CASE REPORTS

Histamine Release Following Intravenous Injection of d-Tubocurarine

M. R. Salem, M.D., Y. Kim, M.D., A. A. El Ete, M.D.*

The first demonstration that histamine can be released from muscle by curare was that of Alam and co-workers who in 1939, injected curare into a limb artery of the dog and found an increase in histamine content of the venous blood associated with a simultaneous decrease in histamine content of the muscle of the injected extremity. Further animal experiments have shown that d-tubocurarine releases significant quantities of histamine, particularly in the guinea-pig. Observations in man appear to be less convincing, although many investigators believe that d-tubocurarine can be a potent cause of bronchospasm in the anesthetized patient.4

Following infusion of d-tubocurarine into the brachial artery of a normal conscious subject, Mongar and Whelan5 failed to find any significant increase in the plasma histamine level of the venous blood draining the affected arm. They also found that the intra-arterial injection of doses as high as 30 mg. failed to mobilize significant quantities of histamine.5 Contrary to the generally accepted concept, they concluded that it is unlikely that relaxant doses of d-tubocurarine injected intravenously can produce side effects from the release of histamine. Measuring the blood level of histamine in a group of patients receiving a rapid intravenous injection of d-tubocurarine, Westgate et al.6 found that three of eleven patients showed a rise in the histamine level which was accompanied by a fall in blood pressure, increased airway resistance, and skin erythema.

The following case history strongly suggests the occurrence of histamine release following the intravenous administration of d-tubocurarine to an anesthetized patient.

CASE REPORT

A 51-year-old man was admitted to the hospital with the diagnosis of a coin lesion in the right upper lobe. He weighed 83 kg. and was essentially healthy except for a history of allergy to penicillin. Preoperative blood pressure was 120/70 mm. Hg; pulse rate 84 per minute; hematocrit 47 per cent. Premedication, consisting of meperidine 50 mg., hydroxyzine 50 mg., and atropine 0.5 mg., was given (90 minutes) before operation. Induction of anesthesia was achieved with pentothal sodium 275 mg. The introduction of a double-lumen Carless tube was facilitated by 100 mg. of succinylcholine. Anesthesia was maintained with 0.4 to 0.5 per cent halothane, 50 per cent nitrous oxide, using a semiclosed system and intermittent positive-pressure respiration. After checking the position of the tube, the patient was turned to the left lateral position. One minute following the intravenous injection of 21 mg. d-tubocurarine, the blood pressure and pulse were not detectable. The anesthetics were discontinued and 100 per cent oxygen was administered. Placing the patient in slight Trendelenburg position did not improve the blood pressure. ECG changes, consisting of ST-segment and T-wave

* Department of Surgery, Section of Anesthesiology, University of Chicago Hospitals, Chicago, Illinois.
abnormalities, and a pulse rate of 120 per minute were seen. Marked flushing and erythema of the skin were noted, especially over the chest and abdomen. After a period of 20 minutes, systolic pressure rose to 70 mm. Hg following intravenous injection of cumulative dose of 15 mg. methoxamine, 4 mg. phenylephrine and 100 mg. hydrocortisone. No wheezing was noted. The Carlen's tube was replaced with an ordinary endotracheal tube, and the patient was turned to the supine position. The hematocrit, at the end of one hour, was 57 per cent, despite administration of 1,000 ml. plasma and 2,000 ml. lactated Ringer's solution in 5 per cent dextrose. At that time, systolic pressure had risen to 80 mm. Hg and pulse rate was 100 per minute. Central venous pressure remained consistently below 10 cm. H_2O. The patient's condition gradually improved, and the flushing disappeared over an interval of three hours. The trachea was extubated and the operation was postponed.

An intradermal skin wheel on the patient's forearm was made with d-tubocurarine, 2 mg. (0.8 ml.), on the next day. A separate wheel was made with normal saline as a control. The site of drug injection exhibited a 2+ wheal and the control site was negative. Eighteen volunteers were subjected to the same skin tests. The results read ten minutes after injection, were as follows:

Size of wheal (d-tubocurarine) 1+ 2+ 3+
Number of volunteers 4 11 3
(3+: more than 2 inches in diameter; 2+: one to two inches; 1+: less than one inch).

Three days later, the patient was brought to the operating room for surgery. The only change in the anesthetic management was the substitution of a succinylcholine drip for d-tubocurarine; a total of 800 mg. was given. Anesthesia was maintained with 50 per cent nitrous oxide and 0.4 to 0.5 per cent halothane. Blood pressure and pulse rate were stable throughout the procedure, during which a right upper lobectomy was performed.

COMMENT

This case history points clearly to the occurrence of histamine release following intravenous injection of d-tubocurarine, as evidenced by extreme hypotension, tachycardia, marked skin erythema, and a rise in hematocrit despite fluid therapy. Although d-tubocurarine may cause hypotension by ganglionic blockade, this does not seem to have played a major role in this instance because of the presence of erythema, hemococoncentration, and lack of response to vasopressors and to the use of Trendelenburg position. Although bronchoconstriction is prominent in rodents and is the cause of death in guinea pigs following release of histamine, it is not prominent in humans in the absence of asthma.

In a comparative study of the release of histamine by the various muscle relaxants in man, Snipe found that the intracutaneous injection of d-tubocurarine produced the greatest response, followed next by dimethyl tubocurarine, gallamine triethiodide and decamethonium. All of our volunteers, as well as the patient cited in this report, had positive skin tests. The majority of the volunteers reacted with the same intensity as the patient, and three volunteers had more severe reactions. One may anticipate that not all volunteers would show evidence of histamine release if given an intravenous dose of d-tubocurarine. It is doubtful that the intradermal skin test with d-tubocurarine is reliable for predicting a significant histamine release during anesthesia.

Various groups of drugs are prone to liberate histamine. The list includes drugs used in anesthesia, such as muscle relaxants, particularly d-tubocurarine, morphine, trimethaphan camphor-sulfonate and, interestingly, various antihistaminic drugs. Although it is generally believed that the release of histamine by succinylcholine is about one one-hundredth of that caused by d-tubocurarine, cases of bronchospasm which may have been due to the liberation of histamine have been reported. It has been suggested that antihistaminic drugs might be used to advantage with d-tubocurarine. In view of the possible connection between d-tubocurarine and histamine liberation, it would seem sensible either to use relatively small doses, injected slowly, or to avoid its use entirely in patients with any reported allergic conditions.

REFERENCES


Cardiac Arrhythmia Induced by Negative Phase in Artificial Ventilation

A. Pace-Floruidia, M.D., F.R.C.P.(C), and A. Galindo, M.D.*

The hemodynamic effects of the negative phase during intermittent positive-negative ventilation have been well documented.1 For example, in certain neurologic disorders such as fracture of cervical spine with quadriplegia, venous return is improved and arterial blood pressure better maintained if a negative phase is introduced during artificial ventilation. Watson et al. also showed that in such disorders subatmospheric pressure applied in expiration during IPPR increased transmural CVP and often increased mean arterial pressure also. We are not aware, however, of any reports of cases in which arrhythmias were induced by the negative phase in intermittent positive-negative ventilation. The following is a report of such a case occurring during hypothermia.

**CASE REPORT**

The patient, a 42-year-old man, was admitted with a history of sudden hemiplegia. He was conscious on admission. He had been on antihypertensive therapy (guanethidine) for two years. Blood pressure was within normal limits and there was no evidence of cardiac disease clinically. The ECG was interpreted as normal. The respiratory system was normal. Cerebral angiograms revealed an arteriovenous malformation in the thalamic region, with an intracerebral hematoma. A left frontal craniotomy was scheduled, to be done under hypothermia. Atrpine 0.6 mg. was given 45 minutes prior to induction of anesthesia with thiopental, 400 mg. and Anectine® 80 mg. Four per cent Xylocaine® spray was applied topically to the glottis and a 9.5 mm. armored cuffed tube inserted. Maintenance consisted of N₂O–O₂ (2:2 L/min.), halothane, and d-tubocurarine with methoxyflurane given for the first 45 minutes after infiltration of the scalp with 1:250,000 adrenaline (while the temperature was still 34° C). Central venous pressure was monitored via a catheter introduced through the left basilic vein. Continuous arterial pressure was monitored via a cathether in right radial artery. Blood gases were determined at intervals. Controlled ventilation was achieved with a Bird Mark IV plus Mark VIII respirator. Positive pressure was kept at 15 cm. H₂O and negative pressure at −5 cm. H₂O to obtain a tidal volume of 550 ml at 16/minute.

The course of the anesthesia was uneventful until a temperature of 30° C was reached. At this point, ventricular bigeminy appeared. This was attributed to the hypothermia; blood gas values were close to normal, with pH 7.44, Pco₂ 33 mm. Hg, Po₂ 175 mm. Hg, HCO₃⁻ 21.7 mEq./l and base deficit 2.0 mEq./l. Lidocaine, 100 mg. (1 perm gel solution, intravenously), given slowly, rapidly corrected the arrhythmia to sinus rhythm. Twenty minutes

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*Department of Anesthesia, Montreal Neurological Institute and Hospital, McGill University, Montreal 2, Quebec, Canada.