THE EFFECTS OF HIGH OXYGEN ATMOSPHERES ON DRUG INDUCED CONVULSIONS * †

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ADMINISTRATION of oxygen has been considered by some to be of value in the management of the critical stages of convulsive syndromes such as tetanus, eclampsia and overdose of strychnine. It appears reasonable that any procedure which increases oxygen tension in the tissues would be helpful since multiple convulsive seizures are considered to prove fatal largely because of the development of anoxia. Special difficulties may be encountered and some contraindications may arise when mechanical methods of artificial respiration are applied under these conditions. Administration of oxygen by mask or by tent may properly come into consideration depending on the estimate of the value of high oxygen atmospheres under such conditions. Obviously, there is not generally a high estimate of such value since oxygen is not routinely used or recommended and, when used, may be intended more particularly for other complications, as atelectasis, pulmonary edema and liver damage. The present study was made in an effort to obtain a quantitative expression of the advantage which may be obtained through free inhalation of high oxygen atmospheres in critical convulsive conditions. Rats and mice were used in order to obtain statistically significant numbers of individual reactions. The convulsant drugs, metrazol, strychnine and sodium cyanide, were administered under conditions designed to compare responses in chambers with high oxygen atmospheres and chambers with ordinary room air. The results demonstrate that there is a substantially increased survival time in the high oxygen atmospheres. There is no pronounced difference, however, in the over-all mortality rate. The development of pulmonary hemorrhages was noted particularly and proved to be most pronounced in the case of the animals surviving for the longer time in the high oxygen atmospheres.

PREVIOUS OBSERVATIONS

The use of oxygen has been mentioned or briefly described as being of value in overcoming the symptoms of anoxia in eclampsia (1, 2, 3, 4, 5, 6), tetanus (7), cyanide poisoning (8) and strychnine poisoning (9).

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Cullen and Gross (10) have recommended the use of oxygen in instances of prolonged convulsions in which hypoxia may be a complicating factor. Oxygen under pressure has been demonstrated to reduce frequency of petit mal seizures (11). There has been an unconvincing claim for the value of oxygen in the treatment of status epilepticus (12). Osterwald (9) in 1900 reviewed laboratory studies on this topic and referred to the report of one clinical case in which freely inspired high oxygen atmospheres reduced the symptoms of strychnine poisoning. He conducted experiments with a limited number of mice, guinea pigs and hens and concluded that high oxygen atmospheres reduced the hyperactive reflexes and convulsions produced by strychnine as contrasted with similar results in room air. At the same time he noted that the strychnine effects in high oxygen atmospheres were more prolonged in the case of mice. No mortality figures were given although it was indicated by the few experiments with guinea pigs that oxygen atmospheres would have the effect of producing much higher survival rates. From a pilot study in this laboratory using mice injected with strychnine, metrazol and cyanide, it was concluded that those in high oxygen atmospheres survived and had convulsions longer than those in room air. There was no difference in convulsive susceptibilities. Those in the high oxygen atmosphere were considered to show a slightly higher survival rate in the case of metrazol and strychnine and a distinctly higher survival rate in the case of cyanide. Results of the present more extensive study have generally agreed with those of the pilot study except that distinctions in survival rate have been reduced to a level which is not considered statistically significant.

As points of corollary interest, it may be noted that Himwich (13) described marked diminution in the arterial oxygen saturation following metrazol convulsions in patients. McCulloch and Roseman (14) reported a marked fall in cortical oxygen tension beginning before the electrical signs of seizure in the case of typical convulsant drugs. Orenstein (15), studying metrazol-induced convulsions in human beings, concluded from electrocardiographic, blood pressure and spinal fluid changes that the observed effects were the result primarily of anoxemia. Also, in reporting effects during and immediately after convulsions induced by metrazol, Cleckley and Eggleston (16) emphasized the extreme degree of cyanosis which occurs in some cases. Abreu and Woodbury (17), in a precise study of cardiovascular effects of strychnine convulsions in dogs, demonstrated that fatal respiratory paralysis was not essentially caused by fatigue of the respiratory center following bombardment with sensory impulses but was more probably the result of anoxemia and, additionally, of hyperacidemia.

Campbell (18) reported that an increase in the oxygen tension in the air breathed markedly increased the oxygen tension in the abdominal cavity and to a lesser degree in the skin. He attributed this rise to an increase of oxygen in physical solution in the blood. Montgomery and

Horwitz (19) concluded that, following the inhalation of 100 per cent oxygen, the oxygen tension of the skin commonly increases from a control of about 50 mm. to 450 mm. of mercury at the peak of oxygen inhalation, depending upon the rate of the circulation and the absence of vascular disease. They also stated that the increment in tissue oxygen tension was usually closely related to the increment in the oxygen breathed.

PROCEDURE AND EXPERIMENTAL CONDITIONS

Each experiment consisted in the observation of a group of 10 animals in a high oxygen atmosphere and simultaneous observation of another 10 closely matched animals in room air. Administration of the drug to each group was made from the same stock solution with alternation of animals from each group. By this procedure the first and last injections in both groups were made at about the same time, the total period for injection of all 20 animals lasting about ten minutes. After administration of the drug, observations were made at frequent intervals and the number in convulsions and the number dead were recorded. These observations were continued for at least thirty minutes after the cessation of convulsions in any of the animals. They were then returned to marked cages and the number of late deaths in the subsequent twenty-four hours was noted. In a considerable number of the experiments, gross postmortem examination was made of the abdominal and thoracic viscera.

In each experiment, all animals were of the same sex. Approximately equal numbers of experiments were carried out with male and female animals. No recognizable differences in responses of the sexes were noted in so far as one experiment could be compared with another. In selecting animals for the two groups of each experiment, an effort was made to divide the animals equally according to weight and also to obtain equal representation from the various litters used. Most of the animals were used only once in these studies although some were survivors of an experiment carried out four or more weeks previously. An effort was made to obtain equal distribution based on this type of past history. The white mice varied in weight from 15 to 35 gm. and the white rats from 125 to 250 gm.

All animals received the same dose of drug per unit of body weight. Aqueous stock solutions of the drugs were made from time to time. The sodium cyanide solutions were made up most frequently. Dilutions prepared at the time of the experiment corresponded to injection volumes of about 0.2 cc. for mice and 0.6 cc. for rats. All solutions were injected subcutaneously in the back rather than over the abdomen, which might have resulted in accidental intraperitoneal injection.

All experiments were conducted in an insulated room with thermostatically controlled air refrigeration machine which maintained room temperature between 25 C. and 26 C. Temperatures within the containers commonly increased about 1 C. over room temperature during

the experiment. The experiments were conducted during the summer months when ordinary room temperatures averaged about 30 C. during the day. Most of the animals were maintained in the stock colony at these ordinary room temperatures although in a few instances some groups were maintained for one to three days in the room with controlled temperature. There was no evidence that susceptibility to the drug was changed by this latter procedure.

The observation chambers consisted of two cylindrical metal containers about 18 inches in diameter and 100 liters in capacity. They were covered with a removable frame fitted with glass for observation and with a trap door for introduction of the animals. High oxygen atmospheres from a commercial gas cylinder were introduced into one of the containers through an opening in the lower part of the container. Before the experiment the gas was passed into the container for ten to fifteen minutes. Concentrations of 95 to 97 per cent were obtained as determined by analysis before the experiment and at random intervals during some of the experiments. Containers of soda lime and of calcium chloride were placed in the experimental chambers to reduce carbon dioxide and humidity.

RESULTS

The appearance of convulsions was generally similar to the detailed description recently given by Cheymol and Thuillier (20). The average time of onset of convulsions was about fifteen minutes after the first injection or, correspondingly, about five minutes after the last animal had been given an injection and placed in the chamber. In terms of the total number of animals having convulsions at the first observation following the injections, there was a higher incidence of convulsions with cyanide (23 per cent) and with metrazol (80 per cent) among the animals in the high oxygen atmosphere as compared with those in the room air. This difference was not noted in the group given strychnine. With each of the drugs, there were no clear differences in the character of the convulsions in the two groups. With each of the drugs it was clearly demonstrated that the convulsions were maintained for a substantially longer time in those groups in high oxygen atmospheres. A survey of the protocols shows that, during the critical interval of the experiments, twice as many animals were recorded as being in convulsions in the groups in high oxygen atmospheres as in the groups in room air. This is a corollary of the data on average survival time presented in table 1. According to these data the average survival time of the groups in high oxygen atmospheres was a little more than twice that in room air.

The data showing incidence of survival do not permit a clear-cut conclusion. Whereas, by comparison with similar groups in room air, the groups in high oxygen atmospheres showed a higher survival rate in the case of cyanide, they showed a more limited improvement in survival rate in the case of strychnine and a lower survival rate in the case

of metrazol. It may also be noted that there are sufficient irregularities in the relations of absolute doses and survival rates that any calculated LD_{50} would have a relatively high standard error.

With strychnine and with metrazol, ordinarily only a very few minutes elapsed between the cessation of convulsions and death of the ani-

EXPERIMENT No. 4

PROTOCOL

Drug: sodium cyanide Animal: mice Room temperature: 25.0 C.
Dose: 9 mg./kg. Sex: male
Time: 10:05 a.m.—injections started
10:11 a.m.—injections completed

	Normal Atmospheric Group		High Oxygen Group	
Time After Beginning of Injections, minutes	Number Dead	Number in Convulsions	Number Dead	Number in Convulsions
11	5	0	2	6
17	6	1	2	7
25	6	1	3	6
60	6	0	4	1
120	6	0	4	1
275	6	0	4	0
310	6	0	5	0
420	6	0	5	0
24 hours	6	—	5	—

EXPERIMENT No. 5

PROTOCOL

Drug: Metrazol Animal: rats Room temperature: 25.0 C.
Dose: 110 mg./kg. Sex: male Relative humidity: 57%
Time: 2:00 p.m.—injections started
2:15 p.m.—injections completed

	Normal Atmospheric Group		High Oxygen Group	
Time After Beginning of Injections, minutes	Number Dead	Number in Convulsions	Number Dead	Number in Convulsions
20	0	0	0	0
24	0	0	0	0
26	0	4	0	6
29	1	2	0	9
33	2	6	0	10
34	3	6	0	10
40	4	3	1	7
65	8	1	6	4
88	8	0	8	2
115	8	0	8	2
130	8	0	9	0
140	8	0	10	0
24 hours	8	—	10	—

TABLE 1

Dose in mg./kg.	Room Atmosphere		High Oxygen Atmosphere		Average Survival Time in Minutes	
	Survivors	Number Used	Survivors	Number Used	Room Atmosphere	High Oxygen Atmosphere
Mice						
Metrazol						
90	24	30	18	30	32	101
100	1	10	4	10	23	—
110	15	60	13	60	22	98
Rats						
110	9	30	3	30	61	79
120	2	20	1	20	44	63
Mice						
Strychnine sulfate						
1 and 1.3	11	30	19	30	15	34
Rats						
1.2, 1.6 and 2.0	28	30	28	30	29	39
2.5 and 3.0	23	30	24	30	47	78
3.5 and 4.0	5	30	1	30	34	79
Mice						
Sodium cyanide						
9	6	30	13	30	16	51
10.5	2	20	3	20	16	24
12	0	10	0	10	14	16
Rats						
9	5	20	5	20	48	94
12	10	40	16	40	67	129

mals. With cyanide, however, a significantly longer period occurred. The animals in high oxygen atmospheres survived an average of forty minutes after convulsions ceased; those in the room air survived an average of twelve minutes. With all the drugs the number of deaths occurring overnight was small (5 per cent) when compared with the total number of deaths. Late deaths were more frequent in the experiments in which metrazol and cyanide were used than in the experiments in which strychnine was given (11 with metrazol, 9 with cyanide and 1 with strychnine).

In two experiments with metrazol and two with cyanide, the effects in a 15 per cent oxygen-85 per cent nitrogen atmosphere were contrasted

with effects in room air. Survival rates were virtually identical in experiments with both drugs. With metrazol the survival time was lower in the case of the 15 per cent oxygen atmosphere (an average of 17 minutes with 15 per cent oxygen contrasted with 23 minutes with room air); no difference in survival times was observed in the experiments with cyanide.

TERMINAL PHASE OF CONVULSIVE DEATHS

In animals which survive for a period after convulsions, it is generally apparent that the heart finally ceases to beat as a result of anoxia. In those animals which undergo extreme spasm followed by no further external respiratory movements, there is reason to consider the possibility that ventricular prefibrillary states or outright ventricular fibrillation might have occurred during this interval of violent stress; anoxia, hypertension, discharge of epinephrine and violent body spasms favor such development. A decisive answer on this point is not readily obtained because of the difficulty of recording valid electrocardiographic effects during the interval of extreme activity of skeletal muscle. Electrocardiographic tracings made during metrazol convulsions in patients have not indicated important fibrillary tendencies in those recordings made directly before and as soon after convulsions as they could be properly recorded (21, 22). We have conducted some further tests of this nature with fatal intravenous strychnine injections in dogs anesthetized with pentobarbital. A direct writing electrocardiograph with special stylus of steel wire and ink-recording tip was used because of the relative durability of such an instrument in the presence of skeletal muscle spasms; the records were obtained from limb lead II with needle electrodes inserted in the skin. Using single doses of strychnine of 4 and 6 mg. per kilogram in 4 intact animals and in 2 with open chest and artificial respiration, we failed to observe important fibrillary tendencies. In the intact animals, a distinct acceleration of heart rate was observed during the early stages of spasm; in each case, however, the heart continued to beat for several minutes during the subsequent terminal apnea. The complexes, as soon as free of disturbing effects of skeletal muscle spasm, were typical of anoxia without special fibrillary tendencies. The usual anoxic picture is that of slow rhythm with sinus node dominance until the final termination when a broad ventricular complex (idioventricular rhythm) develops, followed by cardiac arrest. During observations of the heart in the two open chest preparations the most conspicuous effect was dilation with subsequent moderate tachycardia.

The general conclusion to be drawn from these observations is that there is no clear indication that antifibrillatory drugs are of value in these conditions.

DISCUSSION

These experiments demonstrate a moderate but limited value in the use of freely inspired high oxygen atmospheres. The value in these

experiments was limited chiefly to the prolonged interval of survival whereas, considering the group of drugs, the ultimate survival rates were not judged to be significantly improved over those obtained when ordinary room atmospheres was inspired. In the experiments, in which cyanide was used, there was a questionably significant improvement in survival rate. With each of the drugs, the prolonged survival time in high oxygen atmospheres was associated with a much longer period of convulsions. This prolonged period of convulsions was undoubtedly the basis for the increased pulmonary hemorrhage noted in these groups and without such effect, the survival rate in these groups might have been higher. It should also be recognized that the reaction of these small animals is probably less sensitive than is the case with higher mammals. It is possible that the moderate advantage noted in favor of the use of high oxygen atmospheres would actually be greater if a series of experiments was carried out with higher mammals. This, however, is strict speculation. It is less speculative to consider that the use of oxygen combined with well-balanced administration of sedatives might favorably influence the outcome in critical borderline cases.

SUMMARY AND CONCLUSIONS

Experiments were conducted to determine whether there were any quantitative differences in the effects of drug-induced convulsions when high oxygen atmospheres were inspired and when ordinary room atmosphere was employed. In each separate experiment, 10 animals which received injections of drugs were observed in a high oxygen atmosphere and 10 animals similarly injected were observed simultaneously in ordinary room air. Thirty-six such experiments were conducted with rats and mice. Fifteen experiments were conducted with metrazol, twelve with strychnine sulfate and twelve with sodium cyanide. In addition, two similar experiments with metrazol and two with strychnine were conducted in which the effects of 15 per cent oxygen atmosphere were contrasted with those of ordinary room air.

High oxygen atmospheres as contrasted with ordinary room air had the effect of increasing the length of survival time but with continuance of convulsions. These time periods were somewhat more than doubled as calculated from an over-all average with the three drugs. Survival rates were not considered to be significantly different in the two types of atmospheres. Pulmonary hemorrhage was consistently observed and was more prominent in those animals maintained in high oxygen atmospheres with corresponding longer intervals of convulsions. Results in 15 per cent oxygen atmospheres were not significantly different from those in ordinary room air, except possibly for a shorter survival interval in the 15 per cent oxygen atmosphere.

Experiments with dogs receiving large intravenous doses of strychnine failed to indicate that antifibrillatory drugs have any particular indication in these conditions.

These experiments, in so far as their implications can be transferred to clinical conditions, indicate that there is a definite but limited advantage in the administration of oxygen by mask during intervals between critical recurrent convulsions.

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