Title: IMPROVEMENT OF THE SEPTIC LUNG LESION BY TREATMENT WITH A PROTEOLYTIC ENZYME INHIBITOR

Authors: D.L. Traber, PH.D., L. Sziebert, B.A., T. Adams, Jr., M.S., N. Henriksen, L.D. Traber, R.M.

Affiliation: Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas, Department of Anesthesia Research, Shriners Burns Institute, Galveston, Texas 77550

Introduction. Death and morbidity from sepsis continues to be a growing problem in the operating room and in Intensive Care Areas. The most serious complication of sepsis is the lung lesion that results in loss of integrity of the pulmonary microcirculation. This can be studied by utilizing the sheep lung lymph-preparation. We have been able to produce sepsis in sheep prepared for study in this manner[1] and have also found that small dosages of endotoxin will reproduce the cardiopulmonary and lymph changes[2]. The lesions can be categorized into two phases. Phase I displays an elevation of protein poor lung lymph and pulmonary hypertension. In phase II the elevation in lung lymph is associated with a higher protein content and lower pulmonary pressure; characteristic of increased vascular permeability to protein. During both phases the hematocrit and total peripheral vascular resistance are elevated and the cardiac output is reduced. These changes occur simultaneously with an elevation of proteolytic enzymes in the lymph and plasma[3]. These enzymes could induce the above mentioned vascular leakiness to protein. We, therefore, decided to determine if a proteolytic enzyme inhibitor could block or obtund these responses. We used the non-peptide proteolytic enzyme inhibitor gabexate mesilate (GM) for this purpose.

Methods. Sheep were prepared surgically for study by implanting catheters for measurement of cardiopulmonary variables and the collection of lung lymph. One week following the last surgical procedure, two hours of base line data were obtained then the animals were given a dose of endotoxin (0.75µg/kg) and studied for an additional six hours. Three days later, this sequence was repeated. With one of the two endotoxin studies the animals were treated with GM. A continuous infusion of 1mg/kg/hr was given following a loading dose of1 mg/kg. Treatment was begun one hour after the administration of endotoxin.

Results. The early cardiopulmonary changes produced by endotoxin (phase I) were little affected by treatment with GM. The phase II changes, though, were greatly affected. Most remarkable was the change in lung lymph flow. Treatment here reduced the response by some 30%.This occured although the pulmonary arterial pressure rose equally in untreated animals. The cardiac index was not as low nor the vascular resistance as high following treatment.

Discussion. Proteolytic enzyme inhibition had little effect on the phase I part of the response to endotoxin as most of this response had subsided by the time treatment was initiated. A large percent of the phase II lymphatic response, must be due to these enzymes since the lymph flow is so much less with treatment. These proteolytic enzymes may be responsible for producing this lesion by changing the microvascular permeability to protein since the lymph flow is reduced without a corresponding reduction in pressure. It is important to note that this damage is not permanent and can be reversed with treatment. This finding offers hope for an already septic patient. The peripheral cardiovascular improvement, however, is disappointing; the modest improvement in cardiac index is apparently the result of a lessening of the elevation in vascular resistance. This suggests that the latter might be due to a vasoactive peptide.

Variable		Control	PhaseII
Lymph Flow ml/hr	E	8.5±2.1	30.5±5.9
	E+S	9.4±2.8	23.5±6.0
Pulmonary Artery pressure mmHg	E	19±1	28±1
	E+S	19±1	29±2
Cardiac Index	E	4.79±0.37	3.58±0.37
	E+S	4.78±0.40	3.69±0.34
Total Vascular Resistance	E	1443±77	2276±210
	E+S	1419±97	2022±159

E - Endotoxin E+S - Endotoxin + GM

References.

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3. R.H. Demling, M. Smith, R. Gunther and T. Wandzilak: Endotoxin-induced lung injury in unanesthetized sheep; effect of methylprednisolone. Circ Shock 8:351360;1981.