Further Studies with Antifoaming Agents in Experimental Pulmonary Edema

By Aldo A. Luisada, M.D. and Luigi Cardi, M.D.

The effect of several antifoaming agents by inhalation in preventing paroxysmal pulmonary edema was tested in a series of rabbits. Three single agents (silicone aerosol, freon, and ethyl alcohol vapor) proved beneficial; their combination did not enhance the beneficial effect. A new agent (silicone aerosol) and a new combination (10 per cent ether in alcohol by aerosol) are now ready for clinical trial.

ANTIFOAMING agents in paroxysmal pulmonary edema were advocated in 1950 by one of us (A.A.L.) following animal experimentation. Several substances having effect on surface tension were tested including ether, octyl alcohol, capryl alcohol, sorbitan trioleate, and ethyl alcohol. Pulmonary edema was induced in rabbits by intravenous injection of epinephrine while the various substances were administered by inhalation by means of an atomizer.

Further experiments were conducted in experimental pulmonary edema of the rat caused by intraperitoneal injection of thiourea, in pulmonary edema of the guinea pig caused by ingestion of ammonium chloride, and in pulmonary edema of the dog caused by rapid intracarotid infusion of physiologic salt solution.

The general conclusion was that the heavy alcohols failed to develop any favorable effect, that ether had a moderate beneficial action, and that ethyl alcohol exerted an important favorable effect. This effect was attributed to modification of the surface tension of the foam followed by decrease of its volume and better oxygenation of the lungs. As systemic effects of the inhaled alcohol vapor were minimal, the method was particularly indicated for patients with pulmonary edema in shock or for those who might develop this syndrome. In the meantime, several antifoaming agents were compared in vitro by Rosenbluth and associates. The same authors found that the inhalation of silicone in ether was beneficial in pulmonary edema induced by epinephrine in rabbits. Silicone in water emulsion was further tried in the same type of experimental pulmonary edema by Howell and co-workers, apparently with good effects. The utility of silicone aerosols was further demonstrated by Curry and Nickerson in experimental pulmonary edema of the rabbit (epinephrine) and rat (chlorine). Studies in clinical cases by means of alcohol vapor were reported by Luisada, Goldmann and Weyl, Goldmann and Primiano, Gootnick, Lipson and Turbin, and Goldmann and Luisada. Another type of alcohol (2-ethyl-hexanol) was further tried by inhalation in clinical cases by Reich and associates with favorable results.

These studies by various authors induced us to undertake an experimental comparison between several antifoaming agents including silicone mixtures.

TECHNIQUE

One hundred fifty-three albino rabbits were used for the study of antifoaming agents in series of 16 for each agent. To these should be added a few normal animals and various controls which were reported in a previous study.

Pulmonary edema was induced by a slow (1 min.) intravenous injection of 2 cc. of epinephrine 1:1000 (Parke and Davis) irrespective of weight, this dose being lethal to 95 per cent of the animals.

The following data were studied: (1) the percentage of survival at one-half the average survival time (7 minutes); (2) the average survival in minutes; (3) the average lung to body ratio. This ratio was obtained by dividing the weight of the excised lungs and trachea in grams, multiplied by 100, by the weight of the body in grams. Whenever spontaneous death did not occur in 60 minutes, the animals were sacrificed at the end of such period in order to ob-
serve the lungs and to obtain the lung to body ratio before dissipation of the edema.

The beneficial effect of any agent was graded from 1 to 4 plus and was based on the three data mentioned above plus the amount of foam, found in the lungs, bronchi and trachea.

All animals were submitted to inhalation of the agent to be tested for 15 minutes before the injection of epinephrine and continued after the injection until spontaneous death of the animal or its sacrifice at 60 minutes. Inhalation was done by putting the animals in a box with a glass top. Oxygen bubbling through a bottle of fluid carried the vapor of the volatile agents. Non-volatile substances or mixtures were usually given by aerosol spray with the use of an atomizer* connected with an oxygen tank. A special mixture of silicone with polyethylene glycol was atomized by a jet of freon emitted from a special container. In such experiments, proper oxygenation of the box was obtained by a jet of oxygen penetrating through a second opening. Ventilation was maintained by a small outlet at the opposite end of the box.

The following drugs or mixtures were studied: alcohol, freon‡, silicone (2, 5 and 10 per cent)§ and their mixtures, in addition to 95 per cent ethyl alcohol (vapor). The fact that the original mixture of silicone included freon and polyethylene glycol made several controls necessary. The useful effect of freon, which was discovered in the first controls, pointed out the need of further studies with a mixture of freon and alcohol.

**Results**

The results of the various drugs in preventing pulmonary edema were based on data obtained in a series of control animals treated with epinephrine alone (Table 1). Oxygen inhalation changed the outcome but slightly. It should be noted that since a few animals were taken out of each batch and used as controls, the data of the entire control series were slightly better than those found with some agents. This was probably because these agents were tried in small series of animals which were

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of Survival (60 min)</th>
<th>Foam (15 min)</th>
<th>Lung/Bd ratio</th>
<th>Beneficial Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal animals*</td>
<td>-</td>
<td>-</td>
<td>0.455 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Epinephrine* (controls)</td>
<td>50</td>
<td>13</td>
<td>1.45 (16)</td>
<td>-</td>
</tr>
<tr>
<td>Epinephrine and oxygen (controls)</td>
<td>50</td>
<td>13.7</td>
<td>1.22 (16)</td>
<td>++</td>
</tr>
<tr>
<td>Freon (vapor)</td>
<td>68</td>
<td>39.9</td>
<td>1.20 (16)</td>
<td>++++</td>
</tr>
<tr>
<td>10% silicone in water (aerosol)</td>
<td>81</td>
<td>23.5</td>
<td>1.48 (16)</td>
<td>++</td>
</tr>
<tr>
<td>95% ethyl alcohol (vapor)</td>
<td>75</td>
<td>41</td>
<td>1.03 (16)</td>
<td>++++</td>
</tr>
</tbody>
</table>

* Controls obtained in previous series.

particularly affected by epinephrine, and then abandoned because the mixtures were found "non-useful."

Three agents were beneficial in the treatment of pulmonary edema: 10 per cent silicone in water (aerosol), freon (vapor), and 95 per cent ethyl alcohol (vapor) (Table 1). The overall rating of beneficial effect was lower for silicone, medium for freon, and inmaximum for alcohol. It should be noted, however, that silicone gave the highest percentage of survival at one-half average survival time among the three agents. Freon and ethyl alcohol rated approximately the same in average survival, but alcohol was superior to freon in percentage of survival at 1/2 avg. survival time and in average lungs to body ratio. A relative impression of the three agents is given by the fact that, in the case of silicone, 4 animals out of 16 survived until killed at 60 minutes; in the case of alcohol, 10 animals out of 16 survived until killed at 60 minutes.

Several mixtures were also tried with the hope of enhancing the antifoaming property of one drug by adding that of another (Table 2). Silicone and freon (plus polyethylene glycol as a solvent) gave only mildly beneficial results. This beneficial effect was admitted because the average survival was increased, the amount of foam was decreased, and 5 out of 16 animals survived up to 60 minutes (only one of the
ANTIFOAMING AGENTS IN PULMONARY EDEMA

Table 2.—Influence of Combinations of Antifoaming Agents on Epinephrine Pulmonary Edema

<table>
<thead>
<tr>
<th>Drug</th>
<th>% of Survival (half average survival time)</th>
<th>Average Survival (minutes)</th>
<th>Average Lung/Body Ratio</th>
<th>No. of Animals</th>
<th>Beneficial Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicone + freon + polyethylene glycol (aerosol)</td>
<td>56</td>
<td>22.8</td>
<td>1.30</td>
<td>16</td>
<td>+</td>
</tr>
<tr>
<td>95% alcohol + freon (vapors)</td>
<td>87</td>
<td>23.4</td>
<td>1.27</td>
<td>16</td>
<td>++</td>
</tr>
<tr>
<td>10% ether in 95% ethyl alcohol (aerosol)</td>
<td>87</td>
<td>26.6</td>
<td>1.32</td>
<td>16</td>
<td>++</td>
</tr>
</tbody>
</table>

Table 3.—Incomplete Series Abandoned because the Mixtures were Found Non-Useful

<table>
<thead>
<tr>
<th>Drug</th>
<th>% of Survival (half average survival time)</th>
<th>Average Survival (minutes)</th>
<th>Average Lung/Body Ratio</th>
<th>No. of Animals</th>
<th>Beneficial Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freon + propyl glycol (aerosol)</td>
<td>66</td>
<td>15.6</td>
<td>1.34</td>
<td>6</td>
<td>+</td>
</tr>
<tr>
<td>10% silicone in 9:1 alcohol-ether (aerosol)</td>
<td>16</td>
<td>5.5</td>
<td>1.27</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>2% silicone in 95% alcohol (aerosol)</td>
<td>25</td>
<td>7.2</td>
<td>1.47</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>10% silicone in 95% alcohol</td>
<td>62</td>
<td>15.6</td>
<td>1.42</td>
<td>8</td>
<td>+</td>
</tr>
</tbody>
</table>

controls reached this limit). The lungs to body ratio was not appreciably affected, indicating severe congestion and hemorrhage.

The combination of alcohol and freon raised the percentage of survival at one-half average survival time up to 87 per cent, i.e. higher than of either agent. The lungs to body ratio and the average survival, however, were lower than those of the series treated with either agent. The same was found in the case of a 10 per cent mixture of ether in alcohol because, in spite of higher initial survival time than in the case of alcohol alone, there was a lower (worse) average survival time and a higher (worse) lung to body ratio.

Table 3 shows the results of experiments with three different solutions of silicone and also that of one control with freon and propyl glycol. As the results were not favorable, it was not considered necessary to increase the number of the animals until the series of 16 was completed.

DISCUSSION

The useful effect of ethyl alcohol vapor by inhalation, previously demonstrated by both animal1, 2, 3 and clinical4, 5, 6, 7 experimentation was further confirmed by this new series of experiments (table 1). The useful effect of silicone, also previously observed in animals7, 8 was further confirmed by the present study. However, the only really helpful preparation of silicone was that in water (table 1) while suspensions in alcohol or alcohol-ether did not seem equally effective (table 3). Inhalation with freon, another effective antifoaming agent, gave beneficial results (table 1) which were slightly inferior to those of alcohol but superior to those of silicone.

At the time of the first experimental study with alcohol, its beneficial action was ascribed mostly or completely to its antifoaming effect. Still, a minimal doubt might be entertained because alcohol is a narcotic and as such it might prevent pulmonary edema through a systemic effect.8 The demonstration that two other antifoaming agents (freon and silicone) having no known systemic effects for short term administration are also useful in preventing pulmonary edema, tends to confirm the initial interpretation. It is undoubtedly possible that continued administration of alcohol by inhalation for several hours may lead to greater absorption and, therefore, to moderate systemic effects. However, continuous administration was not advocated in the above quoted publications3, 6.

Association of drugs was tried with the hope of a synergistic effect of various antifoaming agents. However, this was disproven by our experiments (tables 2 and 3). Actually, combination of two of these agents plus water, which is always present in the bronchi, probably leads to weakening of the action on surface tension of the single agents. On one count only was the percentage of survival using two mixtures at half-average survival time, superior.
The effect of several antifoaming agents by inhalation in preventing acute pulmonary edema caused by intravenous epinephrine was tested in 153 rabbits.

Three agents were definitely beneficial: 10 per cent silicone in water, freon, and ethyl alcohol. While inhaled alcohol has mild systemic effects, silicone and freon (in short period of administration) have none. Therefore, the effectiveness of antifoaming therapy in general was confirmed.

Mixtures of antifoaming agents, tested in search of a possible synergistic effect, did not prove superior to the single agents. Even 10 per cent ether in alcohol, in spite of some sedative effect, did not prove to be more effective than alcohol.

As epinephrine pulmonary edema is different from several types of clinical pulmonary edema, and freon should be excluded because it might have toxic effects if administered for several hours, a clinical trial with silicone (aerosol) and ether-alcohol (aerosol), seems indicated.

REFERENCES

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