EFFECT OF MORPHINE AND CYCLOPROPANE UPON CARDIOVASCULAR FUNCTIONS IN THE DOG

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THE CARDIOVASCULAR effects of cyclopropane-oxygen anesthesia without preanesthetic agents have been reported (1).

The purpose of the present investigation was to determine the change in the above effects owing to the subcutaneous administration of morphine sulfate (3 mg./kg.) about 35 minutes before the inhalation of cyclopropane was begun. As stated previously (2), this dose of morphine was selected on the basis of personal experience, as it tranquilizes dogs without depressing respiratory functions. Although this dose seems exceedingly large when compared with the human dose, it is smaller than that used by many investigators. Schmidt and Livingston (3) considered any dose up to 10 mg./kg. a small dose, and 75 to 100 mg./kg. a moderately large dose. Doses of 20 to more than 100 mg./kg. have been used (4–7). Issekutz (8) used a dose identical with ours.

The fact that morphine alone may initiate cardiac irregularities in dogs is well known, as is the fact that cyclopropane after morphine accentuates the irregularities. Eyster and Meek (9) found a slow heart rate and either an S-A or A-V block, with ectopic beats in some of their dogs. McCrea and Meek (10) found that etherization abolished the effect of morphine on the dog's heart.

Robbins and his coworkers emphasized the augmentation of morphine effects by cyclopropane (11) and also the abolition of such effects by ether. They used 5 to 8 mg./kg. of morphine. Amobarbital, likewise, was reported to abolish the irregularities produced by morphine and cyclopropane (12). The slow, irregular heart after morphine and cyclopropane was accompanied by low blood pressure (13). It was suggested long ago that the type of preanesthetic medication was important not only in dogs but also in man (14).

Morphine produces effects similar to parasympathetic stimulation (15) and thus slows the heart rate. Cyclopropane augments the vagal effect (11, 15), and probably increases the excitability of the automatic tissue of the heart (16).

Our experience is in agreement with earlier investigators in that in 6 of our 13 dogs we found cardiac irregularities, consisting of partial or complete A-V block, nodal rhythms, and premature ventricular beats.

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Methods

Mongrel dogs were used. Morphine was injected subcutaneously. After the usual response (vomiting or defecation or both) was completed, a sample of blood was drawn to serve as a nitrogen blank for cyclopropane determinations. Then a tracheal cannula was inserted under local anesthesia (2–3 cc. of 2 per cent procaine hydrochloride, intradermally).

About 35 minutes after the administration of morphine the inhalation of cyclopropane-oxygen was begun. The bag of the anesthesia machine (Heidbrink Kinet-O-Meter) was filled with 50 per cent cyclopropane and 50 per cent oxygen before it was connected with the tracheal cannula. Usually within one and one-half to two minutes, after a very smooth induction, muscular relaxation was noted. At this time, the bag was flushed and the cyclopropane lowered to 20 per cent (gauge set at 50 cc./min.). It was kept here or below throughout the experiment and the flow of oxygen was kept at 200 cc./min.; therefore, the total flow of oxygen and cyclopropane combined was about 250 cc./min. When the bag became distended it was partially emptied. Less cyclopropane was needed to maintain the animals in light surgical anesthesia after morphine than in unpremedicated dogs. This was evident by the concentration of cyclopropane in the arterial blood. In dogs not receiving premedication the range of cyclopropane concentration in arterial blood was 9.46 to 29.02 (intentionally) with a mean of 19.70 $\pm$ 0.60 mg./100 cc., and a standard deviation of 7.02. In the series after morphine premedication, the range was 4.14–15.15, with a mean of 9.87 $\pm$ 0.15 mg./100 cc. and a standard deviation of 1.35.

All the dogs breathed spontaneously throughout the period of observation. We considered the pulmonary ventilation satisfactory since there was not a marked increase in either heart rate or mean arterial blood pressure. One of the important indications of an increase in carbon dioxide tension (owing to inadequate pulmonary ventilation) is a rise in both systolic and diastolic blood pressures (17–23), under anesthesia or in unanesthetized animals.

The left external jugular vein was catheterized for injection of dye (T-1824). The left femoral artery was connected with the cuvette oximeter and strain gauge by means of an indwelling needle. When not recording, 0.9 per cent sodium chloride containing 0.1 mg. per cent of liquaemin (heparin) was permitted to drip slowly into the artery from a pressure bottle. The method of recording, injecting dye, calibrating the cuvette oximeter and measuring the dye curves for calculation of cardiac output has been described by Nicholson and Wood (24). This method was used by the authors. The method used for determination of cyclopropane concentration in arterial blood was suggested by Dr. Kety. Details of the method have been published (1). Electrocardiographic tracings were recorded, using lead II.

Six successive determinations of cardiovascular functions were

TABLE 1

RESULTS OF A SERIES OF 6 SUCCESSIVE DETERMINATIONS OF CARDIAC OUTPUT, GIVING RANGE AND MEAN VALUES FOR EACH CARDIOVASCULAR FUNCTION

Dye Injection	Cardiac Index (liters/min./m.²)	Blood Pressure (mm. Hg)			Peripheral Resistance		Heart Rate (beats/min.)	Stroke Index (cc./beat/m.²)	Concentration of Cyclopropane in Arterial Blood		Amount of Dye Injected (mg.)	Duration of Cyclopropane Anesthesia (min.)	Number of Observations
		Systolic	Diastolic	Mean	Bazett Formula	Dynes/sec./cm.⁻⁵			Vols./100 cc.	Mg./100 cc.			
1. (Range)	1.21–2.39	105–181	34–96	57–121	91–268	4,414–12,295	46–98	17–33	4.31–7.78	8.09–14.61	6.99–9.57	27–34	
(Mean)	1.81	160	74	102	181	7,746	69	27	5.39	10.11	8.28	30	12
2. (Range)	1.41–3.06	124–190	50–103	74–125	91–266	4,381–9,624	46–98	18–38	4.06–7.74	7.63–14.52	7.73–10.21	37–44	
(Mean)	1.99	163	72	102	162	6,980	70	29	5.35	10.04	9.15	40	13
3. (Range)	1.53–3.91	113–193	40–95	64–128	58–224	2,795–9,360	46–101	22–49	4.38–8.09	8.22–15.15	4.51–10.07	46–56	
(Mean)	2.43	165	71	102	138	5,968	70	35	5.57	10.45	8.98	50	13
4. (Range)	1.68–3.91	141–198	48–104	82–135	71–241	3,321–8,729	46–101	21–55	2.98–8.06	5.60–15.12	6.87–10.38	55–66	
(Mean)	2.52	166	72	103	132	5,719	71	36	5.36	10.06	8.89	60	13
5. (Range)	1.80–3.51	136–204	58–104	85–137	73–228	3,420–8,449	46–101	24–52	3.64–5.91	6.83–11.09	9.09–10.27	64–78	
(Mean)	2.58	171	72	105	132	5,665	71	37	5.04	9.46	9.60	69	11
6. (Range)	1.73–4.11	138–204	53–98	82–138	60–199	2,889–7,577	46–109	22–72	2.21–6.05	4.14–11.36	6.13–9.80	73–87	
(Mean)	2.80	173	68	103	119	5,206	72	40	4.80	9.02	8.67	79	12

made on each animal within one-half to one and one-half hours after cyclopropane administration was begun. Although one bout of emesis or defecation or both occurred within 5 to 10 minutes after the administration of morphine, the first observations on cardiovascular functions were made 50 to 60 minutes later, and the above side actions of morphine were considered in no way responsible for any effects noted.

Results

Seventy-eight determinations were made on 13 dogs, but in 4 cases there was difficulty with dye injection or recording, so the report is based on 74 satisfactory observations.

The mean cardiac index was 2.35 ± 0.08 liters/m.^{2}/min. with a standard deviation of 0.68.

The mean systolic blood pressure was 166 ± 2 mm. of Hg, with a standard deviation of 19.

The mean diastolic blood pressure was 72 ±1 mm. of Hg, with a standard deviation of 12.

The mean of the mean blood pressures was 103 ± 1 mm. of Hg, with a standard deviation of 13.

The mean total peripheral resistance was 6,222 ± 226 dynes/sec./cm.$^{-5}$, with a standard deviation of 1,940. By Bazett's formula the mean total peripheral resistance was 144 ± 6, with a standard deviation of 50.

The mean heart rate was 70 ± 2 beats per minute, with a standard deviation of 20.

The mean stroke index was 34 ± 1 cc./beat/m.^{2}, with a standard deviation of 9.

The mean concentration of cyclopropane in arterial blood was 9.87 ± 0.15 milligrams per cent with a standard deviation of 1.35. In terms of volumes per cent the mean concentration of cyclopropane was 5.26 ± 0.11, with a standard deviation of 0.97.

The mean concentration of dye injected per observation was 8.92 ± 0.12 mg. with a standard deviation of 1.35.

Cardiac irregularities were noted in 6 of the 13 dogs, as stated in the introduction. In the dogs in which there was no indication of S-A block, A-V block or ectopic beats, there was a peculiar grouping of beats which could not be attributed to sinus arrhythmia. The R wave was of low amplitude in some dogs, and there was often a deep S wave. In order to test the variability of cardiovascular functions during the course of anesthesia, a series of 6 successive determinations was made on each dog, at approximately ten-minute intervals. The range and means found on the successive determinations are presented in table 1.

Discussion

When the mean results of these 74 observations in which administration of cyclopropane-oxygen followed preanesthetic administration

of morphine were compared with the 103 observations in which no morphine was given (1), the following differences were noted. When morphine was given, the mean cardiac index was 27.7 per cent lower, systolic blood pressure 18.6 per cent lower, diastolic blood pressure 39.0 per cent lower, mean blood pressure 29.9 per cent lower, total peripheral resistance 9.4 per cent lower, heart rate 45.3 per cent lower, and stroke index 36.0 per cent higher. Many cardiovascular functions are markedly lower when morphine is used as a preanesthetic agent before cyclopropane-oxygen anesthesia than when cyclopropane is used alone.

TABLE 2

COMPARISON OF CHANGES IN CARDIOVASCULAR FUNCTIONS DURING CYCLOPROPANE-OXYGEN ANESTHESIA WITH AND WITHOUT MORPHINE *

	Cyclopropane after Morphine			Cyclopropane without Premedication		
	First Determination	Sixth Determination	Per Cent Change	First Determination	Sixth Determination	Per Cent Change
Concentration of cyclopropane in arterial blood in mg./100 cc.	10.1	4.8		17.9	18.3	
Duration of anesthesia	30 min.	79		30 min.	68	
Cardiac index, liters/min./m.^{2}	1.81	2.81	+55.2	3.07	3.66	+19.2
Systolic blood pressure	161	174	+8.1	210	214	+1.9
Diastolic blood pressure	75	69	−8.0	120	121	+0.8
Mean blood pressure	104	104	0	150	153	+2.0
Total peripheral resistance in dynes/sec./cm. ^{5}	7,886	5,285	−33.0	6,303	5,977	−4.8
Heart rate	71	73	+2.8	121	120	−0.8
Stroke index, cc./beat/m.^{2}	26	40	+53.8	26	30	+15.4

* There were 11 dogs in each series in which satisfactory observations were made on the first and sixth sets of observations. The mean values in the first and sixth observations on the same dogs, together with the direction and extent of change are shown. With the exception of peripheral resistance and stroke index, the mean values were lower in the morphine series and, with the exception of mean blood pressure, the changes in this series were greater during anesthesia.

The concentration of cyclopropane in arterial blood was 49.9 per cent lower when morphine was used as a preanesthetic agent, than when cyclopropane was used without any preanesthetic agent. This is in close agreement with the results published by Seevers and his coworkers (25), who used an average concentration of 24.7 per cent in inspired air without premedication and 12.7 per cent after premedication with morphine, to bring about complete muscular relaxation. The concentrations of cyclopropane in arterial blood were not determined by Seevers, but the decrease in concentration in inspired air was 48.5 per cent.

The change in each cardiovascular function during the course of cyclopropane-oxygen anesthesia when morphine was given as premedication differed from the change observed when no morphine was

used, as shown in table 2, in which the means found in the first and sixth dye injections in 11 dogs in the former series are compared with 11 in the latter. Each cardiovascular function except mean blood pressure is more variable during cyclopropane-oxygen anesthesia if morphine has been used than if cyclopropane-oxygen is administered without any preanesthetic agent. This is in striking contrast to the results found when morphine is used before thiopental (26) and ether (2); in these cases many cardiovascular functions changed less markedly when morphine was used.

With respect to cardiac irregularities, we found that the effects of morphine on the heart were counteracted to some extent by thiopental (26), as well as by ether (2), in that no S-A blocks, A-V blocks or ectopic beats were noted in those studies. However, the amplitude of the R wave was small, the S wave was deep, and the T wave was of great amplitude in some of the dogs. In others the P wave was of great amplitude and the T wave inverted and of great amplitude. In none of the animals was there an entirely normal electrocardiogram.

Summary

Several cardiovascular functions were observed in dogs under morphine and cyclopropane-oxygen anesthesia. The results were compared with those observed in dogs under cyclopropane-oxygen anesthesia without preanesthetic agents. The most striking differences were the lower mean values for all cardiovascular functions except stroke index in the morphine series. There was a high incidence of cardiac irregularities after the use of morphine. The changes observed during comparable periods of anesthesia were more marked after the use of morphine. Since cyclopropane and morphine exert similar effects on the heart, the combination is particularly unsatisfactory for dogs.

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