STUDIES OF VINETHENE AS AN ANESTHETIC AGENT [1]

O. S. Orth, H. C. Slocum, J. W. Stutzman and W. J. Meek

Departments of Physiology and Anesthesia, University of Wisconsin Medical School, Madison, Wisconsin

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

Introduction

Studies of the effect of vinethene on cardiac automaticity as measured by the response to the injection of various sympathomimetic drugs were begun in an attempt to compare this agent to cyclopropane, chloroform, and diethyl ether, as previously reported (1), (2). The plan was to determine the effects produced by adrenalin, cobefrin, and neosynephrin on the same animals, as had been done with the other anesthetic agents. Early difficulties encountered led to further studies. This report deals not only with cardiac effects during vinethene anesthesia, but also with its effects on blood pressure, gastro-intestinal activity, nervous stimulation, kidney function, and liver damage in the dog.

Procedure and Results

Vinethene, which consists of divinyl ether 96.5 per cent. and ethyl alcohol 3.5 per cent. with 0.01 per cent. phenyl-alpha-naphthylamine as a preservative, was used in all the studies here reported.

Each vinethene induction was made by the open drop technique. Then an endotracheal tube with an inflatable cuff was inserted. Unless otherwise indicated anesthesia in the dog was maintained by the closed system as previously employed (1), the animal being connected to the anesthetic reservoir by way of a soda-lime carbon dioxide absorber.

The anesthetic mixture was supplied from a large Tissot spirometer. Freshly opened vinethene which had not passed date of expiration was always used. Vaporization was brought about by passing pure oxygen through 60 to 75 cc. of vinethene, to make a total volume of 75 liters. The volume was kept constant by replacing oxygen as it was used metabolically. The animals were maintained in surgical anesthesia so that there was only partial intercostal paralysis. The concentration of vinethene in the spirometer required for such anesthesia was determined routinely with the iodine-pentoxide train and found to be 10 to 12 per cent. If the animals were premedicated, a concentration of 8 to 9 per cent. vinethene was found to be adequate. Each anesthetization was carried out by an experienced member of the department of anesthesiology.

[1] Aided in part by grants from the Wisconsin Alumni Research Foundation, and Merck & Co., Inc.

Cardiac Automaticity and Conduction

Electrocardiograms taken before anesthetization and again after 40 minutes' surgical anesthesia were compared for the first 10 animals for rate, rhythm, P-R interval, and height of QRS complex and T wave. As indicated in Table 1, surgical anesthesia with vinethene caused S-A

TABLE 1

ELECTROCARDIOGRAPHIC FINDINGS IN LEAD II IN THE DOG BEFORE (CONTROL) AND DURING DEEP SURGICAL VINETHENE, AFTER 40 MINUTES' EQUILIBRATION AGAINST A CONSTANT MIXTURE

Dog	S-A Rate		P-R Interval (Seconds)		QRS (Millivolts)		*T Wave (Millivolts)	
	Control	Vinethene	Control	Vinethene	Control	Vinethene	Control	Vinethene
1	130	175	0.11	0.09	3.2	3.2	+0.2	−0.6
2	107	200	.08	.09	3.4	3.0	−0.6, 0.4	−1.0
3	110	167	.11	.09	3.2	3.2	0.6	+0.8
4	110	150	.10	.08	3.2	2.6	1.0	−0.6, 0.4
5	185	225	.10	.10	2.0	1.4	0.2	0, 0
6	130	150	.10	.08	3.4	3.2	−0.2, 0.2	−0.3
7	136	180	.10	.09	2.6	2.6	1.2	0.4
8	115	180	.10	.08	1.6	1.8	0.2	−0.4
9	110	167	.12	.11	3.5	1.2	1.2	−0.1, 1.0
10	118	200	.11	.08	2.4	1.0	−0.1, 0.1	0.2
Averages	~~130~~ 125	179	0.103	0.089	2.85	2.32		

* Both negative and positive readings are indicative of a diphasic wave.

acceleration in every animal. In 8 of the 10 the P-R interval decreased by 0.01 to 0.03 second; in one instance there was no change, and in the other there was an increase of 0.01 second. The shortened P-R interval was undoubtedly due to the faster heart rate. The QRS complexes decreased in 6 of the 10 experiments by 0.2 to 2.3 millivolts. The T wave became more positive by 0.1 to 0.8 millivolt in 8 of the 10 anesthetizations and more negative by 0.2 millivolt in the other 2. Irregularities were not noted even in anesthesia that was prolonged for 2 to 3 hours.

The stimulating or sensitizing effect of vinethene on the automatic tissue of the dog's heart as measured by the occurrence of arrhythmias following a standard injection of adrenalin was determined as reported for other agents (1). Lead II electrocardiograms were taken throughout, and 40 minutes' minimal time was allowed for equilibration against the constant anesthetic mixture. Responses to the injection of equivalent pressor doses of neosynephrin and cobefrin also were observed. Toxic effects of marked weight loss, depression, and bloody diarrhea resulted in the death of 12 animals from a group of 17, and only 4 could be tested with all 3 sympathomimetic amines.

From Table 2 it will be seen that the control injection of 0.01 mgm. per kilogram of adrenalin in 5 cc. saline at the rate of 1 cc. per 10

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

seconds, which had been found previously as the desirable dose and rate of injection in studies of cardiac automaticity, caused A-V block in 9 experiments; A-V extrasystoles in 7; A-V rhythm in 9; ventricular extrasystoles in 7; slow ventricular rhythm in 2; and ventricular tachycardia in 2 experiments. Injection of the same dose of the amine into 12 animals under vinethene produced A-V extrasystoles in 2 instances and A-V rhythm in 4. When 11 of the dogs were premedicated with 1 mgm. morphine sulphate and 0.04 mgm. scopolamine per kilogram subcutaneously 45 minutes before induction, A-V block occurred once; A-V rhythm 5 times; ventricular extrasystoles and tachycardia once each and S-A acceleration 4 times.

TABLE 2

CARDIAC ARRHYTHMIAS RESULTING FROM INJECTION OF BLOOD PRESSURE RAISING DRUGS IN DOSES EQUIVALENT IN EFFECTIVENESS TO THE STANDARD ADRENALIN DOSAGE DURING DEEP SURGICAL VINETHENE ANESTHESIA AND IN VINETHENE ANESTHESIA FOLLOWING PREMEDICATION WITH MORPHINE 1.0 MGM./KG. AND SCOPOLAMINE 0.04 MGM./KG.

Procedure		Number of Animals	Equivalent Pressor Dosage to 0.01 Adrenalin	A-V block	A-V Extrasystoles	A-V Rhythm	Ventricular Extrasystoles	Slow Ventrical Rhythm	Ventricular Tachycardia	S-A Tachycardia
			mgm./Kg.							
Adrenalin	Control	13	0.01	9	7	9	7	2	2	0
	With vinethene	12	0.01	0	2	4	0	0	0	0
	Premedication with vinethene	11	0.01	1	0	5	1	0	1	4
Neosynephrin	Control	6	0.05	5	1	0	1	0	1	0
	With vinethene	5	0.05	0	2	2	1	0	0	0
Cobefrin	Control	5	0.025 to .0375	4	5	3	1	2	1	0
	With vinethene	5	0.025 to .0375	0	0	2	0	0	0	2

Control injection of the comparable pressor dosage of neosynephrin (0.05 mgm. per kilogram) in 6 animals produced A-V block 5 times; and A-V extrasystoles, ventricular extrasystoles, and ventricular tachycardia once each. In 5 of the animals anesthetized with vinethene, injection of neosynephrin was followed by 2 instances each of A-V extrasystoles and A-V rhythm and one of ventricular extrasystoles. Control injection of cobefrin (0.025 to 0.0375 mgm. per kilogram) into 5 animals gave results comparable to those with adrenalin. A-V block occurred 4 times; A-V extrasystoles 5; A-V rhythm 3; slow ventricular rhythm 2; and ventricular extrasystoles and tachycardia once each. Injection under vinethene elicited A-V rhythm and S-A tachycardia twice each.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

It is evident that vinethene gave no evidence of having sensitized the heart to these drugs.

Blood Pressure and Blood Oxygen

Blood oxygen determinations were made by the van Slyke-Neill manometric method as modified by Shaw and Downing for diethyl ether (3). Duplicate analyses were done routinely. The first sample under vinethene was never drawn until at least 40 minutes of equilibration against the constant mixture. Depth of anesthesia was then varied by open drop administration and blood pressure recorded by the usual method of arterial cannulation. Blood samples were drawn at various planes of anesthesia. Figure 1 indicates blood pressure decreased with

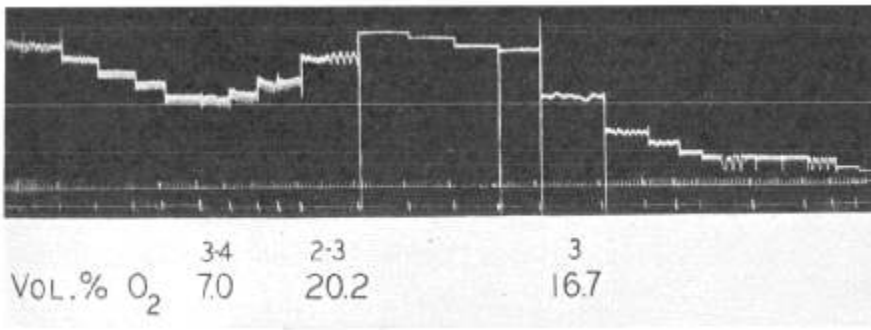

FIG. 1. Blood pressure variation with alteration in depth of vinethene anesthesia. Upper numerals are the planes of surgical anesthesia as given in Table 3. Vol. per cent. O_2 are averages of duplicate analyses of blood oxygen content.

TABLE 3

VOLUMES PER CENT. OF OXYGEN IN ARTERIAL BLOOD FROM DOGS BEFORE AND DURING VINETHENE ANESTHESIA MAINTAINED BY OPEN DROP TECHNIQUE. ALL FIGURES ARE AVERAGES OF DUPLICATE ANALYSES.

Dog No.	Arterial Blood Oxygen Content		Plane of Surgical Anesthesia*	Remarks
	Control	Vinethene		
	Volumes Per cent.	Volumes Per cent.		
T	14.6	21.4	2	
U	21.0	16.8	3	
V	20.7	19.6	3	
W	18.5	16.7	3	
X	15.2	9.8	3—4	Anesthesia deepened until running movements abolished
Y	21.8	7.0 20.2 16.7	3—4 2—3 3	Anesthesia deepened until running movements abolished, then lightened, and again deepened slightly

* Varying from no intercostal involvement (plane 2) to complete intercostal paralysis (plane 4).

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

increased depth of anesthesia. Table 3 shows that adequate oxygenation was maintained under vinethene except when the depth of anesthesia was carried to complete intercostal paralysis which was done with dogs X and Y to study running movements and blood pressure effects.

Running Movements

In each of 108 surgical vinethene anesthetizations to 46 dogs, there was some degree of aberrant muscular movement, which ranged from twitches to coordinated activity of all 4 extremities, simulating running movements. Not until there was complete intercostal paralysis could these be eliminated in all animals. The activity usually disappeared in the fore limbs before the hind limbs. This type of coordinated muscular response has never occurred in over 400 anesthetizations with chloroform, cyclopropane or diethyl ether. In 4 of 13 animals premedicated with morphine-scopolamine such responses also were noted under vinethene.

In an attempt to determine the site of stimulation for such muscular activity 4 dogs were anesthetized with vinethene and then decerebrated by the "bloodless" method of Sollmann (4). Transection of the brain stem at the level of the corpora quadrigemina was verified by examination after formalin fixation. The aberrant movements continued in 3 of the 4 cases. Further localization was evident when 1 of 3 animals in which the spinal cord had been transected at T-10 had continuation of the movements in the hind limbs. In this latter group there was a 5-day interval between cord transection and vinethene administration. Evidently the stimulation which gives these movements is in the cord itself.

Gastro-intestinal Activity

Two dogs were prepared with Thiry and Thiry-Vella loops of the jejunum for recording activity by the balloon-mercury-manometer and bolus propulsion methods. Gastric activity was determined simultaneously by means of a balloon-water-manometer-tambour system.

The unpremedicated dogs were trained to lie on the table unrestrained while breathing through a mask which could be coupled to the spirometer containing the vinethene-oxygen mixture. In this manner records could be obtained with a minimum of excitement during induction. They were then maintained at any desired plane of surgical anesthesia. The animals were anesthetized not more than once in two weeks for periods varying from 25 to 75 minutes.

Gastric tonus increased slightly with surgical anesthesia. Occasionally after discontinuing the agent there was an abrupt fall of tonus, which soon returned to the preanesthetic level. Gastric contractions were inhibited completely by anesthesia. Recovery began in 1 to 5 minutes after discontinuing the vinethene but usually it was not com-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

plete in less than one hour. An esophageal cuff around the tube to the stomach balloon facilitated the aspiration of the profuse salivary secretion produced by vinethene. With this procedure the usual retching and vomiting during recovery was prevented, thus permitting studies in this period.

There was complete inhibition of propulsive and non-propulsive movements of the intestine and a marked loss of tonus in all planes of vinethene anesthesia. Thiry-Vella loops that normally closely accommodated sponge rubber boluses which measured 1 × 2 cm. would readily permit the introduction of the middle finger. When a bolus was introduced immediately before induction, it did not reappear until several minutes after the anesthetic was discontinued. For more than half an hour after anesthetization propulsion times were 1 to 5 minutes longer than the controls. Recovery of non-propulsive movements began within 4 minutes and was complete within 10 minutes after cessation of the administration of vinethene. When the animals were premedicated with morphine-scopolamine, non-propulsive activity of the intestine continued until the third plane of surgical anesthesia was reached.

Kidney Function

Oliguria or anuria occurred in 13 administrations to 5 dogs in which normal urine flows had been determined before anesthetization, as had

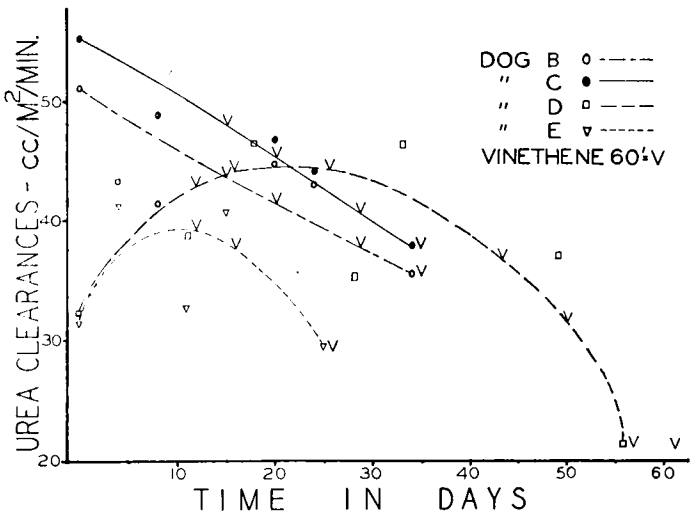

FIG. 2. Effect of vinethene on kidney function as determined by maximal urea clearances. Anesthesia was given for one hour each week, oxygen being used as the diluent for the agent. Each value is the average of clearances for three 20-to-30-minute periods. Dogs B and C died of acute yellow atrophy.

been observed previously with the other agents studied. The effects of vinethene on kidney function, as measured by urea clearance tests, were

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

determined on 4 dogs, employing the technique for maximal clearances as previously used (5). The control clearances of at least 3 sets of 3 periods each averaged 42.6 cc./M.²/minute. The average of the final set obtainable from the animals was 32.0 cc./M.²/minute. Anurias of several days' duration following the sixth and seventh administrations prevented further determinations in dog D. It may be noted from Fig. 2 that the smoothed curve for each animal declines progressively. Using the clearance method vinethene is thus shown to interfere with kidney function.

Dog F was followed before and after each of 7 hourly chloroform anesthetizations given at intervals of a week. The control urea clearances averaged 58.3 and those following anesthetization 57.2 cc./M.²/minute.

Liver Pathology

Eighteen rats in two different groups were used to study the effects of vinethene on the liver. Animals of each group were killed without any anesthesia in order to obtain control liver sections. The remaining animals were anesthetized from 1 to 16 times for periods of 10, 20, or 30 minutes every third day, after which liver sections were also obtained. The only significant difference between the control liver sections and those obtained from the vinethene-anesthetized animals was increased activity of the von Kupffer cells in some of the anesthetized animals. These results were quite different from those found when the dog was used as the experimental animal.

After 7 dogs in the cardiac series died in their pens 24 to 48 hours following anesthetizations given at least 3 days apart, a controlled pathologic study of vinethene toxicity was begun. On these dogs liver biopsies were obtained at the first anesthetization for control sections. Additional periods of vinethene of various duration and at various intervals were given, then samples obtained again at biopsy or post mortem. Table 4 shows the results. No abnormality was evident in any of the control sections. Of the animals given vinethene for 30-minute periods none showed any pathologic effects at the end of a week, but at the end of the second week degeneration was present. These administrations were by open drop technique, as recommended by the Council on Pharmacy and Chemistry of the American Medical Association in its acceptance of vinethene (6).

There was marked liver involvement after 3 anesthetizations in the animals receiving vinethene for an hour each week. These administrations were with approximately 88 per cent. of oxygen in addition to the required vinethene. The terminal picture and pertinent post mortem findings for dog E are:

In great respiratory difficulties last 2 days, very weak, unable to move hind legs, unsuccessful in attempts to drink water. Anuria existed for the 2 days ante mortem. Bleeding time prolonged to 10–12 minutes.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

TABLE 4

PATHOLOGIC FINDINGS IN DOGS AFTER VINETHENE ANESTHETIZATIONS. ADMINISTRATION OF VINETHENE AS DESCRIBED IN TEXT

Animal	Vinethene Anesthetizations			Liver Pathology	Other Pathology	Remarks
	Number of Administrations	Duration of Each Administration	Sequence of Administrations			
		min.				
III	1	60	Once	None	Not examined	Biopsy section normal. Killed 7 days after first administration
E	3	60	Every 7 days	Less extensive necrosis than B, C and D with some definite hepatic proliferation in attempts at regeneration	Kidneys—as for B, C and D Spleen—as for B, C and D	See text for typical post mortem findings (*) Weight change 17.1 to 15.1 kilograms
IV	3	60	Every 7 days	Central zonal necrosis	Not examined	Biopsy studies normal. Killed 7 days after last vinethene. Wt. change 9.5 to 7.8 kilo.
B	4	60	Every 7 days	Acute yellow atrophy	Kidney—albuminuria, moderately severe tubular cloudy swelling with obstruction and glomerular distention with membrane thickening and proliferation of cells of tufts Spleen—corpuscles atrophic, congestion edema, patchy necrosis with sinusoids standing out prominently	Died 2 days after fourth vinethene, death preceding by 3 hours that of litter mate C Post mortem findings as for E in text of paper
C	4	60	Every 7 days	Acute yellow atrophy, damage more severe than for litter mate B	Heart—necrosis of fibers, destruction of nuclei in wide areas. Other organs as for B.	Died 2 days after fourth vinethene, 3 hours after that of her litter mate B

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

TABLE 4—(*Continued*)

Animal	Vinethene Anesthetizations			Liver Pathology	Other Pathology	Remarks
	Number of Administrations	Duration of Each Administration	Sequence of Administrations			
		min.				
D	7	60	Every 7 days	Diffuse severe vacuolar degeneration	Kidney—more congestion, glomerular distention and cloudy swelling of tubules than B. Glomeruli show endothelial proliferation and early adhesions. Spleen—as for B and C	One week omitted in vinethene administration after third anesthetization
J	2	30	Every 3½ days	None	Not examined	Control biopsy normal. Biopsy at 5th day (after 1) and 8th day (after 2 anesthetizations)
K	5	30	Every 3½ days	None	Not examined	Control biopsy normal. Biopsy at 14th day (after 4) and 18th day (after 5 anesthetizations)
H	7	30	Daily	Normal except for marked cloudy swelling and slight atrophy at central areas	Kidney—cloudy swelling minimal, albuminuria pronounced	Biopsy control normal. Killed on 8th day. Weight change from 8.1 to 7.2 kilograms
G	14	30	Daily	Marked diffuse fatty degeneration, most marked in the central zones	Not examined	Control biopsy normal. Killed on 18th day. Weight change from 9.2 to 5.8 kilograms

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

Abdominal cavity contained ± 700 cc. of a thin, hemorrhagic fluid. Liver greatly congested, quite friable, with a marked greenish-yellow cast. Gall bladder greatly distended, containing 70–75 cc. reddish bile. Kidneys congested, differentiation and markings poor. Urinary bladder constricted into a solid muscular mass. Spleen distended. Mesenteric nodes enlarged and hemorrhagic. Petechial hemorrhages from duodenum downward over small and large intestine, particularly in the colon. Internally the G-I tract was coated with a pasty, bloody mucus from duodenum to rectum.

Lungs with pneumonic patches. Mediastinal nodes enlarged and hemorrhagic. Heart appeared normal.

These findings varied only in degree also for dogs B, C, and D. Figure 3 shows the central zonal necrosis commonly present and Fig. 4 is representative of the acute yellow atrophy found in dogs B and C.

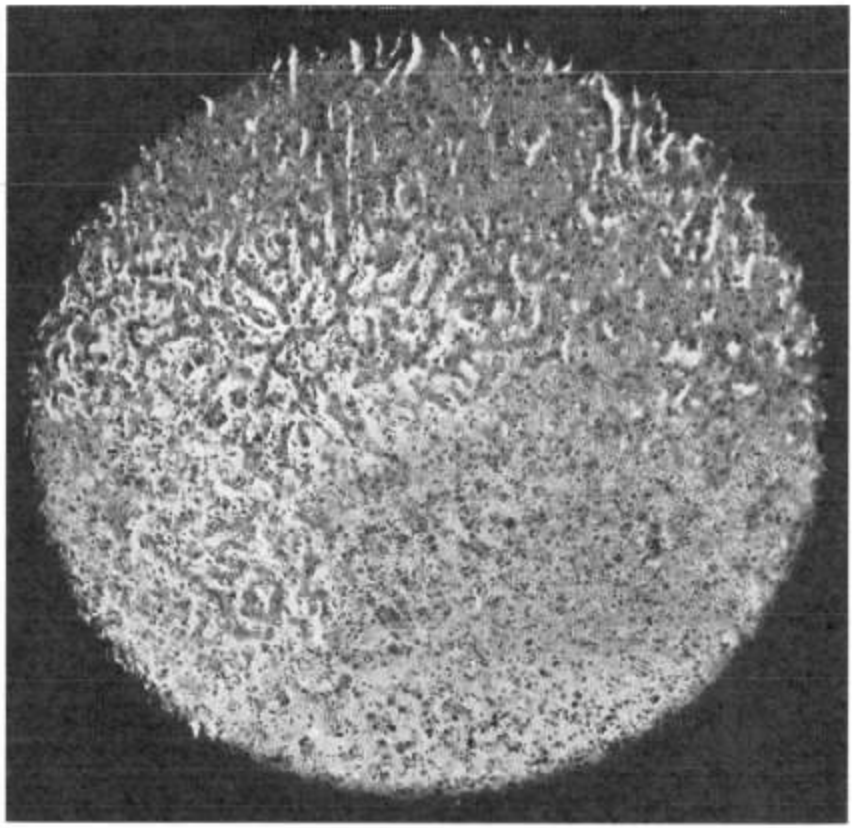

FIG. 3. Severe central zonal necrosis of the liver produced in dog E by one hour of vinethene anesthesia each week for three weeks.

Due to its known toxic action on the liver, chloroform was used for comparison with vinethene. After hourly anesthetizations of chloroform by open drop technique once weekly for 7 periods a biopsy re-

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

vealed a mild vacuolar degeneration. Administration was not continued since this was the greatest number of similarly given vinethene anesthetizations required to kill any animal.

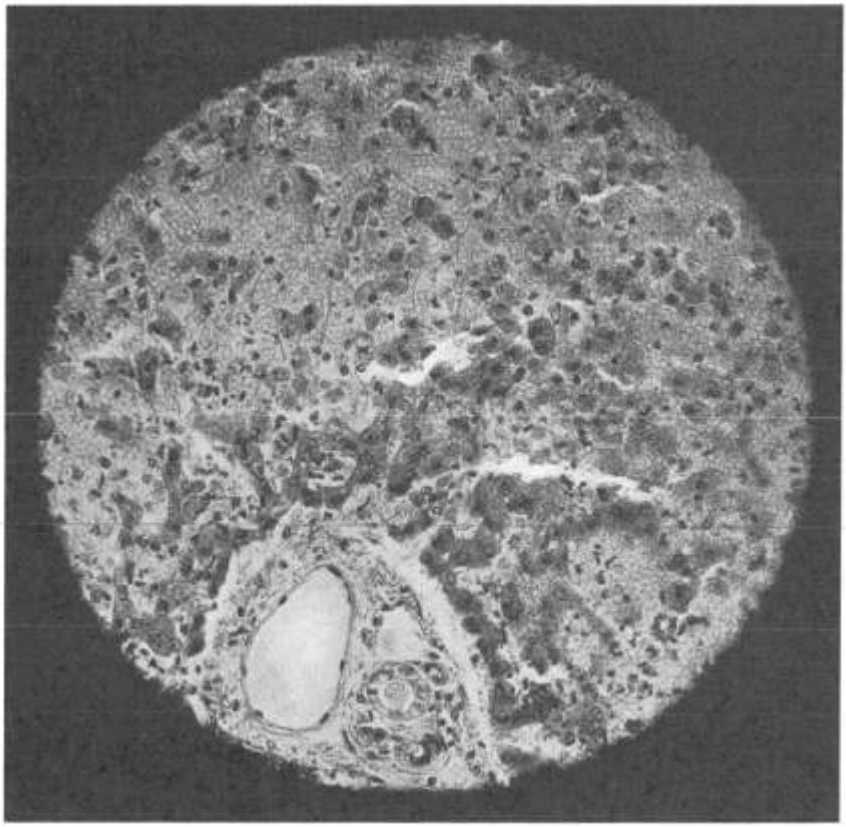

FIG. 4. Acute yellow atrophy of the liver produced by four vinethene administrations of one hour each at weekly intervals to dog B.

At the suggestion of Dr. Hans Moliter diethyl ether also was used for comparison. After control biopsies 2 animals were anesthetized for 6 one-hour periods at intervals of a week and biopsies taken again. No significant pathologic changes were found. In previous studies (2) 5 animals had received at least 5 ether and 4 chloroform anesthetizations each without any of the weight loss, depression, or other symptoms so obvious after only a few anesthetizations with vinethene.

DISCUSSION

From the results of tests with adrenalin, cobefrin, and neosynephrin during vinethene anesthetization it is evident that this agent does not seriously affect cardiac automaticity, in this respect being more similar to diethyl ether than chloroform or cyclopropane as previously studied

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

(1, 2). Failure of lower centers to be made automatic by the action of adrenalin on the heart is interpreted to mean a lack of sympathetic stimulation from higher centers, which has been demonstrated recently to occur with cyclopropane (7). As previously noted with cyclopropane, morphine-scopolamine premedication did not alter the automaticity of the heart significantly.

The marked reduction in the P-R interval with the accompanying average increase of almost 50 beats per minute in heart rate is explainable on the basis of inhibited vagal effects, such as is known to occur with diethyl ether. Decreases in QRS voltage and a similar change in the majority of cases with respect to the T wave may be indicative of some effects on the properties of conductivity and irritability in the myocardium and conducting system.

Anoxemia has been considered necessary before pathologic effects of vinethene occurred (8), and the delayed onset of hepatic damage when the agent was administered with high oxygen atmospheres has been noted (9). This led to our use of pure oxygen as a diluent. The routine employment of the carbon dioxide absorption technique, with endotracheal intubation providing for a patent airway, was considered a further safeguard against alteration of normal blood gases. With these precautions and adequate respiratory exchange, determinations of blood oxygen would not seem necessary but were done to prevent any explanation of the results as due to anoxemia. Routine duplicate analyses agreed within less than 0.5 volumes per cent. As a check on the technique of transfer to the modified Hempel pipette, control samples were analyzed by the routine method for blood oxygen as well as by the modified procedure.

That blood oxygen was adequate is indicated from Table 3. Only when the animals purposely were carried into the lower levels of surgical anesthesia in an attempt to abolish running movements or study blood pressure effects (dogs X and Y) was there a significant lowering of blood oxygen. This deep plane of anesthesia was never permitted in any routine experiment.

Due to the earlier disappearance of the running movements from the fore limbs, in contra-distinction to the accepted order of depression of the central nervous system in anesthesia, these movements were thought to be due to stimulation of lower centers or even to cord irritation. Their presence in all but one of the animals following separation of the cortex and basal ganglia from the cord, and their occurrence in the hind limbs of one of the animals with a complete cord transection at T-10, substantiate this opinion.

The possibility of these movements being caused by a breakdown of vinethene to related furan compounds seems quite possible, in view of the reports of the action of these substances by Johnston and by Henderson and Smith (10), (11).

As Burstein has shown there is a loss of intestinal tonus in all planes

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

of surgical anesthesia with vinethene (12). Our practically constant finding of a rise in gastric tonus was anticipated in view of the spontaneous flow of vomitus frequently observed during surgical anesthesia and often beginning 15 to 20 minutes after induction. Persistence of non-propulsive intestinal movements in the premedicated animals in light vinethene anesthesia corresponds to the results of Youmans et al. with cyclopropane (13). Absence of propulsive activity has not been reported previously.

Histologically the kidneys showed albuminuria, moderately severe cloudy swelling of the tubules, glomerular congestion, endothelial proliferation and early adhesions. It will be noted that in each of the 4 dogs on which urea clearances were determined there was a progressive decrease in kidney function after the first or second weekly period of an hour of vinethene. This is in marked contrast to cyclopropane, diethyl ether, and chloroform, which had been found not to alter kidney function (5). The clearances in dog F following chloroform did not differ essentially from the control values.

As previously reported by Molitor (14) liver damage after vinethene is not demonstrated in the rat. In our series of animals we likewise failed to find any effects with vinethene on this species. This seems explainable due to the marked power of regeneration of the liver in this animal.

Our controlled pathologic studies on the dog agree with the observations of Goldschmidt et al. (15) that there is a minimal duration of vinethene anesthesia necessary to elicit liver damage. This is evident from the lack of any severe effects with 7 daily administrations but fatty degeneration after 14 days. Since dog E died after 3 hourly periods at intervals of a week while dog D withstood this agent for 7 weeks before dying, it seems impossible to predict which animal will show an early response and which will be more resistant.

It is our belief that central zonal necrosis can be produced routinely by vinethene administration. It has been proved that this effect is not due to anoxemia. Since 7 anesthetizations with chloroform caused only mild vacuolar degeneration of the liver in one animal and since the 5 other dogs subjected to numerous diethyl ether and chloroform anesthetizations administered by the same technique and to the same depth of anesthesia showed no ill effects, the more marked pathology following vinethene is attributed to the greater toxicity of this agent.

There have been reported 5 clinical post mortems following the use of vinethene, 3 of which showed liver damage (15), (16). Each author has discounted the responsibility of vinethene for such pathology. In the two cases with liver damage reported by Goldschmidt et al. one subject received only 1 hour and 39 minutes, and the other 2 hours and 40 minutes of vinethene. In a later publication by the same workers it is stated, "There have been no instances of liver necrosis in the entire series" (17). It would seem that such a conclusion was in error. With

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

a new agent every blame should be placed on it until it has been proved definitely *not* to be responsible.

SUMMARY

1. Vinethene does not significantly affect cardiac automaticity in the dog, as tested with equivalent blood pressure-raising doses of adrenalin, cobefrin, and neosynephrin.

2. Anoxemia did not occur in the planes of surgical anesthesia routinely used in this study.

3. Aberrant twitches to running movements occurred in all vinethene anesthetizations. It is believed that they are due to stimulation of the central nervous system below the level of the corpora quadrigemina. In the majority of instances they were prevented by premedication with morphine-scopolamine.

4. Vinethene causes increased gastric and decreased intestinal tonus. Propulsive and non-propulsive movements of the jejunum are inhibited by surgical vinethene anesthesia.

5. Vinethene caused a progressive decrease in kidney function as measured by urea clearances.

6. In the dog vinethene has been found to produce central zonal necrosis of the liver and to be more toxic in this respect than chloroform. From post mortem reports in the literature it is suggested that a similar relationship exists in the human.

We wish to thank the Department of Pathology for inspection and confirmation of diagnoses of the histologic sections.

REFERENCES

1. Meek, W. J.; Hathaway, H. R., and Orth, O. S.: The Effects of Ether, Chloroform, and Cyclopropane on Cardiac Automaticity, J. Pharmacol. & Exper. Therap. **61**: 240 (Nov.) 1937.
2. Orth, O. S.; Leigh, M. D., Mellish, C. H., and Stutzman, J. W.: Action of Sympathomimetic Amines in Cyclopropane, Ether, and Chloroform Anesthesia, J. Pharmacol. & Exper. Therap. **67**: 1 (Sept.) 1939.
3. Shaw, J. L., and Downing, V.: Determination of Oxygen in Blood in Presence of Ether by Modification of van Slyke-Neill Technique, J. Biol. Chem. **109**: 405 (April) 1935.
4. Sollmann, T.: A Method of Bloodless Decerebration, J. Pharmacol. & Exper. Therap. **23**: 153 (March) 1924.
5. Orth, O. S., and Stutzman, J. W.: Constancy of Urea Clearances in Dogs Following Surgical Anesthesias with Cyclopropane, Ether and Chloroform, Proc. Soc. Exper. Biol. & Med. **39**: 403 (Nov.) 1938.
6. Council on Pharmacy and Chemistry, J. A. M. A. **109**: 658 (Aug. 28) 1937.
7. Allen, C. R.; Stutzman, J. W., and Meek, W. J.: The Production of Ventricular Tachycardia by Adrenalin in Cyclopropane Anesthesia, Anesthesiology **1**: 158 (Sept.) 1940.
8. Leake, C. D.; Knoefel, P. K., and Guedel, A. E.: Anesthetic Action of Divinyl Oxide in Animals, J. Pharmacol. & Exper. Therap. **47**: 5 (Jan.) 1933.
9. Goldschmidt, S.; Ravdin, I. S., and Lucke, B.: Anesthesia and Liver Damage; Protective Action of Oxygen Against Necrotizing Effect of Certain Anesthetics on Liver, J. Pharmacol. & Exper. Therap. **59**: 1 (Jan.) 1937.
10. Johnston, J. F. A.: On Anesthetic Action of Furan, J. Pharmacol. & Exper. Therap. **43**: 85 (Sept.) 1931.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024

11. Henderson, V. E., and Smith, A. H. R.: Anesthetic Effects of Some Furan Derivatives, J. Pharmacol. & Exper. Therap. 57: 394 (Aug.) 1936.
12. Burstein, C. L.: Effect of Divinyl Oxide on Intestinal Activity in Vivo, Proc. Soc. Exper. Biol. & Med. 39: 396 (Nov.) 1938.
13. Weisel, W.; Youmans, W. B., and Cassels, W. H.: Effect on Intestinal Motility of Cyclopropane Anesthesia Alone and After Morphine-Scopolamine Premedication, J. Pharmacol. & Exper. Therap. 63: 391 (Aug.) 1938.
14. Molitor, H.: Some Pharmacological and Toxicological Properties of Vinyl Ether, J. Pharmacol. & Exper. Therap. 57: 274 (July) 1936.
15. Goldschmidt, S.; Ravdin, I. S.; Lucke, B.; Muller, G. P.; Johnston, C. G., and Ruigh, W. L.: Divinyl Ether, Clinical and Experimental Studies, J. A. M. A. 102: 21 (Jan. 6) 1934.
16. von Brandis, H. J.: Vergleichende Untersuchungen über die Toxizität des Vinethens, Schmerz Narkos-Anaesth. 8: 84 (Oct.) 1935.
17. Ravdin, I. S.; Eliason, E. L.; Coates, G. M.; Halloway, T. B.; Ferguson, L. J.; Gill, A. B., and Cook, T. J.: Further Experiences with Vinethene Anesthesia, Anesth. & Analg. 17: 176 (May–June) 1938.

SCIENTIFIC PROGRAM OF REGULAR MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS

745 FIFTH AVENUE, NEW YORK CITY

December 12, 1940—8 P.M.

1. The Fire and Explosion Hazard in Anesthesia: Report of a Clinical Investigation Based on Known Cases—30 minutes.

   By

   Barnett A. Greene, M.D., Chairman, Committee on Anesthetic Hazards. Director, Department of Anesthesia, Prospect Heights Hospital, Brooklyn, New York.

2. The Elimination of Explosive Anesthetic Mixtures by the Addition of Helium (Demonstration)—40 minutes.

   By

   George J. Thomas, M.D. and G. W. Jones (by invitation), Bureau of Mines, Pittsburgh, Pennsylvania.

3. A Report of the Committee on Hospital Research—50 minutes.

   By

   Professor J. Warren Horton (by invitation), Massachusetts Institute of Technology. Discussion to be opened by Everett A. Tyler, M.D., Philadelphia, Pennsylvania and H. Sidney Newcomer, M.D. (by invitation), New York City.

Downloaded from http://asa2.silverchair.com/anesthesiology/article-pdf/1/3/246/244312/0000542-194011000-00002.pdf by guest on 10 April 2024