APNEIC AND HYPOTENSIVE EFFECTS OF LOCAL ANESTHETIC DRUGS IN DOGS AND MICE UNDER GENERAL ANESTHESIA

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During tissue distribution studies on cocaine the observation was made that dogs anesthetized with ether or thiopental tolerated less cocaine injected intravenously than unanesthetized animals. Death resulted from respiratory failure without any evidence of convulsions, and the heart continued to beat in an apparently normal manner for several minutes after the appearance of apnea. Further investigation revealed the simultaneous occurrence of hypotension which persisted for minutes or, when artificial respiration was maintained, for hours. The actions of respiratory depression, hypotension, or increased toxicity have been described for local anesthetic agents administered to animals anesthetized with ether, chloroform, cyclopropane, or barbiturates (1–12). Further quantitative information on the apnea-inducing and hypotensive actions of the local anesthetic agents in animals under general anesthesia is presented in this communication. Some observations on the mechanisms by which these phenomena become manifest in the dog are also included.

Methods

Mouse Experiments.—The intravenous LD_{50} values for cocaine, procaine, lidocaine, and pentylenetetrazol were determined in unanesthetized mice and in mice anesthetized with ether, chloroform, thiopental, or pentobarbital. (All the dosages of the local anesthetic agents reported in this paper were calculated and administered as the amine hydrochloride.) Webster strain Swiss mice ranging in weight from 20–25 Gm. were used. Pentylenetetrazol was included as a convulsive agent without local anesthetic activity. At least 40 mice were used for each LD_{50} determination, and all results were analyzed statistically with the method of Litchfield and Wilcoxon (13).

A simple apparatus (fig. 1) was used for anesthetizing the mice with ether or chloroform. The air flow was maintained in excess and was kept uniform by inspection of a bubble counter and adjustment of a screw-clamp. The amount of air passing through the anesthetic bottle, or the by-pass, was controlled by suitable adjustment of the two screw clamps. The air-anesthetic mixture was passed through glass tubing held by a 1-hole rubber stopper into the mouse chamber, prepared from a short piece of glass tubing of sufficient length and diameter to accom-

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modate a mouse and prevent the animal from turning. A 2-hole rubber stopper was placed at the other end of the mouse chamber, and the tail of the mouse was extended through 1 hole. From the other hole rubber tubing carried away the anesthetic vapors. Each mouse was well equilibrated under deep anesthesia before injection. Respiratory rate was the principal criterion for depth of anesthesia. Cyanosis was carefully avoided. Mice anesthetized with ether were equilibrated at a respiratory rate of 7 to 13 per five seconds, and with chloroform, at 10 to 15 per five seconds. Mice equilibrated in this manner could be maintained for thirty minutes (the longest period tested) and in all instances recovered completely upon removal from the chamber.

Anesthesia with thiopental or pentobarbital was obtained by injection of the barbiturate into the tail vein five minutes before the administration of local anesthetic. The dose of sodium thiopental was 100 mg./kg. and that of sodium pentobarbital, 50 mg./kg.

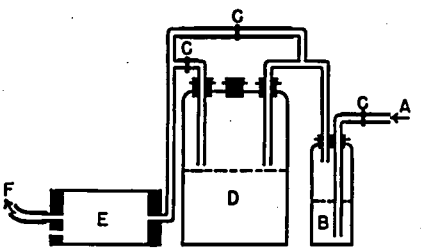

FIG. 1. Diagram of the apparatus employed for anesthetizing mice. All connections were made with appropriate glass and rubber tubing and rubber stoppers. A, compressed air. C, screw-clamps on rubber tubing. B, bottle one-half filled with water to serve as a bubble counter. D, bottle containing the volatile anesthetic agent. E, mouse chamber. F, rubber tubing to carry anesthetic vapors to a fume hood. The entry and exit glass tubes in bottle D were placed 0.5 to 1 inch above the level of the anesthetic liquid. The anesthetic agent was introduced through the middle hole of bottle D after removal of the rubber stopper.

All LD_{50} values of cocaine, lidocaine, procaine, and pentylenetetrazol were determined with a uniform technique of injection. These agents were prepared in physiological saline solution in graduated concentrations and injected in a standard volume, 0.002 ml./Gm. of body weight, into the tail vein at a standard rate of 0.01 ml. per second. Control saline injections had no effect on the anesthetized mice.

Dog Experiments.—The intravenous LD_{50} value for cocaine was determined in 22 unanesthetized mongrel dogs. In addition, 57 dogs were anesthetized with ether to various planes of anesthesia and one of the agents, cocaine, procaine, lidocaine, or procaine amide, was injected intravenously at a constant rate of 0.2 ml. per second. Ether and oxygen were administered to each of the dogs using a clinical anesthesia apparatus with a suitable arrangement of one-way valves connected to a

cannula placed in the trachea of the animal. The ether-oxygen mixture was not recycled. When necessary, mechanical positive pressure artificial respiration was instituted using the ether-oxygen mixture obtained from the anesthesia apparatus and applied through the tracheal cannula. Dead air space in the apparatus was kept at an absolute minimum. In 8 experiments the local anesthetic agent was administered to dogs anesthetized with intravenous pentobarbital or thiopental. Pneumographic tracings were obtained from all of the animals, and mean carotid pressure was recorded from 34 dogs equilibrated under deep ether anesthesia. In several of the animals from which blood pressure was registered, electrocardiograms were taken before, during, and after each injection. Jugular pressure tracings were obtained

TABLE 1

COMPARISON OF INTRAVENOUS LD_{50} VALUES OF COCAINE, PROCAINE, LIDOCAINE AND PENTYLENETETRAZOL IN MICE ANESTHETIZED WITH VARIOUS AGENTS

Drugs	Control No Anesthesia (mg./kg.)	General Anesthetics			
		Ether (mg./kg.)	Chloroform (mg./kg.)	Thiopental (mg./kg.)	Pentobarbital (mg./kg.)
Cocaine-HCl	14* (13–15)† 18* (15–21)	3.3 (2.7–3.9)	2.7 (2.0–3.6)	21 (17–27)	17 (15–20)
Procaine-HCl	37 (31–45)	6.4 (3.2–13)	12 (9.8–14)	75 (67–83)	75 (50–100)
Lidocaine-HCl	21 (20–22)	1.8 (1.1–3.1)	1.6 (1.2–2.0)	20 (17–23)	22 (19–25)
Pentylenetetrazol	43 (35–51)	19 (17–20)	25 (22–29)	over 900	Over 500

* Cocaine LD_{50} values determined at different times to check variations in animals, temperature, and time.

† The figures in parentheses represent the 19/20 confidence limits of the LD_{50} values ($p = 0.05$).

from 7 of the animals. In 11 experiments attempts were made to reestablish normal respiratory effort by withdrawal of ether or administration of nikethamide, pentylenetetrazol, or 10 per cent carbon dioxide. The vagal and glossopharyngeal nerves were sectioned and the carotid sinuses stripped in 3 dogs before the injection of the local anesthetic agent.

Nineteen dogs maintained at approximately plane 3 of anesthesia with ether-oxygen were successively administered intravenous epinephrine, 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP, a ganglion stimulating agent described by Chen, Portman and Wickel (14)), and tetraethylammonium (TEA) chloride before and after the injection of cocaine, procaine, lidocaine, or procaine amide. Artificial respiration

was instituted to maintain the administration of ether and oxygen at a uniform rate after the onset of apnea induced by the injection of the local anesthetic agent.

At the conclusion of some experiments, the thorax was opened to permit observation of the heart size during hypotension.

Results

In Mice.—The LD_{50} values for intravenous cocaine, procaine, lidocaine, and pentylenetetrazol in normal mice anesthetized with the various general anesthetic agents are summarized in table 1. Ether and

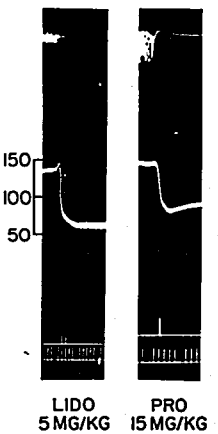

FIG. 2. Effect of intravenous lidocaine and procaine on respiration (upper tracing) and carotid blood pressure (middle tracing) in a dog anesthetized with ether.

chloroform increased considerably the lethal potency of all of the agents, lidocaine, cocaine, procaine, and pentylenetetrazol. For example, the LD_{50} value for lidocaine in mice anesthetized with ether was one-twelfth the value obtained in unanesthetized animals.

Pentobarbital or thiopental anesthesia did not alter the toxicity of cocaine or lidocaine, but significantly decreased the toxicity of procaine and pentylenetetrazol. Convulsions were observed only in the mice anesthetized with thiopental or pentobarbital and administered pentylenetetrazol. All the other animals died during the period of primary depression.

Direct observation of the hearts of a few mice from each group after the cessation of respiration revealed a strong beat with regular rhythm. In a few of the mice which were administered cocaine, cardiac arrest had occurred by the time the thorax was opened.

In Dogs.—Typical results following the intravenous injection of a

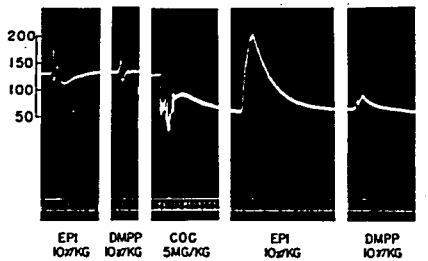

FIG. 3. Effect of intravenous epinephrine and 1,1dimethyl-4-phenylpiperazinium iodide (DMPP) on carotid blood pressure before and after cocaine in a dog anesthetized with ether.

local anesthetic agent into a dog anesthetized with ether are illustrated in figure 2. Procaine, lidocaine, procaine amide and cocaine produced a similar pattern of effect, with the exception that ventricular irregularities usually occurred after the administration of cocaine (fig. 3).

Bilateral vagal section, interruption of carotid and aortic sinus pathways, or a combination of both procedures failed to prevent the apneic or circulatory responses to the local anesthetic agents.

Table 2 summarizes the respiratory effects observed when cocaine, procaine, lidocaine, or procaine amide was injected into dogs anesthetized with ether at various levels of anesthesia. The intravenous LD_{50} for cocaine in dogs was found to be 11 mg./kg. (19/20 confidence limits, 10.1 to 12.3 mg./kg.). Thus the toxicity of cocaine is approximately two-fold greater in dogs deeply anesthetized with ether than in unanesthetized animals. A dose of 5 mg./kg. of cocaine produced apnea and death in 1 of 5 animals in the second stage of anesthesia. At the latter level of anesthesia larger doses of cocaine, 15 and 17 mg./kg., produced very mild convulsions and irreversible apnea.

Apnea was produced in dogs under deep ether anesthesia by 13–25 mg./kg. of procaine, 2.5–5.0 mg./kg. of lidocaine, and 15–45 mg./kg. of

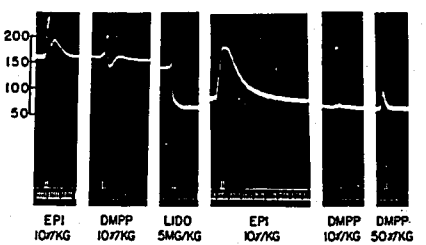

FIG. 4. Effect of intravenous epinephrine and 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) on carotid blood pressure before and after lidocaine in a dog anesthetized with ether.

procaine amide. These doses of procaine, lidocaine, and procaine amide are significantly lower than those which have little or no effect on unanesthetized dogs (15–17). In dogs anesthetized with thiopental or pentobarbital, intravenous injection of the local anesthetic agents rarely produces apnea and then only during very marked respiratory depression with thiopental or pentobarbital.

TABLE 2

SUMMARY OF THE EFFECTS OF THE INTRAVENOUS INJECTION OF THE LOCAL ANESTHETIC AGENTS INTO DOGS ANESTHETIZED WITH ETHER AT VARIOUS LEVELS OF ANESTHESIA

Anesthesia Level	Dose (mg./kg.)	Number of Dogs	Number of Dogs with Respiratory Apnea	Dose (mg./kg.)	Number of Dogs	Number of Dogs with Respiratory Apnea
	Cocaine			Procaine		
Light—muscle tremors, body movement (Stage II to plane 1 of Stage III)	3	1	0			
	5	5	1			
	15	1	1*			
	17	2	2*			
Moderate—dog completely relaxed, full abdominal and thoracic respiration (plane 2)	5	2	2*			
	7	1	1*			
Deep—paralysis of intercostal muscle (plane 3–4)	1.6	1	0	10	1	0
	2.5	2	0	13	1†	1
	4.0	4	1	15	1	1
	5.0	5	3	15	8†	7
	5.0	2†	2	20	1	1
	5.0	4‡	3	25	2†	2
	10	1	1			
	Lidocaine			Procaine Amide		
Deep—paralysis of intercostal muscles (plane 3–4)	2.5	3	1	15	1†	1
	5.0	3	2	30	1†	0
	5.0	2†	2	45	2†	2

* The dogs exhibited mild convulsions.

† Pure oxygen was administered, and after the onset of apnea, artificial respiration was used to maintain animals for vascular studies.

‡ Section of cranial nerves 9 and 10 was performed in order to abolish chemo-reflexes and presso-reflexes. In 3 animals the carotid sinus was stripped and sinus nerve cut.

Attempts to antagonize the apnea produced by local anesthetic drugs in dogs anesthetized with ether have been unsuccessful, as were similar attempts by Hulpieu and Cole (3), as long as the administration of ether was continued. Ten per cent carbon dioxide (with 90 per cent oxygen) administered by a positive pressure pump, along with the amount of ether previously required for maintenance of the anesthetic level, did not initiate spontaneous respiration. Intravenous adminis-

tration of 20 mg./kg. of pentylenetetrazol or nikethamide was likewise ineffective in stimulating respiration although this dose of pentylenetetrazol produced tremors and convulsive movements.

The hypotensive effect of local anesthetic drugs in dogs anesthetized with ether parallels the respiratory depression. When artificial respiration is instituted with continued administration of the previous concentration of ether, the hypotension may be maintained for 1 to 2 hours, affording an ideal preparation for the study of the mechanism of the hypotension.

Typical results from the autonomic test agents are presented in figures 3 to 5. All of the local anesthetic agents potentiated the pressor action of epinephrine. The effect of cocaine was more pronounced in this respect and is consistent with the well-known potentiation of the pressor effect of epinephrine by cocaine. The results also suggest that the local anesthetic drugs reduce compensatory reflex activity following

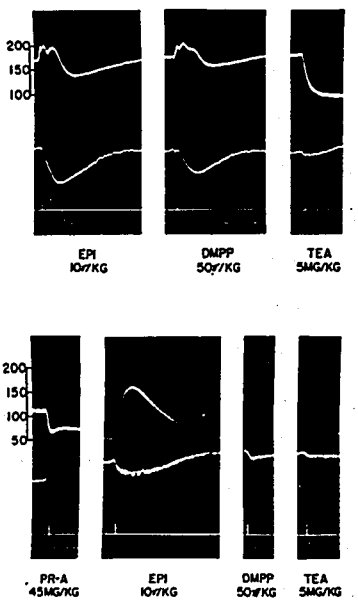

FIG. 5. Effect of intravenous epinephrine, 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP), and tetraethylammonium chloride (TEA) on carotid blood pressure (upper tracings) and jugular venous pressure (middle tracings) before and after procaine amide in a dog anesthetized with ether. No scale was provided for venous pressure inasmuch as changes were of primary concern.

the administration of epinephrine. All of the local anesthetic agents studied, except cocaine, decreased the ganglion stimulating action of DMPP. Ganglion blockade doses of TEA did not accentuate the hypotension produced by any of the local anesthetics. On the contrary, the administration of TEA resulted in a very slight increase in blood pressure of short duration. Typical results from TEA administration are shown in figure 5. A second or third injection of the local anesthetic agent into the dog anesthetized with ether never produced more than a slight transitory additional hypotensive response. Venous pressure recorded from the jugular vein was not altered appreciably (fig. 5). No significant dilatation was observed in those hearts examined during the hypotension.

Electrocardiograms indicated that injection of local anesthetic agents usually decreased the fast pulse rate of dogs anesthetized with ether to a rate near normal and decreased the rate of conduction, except in the case of cocaine, which produced consistent irregularities in rhythm which persisted for 1 or 2 minutes.

Discussion

The observed apnea produced by local anesthetic agents in dogs anesthetized with ether could conceivably result from (1) stimulation of afferent reflexes altering brain stem function, (2) direct depression of the respiratory center, or (3) paralysis of respiratory muscles by neuromuscular blockade. Afferent reflex involvement may be ruled out on the basis that vagal section and interruption of the special sensory pathways from the carotid and aortic areas do not alter the apnea. Other chemoreceptor mechanisms are unlikely, but possible. Since either ether or the local anesthetic agents may reduce neuromuscular transmission, it is conceivable that the combination of the two produces apnea on the basis of neuromuscular paralysis. The administration of pentylenetetrazol in doses sufficient to induce skeletal muscle tremors without resulting in any spontaneous respiratory effort indicates, but does not prove conclusively, that skeletal muscle paralysis is not the primary cause of apnea. An alternative explanation is an additive or synergistic depression of the respiratory centers by ether and the local anesthetic agent. This postulate is substantiated by the fact that procaine (18) or cocaine (19) administered to the medulla and lower brain centers of the rabbit produces respiratory arrest without evidence of stimulation. Although the depression of the respiratory centers would appear to be the best explanation of the apneic effects of the local anesthetic drugs in dogs anesthetized with ether, it is not possible to rule out neuromuscular blockade on the basis of the present experiments.

During the hypotension produced by the local anesthetic drugs in dogs anesthetized with ether, the administration of blockade doses of TEA, or additional amounts of the local anesthetic agents, did not further reduce blood pressure indicating that nerve-mediated vasomotor

tone had been lost. That a direct effect of the local anesthetic drug on the myocardium is responsible for the hypotension is unlikely. It is well known that the local anesthetic agents exert actions on cardiac muscle and, indeed, in the experiments described above, a decrease in rate of conduction was apparent from the electrocardiograms. However, venous pressure was not increased and direct inspection of the heart showed absence of dilatation which would indicate that contractibility was not altered appreciably and that the heart was not in failure. Furthermore, Wollenberger and Krayer (20) have reported that in heart-lung preparations of the dogs, cocaine or procaine produces heart failure in concentrations considerably higher than minimum lethal concentrations after intravenous administration to the intact animal. It should be emphasized that the dose of cocaine or procaine required to produce hypotension in the dog anesthetized with ether is less than the lethal dose in the intact animal. A reflex of the Bezold type may be dismissed on the basis that vagal section and denervation of carotid reflex pathways did not alter the hypotension. Partial blockade of the pressor action of DMPP by procaine, procaine amide and lidocaine suggests a component of ganglionic blockade with these 3 agents, although cocaine did not show such an effect. Accordingly, a combination of partial ganglionic blockade and central vasomotor depression appears to be the best explanation of the hypotension produced by procaine, procaine amide and lidocaine, but just a central effect for the action of cocaine.

Obviously, the local anesthetic drugs exert both overt stimulant and depressant actions on the central nervous system. The general anesthetic agents ether and chloroform antagonize the stimulant action of the local anesthetic drugs on the higher brain centers, but apparently may act in an additive or synergistic manner with the depressant action of the local anesthetic agents on the brain centers of circulation and respiration.

Summary

The lethal potencies (LD_{50}) of cocaine, procaine, lidocaine and pentylenetetrazol in mice are increased considerably when these agents are administered intravenously to animals deeply anesthetized with ether or chloroform. Death results primarily from respiratory failure, convulsions not being observed. Thiopental or pentobarbital anesthesia protect significantly against procaine and pentylenetetrazol toxicity but not against cocaine or lidocaine.

Cocaine, procaine, lidocaine or procaine amide, in doses which have little or no effect in unanesthetized animals, produce apnea in dogs anesthetized with ether. This apnea fails to respond to nikethamide, pentylenetetrazol, or forced inspiration of carbon dioxide. Removal of ether from the administered gas is apparently the best treatment for reversing the apnea.

In dogs anesthetized with ether the apnea produced by intravenous

administration of cocaine, procaine, lidocaine, or procaine amide is accompanied by a hypotension which persists for several hours, provided artificial respiration is maintained. With the latter 3 agents the hypotension is due in part to ganglionic blockade. Central depression of the vasomotor centers appears to be the primary factor with all 4 agents.

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