9 μ g of antibody N per milliliter, which is below the sensitivity of the system used in this paper.⁷

In 1960, Nowell¹⁵ showed that leukocytes incubated with phytohemagglutinin underwent a change which morphologically appeared to be a transformation to a blast type of cell. Later it was found that cells from individuals sensitive to specific antigens would also undergo blast transformation when incubated with a specific antigen.¹⁶⁻¹⁹ The lymphocyte blast transformation reaction apparently occurs with both delayed and immediate type hypersensitivities, since it has been demonstrated with such antigens as tuberculin, tetanus toxoid, diphtheria, penicillin, ragweed, and others.^{20, 21} By the criterion of lymphocyte blast transformation, none of our patients showed evidence of an immunological reaction. This was surprising in that the clinical picture closely resembled that seen in classical anaphylactic reactions. It was also shown that dextran does not inhibit the lymphocyte blast transformation reaction.

Many of the features of the clinical reactions observed in our patients and described by others could be accounted for by the release of pharmacologically active substances such as histamine.²² Other investigators^{4, 5} have also suggested that dextran reactions could be due to a histamine release phenomenon. Another mechanism has been suggested by experiments in albino rats in which dextran releases histamine directly without an antigen-antibody reaction.²³ The mechanism of this reaction is not completely understood. Rocha and associates²⁴ discuss a substance called anaphylatoxin, which is a histamine liberator released by the incubation of normal sera with agar and other polysaccharides. Kabat and associates¹⁴ offer another possible explanation for the negative results obtained in this paper. Clinical dextran is not homogeneous but has small amounts of larger or branched-chain molecules with $\alpha_1, 4$, $\alpha_1, 2$, or $\alpha_1, 3$ linkage. It is possible that the clinical reactions were due to these contaminants²⁵ which were not present in large enough quantities to give positive laboratory tests; this was not evaluated.

In none of our cases, however, could we demonstrate histamine release *in vitro*, and so, by this criterion, we were unable to show an immunologic reaction as the basis for the clinical findings. A number of other substances, such as bradykinin (one of the plasma kinins) have been implicated as mediators of allergic reactions following antigen-antibody reactions.²⁶ It is entirely possible that some other substance such as bradykinin could be involved in the genesis of dextran reactions. At this time, there is no evidence to support or refute this idea.

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