Therapy of Paroxysmal Pulmonary Edema by Antifoaming Agents

By Aldo A. Luisada, M.D.

Inhalation of certain volatile substances decreases the amount of foam in the respiratory passages and may be helpful in acute pulmonary edema. Experiments with several agents were performed in animals with different types of acute edema of the lungs. The best results were obtained with ethyl alcohol, which decreased the severity of the edema and prolonged the survival of the animals. Alcohol, while acting as an antifoaming agent, has no untoward side effects and is well tolerated. This method of therapy is now undergoing clinical tests.

In Spite of many accepted therapeutic measures, paroxysmal pulmonary edema still has a high mortality. Emergency treatment is complicated by the fact that some of the drugs which are useful in certain types of pulmonary edema might be detrimental in others. Morphine, barbiturates and chloral, advocated in cardiac patients \(^1\) \(^2\) are not advocated in pulmonary edema following injury to the central nervous system on account of their depressing action on the nerve centers. Intravenous strophanthin \(^3\) might cause ectopic rhythms in pulmonary edema following coronary occlusion. Venesection, mercurial diuretics, \(^4\) spinal anesthesia, \(^5\) and possibly morphine \(^6\) should not be used in pulmonary edema accompanied by shock because they further reduce venous return and cardiac output. Oxygen under pressure \(^7\) may not be well tolerated by patients with emphysema. A new therapy which could be used in any case of paroxysmal pulmonary edema, irrespective of the cause, would be of great help and probably save many lives. For this reason, a new approach has been followed.

Part I. Studies on Pulmonary Edema Caused by Adrenaline

It has been known for a long time \(^8\) \(^9\) that fairly large amounts of fluid may be tolerated in the respiratory passages as long as no foam is formed. When the latter develops, increased volume of the air-fluid mixture and modified physical properties lead to severe effects by blocking the small bronchi. Anoxia then develops and is followed by higher pressure in the pulmonary artery \(^10\) and increased transudation. \(^11\) A vicious circle is then created which gradually increases the severity of the edema. When foam accumulates in the trachea, the effects are extreme and suffocation causes death. Therefore, the application of antifoaming agents was considered.*

Starting from this assumption, a systematic study was made in acute pulmonary edema induced by adrenaline in the rabbit, this being one of the easiest to produce and one of the most constant types of experimental pulmonary edema. The results of this study have been reported in a preliminary note. \(^12\)

Material and Method

Adrenaline induces a fulminating type of pulmonary edema when injected intravenously in the rabbit, as proved long ago by Emerson. \(^13\) It fails to do so in other species. The study was made in a series of 109 white, male rabbits weighing between 1.5 and 2.5 kilograms. Paroxysmal pulmonary edema was induced by a standard method previously used by the author \(^1\) and slightly modified by Glass, \(^14\) namely by the injection of 2 cc. of a 1:1000 solution of adrenaline into the marginal vein of the ear, irrespective of the animal’s weight. The injection time was kept as close to one minute as possible.

 Twelve rabbits were used as controls, one or more

* In vitro studies on antifoaming agents are being made by Epstein and co-workers. \(^15\)
for each series of experiments. Only 1 out of 12 survived and presented no edema of the lungs.

Evaluation of the edema was done in the following way: (1) Observation of the animal for evidence of discharge of bloody foam from the nostrils or mouth. (2) Survival time. Usually, 50 per cent of the rabbits died within the first six minutes and nearly all within 30 minutes of the time of injection, as was confirmed by the controls in this particular batch of animals. If survival was longer, a maximum of 60 minutes was arbitrarily set, after which the animal was killed quickly, and the lungs examined. (3) Appearance of the lungs. When the lungs were removed, their gross appearance was noted and they were examined for the presence of foam in the trachea and on cut surfaces of the parenchyma. (4) Weight of the lungs. The lungs were weighed after removal of most of the trachea and of all other mediastinal organs. The lungs:body ratio was determined by dividing the weight of the lungs in grams by that of the animal in grams and multiplying the result by 100. Control studies on normal rabbits showed that, by this method, the average ratio is 0.45.

Inhalation of antifoaming agents was obtained in the following way. The rabbits were put into a box with a glass cover. The drug was sprayed at frequent intervals into the box through a hole, by means of an atomizer. Because the appearance of the pulmonary edema is abrupt, the animal was exposed to vapors of the antifoaming agent for ten minutes prior to injection of adrenaline, and after the injection until death, or for 60 minutes.

The following antifoaming agents were tested: Ether, n-octyl alcohol* (octyl alcohol), methyl-n-hexacarbinol† (capryl alcohol), 95 per cent ethanol, and sorbitan triolatet (Span 89). None of these substances led to important general side effects. Ether and 95 per cent alcohol, after an initial period of excitement, caused mild sedation. The dose of ether and alcohol was kept below that causing anesthesia. Octyl and capryl alcohol seemed to cause some excitement in the animals.

In order to control the action of ethyl alcohol, this was also given intravenously in a subanesthetic dose (5 cc. per Kg. of a 25 per cent solution); by stomach or rectum in an anesthetic dose (8 to 10 cc. per Kg. of a 50 per cent solution); or with morphine sulfate. The latter was given in a dose of 10 mg. per Kg. by subcutaneous injection, as used in previous experiments of the author; adrenaline was administered 30 to 40 minutes later.

Further control studies were made with morphine sulfate plus oxygen under pressure. Pure oxygen was given under a pressure of 30 to 40 mm. of water through a tracheal cannula in morphinized rabbits. Adrenaline was injected soon after starting the oxygen jet.

Results

The results of these experiments are summarized in Table 1. Span 85 did not change the severity of pulmonary congestion and edema; it abbreviated the survival time. The heavy alcohols (capryl and octyl alcohol) slightly increased the survival time and decreased the severity of the edema. Ether also had a mild beneficial action.

The action of ethyl alcohol by inhalation was far more marked than that of the other substances, as revealed by the fact that, after 6 minutes, 90 per cent of the animals were still alive; the average survival time was doubled; and the average lungs:body ratio was decreased from three times to twice the normal. This effect of ethyl alcohol was comparable to that of morphine.

Equivalent, subanesthetic doses of alcohol by intravenous injection had a less favorable effect. On the other hand, larger doses of alcohol, given by gavage or enema in sufficient amounts to induce a mild anesthesia, had a beneficial effect which was slightly superior to that of inhalation alcohol in a smaller dose.

Combined therapy was found to give the most beneficial results. Alcohol by inhalation associated with morphine by injection gave excellent results. This was comparable to that obtained by using oxygen under pressure associated with morphine by injection, as proved by the long survival time and the lack of edema.

Discussion

The stability of a foam is based upon the character of the air-fluid interface, namely on the surface tension of the fluid. Any substance capable of modifying the surface tension in such a way as to decrease the foam, is called an antifoaming agent. Some of these agents are oily, poorly volatile substances, like sorbitan triolate, and both capryl and octyl alcohol. Others, like ether and ethyl alcohol, are light and extremely volatile. This fact alone may influence their effectiveness, because penetration into the air passages and mixture with the foam is definitely more difficult with the former types than with the latter.

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* Supplied by Eastman Kodak Co.
† Obtained through the courtesy of the Atlas Powder Co.
The unfavorable action of Span 85, which abbreviated the survival time, may be explained by the possibility that droplets of this oily substance were formed in the bronchi coating the mucosa and contributing to the obstruction of the air passages.

Heavy alcohols had a certain action on the foam revealed by the gross appearance of the cut lungs and by the scanty foam found in the trachea and bronchi. Still, the result was not remarkable, possibly because of toxicity and stimulation of the central nervous system.

Ether had a certain beneficial action. It is possible that congestion of the lungs and irritation of the bronchial mucosa somewhat counteracted the useful effect of decreasing the amount of foam.

Ethyl alcohol proved to be the best among the antifoaming agents. Controls with equivalent subanesthetic doses injected by vein and with larger anesthetic doses given via the gastrointestinal tract revealed that inhalation with alcohol is followed by two different effects. One is local and is due to the antifoaming property of this substance. The other is general and consists of depression of the nerve centers. The latter may result in peripheral vasodilation, decreased dyspnea, and other favorable effects similar to those obtained by other narcotics and anesthetics, as proved by the author in the same type of experimental pulmonary edema.¹

The central action of alcohol explains only in part its useful effect by inhalation. This is proved by the fact that, in order to obtain comparable results, alcohol when administered parenterally has to be given in much larger doses than when it is inhaled. This shows that its antifoaming property is an important factor in the outcome.

**TABLE 1.—Influence of Various Antifoaming Agents on Adrenaline Pulmonary Edema of the Rabbit**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Per cent at L.D./50* (6 min.)</th>
<th>Average Survival (min.)</th>
<th>Average Lungs: Body Ratio and Standard Error</th>
<th>Per cent Developing Pulmonary Edema</th>
<th>Beneficial Effect</th>
<th>No. of Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Normal Animals) . . . . . . . . . . . . . . .</td>
<td>—</td>
<td>—</td>
<td>0.455 ± 0.021</td>
<td>—</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Adrenaline (controls) . . . . . . . . . . . .</td>
<td>50</td>
<td>15.5</td>
<td>1.35 ± 0.035</td>
<td>92</td>
<td>—</td>
<td>12</td>
</tr>
<tr>
<td>Span 85 . . . . . . . . . . . . . . . . . . .</td>
<td>25</td>
<td>6</td>
<td>1.48 ± 0.094</td>
<td>100</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Heavy alcohols (inhalation) . . . . . . . .</td>
<td>70</td>
<td>20.6</td>
<td>1.30 ± 0.098</td>
<td>90</td>
<td>x</td>
<td>10</td>
</tr>
<tr>
<td>Ether (inhalation) . . . . . . . . . . . .</td>
<td>100</td>
<td>29</td>
<td>1.15 ± 0.268</td>
<td>70</td>
<td>x</td>
<td>5</td>
</tr>
<tr>
<td>Morphine (subcutaneous) . . . . . . . . . . .</td>
<td>90</td>
<td>35</td>
<td>1.01 ± 0.109</td>
<td>50</td>
<td>xx</td>
<td>10</td>
</tr>
<tr>
<td>Ethyl alcohol (inhal.) (subanesthetic dose) .</td>
<td>90</td>
<td>35</td>
<td>0.95 ± 0.062</td>
<td>65</td>
<td>xx</td>
<td>20</td>
</tr>
<tr>
<td>Morphine (subcutaneous) plus ethyl cohol (inhal.)</td>
<td>100</td>
<td>42.4</td>
<td>0.68 ± 0.048</td>
<td>0</td>
<td>xxxx</td>
<td>10</td>
</tr>
<tr>
<td>Morphine (subcutaneous) plus oxygen under pressure . . . . . . . .</td>
<td>100</td>
<td>43.6</td>
<td>0.60 ± 0.051</td>
<td>0</td>
<td>xxxx</td>
<td>5</td>
</tr>
</tbody>
</table>

* One half the lethal dose.

† Standard Error \( = \sqrt{\frac{\sum \Delta^2}{(n)(n-1)}} \)
The useful action of inhaled alcohol is less apparent in the observation of the average results than in that of the single experiments. It should be kept in mind that adrenaline pulmonary edema is a fulminating syndrome which kills 92 per cent of the animals in 60 minutes and 30 per cent of them in 6 minutes. When treated with alcohol by inhalation, only 65 per cent of the animals had edema of the lungs; 35 per cent survived more than 60 minutes; and 90 per cent survived more than 6 minutes; only 1 out of 20 (5 per cent) discharged bloody foam from the nostrils. The useful action is even further demonstrated by the fact that it is equivalent to that of morphine sulfate.

The combination of parenteral morphine with alcohol by inhalation gave excellent results; all animals survived 6 minutes; 50 per cent survived 60 minutes; practically no edema of the lungs was found in any of the animals (table 1, figs. 1 and 2). The still existing mortality of a large percentage of rabbits is explained by toxic effect of the extremely large dose of adrenaline.

Statistical analysis was made of the data obtained in two series of experiments comparing alcohol by inhalation with alcohol by inhalation plus parenteral morphine. It was proved statistically that the means of lungs: body ratios in the two series are different and that the combination of the two drugs is superior to each of them alone (see table 1 and figs. 1 and 2).

As shown by previous studies, air and oxygen under pressure are effective in the treatment of adrenaline pulmonary edema of the rabbit.\textsuperscript{7, 13} In our experiments, oxygen under pressure plus morphine saved a high percentage of animals. Comparison between this series and that of the animals treated by parenteral morphine plus alcohol by inhalation showed that the results obtained by using the two methods are equivalent.

The combination of the three remedies, morphine, oxygen under pressure, and alcohol vapor seems, therefore, to be indicated in many clinical cases, while oxygen under pressure and alcohol vapors, morphine being excluded, should be used in others.

Conclusions

Experiments were performed in rabbits with a series of antifoaming agents administered by inhalation in order to decrease the severity of pulmonary edema caused by a standard dose of intravenous adrenaline.

Poorly volatile drugs (heavy alcohols, Span 85) failed to exert any favorable effect. Ether gave only a slight benefit.

Ethyl alcohol exerted an important favorable action due to its antifoaming property; its action on the central nervous system, though slight on account of the dose used, may enhance the effect. The favorable effect of alcohol is comparable to that of morphine.

Combination of morphine by injection with alcohol by inhalation gave excellent results, equivalent to those obtained by morphine plus oxygen under pressure.

Part II. The Action of Alcohol in Several Types of Experimental Pulmonary Edema

A comparison of the action of several antifoaming agents was made by using as a standard method the acute pulmonary edema induced by adrenaline in the rabbit (part I). It was shown that ethyl alcohol by inhalation was the best, adding a mild general action (central sedation, possibly vasodilation) to a more im-
important local action (antifoaming effect). Before suggesting clinical applications of this method, it was considered necessary to try the effect of alcohol vapor in several other types of pulmonary edema.

The following types of pulmonary edema were considered: (a) the edema caused in the rat by an intraperitoneal injection of thiourea, described by MacKenzie and MacKenzie; (b) the edema caused in the guinea pig by ingestion of ammonium chloride, described by Koenig and Koenig; (c) the edema caused by the rapid intracarotid infusion of physiologic salt solution, described by Luisada and Sarnoff in the dog and confirmed by Cheng in the rabbit.

Technic

Thiourea was injected by MacKenzie and MacKenzie in the adult rat (250–300 Gm.) by intraperitoneal injection in doses of 200 mg. per Kg. Pulmonary edema occurred in general within 16 to 24 hours, but sometimes earlier, within five hours.

In our experiments, white, adult rats weighing between 250 and 350 Gm. were used. Thiourea was used in a 10 per cent solution and 250 mg. per Kg. was the dose employed in the entire series of animals. Five of them were kept as controls; the other 5 were placed in a box containing a jar of alcohol-soaked gauze which evaporated readily, and were left there until death or for 22 hours. After this interval the surviving rats were killed and their lungs were examined.

Ammonium chloride was used by Koenig and Koenig to induce pulmonary edema in the guinea pig in the following doses: by intraperitoneal injection, 50 to 70 mg. per 100 Gm. of body weight; by gavage, 90 to 120 mg. per 100 Gm. of body weight.

A 10 per cent solution of ammonium chloride was made. In a first series of animals, 60 mg. per 100 Gm. of body weight were injected into the peritoneal cavity. In a second series, 100 to 120 mg. per 100 Gm. of body weight were given by gavage. Alcohol inhalation was obtained by placing the guinea pigs in a box into which alcohol was sprayed at frequent intervals. If the animals survived, they were killed after 60 minutes and their lungs were inspected and weighed.

The method of rapid injection of physiologic salt solution into the carotid arteries toward the brain was described by the author with Sarnoff. The same technic was used in the present experiments: anesthesia with a small dose of morphine (3 mg./Kg. subcutaneously) and urethane (1 Gm./Kg. by gavage); intracarotid infusion under a pressure of 280 to 300 mm. Hg. Three infusions were given: the first, equivalent to 85 per cent of the blood volume; the second, to 80 per cent, 10 minutes later; and the third, equivalent to 65 per cent, 5 minutes later. The total infusion amounted to 2.3 times the blood volume, the latter being estimated as 10 per cent of the body weight. As a modification of technic, tracheotomy was performed in all our animals. Several squares of gauze were put into a flask partly filled with 95 per cent alcohol. The tubes from the tracheal cannula were suspended in the air chamber of the flask, and the top of this was lightly covered with alcohol-soaked gauze. The alcohol rapidly evaporating in the flask was thus inhaled. If the animal survived the procedure, it was killed 7 minutes after the end of the third infusion and the lungs were removed, inspected and weighed.

Discussion

Previous experiments showed the good results of alcohol administered by inhalation in the acute pulmonary edema of the rabbit and its superiority over other antifoaming agents. Present experiments dealt only with the use of alcohol in other types of experimental pulmonary edema.

Pulmonary edema caused by thiourea in the rat, as described by MacKenzie and MacKenzie did not seem to be constant, because only 1 out of 5 controls developed the syndrome within 22 hours. Moreover, its late appearance made a therapeutic study more difficult. For this reason, the method was abandoned.

Pulmonary edema caused by ammonium chloride in the guinea pig, as described by Koenig and Koenig was not constant when
the drug was injected. It always resulted in death of the animals within a half hour when the drug was ingested (average survival time: 28.7 minutes). Postmortem study revealed a practically constant and severe lesion of the lungs consisting of hemorrhage, congestion and edema and a lungs:body ratio over twice that of normal animals. Treatment with alcohol vapor did not change the lungs:body ratio (table 2) although no foam was found in the bronchi or on the cut surface of the lungs in a large percentage of animals (50 per cent). On the other hand, 80 per cent of the animals were still alive after 30 minutes (20 per cent only of the controls) and 50 per cent were alive after 60 minutes (none of the controls). The average survival time was raised, therefore, from 28.7 minutes (controls) to 47 minutes for these reasons, treatment with alcohol was considered fairly successful in pulmonary edema produced by ammonium chloride.

Acute pulmonary edema caused by rapid intracarotid infusion of physiologic salt solution is an invariably lethal procedure\(^{18}\) and edema of the lungs is constantly caused by this method. Three control animals presented a lungs:body ratio of 5.62 indicating that their lungs were about six times heavier than the normal lungs. Foam poured abundantly out of the trachea and from the cut surface of the lungs. Four animals were submitted to alcohol inhalation, None of them presented edema of the lungs (table 3). Their average lungs:body ratio was 1.25 indicating merely an increased content of blood in the pulmonary vessels and no edema, as proven by Luisada and Sarnoff.\(^{19}\) Therefore, the result of the above experiments was highly successful and further proved the efficacy of alcohol as an antifoaming agent.

**Conclusions**

Experiments were performed in three types of experimental pulmonary edema in order to test further the action of alcohol by inhalation.

Pulmonary edema caused by thiourea in the rat was found to be inconstant. This method of producing pulmonary edema was abandoned.

**Table 3.—Acute Pulmonary Edema in Dogs Caused by Rapid Intracarotid Infusion of Physiologic Salt Solution**

<table>
<thead>
<tr>
<th></th>
<th>Average Lungs: Body Ratio</th>
<th>Beneficial Action</th>
<th>No. of Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal dogs</td>
<td>0.80</td>
<td>—</td>
<td>4</td>
</tr>
<tr>
<td>Controls</td>
<td>5.62</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Treated with Alcohol</td>
<td>1.25</td>
<td>xxx</td>
<td>4</td>
</tr>
</tbody>
</table>

Pulmonary edema caused in the guinea pig by ingestion of ammonium chloride did lend itself to a therapeutic study. Inhalation of alcohol vapor did not change the average lungs:body ratio. However, it decreased the percentage of animals developing pulmonary edema and improved remarkably the survival time of the animals.

Pulmonary edema caused by rapid intracarotid infusion of physiologic salt solution in the dog can be used only for study of the lungs, as the animals are sacrificed soon after the end of the experiment. Inhalation of alcohol vapors, tried on 4 animals, gave a striking result, entirely preventing the development of pulmonary edema.

**Clinical Application**

The favorable action of alcohol by inhalation in experimental pulmonary edema suggested its clinical trial in patients with this syndrome.
A preliminary study indicated the tolerance for inhaled alcohol vapor by normal subjects and cardiac patients; it also showed that the amount of alcohol absorbed through the mucosa of the respiratory passages is moderate and inadequate to induce anesthesia. Clinical treatment with alcohol by inhalation is now being tried at Mount Sinai Hospital. A report of the results will be made upon collection of sufficient evidence.

**Summary**

Experiments were performed in rabbits in which a series of antifoaming agents were administered by inhalation in order to decrease the severity of pulmonary edema caused by a standard dose of intravenous adrenaline. Poorly volatile drugs (heavy alcohols, Span 85) failed to exert any favorable effect. Ether gave only a slight benefit.

Ethyl alcohol exerted an important favorable action, due to the antifoaming property of alcohol; its action on the central nervous system, though slight because of the small dose used, may have enhanced the effect. The favorable effect of alcohol was comparable to that of morphine. Combination of morphine by injection with alcohol by inhalation gave excellent results, equivalent to those obtained by morphine plus oxygen under pressure.

Experiments were further performed in three other types of experimental pulmonary edema in order to test further the action of alcohol by inhalation.

Pulmonary edema caused by thiourea in the rat was found inconstant and the method was abandoned. Pulmonary edema caused in the guinea pig by ingestion of ammonium chloride proved to lend itself to a therapeutic study. Inhalation of alcohol vapor did not change the average lungs:body ratio. However, this therapy decreased the percentage of animals developing pulmonary edema and improved remarkably the survival time of the animals.

Pulmonary edema caused by rapid intracarotid infusion of physiologic salt solution in the dog can be used only for study of the lungs, as the animals are sacrificed soon after the end of the experiment. Inhalation of alcohol vapor, tried in four animals, gave striking results, entirely preventing the development of pulmonary edema.

Clinical treatment with alcohol by inhalation is now being tried and the results will be reported at a later date.

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