


Naloxone Administration To Patients With Acute Stroke

JOSEPH JABAILY, M.D.* AND JAMES N. DAVIS, M.D.

SUMMARY Naloxone, an opiate antagonist, has recently been reported to temporarily reverse neurologic deficits associated with subarachnoid hemorrhage. To determine if this unexpected effect of naloxone might also occur in other forms of cerebrovascular diseases, 13 patients who presented with acute neurologic deficits were administered intravenous naloxone. In 3 of these patients, coincidental improvement in neurologic status was seen. In one patient the improvement was permanent. Ten of the 11 patients with non-fatal neurologic damage improved later in their hospital course — 7 of them to their pre-admission state. The only side effect noted was the temporally related onset of a single focal seizure in an ethanol intoxicated patient with an intracerebral hemorrhage.

Naloxone is a well known and commonly used morphine antagonist. Recently several reports of other possible clinical uses for naloxone have been proposed. These include treatment for septic shock, hypovolemic shock, ethanol induced coma and spinal cord trauma. Our attention was caught by the dramatic report of reversal of cerebral ischemia in gerbils and in two humans. These workers report rapid (within 5 minutes) but temporary (less than 20 minutes) reversal of hemiplegia in two patients with subarachnoid hemorrhages. They noted a similar reversal of hemiplegia in experimentally induced stroke in gerbils. A subsequent report of naloxone reversal of hemiplegia has, also, emerged. In addition, Faden has found naloxone may be capable of limiting the extent of cerebral ischemic injury in the canine embolic model of stroke.

Based on these reports, we undertook a pilot study of hospitalized patients with acute neurologic deficits. We treated 13 consecutive patients within 24 hours of the onset of deficit with naloxone. We now report that naloxone administration coincides with neurologic improvement in a few of these patients.
NALOXONE TREATMENT IN CVDUabaik and Davis

Methods

Thirteen patients at either Duke University Medical Center or the Durham Veterans Administration Hospital who suffered recent (3 to 24 hours) focal neurologic deficits were studied. Their deficits ranged from isolated aphasia to coma. The etiologies of the deficits included intracerebral hemorrhage, presumed thrombosis and presumed embolic events (including a case of deficit which occurred during cerebral angiography).

Patients who had no medical contraindications for naloxone gave informed consent to receive the drug experimentally for a non-indicated usage, while the next of kin gave the informed consent for aphaic patients. The study was single blind; the patient not knowing whether naloxone or saline was being administered. Saline (2 ml) was given first intravenously and observations made for ten minutes. Patients were then administered either two or three ampules of naloxone (0.8 to 1.2 mg) at intervals of ten minutes. Those patients who had an alteration in consciousness or who demonstrated a reversal of deficit received 0.8 mg of naloxone. All other patients received 1.2 mg. Vital signs were monitored and neurologic examinations were repeated at ten minute intervals. Computerized axial tomograms (CT) of the head were performed in all but one of the patients.

Results

Our findings are summarized in Table 1. No patients responded to saline administration. In 3 of 13 patients improved neurologic status within minutes of naloxone administration was unequivocably present. In case 2, who had suffered a brainstem infarct, resolution of rotary nystagmus, improvement in vertigo and improvement in paretic limb strength occurred within two minutes after 0.4 mg of naloxone and lasted for 20 minutes. This improvement was obtained again the next day with the same dose.

Case 4 developed neurological symptoms 3 hours earlier at the time of cerebral angiography. Definite improvement but not complete resolution was noted in left arm and leg hemiplegia within 5 minutes of naloxone (0.4 mg) administration and lasted approximately 15 minutes. This reversal repeated when naloxone was given a second time an hour later. A CT scan several days later showed a hypodense area in the right middle cerebral artery distribution.

Case 6 presented with the sudden onset, six hours earlier, of left hemiparesis, dysphasia, and left homonymous hemianopia. He was given 0.8 mg of naloxone, and marked resolution was noted 15 minutes later. He continued to improve and by the next morning the patient had returned to his premorbid state. In this case the improvement could have been spontaneous; that is, the patient may have had a transient ischemic attack and the relationship of improvement to the naloxone administration could have been coincidental.

The possibility of harmful side effects from naloxone administration was raised by case 13. This patient was a known alcoholic with a history of one previous ethanol-withdrawal seizure. He presented in an agitated state with a blood alcohol level in the intoxicated range and an apparent Wernicke’s aphasia. This patient had a single right focal seizure within one minute of receiving his third ampule of naloxone (1.2 mg). The seizure lasted less than one minute. A left temporal intracerebral hemorrhage was diagnosed by computerized tomography. Subsequently the patient had a bout of delirium tremens, but no further seizures. He had a near total improvement of his aphasia by the 7th hospital day. Two months later his aphasia had totally resolved.

Discussion

Taken together with the cases reported by others,7,9 those reported here suggest that naloxone administration may alter the neurologic deficit seen in some patients with cerebrovascular disease. In our patients cerebral infarction or ischemia was the most common cause of neurologic deficit and was the cause in all of the patients who improved after naloxone. However great care must be taken in interpreting our results.

Although 3 of our 13 patients demonstrated a reversal of neurologic deficit coincident with naloxone administration, in one patient the reversal was permanent and may have represented the spontaneous resolution of a transient ischemic attack. Thus we can be certain of naloxone reversal in only 2 patients. Furthermore Bredesen et al.11 carried out a similar study and did not observe reversal in any of 10 patients. Thus naloxone reversal appears to be a rare occurrence.

It is possible that the lack of neurologic response in some of our patients may be a result of inadequate dosages. Subclasses of opiate receptors exist10,12 and with variable sensitivity to naloxone. Hence the dosage of naloxone sufficient for morphine reversal may not be adequate for the reversal of cerebral ischemic effects.

Naloxone, in the doses we used, had no recognized systemic effects. In particular we saw no alteration in blood pressure or heart rate. This agrees with the findings of Volzuka et al13 who gave 20 mg of naloxone to normal volunteers. They did note, however, changes in certain peripheral hormonal concentrations which began 25 minutes after injection.

The fact that a seizure was observed concurrent with naloxone administration raises a concern about administering this agent. This may represent a clinical manifestation of the experimental reports that naloxone increases audiogenic seizure severity in predisposed mice14 and that naloxone facilitates amygdaloid kindling in rats.15

It should be noted that ten of the eleven patients with non-fatal infarcts improved. In seven of these their deficits completely resolved. This degree of improvement and resolution is unusual for an unselected group of consecutive patients admitted to our hospitals and is also more favorable than would be expected from larger national studies.14,15 Therefore it is intriguing to speculate whether the administration of naloxone with-
in the first 24 hours of deficit had a beneficial effect on both morbidity and mortality.

We emphasize again that care should be taken in the interpretation of these results. Naloxone-reversal of neurologic deficit is a rare event. When this series and the results of Bredeson et al.11 are considered together naloxone reversal occurred in only two or three patients of twenty-three patients tested. This occurrence is so unusual that more detailed and conclusive studies would require large numbers of patients. Furthermore the results certainly do not support the routine administration of this drug in patients with neurologic deficit. Until a double-blind study is performed, the objective benefits for naloxone cannot be properly assessed.

These preliminary data do indicate that naloxone can partially, temporarily reverse clinically apparent neurologic deficits in some patients. This would agree with the observations of Baskin and Hosobuchi.7 The fact that neurological deficits could be pharmacologically reversed even days after their acute onset offers hope to stroke patients.

Acknowledgment

The authors wish to gratefully acknowledge the expert secretarial assistance of Ms. Nanci Demarco.

References


---

### Table 1 Summary of Patients with Recent Focal Neurologic Deficits Treated with Intravenous Naloxone

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>BP</th>
<th>Presenting neurologic deficits</th>
<th>CT diagnosis</th>
<th>Hours elapsed prior to naloxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>M</td>
<td>194/114</td>
<td>stupor, left hemiplegia</td>
<td>right middle cerebral artery infarct with shift of midline structures</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>M</td>
<td>140/94</td>
<td>cranial nerve dysfunction hemiplegia</td>
<td>brainstem infarct</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>M</td>
<td>120/80</td>
<td>left hemiparesis</td>
<td>not done</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>150/90</td>
<td>left hemiparesis</td>
<td>right middle cerebral artery infarct</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>176/88</td>
<td>left hemiparesis</td>
<td>right middle cerebral artery infarct</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>M</td>
<td>170/100</td>
<td>left hemiparesis, hemianopia</td>
<td>normal</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>120/70</td>
<td>left hemianopia, hemiparesis, sensory deficit</td>
<td>right posterior cerebral artery infarct</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>59</td>
<td>M</td>
<td>125/85</td>
<td>left hemiparesis</td>
<td>right middle cerebral artery infarct</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>63</td>
<td>M</td>
<td>152/102</td>
<td>aphasia</td>
<td>left middle cerebral artery infarct, luxury perfusion</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>92</td>
<td>M</td>
<td>200/110</td>
<td>left hemiplegia</td>
<td>right capsular infarct</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>M</td>
<td>158/86</td>
<td>coma, probable brainstem infarct</td>
<td>no abnormalities detected</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>75</td>
<td>F</td>
<td>180/110</td>
<td>left hemiparesis</td>
<td>right occipital intracranial hemorrhage</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>57</td>
<td>M</td>
<td>150/90</td>
<td>aphasia</td>
<td>left temporal intracranial hemorrhage</td>
<td>4</td>
</tr>
<tr>
<td>Naloxone response</td>
<td>Associated medical problems</td>
<td>Adjunct therapy</td>
<td>Follow up (3 weeks to 3 months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>unknown</td>
<td>none</td>
<td>expired</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>temporarily improved</td>
<td>hypertension, previous strokes</td>
<td>coumadin</td>
<td>deficit resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>ethanolism</td>
<td>aspirin</td>
<td>improved (ambulatory)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>temporarily improved</td>
<td>hypertension, TIA</td>
<td>dexamethasone (temporarily)</td>
<td>improved (ambulatory)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>ethanolism, hypertension, diabetes mellitus</td>
<td>none</td>
<td>deficit resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>permanently improved</td>
<td>atrial fibrillation, hypertension, congestive heart failure</td>
<td>after improvement begun on heparin, then coumadin</td>
<td>deficit resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>atrial fibrillation, previous stroke</td>
<td></td>
<td>deficit resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>hypertension, angina pectoris</td>
<td>coumadin</td>
<td>deficit resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>hypertension, cryptococcal meningitis (resolved)</td>
<td>none</td>
<td>deficit resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>hypertension, dementia</td>
<td>none</td>
<td>unimproved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>hypertension, previous stroke</td>
<td>none</td>
<td>expired</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>none</td>
<td>hypertension, previous stroke dementia</td>
<td>none</td>
<td>improved (ambulatory)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>seized</td>
<td>ethanolism, hypertension</td>
<td>none</td>
<td>deficit resolved</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Naloxone administration to patients with acute stroke.
J Jabaily and J N Davis

Stroke. 1984;15:36-39
doi: 10.1161/01.STR.15.1.36

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/15/1/36

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/