The meeting closed after a general discussion during which all participants were given an opportunity to restate their respective viewpoints on various inconsistencies which had not been resolved during lunch or dinner recesses.

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Lung Function Studies after the Intralymphatic Injection of Emulsions of Ethiodol in Dogs

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Originally we became interested in developing an emulsion of Ethiodol in an effort to speed up the procedure of lymphography. With the viscous Ethiodol 45 to 60 minutes are required for injection. Certain low viscosity emulsions can be prepared, allowing much more rapid introduction. These emulsions are equal or superior to Ethiodol in definition of lymphatic structure and certain of them are equally long retained in the nodes for long term radiographic studies (3).

The search for an emulsion takes on added importance since Ethiodol globules embolize in the lungs to greater or lesser degree when lymphography is performed in man or animal, the globules reaching the lungs via the thoracic duct or by lymphatico-venous anastomoses. In most instances this is of no consequence but rarely a patient with concurrent lung disease or with lungs damaged by prior disease or radiation develops acute respiratory difficulties. Unassailable evidence of decrease in pulmonary diffusing capacity after lymphography has been obtained and this appears to be mainly due to a decrease in pulmonary capillary volume (5, 6). Pulmonary oil embolism ought not to occur if the particles of the emulsion are below the diameter of a lung capillary. Pulmonary function following lymphography with Ethiodol emulsions was therefore examined using the dog as an experimental animal.

Methods

Pulmonary function studies were performed on twelve dogs in the laboratory before lymphography, within the first two hours postlymphography, and at 24, 48 and 72 hours and 7 days after lymphography.

The dogs were of both sexes and weighed 14 to 20 kg. All pulmonary function tests were performed under Nembutal anesthesia. Expired gas was collected in a Douglas bag for 3 minutes and arterial blood samples were obtained simultaneously. Diffusing capacity was determined in duplicate using the method of Ogilvie, et al. (8). One liter

of a CO gas mixture was introduced into the lungs with a calibrated metal syringe and the breath held for 10 seconds. An alveolar sample was obtained by a modification of the technique described by Young, et al. (10).

Arterial oxygen tension was measured using a Clark electrode, and arterial pH and PCO_2 using the Astrup technique (1). From the measured data, minute ventilation, alveolar and dead space ventilation, and oxygen consumption and CO_2 production were calculated using standard techniques (2).

On four dogs lymphography was performed by injecting 5 ml of Ethiodol into a lymph trunk of each hind leg, a total of 10 ml per dog. In four other dogs 10 ml of Ethiodol emulsion prepared in our own laboratory was injected into a lymph trunk of each hind leg and in another four dogs, the same injection procedure was carried out with 10 ml of an emulsion prepared by the Leo Company in Sweden. Each of these animals thereby received 20 ml of emulsion. Since the emulsions are 50% water, the same amount of Ethiodol was injected in each set of dogs. After each lymphatic injection, the dog's hind legs were exercised so that a minimum amount of contrast media was allowed to linger in the lymph trunks and a maximum amount entered the systemic venous circulation and traveled to the lungs. A radiographic check film confirmed this. Four additional dogs were anesthetized with Nembutal on the initial day and again anesthetized at 24, 48 and 72 hours and at seven days and on each day carbon monoxide diffusion studies performed in the same manner. No lymphography was performed on these four.

The emulsion of the Iowa laboratory was prepared from 50% Ethiodol and 50% of aqueous phase by volume. The aqueous phase consisted of buffer and preservative in distilled water. Emulsifying agents Pluronic F 68 (polyoxyethylene polypropylene glycol) and soybean lecithin were present in 3% total concentration with ratio of the two, 78/22. The emulsion was prepared in the Branson ultrasonic generator, at power level 6 for four minutes. The pH was 7.3 to 7.4. The vast majority of particles are below 6 μ in size, but rarely are as large as 75 μ.

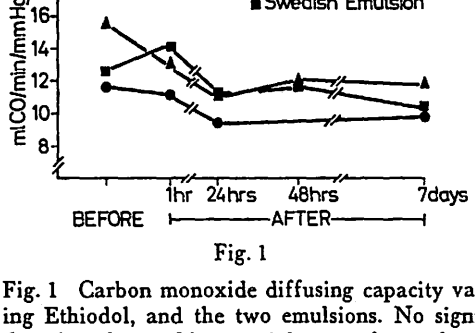

Fig. 1

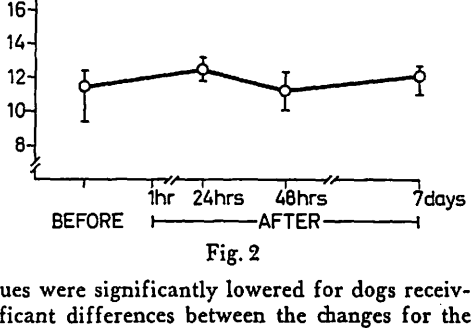

Fig. 2

Fig. 1 Carbon monoxide diffusing capacity values were significantly lowered for dogs receiving Ethiodol, and the two emulsions. No significant differences between the changes for the three lymphographic materials were observed.

Fig. 2 Carbon monoxide diffusing capacities of the four un-injected dogs did not decrease significantly in the period of observation.

The Swedish emulsion is likewise composed of iodinated ethyl ester of poppyseed oil (Ethiodol, Lipiodol F), but is initially prepared in glycerol with soybean lecithin as an emulsifying agent. The base emulsion contains 0.25 gm of iodine per ml. Mixing two parts of base emulsion with one part 5% glucose in water produces an emulsion of 0.17 gm iodine per ml, comparable to Iowa's emulsion's 0.18 gm iodine per ml. The particles are said to never exceed 1 μ and the vast majority are smaller than 0.5 μ. The viscosity is above 16 cps (BROOKFIELD).

The statistical procedure used was a two factor analysis of variance for unweighted means, since not all cells were of the same size.

Tab. 1 Lung Diffusing Capacity After Lymphography (Single Breath Carbon Monoxide (Method) ml/min/mm Hg.

	Dog Nr.	Pre-Injection	1 hr.	24 hrs.	48 hrs.	7 days
Ethiodol	561	13.7	17.9	9.4	–	10.8
	564	9.7	9.0	6.8	–	8.0
	566	9.3	9.9	9.5	8.7	8.7
	568	14.2	7.9	11.6	9.3	12.2
	mean	**11.7**	**11.2**	**9.3**	**9.0**	**9.9**
	S. E.	1.3	2.3	1.0	–	1.0
Iowa	572	16.3	13.0	13.0	10.4	14.9
Emulsion	580	13.8	13.4	10.8	12.1	8.5
	588	14.1	9.0	9.7	11.2	10.5
	594	18.1	16.4	10.6	14.1	12.8
	mean	**15.6**	**12.9**	**11.0**	**12.0**	**11.7**
	S. E.	1.0	1.6	0.7	0.8	1.4
Swedish	582	13.7	14.6	10.2	11.2	10.8
Emulsion	583	10.3	12.3	11.2	11.9	10.2
	585	10.4	11.0	9.2	9.5	8.4
	602	16.0	18.1	14.1	13.5	12.8
	mean	**12.6**	**14.0**	**11.2**	**11.6**	**10.5**
	S. E.	1.4	1.6	1.1	0.8	0.9
Controls	603	12.5	–	11.7	10.8	12.8
	604	12.8	–	12.5	12.6	12.9
	605	10.2	–	12.2	10.2	11.1
	606	9.5	–	13.3	11.4	12.5
	mean	**11.3**	–	**12.4**	**11.3**	**12.3**
	S. E.	0.8	–	0.33	0.5	0.4

Results

Minute ventilation, arterial and carbon dioxide tension, blood pH, calculated oxygen consumption, carbon dioxide production, alveolar ventilation, and physiologic dead space values did not change significantly from pre-injection values in the animals receiving Ethiodol, the Iowa emulsion, or the Swedish emulsion.

The single breath carbon monoxide diffusing capacity values were significantly lowered from pre-injection values for the animals receiving Ethiodol. They were also

significantly lowered for the animals receiving the Iowa emulsion, and the animals receiving the Swedish emulsion (Table 1, Fig. 1). The four control animals, subjected to identical periods of anesthesia but not to lymphography did not show decrease in carbon monoxide diffusing capacity (Fig. 2). There were no statistically significant differences between the decreases for the three lymphographic materials.

Discussion

The decrease of about 16% in diffusing capacity following intralymphatic injection of Ethiodol in the dog is in the same range (12–60%) as reported in seven cases in man (6). The dose used in these dogs, however, was larger than in man, 0.5 ml/kg as compared to 0.28 ml/kg. The decrease in diffusing capacity following the intralymphatic injection of an emulsion of Ethiodol prepared in the Radiology Laboratory at the University of Iowa and the emulsion prepared by the Leo Company, Hälsingborg, Sweden, must be considered in the light of the characteristics of the emulsions and the responses of the body to the introduction of foreign particles. Although most of the particles in the Iowa emulsion were below the size presumably small enough to pass through the lung capillaries, it contained a number of fat globules of size sufficient to lodge in a small arteriole or a capillary. Even so, one would think the embolization should be less than with the Ethiodol, but possibly the unemulsified Ethiodol is composed of fewer and larger globules and is trapped to a greater degree in the node or in larger lung vessels than the emulsion globules. Histologically the oil globules of Ethiodol are said to be in the lung capillaries. However, it has been calculated that 20 ml of Ethiodol if reduced to globules 10 μ in diameter could occlude twice the number of capillaries the human lung is assumed to have (6). All particles of the Swedish emulsion are of fine enough size so that they should pass unobstructed through the lung capillaries. The Swedish emulsion has been observed to pass through lung capillaries of the rabbit without causing infarction (7). However, the same emulsion when used for selective renal angiography in dogs revealed injury for which no satisfactory explanation was offered. Why then is a decrease in diffusing capacity seen with the use of emulsions?

Possibly the size of the particle of emulsion reaching the lungs might be larger than its size when initially introduced into the lymph vessel. Foreign particles with certain surface characteristics are thought to interact with blood proteins, acquiring a coating of protein and thereby increasing in size. Clumping together of two or more particles by virtue of adhesiveness of the protein coat may occur, converting very small particles into agglomerations which could easily plug capillaries. Observations with electron microscopy of lung sections of the mouse given emulsion intravenously revealed clumps of platelets associated with oil globules in lung vessels, suggesting another mechanism whereby pulmonary embolization might occur (4). Another possibility to consider is that the measured decrease in diffusing capacity is due to a chemical pneumonitis hindering membrane permeability. Certainly the oil can shift from the lung capillaries into the interstitial tissue and into the aveolar spaces, but if the globules are not first trapped in the lung capillaries it is difficult to see how this could be a significant factor. At the present time, we do not know if the dog lung responds in essentially the same way as the human lung does to the embolization of

Ethiodol. An earlier iodinated emulsion was found unsuitable for use because one of its components tended to precipitate in the presence of blood and form flakes of considerable size (9). The two emulsions with their smaller particles theoretically should not have produced as much embolization of the lung vessels as Ethiodol itself, but differences between the three tested agents might have been concealed by use of two large a dose of contrast material in the animals. Other sources of experimental error are not apparent at this time.

Summary

Lung function studies were performed in twelve dogs receiving lymphographic contrast media. Animals receiving Ethiodol and two prepared Ethiodol emulsions showed decrease in carbon monoxide diffusion capacity compared to controls. Significant differences between the three contrast agents were not shown. The possible explanations for these observations are discussed.

Acknowledgements

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