TABLE II.
Reversibility of Propazone Inhibition of Oxygen Consumption in Rat Kidney Cortex Slices.
Medium: Ringer's-phosphate-glucose, pH 7.4, Temp. 37.5°C.

	Propazone sodium, 500 mg%	Control
Mean Q_{O_2} before addition of propazone	5.30	4.60
Mean Q_{O_2} 35 min. after addition of propazone	1.80	4.60
Mean Q_{O_2} 45 min. after washing slices	3.20	3.95

Conclusions. Propazone sodium inhibits the oxygen consumption of rat kidney cortex, liver and cerebral cortex slices *in vitro*. For a given concentration of propazone, this inhibition is much more marked in media containing glucose than in those containing succinate or p-phenylenediamine. In kidney cortex the inhibition is about 70% reversible.

13570

Drug Prophylaxis Against Lethal Effects of Severe Anoxia. II. Alcohol, Amytal and Pentobarbital.

G. A. EMERSON, E. J. VAN LIERE AND JAMES L. MORRISON.

From the Departments of Pharmacology and Physiology, West Virginia University School of Medicine, Morgantown.

Effects of certain respiratory stimulants and other convulsants as antagonists to the lethal effects of acute anoxia have been reported.[1] Comparison of prophylactic effects of other types of agents through a standardized technic[2] is desirable, since many of the compounds previously reviewed[1] exhibit their protective action only under special conditions. Inasmuch as none of the convulsants affords complete prophylaxis against lethal effects of acute anoxia, it is of interest to observe the influence of various representative narcotics.

It was postulated[1] that, among others, an agent inhibiting the tendency toward convulsions in acute anoxia and an agent easily utilized as a nutrient under anoxic conditions might be of value if such agents did not unduly depress the nervous mechanisms governing respiration. Proper doses of ethyl alcohol may combine these 2 characteristics without too great respiratory depression. Accord-

[1] Emerson, G. A., and Van Liere, E. J., *Arch. internat. Pharmacodyn.*, 1940, **64**, 239.

[2] Emerson, G. A., Van Liere, E. J., and Morrison, J. L., to be published.

ingly, different doses of ethanol were administered to young adult white mice and tranquillizing and narcotic doses of a moderately long-acting and of a moderately short-acting barbiturate were administered to other mice, before exposure to anoxic anoxia. The barbiturates do not act as nutrients and thus serve as controls for the simple tranquillizing and narcotic effects of ethanol.

All agents were administered intraperitoneally. A 10% solution of absolute ethanol in physiologic saline, by volume, was injected as noted in Table I, and 60 cc/kg of saline were injected in other mice to control the effects of hydration. It was previously shown that treatment with 50 cc/kg of saline does not significantly alter the susceptibility of mice to lethal effects of anoxia.[1] Na amytal and Na pentobarbital were injected with 50 cc/kg of saline, and 50 cc/kg of saline were injected into control mice subjected simultaneously to anoxia.

Anoxic anoxia was produced in a decompression chamber resembling that described by Kolls and Loevenhart.[3] Since previous experience[1] demonstrated that the lethal range of anoxia is variable for mice on different days, each experiment was controlled by inclusion of a group of mice treated with saline, with simultaneous exposure to anoxia of these control mice and others receiving drugs. Anoxia was rapidly induced by reducing the tank pressure to a level simulating an altitude of about 10,000 ft. The mice were then maintained at this degree of anoxia for 10 minutes. It is felt that this treatment obviates any hazard of the occurrence of aeroembolism later.[2] The pressure in the tank was then reduced at a rate simu-

TABLE I.
Influence of Alcohol and Barbiturates on Resistance to Lethal Effects of Anoxia.

Agent	Dose	Time before exposure to anoxia, hours	Mortality ratio	Mean body wt of mice, g	
				Surviving	Dying
Ethanol	6.0 cc/kg	1	12/70	15.7	17.1
Saline	60. ''	1	32/70	14.6	14.8
Ethanol	6.0 ''	1	6/30	15.9	17.7
''	6.0 ''	14	14/30	16.3	18.4
''	3.0 ''	1	16/30	15.9	17.1
Saline	60. ''	1	16/30	17.7	18.3
Na amytal	40. mg/kg	1	3/20	—	—
'' ''	80. ''	1	7/20	—	—
'' pentobarbital	25. ''	1	6/20	—	—
'' ''	50. ''	1	1/20	—	—
Saline	50. cc/kg	1	7/20	—	—

[3] Kolls, A. C., and Loevenhart, A. S., *Am. J. Physiol.*, 1915, **39**, 67.

lating an increase in altitude of about 1000 ft/min., until a simulated altitude of about 38,000 ft. was attained. At this pressure of 155 mm Hg, with a pO_2 of 31 mm, approximately half of the control mice succumbed in each instance. With corrections of readings of an open Hg manometer for barometric pressure, this level of anoxia corresponds to a simulated altitude of about 40,000 ft., or an atmospheric pressure of 141 mm, or a partial pressure of O_2 of 28 mm.

Three such experiments were carried out, with the results noted in Table I. Seventy mice treated with 60 cc/kg of 10% ethanol and 70 treated with 60 cc/kg of saline were simultaneously exposed to anoxia. Four groups of 30 mice each were also subjected to anoxia simultaneously; one group was treated with 60 cc/kg of 10% ethanol 1 hour before exposure to anoxia, another was similarly treated 14 hours before exposure to anoxia, a third group was treated with 30 cc/kg of 10% ethanol and a fourth group was treated with 60 cc/kg of saline, both of the latter groups 1 hour prior to exposure to anoxia. Finally, 4 groups of 20 mice each which had received barbiturates as noted in Table I, in 50 cc/kg of saline, and a control group of 20 mice which received 50 cc/kg of saline alone, were simultaneously exposed to anoxia.

Examination of Table I indicates that premedication with 6 cc/kg of ethanol 1 hour before exposure to anoxia greatly reduces mortality, from 48 of 100 control mice to 18 of 100 mice treated with ethanol. This reduction in the lethal effect of acute anoxia is highly significant statistically, with a p much less than 0.005, according to the criteria of Loewenthal and Wilson.[4] However, the same dose of ethanol given 14 hours prior to exposure to anoxia does not significantly alter mortality, nor does half the dose when administered 1 hour before exposure to anoxia. Mice treated with the higher dose of ethanol are in coma for several hours, but recover to apparently normal activity within 14 hours. Mice treated with the lower dose of ethanol are merely ataxic and somewhat more quiet than control mice before and during the exposure to anoxia. No further deaths occurred within 48 hours after the mice were subjected to anoxia.

Of the results with mice treated with barbiturates, only those of the group treated with 50 mg/kg of Na pentobarbital exhibit a significant reduction in mortality. The p for the significance of this reduction is exactly 0.05.

Also included in Table I are the mean body weights of the larger groups of mice surviving and succumbing under identical conditions

[4] Loewenthal, L. J. A., and Wilson, W. A., *Brit. Med. J.*, 1939, **2**, 110.

of treatment. These data tend to the conclusion that lighter mice are more resistant to lethal effects of anoxia than are heavier mice, but none of the differences in mean body weight is significant. The problem of correlation of body weight with susceptibility to anoxia is considered in more detail elsewhere.[2]

Comparison of the prophylactic effects of ethanol and the barbiturates indicates that the superiority of ethanol in this regard is dependent upon factors other than simple tranquillization of narcosis. Utilization of ethanol as a nutrient by anoxic tissues may be an important factor, but other differences in pharmacological action of the 2 types of narcotics must be sought for in larger anoxic mammals before definite conclusions may be drawn. Observations of the resistance to lethal effects of anoxia in mice treated with more selective depressants are in progress.

Within the range of doses used, it is improbable that ethanol or the barbiturates cause any appreciable histotoxic anoxia, for there is a complete lack of synergism of these agents with anoxic anoxia. These narcotics may cause a true histotoxic effect when applied to isolated tissues in high concentrations but there is no indication that a significant degree of histotoxic anoxia is produced by the sublethal amounts administered in the present study.

Since these studies are concerned with lethal effects of severe anoxic anoxia and only full narcotic doses of ethanol were found to be protective, no immediate applications to therapy in man are possible. The present results should not be construed to apply to milder degrees of anoxia, particularly as encountered in aviation practice, where alcohol is contra-indicated.[5, 6]

Summary. Full narcotic doses of ethyl alcohol significantly reduce the lethal effects of severe acute anoxic anoxia in mice if administered 1 hour prior to exposure to anoxia but not if administered 14 hours before exposure. Amytal and pentobarbital do not produce comparable prophylactic effects.

[5] Armstrong, H. G., *Principles and Practice of Aviation Medicine,* Baltimore, 1939.

[6] Barcroft, J., *Lancet,* 1920, **2**, 485.