CHANGES IN HISTAMINE BLOOD LEVELS FOLLOWING *d*-TUBOCURARINE ADMINISTRATION*

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ONE OF THE ACTIONS of *d*-tubocurarine is said to be a significant release of histamine from the skeletal muscles. Alam in 1939 first demonstrated that *d*-tubocurarine was capable of releasing histamine from the dog gastrocnemius muscle.[1] The histamine blood level of the dog rose as the rate of *d*-tubocurarine injection increased, and the blood pressure decreased in proportion to the rate of injection. Since Alam's report other investigators have quantitated the histamine released from the skeletal muscles of experimental animals following both curare and *d*-tubocurarine administration.[2–5]

Mongar and Whelan[6] could not demonstrate any histamine release from human muscle. These authors cannulated a vein from a forearm muscle and injected *d*-tubocurarine into the artery supplying the muscle. No histamine release could be recorded on injecting up to 50 mg. of *d*-tubocurarine unless the circulation to the muscle was occluded for at least two minutes. Histamine release in the human secondary to the administration of curare compounds has been implied by other investigators[7–9] (although no measurements of blood histamine have been made). This report is based on a study carried out on humans to determine the effect on histamine blood levels of intravenously administered *d*-tubocurarine.

METHOD

Seventeen patients scheduled for elective surgical procedures constituted the study group. None of the subjects had a history of allergy and all were free of clinical or laboratory evidence of cardiac and respiratory disease. Preoperative medication was pentobarbital, 4 mg. per kg. of body weight, given intramuscularly 90 minutes before the induction of anaesthesia, and atropine, 0.01 mg. per kg. of body weight, given intravenously 15 minutes prior to the induction of anaesthesia. In the control group (six subjects) an initial blood sample was drawn from each subject 15 minutes after the intravenous atropine and three more blood samples were drawn at 2-minute intervals.

The remaining 11 subjects formed the study group. These patients received thiopental intravenously in 5-cc. increments to a dose of 8 mg. per kg. of body weight. Five minutes after the last incremental dose a blood sample was taken to establish a control blood histamine concentration. *d*-Tubocurarine 0.44 mg. per kg. of body weight, was then given intravenously in a single rapid injection. If no side-effects of *d*-tubocurarine administration, such as an elevated pulse rate,

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systolic hypotension, bronchoconstriction, decreased compliance, or skin erythema, were present, a second blood sample was taken 5 minutes after the *d*-tubocurarine injection. From patients showing any of the above signs the second sample was taken when the signs were well established. In these cases the average time interval between the injection of *d*-tubocurarine and the maximum severity of the signs was 4 to 5 minutes.

The interval of 5 minutes between the administration of the *d*-tubocurarine and the blood sampling was chosen for the following reasons. The maximal effect of intravenously administered *d*-tubocurarine is seen in 3 to 5 minutes.[10,11] Changes in blood levels of histamine occur after only the time of one circulation[3] and persist for periods much longer than 5 minutes.[12,13] Electromyographic studies done by us indicate that the neuromuscular block produced by *d*-tubocurarine is usually maximal by 3 minutes.

Histamine analysis was done using the spectrophotometric technique described by Code and McIntire.[14] This method gives values slightly below those obtained using biological methods in similar samples. Using this method a maximum of 85 per cent of the histamine present in any sample can be measured. Samples containing a known quantity of added histamine base were analysed until we consistently obtained terminal amounts of histamine of not less than 80 per cent of the added amount.

All blood samples for histamine determinations were drawn in syringes containing one-tenth volume of 1.76 per cent potassium oxalate. The syringes were immersed in ice water and analysis was begun within 20 minutes of taking the final sample. All analyses were carried out in quadruplicate.

Results

The means and standard deviations of the blood histamine levels of the four samples from each of the six control patients are given in Table I. By referring to Table II normal blood histamine values as determined by others can be compared with our mean value.

The histamine blood levels of the patients of the study group before and after intravenous *d*-tubocurarine are listed in Table III.

TABLE I

HISTAMINE BLOOD LEVELS IN μG. OF BASE PER CC. OF BLOOD IN CONTROL PATIENTS PREMEDICATED WITH ATROPINE AND PENTOBARBITAL

Patient	Age (yr.)	Mean histamine level	S.D.	No. of samples
1	20	0 033	0 001	16
2	60	0 055	0 003	12
3	84	0 087	0 004	12
4	35	0 106	0 005	16
5	72	0 039	0 004	12
6	50	0 085	0 004	14
Mean	53	0 067	0 027*	

*Standard error of the mean.

TABLE II

MEAN BLOOD HISTAMINE LEVELS IN μG. OF BASE PER CC. OF BLOOD AS REPORTED BY OTHER AUTHORS

Author	Mean histamine level	Range	No. pts.
Nilzen[12]	0 06	0 045–0 084	30
Rose[19]	0 04	0 020–0 075	50
Tarras-Wahlberg[24]	—	Trace–0 050	20
Randolph-Rackermann[25]	0 045	0 019–0 071	50
Cerqua[26]	0 085	0 07 –0 100	—
El-Sayed[27]	0 055	—	—

TABLE III

HISTAMINE BLOOD LEVELS BFFORE AND AFTER INTRAVENOUS D-TUBOCURARINE

No.	Age (yr.)	Wt. (kg.)	Curare (mg.)	Blood sample before curare histamine in μg./ml.	Blood sample after curare histamine in μg./ml.	$\bar{x}_b - \bar{x}_a$	(T)	Clinical signs
1	41	39	21	0 042	0 043	−0 001	0 23	None
2	48	72 6	45	0.106	0 108	+0 002	0 45	None
3	72	52	30	0 052	0 049	−0 003	0.68	None
4	52	97	40	0 093	0 094	+0 001	0.23	None
5	19	53	30	0 092	0 142	+0 050	11 3	None
6	49	52	30	0 024	0 061	+0 037	8 4	None
7	74	45.4	24	0 045	0 060	+0 015	3 4	None
8	75	64 9	30	0 096	0 144	+0 048	10 8	None
9	57	82 6	40	0 058	0 026	−0 032	7 2	Chest erythema, B.P. fall 160/80 to 100/70
10	52	45 4	21	0.058	0 042	−0 016	3 6	Questionable erythema, B.P. fall 200/100 to 160/95
11	48	95.7	45	0 118	0 072	−0 046	10 4	Generalized erythema, B.P. fall 120/75 to 80/50—prolonged expiration

DISCUSSION

Our normal mean of 0.067 μg. of base per ml. of blood is slightly higher than that obtained by others. The patients used by us were premedicated with atropine, which is capable of raising blood histamine levels.[15] Values reported by other authors were obtained from unpremedicated individuals.

Stagnant hypoxia of muscle, such as occurs when a tourniquet is left on during withdrawal of a blood sample, can cause an elevation in the blood histamine level.[16] Samples were withdrawn in most cases without using a tourniquet but in some this was not possible. In these latter cases the tourniquet was applied, a partial sample taken, the tourniquet released, and the process repeated until an adequate sample was obtained.

Changes in blood histamine produced by the psychological stress of being brought to the operating room and having an intravenous started probably are

minimal. Selye has shown that stressful circumstances do produce an initial release of histamine but that the blood concentration decreases as stress continues. These factors may account for the higher mean blood histamine value obtained by us.

The data obtained from the patients in the study group can be divided into three groups according to the changes seen in the histamine blood level following intravenous *d*-tubocurarine. In the first group no change in the concentration of histamine occurred; in the second group an elevation occurred; and in the third group a decrease in the blood histamine occurred. The three patients in the third group also showed the secondary signs of curarization. The magnitude of the clinical signs was proportional to the drop in the histamine blood level but the size of the group precludes any conclusions.

The data obtained from the patients in the second group demonstrate that the intravenous administration of *d*-tubocurarine in clinical doses is capable of causing a rise in blood histamine. The elevation in blood histamine, however, was without clinical significance. The direction of the change in blood histamine was not related to the weight or the age of the patient or to the amount of *d*-tubocurarine injected. The initial blood histamine value in itself was not significant and the rate of injection of *d*-tubocurarine was approximately the same in all cases.

The decrease in the blood histamine concentration following the administration of *d*-tubocurarine may be explained in several ways. First, one may assume that no histamine was released and the clinical signs were due to *d*-tubocurarine reducing the thresholds of the effector end-organs to such a degree that the physiologically active histamine already present in the blood produced a reaction. Evidence for or against such a mechanism does not exist as yet. Similarly there is no evidence to indicate that any other substance capable of producing the clinical signs was present or released at the time of the *d*-tubocurarine injection.

A second explanation that has been offered is that the clinical signs are a result of ganglionic blockade. Sympathetic ganglionic paralysis following curare administration does not occur until five to ten times the dose required for muscle paralysis has been given.[17] Atropine, which will block the muscarinic effects of acetylcholine, and neostigmine cannot block the vasodilatory effect of intravenous or intra-arterial curare. Prior injection of tripelennamine or diphenhydramine will block this vasodilation.[9] Goodman and Gilman make the statement that "inasmuch as considerably larger doses of curare are required for blocking synaptic transmission than for blocking neuromuscular transmission, it is unlikely that the therapeutic use of curare entails any significant element of autonomic ganglionic blockade."[18]

The third explanation, the explanation which we believe is correct, is that histamine was released by *d*-tubocurarine and the clinical signs were due to the uptake of histamine by effector end-organs. That *d*-tubocurarine is capable of releasing histamine was shown to be true by the elevated blood histamine in the second group of subjects. It is conceivable that histamine was released into the blood by *d*-tubocurarine and was rapidly taken up by the histamine effector end-organs of the body, e.g., smooth muscle of cutaneous arterioles, bronchial musculature, and gastric mucosal glands.

Studies of blood histamine levels with concomitant allergic reactions are numerous but they give a varied picture of the blood histamine changes. Nilzen found that when a patient had clinical signs of an allergic response to arsphenamine (erythema, facial oedema) the histamine blood level dropped from 0.12 to 0.05 μg. per ml. of blood. Following subsidence of the reaction the blood histamine rose to 120 μg. per ml. and later returned to normal.[12] Rose has described two cases of urticarial reactions following sulphamethylthiozole and torantil in which blood histamine levels dropped with the onset of skin manifestations.[16] This same author has also described decreases in blood histamine following surgical shock[19] and in cases of angioneurotic oedema.[20, 21] During acute asthmatic attacks the level of blood histamine has been shown to rise or remain unchanged.[21] We have reported a case of urticaria and angioneurotic oedema following *d*-tubocurarine administration with a rise in the blood level of histamine.[13] The reaction in this patient, however, was confined to localized areas, a recent skin graft on the head and neck.

Histamine binding sites have been demonstrated to be abnormal in the serum of allergic patients.[22] It has also been shown that in asthmatics the histamine-activated end-organs are abnormally sensitive.[23] Whether either of these two factors is present in the patients in the third group cannot be proved by our studies, but all patients were free of any allergic symptoms or history.

The method used to determine blood histamine does not differentiate the *in vivo* nature of the histamine. A varying proportion of the histamine may be in the bound and/or conjugated form. Therefore a high blood histamine level may not be indicative of a high blood level of physiologically active histamine. Conversely very small elevations of blood histamine may cause symptoms if the binding sites are abnormal or saturated with histamine.[17] This fact can explain the difference between the second group, where all histamine released was either bound (e.g. to the globulin fraction of the plasma proteins), or was in a conjugated state, and the third group, where the histamine released was not bound and was taken up by effector end-organs.

Summary and Conclusion

The blood level of histamine was measured in six control patients scheduled for elective surgery. In eleven patients the histamine blood level was measured before and five minutes after the rapid intravenous injection of 0.44 mg. per kg. body weight of *d*-tubocurarine. There was no change in the histamine blood level of four patients, a rise in the histamine blood level of four patients, and a decrease in the histamine blood levels of three patients. The last group of patients all showed evidence of systolic hypotension, increased airway resistance, and skin erythema.

Histamine may be released from endogenous sources by *d*-tubocurarine. The significance of this release is determined by the sensitivity of the histamine effector cells and by the state of the histamine binding sites. When these are abnormal, such as in asthmatic or "ectopic" individuals, it is wise to use relaxants other than *d*-tubocurarine.

RÉSUMÉ

Le taux d'histamine dans le sang fut mesuré chez six malades témoins devant subir une chirurgie élective. Chez onze malades, le taux d'histamine fut mesuré avant, et cinq minutes après l'injection rapide de *d*-tubocurarine par voie I.V., à raison de 0.44 mg./kg. de poids corporel. Il n'y eut aucun changement du taux d'histamine chez quatre malades; il y eut une élévation chez quatre autres malades, et une diminution chez trois malades. Chez ces derniers, on constata une hypotension systolique, une résistance augmentée du "airway," et de l'érythème.

La *d*-tubo peut provoquer la libération d'histamine à partir de sources endogènes.

L'explication de cette libération nous serait donnée par la sensibilité des cellules effectrices de l'histamine, et par l'état des récepteurs d'histamine. Quand ceux-ci sont anormaux, comme chez les asthmatiques, il est sage de se servir de myorésolutifs autres que la *d*-tubocurarine.

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