A Double Blind Trial of Naloxone in the Treatment of Acute Stroke

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SUMMARY Naloxone has been reported to have potential benefit in the treatment of stroke. We evaluated the effect of naloxone in a double-blind trial conducted with 15 stroke patients whose deficits ranged from 8 to 60 hours in duration. All but one patient sustained a cerebral infarction. Neurologic function was assessed before and five minutes after each of two injections given to each patient in a double-blind fashion. The injections consisted of naloxone (0.4 mg in 3 patients and 4.0 mg in 12 patients) and saline. Prior to the trial, samples of plasma were obtained for determination of immunoreactive beta-endorphin for each patient. Four patients showed minimal improvement following injection of naloxone, while five patients exhibited a slightly greater improvement following saline injection. There were no significant elevations of plasma beta-endorphin among stroke patients. We conclude that naloxone may not have a significant therapeutic role for stroke in the clinical setting.

THE ENDOGENOUS OPIATE SYSTEM may play a role in the pathogenesis of a number of disease entities, including spinal cord contusion and a variety of shock syndromes. Recently, the opiate antagonist naloxone has been used to treat cerebral ischemia in both limited clinical trials and in animal models of stroke. Naloxone was initially reported to be of benefit in human cerebral ischemia, but further studies, using the drug in doses up to 1.2 mg, have produced conflicting results. In an attempt to define the clinical efficacy of naloxone, we undertook a prospective, double-blind trial of this agent at doses of up to ten times those initially reported to be of benefit in acute stroke patients.

Methods

Patients admitted to Los Angeles County University of Southern California Medical Center with stroke of less than 72 hours in duration were studied after informed consent was obtained. Exclusion criteria consisted of pregnancy, use of narcotic drugs, shock, spinal cord injury and other recent trauma. All patients received head CT scans. The neurologic function of each patient was scored according to a standardized examination immediately before and five minutes after each of two injections given one hour apart in double-blind fashion. The injections consisted of naloxone and normal saline. The first three patients in the study received 0.4 mg naloxone and the remaining subjects received 4.0 mg. Blood pressures were monitored
using an arm pressure cuff prior to, and five minutes after, each injection. The standardized examination used to give neurological scores to patients consisted of the following: Five points maximum for strength of each deltoid, iliopsoas, tibialis anterior, and each pair of wrist extensors (extensor carpi ulnaris and radialis); two points maximum for facial movement (each side) and for speech; four points maximum for level of consciousness. The maximum total score was 50 points. Immediately prior to each trial, a sample of plasma was obtained from each patient and stored at −20 degrees centigrade for later determination of immunoreactive beta-endorphin. Immunoreactive beta-endorphin was assayed by a modification of the method described by Shaaban et al.9 Briefly, a direct radioimmunoassay was performed on the plasma samples after an adjustment of the pH to 6.5. Using this method the cross-reactivity with beta-lipotropin was shown to be not more than 10% on a molar basis. The levels of beta-endorphin measured in this way were similar to those obtained after plasma extraction and chromatography. Plasma for the determination of control values of immunoreactive beta-endorphin was obtained from 17 patients hospitalized for a variety of reasons unrelated to cerebral vascular disease, narcotic use, shock, and spinal cord contusion. Paired and unpaired t-tests were used for data analysis.

**Results**

Fifteen patients, six males and nine females, were admitted to the study. The mean age of the patient group was 57.1 years. The duration of deficit at the time of entry into the study ranged from 8 to 60 hours, with a mean of 37 hours. Normal CT scans were obtained in four cases, while the remainder were abnormal. The abnormalities consisted of regions of decreased density in cortical areas (six), low density subcortical lesion (four), and intracerebral hemorrhage (one).

There was no significant difference in neurological function following the administration of either naloxone or saline (fig. 1). The neurological scores before saline were 34.0 ± 8.2 (mean ± S.D.) and 34.6 ± 8.7 after saline. Neurological scores before naloxone were 34.4 ± 8.4 while after naloxone injection the scores were 34.1 ± 9.0. Four patients showed minimal improvement following naloxone injection, with an average score increase of 1.5 points. These patients had an average duration of deficit of 41.5 hours and two had normal CT scans. Following injection of saline, five patients showed improved neurological function, with an average increase of neurological score of 2.6 points. Mean arterial blood pressure (MAP) before naloxone was 115 ± 22 mm Hg (mean ± S.D.) and 114 ± 21 mm Hg five minutes after. Mean arterial pressure before saline was 115 ± 21 mm Hg and 113 ± 21 mm Hg after. Blood pressure recordings were not routinely performed beyond five minutes after injection. However, eight patients, whose first injection was of naloxone, had recordings performed one hour after the initial injection (i.e., just prior to saline injection). For these patients, baseline MAP was 120 ± 23 mm Hg and measurements one hour post-injection averaged 120 ± 21 mm Hg.

The plasma immunoreactive beta-endorphin level for the control group (nine males, eight females, average age 55.6) was 10.9 ± 9.8 fmol/ml (mean ± S.D.). The plasma beta-endorphin levels for the stroke patients was 9.6 ± 6.3 fmol/ml which was not significantly different than controls. No individual patient had a plasma beta-endorphin level greater than two standard deviations above the control mean.

The lot number of naloxone used in this study was assayed for biological activity in C57/B1 mice by a modified hot plate latency test.10 The lot of naloxone normalized the prolonged latencies induced by 4 mg/kg intravenous morphine within 10 seconds.

**Discussion**

In this double-blind trial, we have found that naloxone is ineffective in reversing the neurologic deficits of acute stroke. We used doses of naloxone of up to ten times that reported to be clinically effective. Nevertheless, there was no significant clinical change following injection of intravenous naloxone.

Beta-endorphin is a powerful endogenous opiate agonist known to exert a profound influence on motor activity, as intra-cisternal infusion of beta-endorphin can elicit akinesia in rats.11 The possible effect of naloxone in stroke has been related to modulation of the endogenous opiate system, including beta-endorphin.12 In the current study, we measured plasma immunoreactive beta-endorphin, reflecting primarily beta-endorphin of pituitary origin.12 There was no significant elevation among the stroke patients.

The benefits of naloxone in septic shock are associated with improvement of hemodynamic variables.13 A recent report describes a 45% mean increase of systolic blood pressure in a group of septic patients, beginning as early as two minutes after bolus injection of 0.4 mg.
naloxone. It has been suggested that one of the mechanisms for a possible beneficial effect of naloxone in spinal injury may be improved perfusion, perhaps due in part to increased systemic blood pressure. In this regard, attempts to demonstrate a pressor response to naloxone in non-septic humans have yielded conflicting results. A saline-controlled trial of naloxone in a normal population, at a dose totaling 1.2 mg by bolus injections, resulted in a small (3 mm Hg) but significant decrease in systolic blood pressure measured two and six minutes after injection. An uncontrolled trial, using three minute infusions of as much as 4 mg/kg naloxone, demonstrated systolic pressure increases averaging as high as 6 mm Hg beginning 15 minutes after injection, while no significant changes were noted for diastolic pressure. Additionally, in dogs subjected to cerebral air embolism, naloxone infusion (2 mg/kg naloxone bolus followed by 2 mg/kg per hour) resulted in an average MAP increase of 16 mm Hg after one to four hours of infusion, compared to a 10 mm Hg MAP increase after an equal volume saline injection. In the current study, we noted no pressor response to naloxone in blood pressure recordings five minutes and one hour after naloxone injection by bolus. While it is conceivable that higher doses of naloxone given as a constant infusion might elicit a pressor response, other pharmacologic agents are currently available that more effectively deal with this parameter in a non-septic patient population.

Two additional parameters worthy of discussion are the duration of the deficit from stroke and the dose of naloxone used. The initial study of naloxone in human cerebral ischemia reported naloxone-reversible weakness occurring as long as ten weeks after the onset of the deficit. In the clinical setting, there is, typically, a delay of hours between the onset of stroke and neurological evaluation of the patient. We noted no difference in the response to naloxone based on the duration of the stroke. The dose of naloxone used in clinical and laboratory studies has been highly variable. We initially chose 0.4 mg naloxone, representing the standard dose used to treat narcotic overdose and the dose initially reported to be effective in cerebral ischemia. When we saw no apparent effect, we completed our study using ten times this dose of naloxone. This proved to be equally ineffective. This study does not exclude the possibility that still higher doses of naloxone may be beneficial. However, we doubt that further dose increases would have any physiologic benefit on the duration of the deficit from stroke and the dose of naloxone used. The initial study of naloxone in human cerebral ischemia reported naloxone-reversible weakness occurring as long as ten weeks after the onset of the deficit. In the clinical setting, there is, typically, a delay of hours between the onset of stroke and neurological evaluation of the patient. We noted no difference in the response to naloxone based on the duration of the stroke. The dose of naloxone used in clinical and laboratory studies has been highly variable. We initially chose 0.4 mg naloxone, representing the standard dose used to treat narcotic overdose and the dose initially reported to be effective in cerebral ischemia. When we saw no apparent effect, we completed our study using ten times this dose of naloxone. This proved to be equally ineffective. This study does not exclude the possibility that still higher doses of naloxone may be beneficial. However, we doubt that further dose increases would have any physiologic benefit based solely on antagonism of morphine receptors, which represent approximately 25% of all identified opiate receptors in guinea-pig brain.

The use of naloxone to treat experimental cerebral ischemia has produced widely conflicting results. In this clinical trial, it is of interest to note the modest improvement in neurological function noted in five patients after saline injection. This suggests that mild, random fluctuations of neurological function are common following stroke. Only rigorous, double-blind trials can make the necessary distinction between these fluctuations and the pharmacological effects of naloxone (or other agent). Our inability to demonstrate a response to naloxone suggests the possibility that naloxone may not have a significant role in the therapy of stroke in the clinical setting.

References
8. Jabarly J, Davis JD: Naloxone partially reverses neurologic deficits in some but not all stroke patients. Neuror (Ny) 32: A197, 1982
A double blind trial of naloxone in the treatment of acute stroke.
R J Fallis, M Fisher and R A Lobo

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