Study of Antifoaming Agents and Preliminary Evaluation of their Use in Experimental Pulmonary Edema. (19733)

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(Introduced by Irving Graef.)
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In some patients who die in an attack of pulmonary edema it seems likely that an important cause of death is asphyxia due to mechanical interference with gaseous interchange due to foam which fills the airways. If this foam could be collapsed, the volume of the resulting liquid would be only a small fraction of the original foam volume. The airways would be cleared to the extent of the difference between these 2 volumes. In certain cases of pulmonary edema the resultant increased effectiveness of administered oxygen could be of great value.

The first phase of this investigation was concerned with the testing of various antifoaming substances on transudate fluid *in vitro,* the second phase with an evaluation of their use in experimental pulmonary edema.

I. *Comparison of antifoaming activity of various substances in vitro. Method.* Foam was produced from ascitic fluid which is considered similar to pulmonary edema fluid. The fluid was poured into a vertical glass cylinder, closed below by a rubber stopper, perforated to permit the passage of a fritted glass tube. Oxygen was bubbled through this tube into the fluid at a constant rate until a given volume of foam was made. Oxygen was then turned off and the rate of foam collapse measured. The foam was then remade to the original volume, the antifoaming agent to be tested was dripped into the tube from a small syringe through a 20-gauge needle and the rate of collapse again measured. The rates of foam collapse before and after addition of the antifoaming agent were expressed as a ratio and termed "Foam Destruction Index" (I_1). Finally, oxygen was once more bubbled through the fluid which now contained antifoaming agent and the rates of foam formation before and after addition of the agent were compared; their ratio was termed "Foam Prevention Index" (I_2). The indices I_1 and I_2 measure the effectiveness of the antifoaming agent in dissolving foam and preventing foam formation, respectively. This method, modified from Bickerman(1), was found to yield reproducible results if care was taken to carry out every step in a suitably standardized manner.

TABLE I.
Antifoaming Activity of Various Agents.

Antifoaming agent	Foam destruction index* I_1	Foam prevention index* I_2
Control	1	1
1. Ether	2	1
2. Ethyl alcohol	2	—
3. Octylic "	16	—
4. DCAA 5% in ether	4.5	1.1
5. " 10 " "	4.5	1
6. TBP 1% in water	2	—
7. " 100%	38.5	—
8. Aerosol 18 5% in water	1	—
9. DCAA 5% + Aerosol 18 2.5% in ether	11.5	2.2
10. DCAA 6.6% + Aerosol OT 3.3% in ether	25	1.8
11. DCAA 3.3% + Aerosol 18 1.7% + TBP .34% in ether		
12. DCAA 6.6% + Aerosol OT 3.3% + TBP .67% in ether	37.5	8

* Each figure is the mean of several determinations. For abbreviations, see text.

Results. Some representative findings obtained by the method described are summarized in Table I. The relative ineffectiveness of ether and ethyl alcohol, pharmacologically suitable, in comparison with octylic alcohol, entirely unsuited for inhalation, prompted a search for agents combining clinical usefulness with efficacy. DC Antifoam A (DCAA), a methylpolysiloxane, has been shown to be non-toxic(2). However, solutions of DCAA in ether are only moderately effective. Tributylphosphate (TBP), although a powerful antifoamer, was irritating on inhala-

TABLE II. Effect of an Antifoaming Agent (DC Antifoam A) on the Development of Adrenaline-Induced Pulmonary Edema in Rabbits.

Agent	Wt, kg	Total adrenaline, mg	Degree of pulm. edema	Lung:body ratio*	Survival time,† min	Mode of death	Pulm. edema Present	Pulm. edema Absent
				Control animals				
Norm. saline	2.5	1.8	2+	.60	20	S	+	
	2.7	2	3+	.84	20	S	+	
	2.3	2	2+	.89	35	S	+	
Ether	2.1	2.5	1+	.64	20	N	+	
	2.4	2.5	2+	.85	10	S	+	
	2.3	2.5	2+	.64	15	S	+	
	2.5	2.5	2+	.73	15	N	+	
None	2.5	2	3+	.80	20	S	+	
	2.5	2.5	3+	1.10	15	N	+	
				Treated animals				
5% DCAA	2.9	2.5	0	.42	15	S		+
	2.4	2.5	?	.56	15	i.v. air		+
	2.5	1.5	2+	.74	15	S	+	
	2.4	2.5	2+	.87	15	N	+	
	2	2	2+	.95	10	S	+	
10% DCAA	3.4	3	?	.44	25	E		+
	2	2.5	0	.52	15	N		+
	3.3	2.5	0	.34	15	S		+
	2.6	2.5	2+	.85	15	N	+	
	2.2	2.5	3+	1.13	15	N	+	

* Lung:body ratio—lung wt × 100/body wt. † Measured from start of adrenaline.
T—trace. S—spontaneous. N—nembutal. E—electrocuted.

tion unless diluted to at least 1% at which point it lost most of its potency. Combinations of DCAA and certain detergents (Aerosol 18 and Aerosol OT), with or without TBP, enhance antifoaming activity to a remarkable extent. Although Aerosol OT (Dioctyl sodium sulphosuccinate) appears to be non-toxic on ingestion(3), inhalation of related aerosols in concentrations over 0.1% was found to be injurious to the lungs(4). The usefulness of this method in determining the antifoaming activity of various agents is suggested by these data.

II. *Effect of antifoaming agent (DC antifoam A) on adrenaline-induced pulmonary edema in rabbits.* Five and 10% solutions of DCAA in ether were the agents studied. More potent agents (Table I) were not used because of their tendency to produce lung damage. Pulmonary edema was produced by the slow intravenous injection of dilute adrenaline solution (0.25 mg per ml). This modification was found to reduce death rate within the first 10 minutes following injection(9,10). Adrenaline and antifoaming agent or control solution were administered in a standard manner. Male rabbits were placed in a holding box and antifoam or control solution directly sprayed into the mouth through a Devilbiss atomizer. After the animal received 3 to 5 squirts per minute for 5 minutes the adrenaline solution was injected into an ear vein at the rate of one ml per minute. The injection was continued until the animal either had received 10 ml (2.5 mg) of adrenaline solution or developed manifest pulmonary edema. During this period the spray was continued at 2 minute intervals. The solutions used were stained with methylene blue and examination of the lungs postmortem showed that satisfactory penetration of the sprayed solution had been obtained. The rabbits that did not die spontaneously were sacrificed after a period of 15 to 25 minutes and autopsied immediately. A total of 19 rabbits were used, of which 10 received the antifoaming agent and 9 received control solutions. A gross estimate of the degree of pulmonary edema was made by observing the lungs and tracheobronchial tree. A more quantitative estimate was obtained by determining the ratio of lung weight to body weight. This ratio in normal untreated rabbits was approximately 0.46 but to account for the presence of pulmonary congestion a

ratio above 0.6 was considered indicative of pulmonary edema. Lung:body ratios seemed to correlate well with the degree of observed pulmonary edema. Since the scope of this study was limited to evaluating the effect of antifoaming agent on the development of gross pulmonary edema, ultimate recovery and survival, and the histologic appearance of the lungs were not studied. The findings are summarized in Table II. All of the control animals developed frank pulmonary edema. In contrast 5 out of 10 antifoam treated animals showed evidence of pulmonary edema. Half of the treated group received 5% solutions of DCAA and the other half 10% solutions. It would seem that the antifoaming agent had significantly reduced the incidence of pulmonary edema.

Comment. The usefulness of antifoaming agents in the treatment of pulmonary edema is suggested by the finding that the condition could be prevented in half of the treated animals. In those animals in which pulmonary edema developed in spite of treatment with antifoaming agent, there is always a certain amount of doubt whether adequate amounts of the agent had penetrated deeply enough. It is felt that the availability of a more satisfactory antifoaming agent and a more efficient way of administering it might have increased the proportion of successfully treated animals beyond the reported 50%.

Summary. 1. The collapse of the foam which fills the tracheobronchial tree in certain cases of pulmonary edema would be advantageous in the management of this condition. This might be accomplished by the use of antifoaming agents. 2. A method for measuring antifoaming activity *in vitro* is described and various antifoaming substances are compared by this method in terms of their foam-destroying power. 3. The inhalation of one of these substances, a solution of the silicone DC Antifoam A, in ether, was shown to reduce the incidence of adrenaline induced pulmonary edema in rabbits by 50%.

DCAA: DC Antifoam A, supplied through courtesy of Dow Corning Corp., Midland, Mich.

Aerosol 18 and Aerosol OT, supplied through courtesy of Am. Cyanamid Co., New York City.

TBP: Tributylphosphate, supplied through courtesy of Commercial Solvents Corp., New York City.

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Received May 21, 1952. P.S.E.B.M., 1952, v80.