High-Dose Intravenous Naloxone for the Treatment of Acute Ischemic Stroke

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To evaluate the safety and possible efficacy of high-dose naloxone for the treatment of acute cerebral ischemia, 38 patients received a loading dose of 160 mg/m² over 15 minutes followed by a 24-hour infusion at the rate of 80 mg/m²/hr. Nausea and/or vomiting were common side effects. Naloxone was discontinued in seven patients (because of hypotension in one, bradycardia and hypotension in two, myoclonus in one, focal seizures in two, and hypertension in one); all seven patients responded to treatment and no permanent sequelae to naloxone were noted. Twelve of the 38 patients showed early neurologic improvement (by completion of the naloxone loading dose). However, there was no correlation between such a loading dose response and clinical outcome at 3 months. Our experience suggests that naloxone is safe at the dose used, but data for efficacy are inconclusive. (Stroke 1990;21:721-725)

Naloxone is an opiate receptor antagonist suggested to have value as a treatment for acute stroke. In animal studies, naloxone inhibits neutrophil superoxide release, alters transmembrane calcium flux, affects lipid peroxidation, has antioxidant actions, stabilizes lysosomal membranes, inhibits proteolysis, and may have several platelet antiaggregatory effects. Naloxone also blocks the cerebral arterial vasoconstrictive effects of norepinephrine and in high concentrations produces vasodilation and increases cerebral blood flow. Finally, naloxone may attenuate cerebral edema.

The potential value of opiate antagonists in treating acute ischemic stroke is suggested by the results of some animal studies and a few human studies. In other small clinical studies, results have ranged from complete reversal of ischemic neurologic deficits to no effect. Patients were few, delays before treatment were often long, and total body doses were lower than those producing a response in animals. None of these studies included a prolonged infusion despite the fact that naloxone's plasma half-life of 30-60 minutes suggests the need for a continuous infusion. A dose-escalation study of naloxone was performed at the Universities of Cincinnati and Iowa from May to September 1984 to determine the highest reasonably tolerated dose for further human study. Well-defined patient selection criteria were used, and the time from stroke onset to initiation of treatment was never more than 48 hours. Naloxone was administered as a loading dose followed by a 24-hour infusion in an attempt to maintain serum levels similar to those showing beneficial effects in animal studies. Loading doses of up to 200 mg/m² (5 mg/kg) were well tolerated, and toxicity was minimal.

A Phase II study was then conducted at the same universities from January through November 1985 to further test the safety of large doses of naloxone in treating patients with acute or progressing ischemic stroke and to determine if the results are sufficiently promising to warrant a randomized prospective double-blind clinical trial. We report the results of the Phase II study.

Subjects and Methods

The entry and exclusion criteria were those used in the previously reported dose-escalation study. Patients aged 35-85 years with acute or progressing ischemic stroke were recruited. We included patients with large-artery atherothrombotic occlusions (LVAT), large-artery embolic occlusions (LVAE, artery-to-
artery or cardiac sources), or small-vessel lacunar infarctions. Treatment began ≤48 hours after the onset or latest progression of the stroke.

Patients had cranial computed tomography (CT) before entry into the study to rule out cerebral hemorrhage. Baseline laboratory evaluation was that used in the previously reported dose-escalation study. The study protocol was approved by the Institutional Review Boards of the participating institutions, and informed consent was obtained from each patient or a family member.

A loading dose of naloxone (160 mg/m²) was given over 15 minutes at a rate not exceeding 10 mg/min. A 24-hour infusion followed immediately at the rate of 80 mg/m²/hr. Naloxone, provided by the pharmaceuticals division of E.I. du Pont de Nemours and Co. (Wilmington, Delaware) was received in a concentration of 50 mg/ml (2-ml ampule) in preservative-free solution. Naloxone was diluted in 500 ml normal saline for the 24-hour infusion. Other treatment consisted of bed rest, supplemental oxygen (2 l/min via nasal prongs), and intravenous saline to maintain urinary output. No food or glucose-containing fluids were given during the 24-hour treatment period. Pretreatment drugs were continued, but additional new therapies (such as anticoagulants) were avoided.

Neurologic and medical assessments designed to detect changes in neurologic condition or signs of naloxone toxicity were performed before treatment and upon 20 minutes and 1, 6, 12, and 24 hours after completion of the loading dose. These assessments were repeated at 2 hours, 24 hours, 7-10 days, and 1 and 3 months after completion of the infusion. Neurologic parameters assessed included National Institutes of Health stroke scale score, level of consciousness, orientation, response to commands, visual fields, gaze, pupillary responses, sensory responses, motor function, limb coordination, plantar reflex, presence of neglect, language, and articulation. The patients’ baseline, completion of loading dose, and 3-month neurologic conditions were categorized as normal (stroke scale score of 0) or mild (1-10), moderate (11-29), or severe (≥30) deficit.

Laboratory studies were repeated at 7-10 days. CT was repeated at 7-10 days and 3 months. CT analysis included assessments for mass effect, edema, shift of midline structures, cortical atrophy, enlarged ventricles, or hypodense lesions due to a stroke. Lesions were localized to arterial distributions and anatomic sites using standardized templates, and lesion volumes were calculated. Three-month follow-up assessments also included performance and discharge disposition. All data were transmitted to Mathematical Statistics, BFSB, IRP, National Institute of Neurological and Communicative Disorders and Stroke, for management and analysis.

We screened 208 patients; 38 (18 men and 20 women) met the inclusion criteria (entry rate=1:5.5). Their mean±SEM age was 63±10.2 (range 41-84) years.

Average time from onset of stroke to initiation of naloxone treatment was 10 hours 36 minutes (48 minutes). Two patients were treated ≤6, 16 were treated 6-12, 15 were treated 12-24, and three were treated 24-48 hours after the onset of stroke. Time data are not available on two patients.

Twenty-one patients (55%) had left hemispheric events, 13 (34%) had right hemispheric events, and four (11%) had infarcts at other sites. By classification of stroke type, 15 patients (40%) had LVAE, 13 (34%) had LVAT, five (13%) had lacunar infarction, and five (13%) had cardiac embolism.

Initial CT findings were positive for stroke in 15 patients and negative in the remaining 23. Twenty-nine of 37 CT examinations done on days 7-10 were abnormal. Two patients with normal baseline CT scans had asymptomatic hemorrhagic transformations detected on their 7-10-day CT scans.

Related disorders observed at baseline were hypertension (n=25), cardiac disorders (n=17), diabetes (n=13), lung disease (n=4), smoking (n=19), and alcohol abuse (n=4); some patients had multiple related disorders at baseline. Cardiac disorders included myocardial infarction (n=9), congestive heart failure (n=6), atrial fibrillation (n=4), cardiomegaly (n=11), and recent cardiac surgery (n=1).

Results

Total naloxone dose for the study population ranged from 344.4 to 4,846.3 mg. Plasma naloxone levels 24 hours after completion of the infusion ranged from 178.64 to 1,426.06 (mean±SEM 582.69±38.98 µg/ml). At 29 hours after completion of the infusion, plasma naloxone levels ranged from 178.64 to 96.76 (mean±SEM 24.23±3.00) µg/ml. Toxicity and outcome were not related to plasma naloxone levels at 24 or 29 hours.

Blood pressure, pulse, respiration rate, and laboratory values (hematocrit, hemoglobin content, platelet count, and leukocyte count) in general remained within normal ranges. Three patients had elevated bilirubin concentrations at the completion of the infusion. The highest bilirubin concentration in any patient was 1.7 mg/dl. Bilirubin concentration returned to normal in all patients by 48 hours.

Baseline stroke scale scores ranged from 3 to 44 (mean±SEM 19.7±12.9), and the 3-month scores ranged from 0 to 31 (mean±SEM 8.0±10.2) (Table 1). Twelve patients had improved by two or more points on the stroke scale between the baseline and the completion of loading dose assessments (Table 1). However, there was no correlation between such a loading dose response and the 3-month outcome. Table 1 also shows each patient’s discharge disposition and performance at the 3-month follow-up.

Possible adverse reactions to naloxone treatment are summarized in Table 2. Twenty-six patients (68%) experienced nausea and/or emesis, which typically occurred after 6-12 hours of naloxone infusion. These complications were controlled with antiemetics, and the naloxone was continued. Behavioral
changes were noted in three patients; two exhibited confusion, and the other became agitated.

The naloxone was prematurely discontinued in seven patients (18%). Focal seizures ipsilateral to the affected hemisphere were seen in two with onset between 6 and 12 hours after initiation of the infusion. Both patients were effectively managed with anticonvulsants. One patient developed myoclonus without frank seizure activity, which subsided after discontinuation of the naloxone. One episode of severe hypertension during the loading dose was noted; the naloxone was discontinued and this patient responded to antihypertensive therapy. Two episodes of hypotension/bradycardia occurred during the loading dose; the drug was discontinued and normal vital signs returned within 40–45 minutes in response to Trendelenburg's position and fluid replacement in one patient and in response to 1 mg atropine, 100 mg dopamine infusion for 10 hours, and fluid replacement in the other. Both patients demon-
strated a transient worsening of their neurologic deficits, which reversed when their blood pressures were normalized. Another episode of hypotension occurred midway during naloxone infusion; the drug was discontinued, and fluid replacement over 110 minutes was required to reestablish previous vital signs in this patient.

By the 3-month follow-up, three patients (8%) had suffered another stroke and three (8%) had died (Table 1). Naloxone was not implicated in any subsequent stroke nor in the deaths.

Discussion

Our results suggest that naloxone is relatively safe at the high doses administered. It is known to be a weak antagonist of γ-aminobutyric acid and may cause seizures at lethal doses in experimental animals. The two cases of focal seizures may not have been related to naloxone. These two patients had relatively large infarcts involving the cortex and were therefore at a higher risk for developing seizures even without naloxone treatment. In both patients the seizures were controlled with phenytoin.

The high incidence of nausea and emesis is clearly drug-related and is to be expected at this dose. In our Phase I dose-escalation study 44% of patients experienced one or both of these side effects. That proportion increased to 68% in the present Phase II high-dose study. The transient mild increase noted in the Phase I study points out the importance of monitoring bilirubin concentration carefully in all patients the seizures were controlled with phenytoin.

Some patients had multiple adverse reactions. No adverse reaction was recorded in 11 patients (29%).

**Results in discontinuation of naloxone.**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>Nausea with emesis</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>Hypotension*</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Emesis without nausea</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Seizures*</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Confusion</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Myoclonus*</td>
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<td>3</td>
</tr>
<tr>
<td>Agitation</td>
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<td>3</td>
</tr>
<tr>
<td>Smothering sensation</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Drug discontinued</td>
<td>7</td>
<td>18</td>
</tr>
</tbody>
</table>

Some patients had multiple adverse reactions. No adverse reaction was recorded in 11 patients (29%).

*Results in discontinuation of naloxone.

We believe that a slower rate of loading dose infusion (≤5 mg/m²/min) will decrease the likelihood of complications such as hypotension and bradycardia. It could also reduce the incidence of nausea, vomiting, and behavioral changes.

Our specific recommendations for a randomized, controlled trial include using the dose described (160 mg/m²) and a slower rate of loading dose infusion (≤5 mg/m²/min). We also recommend development of an acute stroke treatment program modeled on existing systems for early trauma care so that treatment can be started ≤4 hours after stroke onset and ≤1 hour after arrival at the hospital.

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