Effect of Anesthetics on Central Nervous System Toxicity of Hyperbaric Oxygen

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Dogs were exposed to oxygen at four atmospheres absolute, unanesthetized or under the influence of thiamylal or halothane. Primary manifestations of oxygen toxicity were related to the central nervous system. The onset of convulsive electroencephalographic activity was delayed in the halothane series as compared to the awake series. Thiamylal prevented convulsions, but was associated with postexposure central nervous system disturbances. Electroencephalographic convulsive activity was associated with severe cardiovascular reactions in the unanesthetized animals, but not in the halothane animals. Safe exposure to oxygen at four atmospheres was found to be of short duration.

OXYGEN poisoning is the principal limiting factor in the clinical application of hyperbaric oxygen. Though the primary lesion of oxygen toxicity effects all tissues of the body and may be enzymatic,[1] clinical manifestations relate particularly to the central nervous system and lungs.[2] Exposure to oxygen at pressures employed for hyperbaric surgery (three or more atmospheres absolute) tends to magnify the acute central nervous system signs (generalized convulsions), and reduces the importance of pulmonary manifestations seen at lower pressures. Delayed central nervous system toxicity consisting of ataxia, postural disturbances and spastic paralysis, which may or may not be reversible, is the third member of the triad of oxygen poisoning. These latter manifestations may appear after exposure in the absence of convulsive activity, and are more severe at higher pressures of oxygen.[3, 4]

Acute central nervous system signs may be delayed or prevented in animals by administration of chloroform, ether, barbiturates, paraldehyde, urethane, and other central nervous system depressants.[5-9] However, pentobarbital markedly increases the incidence of delayed central nervous system toxicity in rats and mice.[4, 9, 10]

The general problems of anesthesia under hyperbaric conditions have been reviewed by Smith,[11] McDowall,[12] and Sluyter.[13] The purpose of this study was to determine to what extent certain anesthetic drugs might modify the course of oxygen toxicity, and thus evaluate their applicability in hyperbaric surgery. Halothane and a thiobarbiturate were selected for investigation.

Method

Mongrel dogs of both sexes weighing 10 to 15 kg. were employed. A group of 7 dogs, serving as controls, were maintained in a quiescent state by means of an initial intravenous dose of succinylcholine 4 mg./kg., with increments of 1 to 2 mg./kg. intravenously as necessary. Two additional groups of 5 and 6 dogs, respectively, were maintained under light general anesthesia, the first group receiving intravenous thiamylal sodium (two exposures in one animal) 15 mg./kg. initially, with supplementary doses of 1.5 to 2.0 mg./kg. as needed, and the other group being administered halothane open drop for induction followed by 1

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to 1.5 per cent, via an FNS vaporizer. Immediately after the animals received succinylcholine or were anesthetized, a cuffed endotracheal tube was inserted and oxygen was administered. The succinylcholine group and the thiamylal group received 100 per cent oxygen; the halothane group received 1 to 1.5 per cent halothane in oxygen. The succinylcholine group of animals were ventilated with a Harvard Pump at a tidal volume of 25 ml./kg. and at a rate of 20 respirations per minute. Except for 2 animals in the thiamylal series and one animal in the halothane series, which had respirations assisted with a Mark 8 Bird Respirator, the experimental animals were allowed to breathe spontaneously. Arterial and central venous catheters were inserted in a femoral artery and an external jugular vein or a femoral vein, using local infiltration of lidocaine 1.0 per cent, 5 to 8 ml., in the succinylcholine group. Continuous monitoring of the direct arterial pressure by means of a Statham strain gauge, lead 2 of the electrocardiogram (ECG), and a frontal occipital electroencephalogram (EEG) was maintained throughout the procedures by means of a multichannel polygraph. Intermittent determinations of arterial and venous blood gases (pH, P_{O_2} and P_{CO_2}) were made inside the Duke Pilot Hyperbaric chamber with a modified Model 113 Instrumentation Laboratories gas analyzer.

After the completion of these procedures, and when a clinically stable level of anesthesia had been attained, the pressure in the Duke Pilot Hyperbaric Chamber was elevated in 8 to 10 minutes to four atmospheres, absolute. Exposure to this pressure while breathing oxygen was continued for 45 to 55 minutes, except in 2 animals of the succinylcholine group which received exposures of 36 and 90 minutes, respectively. The animals were accompanied during all phases of compression and decompression by one of the authors. Decompression was carried out according to the stages described in the standard Navy Diving Tables.

In animals which exhibited convulsive activity by the EEG at pressure, room air was substituted for oxygen during decompression. Three animals of the succinylcholine group which developed ventricular tachycardia and hypotension were treated with combinations of intravenous calcium gluconate, procaine amide, isoproterenol, deslanoside and external electrical d.-c. shock in efforts to re-establish an effective cardiac output. Barbiturates and/or diphenylhydantoin were administered intravenously during decompression to animals that showed continuing convulsive activity on the EEG.

Surviving animals were observed daily for evidence of neurologic or pulmonary damage. Animals which survived 5 days were sacrificed on the fifth to seventh day after exposure and postmortem examinations were performed.

Results

Vital Signs. No significant difference in the vital signs was observed in the animals breathing oxygen at ambient pressure and breathing oxygen at four atmospheres absolute. The dogs anesthetized with halothane had lower arterial pressures, while those under succinylcholine had higher arterial pressures than the animals anesthetized with thiamylal sodium. Marked elevation of pulse rates and arterial pressures occurred in association with convulsive activity on the EEG in unanesthetized animals, but not in the anesthetized animals which exhibited convulsions. A summary of the vital signs observed is shown in table 1.

Blood Gases and pH. Arterial oxygen tensions at four atmospheres absolute were comparable in the three groups of dogs. Controlled hyperventilation with positive pressure in the succinylcholine group produced hypocarbia, but did not result in greater arterial oxygen tensions than in the animals breathing spontaneously, either at ambient pressure or at four atmospheres absolute. The results of blood gas analyses are summarized in table 2.

Toxic Symptoms. The toxic responses of the three groups of animals are summarized in table 3. Four of 7 animals in the succinylcholine group demonstrated EEG evidence of convulsive activity. This activity consisted of the sudden development of continuous 10–15 cycles per second asynchronous spikes greater than 250 microvolts. The time to onset of seizure activity after initiation of hyperbaric conditions averaged 18 minutes in these 4 animals. Associated with the seizure activity

TABLE 1. Summary of Vital Signs

Dog	Ambient Pressure			4 Atmospheres Absolute			During Convulsions		
	B.P.	Pulse	Resp.	B.P.	Pulse	Resp.	B.P.	Pulse	Resp.
Succinylcholine*									
602	150/110	120	20	240/170	128	20	280/155	220	20
609	230/120	160	20	240/120	144	20	300/220	330	20
617	—	—	20	230/95	80	20	No convulsions		
620	235/130	136	20	270/170	104	20	300/270	300	20
631	—	—	20	210/110	80	20	300/230	222	20
638	184/78	70	20	196/120	90	20	No convulsions		
642	204/110	40	20	204/112	40	20	No convulsions		
Mean	201/109	105	20	227/128	95	20	295/219	268	20
Thiamylal									
479†	180/100	150	24	120/70	60	20	No convulsions		
502†	130/100	105	18	130/100	96	16	No convulsions		
515‡	170/90	102	24	150/110	180	50	No convulsions		
515‡ 5 2 wks.	120/84	170	18	180/120	120	20	No convulsions		
544‡	140/90	119	26	130/86	170	20	No convulsions		
722‡	190/116	72	30	200/120	72	24	No convulsions		
Mean	155/97	120	23	152/101	116	25			
Halothane									
497‡	100/70	120	44	100/60	160	40	No convulsions		
533‡§	104/80	70	14	114/76	100	18	140/90	96	48
580‡	200/120	112	24	240/140	92	24	240/100	92	20
603‡	90/55	120	—	90/40	100	20	84/40	190	20
610‡	120/90	110	20	80/40	126	28	No convulsions		
627‡	90/50	88	30	70/40	70	30	120/90	90	30
Mean	117/78	100	26	114/66	108	27	146/80	117	30

* All succinylcholine animals on controlled respirations at 20/min.
† Respirations assisted with Bird Respirator.
‡ Spontaneous Respirations.
§ Off O_2 for 8 minutes at 45 p.s.i.g. with onset of convulsions.

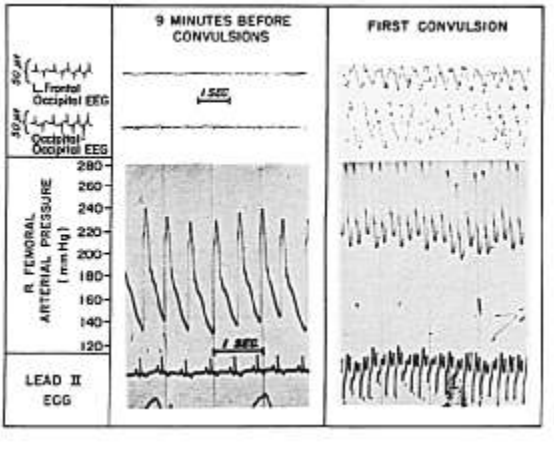

FIG. 1. Dog 609—Comparison of EEG, ECG and right femoral arterial pressure before and during convulsive activity in dog pretreated with succinylcholine and ventilated on oxygen at four atmospheres absolute.

TABLE 2. Arterial Blood Gases and *p*H

Dog	Ambient Pressure on O_2			4 Atmospheres Absolute		
	Pa_{O_2}	$PaCo_2$	*p*H	Pa_{O_2}	$PaCo_2$	*p*H
Succinylcholine‡						
602	345¶	16.5	7.75	960¶	18	7.73
609	450	21.4	7.46	2,040	24.0	7.46
617	425	13.2	7.63	2,140	11.8	7.54
620	490	15.5	7.58	2,340	20.5	7.52
631	495	18.5	7.55	2,160	23.0	7.42
638	450	12.5	7.64	2,040	16.0	7.65
642	420	16	7.60	2,300	19.0	7.50
Mean	455	16.5	7.60	2,177	18.9	7.55
Thiamylal						
479*	425	31.5	—	2,400	28	7.67
502*	430	19	7.63	2,200	36	7.53
515†	430	52	7.38	2,400	62	7.38
515† p 2 wks.	460	35	7.38	2,100	43	7.35
544†	435	38	7.36	—	—	—
722	440	35.5	7.375	2,220	20.5	7.60
Mean	436	35.1	7.42	2,264	37.9	7.51
Halothane						
497*	420	17.5	7.59	1,860	34.5	7.45
553†§	—	41	7.44	—	—	—
580†	520	30.5	7.39	2,720	39	7.42
603†	525	44.5	7.33	2,680	52.5	7.31
610†	430	29	7.34	2,380	26	7.23
627†	505	27.5	7.39	2,360	31	7.32
Mean	480	31.7	7.41	2,400	37	7.35

* Respirations assisted with Bird Respirator.
† Spontaneous respirations.
‡ Controlled respirations with Harvard Ventilator.
§ Dog 553 off O_2 for 8 min. and on air at 45 p.s.i.g. with onset of convulsions.
¶ Difficulty with I.L. Analyzer O_2 membrane. Oxygen thought to be inaccurate and not included in mean.

there appeared sinus tachycardia, elevation of arterial pressure, and ECG changes including premature ventricular contractions, ventricular tachycardia, and in one animal ventricular fibrillation (fig. 1). Three of the 4 animals which exhibited convulsive activity died in the immediate postexposure period. In each instance, death was attributed to cardiovascular collapse, the blood gases being both hyperoxic and hypocarbic at the time of death. The single animal (631) which survived seizure activity showed spastic paralysis of the hind legs in 24 hours and died 48 hours after exposure.

In the series anesthetized with thiamylal sodium, no convulsive movements were observed. The EEG patterns were characteristic of thiobarbiturate anesthesia throughout the hyperoxic exposure, and no abnormal activity was noted. The ECG tracings showed occasional episodes of bigeminy, but these appeared with comparable frequency before, during, and after hyperbaria. All animals survived the exposure. However, in four of the six experiments, ataxia and nonspastic motor weakness of the hind legs developed following exposure. These animals demonstrated disequilibrium and appeared to have loss of proprioceptive function; these signs persisted for 24 to 72 hours and then were followed by a complete clinical return to normal function.

Four of the 6 animals anesthetized with halothane developed convulsions. The time of onset after exposure to pressure averaged 48 minutes. The EEG recordings during the convulsions were distorted by motor artifact, but typical seizure patterns could be demonstrated.

TABLE 3. Toxic Responses of Dogs Subjected to O_2 at 4 Atmospheres Absolute

Dog	Time in Minutes After Compression Signs Appeared	Toxic Response	Postexposure Signs
Succinylcholine			
602	26	Convulsions, ventricular tachycardia leading to ventricular fibrillation	Died despite resuscitative attempts during decompression
609			
609	14	Convulsions, ventricular tachycardia, hypertension	Died despite resuscitative attempts during decompression
617	—	ST depression on ECG	None
620	22	Convulsions, ventricular tachycardia, hypertension	Died in ventricular tachycardia and shock 2 hours after decompression
631	11	Convulsions, PVCs, hypertension	Hind extremity spasticity; died 48 hours after exposure
638	—	None	None
642	—	None	None
Thiamylal			
479	40	Hyperpnea	Ataxia and incoordination for 24 hours after exposure
502	15	PVCs	Ataxia and incoordination for 24 hours after exposure
515	30	Inspiratory twitching*	None
515 p 2 wks.	—	None	None
544	35	Inspiratory twitching, vomiting	Ataxia and incoordination for 72 hours after exposure
722	24	Hyperpnea	Ataxia and incoordination for 96 hours after exposure
Halothane			
497	—	Perioral twitching on decompression	None
553	25	Convulsions	None
580	50	Convulsions	Died at completion of decompression
603	48	Convulsions, sinus tachycardia	Status epilepticus; died 48 hours after decompression
610	—	None	None
627	45	Convulsions	Required barbiturates for convulsions for 48 hours

* Generalized myoclonic activity of rapid frequency seen only during inspiration.

Convulsive activity was not associated with the marked cardiovascular changes observed in the succinylcholine group. The ECG patterns, blood pressure and pulse rate remained unchanged during seizure activity. Of the animals exhibiting convulsions, one died immediately following decompression, and a second died 48 hours after exposure in status epilepticus. In the 2 animals which survived the convulsions, one required heavy barbiturate sedation for status epilepticus which persisted for 24 hours, while the other was clinically normal following decompression. No residual muscle weakness or ataxia was noted in the 4 surviving animals of the halothane series.

Discussion

Previous investigators have observed great variability in the susceptibility of both animals and man to central nervous system toxicity associated with hyperoxia.[7, 14, 15] The above data further confirm this variability.

While halothane anesthesia delays the onset of convulsions, it does not reduce their incidence. Furthermore, while it has previously been believed that discontinuance of oxygen and substitution of room air rapidly reverses the process of oxygen toxicity, this is untrue in the anesthetized animal. In 2 animals of the halothane series (603 and 627), the onset of convulsive activity coincided with the time

for termination of the hyperoxic exposure, yet sufficiently severe central nervous system changes had already developed to produce prolonged status epilepticus.

The marked hypertension, tachycardia, and cardiac arrhythmias noted in association with seizure activity in the succinylcholine control series has not been reported previously. However, convulsive activity produced by drugs and electroshock is known to be associated with similar cardiovascular changes.[16, 17, 14] Why these seizure-associated arrhythmias were absent in halothane anesthetized animals is unclear. Reduction of arterial pressure has been shown to mitigate against catecholamine-induced arrhythmias. The lower arterial pressures in the halothane anesthetized animals may thus afford partial explanation.

Acute convulsive manifestations of oxygen poisoning were absent in the thiamylal series, indicating that thiamylal sodium provides protection against these acute mainfestations similar to those previously reported for oxybarbiturates.[4, 7, 10] On the other hand, while delayed central nervous system oxygen poisoning was absent in the 5 animals of the control and halothane series which failed to develop acute signs of central nervous system toxicity, four of the six experiments in which thiamylal anesthesia was used were followed by evidence of delayed toxicity. These observations agree with those of Van den Brenk and Jamieson [10] and Kydd and Betz [4] that barbiturates may, while preventing acute central nervous system toxicity, potentiate delayed central nervous system toxicity. It is possible that barbiturates may increase the incidence of delayed central nervous system toxicity primarily by decreasing acute toxicity and death.

It may be argued that the lower Pa_{CO_2} values recorded in the control series, as opposed to the groups under general anesthesia, played a part in the development of convulsive activity. It has been shown[9, 19] that elevation of Pa_{CO_2} increases susceptibility to all forms of oxygen toxicity. Furthermore, Bohr and Bean [20] have demonstrated that hypocarbia produced by hyperventilation exerts a protective effect on the manifestations of oxygen poisoning. If anything, the hyperventilation in the control series of animals acted in a salutary manner.

One can conclude from this study that exposure times to high pressures of oxygen must be brief. Relatively short exposures to oxygen tensions of four atmospheres absolute proved fatal to both awake and anesthetized dogs.

EEG and ECG should be monitored in all individuals exposed to high tensions of oxygen, whether they be awake or anesthetized. Evidence of convulsive activity would indicate that hyperoxia be terminated immediately. Anticonvulsant therapy should be instituted to prevent further central nervous system and cardiovascular sequelae.

At the present time there is no adequate means of predicting the development of delayed central nervous system toxicity. Before prolonged exposure of human beings to oxygen tensions in excess of three atmospheres absolute is carried out, methods of detecting and preventing this form of oxygen poisoning must be found.

No conclusions can be drawn regarding the proper selection of anesthetic drugs for use under hyperbaric conditions. Both halothane and thiamylal sodium modify the course of oxygen poisoning in animals, but neither drug offers complete protection at four atmospheres absolute.

Summary

Eighteen dogs were exposed to oxygen at four atmospheres absolute. Seven animals rendered quiescent with succinylcholine served as controls. Five animals (six exposures) were anesthetized with thiamylal sodium and 6 animals were anesthetized with halothane. All groups showed evidence of central nervous system oxygen poisoning. In the control dogs, toxicity was manifested in 3 animals by convulsions and cardiovascular collapse, while a fourth animal had convulsions followed by spastic hind limb paralysis. Convulsions developed in 4 animals anesthetized with halothane after more prolonged exposures, but associated cardiovascular symptoms were absent. While no evidence of convulsions was observed in the thiamylal series, 4 of the 5 animals showed evidence of delayed central nervous

system toxicity. The data suggest that safe exposures to oxygen tensions of four atmospheres absolute must be brief, and that no adequate means for the detection of delayed central nervous system oxygen poisoning is presently available.

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PROFOUND HYPOTHEMIA When hemostasis is expected to be a very difficult problem during intracranial surgery, a combination of profound hypothermia and cardiac bypass may be used. Cerebral blood flow may be safely interrupted for one hour. Cannulas drain blood from the cavas and a pump oxygenator returns the blood to the iliac artery. The pump is primed with blood and Ringer's solution. A heat exchanger cools the blood and flow is maintained at 1.5 to 2 liters per square meter per minute. When the esophageal temperature is 12° to 15° C., the pump is slowed and most of the patient's blood is drained into the oxygenator. Absolute hemostasis must be achieved after normal circulation has been restored. The 3 deaths in a series of 8 cases were not related to the special techniques. (*St. Ville, J. M., and Tobias, E.: Intracranial Surgery, Arch. Surg. 92: 573 (Apr.) 1966.*)