Effect of Mescaline on Cardiopulmonary Dynamics

Method for Determination of Right Ventricular Pressure in the Guinea Pig

By VINCENT DE PAUL LYNCH, EMMETT CLEMENTE, and STEVEN CARSON*

The effect of mescaline on respiratory dynamics, right ventricular pressure, and the ECG in the guinea pig is presented. A procedure for the acquisition of normal right ventricular pressure is described. The mean value for the latter was 13.4 ± 4.6 mm. Hg. Mescaline in low dosages (1 to 20 mg./Kg.) produced a slight increase in heart rate; higher dosages (50 to 240 mg./Kg.) induced bradycardia and conduction disturbances. Respiratory rate, resistance of the airways, and minute volume increased significantly, while tidal volume and compliance decreased. The decrease in compliance was near maximum (−70 and −77 per cent) with high dosages (50 and 100 mg./Kg.). Right ventricular pressure increased, average 45 per cent, following moderate dosages of mescaline (25 mg./Kg.). Diphenhydramine and chlorpheniramine (range 0.4 to 0.7 mg./Kg.) in sufficient concentration to block the effect of histamine (4 mg./Kg.) were utilized to observe possible mescaline antagonistic activity. However, the antihistamines were ineffective against mescaline. It appears probable that mescaline does not owe its activity on these parameters to histaminic receptor stimulation.

ALTHOUGH the effects of mescaline on the central nervous system (CNS) are well documented, its mode of action is unclear (1–3). Unfortunately, the peripheral activities of mescaline have not been subject to as much critical evaluation. It must be emphasized that while analogies are often misleading and erroneous, when comparing peripheral to central effects, a valid working hypothesis may be obtained. Moreover, the current theory concerning the mechanism of action (central) of LSD had, in large part, developed from peripheral studies (4–7). In view of this concept, studies were conducted to observe the effect of mescaline on the cardiopulmonary system in the guinea pig. The investigation was divided into three phases: the effect of mescaline on (*a*) the electrocardiogram, (*b*) right ventricular pressure, and (*c*) respiratory dynamics.

Deniker (8), in studies designed to determine electrolyte alterations induced by mescaline in man, reported a significant decrease in serum potassium. Speck (9) determined heart rate and blood glucose levels in rats challenged with mescaline. She reported that both parameters decreased significantly following intermediate and high doses. Wolbach *et al.* (10) noted that mescaline had a variable effect on pulse rate in man.

The ECG was monitored in the present study since any of the above phenomena could be reflected in this parameter (11). Furthermore, at present there are no available data concerning the effect of mescaline on the guinea pig ECG.

Cochin *et al.* (12) conducted distribution studies in the dog and observed that mescaline entered ventricular tissue. While such findings do not signify that mescaline has an effect on cardiac tissue, it was necessary nevertheless to take cognizance of this possibility. This is true especially in light of reports that mescaline has a variable effect on pulse rate and blood pressure (8, 10, 13). Most investigators agree that systemic blood pressure rises following high doses of mescaline (9, 14–16). It has been established that changes in blood pressure are accompanied by alterations in cardiac activity and respiratory function. It was reasoned, therefore, that if right ventricular pressure was monitored, variations in all related systems would be manifested in this parameter. However, an investigation of this nature could not immediately be undertaken because there are no unequivocal data available regarding the normal variations and mean value of this parameter in the guinea pig. Consequently, this research was designed to obtain the latter information as an initial step. After this was accomplished, an evaluation of the effect of mescaline on the same system was commenced.

The availability of techniques for the cannulation of various vascular networks has facilitated the investigation of cardiopulmonary function (17, 18). Whereas most investigators have used the rat as the test animal (19, 20), the guinea pig was chosen in the present study because of its

Received October 3, 1966, from the Department of Pharmacognosy, Pharmacology and Allied Sciences, College of Pharmacy, St. John's University, Jamaica, NY 11432, and the * Food and Drug Research Laboratories, Inc., Maspeth, NY 11378

Accepted for publication December 30, 1966.

The authors acknowledge the American Medical Association, Education and Research Foundation, for support of a major portion of this work.

Abstracted in part from a thesis submitted by Emmett Clemente to the Graduate School, St. John's University, Jamaica, N. Y., in partial fulfillment of Doctor of Philosophy degree requirements.

susceptibility to respiratory stress (21) in addition to the aforementioned reasons.

During the course of experiments involving the initial phase in this study, mescaline was observed to exert a potent effect on respiration. Doses comparable to those used in human experimentation, and previously reported to have little effect on this parameter in other species (10, 15, 22), were observed to cause a pronounced effect. Moreover, the induced changes closely resembled those produced by histamine (23). In view of these findings, this study was expanded ultimately to observe the action of mescaline on the cardiopulmonary system, its similiarity to histamine, and the possible antagonism of antihistamines upon induced alterations.

MATERIALS AND METHODS

Measurement of Right Ventricular Pressure—Adult male and female guinea pigs, weighing between 700 and 1000 Gm., were anesthetized intraperitoneally with sodium pentobarbital (35 mg./Kg.). The preparation of ventricular catheters and surgical procedures of Popovic (24) were modified in these studies according to the following procedures.

Ventricular catheters (polyethylene tubing, 0.011 in. i.d. × 0.024 in. o.d., No. P.E. 10, Clay-Adams) were prepared at least 24 hr. prior to intubation and allowed to soak in an antiseptic solution of benzalkonium chloride[1] (1:120). The tip of the catheter was shaped in the form of a right angle with the aid of a pencil soldering iron. The angled flexure was approximately 3 mm. from the tip. A small bulb (formed by rotating the catheter over a heat source) was placed a critical distance from the flanged tip of the catheter contingent upon the weight or size of the animal (Table I). The flange was produced with the soldering pencil and served the purpose of minimizing damage to the vessel linings (Fig. 1). The length of the catheter (20 cm.) was held constant so that changes in pressure could not be attributed to a variability in the tubing length. A 22-cm. stainless steel stylet (No. 32 gauge) was inserted into the catheter up to the flexure. The catheter was filled with heparinized saline (4 mg./ml.) and the external tip flame-sealed around the stylet.

An incision of approximately 2 cm. was made so that the midpoint of the incision coincided with the point at which the right transverse scapular vein joined the right external jugular vein. The jugular vein was dissected free and the cephalad portion permanently ligated while the peripheral end was secured with a loose ligature. The catheter was introduced distally into the vessel as close as possible to the junction of the right external jugular and right transverse scapular veins, and then advanced toward the heart. The loose ligature was secured after the bulb of the catheter had entered the vessel, the stylet removed, and the catheter flushed with a volume of saline slightly in excess of the capacity of the catheter (0.02 ml.). The validity of correct placement of the catheter was ascertained by raising the tip of the catheter approximately 5 cm. above the level of the heart and observing the ventricular pattern which was produced after the catheter was connected to a pressure transducer and monitored by a direct writing recorder (Fig. 2, C). It was then flushed with heparinized saline and sealed. This was accomplished by the application of a hemostat approximately 6 cm. from the tip of the catheter and the insertion of a 5-cm. piece of stainless steel wire (No. 30 gauge). This procedure eliminated the necessity of cutting the tip of the catheter before each pressure determination or blood sample withdrawal which would be required if heat sealing were used. The catheter was exteriorized by placing it into the lumen of a needle (No. 13 gauge) and pushing the needle underneath the skin around the

[1] Marketed as Zephiran by Winthrop Laboratories, New York, N. Y.

TABLE I—DISTANCE OF BULB FROM CATHETER TIP

Body Wt., Gm.	Distance, cm.
700–750	3.9–4.1
750–800	4.1–4.3
800–850	4.3–4.5
850–900	4.5–4.7
900–950	4.8–5.0
950–1000	5.0–5.2

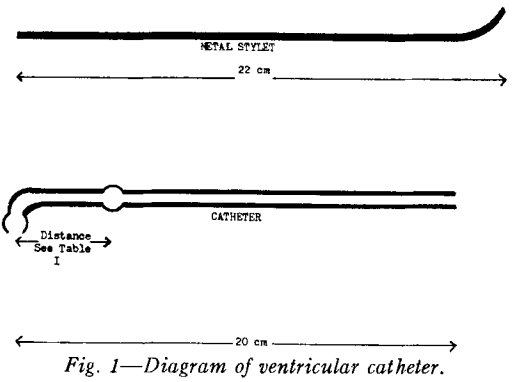

Fig. 1—Diagram of ventricular catheter.

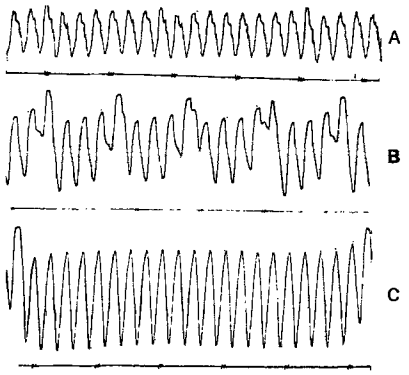

Fig. 2—Patterns of right ventricular pressure. Key: A, catheter in close proximity of pulmonary artery; B, catheter positioned in lower two-thirds of ventricular lumen; C, catheter positioned in upper third of ventricular lumen.

TABLE II—EFFECT OF ANTIHISTAMINES ON RIGHT VENTRICULAR PRESSURE CHANGES INDUCED BY MESCALINE AND HISTAMINE IN THE ANESTHETIZED GUINEA PIG

Compd.[a]	Dosage, mg./Kg.	Animals, No.	Treatment with Antihistaminics, mg./Kg., 15 min. Prior to Challenge	% Change in Right Ventricular Pressure at Max. Effect (Range)
Histamine	4.0	2	[c]	+70-75[b]
Diphenhydramine	0.7	1	[c]	No change
Histamine	4.0	1	Diphenhydramine 0.4	No change
Histamine	4.0	1	Diphenhydramine 0.7	+10.0
Chlorpheniramine	0.8	1	[c]	No change
Histamine	4.0	1	Chlorpheniramine 0.8	+20.0
Mescaline	25.0	6	[c]	+26-86[b]
Mescaline	25.0	1	Diphenhydramine 0.7	+50.0
Mescaline	25.0	1	Chlorpheniramine 0.4	+83.0

[a] Compounds were administered intraperitoneally as their salts. [b] Range value. [c] Animal not pretreated.

TABLE III—EFFECT OF DRUGS ON RESPIRATORY DYNAMICS IN THE GUINEA PIG

Animal, No. and Sex	Pretreatment with Diphenhydramine, mg./Kg.	Mescaline, mg./Kg.	Tidal Vol.	Respiratory Rate	min. Vol.	% Change from Control Compliance	Resistance
1M	[c]	5.0	±[d]	+	+	−33	+9
2M	−	25.0	±	±	±	−66	+140
3M	−	50.0	±	±	±	−70	+63
4M	−	100.0	−	+	+	−77	+200
5M	0.7	25.0	−	+	±	−64	+70
6M	0.7	25.0	±	NC	±	−60	+164
7M	0.7	−	NC[a]	NC	NC	+16[b]	+31[b]

[a] NC, no change. [b] Average value. [c] Compound not administered. [d] ±, fluctuation in response; increase followed by decrease.

neck until the desired area for immobilization was reached.

A Sanborn fluid pressure transducer, model 368B (range ±40 mm. Hg), was connected to a Sanborn recorder, model 350, for the sensing and recording of the ventricular pressure. Lead II was monitored with a Sanborn Twin-Viso recorder (model M-60-13000B, series 203). Connection between the catheter and transducer was accomplished according to the following procedure.

A needle adaptor was connected between the catheter and a short piece (5 cm.) of coiled polyethylene tubing (P.E. No. 10). A gasket was formed on the free end of the coiled tubing and sealed within a male-female B-D adaptor (size A for P.E. 10–50). The final connection was made by placing a male to male Luer adaptor between the female end of the B-D adaptor and the female adaptor of the transducer. The transducer was calibrated to record the pressures within the transducer limits at various attenuation settings.

After the surgical procedure had been completed, the animal was placed into a cylindrical Lucite chamber. The electrodes utilized for the conventional electrocardiographic (ECG) recordings were strategically placed in the chamber so that contact with the electrodes was achieved in the normal resting position. This apparatus facilitated simultaneous recording of right ventricular pressure and electrocardiographic leads I, II, or III. Provisions for obtaining intraventricular ECG recordings had been initiated, but were not completed during the study.

Drug Effects on Right Ventricular Pressures—Anesthetized guinea pigs, weighing between 750 and 1000 Gm., were utilized when studying the effect of antihistamines on the changes induced by histamine and mescaline on this parameter. A control period of 60 min. was maintained prior to injection of the test compound. Readings were obtained at a definite interval to correlate with those taken in the respiratory phases. Antihistamines (chlorpheniramine and diphenhydramine, dosage range 0.4 to 0.8 mg./Kg. i.p.) were administered to observe possible antagonistic action against histamine (4 mg./Kg.) and mescaline (25 mg./Kg.). The antihistamines were administered 15 min. prior to the histamine or mescaline challenge (Table II).

Electrocardiographic Recordings—Unanesthetized male and female guinea pigs, weighing between 700 and 1000 Gm., were used. To record the heart rate, the animal was confined in a plastic container in a prone position. The leads were secured to the forelegs so that lead I could be recorded. An arbitrary time period of 15 min. was allowed to elapse before the ECG recordings were begun. The animal was then removed from the container and injected intraperitoneally with mescaline or with the solvent (water). The latter served as the control. Various dosages of the drug were administered (ranging from 1 to 240 mg./Kg.), and the influence on the ECG was recorded at specific

TABLE IV—EFFECT OF MESCALINE ON THE RESPIRATORY RATE IN THE INTACT GUINEA PIG

	5–20 min.		5–60 min.	
	Mean Resp./ min.	S. D.	Mean Resp./ min.	S. D.
Control[a] mg./Kg.[b]	69.2		67.6	
5	90.4	± 7.94	87.2	± 7.55
25	98.0	±10.95	88.6	± 7.94
100	103.5	±12.92	96.5	±10.95

[a] Twelve animals in control group. [b] Four animals per dosage level.

TABLE V—EFFECT OF DIPHENHYDRAMINE ON RESPIRATORY RATE CHANGES INDUCED BY MESCALINE AND HISTAMINE IN THE UNANESTHETIZED GUINEA PIG

Compd.[a]	Dosage,[c] mg./Kg.	Treatment with Diphenhydramine, mg./Kg., 15 min. Prior to Challenge	% Change in Respiratory Rate at Max. Effect
Histamine	4.0	[b]	+20
Diphenhydramine	0.7	[b]	No change
Histamine	4.0	0.7	+6
Mescaline	25.0	[b]	+33
Mescaline	25.0	0.7	+36

[a] Compounds were administered intraperitoneally as their salts. [b] Compound not administered. [c] Two animals per dosage level.

intervals over a 240-min. period following injection.

Measurement of Respiratory Dynamics Utilizing the Amdur Technique—Tidal volume, respiratory rate, minute volume, compliance, resistance, and flow rate were recorded in the anesthetized guinea pig (weighing between 230–290 Gm.). The technique utilized was a modification of the Amdur method (25). Control readings were begun following a 30-min. recovery from catheterization. Control readings were taken every 3 min. for a period of 15 min. to insure parameter stability. The animal was then injected intraperitoneally with drugs of varying doses (Table III), and tracings were obtained at the specified intervals for a period of 1 hr.

Drug Effects on Respiration in the Intact Animal—In order to evaluate the effect of mescaline on the respiration of the intact animal, 12 animals in groups of four were given mescaline in doses of 5, 25, and 100 mg./Kg. intraperitoneally. Respiratory rate was counted at specific intervals over a 1-hr. period; the same procedure was followed for the control values (Table IV). Six animals were used to demonstrate the effect of diphenhydramine on the per cent change in the respiratory rate at peak responses to a histamine or mescaline challenge. The drugs and doses used are given in Table V.

RESULTS

Measurement of Right Ventricular Pressure—Normal right ventricular measurements were carried out in a series of 49 anesthetized guinea pigs. Electrocardiograms as well as right ventricular pressure was monitored in 16 animals at specific intervals for a period of 3 hr. Lead II was recorded simultaneously with the ventricular pressure at 0, 15, 30, 45, 60, 90, 120, 150, and 180 min. after cannulation. Due to instrument difficulty, ECG data have been compiled in nine of the 16 runs mentioned above.

Frequency distribution histograms were plotted for pressure values obtained immediately after cannulation (Fig. 3, A) and for the average value obtained during the 3-hr. exposure periods (Fig. 3, B). Histogram A exhibits a normal distribution pattern. The arithmetic mean was 13.4 mm. Hg, with a standard deviation of ±4.6 mm. Hg. Observation of the difference between the pressure immediately after cannulation and the average value after the 3-hr. exposure period was made and found in most instances to be small. In the majority of cases, the difference recorded was less than 1.0 mm. Hg (ranging from −1.1 to +2.5). Generally, when the difference was greater than +1.0 mm. Hg, the animal exhibited signs of partial recovery from the initial level of anesthesia. Marshall and Hanna (26) stated that under general anesthesia the mean arterial blood pressure in the guinea pig was lower than when the animal was conscious and active. More recently, Rudolph and Scarpelli (27) observed reduction in blood pressure after intravenous administration of pentobarbital in the unanesthetized dog. Popovic and Kent (28) have demonstrated the effect of anesthesia upon cardiac output presenting evidence that cardiac output is reduced under anesthesia. The ECG data and heart rate values obtained in these experiments correspond closely with those described by Lombard (29).

Drug Effects on Right Ventricular Pressure—Six anesthetized animals (35 mg./Kg. sodium pentobarbital) were injected intraperitoneally with mescaline and right ventricular pressure and lead II were monitored. In all cases a rise in pressure was noted in approximately 2 min. following injection. The rise in pressure correlates remarkably well with the onset of hyperpnea in the respiratory phase. The magnitude and duration of the pressure rise varied from animal to animal; however, the return to control values was initiated at about 30 min. after administration of the compound. During the entire test period there appeared compensatory changes, although this phenomenon was not observed during the control period (60 min.).

Animals exhibiting marked changes in pressure also demonstrated ECG alterations. In general, there was no significant change in pulse rate while marked changes occurred in conduction. One animal exhibited A-V block and inversion as well as diphasic "T" wave changes. Overall, the changes in ECG were not consistent. In some animals, the "T" wave was observed to reverse polarity and appear "tented," while in others it became more negative. However, the effect observed on the ECG was noted to occur between 5 and 10 min. after mescaline injection in all cases.

Three animals were injected with histamine. The ventricular pressure was observed to both rise and fall dramatically throughout the first 10 min. following administration. Following this phase, the pressure usually fell with an abrupt cessation of cardiac activity a few minutes thereafter. It is noteworthy to mention that this marked fluctuation in pressure was also observed with mescaline.

In order to assess the effect of antihistamines on

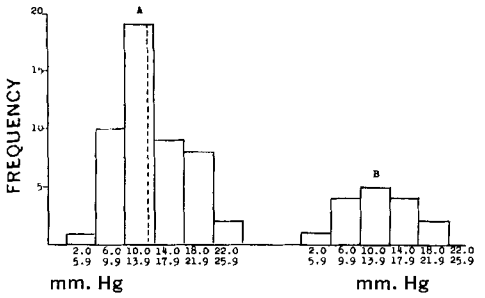

Fig. 3—Frequency histograms: ventricular pressures. Key: A, *values (49 animals) immediately after cannulation;* B, *average values for nine readings of right ventricular pressure for 3 hr. (16 animals);* - - - -, *mean pressure value (13.4 mm. Hg).*

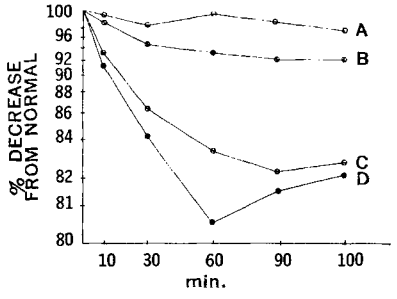

Fig. 4—Effect of mescaline on heart rate in the unanesthetized guinea pig. Key: A, *50 mg./Kg.;* B, *100 mg./Kg.;* C, *200 mg./Kg.;* D, *240 mg./Kg.*

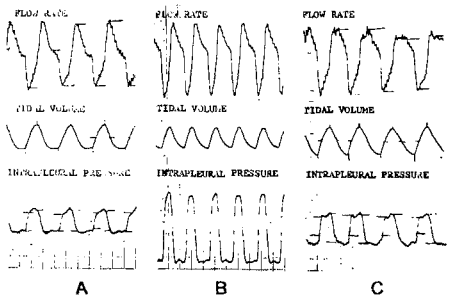

Fig. 5—Simultaneous effect of mescaline on various respiratory parameters in the unanesthetized guinea pig. Key: A, *control;* B, *test period, 5 min. following 100 mg./Kg i.p. of mescaline;* C, *recovery at 60 min.*

mescaline, the compounds were first tested on histamine challenged animals. As can be observed in Table III, the antihistamines blocked the previously pressor and lethal effects of histamine. The antihistamines did not effectually block the action of mescaline either on the rise in ventricular pressure or in respiratory rate, in dosages which were sufficient to curtail the effects of histamine. These findings are also borne out in the respiratory study on the intact animal.

Electrocardiographic Recordings—A series of 12 animals was used for this phase. Administration of mescaline in dosages of 1, 3, 8, 10, and 20 mg./Kg. did not exhibit a significant change in pulse rate or in wave characteristics when compared with control. However, when higher dosages were administered (50, 100, 200, and 240 mg./Kg.) there appeared to be a significant decrease in rate beginning at 10 min. and lasting for approximately 1 hr. (Fig. 4). In most of the latter cases, a "T" wave change was evident at 10 min. and was terminated at approximately 60 min. In general, low doses produced no significant change in the above parameters; high doses had a rather rapid but transient effect on pulse rate and "T" wave of the guinea pig ECG. A more critical evaluation of the electrical characteristics was limited due to instrument inefficiency.

Respiratory Data Utilizing the Amdur Technique—In all animals tested and with all dosages employed (5, 25, 50, and 100 mg./Kg.), there was exhibited an increase in respiratory rate and resistance; however, tidal volume and compliance decreased. Because of the marked increase in respiratory rate, the minute volume also increased. The changes in the above parameters occurred rapidly, usually within the first 3 min. The magnitude of the effect was observed to be dependent upon the dose. The maximum effect was demonstrated to range from 10 to 30 min. following administration of the compound. A return to control values usually began after 30 min. and was complete by 60 min. (Fig. 5). Furthermore, a considerable amount of compensation occurred throughout the test period, which was reflected in a "see-saw" activity of the respiratory rate and the dependent minute volume as well as in the other parameters monitored.

The most consistent change was observed in the compliance decrease. The per cent decrease in compliance at maximum effect for 5, 25, 50, and 100 mg./Kg. of mescaline was 33, 66, 70, and 77, respectively. It was noted on many occasions that the effect of this compound was in large part dependent upon the susceptibility of the animal, which in turn was dependent upon the physical state. Indeed, an animal with respiratory disturbances will, in many instances, not respond typically to the compound.

Pretreatment with diphenhydramine (0.7 mg./Kg.) did not alter the decrease in compliance following the administration of mescaline (25 mg./Kg.). Diphenhydramine alone was observed to cause either an increase or no change in compliance (Table II).

Drug Effects on Respiration in the Intact Animal—With all dosages employed, mescaline produced a significant increase in respiratory rate and activity of the animals. The effect was very rapid at all dose levels beginning at approximately 1 to 3 min. Termination of the effect was observed to occur between 20 and 30 min. after injection. The respiratory rate at the end of the test period (60 min.) was usually below control rate. This was also observed in the catheterized animals. The average per cent increase in respiratory rate for a total of 1 hr. at 5, 25, and 100 mg./Kg. was 23.2, 33.2, and 51.6, respectively. However, if only the first 20 min. were considered, the per cent increase was greater because the major effect of the compound was occurring during this period (Table IV). It is interesting to note that several animals in all dosage groups exhibited both coughing and very strong abdominal contractions. At times, the con-

tractions were so powerful as to propel the animal forward.

The effect elicited by mescaline on compliance of the lung and airway resistance is quite similar to that which has been observed for histamine (25). In order to observe the effect of antihistamine pretreatment on the respiratory changes produced by mescaline, without the influence of anesthesia and surgical trauma, several animals were given diphenhydramine (0.7 mg./Kg.) 15 min. prior to mescaline (25 mg./Kg.) or histamine (4.0 mg./Kg.). There were no significant changes induced by diphenhydramine alone; however, mescaline produced its characteristic symptoms with or without pretreatment of the antihistamine. Marked hyperpnea and coughing were noted within 5 min., the maximum occurring between 10 and 20 min. The effect of histamine was antagonized by the antihistamine (Table V).

DISCUSSION

Patterns of Right Ventricular Pressure—Observation of the pressure waves indicated that they could be grouped into three basic forms. The first demonstrated a typical peripheral pulse pattern (Fig. 2, A). The second showed a smoother wave with a slight flattening of the apical region (Fig. 2, B), and the third, which though similar to the second, was devoid of flattening of the apical region (Fig. 2, C). Dissection of the site of catheter insertion revealed that where the first wave formation was present, the catheter resided in the ventricle in proximity to the valve of the pulmonary artery. The other two pressure patterns differed only with respect to their location within the ventricular lumen, the former lying in the lower third and the latter in the upper third of the lumen. From an examination of the tracings of the former situation, the flattened apical region could be accounted for by assuming that at the peak of systole the catheter was forced against the ventricular wall (because of the narrowness of the lumen in that area) and resulted in a momentary interference with blood flow through the catheter. The apically flattened curves resulted from the catheter positioned in the narrower area of the ventricle, whereas the smooth waves described above resulted from the positioning of the catheter in the wider portion of the ventricle. The results indicated that slight movement of the catheter within the right ventricle may lead to a fourfold difference in pressure. There appeared to be an "optimal-position pressure relationship." When the catheter lay in the upper third of the ventricular lumen, the pressure was higher than that found when the catheters were positioned in the lower two-thirds of the ventricle.

In these studies, the ventricular pressure was determined to be less than 4.0 mm. Hg when the catheter tip lay under the papillary muscle. In this situation, the catheter could not, as a rule, be repositioned without damage to the overlying musculature. The ventricular pattern was characteristic when this occurred. The wave was small (low pressure) and considerably wider, whereas the apex of the wave was usually flattened. If the catheter was found to be pressing against the tissue anywhere within the ventricle, the wave formed was relatively wide and the pressure low (lower than 5.0 mm. Hg). In these studies, lead II was monitored simultaneously with pressure determination. These data are in accord with previously published reports.

Ventricular pressure variations reported in the literature seem to have been dependent upon positioning of the catheter as well as the methodological problems having little or nothing to do with the normal physiological state of the test animal.

The changes (decrease) in compliance observed with the higher dosages of mescaline (50 and 100 mg./Kg.) reflect near maximal decrease in this parameter (30–33). Concomitantly, the resistance in the airways increased. Moreover, because both effects occur at approximately the same time, it is difficult to assess the primary response. However, if mescaline exerts its respiratory effects in a fashion similar to other compounds, *e.g.*, serotonin or histamine (4), which induce a rapid and shallow respiratory pattern, one can attribute these effects to a primary change in compliance rather than resistance. If the respiration were deep and slow, this would tend to implicate the changes in resistance as the more susceptible function (31).

Decrease in compliance has been attributed to increased permeability and accumulation of blood in the pulmonary-capillary network of the lungs for histamine by Hughes, May, and Wittecombe (34, 35). However, spasm of the vascular network has also been demonstrated to cause the compliance to decrease. The effect of mescaline in low doses could be explained from the latter observations since the intrapleural pressure, although increased significantly, would at times approach control level. However, when higher doses were employed, the possible spasmogenic effect could not be compensated. Aviado (36) stated that methoxamine could influence pulmonary blood flow, but not directly influence the bronchiolar and pulmonary vascular smooth muscles. The consequences of a primary systemic pressor action, however, include reflex increase in vagal tone which can include bronchoconstriction. Moreover, the pressor effect of mescaline might serve to explain the changes observed, if an analogy can be made with methoxamine. Furthermore, Speck (9) demonstrated that bradycardia was produced following mescaline administration. This effect has been confirmed in this study. The possibility of reflex bronchoconstriction accounting, at least in part, for the action of mescaline on respiration has merit. Luduena, O'Malley, and Ogen (37) have demonstrated that lung edema can be produced by intravenous administration of epinephrine into rabbits. They attributed the edema to the intense and sustained high arterial blood pressure with increased left ventricular work load leading to elevated capillary pressure and then edema. It has been demonstrated that the edema produced in the dog by epinephrine is probably mediated by its peripheral action only.

Mescaline has been observed to increase systemic blood pressure in the cat (38), to cause severe peripheral vasoconstriction in the rat (9), and to produce constriction of various smooth muscle preparations *in vitro* (4, 6, 7); the latter effect has also been confirmed in this laboratory. The possibility exists that the lung edema observed in this study following intermediate and high dosages of mescaline (25 to 100 mg./Kg.) could be attributed to a similar mechanism as that postulated for epinephrine.

Because of the similarity with the observed respiratory change (in cannulated and intact animals) and the ventricular pressure between histamine and mescaline, antihistamines were employed in concentrations sufficient to block the effect of histamine. The results demonstrate that the antihistamines were not effective against mescaline; therefore, mescaline is probably not liberating histamine or stimulating histaminic receptor sites. It may be plausible that some of the effects on right ventricular pressure may be explained on a physical basis, due to the marked forcefulness induced by mescaline on respiratory movements. Moreover, this effect appears to be multifaceted: a combination of facilitated venous return, due to severe respiratory movements, increased peripheral vasoconstriction, and possibly a spasmogenic effect on the pulmonary vascular network.

Low doses of mescaline produced a slight increase in heart rate; however, higher doses produced bradycardia. The latter effect was also reported by Speck (9). Because the rise in blood pressure parallels the fall in heart rate, a baroreceptor mechanism appears to be, at least partly, responsible for the bradycardia. The effect of mescaline on the ECG was not remarkable at low dosages (1, 3, 8, 10, and 20 mg./Kg.). However, at higher doses in the intact and cannulated animal, conduction changes were evident. The most prominent effect was observed as an increase in positive polarity of the "T" wave. This effect is quite similar to those reported for various sympathomimetic amines, especially phenylephrine (39). The observed changes could have been mediated *via* a central and/or peripheral mechanism as has been demonstrated for phenylephrine. Because mescaline exerts a strong influence on the central nervous system, the effect on the cardiopulmonary system *via* central mechanisms cannot be dismissed. The "T" wave appeared to be "tented," a phenomenon observed when the serum potassium level is elevated (11). However, Deniker (8) reported that in humans, the serum potassium level fell within the first 10 min. and the effect was maximum between 30 and 60 min. following the intravenous administration of mescaline (10 mg./Kg.).

SUMMARY

The effect of mescaline on respiratory dynamics and the electrocardiogram in the unanesthetized guinea pig was determined. A procedure is described for the acquisition of normal right ventricular pressure in the anesthetized guinea pig and the action of mescaline on this parameter.

1. The mean value obtained for right ventricular pressure was 13.4 ± 4.6 mm. Hg.

2. Mescaline (25 mg./Kg.) and histamine (4.0 mm. Hg) caused a marked increase in right ventricular pressure. Pretreatment with antihistamines in sufficient concentration to curtail the effects of histamine did not antagonize the action of mescaline.

3. The action of mescaline on respiratory dynamics (compliance, resistance of the airways, tidal volume, minute volume, flow rate, and respiratory rate) in the unanesthetized animal resembled the effect of histamine. However, pretreatment with diphenhydramine did not alter these responses to mescaline. Mescaline, in various doses, including that used in human experimentation, produced a marked increase in the respiratory rate in the intact guinea pig. Diphenhydramine effectively antagonized the action of histamine but not of mescaline on this parameter in the intact animal.

4. Control ECG data obtained in these experiments are in accord with previously published reports. Mescaline did not significantly alter heart rate in low to intermediate dosages (1 to 25 mg./Kg.); however, bradycardia was apparent with higher dosages (50 to 240 mg./Kg.). Conduction disturbances were manifested at the high dose levels, the most consistent being a "T" wave alteration.

REFERENCES

(1) Denber, H. C., Teller, D., Rajotte, P., and Kaufman, D., *Ann. N. Y. Acad. Sci.*, **96**, 14(1962).
(2) Giarman, N., and Freedman, D., *Pharmacol. Rev.*, **17**, 1(1965).
(3) Takeo, Y., and Himwich, H., *Science*, **150**, 1309 (1965).
(4) Gaddum, J. H., Hebb, C. O., Silver, A., and Swan, A., *Quart. J. Expll. Physiol.*, **38**, 255(1953).
(5) Gaddum, J. H., and Hameed, K. A., *Brit. J. Pharmacol.*, **9**, 240(1954).
(6) Åström, A., and Sameleus, U., *ibid.*, **12**, 410(1957).
(7) Costa, E., *Proc. Soc. Expll. Biol. Med.*, **91**, 39(1956).
(8) Deniker, P., *J. Nervous Mental Disease*, **125**, 427 (1957).
(9) Speck, L., *J. Pharmacol. Exptl. Therap.*, **119**, 78 (1957).
(10) Wolbach, A. B., Jr., Miner, E. J., and Isbell, H., *Psychopharmacologia*, **3**, 219(1962).
(11) Goldman, M., "Principles of Clinical Electrocardiography," 5th ed., Lange Medical Publications, Los Altos, Calif., 1965, pp. 377–380.
(12) Cochin, J., Woods, L. A., and Seevers, M. A., *J. Pharmacol. Exptl. Therap.*, **101**, 205(1951).
(13) Wolbach, A. B., Jr., Isbell, H., and Miner, E. J., *Psychopharmacologia*, **3**, 1(1962).
(14) Grace, G. S., *J. Pharmacol. Exptl. Therap.*, **50**, 359 (1934).
(15) Deniker, P., *J. Nervous Mental Disease*, **124**, 371 (1956).
(16) Parker, J. M., and Hildebrand, N., *Federation Proc.*, **21**, 419(1962).
(17) Halmagyi, D. J., Colebatch, H. J. H., and Starzecki, B., *J. Appl. Physiol.*, **19**, 105(1964).
(18) Popovic, V., *Am. J. Physiol.*, **207**, 1345(1964).
(19) Popovic, V., and Kent, K. M., *ibid.*, **207**, 767(1964).
(20) Weeks, J. R., and Davis, J. D., *J. Appl. Physiol.*, **19**, 540(1964).
(21) Carson, S., Goldhamer, R. E., Mackars, A., and Silson, J. E., *Arch. Environ. Health*, **11**, 635(1965).
(22) Friedhoff, A. F., and Goldstein, M., *Ann. N. Y. Acad. Sci.*, **96**, 5(1962).
(23) Amdur, M., and Mead, J., *Am. J. Physiol.*, **192**, 364 (1958).
(24) Popovic, V., and Popovic, P., *J. Appl. Physiol.*, **15**, 727(1960).
(25) Amdur, M., and Mead, J., *Proc. Third Natl. Air Pollution Symp.*, 1955.
(26) Marshall, L. H., and Hanna, C. H., *Proc. Soc. Expll. Biol. Med.*, **92**, 31(1956).
(27) Rudolph, A. M., and Scarpelli, E. M., *Am. J. Physiol.*, **206**, 1201(1964).
(28) Popovic, V., Kent, K., and Popovic, P., *Proc. Soc. Expll. Biol. Med.*, **113**, 599(1963).
(29) Lombard, E. A., *Am. J. Physiol.*, **171**, 182(1952).
(30) Carson, S., unpublished data.
(31) Mead, J., *J. Appl. Physiol.*, **15**, 325(1960).
(32) Murphy, S. D., and Uhlrich, C. E., *J. Am. Ind. Hygiene Assoc.*, **25**, 28(1964).
(33) Swann, H. E., Jr., Brunol, D., and Balchum, O., *Arch. Environ. Health*, **10**, 24(1965).
(34) Hughes, R., May, A. J., and Wittecombe, J. G., *J. Physiol.*, **142**, 306(1958).
(35) Cook, C. D., Mead, J., Schreiner, G., Frank, N., and Craig, J. M., *J. Appl. Physiol.*, **14**, 177(1959).
(36) Aviado, D. M., Jr., *J. Pharm. Sci.*, **51**, 191(1962).
(37) Luduena, F. P., O'Malley, E., and Ogen, I. H., *Arch. Intern. Pharmacodyn.*, **162**, 111(1959).
(38) Jacobsen, E., *Clin. Pharmacol. Therap.*, **4**, 480(1963).
(39) Keys, A., and Violante, A., *J. Clin. Invest.*, **21**, 1 (1942).