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 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.

SEVERAL CONTROVERSIAL REPORTS regarding the use of naloxone in acute cerebral ischemia have recently appeared1, 2, 3, 9 Baskin and Hosobuchi1 found that two patients with focal cerebral ischemia had dramatic improvement with the intravenous administration of naloxone. Jabaily and Davis2 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 al3 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 al7 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. Faden8 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. with symptoms longer than 7 days duration (range 7–15 days); 2) patients with hypertensive intracerebral hematomas proven by C.T. the naloxone being given within the first 24 hours of the inception of the symptoms; 3) patients with acute cerebral ischemia of less than twenty-four hours duration (normal C.T. and lumbar puncture in the first 24 hours); 4) patients with hyperacute focal cerebral ischemia secondary to angiographic accidents; the naloxone was given within the first ten minutes of the onset of the ischemia.

Patients and Methods
The first group were 20 patients with C.T. proven cerebral infarct of more than 7 days’ duration (range...
hemorrhage. A complete neurological examination

The mean age was 52.7 years with a range

between 32 and 84 years. All these patients had imme-

diately received a lumbar puncture and a C.T. scan to

record each five minutes. No other medications

gists did not change significantly after the administra-

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 nal-

oxone 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 imme-

diately 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, nalox-

one 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 exami-

nation was performed. At the time of discharge the

patients were again evaluated.

The third group of patients had hypertensive intra-

cerebral hematomas in the putamen and internal cap-

sule. 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 devel-

oped signs of focal cerebral ischemia during the per-

formance 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 be-

fore 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 neurolo-

gists did not change significantly after the administra-

I.V. NALOXONE AND CEREBRAL ISCHEMIA/Estanol et al

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 sev-

days. The mean duration of the symptoms was 9.5
days. The degree of weakness was graded according to

the intravenous administration of naloxone. Six 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 improve-

ment 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 ex-

tremity 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 ische-

mia 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 respond-
ed 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 intrave-

nous naloxone (table 1). The C.T. studies were per-

formed 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 im-

provement. The rest of the patients were discharged

improved with respect to their condition on admis-

sion although some had important neurological se-

quelae. The five patients with C.T. proven hyperten-
sive 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 pa-

tients 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 nalox-
one. Thereafter 0.4 mgs of naloxone was given inter-

venously each hour. These patients were discharged

without residual neurological deficit. Table 2 summa-

rizes 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. Faden8 suggest-
ed that an inadequate selection of patients may be a
### TABLE 1 Response of neurological deficit.

<table>
<thead>
<tr>
<th>Age (years)</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</td>
<td>complete</td>
<td>normal</td>
<td>recovered</td>
</tr>
<tr>
<td>46</td>
<td>2</td>
<td>complete</td>
<td>normal</td>
<td>recovered</td>
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<td>partial</td>
<td>left parietal infarct</td>
<td>improved</td>
</tr>
<tr>
<td>47</td>
<td>10</td>
<td>none</td>
<td>left capsular infarct</td>
<td>not improved</td>
</tr>
<tr>
<td>39</td>
<td>7</td>
<td>none</td>
<td>left capsular infarct</td>
<td>not improved</td>
</tr>
<tr>
<td>84</td>
<td>4</td>
<td>none</td>
<td>left fronto-parietal infarct</td>
<td>improved</td>
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<td>49</td>
<td>22</td>
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<td>left parietal infarct</td>
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</tr>
<tr>
<td>70</td>
<td>6</td>
<td>none</td>
<td>right fronto-parietal infarct</td>
<td>improved</td>
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<td>42</td>
<td>8</td>
<td>complete</td>
<td>normal</td>
<td>recovered</td>
</tr>
<tr>
<td>66</td>
<td>24</td>
<td>none</td>
<td>capsular infarct</td>
<td>improved</td>
</tr>
<tr>
<td>58</td>
<td>20</td>
<td>partial</td>
<td>left fronto-temporal infarct</td>
<td>improved</td>
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<td>38</td>
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</tr>
<tr>
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<tr>
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<tr>
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<td>normal</td>
<td>recovered</td>
</tr>
<tr>
<td>52</td>
<td>18</td>
<td>partial</td>
<td>left fronto-parietal infarct</td>
<td>improved</td>
</tr>
</tbody>
</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. 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 the ischemia who responded poorly or not at all to naloxone were subsequently shown to have a cerebral infarction by C.T. scanning. The seven patients who had the most favorable response to intravenous naloxone 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 al and why some patients of Jabaily and Davis did not have any improvement. The patients of Baskin and Hosobuchi 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 reported 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 pate...
"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 possible we are using inadequate amounts of the drug.

Our data show that 0.8 mgs of naloxone in bolus is adequate to revert ischemic deficits in some patients without undesirable effects. This dose is much less than the 10 mgs/kg used in experimental animals. 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.

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Stroke. 1985;16:1006-1009
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