

BRIEF COMMUNICATIONS

Immediate hypersensitivity reaction to aminophylline

Report of a case with immunologic confirmation by an in vitro procedure

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A twelve-year-old asthmatic boy is reported who had a urticarial reaction associated with generalized pruritus following the intravenous administration of aminophylline. An identical clinical reaction occurred after a fortuitous challenge with a second dose of the drug. An immediate wheal and flare reaction to aminophylline was obtained, which could be passively transferred using the Prausnitz-Küstner procedure. To confirm the immunologic nature of the reaction, the rat mast cell degranulation technique was applied using the patient's serum and aminophylline or anti-IgE. Positive results were obtained with aminophylline as well as with anti-IgE, suggesting that the immediate reaction observed may have been mediated by aminophylline. Whether the IgE detected by this method was specific or not for aminophylline is not established.

Aminophylline has played a major role in the treatment of asthma by virtue of its bronchodilator action. Toxic reactions are not uncommon, and occasional deaths from this drug, especially in the pediatric population, have been reported.¹ However, allergic reactions of the immediate type following the therapeutic administration of this drug have not been previously reported to the best of our knowledge.

Tas and Weissberg² in 1958 published a case of allergy to aminophylline occurring in a pharmacist handling aminophylline preparations (suppositories) who developed dermatitis of the contact type. Other features of the clinical untoward reaction included rhinitis and bronchial asthma. Baer and associates³ reported in 1959 on another pharmacist who developed eczematous contact dermatitis due to aminophylline. We recently encountered a patient who exhibited generalized pruritus and an urticarial reaction following aminophylline therapy.

CASE REPORT

This 12-year-old Negro boy had been known to be asthmatic since the age of 5. He was under the care of his private physician and was fairly well controlled on sublingual

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isoproterenol, promethazine hydrochloride elixir, and theophylline-potassium iodide elixir. On September 22, 1970, he was seen in the Los Angeles County-University of Southern California Medical Center Emergency Room for an acute asthmatic attack. He was treated with aqueous epinephrine (1:1,000), 0.3 ml. subcutaneously, and intermittent positive-pressure breathing with 0.25 ml. isoproterenol (1:200) without much improvement and was, therefore, hospitalized.

His past history indicated that he had had one episode of pneumonia and one previous hospitalization for asthma. He had no known drug allergies. Physical examination revealed a well-developed, well-nourished Negro boy in mild to moderate respiratory distress. His vital signs included a temperature of 96.4° F., pulse rate of 120, and respiratory rate of 28. There was no evidence of cyanosis. His pharynx was slightly injected. There were bilateral wheezes, both inspiratory and expiratory, but no rales. Examination of the heart revealed normal sinus rhythm and no murmurs. The remainder of the physical examination was within normal limits.

Laboratory studies performed on admission revealed a hemoglobin of 14.1 Gm. per cent, white blood cell count of 9,200 with 59 per cent segmented neutrophils, 25 per cent lymphocytes, 10 per cent monocytes, and 6 per cent eosinophils. Routine urinalysis showed a specific gravity of 1.001, pH 6.5, and negative albumin and sugar. Microscopic examination of the urine was negative. The blood sugar was 83 mg. per cent, blood urea nitrogen 6 mg. per cent, sodium 135 mEq. per liter, potassium 4.8 mEq. per liter, and bicarbonate 18 mEq. per liter. Both the throat culture and sputum culture were unremarkable. His chest x-ray revealed no infiltrate.

The patient was treated with intravenous fluid ($\frac{1}{4}$ normal saline), intermittent positive-pressure breathing with isoproterenol (0.25 ml. of 1:200), ephedrine with hydriodic acid, and aminophylline (3 mg. per kilogram by intravenous push). A few minutes after receiving a dose of 125 mg. of aminophylline in an intravenous push, the patient developed generalized pruritis associated with urticarial lesions on his trunk. His symptoms gradually subsided, but a dose of 5 mg. aminophylline given intravenously several hours later resulted in recurrence of the same urticarial reaction. Aminophylline was then discontinued, and his urticarial lesions were controlled with diphenhydramine.

Prior to his discharge, we were asked to evaluate this patient. On further questioning, he stated that he had had these symptoms previously, i.e., generalized pruritis and a similar "rash." This had occurred on three separate occasions about one hour after taking PET tablets orally. (Each PET tablet contains phenobarbital 8 mg., ephedrine 24 mg., and theophylline 130 mg.) The last episode of this type occurred 3 days prior to admission.

Routine skin testing revealed significant positive results only by the intradermal method. He displayed a wheal and flare reaction to house dust (3+), to mixed grass (3+), to mixed molds (3+), to mixed weeds (2+), and to dog dander (2+). Our criteria for measuring this reaction are the following: 0 = all reactions equal to control; 1+ = erythema and 0.5 cm. wheal; 2+ = erythema and 1 cm. wheal, no pseudopods; 3+ = erythema, 1.5 cm. wheal, and pseudopods; and 4+ = erythema, 2 cm. wheal, and pseudopods. Skin test to aminophylline was also done using the undiluted solution (25 mg. per milliliter). The scratch test was negative. However, an intradermal test revealed wheal and flare (2+) to aminophylline and to histamine control (3+). Two atopic individuals known to have received aminophylline repeatedly in the past were also tested to aminophylline, and no wheal and flare reaction was found at the same concentration.

Passive transfer of the immediate wheal and flare reaction (Prausnitz-Küstner) to aminophylline was attempted to provide additional confirmatory evidence. A nonatopic recipient was selected and was found to have negative skin tests to aminophylline by both scratch and intradermal methods. Serial dilutions of the patient's serum (0.1 ml.) were then injected intradermally into the nonatopic subject. After 24 hours, the sites were challenged with aminophylline (0.02 ml.). The skin tests were read at 20 minutes and the diameters of the wheal and erythema were measured. The passive transfer test was interpreted as positive by an unbiased observer (Table I).

TABLE I

Serum	Challenge	Wheal (mm.)	Erythema (mm.)
Undiluted	Normal saline	2	0
Undiluted	Aminophylline*	9	30
1:2 Dilution	Aminophylline	6	28
1:4 Dilution	Aminophylline	3	14
No serum	Aminophylline	2	5

*25 mg. per milliliter.

In an attempt to ascertain the immunologic nature of the urticarial reaction observed with the xanthine therapy, a sample of the serum was tested by our rat mast cell degranulation (RMCD) technique.^{4, 5}

METHOD

A suspension of rat mast cells (RMC) (0.05 ml.) was incubated with 0.05 ml. of the patient's serum and challenged with either aminophylline* (12.5 mg. per milliliter), ephedrine (12.5 mg. per milliliter), or phenobarbital (65 mg. per milliliter). Control preparations consisting of RMC and nonatopic sera, and RMC with each drug alone were included. Sera of 2 chronic asthmatic patients (AS₁ and AS₂) who had received multiple doses of intravenous aminophylline were also used as controls. In addition, RMC were incubated with the patient's serum and challenged with anti-IgG, IgA, IgM and IgE (0.3 μ g antibody N per milliliter). Antigens giving significant positive intradermal tests in our patient were also used as the challenging antigen in the in vitro test as positive controls.

RESULTS

Of the three drugs utilized, only aminophylline gave a significant degree of degranulation in the presence of the patient's serum (Table II). Aminophylline gave almost six times as much degranulation as did the control. In our laboratory, three times the control or greater is considered to be a positive test. Negative results were obtained with both phenobarbital and ephedrine. When the sera of the 2 control atopic patients (AS₁ and AS₂) were tested with aminophylline, no significant degranulation was observed.

Both weeds (500 protein nitrogen units [PNU] per milliliter) and molds (500 PNU per milliliter) gave degranulation three times or greater than control in the presence of the patient's serum (Table III). Significant degranulation was obtained with anti-IgE and the patient's serum (over 5 times control) but not with antisera to the other immunoglobulins (Table IV).

DISCUSSION

This patient demonstrated a clinical reaction of the immediate hypersensitivity type to a therapeutic dose of intravenous aminophylline and an identical reaction upon challenge with a subsequent dose of the same drug by the intravenous route. It is interesting that 3 days preceding his admission he

*The dose of each drug used in vitro was determined by performing the test with serial dilutions of the drug alone and selecting the highest concentration not giving significant degranulation.

TABLE II. Per cent degranulation of RMC

Test	% Degranulation
Control	
RMC + PS	6
RMC + NAS	8
RMC + AS ₁	3
RMC + AS ₂	4
RMC + Aminophylline	11
RMC + Ephedrine	8
RMC + Phenobarbital	5
Challenge	
RMC + PS + Aminophylline	60
RMC + PS + Ephedrine	9
RMC + PS + Phenobarbital	7
RMC + AS ₁ + Aminophylline	6
RMC + AS ₂ + Aminophylline	5
RMC + NAS + Aminophylline	10

PS = patient's serum, NAS = nonatopic serum, AS = atopic serum (two patients), RMC = rat mast cell. Aminophylline, 12.5 mg. per milliliter; ephedrine, 12.5 mg. per milliliter; phenobarbital, 65 mg. per milliliter.

TABLE III. Per cent degranulation of RMC

Test	% Degranulation
Control	
RMC + NAS	8
RMC + PS	4
RMC + mold	5
RMC + grass	3
RMC + weed	4
Challenge	
RMC + PS + mold	25
RMC + PS + grass	16
RMC + PS + weed	35

NAS = Nonatopic serum, PS = patient's serum, RMC = rat mast cell.

TABLE IV. Per cent degranulation of RMC

Test	% Degranulation
Control	
RMC + NAS	8
RMC + PS	4
RMC + anti-IgE	6
Challenge	
RMC + PS + anti-IgE	44
RMC + PS + anti-IgG	10
RMC + PS + anti-IgA	12
RMC + PS + anti-IgM	9
RMC + NAS + anti-IgE	9

NAS = Nonatopic serum, PS = patient's serum, RMC = rat mast cell.

had had an identical reaction one hour following ingestion of a preparation containing theophylline, ephedrine, and phenobarbital. This suggests that the theophylline component of aminophylline was the allergen in this case rather than the ethylenediamine portion. While a possible clinical reaction to ephedrine or phenobarbital also needed to be considered, both of these drugs failed

to cause significant degranulation of the rat mast cells in the presence of the patient's serum. In the experience of this laboratory, the modified RMCD, as described previously by Perelmutter and Khera,^{6, 7} Korotzer and associates,^{4, 5} and Haddad and Korotzer,⁸ has proved to be a reproducible in vitro immunologic test correlated with immediate hypersensitivity to a gamut of allergens.

Most drugs appear to act as haptens in producing hypersensitivity reactions of the immediate type. This mechanism is generally thought to require a multivalent antigen. However, recent reports by several investigators⁹⁻¹¹ have alluded to the possibility that univalent antigens may elicit anaphylactic reactions. Frick and associates¹⁰ postulated that a portion of the anaphylactogenic univalent hapten molecule adjacent to the determinant site somehow may interact with other parts of the antibody molecule, or with the cell, producing some change in the antibody-cell configuration resulting in the release of histamine. Thus, aminophylline, acting as a univalent hapten, may have the potential of eliciting a hypersensitivity reaction of the immediate type.

Reactions of this type are mediated largely by immunoglobulin E. While various pollens, molds, and aminophylline or anti-IgE produced degranulation of the rat mast cell in the presence of the patient's serum, suggesting the presence of IgE antibodies in the serum, one cannot conclude that the degranulation produced by aminophylline was necessarily mediated by aminophylline-specific IgE.

It should be mentioned that, using the human basophil leukocyte system, Lichtenstein and Margolis¹² reported an inhibitory effect of aminophylline on histamine release. It is of interest that, at least in our case, aminophylline has no such inhibitory action on rat mast cell degranulation. This may reflect another difference in the two biological systems, as disodium cromoglycate has been also shown to inhibit histamine release from rat mast cells¹³ but not from human basophil leukocytes.¹⁴

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