

THE EFFECTS OF PREMEDICATION UPON THE SIGNS OF ASPHYXIA DURING NITROUS OXIDE-OXYGEN ANESTHESIA *

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Received for publication August 29, 1947

THE question of whether nitrous oxide deserves to retain a place among other agents in the armamentarium of the anesthesiologist has not been settled. It is said to possess certain qualities which surpass in some ways other anesthetic agents. Some anesthesiologists believe that when this gas is properly administered, it is one of our safest drugs (1, 2, 3). Others insist that nitrous oxide has been too closely associated with death from asphyxia and with transient or permanent injuries of the central nervous system to justify its further use (4). It is generally agreed that the damage that occurs during nitrous oxide anesthesia is due to hypoxia rather than to the anesthetic agent *per se* (4).

Certain of the preanesthetic drugs tend to suppress the clinical signs of asphyxia (5). It is the purpose in this paper to demonstrate their potential dangers during nitrous oxide anesthesia.

As the more potent anesthetic agents were employed in the operating room, surgeons came to appreciate the advantages of good muscular relaxation. In the effort to obtain this desirable condition during nitrous oxide anesthesia, two technics were developed. One method advocated a reduction in the oxygen content of the anesthetic mixture, thereby imposing the effects of hypoxia on those of nitrous oxide. The advocates of this method realize that hypoxia is present but insist it is of little consequence, since the appearance of the signs of severe oxygen-lack would indicate the need for oxygen at a time when the damage is completely reversible (4).

This assumption is undoubtedly true for normal unpremedicated patients, but an individual who suffers from chronic hypoxia may react so quickly and so severely to a further reduction in available oxygen that death will occur before corrective measures can be instituted. This technic of deliberately imposing hypoxia upon nitrous-oxide anesthesia should be avoided whenever certain disease states are present,

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such as low cardiac reserve, anemia, shock, hyperthermia or pulmonary lesions which interfere with the transport of gases to aerate the blood.

The other technic consists of the administration of a nitrous oxide-oxygen mixture of 80:20 or 85:15 proportions after premedication with morphine, atropine, scopolamine, barbiturates, and so forth, separately or in various combinations. In many of the reports of deaths during nitrous oxide anesthesia, premedication was not mentioned. The more detailed reports, however, indicate that in many instances such drugs were employed (6, 7, 8).

Partial obstruction to the airway, respiratory depression, pulmonary disease, a sluggish circulation or anemia may result in hypoxia even though the mixture to be inspired contains 15 per cent oxygen. It seems logical to suspect that if other drugs are present in such instances and suppress the signs of severe oxygen-want, irreversible damage may occur to the central nervous system and the anesthetist may not be aware of the period of distress. Under such conditions, death may occur "suddenly" during the course of an operation.

PROCEDURE AND RESULTS

Thirty-five normal dogs were used. The animals were anesthetized with a nitrous oxide-oxygen mixture. After intubation, the endotracheal tube was connected to a carbon dioxide absorber attached to a 100 liter bag containing an 80:20 mixture of nitrous oxide-oxygen. After a period of thirty minutes of anesthesia, the endotracheal tube was connected directly to a 1 liter rubber bag containing the 80:20 mixture. Asphyxia was produced by allowing the dog to rebreath the mixture in the small bag.

Arterial blood pressure was recorded in each experiment by means of a mercury manometer connected to a cannula in the femoral artery. Respiratory variations were determined by recording pressure changes through a side arm of the endotracheal tube. Electrocardiograms and stethocardiograms were recorded simultaneously to determine the heart rates. The heart sounds disappeared when the blood pressure reached zero mm. of mercury.

The circulatory and respiratory signs of asphyxia are the same in dogs asphyxiated during nitrous oxide-oxygen anesthesia as in unanesthetized animals sacrificed in the same manner (5).

Five unpremedicated dogs were asphyxiated during nitrous oxide-oxygen anesthesia. Figure 1 shows the typical responses. During the progressive increase in the degree of asphyxia three stages are suggested. The precrisis stage is evident when the inspired mixture contains about 12 volumes per cent of oxygen. There is an increase in both the rate and depth of respiration owing to the stimulation of the respiratory center by the increased carbon dioxide content of the blood and also owing to the response of the aortic and carotid bodies to oxygen lack. The heart rate is rapid because of a slight reduction in vagal

tone and a slight increase in cardio-accelerator activity (9, 10). The pulse pressure is increased.

When the blood oxygen concentration is reduced to about 9 volumes per cent, the heart begins to dilate, the systolic pressure begins to fall, a marked bradycardia develops, and the stage of circulatory crisis is evident (9, 10). This slow, full, bounding pulse of oxygen-want is produced by an increase in vagal impulses. If the lungs are inflated with oxygen at this time or if the vagi are cut, the pulse will immediately return to its former rate or even a faster one. Soon after the beginning of the second stage, breathing ceases. After a brief period of apnea, a period of asphyxial gasping ensues. The arterial pressure gradually

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA IN UNPREMEDICATED DOGS

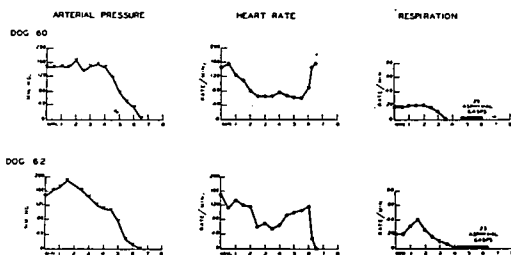


FIG. 1.

falls throughout this stage and venous pressure rises. There is a gradual increase in pulse rate in the latter part of the period as the cardio-inhibitory center is depressed.

The third stage is the terminal one and is consummated with great rapidity. It occurs after the blood oxygen concentration has been reduced to 4 volumes per cent or less. There is a cessation of asphyxial gasping, a rapid fall in arterial blood pressure to zero, and a terminal slowing of the pulse. The effects of hypoxia are readily reversible during the first two stages of asphyxia, but in stage III when the heart fails and stops because of direct myocardial hypoxia, the responses to the usual attempts at resuscitation are not satisfactory.

Three dogs, after being premedicated with 0.64 mg. of atropine for thirty minutes, were anesthetized with an 80:20 mixture of nitrous oxide-oxygen for thirty minutes and then asphyxiated. The various responses of 2 of these animals are shown in figure 2. There was a rise in arterial pressure followed by an abrupt fall. Bradycardia did

not occur in response to asphyxia. The period of asphyxial gasping was about half that of the unpremedicated controls.

Three other dogs were premedicated with 20 mg. of morphine and 0.64 mg. of atropine, thirty minutes before the beginning of anesthesia. Thirty minutes later, asphyxia was produced as previously described.

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA IN DOGS PREMEDICATED WITH ATROPINE

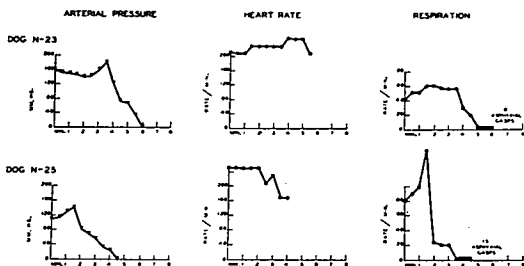


Fig. 2.

The responses of 2 dogs are shown in figure 3 and are essentially the same as those shown in figure 2 when atropine alone was the premedicant drug.

The responses to asphyxia by 3 animals premedicated with 5 mg. of morphine per kilogram were similar to those of the unpremedicated

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA IN DOGS PREMEDICATED WITH MORPHINE AND ATROPINE

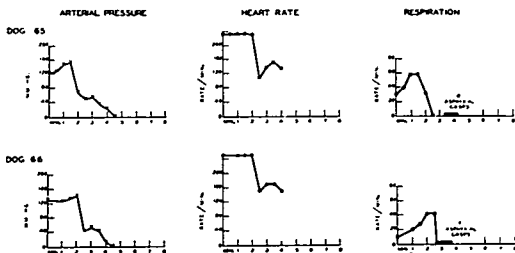


Fig. 3.

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA
IN DOGS PREMEDICATED WITH MORPHINE

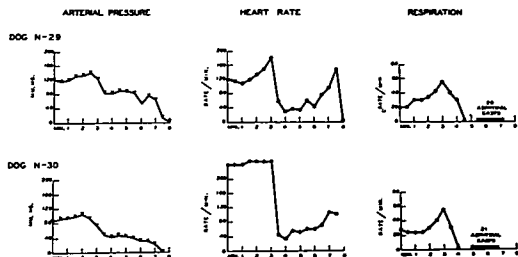


FIG. 4.

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA
IN DOGS PREMEDICATED WITH MORPHINE - SCOPOLAMINE

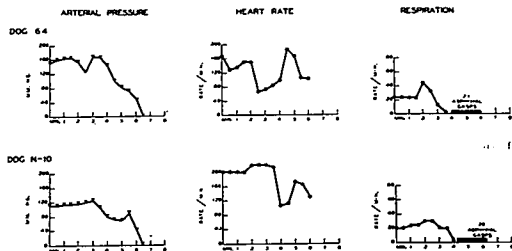


FIG. 5.

dogs. The bradycardia of stage II was marked. Figure 4 illustrates the signs of asphyxia when morphine alone was used for premedication.

Three dogs were premedicated with 20 mg. of morphine and 0.64 mg. or 0.44 mg. of scopolamine. One hour later, they were asphyxiated during nitrous oxide anesthesia. The bradycardia of the second stage of oxygen-want was not so profound as when no premedication or only morphine premedication was employed. Otherwise, the signs of asphyxia were about the same as those of the control dogs. Figure 5 shows typical responses.

A dose of 25 mg. of demerol per kilogram administered intravenously to each of 3 dogs caused convulsions, vocalization and opisthotonos. This condition persisted until the animals were anesthetized

with the nitrous oxide-oxygen mixture. Marked hypotension and tachycardias of over 200 were present throughout the period of saturation with the anesthetic gas. The arterial pressure rise in response to asphyxia was retarded. The heart rate did not accelerate in response to early hypoxia. Although a bradycardia of vagal origin did occur the time of appearance was delayed and the duration of bradycardia markedly shortened. The respiratory response was an increase in both rate and depth. The period of asphyxial gasping was about half that of the unpremedicated dogs. Typical responses may be seen in figure 6.

It is generally believed that almost all of the barbiturates in clinical

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA IN DOGS PREMEDITATED WITH DEMEROL

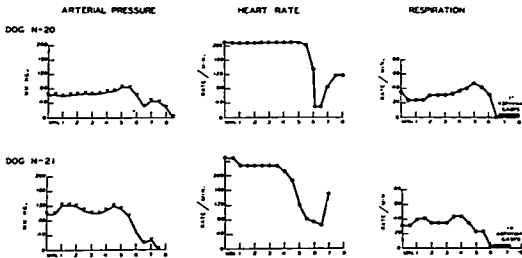


FIG. 6.

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA IN DOGS PREMEDITATED WITH NEMBUTAL

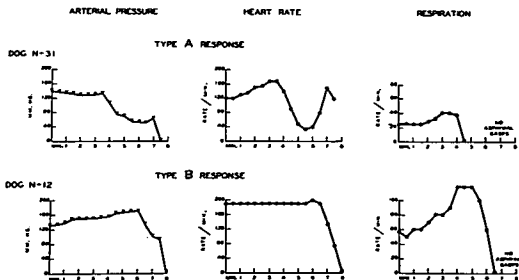


FIG. 7.

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA
IN DOGS PREMEDICATED WITH NEMBUTAL AND DEMEROL

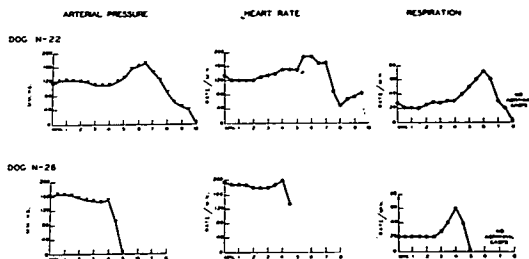


FIG. 8.

RESPONSE TO ASPHYXIA DURING NITROUS OXIDE ANESTHESIA
IN DOGS PREMEDICATED WITH SODIUM AMYTAL

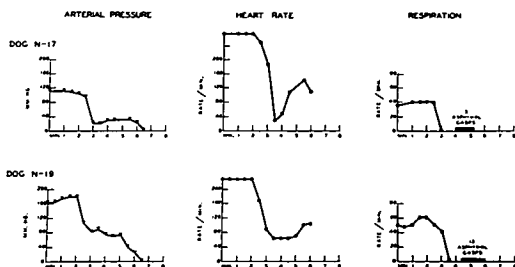


FIG. 9.

use with the exception of sodium phenobarbital depress the vagal cardio-inhibitory effects (11-15). Five dogs were premedicated with sodium pentobarbital in doses ranging from 15 to 35 mg. per kilogram. In 4 of the dogs, asphyxia during nitrous oxide anesthesia resulted in the Type A response of figure 7, while only one dog gave the Type B response which one would anticipate with drugs which depress vagal tone. In none of the dogs did asphyxial gasping develop.

The combined premedication of demerol, 12 mg. per kilogram, and sodium pentobarbital, 15 mg. per kilogram, showed a tendency to prevent the occurrence of the slow bounding pulse of the second stage. As is shown in figure 8, the response of Dog N-26 was very similar to that

of Dog N-12 of figure 7. None of this series of dogs developed asphyxial gasping.

Three animals were premedicated with doses of 17 to 28 mg. of sodium amytal per kilogram, administered intravenously. After thirty minutes, the animals were anesthetized with nitrous oxide-oxygen for thirty minutes and then asphyxiated. Although the heart rates before the period of asphyxia were well over 200 per minute and suggestive of low vagal tonus, marked bradycardia developed during the second stage of oxygen-want. The arterial pressure response to asphyxia was primarily that of depression. The period of gasping respiration was reduced to about half that developed by unpremedicated dogs. Figure 9 shows the responses of two of the animals premedicated with sodium amytal.

EFFECTS OF PREANESTHETIC AGENTS UPON THE SIGNS OF ASPHYXIA IN DOGS DURING NITROUS OXIDE ANESTHESIA

	HEART RATE				ARTERIAL BLOOD PRESSURE			RESPIRATION Number of breaths in 15 sec. at 100 mm. Hg. O ₂
	INITIAL RATE PER MINUTE	BRADYCARDIA OF OXYGEN WANT		INITIAL PRESSURE MM. Hg.	PRESSURE ELEVATION AT 15 MIN.	TENSING FALL TO 15 MIN.		
UNANESTHETIZED	110	36	+	132	+++	+++	18	
UNPREMEDICATED	148	56	+	145	++	++	17	
MORPHINE	195	34	+	102	+	+++	20	
MORPHINE - SCOPOLAMINE	184	69	+	137	+	++	16	
ATROPINE	241	NONE	+	131	++	+	8	
MORPHINE - ATROPINE	244	NONE	+	127	+	++	7	
NEMBUTAL	163		+ OR +	136	+	+ OR +	0	
DEMEROL	191	53	+	93	+	+	8	
NEMBUTAL - DEMEROL	165		+ OR +	135	+	+ OR +	0	
SODIUM AMYTAL	230	43	+	136	+	++	9	

* ALL DOGS SHOWED AN INCREASE IN RESPIRATORY RATE AND TIDAL VOLUME IN RESPONSE TO ASPHYXIA

Fig. 10.

The effects of the preanesthetic drugs upon the signs of asphyxia in dogs during nitrous oxide-oxygen anesthesia are summarized in figure 10.

DISCUSSION

The extensive studies of Courville (2, 3) suggest that serious or even fatal results may follow nitrous oxide anesthesia, even though it is administered without gross error and by accepted technics. The fact that the premedication can mask the signs of asphyxia may help to explain why even experienced anesthetists have allowed irreversible damage to develop without recognizing the period of distress.

Of all the preanesthetic agents tested, atropine appears to be the most dangerous, especially if the anesthetist is relying primarily upon

pulse changes to warn him of impending disaster. The hypodermic dose of 0.5 to 1.0 mg. of atropine produces either no effect or moderate slowing of the heart in the average man. Slightly larger doses in these same individuals or small amounts in more susceptible patients produce a very transient slowing followed by cardiac acceleration. This acceleration is caused by direct vagal depression by atropine and in many instances of overdose, the cardio-inhibitory fibers are completely blocked (16, 17). In patients thus affected by such premedication, there may be no development of a slow bounding pulse even though the asphyxia progresses to completion.

In comparison to atropine, scopolamine is a relatively weak depressor of the vagus (18). Moreover, because of the psychic depression produced by the scopolamine, the amount of morphine which usually accompanies it is significantly less than that used with atropine. Thus, the depressant effects of the opiate are lessened.

Morphine does not appear to interfere with pulse changes. It does, however, tend to depress the blood pressure and its response to asphyxia. Anesthetists are frequently confronted with patients who have been overpremedicated with this drug. In hospitals where it is routine for all patients to receive from 10 to 16 mg. of morphine before anesthesia, it is not uncommon to find debilitated, aged or very young patients in the precrisis stage of asphyxia because of respiratory depression. Such individuals may react severely to the imposition of an induction with pure nitrous oxide, and a permanent apnea may ensue.

The dose of morphine that is prescribed in conjunction with atropine or scopolamine premedication should usually be only one half or one third the amount that would be desired for the relief of pain in the same individual. If such doses of morphine are administered at least one and one half hours before anesthesia, the respiratory and circulatory depression will have been dissipated by the time the patient arrives in the operating room.

All of the dogs premedicated with sodium pentobarbital (with or without the addition of demerol) died of asphyxia without producing the asphyxial or gasping type of breathing. Those who depend only upon the type of breathing to prevent severe oxygen-want during nitrous oxide anesthesia should not premedicate their patients with this barbiturate. Pulse changes were usually similar to those of unpremedicated animals, but the fact that Dog N-26 (fig. 8) and Dog N-12 (fig. 7) showed no pulse slowing until the terminal period of asphyxia deserves considerable thought.

Since sodium amytal is believed to be the most profound vagal depressant of the barbiturate group, the responses of the animals premedicated with this drug were not what we had anticipated. The pulse rates of over 200 per minute suggested a vagal block, but the development of marked periods of bradycardia during the second stage of asphyxia indicates a strong response of the vagal center to asphyxia.

The atropine-like qualities of demerol appeared to cause little variation in the signs of asphyxia. The hypotension of the dogs was possibly owing to a species sensitivity. The responses to this drug seemed to indicate a general depression of the respiratory and cardiovascular systems.

SUMMARY

When atropine is used in premedication, the slow bounding pulse of oxygen-want may not be present during nitrous oxide anesthesia even though the processes of asphyxia are progressing to the stage of irreversibility.

If sufficient sodium pentobarbital is present in the tissues, the asphyxial or gasping type of breathing will not develop to warn of impending death from anoxia. In some instances sodium pentobarbital tends to mask the circulatory signs of asphyxia.

Morphine, sodium amytal or demerol, alone, does not appear to mask the clinical signs of asphyxia during nitrous oxide anesthesia provided the drug has been administered one hour or more prior to the period of asphyxia.

Morphine-scopolamine premedication seems to have fewer masking effect upon the signs of asphyxia than morphine-atropine.

In clinical anesthesia, two points should be emphasized: (a) premedication prior to nitrous oxide must be adequate to alleviate the necessity for low concentrations of oxygen, and (b) the use of certain premedicant drugs in doses which may mask the signs of hypoxia or asphyxia during nitrous oxide anesthesia is dangerous.

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The Annual Meeting of the Massachusetts Medical Society will be held on May 24, 25, and 26, 1949, in the Worcester Memorial Auditorium, Worcester, Mass.

The Section on Anesthesiology of the Massachusetts Medical Society will meet in the Worcester Memorial Auditorium on Thursday, May 26, 1949, between the hours of 12:00 noon and 2:00 p.m. This will be a luncheon meeting, and Dr. Robert D. Dripps, Head of the Department of Anesthesiology at the University of Pennsylvania, will discuss. "A New Plan for Graduate Teaching of Anesthesiology."

On Thursday, May 26, 1949, at 2:25 p.m. Dr. Dripps will also speak on the General Session of the Massachusetts Medical Society, and his topic will be. "Pitfalls in Anesthesiology."