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Absorption and Diuretic Effects of Nebulized Ethanol in Dogs[1] (38407)

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Acute pulmonary edema is a medical emergency requiring prompt therapeutic intervention. Administration of oxygen, bronchodilators, cardiac glycosides, morphine, and diuretics, along with the application of tourniquets or phlebotomy, is required in the more seriously ill patients. In addition, positive pressure ventilation, with or without control of ventilation or its volume, is often of great value. However, positive pressure breathing has the adverse effect of antidiuresis secondary to its known stimulation of ADH release (1–3).

Alcohol, in vapor form, has also been advocated for the treatment of acute pulmonary edema. Although it was introduced clinically more than 20 years ago, the mechanism of action of nebulized alcohol and its therapeutic value in pulmonary edema remain controversial. Its known beneficial effects are local and include stabilization of lung surfactant and an antifoaming action (4–6). Recently, successful resuscitation following the administration of nebulized alcohol to patients refractory to routine therapy has caused the authors to consider a possible new role for inhalation alcohol in acute pulmonary edema. If sufficient nebulized alcohol is absorbed during inhalation therapy, the systemic effects of sedation and inhibition of ADH release represent potential unrecognized benefits. The present study evaluates the absorption of nebulized alcohol in dogs, when administered as it would be to a patient with acute pulmonary edema, and its capacity to offset the release of ADH secondary to positive pressure breathing.

Methods. Twenty adult mongrel dogs were fasted overnight to obtain maximal concentration of the urine. Animals were paralyzed with decamethonium bromide (10 mg), intubated, and ventilated with a Harvard respirator. Utilizing a semiopen anesthetic technique, each dog was ventilated with a mixture of nitrous oxide (4 liters/min) and oxygen (2 liters/min). Femoral artery cannulation allowed continuous monitoring of systemic blood pressure and serial sampling of arterial blood. Through a small suprapubic incision the distal portion of each ureter was isolated and cannulated with a polyethylene catheter. The placement of ureteral catheters allowed the determination of the volume and the osmolality of urine collections made at 15-min intervals. After a 30-min period of stabilization, all animals underwent a 30-min period of intermittent positive pressure breathing (20 cm H_2O) using room air and a Bennett Inhalation Therapy Unit (Model TV-2P). Control animals (five dogs) underwent sham nebulization with room air during this period. Test animals (15 dogs) received combined positive pressure and nebulization of 95% ethyl alcohol (1.5 ml/kg) for 30 min. Serial samples of arterial blood obtained at 5, 15, and 30 min during nebulization and at 30 and 60 min after nebulization were analyzed for alcohol by gas chromatography (7).

Urine collections were continued for a period of 120 min following nebulization. The osmolality of each urine collection was determined using an Osmett A Automatic Osmometer (Precision Systems). Urine flow (V_u) and tubular clearance of water (Tc_{H_2O}) were calculated for each sample.

Results. All test animals receiving nebulized alcohol developed significant blood alcohol levels (Table I). The concentration of alcohol in the blood averaged 23.3 mg/100 ml at 5 min, increasing to 40.7 mg/100 ml at 15 min, and 58.7 mg/100 ml at 30 min. The average concentration of alcohol in the blood subsequently declined to 28.3 and 16.7 mg/100 ml at 30 and 60 min postnebulization, respectively.

Control animals showed the expected concentration of the urine following overnight fast-

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TABLE I. Average Blood Alcohol (mg/100 ml) during and Postnebulization.

	Blood alcohol (mg/100 ml)				
	During nebulization (min)			Postnebulization (min)	
Time	5 min	15 min	30 min	30 min	60 min
$\bar{X} \pm$ SEM	23 ± 2.3	41 ± 2.2	59 ± 2.6	28 ± 2.2	17 ± 2.1

ing (Table II). The average base-line osmolality of 1821 mOsm/liter gradually increased with each subsequent 15-min period of observation. Maximal concentration of the urine occurred at 120 min with 2393 mOsm/liter representing a 31% increase over base-line values. The urine volume and urine flow per 15-min period showed no significant change from base-line values following sham nebulization. A base-line Tc_{H_2O} of −0.58 ml/min had significantly decreased to −0.83 ml/min at 120 min ($P < 0.05$).

The urine of test animals averaged 1981 mOsm/liter following overnight fasting (Table II). After nebulization of 95% ethyl alcohol for 30 min, urine osmolality gradually decreased to 1691 mOsm/liter at 45 min postnebulization (a 14% decrease from the average base-line value). The average osmolality then increased to 1812 mOsm/liter at 120 min as the blood alcohol level diminished. Urine volume and flow had increased 21% at 120 min, however, values were not significantly different from base-line recordings. The Tc_{H_2O} was not significantly changed following alcohol nebulization.

There was essentially no change observed in arterial blood pressure and heart rate of either control or test animals during the period of observation.

Discussion. The exact mode of action of inhaled alcohol in the treatment of acute pulmonary edema remains conjectural. Luisada and his colleagues, who introduced the procedure into clinical practice, attributed its favorable action to antifoaming properties (10). More recently, McClenahan *et al.* demonstrated that lungs with decreased compliance could be restored to normal by ventilation with ethyl alcohol vapor, and proposed that it stabilized lung surfactant (11). If, however, ethanol is absorbed in sufficient amounts via the pulmonary route, it is possible that the therapeutic efficacy of alcohol vapor inhalation during acute pulmonary edema may in part result from the systemic effects of alcohol. The local pulmonary effects may then be complemented by the systemic effects of sedation, diuresis, and vasodilatation. In order to ascertain if systemically effective blood concentrations occur during inhalation therapy, our experiments were designed to administer ethanol vapor to dogs in a manner simulating the treatment of a human patient with acute pulmonary edema.

Moore and Karp in 1945 reported sedation in obstetrical patients given intravenous ethanol to blood levels of 50–70 mg/100 ml (12). Johnstone and Reier infused intravenous ethanol at 0.35, 0.70, and 1.05 ml/kg over 60 min to normal human subjects, and found peak blood concentrations averaging 40, 99, and 121 mg/100 ml. The subjects showed various degrees of euphoria, intoxication, and sedation with little evidence of respiratory depression compared with other sedative and analgesic drugs (13). In the present study, blood alcohol levels in our experimental animals were in the lower range of those reported to cause sedation. Therefore, inhalation of alcohol during acute pulmonary edema might be beneficial in reducing anxiety without impairing respiration, supplementing morphine which is commonly used.

Left ventricular failure is the most common cause of acute pulmonary edema. Therefore the cardiovascular effects of blood alcohol levels attained by nebulization are of paramount importance. Unfortunately, the literature on this subject is controversial, with effects varying with dosage, anesthesia, whether the chest is opened or closed, and whether or not there is preexisting heart disease (14–17). There is some evidence for a vasodilator effect in dogs (16). In contrast, Conway found the hemodynamic effects of blood alcohol levels ranging from 30 to 100 mg/100 ml to be deleterious in human patients with coronary heart disease (17). Patients with pulmonary edema would probably react to ethanol in a manner similar to Conway's subjects.

TABLE II. Average Urine Osmolality (mOsm) for Control and Test Animals.[a]

Experimental group	Base line	Nebulization	Postnebulization (min)					
			15 min	30 min	45 min	60 min	90 min	120 min
Control								
$\bar{X} \pm$ SEM	1821 ± 150	1915 ± 175	1968 ± 192	1895 ± 187	1885 ± 186	1973 ± 260	2156[b] ± 181	2393[b] ± 225
Ethyl alcohol								
$\bar{X} \pm$ SEM	1981 ± 78	1925 ± 83	1826[b] ± 79	1723[c] ± 82	1691[c] ± 72	1723[c] ± 85	1803[b] ± 77	1812[b] ± 84

[a] Statistical significance refers to comparison to baseline values.
[b] $P < 0.05$.
[c] $P < 0.01$.

However, at the low blood concentrations achieved by ethanol inhalation, the hemodynamic effects would probably be minimal.

Positive pressure breathing with or without controlled ventilation may be employed in the acute phase of pulmonary edema to facilitate the transport of oxygen across the alveolar–capillary membrane. Its potential therapeutic role is complicated by its known stimulation of antidiuretic hormone release (1–3). The effect is not impressive in our control animals because they were already in a state of almost maximum antidiuresis. Ethanol, in blood concentrations similar to those in our experiments, is known to inhibit the release of antidiuretic hormone (18). In the present studies, although ethanol-treated showed a significant decrease in urine osmolality compared with control animals (Table II), there was never a water diuresis, *i.e.*, a positive clearance of water. In addition, the change in net tubular reabsorption of water (Tc_{H_2O}) was not of an important magnitude (< 0.2 ml/min). Therefore, it appears that in this situation, with anesthesia and positive pressure respiration, antidiuresis is maintained in spite of the presence of ethanol in the blood.

Summary. (1) Dogs anesthetized with nitrous oxide were given positive pressure respiration and nebulized ethanol for 30 min in a manner similar to that used in treating human subjects for acute pulmonary edema. A control group was given the same treatment without the ethanol. Blood and urine samples were collected during this 30-min period and for 2 hr afterward while the animals were maintained under anesthesia and artificial respiration.

(2) Blood alcohol levels reached an average of 59 mg/100 ml in 30 min and diminished to 17 mg/100 ml at the end of the 1 hr postnebulization period. It is considered that these concentrations are high enough to have important systemic effects on sedation but probably have little hemodynamic effect.

(3) The urine of the dogs breathing ethanol vapor showed a significant decrease in osmolality in contrast to the increased osmolality of the urine of the control dogs. The fact that they did not develop a positive clearance of free water is attributed to the antidiuretic effects of positive pressure respiration and the anesthesia.

1. Baratz, R. A., and Ingraham, R. C., Amer. J.

Physiol. **198,** 565 (1960).

2. Baratz, R. A., Philbin, D. M., and Patterson, R. W., Anesthesiology **32,** 17 (1970).

3. Philbin, D. M., Baratz, R. A., and Patterson, R. W., Anesthesiology **33,** 345 (1970).

4. Heinemann, H. O., Adv. Intern. Med. **14,** 83 (1968).

5. Avery, M. E., and Said, S., Medicine **44,** 503 (1966).

6. Cook, C. D., Mead, J., Schreiner, G. L., Frank, N. R., and Craig, J. M., J. Appl. Physiol. **14,** 177 (1959).

7. Jain, N. C., Clin. Chem. **17,** 82 (1971).

8. Robin, E. D., Cross, C. E., and Zelia, R., New Eng. J. Med. **288,** 239 (1973).

9. Robin, E. D., Cross, C. E., and Zelia, R., New Eng. J. Med. **288,** 292 (1973).

10. Luisada, A. A., Goldmann, M. A., and Weyl, R., Circulation **5,** 363 (1952).

11. McClenahan, J. B., Mussenden, R., and Ohlsen, J. D., J. Appl. Physiol. **27,** 90 (1969).

12. Moore, D. C., and Karp, M., Surg. Gynecol. Obstet. **80,** 523 (1945).

13. Johnstone, R. E., and Reier, C. E., Clin. Pharmacol. Ther. **14,** 501 (1973).

14. Mitchell, J. H., and Cohen, L. S., Mod. Conc. Cardiovas. Dis. **39,** 109 (1970).

15. Riff, D. P., Jain, A. C., and Doyle, J. J., Amer. Heart J. **78,** 592 (1969).

16. Pitt, B., Sugishita, Y., Green, H. L., and Friesinger, G. C., Amer. J. Physiol. **219,** 175 (1970).

17. Conway, N., Brit. Heart J. **30,** 638 (1968).

18. Kleeman, C. R., Rubini, M. E., Lamdin, E., and Epstein, F. H., J. Clin. Invest. **34,** 448 (1955).

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