Opiate Antagonists: A Role in the Treatment of Hypovolemic Shock

Abstract. *The opiate antagonist naloxone has been used to treat shock following acute blood loss in conscious rats. Naloxone treatment rapidly increased mean arterial pressure and pulse pressure in this new shock model. More importantly, these blood pressure changes were sustained and survival was significantly increased with naloxone as compared with placebo treatment. From these findings, it may be inferred that endorphins may play a role in the pathophysiology of hypovolemic shock. It is suggested that narcotic antagonists may prove to be of therapeutic value in the treatment of shock.*

Endogenous opiates (endorphins) may function in a variety of physiological systems (*1*) in addition to their role in modulating the perception of painful stimuli (*2*). We recently demonstrated that the opiate antagonist naloxone is able to reverse the hypotension of endotoxin shock (*3*). The underlying theoretical considerations that prompted those studies were twofold: (i) endorphins are released in response to stress (*4*) and (ii) even small doses of opiates are able to depress blood pressure (*5*). From the results of the endotoxin studies, we suggested that endorphins might be involved in the pathophysiology of septic shock. However, the possibility existed that these beneficial effects of naloxone were unique to an interaction with endotoxins and not generalizable to other forms of shock. The purpose of the present studies was to evaluate the efficacy of naloxone in another model of shock (hypovolemia) and to determine whether this opiate antagonist improved survival as well as physiological parameters in hypovolemic shock.

Thirty male Sprague-Dawley rats (Zivic-Miller Laboratories, Allison Park, Pennsylvania) weighing 250 to 300 g were studied. Following intraperitoneal pentobarbital anesthetization (50 mg/kg), cannulas were placed in the tail artery and external jugular vein; these cannulas were passed subcutaneously to emerge from the posterior neck to permit the animals subsequent freedom of movement (*6*). The rats were maintained before and after surgery at 24°C on a 12-hour light-dark cycle with free access to food and water. At 24 hours after surgery, these freely mobile, conscious rats were studied in their home cages. Arterial lines were connected to a Narco Bio-Systems microtransducer (model RP1500) and blood pressure (BP) and heart rate (HR) were recorded on a Beckman dynograph (type R). Hypovolemic shock was produced by withdrawing blood from the venous catheter into a 10-ml heparinized syringe. Mean arterial pressure (MAP) was maintained at 40 mm-Hg for 20 minutes through intermittent bleeding (*7*). On retrospective analysis, an equivalent volume of blood [approximately 50 percent of total blood volume (*8*)] was withdrawn from each group of animals: naloxone rats, 8.87 ± 0.35 ml (mean ± standard error), and saline rats, 9.29 ± 0.44 ml (Student's t-test, $P = .75$, not significant). Following this period of hypotension, either saline or a dose of 1 mg of naloxone-HCl per kilogram (*9*) (Endo Laboratories, Garden City, New York) was given by intravenous bolus in a milliliter volume equal to grams of body weight $\times 10^{-3}$. These injections were followed by a 0.2-ml intravenous saline cannula flush to ensure that all of the drug had been infused; blood was not returned. Fifteen animals each were assigned to either the saline or the naloxone treatment group; animals were matched in pairs according to pretreatment MAP. The BP and HR were recorded for 2 hours after treatment and survival was determined at 24 hours.

Figure 1 shows representative dynographic recordings for saline and naloxone rats. Administration of naloxone-HCl (1 mg/kg) resulted in a prompt and sustained increase in MAP and pulse pressure (PP); saline injections of equivalent volume produced little change in either parameter (*10*). These effects are clearly illustrated in Fig. 2, which shows grouped data comparing the effects of the two treatments on MAP, PP, HR, and survival. The MAP and PP were higher in naloxone-treated animals as early as 5 seconds after treatment and remained higher than those of saline-treated animals over the entire 2-hour period of monitoring. Analysis of variance with repeated measures showed that the differences in MAP and PP between the groups were significant ($P < .05$). These differences were even more striking when the data were averaged across time and adjusted for experiment-to-experiment variability (Mann-Whitney U test, $P < .001$). The naloxone effect appeared to become less

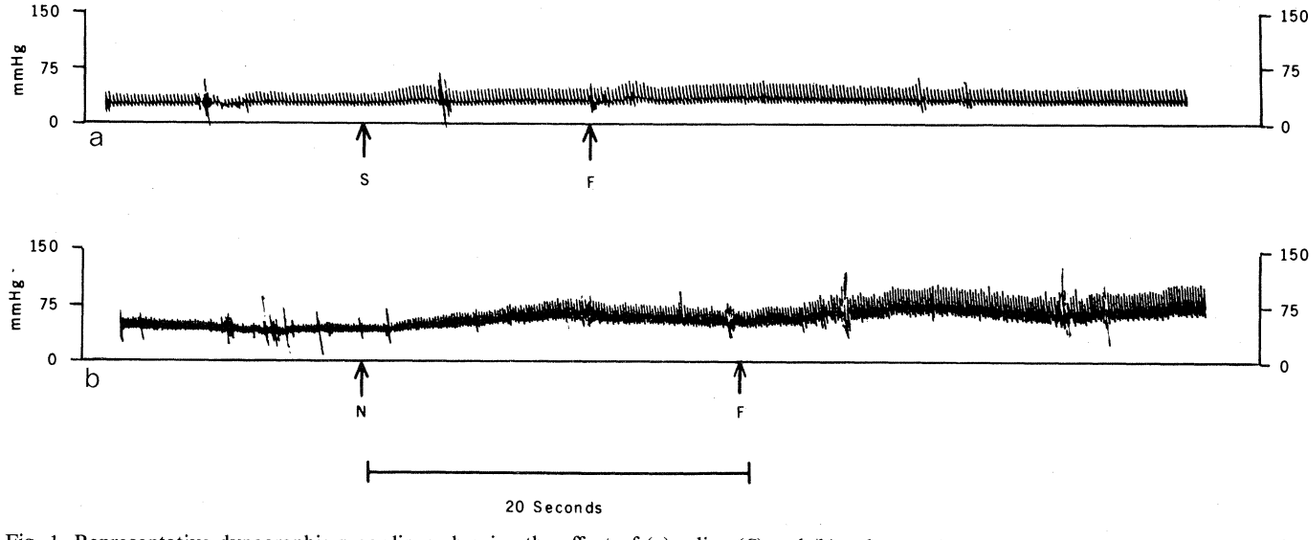

Fig. 1. Representative dynographic recordings showing the effect of (a) saline (*S*) and (b) naloxone (*N*) on blood pressure after hypotension induced by bleeding. A 0.3-ml saline flush (*F*) was used to ensure complete drug delivery.

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marked in the period 60 to 120 minutes, but this may be an artifact related to the greater mortality in saline animals (*11*). More importantly, however, survival was significantly increased by naloxone treatment (Fig. 2), with 13 of 15 naloxone-treated and 8 of 15 saline-treated animals surviving 24 hours (Fisher's exact probability test, $P < .05$). Moreover, the two naloxone-treated rats that died appeared to have more prolonged survival, having lived 85 minutes and 12 hours after treatment. In contrast, most of the deaths in the saline group occurred within the first 60 minutes after treatment, with only one animal living as long as 85 minutes after treatment. Despite the effect of naloxone on pressure, there appeared to be little difference in HR responses between the two groups (analysis of variance, not significant). Interestingly, the HR responses in the saline group had a bimodal distribution, with surviving animals having significantly lower heart rates (362 ± 28 beats per minute) than animals that subsequently died (473 ± 8 beats per minute; unpaired *t*-test, $P < .01$).

The choice of the present hypovolemic model in lieu of the more standard rat hypovolemic model (*12*) resulted from several considerations. First, we studied conscious animals, whereas other rat hypovolemic models have been developed and used for anesthetized animals. Anesthesia suppresses many compensatory cardiovascular reflexes that are present in conscious animals (*13*), and our attempts to fulfill accepted hypovolemic criteria in conscious rats have resulted in death long before the period of hypotension defined for anesthetized animals (*12, 14*). Barbiturate suppression of pituitary function (*15*) as well as other possible barbiturate-endorphin interactions (*16*) also suggested that the use of barbiturates or other anesthetics would complicate the interpretation of any naloxone effect. Second, our hypovolemic model followed from endotoxin studies, which suggested that the effects of endorphins were most important early in shock and that naloxone was maximally effective at this time (*17*). Finally, the use of a more acute model of hypovolemia better paralleled the clinical situation in humans.

The dosage of naloxone used in these experiments (1.0 mg/kg) was an order of magnitude less than that previously reported to be efficacious in treating endotoxic shock (*3*). In more recent studies, a naloxone dose as small as 0.1 mg/kg was effective in restoring BP following endotoxic shock (*17*). Moreover, this effect of naloxone was found to be stereospecific and therefore probably mediated at the opiate receptor.

The findings of this study demonstrate that naloxone treatment can significantly increase both BP and survival in hypovolemic shock. Since naloxone blocks the opiate receptor, its ability to modify physiological events has been used to infer endorphin activity (*18*). With this assumption, the present findings are consistent with the hypothesis that endorphins are hypotensive factors in hypovolemic shock. In further support of this premise, we recently showed that intravenously administered β-endorphin produces a naloxone-reversible hypotension in conscious rats (*17*). It has been suggested that endogenous factors might be important in the cardiovascular pathophysiology of shock (*19*); endorphins appear to be such factors.

The effect of naloxone in reversing the hypotension of both endotoxin and hypovolemic shock suggests that endorphins might be critical hypotensive factors in other forms of shock (burn shock, neurogenic shock, and so on). The fact that this agent has been extensively used in humans for opiate overdose, along with its low toxicity and rapid onset of action, makes it a particularly attractive potential therapeutic agent (*20*). However, these findings must be replicated in larger species, including primates, before use of naloxone in human shock states can be considered.

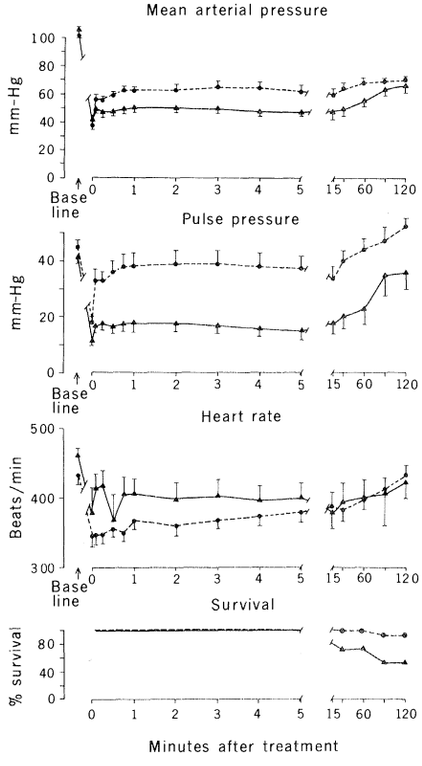

Fig. 2. Effects of (●) naloxone and (▲) saline treatment on mean arterial pressure, pulse pressure, heart rate, and survival following hypotension induced by bleeding. Naloxone treatment significantly increased mean arterial pressure, pulse pressure, and survival compared to saline controls and significantly decreased heart rate. Points represent averaged values ($N = 15$) ± standard errors.

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7. This model was based on pilot studies which showed that the parameters used resulted in an adequate mortality rate (approximately 50 percent) in saline-treated animals.
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9. A dose of 1 mg/kg was based on dose-response data from the endotoxin model. It was maximally effective without signs of toxicity (A. I. Faden and J. W. Holaday, in preparation).
10. We found that naloxone-HCl in doses up to 10 mg/kg is without effect on MAP, PP, or HR in normal conscious rats.
11. The greater mortality of saline-treated rats during the first 60 minutes resulted in exclusion of a number of hypotensive animals, thereby selecting saline rats with higher BP values.
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