APNEA DURING ANESTHESIA

2. Influence of Morphine Alone and Combined with Atropine or Scopolamine *

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In previous communications (1, 2) it was shown that apnea may occur during general anesthesia in subjects depressed by preanesthetic morphinization. It was concluded that general anesthesia may so enhance the depression of the respiratory center caused by excessive morphine that respiratory movements are then maintained principally by the hypoxemic stimulation of the chemoreceptors of the body. Removal of the "anoxemic stimulus" (3) following the inhalation of sufficient oxygen, under these conditions, inactivates the chemoreceptor mechanism, leaving an uncompensated depressed respiratory center, and apnea results.

Since preanesthetic medication frequently includes either atropine or scopolamine in addition to morphine, laboratory experiments were performed to study the effects of combinations of these drugs upon the production of this type of apnea.

Method

Forty-seven experiments were completed upon 17 dogs of 12 to 15 Kg. of body weight. The various combinations of drugs were used upon each animal. Five to seven days were allowed between experiments and the order of drug administration was varied in order to obviate possible cumulative effects. The dose of morphine sulfate used was 10 mg. per Kg. of body weight. This amount, in the dog, results in a state of depression characterized by stupor without loss of consciousness. The dose of atropine sulfate or scopolamine hydrobromide was 0.4 mg. per Kg. All drugs were rapidly administered intravenously. After ten minutes the animal was sufficiently depressed to permit a catheter, 16 mm. in diameter and 30 cm. in length, to be passed translaryngeally into the trachea. Recording pneumographs were applied to the chest and abdomen. Fifteen minutes after drug administration connections were made for the utilization of the carbon dioxide absorption technic and a constant mixture of cyclopropane in oxygen was delivered by means of an accurately calibrated appliance. The anesthetic mixture administered consisted of oxygen flowing at the rate

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of 1200 cc. per minute and cyclopropane 500 cc. per minute. This mixture was administered for approximately two minutes, each animal receiving an identical amount every time it was employed for the various combinations of drugs. Cyclopropane was then discontinued and the flow of oxygen was reduced to approximately 200 cc. per minute, an amount sufficient for metabolic requirements only. Onset and duration of apnea were recorded. Several minutes after spontaneous respiratory movements were resumed the breathing mixture was emptied and replaced by nitrogen until cyanosis of the tongue was evident. Nitrogen was then discontinued and oxygen was again administered at the rate of 2 liters per minute for two or three minutes.

RESULTS

1. *Onset of Apnea.*—A summary of the experiments is presented in Table 1. The onset of apnea following the administration of small quantities of cyclopropane in excess oxygen was more rapid when

TABLE 1

ONSET OF APNEA

Dog No.	Morphine Only	Morphine and Scopolamine	Morphine and Atropine
1	92 seconds	64 seconds	62 seconds
2	80 "		60 "
3	115 "	70 "	64 "
4	100 "	40 "	48 "
5	102 "	50 "	44 "
6	120 "	58 "	50 "
7	240 "	180 "	165 "
8	110 "		36 "
9	175 "	72 "	40 "
10	91 "		54 "
11	59 "	19 "	14 "
12	101 "	43 "	36 "
13	104 "	98 "	76 "
14	75 "	38 "	34 "
15	136 "	116 "	110 "
16	120 "	110 "	100 "
17	110 "	100 "	90 "

scopolamine had been given with morphine, and even more rapid when atropine was combined with morphine than when morphine had been injected alone. The average values for the time of onset of this apnea were one hundred eight seconds when morphine had been given, seventy-five seconds after morphine-scopolamine, and sixty-four seconds after morphine-atropine administration.

To demonstrate that the cessation of respiratory movements was not respiratory arrest from overdose of the anesthetic drug, thoracic and abdominal respiratory movements were recorded simultaneously. Figure 1 illustrates this point. It may be seen that both thoracic (*A*) and

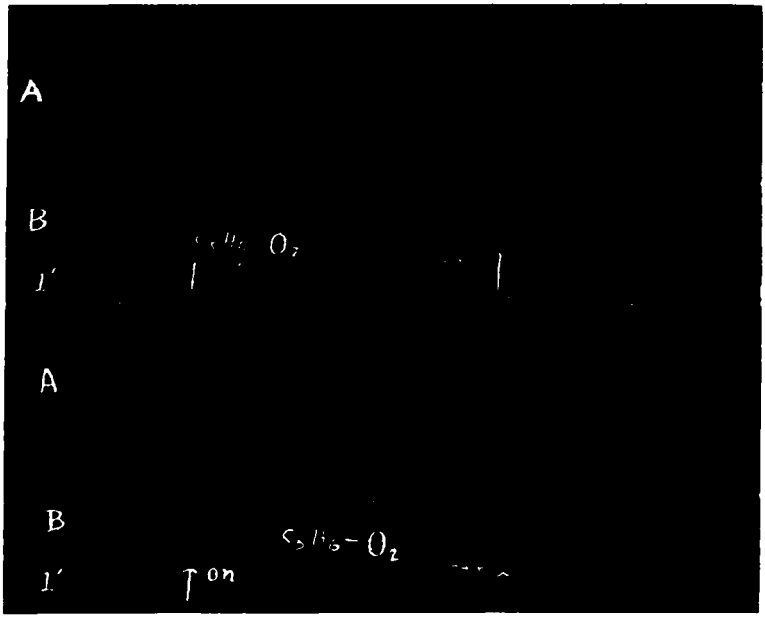

FIG. 1. Tracings showing onset of apnea. Upper tracing; dog prepared with morphine. Lower tracing; dog prepared with morphine and atropine. *A*, thoracic pneumogram. *B*, abdominal pneumogram. Time, in second intervals. Cyclopropane and oxygen were administered between arrows for 70 seconds. Note the simultaneous cessation and simultaneous return of both thoracic and abdominal respiratory movements indicative of apnea. . . . Note the earlier onset and more prolonged duration of apnea in the lower tracing (morphine-atropine preparation).

abdominal (*B*) movements cease and recur at the same time, unlike that which occurs in anesthetic overdose, where thoracic respiratory movements become paralyzed in more profound anesthesia.

Further proof that these apneas were not due to anesthetic overdose was obtained by determining cyclopropane concentrations in the arterial blood. During the periods of apnea the amounts of cyclopropane were from 10.16 to 16.8 mg. per 100 cc., whereas when the same animals were anesthetized with cyclopropane and a minimum of oxygen, the cyclopropane concentrations at the time of respiratory arrest were from 30.9 to 36.3 mg. per 100 cc. The latter preparations exhibited the typical signs of anesthetic overdose, characterized by intercostal paralysis and followed by progressively diminishing diaphragmatic activity.

2. *Duration of Apnea.*—Addition of either atropine or scopolamine to morphine increased in every case the duration of apnea when the

cyclopropane-oxygen mixture was subsequently administered. A summary of the results of these experiments is given in Table 2. The average values were found to be sixty-three seconds for morphine alone, one hundred twenty-one seconds for morphine-scopolamine, and two hundred twenty-two seconds for the morphine-atropine combination.

3. *Effect of Oxygen Deprivation.*—An interesting difference in respiratory reaction was observed when the various animal preparations were subjected to oxygen lack by the replacement of oxygen in the breathing mixture with nitrogen until marked cyanosis was evident on

TABLE 2

DURATION OF APNEA

Dog No.	Morphine Only	Morphine and Scopolamine	Morphine and Atropine
1	120 seconds	190 seconds	245 seconds
2	115 "		225 "
3	D.R.*	150 "	185 "
4	73 "	110 "	233 "
5	D.R.*		234 "
6	40 "	75 "	105 "
7	30 "	82 "	90 "
8	D.R.*		710 "
9	210 "	303 "	508 "
10	33 "		61 "
11	45 "	102 "	192 "
12	21 "	97 "	244 "
13	27 "	50 "	64 "
14	D.R.*	33 "	37 "
15	88 "	134 "	172 "
16	30 "	48 "	54 "
17	236 "	345 "	426 "

* "D.R." indicates "depressed respiration"; i.e., respiratory movements at the rate of 5 to 12 per minute without actual apnea.

the tongue and other mucous membranes. In the group prepared with morphine alone, even mild degrees of cyanosis resulted in marked hyperpnea characterized by increased rate and augmented amplitude of respiratory movements. When the same animals were prepared with atropine or scopolamine in addition to morphine, oxygen deprivation resulted in a contrasting lesser degree of hyperpnea. Four of the animals—one prepared with morphine-scopolamine and 3 with morphine-atropine—died rapidly without showing any hyperpneic reaction when oxygen lack was induced. In each of these 4 cases immediate attempts at resuscitation by rhythmic pulmonic inflation with oxygen as soon as the pulse became impalpable were of no avail; death apparently was due to medullary paralysis.

DISCUSSION

With these experiments, it has been shown that in the dog the type of apnea studied was produced more rapidly and was more prolonged

when either atropine or scopolamine had been added to morphine in the preanesthetic medication. Furthermore, oxygen deprivation caused little or no respiratory stimulation when atropine or scopolamine had previously been administered. This latter observation is to be expected since Wright (4) and others have demonstrated that after carotid body denervation anoxia depresses respiration in contrast to the stimulation observed in the intact animal. Heymans (5) has shown that atropine diminishes sensitivity of the carotid reflexes. In 4 of the animals used in this study, the dose of atropine and scopolamine seemed to have paralyzed the chemoreceptors completely since oxygen lack resulted in respiratory failure followed by circulatory failure and death.

The more prolonged period of apnea when atropine or scopolamine was added to morphine may likewise be explained by the depressing effect of these drugs upon the chemoreceptors so that a greater degree of hypoxia seemed necessary to produce the "anoxemic stimulus" for respiration.

SUMMARY

1. The effects of morphine, morphine-atropine, and morphine-scopolamine on the production of apnea during cyclopropane anesthesia were examined in the dog.

2. Onset of apnea was more rapid and the duration was prolonged when atropine or scopolamine was given with morphine for preanesthetic medication.

3. The hyperpneic response to oxygen deprivation was reduced or absent when atropine or scopolamine had been administered with morphine and resulted in death of some of the animals.

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