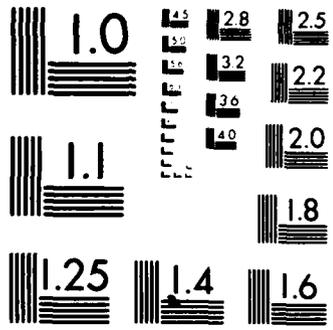


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CORTICOSTEROID/ANTIBIOTIC TREATMENT
OF SEPTIC SHOCK: AN EVALUATION OF MECHANISMS

Annual Summary Report

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Research Career Scientist

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administration of corticosteroid can compromise the host; whereas, 1-2 day corticosteroid administration is protective of the host. Why naloxone is an efficacious therapy for dogs but causes no benefit in baboons and what causes death in the adrenalectomized dog in LD₁₀₀ E. coli-induced shock remains challenges for us to further investigate. Finally, plasma β -endorphin concentrations do not appear to be of prognostic value in determining final outcome of shock.

FORWARD

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

CORTICOSTEROID/ANTIBIOTIC TREATMENT OF SEPTIC SHOCK:
AN EVALUATION OF MECHANISMS

STATEMENT OF THE PROBLEM

Gram-negative septicemia occurs in approximately 1 of every 100 hospitalized patients in the United States (1, 2). The serious nature of bacteremic sepsis has been underscored by McCabe (2) who pointed out that the number of cases and deaths from bacteremia continues to increase progressively each year. Mortality rates in patients remain between 20-80% for septicemia (2, 3), and as high as 80-90% for septic shock (3-6). We have succeeded in developing the first effective therapy to prevent death (>7 days) from septic shock induced by a 100% lethal dose (LD₁₀₀) of live E. coli organisms administered intravenously to dogs and baboons. The therapy consists of intermittent infusions of the corticosteroid, methylprednisolone sodium succinate (MPSS), and the aminoglycoside antibiotic, gentamicin sulfate (GS) (7-11). The problem we are addressing in this proposal is to determine the mechanisms of protection and strengths and limitations of MPSS/GS therapy.

BACKGROUND

We selected the corticosteroid, methylprednisolone sodium succinate (MPSS), to test as a therapy for experimental septic shock because we reasoned that it might correct or prevent the various defects of shock, including the maldistribution of blood flow and volume, metabolic abnormalities, coagulation and host-defense defects, and pathologic tissue changes (12-29).

We evaluated the separate and combined effects of steroid and antibiotic in dogs given LD₁₀₀ E. coli. Infusions of MPSS and gentamicin sulfate prevented death in all dogs. Dogs that received either antibiotic or steroid alone were not protected and could not be distinguished from the group that received E. coli only (7).

Utilizing the lethal septic shock baboon model developed in our laboratory (30-31), we sequentially analyzed the effectiveness of our combination MPSS/GS regimen. Results demonstrated that the earlier the steroid/antibiotic regimen is given the more likely an animal is to survive the lethal effects of LD₁₀₀ E. coli-induced shock. The MPSS/GS therapy prevented the hypoglycemia and corrected the hypoinsulinemia of septic shock. MPSS/GS infusion also lowered BUN blood levels, prevented anuria, lowered heart rate, and increased concentrations of circulating mature and immature neutrophils (7-10) after E. coli administration. Moreover, MPSS/GS prevented or ameliorated all significant organ damage in baboons that survived (29). These observations suggest that the responses of the adrenal gland, liver, the host-defense system, and the cardiovascular system are interdependent as they influence the outcome of septic shock. We propose to delineate the mechanisms underlying these phenomena.

We are in a unique position to advance the research of septic shock and its therapy because:

1. We have developed the first treatment (MPSS/GS) that prevents the death of dogs and nonhuman primates infused with 100% lethal doses of live E. coli organisms. There are no other therapy studies using nonhuman primates challenged with live organisms that result in permanent survival.

2. Our criterion that an animal must survive more than seven days after the septic challenge to be defined a "survivor" is the most stringent survival standard in the shock literature.

3. The animal slowly infused with live organisms is a clinically relevant shock model.

4. The effectiveness of MPSS/GS treatment is not limited to a specific species since both dogs and baboons are protected.

5. Even delayed MPSS/GS therapy is effective for baboons given LD₁₀₀ E. coli. MPSS infusion initiated 2 hours and 4 hours post onset of E. coli infusion results in survival rates of 85% and 65% respectively (9-10).

6. We now can use our well-controlled experimental animal septic models to investigate the mechanisms of protection of the MPSS/GS therapy which would be difficult to sort out in a human clinical study because of differing degrees of debilitation, various sites of infection, multiple organisms, and other factors.

APPROACH TO THE PROBLEM

A. Specific Objectives:

1. The long-term objective of this proposal is to identify the mechanisms of action of protection of our MPSS/GS therapy for LD₁₀₀ E. coli-induced shock in the dog and baboon so that the information can be used effectively in the treatment of humans with severe sepsis and thereby prevent septic shock.

2. Short-term objectives are:

a. To determine if our MPSS/GS therapy blocks complement activation or granulocyte ability to respond to C5a in our E. coli-shock models and thereby prevents or reverses granulocyte margination, aggregation, and subsequent endothelial damage.

b. To determine the role of endogenous versus exogenous corticosteroid in conjunction with antibiotic in preventing granulocyte-mediated organ damage and in preserving gluconeogenesis after E. coli shock.

c. To ascertain if our MPSS/GS therapy enhances or inhibits in vitro phagocytosis by mature or immature neutrophils in animals challenged with LD₁₀₀ E. coli.

d. To determine if our MPSS/GS therapy affects the release of β -endorphins, thromboxane A₂, and protacyclin.

e. To determine whether platelet aggregation and/or release of vasoactive agents is prevented in our E. coli shock models by our MPSS/GS therapy.

f. To determine if our MPSS/GS therapy can prevent myocardial dysfunction since we have documented that the heart fails in 75% of the dogs subjected to E. coli-induced shock.

g. To determine if venous return is augmented toward control levels by MPSS/GS therapy after E. coli challenge.

h. To determine if MPSS/GS therapy in our E. coli shock models preserves renal hemodynamics and function.

i. To determine if MPSS therapy enhances microcirculatory delivery and distribution of antibiotic in our E. coli shock models.

j. To determine the strengths and limitations of our MPSS/GS therapy in E. coli shock and to delineate the times and methods of administration vital to preserve life.

B. Key Questions to Answer Are:

1. Is the maldistribution of blood volume and blood flow caused by peripheral pooling, pre- and postcapillary constriction, and decreased cardiac output in experimental septic shock prevented or reversed by our MPSS/GS therapy?

2. To what extent does endotoxin activation of complement (with subsequent margination and aggregation of WBCs, endothelial injury and disseminated intravascular coagulation) contribute to the cardiovascular dysfunction observed in septic shock and does our MPSS/GS therapy interfere with this sequence of events?

3. Does a relative adrenal insufficiency occur during septic shock and adversely affect neutrophil function (phagocytosis and killing of bacteria and glucose utilization) and liver function (gluconeogenesis)? If so, does our exogenous corticosteroid administration compensate for the adrenal insufficiency and/or prevent adrenal damage?

4. If an animal has undergone chronic steroid administration, will his response to E. coli challenge and to MPSS/GS therapy be altered?

5. Does steroid enhance the peripheral distribution of antibiotic in animals when treated with our MPSS/GS therapy? If so, is the improved distribution due to increased peripheral vascular flow?

6. Do animals survive E. coli shock when treated with our MPSS/GS therapy because the therapy prevents myocardial dysfunction?

7. Does our MPSS/GS therapy for E. coli shock prevent renal histopathology and functional impairment and enhance antibiotic excretion?

8. What are the limits of MPSS/GS therapy related to dose, time and means of administration of MPSS/GS during E. coli-induced shock?

RESULTS AND DISCUSSION

Objective A. To Delineate the Exact Mechanisms of Protection of Our Corticosteroid/Antibiotic Therapy for E. coli-Induced Shock:

A. Myocardial function. Cardiac depression and/or failure have been reported in both animal and human septic shock reports. A key goal in our project is to determine the effect of our therapy on myocardial function. We have completed ten experiments and preliminary results indicate that myocardial dysfunction in E. coli-induced shock is prevented by large acutely administered infusions of methylprednisolone sodium succinate (MPSS) and gentamicin sulfate (GS).

We have documented that all dogs survive LD₁₀₀ E. coli-induced shock when administered MPSS/GS early after onset of E. coli infusion. If MPSS/GS treatment prevents myocardial failure this would suggest that the dysfunction contributes to the lethal effects of LD₁₀₀ E. coli-induced shock. If, on the other hand, the myocardial failure still occurs after MPSS/GS therapy, we could conclude that this degree of cardiac dysfunction may not significantly contribute to lethality.

B. Adrenal gland function: role of corticosteroid. Pharmacologic doses of the corticosteroid, methylprednisolone sodium succinate (MPSS), combined with gentamicin sulfate (GS) promote complete recovery of dogs administered LD₁₀₀ E. coli. We recently completed a study which more clearly delineates the role of corticosteroid in severe sepsis and which compares the disappearance rates of endogenous cortisol in septic and nonseptic animals. Anesthetized dogs were acutely adrenalectomized then infused with saline, E. coli, or E. coli plus GS and pharmacologic doses of MPSS. Adrenalectomized dogs given E. coli died in 3 hours, while those given saline or E. coli plus MPSS/GS survived 126 and 112 hours respectively. MPSS/GS supported arterial pressure, pH and pO₂, reduced hemoconcentration and lactate accumulation, and maintained blood glucose (p<0.05), but did not affect numbers of circulating bacteria. Dogs

given E. coli had higher cortisol levels and longer cortisol half-lives than those given saline ($p < 0.05$). An inverse relationship between survival time and cortisol half-life was observed in untreated septic dogs. Findings confirm the decisive role of corticosteroid in sepsis and therapy.

C. Hepatic function: carbohydrate metabolism. During sepsis/septic shock, metabolic alterations, including glycogen depletion and diminished gluconeogenesis, occur at a time when plasma glucocorticoids, glucagon, and epinephrine levels are elevated. In addition, hypoglycemia accompanies lethal septic shock, whereas normo- to hyperglycemia is associated with survival. Steroidogenesis does not seem to be altered, but the intracellular mode of steroid action is perturbed in shocked animals. These observations emphasized the need to consider molecular events involved in the host response to acute bacterial sepsis, and we have subsequently begun a project designed to determine the mechanisms by which carbohydrate metabolism is perturbed during gram-negative sepsis. These studies are being carried out with the collaboration of Drs. R. D. Stith and R. E. McCallum of the University of Oklahoma Health Sciences Center. Our plans are to elucidate the mechanism(s) whereby combined exogenous steroid therapy and antibiotic treatment improve survival in adrenalectomized dogs administered Escherichia coli. An adrenalectomized animal may exhibit near normal plasma glucose concentrations in basal or resting states. However, in a state of stress such as gram-negative septic shock the ability of that animal to produce glucose is impaired. This is undoubtedly due to a failure of hepatic and renal gluconeogenesis. Control of phosphoenolpyruvate carboxykinase (a rate-limiting gluconeogenic enzyme) synthesis is probably a major mechanism by which glucocorticoids regulate gluconeogenesis.

In this series of studies, we have completed six experiments with E. coli and four control (no E. coli) experiments. In the E. coli-treated animals, since time of death was 90 min for three animals, the final blood samples were taken at an average of 102 minutes post-onset of E. coli infusion whereas in control animals final blood samples were drawn at 120 minutes post-onset of saline infusion. Tissue biopsies of liver, ileum, spleen, lung and left ventricle were completed within 30 additional minutes. Plasma nor-epinephrine concentrations increased in both control and E. coli-infused adrenalectomized dogs but these final values were not significantly different between the two groups. Results from these studies demonstrate decreased specific, high-affinity binding of ^3H -dexamethasone in cytosol preparations especially of liver obtained from E. coli-infused adrenalectomized dogs. Decreased binding occurred at a time after E. coli infusion when hepatic phosphoenolpyruvate carboxykinase (PEPCK) activity was diminished. Although steroid binding and PEPCK activity were decreased, liver glycogen content in E. coli and control animals were $+18.1 \pm 5.9$ and $+23.3 \pm 6.7$ mg/gm of liver, respectively. Insulin and glucagon values appear to be increasing in the E. coli-infused animals but the insulin/glucagon ratios and blood glucose concentrations remained relatively unchanged in both groups of animals. Analysis of the data to date suggest to us that although certain critical events that lead to

metabolic death during lethal septic shock are manifested in the animals challenged with E. coli (e.g., decreased steroid binding and PEPCCK activity), the constancy of blood glucose values reveal that in the acutely adrenalectomized animal, metabolic derangements are not the cause of death. These complex mechanistic studies have stimulated us to begin designing studies that would explore early cardiovascular events as the probable cause of death in adrenalectomized animal.

Objective B. Evaluate Therapy Interaction with Adrenal Cortex, Lung, Liver and Leukocytes.

A. Adrenal gland function: role of corticosteroid. Our recent results from adrenalectomized dogs administered E. coli demonstrate decreased specific, high-affinity binding of corticosteroid in the lung and liver. These findings stimulated us to determine if exogenous steroid (methylprednisolone) and antibiotic therapy would reverse this action. Our hypothesis is that gram-negative septicemia interferes with the normal action of glucocorticoids and that exogenous high-dose steroid treatment will reverse the perturbation. We are now conducting studies to explore this possibility.

B. Maintenance of multiple organ integrity: role of corticosteroid and the mode of administration of antibiotic. Powell et al. (32) recently administered tobramycin (average 78 mg/kg/dog) to control dogs either once daily, every four hours or by continuous infusion. By measuring glomerular filtration and concentration of aminoglycoside found in the kidney they concluded that intermittent doses with large maximum serum aminoglycoside concentrations do not produce toxicity as much as comparable doses given as continuous infusions. Furthermore, the efficacy of once-daily aminoglycoside doses in some models is as great as or even greater than continuous infusion. This finding implies an improvement in the benefit-to-risk ratio with once-daily dosing.

These results have stimulated us to investigate if in fact the method of administration of the aminoglycoside antibiotic, tobramycin (Tobra), alters its therapeutic effectiveness, with or without methylprednisolone sodium succinate in dogs challenged with LD₁₀₀ E. coli. In studies in progress dogs have been divided into five groups:

- Group A - LD₁₀₀ E. coli only
- Group B - E. coli + Tobra (bolus)*
- Group C - E. coli + Tobra (infusion)†
- Group D - E. coli + Tobra (bolus) + MPSS (infusion)**
- Group E - E. coli + Tobra (infusion) + MPSS (infusion)††

*Tobra (45 mg/kg 10 min i.v. injection @ 65 min and 11.25 mg/kg i.v. injections @ 24, 48, 72 and 96 hr).

†Tobra (3 mg/kg 10 min i.v. injection @ 65 min, 1.65 mg/kg/hr i.v. infusion from 75 to 360 min, and 11.25 mg/kg i.m. injections @ 6, 12, 18, 24, 48, 72 and 96 hr).

**Tobra (45 mg/kg 10 min i.v. injection @ 65 min and 11.25 mg/kg i.v. injections @ 24, 48, 72 and 96 hr) plus MPSS (30 mg/kg 15 min i.v. injection @ 15 min and 30 mg/kg i.v. infusion from 30 to 360 min).

††Tobra (3 mg/kg 10 min i.v. injection @ 65 min, 1.65 mg/kg/hr i.v. infusion from 75 to 360 min, and 11.25 mg/kg i.m. injections @ 6, 12, 18, 24, 48, 72 and 96 hr) plus MPSS (30 mg/kg 15 min i.v. injection @ 15 min and 30 mg/kg i.v. infusion from 30 and 360 min).

Results of percent survival/mean survival times of the animals completed in each group are as follows: Group A - 0%/22 hours; Group B - 0%/25 hours; Group C - 0%/17 hours; Group D - 50%/141 hours; and Group E - 100%/permanent survival (>7 days).

These results demonstrate that it is imperative to give MPSS in combination with antibiotic to decrease mortality in LD₁₀₀ E. coli-induced shock. They further suggest that giving tobramycin by infusion is more effective than by bolus against the lethal effects of E. coli-induced shock.

Objective C. Evaluate the Roles of Granulocytes in Live Organism-Induced Shock and Assay the Role of Corticosteroid in Prevention of the Injury.

We have completed a study evaluating acute (1-2 day) and chronic (8 day) daily administration of a large dose of corticosteroid, methyl-prednisolone sodium succinate (30 mg/kg/day), given prior to E. coli administration, on an animal's subsequent response to LD₁₀₀ E. coli infusion. Results show that animals given MPSS for 1-2 days prior to endotoxin challenge survive significantly longer ($p < 0.05$) than those given E. coli alone (91 hours vs. 17 hours). However, those receiving corticosteroid daily for eight days respond poorly to E. coli, survival time averaging 12 hours, and only minimal benefit is obtained by treatment with MPSS/GS after E. coli infusion. Leukocyte concentrations of animals receiving steroid for 1-2 days are significantly higher than those receiving E. coli alone, and those given daily steroid injections for eight days demonstrate a severe sustained degree of leukopenia for six hours following E. coli challenge. No evidence was found for a detrimental effect of short term (1-2 days) administration of large doses of corticosteroid prior to challenge with lethal E. coli; however, long term daily administrations (8 days) reveal definite detrimental effects on animals subsequently challenged by E. coli.

Objective D. Assay the Significance of Beta-Endorphins in the Pathogenesis of Shock and Effectiveness of Therapy.

A. Naloxone therapy: survival results. We have completed studies in which dogs and baboons were intravenously infused with the opiate antagonist, naloxone, and the antibiotic, gentamicin, to determine the therapeutic efficacy of naloxone. Naloxone, 2 mg/kg, was injected intravenously when one-fourth of the E. coli had been infused and then infused at 2 mg/kg/hr (six hours for dogs and twelve hours for baboons). Naloxone provided marked improvement for dogs: 4 of 5 naloxone-treated dogs permanently survived (>7 days); whereas, all dogs given only E. coli died. In contrast, naloxone did not benefit baboons: all died within 42 hours. The explanation for the marked differences between the species is not clear, but the sympathoadrenal response of the baboon to E. coli and naloxone appears to be different from that of the dog.

B. Naloxone therapy: plasma endorphin concentrations. We have completed a study measuring the plasma concentrations of β -endorphin in dogs and baboons in collaboration with Dr. Robert A. Lahti, CNS Diseases Research, The Upjohn Company. Fourteen of sixteen baboons showed elevated endorphin levels during the post E. coli period regardless of whether or not naloxone was administered.

C. Adrenalectomy/E. coli-induced shock study: plasma endorphin concentrations. Seven of nine dogs demonstrated increases of endorphin concentrations following adrenalectomy, while five of these nine dogs also showed increases in endorphin concentrations during a six hour period following subsequent lethal E. coli infusion.

CONCLUSIONS

The purpose of this study was to delineate the exact mechanisms of protection of our corticosteroid/antibiotic therapy including how it is involved with the cardiovascular, metabolic, endocrinologic and host-defense systems of the septic animal. We have particularly emphasized evaluation of therapy interaction with adrenal cortex, lung, liver, and leukocytes. We have evaluated the roles of granulocytes and complement in tissue injury in live organism-induced shock and assayed the role of corticosteroid in prevention of such injury. We have also assessed the significance of β -endorphins in the pathogenesis of shock and effectiveness of therapy. To achieve these goals using dogs, we have developed intact catheterized, adrenalectomized, and isolated working left ventricular preparations. Results underscore the following: methyprednisolone sodium succinate/gentamicin sulfate therapy may prevent the myocardial dysfunction in E. coli-induced shock; corticosteroids perform a decisive role in sepsis and therapy; metabolic derangements are not the cause of death in the adrenalectomized animal challenged with LD₁₀₀ E. coli, but early cardiovascular derangements may take precedence; a decrease in phosphoenolpyruvate-carboxykinase activity contributes to the depression of hepatic and renal gluconeogenesis in lethal septic shock which leads to a metabolic death; the method of administration of antibiotic may prove extremely important in determining its effectiveness against the lethal effects of live organism-induced shock; short term (1-2 days) administration of large doses of corticosteroid prior to challenge with lethal E. coli causes no detrimental effects, however, long term daily administration (8 days) was harmful in animals subsequently challenged with E. coli; 20% of dogs and 100% of baboons* treated with naloxone die when challenged with lethal E. coli; and finally plasma β -endorphin concentrations increase in the baboon subjected to lethal E. coli-induced shock with or without naloxone therapy.

In conclusion, to increase survival of animals in lethal septic shock it is critical to prevent myocardial dysfunction, preserve phosphoenolpyruvate-carboxykinase synthesis, and maintain cortico-

* (experiments conducted by means of separate funding.)

corticosteroid and antibiotic concentrations. On the other hand, 8 day administration of corticosteroid can compromise the host; whereas, 1-2 day corticosteroid administration is protective of the host. Why naloxone is an efficacious therapy for dogs but causes no benefit in baboons and what causes death in the adrenalectomized dog in LD₁₀₀ E. coli-induced shock remain challenges for us to further investigate. Finally, plasma β -endorphin concentrations do not appear to be of prognostic value in determining final outcome of shock.

RECOMMENDATIONS (PLANS FOR FUTURE RESEARCH)

1. Experiments recently begun are being continued to determine if the myocardial dysfunction of E. coli-induced shock is prevented by treatment with infusions of corticosteroid/antibiotic. If protection is documented, the mechanisms of action of the corticosteroid/antibiotic treatment will be determined from analysis of the changes in the parameters of myocardial function.
2. Studies will be continued to determine the mechanisms by which carbohydrate metabolism is perturbed during gram-negative sepsis. Future work will be directed at determining if exogenous steroid (methylprednisolone) and antibiotic therapy will reverse the recently identified perturbances of steroid action (see above). Our hypothesis is that gram-negative septicemia interferes with the normal actions of glucocorticoids and that the resultant adverse effects will be reversed or prevented by high-dose corticosteroid treatment.
3. Studies will be designed to explore early cardiovascular events as the probable cause of death in the adrenalectomized animal subjected to lethal doses of E. coli.
4. Expansion of the role of MPSS in the peripheral distribution of antibiotics will be emphasized.
5. There will be expanded use of special chemical procedures for measurement of cortisol, exogenously administered corticosteroid, endorphin and endotoxin in the blood and/or tissue of animals subjected to E. coli shock.

PUBLICATIONS (RESULTING FROM THIS PROJECT)

Full length manuscripts:

1. Hinshaw, L. B., B. K. Beller, A. C. K. Chang, D. J. Flournoy, R. B. Passey, and L. T. Archer. Evaluation of naloxone for therapy of E. coli shock: species differences. (Submitted.)
2. Hinshaw, L. B., B. K. Beller, A. C. K. Chang, R. B. Passey, and L. T. Archer. Adrenalectomy confirms decisive role of corticosteroid in septic shock therapy (submitted).
3. Archer, L. T., B. K. Beller, A. C. K. Chang, E. H. Brown, R. B. Passey, and L. B. Hinshaw. Does prior steroid administration effect survival time of canines challenged with lethal sepsis? (In preparation.)

Abstracts:

1. Hinshaw, L. B., B. K. Beller, A. C. K. Chang, R. B. Passey, D. J. Flournoy, and L. T. Archer. Naloxone treatment for E. coli-induced shock benefits dogs, but fails to prevent death of baboons. Fed. Proc. 43:414, 1984.
2. Hinshaw, L. B., and B. K. Beller, A. C. K. Chang, R. B. Passey, D. J. Flournoy, and L. T. Archer. Corticosteroid/antibiotic treatment protects adrenalectomized dogs challenged with lethal E. coli. Circ. Shock 13:87, 1984.

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