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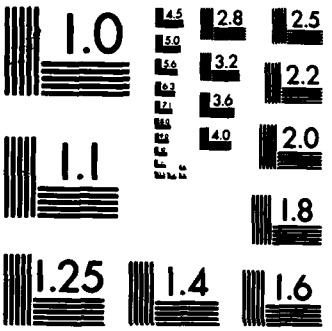

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PROSPECTIVE RANDOMIZED TRIAL OF NALOXONE VERSUS DOPAMINE AS ADJUNCTIVE THERAPY FOR BACTEREMIC SHOCK

ANNUAL REPORT

Merle A. Sande, Gerard P. Aurigemma, Neal Benowitz, Henry F. Chambers, Howard Fullman, David N. Gilbert, D. Lynn Morris, and J. Marcus Wharton

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18. SUPPLEMENTARY NOTES

Cooperative studies were performed at San Francisco General Medical Center, San Francisco, CA 94110 and Providence Medical Center, Portland, OR 97213.

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

NALOXONE vs. PLACEBO, ANLOXONE vs. DOPAMINE, BACTEREMIC SHOCK

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The purpose of this study was to assess the efficacy of naloxone in the therapy of septic shock. The operating protocol was revised during this first year of the study. (See reverse.)

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BLOCK 20 (cont'd)

The original protocol (protocol I), patients (7) were randomized to receive either dopamine or naloxone in increasing bolus doses up to 1 mg/kg followed by continuous naloxone infusion. Of 4 patients given naloxone, 2 responded, with increases in mean arterial pressure (MAP) of 30 % within 10 minutes. Pressures fell however after 70 minutes and 6 hours despite continued drug infusion. Three patients given dopamine responded, although this occurred more slowly (1-2 hours). Survival was unrelated to therapy or hemodynamic response. Infections were present in 4 of 7 patients.

In the revised protocol (protocol II), patients received naloxone or a placebo, (double-blinded and randomized), designated A or B (code not yet broken), given as a single IV bolus of 1 mg/kg followed by a continuous IV infusion of 70% of the bolus dose. If a hemodynamic response does not occur within 10 minutes, the patient then receives conventional therapy.

Seven patients entered protocol II without having prior pressor therapy. Five received drug A, and 3 responded, all within 5 minutes. MAP increased from 64 to 79 mmHg with therapy. However, blood pressure was maintained for an extended period of time (6 hours) in only one patient. Neither of 2 patients given drug B responded. Four of 7 patients survived, unrelated to either therapy or hemodynamic response. Four of 7 had bacterial infections.

Seven patients entered protocol II having failed dopamine, and none responded to drug A (6) or B (1). Two of 7 patients survived; 5 of 6 had bacterial infections.

Based on results from the original protocol, naloxone appears effective in some patients, although on occasion only transiently. The study is currently following protocol II. Some patients appear to respond to drug A, and no adverse side effects have been noted for either drug A or B. We consider it appropriate to continue the study under this protocol.

A-1

Summary.

This study assess the efficacy of naloxone in the therapy of septic shock. The operating protocol was revised during this first year of the study.

The original protocol (protocol I), patients (7) were randomized to receive either dopamine or naloxone in increasing bolus doses up to 1 mg/kg followed by continuous naloxone infusion. Of 4 patients given naloxone, 2 responded, with increases in mean arterial pressure (MAP) of 30 % within 10 minutes. Pressures fell however after 70 minutes and 6 hours despite continued drug infusion. Three patients given dopamine responded, although this occurred more slowly (1-2 hours). Survival was unrelated to therapy or hemodynamic response. Infections were present in 4 of 7 patients.

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Seven patients entered protocol II having failed dopamine, and none responded to drug A (6) or B (1). Two of 7 patients survived; 5 of 6 had bacterial infections.

Based on results from the original protocol, naloxone appears effective in some patients, although on occasion only transiently. The study is currently following protocol II. Some patients appear to respond to drug A, and no adverse side effects have been noted for either drug A or B. We consider it appropriate to continue the study under this protocol.

FORWARD

Septic shock is a clinical syndrome manifested by systemic aberrations of hemodynamic and metabolic parameters caused by bacterial infections. This syndrome, seen in both Gram-negative and Gram-positive bacterial infections, is associated with significant in-hospital mortality.

Preliminary experimental animal studies and open clinical trials in humans with bacteremic shock have suggested hemodymanic and metabolic improvement with naloxone. In this study we assess the efficacy of naloxone in the therapy of septic shock

For protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46. Both research protocols I and II have been reviewed and approved by the Commitee on Human Experimentation at the University of California, San Francisco (approval number 243102-02A, HHS 596).

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BODY OF REPORT

Introduction and Study Design

Septic shock is a clinical syndrome manifested by systemic aberrations of hemodynamic and metabolic parameters caused by a bacterial infection. This syndrome, seen in both Gram-negative and Gram-positive bacterial infections, is associated with significant in-hospital mortality. Despite recent advances in management of critically ill patients, mortality for septic shock is high, ranging from 20-60% in published series to 50-60% in our experience at San Francisco General Hospital.

Current management practice stresses the role of adequate fluid replacement as peripheral vasopressor responses are blunted with low systemic vascular resistance and a relative hypovolemia exacubated by sequestration of fluid at sites of inflammation, fever, vomiting and diarrhea. Patients not responding to fluid alone are given a vasopressor, such as dopamine, to improve cardiac index, systemic vascular resistance, and visceral perfusion. Some patients still do not respond even at large doses, which can cause excessive vasocontriction accompanied by worsening perfusion and acidosis. In addition, at these high doses significant arrhythmias may ensue and further complicate management. A variety of vasoactive agents other than dopamine (e.g. isoproterenol, norepinephrine, dobutamine, and metaraminol) are available but all have serious side-effects. New and less toxic drugs would therefore be useful in the management of shock.

The mechanism responsible for the clinical syndrome of septic shock and its metabolic derangements involve complex interactions of several mediator substances. Beta-endorphin, an endogenous opiate stored with ACTH and released during stress, has been implicated in the hypotension associated with shock states (1). Preliminary animal and clinical studies have shown significant improvement in hemodynamic and cardiovascular function after administration of naloxone in endotoxic/bacteremic, hypovolemic, and spinal shock (1-13). In addition, naloxone is very safe and therefore the therapeutic potential is great if naloxone is indeed effective for shock states. Moreover, if naloxone proved to be of value in patients failing vasopressor therapy, it could significantly alter our approach to this disease and might effectively reduce mortality.

The major purposes of this study (revised protocol-protocol 1) are (1) to evaluate the potential role of naloxone in the early stage of septic shock, (2) to determine if it is useful to treat septic shock in patients unresponsive to vasopressor drugs, and (3) to determine the effect on survival of naloxone compared to conventional therapy in bacteremic shock. The study (revised protocol) consists of two phases. In the first phase, naloxone is compared to blinded placebo (saline, provided by Dupont Laboratories), for bacteremic shock in patients not responding to therapy with fluid resuscitation. Hemodynamic and metabolic responses will be used as a measure of tissue perfusion and these variables will be compared for patients randomized either to intravenous naloxone or to intravenous blinded placebo during the first 24 hours of therapy for bacteremic shock. In addition, survival at 24, 48, and 72 hours and during the period of hospitalization will be compared between the two groups.

In the second phase of this study, the efficacy of naloxone will be compared to a placebo in patients who do not respond to dopamine alone. A beneficial effect of naloxone in this extremely ill patient population would represent a major contribution in the management of septic shock.

Details of the study design and methods are stated in the study protocol (revised protocol 10-21-83), and summarized in the appropriate

portions of the Results section. The original protocol (protocol I) compared naloxone with dopamine in a randomized but non-blinded manner. This protocol was revised because it was cumbersome to administer and difficult to enroll sufficient numbers of patients. Results for both the original and revised protocol are given below.

Results.

In this section, the original protocol is designated Protocol I, and the revised protocol, currently being followed, is designated Protocol II. Results for each are presented separately. Hemodynamic and metabolic parameters measured are given. Blood samples have been obtained but not yet assayed, for endorphins, cortisol, and where appropriate, dopamine.

Protocol I: Naloxone versus Dopamine

Seven patients entered the study under this protocol, in which patients were randomized to receive naloxone versus dopamine in an unblinded fashion. Naloxone was administered in 3 graduated bolus doses of 0.05 mg/kg, 0.5 mg/kg, and 1.0 mg/kg. If after 10 minutes the desired hemodynamic response was not achieved, the next graduated bolus dose was given. If the desired hemodynamic response was obtained then a 24 hour infusion of 70% the effective bolus was given.

Dopamine was administered by continuous IV infusion at a starting dose of 0.5 mcg/kg/min. This dose was adjusted until either the desired hemodynamic response was achieved or a dose of 20 mcg/kg/min was reached without an appropriate response observed.

Naloxone: Four patients were randomized to naloxone, and two of the 4 had a blood pressure response to the initial low dose bolus (0.05 mg/kg). Responses were observed within 10 minutes of administration. With subsequent continuous naloxone infusion, blood pressures were maintained for 70 minutes and 6 hours respectively, but then began to fall toward baseline and naloxone was discontinued. One of these patients survived and one expired; only one had a documented bacterial infections (Staphylococcus aureus sepsis). Pertinent parameters before and after treatment for the responders are (mean ± SD; n=number of patients for whom data are available):

	BASELINE	(n)	TREATMENT	(n)	% CHANGE		TIME
MAP (mmHg)	58.5±7.8	(2)	76.5±19.1	(2)	30%	inc.	10 min
HR	139.5±28.9	(2)	145.0±20.0	(2)	3%	inc.	10 min
SYS BP (mmHg)	83	(1)	105	(1)	26%	inc.	20 min
DIAS BP (mmHg)	41	(1)	30	(1)	26%	dec.	10 min
LACTATE (mg/dl)	47	(1)	37	(1)	21%	dec.	1 hr
HCO3 (mEq/l)	12.0	(1)	9.2	(1)	23%	dec.	3 1/2 hr

	BASELINE	(n)	TREATMENT	(n)	% CHANGE	TIME
ABG-PH	7.42±0.02	(2)	---	---	-- --	---
ABG-pCO2 (mmHg)	31.6±4.0	(2)	---	---	-- --	---

Of the two patients who did not respond to naloxone, one survived and one expired. Both patients had gram negative bacterial sepsis. Pertinent parameters before and after therapy are listed above:

	BASELINE	n)	TREATMENT	(n)	% CHANGE	TIME
MAP (mmHg)	62.5±17.6	(2)	62.0±21.2	(2)	0.8% dec.	10 min
HR	116.5±10.6	((2)	109.5±0.7	(2)	6% dec.	10 min
SYS BP (mmHg)	98.5±2.1	(2)	90.0±5.6	(2)	8% dec.	10 min
DIAS BP (mmHg)	45.0±26.8	(2)	52.0±25.4	(2)	15% inc.	10 min
RAP (mmHg)	15	(1)	12	(1)	2% dec	20 min
PCWP (mmHg)	18	(1)	18	(1)	0% ---	10 min
ANION GAP (mEq/l)	9.0±1.4	(2)	---	---	---- ---	---
LACTATE (mg/dl)	23.2±1.7	(2)	17.8±9.6	(2)	23% dec.	40 min
HCO3 (mEq/l)	20.3±5.0	(2)	15.5±6.4	(2)	23% dec.	10 min
ABG-PH	7.42±0.18	(2)	7.37+.24	(2)	.6% dec.	10 min
ABG-pCO2 (mmHg)	24.5±2.1	(2)	26±4.2	(2)	6% inc.	10 min

Dopamine: Three patients were randomized to receive dopamine. All 3 had a blood pressure response, occurring within 1, 2, 6 hours of administration respectively. Blood pressures were maintained for 24 hours or more, however 2 of the 3 patients died. Only one had a documented bacterial infection (*Pseudomonas aeruginosa*, pancreas). Parameters (as above) are:

	BASELINE	(n)	TREATMENT	(n)	% CHANGE	TIME
MAP (mmHg)	46.0±3.0	(3)	57.0±6.5	(2)	23% inc.	1-2 hr
HR	84.4±16.9	(3)	100.0±14.1	(2)	18% inc.	1 hr
SYS BP (mmHg)	73.3±14.2	(3)	84.0±0.0	(2)	14% inc.	1 hr
DIAS BP (mmHg)	34.6±5.0	(3)	63.0±46.6	(2)	81% inc.	1 hr
RAP (mmHg)	7.0±8.5	(2)	7.0±7.1	(2)	0% --	24 hr
PCWP (mmHg)	9.0±9.9	(2)	13.5±9.2	(2)	5% inc.	24 hr

	BASELINE	(n)	TREATMENT	(n)	% CHANGE		TIME
CO L/min	6.2±0.8	(2)	----	--	---	--	---
LACTATE (mg/dl)	43.0±60.8	(2)	50.0±50.9	(2)	16%	inc.	1 hr
ABG-PH	7.33±0.01	(3)	7.33±0.12	(2)	0%		1 hr
ABG-pCO2 (mmHg)	21.6±7.6	(3)	22.5±6.2	(2)	4%	inc.	1 hr

Protocol II: Naloxone versus blinded placebo.

In this protocol, patients received either naloxone or a physically identical placebo in a randomized double blinded manner. The drugs are coded as "A" or "B" and the identity of each is unknown to us at this time. Each is administered as a single bolus of 1.0 mg/kg followed immediately by a continuous infusion of 70% of the bolus dose. The infusion is discontinued and alternate therapy initiated if no response is observed within 10 minutes. Patients enter the protocol when first observed to be in shock, or after failing to respond to dopamine infusion. These groups are analyzed separately.

Naloxone versus Blinded Placebo-no prior pressor therapy

Drug A. Five patients were randomized to receive drug A, and 3 demonstrated a blood pressure response, all within 5 minutes. One patient, blood pressure fell to baseline after 20 minutes, despite continued drug infusion. In a second patient, the blood pressure remained elevated for 6 hours, but fell when drug A infusion was stopped. In the third, therapy was switched to dopamine shortly after a response was obtained, for reasons unrelated to the study protocol. Two of the three patients survived. Infections were present in 2 (Escherichia coli sepsis, mixed bacterial pneumonia). Data for the 3 responders are (as above):

	BASELINE	(n)	TREATMENT	(n)	% CHANGE		TIME
MAP (mmHg)	64.0±8.4	(2)	79.3±16.3	(3)	23%	inc.	5 min
HR	120.0±28.2	(2)	115.0±7.1	(2)	4%	dec.	5 min
SYS BP (mmHg)	88.0±14.6	(3)	99.6±4.7	(3)	13%	inc.	5 min
DIAS BP (mmHg)	55.0±14.8	(2)	70.0±21.8	(3)	27%	inc.	5 min
HCO3 (mEq/l)	22.0±3.1	(3)	---	--	--	--	---
ABG-PH	7.46±0.02	(3)	---	--	--	--	---
ABG-pCO2 (mmHg)	31.5±4.0	(3)	---	--	--	--	---

Of the two patients who did not respond to Drug A, one survived. Bacterial infection (mixed anaerobic bacteremia) was present in one patient. Parameters (as above) are:

	BASELINE	(n)	TREATMENT	(n)	% CHANGE	TIME
MAP (mmHg)	61.5±12.0	(2)	61.5±13.4	(2)	0%	5 min
HR	75.2±25.2	(2)	-----	--	---- ---	---
SYS BP (mmHg)	91.5±12.0	(2)	92.0±12.7	(2)	0.5% inc.	5 min
DIAS BP (mmHg)	43.5±9.2	(2)	43.5±10.6	(2)	0%	5 min
RAP (mmHg)	15	(1)	20	(1)	33% inc.	1 hr
PCWP (mmHg)	18	(1)	20	(1)	11% inc.	1 hr
LACTATE (mg/dl)	13.7±18.9	(2)	---	---	--- ---	---
ABG-PH	7.26±0.12	(2)	---	---	--- ---	---
ABG-pCO2 (mmHg)	25.0±2.8	(2)	---	---	--- ---	---

Drug B. Two patients were randomized to Drug B, and neither responded. One had a bacterial infection (Escherichia coli peritonitis). One survived and one expired. Parameters (as above) are:

	BASELINE	(n)	TREATMENT	(n)	% CHANGE	TIME
MAP (mmHg)	70.0±2.1	(2)	69.5±0.7	(2)	0.7% dec.	5 min
HR	84.5±34.6	(2)	82.0±31.1	(2)	2.9% dec.	5 min
SYS BP (mmHg)	82.0±5.6	(2)	84.0±1.4	(2)	2% inc.	5 min
DIAS BP (mmHg)	63.0±2.8	(2)	58.5±9.2	(2)	7% inc.	5 min
ABG-PH	7.39±0.21	(2)	---	--	--- ---	---
ABG-pCO2 (mmHg)	28.4±0.6	(2)	---	--	--- ---	---

Naloxone versus Blinded Placebo after Dopamine Therapy Failure

Drug A. Six of 7 patients were randomized to drug A, and no patient responded to the drug. Five of 6 patients had bacterial infections. Two patients survived and 4 expired. Parameters (as above) are:

	BASELINE	(n)	TREATMENT	(n)	% CHANGE	TIME
MAP (mmHg)	53.2±10.1	(6)	51.3±12.6	(6)	3% dec.	5-10 min
HR	125.6±18.6	(5)	132.7±14.7	(4)	5% inc.	5-10 min
SYS BP (mmHg)	72.6±12.2	(6)	69.2±16.7	(6)	4% dec.	5-10 min
DIAS BP (mmHg)	40.8±6.1	(6)	42.2±8.7	(6)	3% inc.	5-10 min
RAP (mmHg)	9	(1)	7	(1)	22% dec.	5 min
PCWP (mmHg)	7	(1)	9	(1)	28% inc.	5 min
CO L/min	8.3	(3)	7.4	(1)	10% dec.	5 min
ANION GAP (mEq/l)	13.5±9.7	(3)	---	--	--- ---	---
LACTATE (mg/dl)	34.3±16.5	(2)	21.8±7.2	(2)	36% dec.	20 min
HCO3 (mEq/l)	15.8±0.9	(3)	13.5±6.0	(3)	14% dec.	5-10 min
ABG-PH	7.37±0.07	(5)	7.41±0.04	(3)	0.5% inc.	5-10 min
ABG-pCO2 (mmHg)	30.0±9.5	(5)	22.0±11.5	(3)	26% dec.	5-10 min

Drug B. The one patient randomized to Drug B did not respond. Drug was administered for 8 minutes but was discontinued when the patient developed severe bradycardia. He had mixed bacterial sepsis.

	BASELINE	(n)
MAP (mmHg)	37	(1)
HR	89	(1)
SYS BP (mmHg)	85	(1)
DIAS BP (mmHg)	26	(1)
ABG-PH	7.04	(1)
ABG-pCO2 (mmHg)	15	(1)

Discussion.

Protocol I: Naloxone versus Dopamine.

Two of 4 patients given naloxone had a definite increase in blood pressure (30% increase in mean arterial pressure) occurring within 10 minutes of drug administration. The naloxone responses were obtained with the lowest dose tested (0.05 mg/kg). The increase in blood pressure were sustained for 70 minutes and 6 hours respectively but then fell despite continued naloxone infusion. Three of 3 patients given dopamine responded with increases in blood pressure, although the increases occurred more slowly than with naloxone. There was a trend toward improvement of metabolic abnormalities but no significant difference could be demonstrated. The presence or absence of documented bacterial infection did not correspond with response to therapy with either naloxone or dopamine. The number of patients assessed is too few to allow any further conclusions, including effects on survival. No dramatic changes were noted in other parameters measured. There were no apparent side effects from the administration of up to 1.0 mg/kg naloxone.

Protocol II: Naloxone versus blinded placebo.

These drugs are administered in a randomized double-blind manner. Three of 5 patients given drug A responded within 5 minutes while neither of 2 patients given drug B responded. As observed in one of the patients given naloxone under protocol I, blood pressure was sustained for only a short time in patients receiving drug A. In another, blood pressure was maintained for 6 hours. When administered to patients who failed dopamine therapy, neither drug A (6 patients) nor drug B (one patient) was effective in producing a blood pressure response. However there was a trend toward improvement of metabolic abnormalities (lactate and arterial pH). Neither drug had apparent side effects, and the presence of documented infection did not correlate with response to therapy. Parameters other than systemic blood pressures were not markedly altered by therapy with either drug . Ultimate survival appeared unrelated to response to therapy.

Conclusions and Recommendations.

Under the current protocol (protocol II--Naloxone versus blinded placebo) there are too few patients entered in the study to determine significant differences in the two groups. Neither drug appears to have adverse side effects, and several patients who received drug A had apparent hemodynamic responses. There also appears to be a trend toward normalization of metabolic adnormalities with drug A, although numbers of patients are too few to demonstrate statistically significant differences. We consider it appropriate to continue the study under the current protocol which is easily administered and now progressing smoothly, there is no reason to break the code at this time.

In the prior protocol (naloxone versus dopamine), two of 4 patients responded to naloxone with significant increases in mean arterial pressure. Responses occurred within 10 minutes of drug administration or opposed to 1-2 hours for comparable responses in patients given dopamine. No adverse effects were noted with administration of up to 1 mg/kg naloxone.

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