SEVERAL CONTROVERSIAL REPORTS regarding the use of naloxone in acute cerebral ischemia have recently appeared. Baskin and Hosobuchi found that two patients with focal cerebral ischemia had dramatic improvement with the intravenous administration of naloxone. Jabaily and Davis gave intravenous naloxone to thirteen patients with acute stroke, treatment given between 4 and 24 hours after the cerebral event. Three out of thirteen patients improved suggesting that naloxone reversal of ischemic cerebral deficits was a rare event. Two had intracerebral hemorrhages that did not respond and one had an immediate and long lasting recovery and was subsequently shown to have a C.T. scan without evidence of a cerebral infarction.

Cutler et al. gave intravenous naloxone to nineteen patients with cerebral ischemia of less than seventy-two hours duration. None of the patients responded to the intravenous naloxone. Two of their patients also had an intracerebral hemorrhage. Fallis, et al. gave intravenous naloxone in a double blind trial to 15 patients with symptoms between 8 and 60 hours in duration. None of the patients responded. One patient had an intracerebral hemorrhage. Faden suggested that the discrepancy of the different trials is partly due to a poor selection of patients, lack of early treatment and use of inadequate doses. In order to elucidate the time factor and the type of patients who respond to intravenous naloxone we conducted a trial in four different populations of stroke patients: 1) patients with an established cerebral infarction proven by C.T. scanner 48 hours after the onset of the cerebral ischemia and were asymptomatic when discharged. The 3 patients with hyperacute cerebral ischemia secondary to angiographic angiography had a dramatic response to the injection of naloxone. These findings suggest that intravenous naloxone may differentiate reversible versus irreversible cerebral ischemia.

Summary

Naloxone was given as an I.V. bolus of 0.8 mgs to four groups of patients with stroke: 1) 20 patients with C.T. proven cerebral infarcts of longer than 7 days duration; 2) 20 patients with acute cerebral ischemia of less than 24 hours; 3) 5 patients with C.T. proven intracerebral hemorrhage of less than 24 hours; and 4) 3 patients with a hyperacute cerebral ischemia which occurred during the performance of a cerebral angiogram. The patients with established cerebral infarctions of more than 7 days duration and the patients with intracerebral hematomas had no response to intravenous naloxone. Of 20 patients with acute cerebral ischemia of less than 24 hours duration, 7 had prompt, complete and long-lasting recovery. These patients had no subsequent evidence of cerebral infarct by C.T. scanner 48 hours after the onset of the cerebral ischemia and were asymptomatic when discharged. The 3 patients with hyperacute cerebral ischemia secondary to cerebral angiography had a dramatic response to the injection of naloxone. These findings suggest that intravenous naloxone may differentiate reversible versus irreversible cerebral ischemia.
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7–15 days). The mean age of the patients was 54 years with a S.D. of 12.32 years (range 45–81 years). 2 c.c. of normal saline was given intravenously as placebo and the patient was evaluated after; 5 minutes if no response was attained naloxone was given by I.V. bolus 0.8 mgs and the patient was evaluated every five minutes during 30 minutes. These patients had focal cerebral ischemic deficits for a period longer than seven days. The mean duration of the symptoms was 9.5 days. The degree of weakness was graded according to the Mayo Clinic score system. Two neurologists examined each patient and scored the deficit independently. Blood pressure, pulse and respiratory rate were recorded each five minutes. No other medications were given to these patients except for antihypertensive medication.

The second group consisted of 20 patients with acute ischemic cerebral deficits seen during the first 24 hours of the inception of the ischemia. The mean duration of the symptoms at the time of the administration of naloxone was 11.1 hours with a range between 2 and 24 hours. The mean age was 52.7 years with a range between 32 and 84 years. All these patients had immediately received a lumbar puncture and a C.T. scan to rule out a subarachnoid hemorrhage or an intracerebral hemorrhage. A complete neurological examination was performed and 2 c.c. of normal saline was given as a placebo. With no response after five minutes, naloxone 0.8 mgs I.V. bolus was given and thereafter a careful motor evaluation was performed every five minutes during 30 minutes. Vital signs were recorded before the administration of the medication and each five minutes thereafter. The patients were examined for progression of the ischemic symptoms every four hours for the first 48 hours. After 48 hours the C.T. scan was repeated and a complete neurological examination was performed. At the time of discharge the patients were again evaluated.

The third group of patients had hypertensive intracerebral hematomas in the putamen and internal capsule. The mean age of the patients was 65 years and the mean duration of the symptoms was 8 hours. Naloxone and placebo were given as in the first group.

The last group comprised three patients who developed signs of focal cerebral ischemia during the performance of a cerebral angiogram. The patients were seen within the first ten minutes of the onset of the ischemia. No placebo was given to these patients. A careful neurological examination was performed before 0.8 mgs of naloxone was given by bolus and every 5 minutes thereafter. The condition at discharge was also evaluated.

Results

No changes in blood pressure, pulse or respiratory rates related to naloxone injection were observed in any of the patients. None of the patients of the first group (established cerebral infarction) improved with the intravenous administration of naloxone. The scores of weakness assessed independently by two neurologists did not change significantly after the administration of the drug in any patient. The patients in the second group (cerebral ischemia of less than 24 hours duration) had no response to the placebo (normal saline) and they had a variable response to the intravenous naloxone. Seven out of twenty patients had a prompt, dramatic response with complete resolution of the symptoms (table 1). The weakness cleared in all these patients in less than ten minutes. The improvement lasted in three patients 30 minutes and in four was long-lasting without recurrence of the weakness.

Four out of 20 patients had a partial response with improvement of the weakness of the paretic lower extremity but had no response in the upper extremity. None of the patients had clouding of consciousness. The mean time elapsed between the onset of the ischemia and the administration of the naloxone was 11.1 ± 8.2 hours with a range between 2 and 24 hours. Six of the patients who responded to the naloxone had focal cerebral ischemia of less than 12 hours. Only one patient who responded well to naloxone had a duration of the ischemic symptoms for 22 hours. The mean duration of the symptoms of the patients who responded to naloxone was 9 hours whereas the mean duration of the symptoms of the patients who had no response was 11.4 hours. This difference was not statistically significant. The C.T. findings after 48 hours of the onset of the ischemia were: 1) no evidence of cerebral infarction in the seven patients who had a full response to naloxone; 2) cerebral infarction in the 13 patients who either responded poorly or not at all to the intravenous naloxone (table 1). The C.T. studies were performed without contrast infusion. The seven patients who responded to the drug were discharged without sequelae three to seven days from the onset of the ischemia. The rest of the patients were discharged with variable neurological sequelae. Two patients with capsular infarcts were discharged without any improvement. The rest of the patients were discharged improved with respect to their condition on admission although some had important neurological sequelae. The five patients with C.T. proven hypertensive putaminal hemorrhages who received naloxone during the first 24 hours of the onset of the symptoms (mean duration 8 hours) had no response to the drug. Two of these patients were obtunded. There was no improvement in the state of consciousness. These patients were discharged unimproved. The three patients who received naloxone during the first ten minutes of the onset of the ischemia were hemiplegic before the administration of naloxone. They all recovered fully during the first 15 minutes after the injection of naloxone. Thereafter 0.4 mgs of naloxone was given intravenously each hour. These patients were discharged without residual neurological deficit. Table 2 summarizes the findings in the second group of patients with cerebral ischemia.

Discussion

It is perplexing that some patients with acute strokes respond to naloxone and some do not. Faden suggest ed that an inadequate selection of patients may be a
TABLE 1  Response of neurological deficit.

<table>
<thead>
<tr>
<th>Age</th>
<th>Hours after onset of cerebral ischemia</th>
<th>Recovery to Naloxone</th>
<th>CT findings 48 hours after</th>
<th>Neurological deficit at discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>11 complete</td>
<td>normal</td>
<td>recovered</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>2 complete</td>
<td>normal</td>
<td>recovered</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>24 partial</td>
<td>left parietal infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>10 none</td>
<td>left capsular infarct</td>
<td>not improved</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>7 none</td>
<td>left capsular infarct</td>
<td>not improved</td>
<td></td>
</tr>
<tr>
<td>84</td>
<td>4 none</td>
<td>left fronto parietal infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>22 none</td>
<td>left parietal infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>6 none</td>
<td>right frontal infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>8 complete</td>
<td>normal</td>
<td>recovered</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td>24 none</td>
<td>capsular infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>20 partial</td>
<td>left fronto-temporal infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>24 none</td>
<td>left capsular infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>67</td>
<td>22 complete</td>
<td>normal</td>
<td>recovered</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>4 none</td>
<td>left parietal infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>64</td>
<td>5 none</td>
<td>left parietal infarct</td>
<td>improved</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>8 complete</td>
<td>normal</td>
<td>recovered</td>
<td></td>
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<tr>
<td>58</td>
<td>12 partial</td>
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<tr>
<td>66</td>
<td>12 complete</td>
<td>normal</td>
<td>recovered</td>
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<tr>
<td>62</td>
<td>2 complete</td>
<td>normal</td>
<td>recovered</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>18 partial</td>
<td>left frontal infarct</td>
<td>improved</td>
<td></td>
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</table>

x 52.7 Range 32–84 years; x 11.1 ± 7.3 hs. Range 2–24 hs.

reason to explain these discrepancies. The present trial provides support to this notion. Patients with established cerebral infarcts did not improve with the administration of intravenous naloxone. The present trial provides support to this notion. Patients with established cerebral infarcts did not improve with the administration of intravenous naloxone. Our twenty patients with C.T. proven cerebral infarcts of more than seven days duration had no response. The thirteen patients with acute cerebral ischemia treated within the first twenty-four hours of the onset of ischemia and were discharged without neurological deficits. These data suggest that the patients who had a dramatic improvement with naloxone had reversible ischemic neurological deficits whereas those patients that did not respond had established cerebral infarcts. These data may explain the findings of Cutler et al³ and why some patients of Jabaily and Davis² did not have any improvement. The patients of Baskin and Hosobuchi¹ who improved with intravenous naloxone had a C.T. scan without evidence of a cerebral infarct. The patient of Jabaily and Davis who had an immediate and long lasting recovery did not have a cerebral infarct by C.T. forty-eight hours after the inception of the ischemia and were discharged without neurological deficits. These data suggest that the patients who had a dramatic improvement with naloxone had reversible ischemic neurological deficits whereas those patients that did not respond had established cerebral infarcts. These data may explain the findings of Cutler et al³ and why some patients of Jabaily and Davis² did not have any improvement. The patients of Baskin and Hosobuchi¹ who improved with intravenous naloxone had a C.T. scan without evidence of a cerebral infarct. The patient of Jabaily and Davis who had an immediate and long lasting recovery did not have a cerebral infarct by C.T.

Patients with hypertensive intracerebral hematomas do not improve with the administration of intravenous naloxone even in the first few hours of the illness. This is suggested by the fact that five of our patients with C.T. proven intracerebral hematomas and those previously reported²–³ had absolutely no improvement. Although the sample size is obviously inadequate the reported evidence supports this contention. Furthermore, a white matter destruction such as that induced by a deep intracerebral hematoma is unlikely to improve with naloxone. In our group of patients with acute ischemia those who had a capsular infarct did not improve with intravenous naloxone suggesting again that patients with white matter lesions do not respond to the drug of the patients who had a poor or partial response, all had cortical cerebral infarcts and this fact favors the hypothesis that naloxone may improve the
TABLE 3  Clinical Studies of Naloxone in Stroke

<table>
<thead>
<tr>
<th>Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baskin, Hosobuchi, 1982</td>
<td>0.4 mgs I.V. improved function</td>
</tr>
<tr>
<td>Cutler and Bredesen, 1982</td>
<td>0.4-0.8 mgs no response</td>
</tr>
<tr>
<td>Jabaily, Davis, 1982</td>
<td>0.4-0.8 mgs I.V. no response</td>
</tr>
<tr>
<td>Fallis, 1983</td>
<td>0.8 mgs I.V. 3/7 improved function</td>
</tr>
<tr>
<td>Estanol, 1984</td>
<td>0.8 mgs I.V. 7/20 improved</td>
</tr>
<tr>
<td>Aguilar Corona</td>
<td></td>
</tr>
</tbody>
</table>

"ischemic penumbra" that surrounds a cortical infarction. We do not know whether intravenous naloxone had a beneficial effect upon the cerebral ischemia and we believe the drug improved only those patients who had reversible ischemic deficits and were going to recover regardless of the therapy. It is important to point out that in the first twenty-four hours or more of a focal cerebral ischemic deficit it is very difficult or impossible to predict whether the patient will recover or will be left with a cerebral deficit. By definition, a T.I.A. is an ischemic focal deficit of less than twenty-four hours duration. C.T. scanning is not helpful in determining whether a patient has an established infarct or a T.I.A. because the C.T. is usually normal in the first twenty-four hours of a cerebral infarction. Our data suggest that naloxone may be useful in predicting the outcome of the patient with acute cerebral ischemia. It is highly unlikely that the response could have been due to spontaneous recovery on a chance basis because none of the patients responded to the placebo and the response to the drug was seen in all cases within the first five minutes of the injection and lasted a mean of thirty minutes. It has been suggested that the dosage of naloxone may be important in the response and that it is possible we are using inadequate amounts of the drug. We did not find undesirable side effects with this dose and it proved effective in seven of the twenty patients. On the other hand, the time at which the drug is given, we believe is of a crucial importance. It is likely that the use of naloxone in the first twelve, six or less hours of the onset of the ischemia will increase the number of patients who respond to naloxone. We gave 0.8 mgs of intravenous naloxone to three patients within the first ten minutes of the onset. These patients had developed ischemic focal cerebral deficits as a complication of a cerebral angiographic procedure. Three patients had a dramatic and sustained improvement with a single dose of naloxone. These findings support the idea despite the sample size, that the best response to naloxone may be seen when the drug is given very early after the inception of the ischemia. The C.T. studies were performed without contrast infusion. If they had been done with enhancement the yield of cerebral infarction probably would have been greater but there was a good clinical correlation between the recovery and the absence of cerebral infarction by C.T. Subsequent trials of naloxone in the first few hours of an acute cerebral ischemic event are urgently needed. Table 3 summarizes the clinical trials of naloxone in acute stroke.

References
Diagnosis of reversible versus irreversible cerebral ischemia by the intravenous administration of naloxone.
B Estañol, F Aguilar and T Corona

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