URTICARIA AND ANGIONEUROTIC EDEMA FOLLOWING *d*-TUBOCURARINE ADMINISTRATION

Report of a Case, With Observations on Blood and Plasma Histamine Levels

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HISTAMINE release has been suggested as a factor in various allergic and circulatory phenomena [1-5] associated with the administration of *d*-tubocurarine in man. However, while increases in concentration of histamine in the blood following injections of curare are well documented in experimental animals,[6-8] and while there is a single report in which direct measurements of histamine have been made in an experimental study in man,[9] values have not been reported following clinical usage of the relaxant. On the basis of this single study, it has been suggested that histamine released as a consequence of clinical doses of *d*-tubocurarine is not in sufficient quantity to evoke symptoms.

We recently have measured elevated blood and plasma histamine values in a patient exhibiting an urticarial reaction while being anesthetized. This reaction and the increased histamine concentrations were probably consequences of *d*-tubocurarine administration. This paper will report this reaction and subsequent investigations on which our conclusions are based.

CASE REPORT

A twenty-five year old man with a history of ten previous anesthesias was scheduled for a tendon transfer of the left arm. Eight of these procedures were within the past eighteen months and are described in table 1.

The results of routine preoperative laboratory examinations (urinalysis, hemoglobin determination, sedimentation rate, leucocyte and differential counts, and serological tests for syphilis) were within normal limits. For the nine most recent procedures preoperative medication consisted of secobarbital (100 mg.) or pentobarbital (100 mg.) given intramuscularly ninety minutes before operation, and atropine sulfate (0.4–0.6 mg.) administered intravenously approximately fifteen minutes prior to the induction of anesthesia. When a regional anesthetic method was elected, meperidine (100 mg.) was given at the same time as the barbiturate. An intravenous infusion of 5 per cent dextrose in water was started through a skin wheal of 1 per cent procaine prior to each anesthesia, and this infusion was maintained throughout operation and during recovery from anesthesia. When endotracheal intubation was performed a water soluble lubricant (cyclomethycaine 0.75 per cent) was used on a cuffed portex tube.

The urticarial reaction occurred when thiopental-*d*-tubocurarine, nitrous oxide-oxygen anesthesia was used. After a 2-ml. test dose of a thiopental-*d*-tubocurarine mixture (thiopental 25 mg., and *d*-tubocurarine 0.75 mg. per ml.) was given, 25 ml. of the mixture were administered in 5-ml. increments. The patient's lungs were ventilated manually with 100 per cent oxygen by means of a bag and a face mask and then through an endotracheal tube.

Immediately after tracheal intubation swelling of the eyelids was noted. Edema of the face and neck ensued rapidly and giant hives appeared over most of the body. The severity of the whealing and flushing was most marked in the area of the previous operative sites. Pharyngeal and epiglottic edema was noted. Because of this edema and the severity of the urticaria at the site of the intended operation the procedure was postponed and the patient was removed to the postanesthesia recovery room. At no time was bronchoconstriction clinically evident nor did the pulse rate and blood pressure vary significantly.

Blood was drawn for histamine analysis and an eosinophil count approximately forty-

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TABLE 1

ANESTHETIC AND OPERATIVE PROCEDURES PRIOR TO THE ALLERGIC RESPONSE

Time Prior to Reported Case (months)	Operation	Anesthesia	Endotracheal Tube	Complication and Comment
18	Closed reduction and fixation of right Colles fracture	Thiopental Succinylcholine N_2O-O_2	No	None
15	Fixation of a compounded fracture of left radius and ulna	Thiopental Gallamine N_2O-O_2	Yes	None
14	Skin graft	Lidocaine 2.0% Tetracaine 0.15% (28 ml)	No	None
12	Internal fixation of fracture attempted	Lidocaine 2.0% Tetracaine 0.15% (30 ml) Thiopental-1,150 mg. Gallamine-224 mg. N_2O-O_2	Yes	None
10	Internal fixation of fracture	Thiopental-1,200 mg Gallamine-245 mg. N_2O-O_2	Yes	Urticaria and hyper-pyrexia following blood transfusion
7	Incision and drainage of left forearm	Thiopental-600 mg. Succinylcholine-20 mg.	No	None
6	Secondary closure of wound	Thiopental-750 mg. Gallamine-150 mg. N_2O-O_2	Yes	None
4	Incision and drainage with osteotomy and removal of internal fixation	Thiopental-425 mg. Meperidine-150 mg. N_2O-O_2	No	None

five minutes after induction of anesthesia. The patient then was given 200 mg. of hydrocortisone and 25 mg. of diphenhydramine intravenously. The reaction gradually began to subside without further treatment and the patient was later discharged to the ward in good condition.

Later that afternoon, the patient acknowledged a history of urticarial reactions. He stated that he occasionally developed hives and that his eyes and lips became swollen when he ate green onions, strawberries, or when he became emotionally upset. None of this information had been volunteered at any of the previous preanesthetic examinations.

METHODS AND PROCEDURES

In an attempt to determine the etiology of the reaction various studies were undertaken when the patient was asymptomatic. A blood sample for histamine determination was drawn ten days after the reaction. Direct intradermal tests on the patient's right forearm also were carried out at this time by separate 0.05-ml. injections of 2.5 per

TABLE 2

HISTAMINE LEVELS OF PATIENT AND NONALLERGIC PERSONS

	Patient		Normal*		Normal†	
	Symptomatic	Asymptomatic	Mean	Range	Mean	Range
Plasma Histamine (μg. base/ml. plasma)	0.145				0.012	0.006–0.020
Blood Histamine (μg. base/ml. blood)	0.286	0.114	0.074	0.031–0.106	0.06 0.04 0.082	0.045–0.084 0.02–0.075 0.07–0.10

* 15 Nonallergic persons who received premedication similar to the patient.
† Values from references 14, 15 and 17.

TABLE 3

RESULTS OF DIRECT SKIN TEST AND PASSIVE IMMUNIZATION TRANSFER TEST

Agent	Allergic Patient		Nonallergic Volunteer			
			Test Arm		Control Arm	
	Erythema	Wheal	Erythema	Wheal	Erythema	Wheal
	(mm. diam.)		(mm. diam.)		(mm. diam.)	
Thiopental 2.5%	6	None	4	None	4	None
Gallamine 0.4%	13.6	5 Concentric	10	5 Concentric	12	5 Concentric
d-Tubocurarine 0.015%	30–40	22–25 Irregular	20	7 Concentric	19	8 Concentric
Control—H_2O	None	None	None	None	None	None

cent thiopental, 0.75 per cent *d*-tubocurarine, 0.4 per cent gallamine and a control of sterile distilled water. Ten weeks following the reaction direct intradermal tests using *d*-tubocurarine and 1:40,000 histamine diphosphate were performed.

Ten days following the reaction a sample of the patient's blood was collected, processed,[10] decanted, and stored at a temperature of 24 C. Three days later, it was injected intradermally on the forearm of a nonallergic volunteer. After five days, the volunteer was skin tested on the test arm and the control arm using drugs identical to those used for the direct skin tests on the patient.

Histamine concentrations were determined by the spectrophotometric method outlined by Lowry *et al.*[11] All blood and plasma histamine values are reported as micrograms of histamine base per milliliter, and all samples were analyzed in quadruplicate. (Levels of histamine obtained by the spectrophotometric method are slightly lower than those by the guinea pig ileum method.)[12]

RESULTS

The data may be seen in tables 2 and 3. The eosinophil count of the blood drawn at the time of the reaction was normal.

DISCUSSION AND CONCLUSIONS

Conclusions drawn from one case are limited. Further, the unexpected occurrence of this reaction precluded preanesthetic histamine determinations. Nevertheless, we believe some inferences may be drawn.

The reaction observed in this patient was, in all probability, a consequence of *d*-tubocurarine administration. Examination of the available anesthetic records (table 1) indicates that the only agent the patient had not received prior to the day of the reaction was *d*-tubocurarine. While thiopental sensitization as a consequence of repeated administrations is a possibility, this seems remote when one considers the results of the skin tests (table 2). Neither the direct skin test nor the indirect passive transfer test indicate hypersensitivity to thiopental. Positive reactions on direct skin testing with curare previously have been reported in man.[4] The wheal and erythema of the direct skin test probably do not indicate true allergy (antigen-antibody reaction) since a past history of *d*-tubocurarine sensitization could not be elicited and *d*-tubocurarine antibodies were not demonstrated with the passive transfer test. The wheal and flush evoked by intradermal *d*-tubocurarine in this patient, while somewhat larger than the control tests, do not differ strikingly from our controls or from those seen in the nonallergic patients described by Comroe and Dripps.[4] Intradermal histamine phosphate evoked similar cutaneous responses in both the patient and in our control subjects. The data in table 3 indicate that the concentration of histamine

in the patient's blood at the time of the reaction was more than twice his normal value and almost four times the mean values found in similarly premedicated nonallergic individuals (table 2). The plasma histamine concentration at the time of the reaction was similarly increased. During the period when the patient was asymptomatic the blood histamine remained slightly above the upper range of normal for nonallergic patients.

The absence of preanesthetic blood histamine measurements in this patient prevents us from stating with certainty that the levels seen at the time of reaction were greater than the preanesthetic levels, but the magnitude of the difference between the values obtained when the patient was asymptomatic and the level at the time of the reaction makes this assumption probable.

The histamine level observed in this patient during the urticaria may be related in part to the urticarial reaction itself. During hypersensitivity reactions in conscious humans, blood histamine levels may rise, fall, or remain unchanged.[13-15] Such erratic responses are determined, at least in part, by the type of reaction and the time of blood sampling. Rose[13] has observed initial rises in blood histamine during the urticaria evoked by physical stimuli such as heat, cold and light. In his series, 8 of 15 patients had initial rises in blood histamine within fifteen minutes of the stimulus, and 4 of these patients exhibited subsequent falls below control levels within thirty minutes. Cerqua[14] observed rises in the levels of the blood histamine of 6 patients during the acute urticarial phase with return to normal in six hours. Gate *et al.*[15] have observed an elevation of blood histamine at the onset of urticaria. In our patient the observed histamine levels may in fact be declining since the initial blood sample was taken forty-five minutes after induction of anesthesia and thirty-five minutes after the onset of urticaria.

"Allergic" side reactions associated with the clinical use of *d*-tubocurarine have been described by several authors[1-3, 5] but histamine assay has not been performed during any of these reactions. Under experimental conditions, Mongar and Whelan[9] studied the histamine release associated with *d*-tubocurarine in 2 conscious and 5 anesthetized nonallergic subjects. These workers injected the drug into the brachial artery and collected samples of the venous return from the forearm of each subject. Using large intra-arterial doses of the relaxant and arresting limb blood flow for 2 minutes following injection they demonstrated increases in plasma histamine concentrations. These were accompanied by flushing and whealing of the skin of the involved limb. However, the authors state . . . "it seems unlikely that relaxant doses of *d*-tubocurarine administered intravenously for clinical purposes, where the concentration in the blood would be less than 1/100th of that present in . . . [these] . . . experiments are ever likely to produce side effects due to the release of histamine. . . ." However, their observations do not preclude the possibility of "allergic" reactions occurring in hypersensitive individuals since it has been shown that small increases in the levels of histamine may evoke reactions in such patients.[16]

The urticarial reaction was greatly accentuated at the site of the patient's previous operations. Regenerating tissue has been shown to be richer in histamine than mature tissue,[18] and one might expect a reaction due to histamine release to be intensified in such areas.

The occurrence of this patient's reaction is of considerable worth from a clinical standpoint. The value of an adequate preoperative history is obvious, but perhaps more attention should be given questioning the patient, in lay terms, about previous allergic reactions. It also illustrates the ineffectiveness of the intravenous test dose of *d*-tubocurarine in eliciting an allergic response in the hypersensitive patient, and demonstrates the postulate that the patient is his own best control. If a patient has had previous anesthetic agents without untoward reactions, these same agents should be given preference for future anesthesias. Different operative procedures, changing physical states, and the introduction of new anesthetic techniques and agents occasionally will modify this clinical principle. Nevertheless this maxim offers a good working premise, especially when dealing with allergic individuals.

SUMMARY

An urticarial reaction associated with abnormally high blood and plasma histamine levels following the clinical administration of *d*-tubocurarine is described. The anesthetic history and subsequent investigations implicate *d*-tubocurarine as a causative factor in the reaction.

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