**Background and Purpose** The aim of this study was to determine the time and dose response of the therapeutic effects of the \(N\)-methyl-\(d\)-aspartate receptor antagonist ketamine in experimental head injury.

**Methods** Sixty-six male Sprague-Dawley rats were divided into eight groups. Groups A, B, and C were surgically prepared but received no trauma. Groups D through H received a nonpenetrating impact to the left cranium. Group A (n=7) received no treatment. Groups B (n=4) and C (n=5) received 60 and 120 mg/kg IP ketamine, respectively. Group D (n=8) received no treatment. Groups E (n=8) and F (n=7) received 120 and 180 mg/kg IP ketamine, respectively, 1 hour after head trauma. Groups G (n=7) and H (n=9) were treated with 180 mg/kg IP ketamine 2 and 4 hours after head trauma, respectively. Neurological severity score (NSS, 0 through 25 from no injury to severe injury) was determined at 1, 24, and 48 hours after head trauma. After death at 48 hours, cortical slices were taken adjacent to the lesion on the traumatized hemisphere and from comparable sites in the contralateral hemisphere for determination of tissue specific gravity and water content.Brains were then placed in 4% formaldehyde, and the volume of hemorrhagic necrosis was measured 4 days later. NSS was compared within and between groups using the Kruskal-Wallis test for repeated measurements and Mann-Whitney \(U\) test for post hoc testing. Water content, specific gravity, and hemorrhagic necrosis were compared within and between groups using two-way ANOVA followed by Fisher’s protected least significant difference procedure. A value of \(P<.05\) was considered statistically significant.

**Results** Head trauma alone increased NSS, decreased specific gravity, increased water content, and caused cerebral infarction in the injured hemisphere. Ketamine given in two time-dose regimens, 180 mg/kg IP at 2 hours (group G) and 120 mg/kg IP at 1 hour (group F) after trauma, improved NSS from 11.6±1.7 and 14.4±0.8 at 1 hour to 4.4±1.3 and 8.0±1.4 (mean±SEM) at 48 hours, respectively \((P<.03)\). Compared with the untreated group (group D), 180 mg/kg IP ketamine given at 2 and 4 hours after head trauma decreased the volume of hemorrhagic necrosis from 37.1±9.5 mm\(^3\) to 10.1±3.8 and 15.3±3.6 mm\(^3\), respectively \((P<.05)\). Brain tissue specific gravity and water content at 48 hours were not significantly different between treated and untreated groups. There was no difference in rectal and temporalis muscle temperature between groups.

**Conclusions** We conclude that 180 mg/kg IP ketamine was effective in ameliorating neurological dysfunction after head trauma in rats when the administration time was delayed for 1 hour to 2 hours but not after 4 hours. When given at 1 hour after head trauma, ketamine at 120 mg/kg but not 60 mg/kg is effective in reducing neurological damage after head trauma. (Stroke. 1994;25:1637-1643.)

**Key Words** • amino acids • \(N\)-methyl-\(d\)-aspartate • brain injuries • rats

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**See Editorial Comment, page 1643**
tenth that of another noncompetitive NMDA antagonist, MK-801. Ketamine also blocked NMDA agonist-induced death of cultures of cortical and hippocampal neurons and swelling of cultures of astrocytes. In vivo, ketamine was reported to significantly increase neuronal survival after ischemia. Recently, we found in our rat HT model that 180 mg/kg ketamine 1 hour after HT improved neurological outcome and decreased the volume of the hemorrhagic necrosis. A companion study showed that the normally increased tissue calcium levels were reduced and the magnesium levels increased.

Thus, ketamine may have therapeutic value in the treatment of traumatic brain injury. However, neither the optimal dose nor the therapeutic time window for ketamine after HT has been delineated. Accordingly, we designed the present studies to determine whether lower doses of ketamine (120 and 60 mg/kg) given at 1 hour and the original dose of 180 mg/kg given at different time intervals (2 and 4 hours) improves neurological outcome after a nonpenetrating cranial impact. Neurological outcome was assessed by measurement of neurological severity score (NSS), volume of hemorrhagic necrosis, and cerebral edema after injury.

Methods

This study was approved by the Animal Care Committee of the University of Washington. Sixty-six male Sprague-Dawley rats weighing 180±15 g (mean±SD) were anesthetized with halothane only. Maintenance of adequate anesthesia for the experimental procedure was confirmed by the loss of corneal and pupillary reflexes. Rats were assigned to one of eight experimental groups using a randomization sequence designed to allocate approximately twice as many rats to groups D through H as to groups A through C. In groups A through C (no cranial trauma), no ketamine was given. In groups B and C, 60 and 120 mg/kg IP ketamine was given 1 hour after anesthesia was discontinued and rats were returned to their cages. In groups D, E, F, G, and H (n=5 in each group), the skull was incised longitudinally and separated to expose the underlying skull. No cranial impact was delivered, and the scalp incision was closed. Anesthesia was discontinued, and rats were returned to their cages where they were allowed free access to chow and water. In group A, no ketamine was given. In groups B and C, 60 and 120 mg/kg IP ketamine was given 1 hour after anesthesia was discontinued and rats were returned to their cages. In groups D, E, F, G, and H (n=10 in each group), the skull was exposed and a cranial impact was delivered at a prefixed point over the left hemisphere 1 to 2 mm lateral from the midline on the skull convexity. The impact was delivered by a free-falling plate, from the center of which protruded a silicone-covered rod that hit the skull. It was previously reported that the energy imparted to the skull by the stereotaxically guided plate was directly and linearly related to the distance of fall and that the nonpenetrating impact caused a reproducible brain injury and deterioration of neurological status. In group D, no ketamine was given. In groups E and F, 60 and 120 mg/kg IP ketamine was given, respectively, 1 hour after anesthesia was discontinued and rats were returned to their cages. In groups G and H, 180 mg/kg IP ketamine was given 2 and 4 hours, respectively, after anesthesia was discontinued and rats were returned to their cages. Table 1 summarizes the group assignments.

Eleven rats in groups D through H died of apnea or excessive bleeding immediately after the impact and were excluded from the study, leaving the group sizes as follows: D, n=8; E, n=8; F, n=7; G, n=7; and H, n=9. Six animals that survived the initial impact died after 24 hours but before the planned death at 48 hours (1 each in groups D through G and 2 in group H). In all rats temperature was measured at the time of neurological assessment at 1, 24, and 48 hours after HT using a rectal (model 73A, Yellow Springs Instruments) and temporal muscle (Yellow Springs Instruments) thermistor probe.

### Table 1. Assignment of Treatment Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Ketamine Dosage</th>
<th>Injection Time</th>
<th>Head Trauma</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>None</td>
<td>. . .</td>
<td>No</td>
<td>7</td>
</tr>
<tr>
<td>B</td>
<td>60 mg/kg IP</td>
<td>1 Hour</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>120 mg/kg IP</td>
<td>1 Hour</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>D</td>
<td>None</td>
<td>. . .</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>E</td>
<td>60 mg/kg IP</td>
<td>1 Hour</td>
<td>Yes</td>
<td>8</td>
</tr>
<tr>
<td>F</td>
<td>120 mg/kg IP</td>
<td>1 Hour</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>G</td>
<td>180 mg/kg IP</td>
<td>2 Hours</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>H</td>
<td>180 mg/kg IP</td>
<td>4 Hours</td>
<td>Yes</td>
<td>9</td>
</tr>
</tbody>
</table>

### Neurological Severity Score

The neurological status of the rats was evaluated 1, 24, and 48 hours after the cranial impact. The neurological assessment was not performed during the first 10 hours because of the anesthetic effect of ketamine in the treatment groups. This evaluation was done using an NSS that was developed to assess the clinical condition of the rats after trauma. Table 2 summarizes the criteria for scoring. The NSS correlates directly with the deterioration of observable neurological status so that a lower score represents nearly intact neurological status and a higher score represents severe neurological dysfunction.

### Volume of Hemorrhagic Necrosis

At the time of death rats were decapitated. The entire brain (excluding the cerebellum) was immediately removed (42±6 seconds) and placed on a frozen plate. Brain tissue samples of 20 to 50 mg were cut from areas just adjacent to the zone of maximal macroscopic damage in the left hemisphere and the corresponding contralateral areas of the right hemisphere in groups D through H. In groups A, B, and C (no cranial impact), brain tissue samples were taken from corresponding left and right hemisphere areas. These small brain tissue samples were used for the determination of tissue specific gravity and water content (see below). The remaining brain tissue was placed in 4% phosphate-buffered formalin for 4 days. After removal from formalin, brains were embedded in a brain tissue slicer (D. Jacobowitz, National Institutes of Health, Bethesda, Md), and identical coronal sections 1 mm wide were made through both frontal lobes. The sections were projected as digitized video images at a final magnification of x4, and the volume of hemorrhagic necrosis in each frontal lobe was calculated by a blinded observer using an automated image-analysis system (Bioquant System-IV) (Fig 1). The values in Fig 2 are the sum in millimeters cubed of five sections in each animal.

### Brain Tissue Specific Gravity

The specific gravity of brain tissue was determined according to the method described by Marmarou et al. In brief, tissue segments were placed on top of linear gradient columns of kerosene and bromobenzene calibrated with K2SO4. Specific gravity of the tissue was determined from a standard curve by measurement of its equilibrium position in the column.

### Brain Tissue Water Content

Each tissue sample was placed on a piece of aluminum foil and weighed for tissue wet weight (WW). It was then dried in a desiccating oven at 105°C for 24 hours and reweighed to obtain the dry weight (DW). Percent brain tissue water was calculated as (WW−DW)/100*WW.
TABLE 2. Grading of Neurological Severity Score

<table>
<thead>
<tr>
<th>Points</th>
<th>At 1 Hour</th>
<th>Other Times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiplegia: inability of rat to resist forced changes in position</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Flexion of hindlimb when raised by the tail</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inability to walk straight when placed on the floor</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inability to walk</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Reflexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of righting reflex for 20 minutes</td>
<td>1</td>
<td>…</td>
</tr>
<tr>
<td>Loss of righting reflex for 40 minutes</td>
<td>1</td>
<td>…</td>
</tr>
<tr>
<td>Loss of righting reflex for &gt;60 minutes</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Limb reflexes: loss of placing reflexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left forelimb</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Right forelimb</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Left hindlimb</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Right hindlimb</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Startle reflex</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clinical grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of seeking behavior</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prostration</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Inability to exit from circle (50 cm in diameter) when left in its center for 30 minutes</td>
<td>1</td>
<td>…</td>
</tr>
<tr>
<td>Inability to exit from circle (50 cm in diameter) when left in its center for 60 minutes</td>
<td>1</td>
<td>…</td>
</tr>
<tr>
<td>Inability to exit from circle (50 cm in diameter) when left in its center for &gt;60 minutes</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Functional test: failure in beam balancing task (1 cm wide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balances with steady posture; paws on top of beam</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grasps sides of beam and/or has shaky movement</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>One or more paws slip off beam</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Attempts to balance on beam but falls off</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Drapes over beam and/or hangs on beam and falls off</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Falls off beam with no attempt to balance or hang on</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Failure in beam walking task</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5-cm wide</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5.0-cm wide</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>8.5-cm wide</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Maximum points</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Statistical Analysis

Data are presented as mean±SEM. Brain tissue specific gravity, water content, volume of hemorrhagic necrosis, and rectal temperature were compared by two-way ANOVA for repeated measures with post hoc testing using Fisher's protected least significant difference multiple comparison procedure. Between-group comparison was done using Student's t test for unpaired data with appropriate Bonferroni correction. To take into consideration the variability in the initial 1 hour NSS between groups and to allow assessment of change in NSS with time for treatment, we normalized the NSS by expressing it at 24 and 48 hours as a percentage of the initial NSS at 1 hour after trauma. Subsequent analysis of the NSS percentage was then performed with Kruskal-Wallis analysis and post hoc testing using the Mann-Whitney U test. A probability value of <.05 was considered significant.

Results

Neurological Severity Score

Table 3 shows the raw NSS of all HT groups at 1 hour. Relative changes in NSS of all rats in which cranial impact was delivered (groups D through H) are shown in Fig 3. Between-group comparisons indicated that at 1 hour after HT and before the animals were treated with ketamine, the groups treated with 60 mg/kg (group E) and 120 mg/kg (group F) had a higher NSS (worse) than other groups (P<.001) (Table 3). At 24 hours after HT,
animals in group E had a higher (worse) NSS than all other groups ($P<.05$). At 48 hours after HT, animals in groups E and H (180 mg/kg 4 hours after HT) had a higher NSS than animals that were treated with 180 mg/kg ketamine 2 hours after HT (group G) ($P<.03$). Normalizing the NSS to 100% at 1 hour after HT, within-group comparisons indicated that NSS in two groups that were treated within the first 2 hours (groups F and G) after cranial impact was significantly improved ($P<.003$) at 48 hours. Moreover, the group treated with 120 mg/kg (group F) was significantly improved by 24 hours after HT. Animals in the control group (group D) and animals that were treated 4 hours after HT (group H) showed no significant improvement over that time period (Fig 3).

**Volume of Hemorrhagic Necrosis**

No cerebral hemorrhagic necrosis occurred in groups A, B, and C (no cranial impact). Fig 2 shows the volume of hemorrhagic necrosis for groups D through H. Among the animals that received cranial impact, the volume of hemorrhagic necrosis in the rats treated with 180 mg/kg ketamine at 2 hours after HT (group G) was $10.06 \pm 3.84$ mm$^3$, a value that is significantly decreased compared with that in rats not treated with ketamine (group D), treated with 120 mg/kg (group F), and treated with 60 mg/kg (group E) ($37.07 \pm 9.55$, $24.72 \pm 3.88$, and $31.37 \pm 4.82$ mm$^3$, respectively) ($P<.003$). When 180 mg/kg ketamine was given 4 hours after HT (group H), the hemorrhagic necrosis volume was $15.34 \pm 3.59$ mm$^3$, which was significantly decreased compared with that in rats without treatment (group D) and rats that received only 60 mg/kg ketamine (group E).

**Edema Formation**

Fig 4 presents the specific gravity and water content of cortical slices taken from the injured and the corresponding contralateral hemispheres in both treated and
untreated rats. Between-group comparisons indicated
that in general specific gravity and water content of the
injured hemisphere from rats in which cranial impact
was delivered and ketamine was given (groups E
through H) were not significantly different from specific
gravity and water content of the injured hemisphere from
the untreated group (group D). Specific gravity and
water content of the uninjured hemisphere from traum-
matized and untreated rats (groups E through H) were not
significantly different from specific gravity and water
content of the uninjured hemisphere from either traum-
matized and untreated rats (group D) or traumatized
rats (groups A, B, and C).

Brain tissue specific gravity and water content in rats
receiving ketamine and no cranial impact (groups B and
C) were not significantly different from those in rats
receiving no ketamine and no cranial impact (group A).
Within-group comparisons indicated that specific gravity
was decreased and water content was increased (P< .01)
in the injured hemisphere compared with those of
the uninjured (right) hemisphere in groups D
through H and as well as those from rats receiving no
cranial impact (groups A, B, and C).

Temperature
There was no statistically significant difference within
or between groups at 1, 24, and 48 hours in either rectal
or temporalis muscle temperature of treated and un-
treated rats.

Discussion
In the present study, a single dose of 180 mg/kg IP
ketamine given 2 hours, but not 4 hours, after HT
significantly improved NSS at 48 hours after injury. On
the other hand, when given at 1 hour after HT, a
decrease in ketamine dosage to 120 but not 60 mg/kg
also significantly improved NSS at 24 and 48 hours after
injury. The residual sedative effect of ketamine admin-
istration prohibited evaluation of NSS at earlier time
periods. Ketamine also reduced neuronal damage, as
indicated by the significant decrease in the volume of
hemorrhagic necrosis in the ketamine-treated group
compared with the untreated group. However, as ex-
pected, the ketamine did not improve brain edema at 48
hours after head injury.

Our results are consistent with previous reports that
ketamine may protect neurons from ischemic injury. Ketamine at 30 mg/kg IP decreased the size of the lesion resulting from hippocampal injection of quino-
linic acid and NMDA in rats.26 Similarly, 100 or 150
mg/kg IP ketamine increased survival rate and 200
mg/kg IP increased the density of the pyramidal cells in
the hippocampus after bilateral carotid occlusion in
gerbils.27 To have therapeutic value, however, the effi-
cacy of delayed administration of ketamine must be
demonstrated, yet few studies have addressed this issue.
In a global ischemia model in rats (bilateral carotid
occlusion combined with hypotension to a mean arterial
blood pressure of 50 mm Hg), this efficacy was demon-
strated; 10 mg/kg IV ketamine given 10 minutes before
ischemia and 0, 15, 30, 45, 60, and 90 minutes after
ischemia followed by 20 mg/kg IP each hour for 7 hours
decreased neuronal loss in the CA1 region of the
hippocampus.28 These results are consistent with our
previous findings in the HT model which demonstrated
that 180 mg/kg IP ketamine given at 1 hour after HT
improved neurological outcome and decreased hemor-
rhagic necrosis volume.22 However, the optimal dosage
and the range of the therapeutic time window are not
known, so the present study was designed to provide
these answers.

In this study we demonstrated that a ketamine dose of
180 mg/kg improved the neurological outcome when
animals were treated as late as 2 hours, but not 4 hours,
after HT. In the dose-response study we found that 120
mg/kg ketamine, but not 60 mg/kg, improved the neu-
rological outcome when animals were treated 1 hour
after HT. Compared with our previous study which
showed that animals treated with 180 mg/kg 1 hour
after HT were neurologically improved by 24 hours,24
the neurological status of animals in groups G and F
(180 mg/kg 2 hours and 120 mg/kg 1 hour after HT)
only improved at 48 hours after the trauma. These
results suggest that in this model of head injury, keta-
mine treatment should be begun as soon as possible
after injury and that the optimal dose is 180 mg/kg.
However, a smaller dose (120 mg/kg) given at 1 hour
as well as delayed treatment with the higher dose at 2
hours after HT can still be of some benefit. These
results also suggest that either the damage from gluta-
mate release after HT is complete by the end of 2 hours
or there is no further accumulation of glutamate after 2
hours. Further studies are required to clarify this issue.
As regards our HT model, the device used in this
study delivered a nonpenetrating impact to an intact
cranial vault. The two other currently used HT models
use fluid percussion and cryogenic injury, respectively.
All three models cause both primary and secondary
neuronal injury. The model used in this study has been
shown previously to produce a highly reproducible
decrease in brain tissue specific gravity, increase in
blood-brain barrier permeability, and characteristic hist-
opathological change in the hemisphere beneath the
area of impact.12,24,29,30

The issue of temperature is important in studies of
cerebral injury. Corbett et al31 and Buchan and Pulsin-
elli32 reported in models of global ischemia in gerbils
that a portion of the "neuroprotective" effect of the
NMDA antagonist MK-801 was due to MK-801-in-
duced hyperthermia and not solely to the drug itself.
Baker et a33 reported in global ischemia in rabbits that
improvement of neurological and neuropathological
outcome caused by decrease of temperature to 29°C was
accompanied by marked attenuation of excitatory
amino acid levels (glutamate, aspartate, and glycine). The
fact that temperature did not differ among groups in
our study indicates that hyperthermia did not contrib-
ute significantly to the decreased NSS and reduced
delayed administration of ketamine must be
demonstrated, yet few studies have addressed this issue.
In a global ischemia model in rats (bilateral carotid
occlusion combined with hypotension to a mean arterial
blood pressure of 50 mm Hg), this efficacy was demon-
strated; 10 mg/kg IV ketamine given 10 minutes before
ischemia and 0, 15, 30, 45, 60, and 90 minutes after
ischemia followed by 20 mg/kg IP each hour for 7 hours
decreased neuronal loss in the CA1 region of the
hippocampus.28 These results are consistent with our
previous findings in the HT model which demonstrated
that 180 mg/kg IP ketamine given at 1 hour after HT
improved neurological outcome and decreased hemor-
rhagic necrosis volume.22 However, the optimal dosage
and the range of the therapeutic time window are not
known, so the present study was designed to provide
these answers.

In this study we demonstrated that a ketamine dose of
180 mg/kg improved the neurological outcome when
animals were treated as late as 2 hours, but not 4 hours,
after HT. In the dose-response study we found that 120
mg/kg ketamine, but not 60 mg/kg, improved the neu-nolescence of amino acid levels (glutamate, aspartate, and glycine). The
fact that temperature did not differ among groups in
our study indicates that hyperthermia did not contrib-
ute significantly to the decreased NSS and reduced
volume of hemorrhagic necrosis in the ketamine-
treated, head-injured group. However, it is possible that
temperature difference developed between 1 and 2
hours and this difference was responsible for the bene-
ficial effect of ketamine, we consider this unlikely be-
cause the first temperature measurement was taken
immediately after ketamine was given in groups B, C, E,
and F. Should ketamine cause the temperature to
decrease, the effect should be maximal at this time.
Moreover, clinically, ketamine is an anesthetic that
maintains sympathetic and muscle tone and therefore is
likely to maintain body temperature, although we know of no clinical studies to substantiate this point.

Another potential concern regarding methodology is that the sedation caused by ketamine was responsible for the improvement of NSS and decrease of infarct size at 24 and 48 hours. Thiopental has been shown to decrease the incidence of neurological dysfunction after cardiopulmonary bypass for valvular heart surgery.34 The protection is presumably on the basis of metabolic suppression and reduction of oxygen requirement. However, there is no evidence that ketamine decreases cerebral metabolism, as most studies report that the cerebral metabolic rate was either unchanged or increased during ketamine anesthesia.35-36 Moreover, in a rat model in which ketamine decreased the percentage of neurons damaged in five hippocampal regions after injection of ibotenic acid into the hippocampus, halothane and pentobarbital, which should decrease the metabolic rate, did not decrease neuronal damage.37 Thus, it seems unlikely that in the present model either sedation or anesthesia per se accounted for the decreased NSS and infarct size with ketamine.

Previous recommendations against the use of ketamine in head-injured patients were based on reports that ketamine increased cerebral metabolic rate, cerebral blood flow, and intracranial pressure.35-37 Although treatments such as thiopental, hypocapnia, benzodiazepines, or opioids may reverse ketamine-induced increases of cerebral metabolic rate, cerebral blood flow, and intracranial pressure in animals or patients without intracranial pathology,38-40 these treatments may not be completely effective in patients with intracranial pathology. In the only study of cerebral metabolic rate after administration of ketamine to patients, Takeshita et al41 reported no change in the metabolic rate despite a 62% increase in cerebral blood flow. In addition, the increase in arterial blood pressure that follows ketamine treatment may have a therapeutic value. Phenylephrine-induced hypertension after middle cerebral artery occlusion in rats has been reported to increase local cerebral blood flow in the area of focal ischemia and reduce the area of histochemical neuronal dysfunction.42-46 However, other reports indicate that hypertension after transient middle cerebral artery occlusion disrupts the blood-brain barrier, increases vasogenic cerebral edema, and increases the risk for intraparenchymal hemorrhage.44-46 Additional studies are needed to clarify the effects of hypertension after HT. Because of the need to perform repetitive neurological assessments, we did not measure blood pressure in our animals after either HT or ketamine treatment. Therefore, we have not ruled out the improvement of cerebral perfusion as a contributing mechanism to the beneficial effect of ketamine. However, if the increase in flow is secondary to an increase in metabolism as reported in some studies,38 then no net benefit should occur.

Although we have not elucidated the precise mechanism of ketamine-induced protection, which may be multifactorial (improved systemic and cerebral perfusion, possible hypothermia), we have demonstrated that delayed treatment with a high dose of ketamine is beneficial and that a lower dose can be administered if given within 1 hour of experimental head injury. However, more investigations are required before we can move from experimental studies to clinical trials. Nevertheless, these studies suggest that there is a therapeutic time window for ketamine after head injury.

Acknowledgments

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References

In this article the authors determine the time and dose response of the therapeutic effects of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine in experimental head injury. They conclude that ketamine (180 mg/kg IP) is able to ameliorate neurological dysfunction after head trauma when the administration time is delayed for 1 to 2 hours but not for 4 hours. They also determine that, when given at 1 hour after head trauma, ketamine at 120 mg/kg but not 60 mg/kg is effective in reducing neurological damage after head trauma. Although the idea that the NMDA receptor antagonists may be involved in the amelioration of neurological dysfunction after head injury is not innovative, the idea of a dose-time response is of some importance. Those of us involved in evaluating a variety of compounds to determine whether these compounds can ameliorate neurological dysfunction after head injury are always interested in the window of opportunity. In this article the window of opportunity is demonstrated, as is the effective ketamine dose. One major distraction of this article is that it does not investigate any specific mechanism of action by which ketamine exerts its positive effect, although the authors discuss several possibilities. The NMDA receptors are clearly involved, but no experiments were performed to investigate this potential mechanism of action. In addition, cerebral blood flow was not measured in these studies, and it is possible that cerebral blood flow, during and after the injury, may be affected differently by ketamine itself. Although it is important from a clinical point of view to demonstrate windows of opportunities and drug doses that are and are not effective, it is also important not to overlook the potential mechanisms of action.

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Therapeutic time window and dose response of the beneficial effects of ketamine in experimental head injury.

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