The Effect of d-Tubocurarine on Respiratory Resistance in Anesthetized Man

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Total respiratory resistance was measured during hyperventilation apnea in normal subjects anesthetized with nitrous oxide and halothane. Subsequent administration of *d*-tubocurarine caused no significant change in respiratory resistance. Bronchoconstriction and increased respiratory resistance are, therefore, not usual or expected responses to administration of *d*-tubocurarine. The mean value for respiratory resistance, 6.2 cm. of water/liter/second is in good agreement with previously reported values in conscious, spontaneously breathing individuals.

EARLY INVESTIGATIONS on the effects of curare by Alam,[1] West,[2,3] Comroe,[4] and Landmesser [5,6] showed that when curare is administered to laboratory animals release of histamine or histamine-like substances from skeletal muscles occurs. Bronchoconstriction, bronchospasm, vasodilatation with resulting hypotension and increased bronchial secretions following administration of *d*-tubocurarine have been attributed to histamine release in anesthetized human subjects.[7,9] Attempts to document histamine release or phenomena attributable to histamine release following administration of *d*-tubocurarine in man by objective measurements have been equivocal. Mongar and Whelan were unable to demonstrate increase in histamine level of venous blood following intra-arterial injection of large doses of *d*-tubocurarine in human subjects.[10] Westgate and VanBergen observed no consistent response to administration of *d*-tubocurarine of blood histamine level in healthy anesthetized human subjects. In their study, however, a significant decrease in blood histamine concentration occurred in those subjects who were perceived to exhibit generalized erythema, decrease in blood pressure or prolonged exhalation following administration of *d*-tubocurarine.[11] The present study was undertaken to determine whether a change in respiratory resistance could be detected after administration of *d*-tubocurarine to normal anesthetized human subjects.

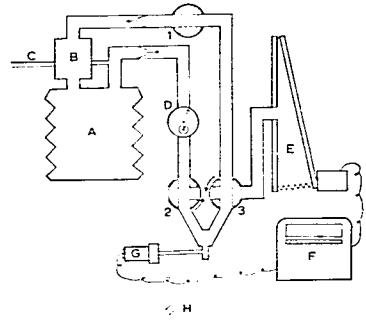

FIG. 1. Diagram of experimental apparatus. For explanation see text.

Method

Subjects of the study were male patients undergoing elective surgery under general anesthesia. All patients denied any allergic reactions. Patients were premedicated according to the desires of the anesthesiologist responsible for clinical management of the case. Unconsciousness was produced with thiopental sodium and endotracheal intubation was facilitated with succinylcholine. A 40 French (inside diameter 1 cm., length 28 cm.) cuffed tube was used in each subject. Anesthesia was subsequently maintained with 60–70 per

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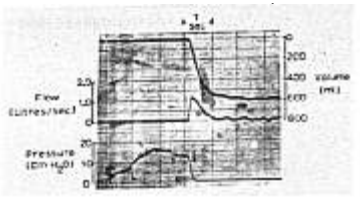

FIG. 2. Airway pressure, expiratory flow rate, and exhaled volume during chest inflation and passive exhalation.

cent nitrous oxide, 30–40 per cent oxygen and 1–2 per cent halothane. When spontaneous respirations had returned and the action of the preceding dose of succinylcholine was thought to be terminated, subjects were made apneic by mechanical hyperventilation and several control measurements of respiratory resistance were made. *d*-Tubocurarine was then administered and respiratory resistance subsequently measured at predetermined intervals following injection. Seven subjects received an initial dose of *d*-tubocurarine of 0.35 mg./kg. and in three others the initial dose was 0.6 mg./kg. Forty-five minutes after the initial dose of *d*-tubocurarine, one half the initial dose was administered and respiratory resistance again measured at intervals. A third injection and period of observation was possible in five of the subjects. Respiratory resistance was measured at intervals over a 45-minute period in three additional patients subjected to an identical anesthetic technique but with no muscle relaxant.

TABLE 1. Effect of *d*-Tubocurarine on Respiratory Resistance in Subjects Anesthetized with Nitrous Oxide and Halothane

Case	Age	Type of Operation	Dose of *d*-Tubocurarine	Control	Total Respiratory Resistance (cm.H₂O/L./sec.) / Minutes After *d*-Tubocurarine Administration						
					3	5	10	15–25	25–35	35–45	Individual Means
Curare Dosage: 0.35 mg./kg.											
1	34	Cholecystectomy	22.0	3.8	—	—	3.4	4.3	5.2	5.0	4.5
			11.0	4.3	—	5.6	3.6	—	3.8	—	4.3
2	44	Vagotomy pyloroplasty	26.2	4.0	4.8	—	4.8	3.9	5.2	6.4	5.0
			13.1	4.7	—	5.8	7.8	5.1	7.4	5.8	6.4
3	44	Lumbar sympathectomy	26.1	4.5	3.4	4.8	4.8	3.4	4.6	4.8	4.3
			13.6	4.4	—	5.0	4.8	4.0	4.5	4.4	4.5
4	40	Cholecystectomy	25.0	6.6	5.8	5.4	6.4	7.0	6.6	6.6	6.3
			12.5	6.3	7.8	—	7.6	7.2	7.6	5.3	7.1
			12.25	7.4	5.8	6.2	7.4	6.0	6.0	—	6.3
5	42	Exploratory laparotomy	21.0	4.5	4.3	4.7	4.4	5.6	5.8	5.6	5.1
			10.5	5.2	6.2	5.0	6.1	4.1	3.9	3.9	4.9
6	47	Inguinal hernia	21.0	6.7	5.8	—	—	7.2	6.6	7.0	6.7
			10.5	7.2	7.7	10.2	9.0	7.1	5.8	6.3	7.7
7	69	Epigastric hernia	30.2	11.8	13.5	13.2	11.4	14.1	13.5	10.2	12.7
			15.1	11.5	10.7	10.0	7.8	13.5	9.3	14.6	11.0
			11.4	8.0	—	—	14.8	7.2	11.8	—	11.3
Curare Dosage: 0.6 mg./kg.											
8	69	Antrectomy	35.4	3.7	—	4.7	3.8	4.6	4.9	4.8	4.6
			17.7	4.7	5.0	5.0	5.7	6.5	6.1	5.7	—
			17.7	6.0	—	6.1	6.7	5.2	5.4	4.5	5.6
9	47	Vagotomy duodenostomy	42.6	7.7	11.8	8.3	7.7	7.8	8.0	6.8	8.7
			21.3	8.2		7.6	5.6	6.7	7.2	7.4	6.9
			21.3	7.0		6.9	7.8	8.3	8.0	6.7	7.5
10	49	Cholecystectomy	24.8	5.4	6.6	5.0	4.2	4.6	5.7	4.3	5.1
			12.4	4.8	6.6	4.6	7.6	5.7	5.8	5.1	5.9
			12.4	6.1	5.4	5.6	4.5	5.0	4.7	4.8	5.0
Group Means			—		6.2	7.1	6.5	6.5	6.4	6.6	6.2	—

TABLE 2. Respiratory Resistance in Subjects Anesthetized with Nitrous Oxide and Halothane Who Received No Muscle Relaxant

Case	Age	Type of Operation	Total Respiratory Resistance (cm.H_2O/L./sec.) Minutes After Induction of Anesthesia								
			10	15	20	25	30	35	40	45	Individual Means
1	40	Herniorraphy	—	2.0	4.4	5.0	4.8	5.6	5.2	4.8	4.5
2	74	Herniorraphy	5.0	5.6	7.0	7.0	7.0	—	6.0	7.0	6.2
3	50	Meniscectomy	5.9	6.6	5.4	5.1	5.2	5.8	5.0	5.0	5.5
Group Means			5.8	4.5	3.1	5.7	5.7	5.7	5.4	5.6	—

Respiratory resistance was determined at a flow of 0.5 liter/second by measuring the transthoracic pressure when expiratory flow rate was 0.5 liter/second The experimental apparatus is illustrated in figure 1. Each subject was artificially ventilated through a tightly-fitting cuffed endotracheal tube (H) using a mechanical ventilator (A) and a semiclosed system with a carbon dioxide absorber (B) in the circuit. Fresh gas (C) was supplied from an anesthesia machine. At the end of an exhalation, the expiratory line was occluded by rotation of a two-way tap (1). The subsequent inspiration was monitored with the ventilation meter (D) and when the desired volume of gas had entered the thorax, the three-way tap in the inspiratory line (2) was rapidly rotated so that this volume of gas was held in the thorax. After a 1–2 second period of sustained pulmonary inflation, the three-way tap in the expiratory line (3) was rotated permitting passive exhalation into the "Wedge" spirometer (E). During exhalation volume and flow rate were continuously measured with the appropriate transducers on the spirometer and recorded on a Minneapolis-Honeywell Visicorder (F). Airway pressure was recorded throughout the respiratory cycle from the output of a Statham PM5TC pressure transducer (G). Following the measurement, all taps were returned to their original positions and regular artificial ventilation was resumed. The "Wedge" spirometer is a ten liter waterless spirometer (Med. Science Electronics) of low resistance and satisfactory frequency response. The volume transducer of this spirometer was calibrated with a 2,000 ml. gas syringe and the flow transducer subsequently calibrated by measuring rate of change of volume during filling of the spirometer at constant flow. The pressure transducer was calibrated against a water manometer. Apparatus resistance was determined using a 10 gallon steel drum as a resistance-free patient analogue and was subtracted from total measured resistance to obtain patient respiratory resistance for each determination.

A representative record of exhaled volume, flow, and airway pressure is illustrated in figure 2. Static compliance was calculated by dividing the volume exhaled (corrected to BTPS) by transthoracic pressure during the period of sustained thoracic inflation. Resistance at 0.5 liter/second was calculated by noting thoracic volume at the instant that this flow occurred and dividing this volume by the static compliance. This calculation gives the transthoracic pressure required to produce an expiratory flow of 0.5 liter/second which is, by definition, the total respiratory resistance at 0.5 liter/second.

Results

Results are summarized in tables 1 and 2. The mean of all control values for respiratory resistance obtained during hyperventilation apnea before administration of *d*-tubocurarine was 6.2 cm. of water/liter seconds. Administration of *d*-tubocurarine caused no significant or consistent alteration in magnitude of respiratory resistance. In subjects studied only during hyperventilation apnea, without muscle relaxant, no consistent change in respiratory resistance with time occurred.

Discussion

Values for respiratory resistance obtained in the present study in both paralyzed and unparalyzed anesthetized subjects are in good agreement with previously published values in both conscious and anesthetized subjects.[12-15] No evidence for increased respiratory resistance following administration of *d*-tubocurarine was found. Variations in respiratory resistance following administration of *d*-tubocurarine were similar in magnitude to random variations in respiratory resistance with time occurring under comparable conditions in subjects who received no *d*-tubocurarine. Variations of the relaxant dose or use of repeated injections did not alter the experimental results. The high respiratory resistance in subject 7 was due to presence of chronic obstructive airway disease.

It is concluded that bronchoconstriction and increased respiratory resistance are not usual or expected responses to administration of *d*-tubocurarine in normal subjects. Mongar and Whelan have also concluded that it is unlikely that relaxant doses of *d*-tubocurarine given intravenously will produce side effects from release of histamine.[10] These conclusions may not be valid in patients with preexisting allergy and a predisposition to develop bronchoconstriction. It is possible that some of the early reports on histamine release following curare administration could be explained by impurities present in preparations of curare then in use. It is also possible that some of the effects of *d*-tubocurarine which have been attributed to histamine release are in fact due to the ganglionic blocking effects of this drug.

Summary

Administration of *d*-tubocurarine to normal patients anesthetized with nitrous oxide and halothane caused no significant change in respiratory resistance. Values for respiratory resistance in anesthetized subjects are in good agreement with previously reported values in conscious, spontaneously breathing individuals.

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