Case Report

Preliminary Evidence That Ketamine Inhibits Spreading Depolarizations in Acute Human Brain Injury

Oliver W. Sakowitz, MD; Karl L. Kiening, MD; Kara L. Krajewski, BA; Asita S. Sarrafzadeh, MD; Martin Fabricius, MD; Anthony J. Strong, MD; Andreas W. Unterberg, MD; Jens P. Dreier, MD

Background and Purpose—Spreading depolarizations, characterized by large propagating, slow potential changes, have been demonstrated with electrocorticography in patients with cerebral hemorrhage and ischemic stroke. Whereas spreading depolarizations are harmless under normal conditions in animals, they cause or augment damage in the ischemic brain. A fraction of spreading depolarizations is abolished by N-methyl-D-aspartate receptor antagonists.

Summary of Case—In 2 patients with severe acute brain injury (traumatic and spontaneous intracranial hemorrhage), spreading depolarizations were inhibited by the noncompetitive N-methyl-D-aspartate receptor antagonist ketamine. This restored electrocorticographic activity.

Conclusions—These anecdotal electrocorticographic findings suggest that ketamine has an inhibitory effect on spreading depolarizations in humans. This is of potential interest for future neuroprotective trials. (Stroke. 2009;40:e519-e522.)

Key Words: electrocorticography ■ intracerebral hemorrhage ■ NMDA receptor antagonists ■ spreading depression ■ traumatic brain injury

Spreading depolarization (SD) of the cerebral gray matter is characterized by dramatic changes in ion distribution reflected by a large but transient negative shift of the extracellular direct current potential. Under physiological conditions, SD is termed cortical spreading depression because it causes reversible depression of the spontaneous electrocorticographic activity (as recorded with AC-coupled amplifiers).1 SD propagates at a characteristic speed of 2 to 5 mm/min, does not cause neuronal damage, and is blocked by N-methyl-D-aspartate receptor (NMDAR) antagonists.2 If observed under conditions of energy compromise such as ischemia, hypoxia, or hypoglycemia, SD is associated with additional neuronal injury.3

SDs have been demonstrated recently in patients with acute neuronal injury. Whether treatment with NMDAR antagonists has an effect on this new clinical phenomenon is unclear.4,5 In 2 cases with traumatic and spontaneous intracerebral hemorrhage, we show here for the first time in human brain that SDs are indeed blocked by the NMDAR antagonist ketamine.

Case Presentations

We describe 2 patients who underwent emergency craniotomy. In addition to routine monitoring, subdural 6-contact linear electrode strips (Wyler, 5/10 mm platinum; Ad-Tech Medical Instrument Corp, Racine, Wisc) were placed adjacent to the injured cortex in a centrifugal orientation. Details of this procedure have been described previously.4 Four bipolar recordings of adjacent electrode pairs were amplified and digitized (sampling rate: 400 Hz, time constant: 100 ms, upper/lower frequency limits: 0.01/200 Hz; Octal Bioamplifier ML138 [or GT205] and Powerlab 16; ADInstruments Pty Ltd, Castle Hill, Australia). Electrocorticography (ECoG) was part of an approved study protocol in accordance with the local Institutional Review Boards (www.cosbid.org), and surrogate consent was obtained from legal representatives.

Case 1

History

A 63-year-old man sustained a severe head injury with a thin left-hemispheric subdural hematoma. The patient deteriorated progressively with a decreased level of consciousness. Follow-up CT demonstrated hemorrhagic transformation of multiple temporal contusions, extension of subdural hemorrhage, and a midline shift (Figure 1A).

Procedure

The patient was intubated and underwent emergency craniotomy for evacuation of a subdural hematoma. A subdural...
electrode strip (located on the pericontusional cortex from the left supramarginal region to the frontal lobe) was implanted intraoperatively (Figure 1B–D).

**Hospital Course**
Postoperatively, the patient remained sedated and on ventilatory support in the neurointensive care unit. From the beginning, SDs were observed spreading spatially along the electrode strip at a characteristic speed of 3 mm/min. The patient was otherwise stable. Frequency of SDs continued to increase and intermittent ECoG background activity changed to an ill-defined burst-suppression pattern with many flat episodes (Figure 1E). Because of increasing tolerance to sedation and a growing demand for catecholamines, ketamine (Ketanest-S, Pfizer Ireland Pharmaceutics, Dun Laoghaire; 2 to 3 mg/kg/h) was added on postoperative Day 2. Immediately after initiation of ketamine, SDs subsided abruptly and did not recur. ECoG background activity recovered to a regular burst-suppression pattern (Figure 1F).

In total, 53 SDs occurred within 40 hours of ECoG monitoring before ketamine was started. There were no SDs within the next 84 hours of monitoring under continuous ketamine infusion (Figure 2). Within the final 6 hours before ketamine was started, SDs recurred at an average frequency of 1.5/h. These SDs were associated with an average ECoG depression period lasting 13.9±6.2 minutes (SD; range, 6.8 to 26.6 minutes).

**Clinical Outcome**
On Day 7 after trauma, the patient died from noncerebral causes after developing pneumonia, sepsis, and multiorgan failure.

**Case 2**

**History**
A 34-year-old man with subarachnoid and intraventricular hemorrhage presented comatose without focal neurological deficits or posturing. Multiple (4) aneurysms of the anterior circulation were detected on cerebral angiography. After attempted coiling of an anterior communicating artery aneurysm, a left internal carotid artery aneurysm ruptured leading to intracerebral hemorrhage requiring surgical evacuation.

**Procedure**
Intraoperatively, a subdural electrode strip was placed on the perihemorrhagic cortex extending over the anterior pole of the frontal lobe.

**Hospital Course**
Postoperatively, the patient displayed SDs from the perihemorrhagic rim into unaffected frontal lobe tissue. These were similar to those shown in Case 1. Because of sustained...
intracranial hypertension, sedation was deemed inadequate and ketamine was added (2 to 3 mg/kg/h) on Day 5 after hemorrhage. Immediately after initiation of ketamine, SDs subsided abruptly. ECoG background activity recovered to a regular burst suppression pattern and SDs did not recur.

In total, 9 SDs occurred within 27 hours of ECoG monitoring before application of ketamine. There was no SD within the next 21 hours of monitoring under continuous ketamine infusion (Figure 2). Within the final 6 hours before ketamine was started, SDs recurred at an average frequency of 0.7/h. These SDs occurred while the ECoG activity remained continuously suppressed.

Clinical Outcome
The patient was discharged after 5 weeks in neurointensive care in a clinically good condition, awake and following commands, but with features of frontal lobe syndrome.

Discussion
The noncompetitive NMDAR antagonist ketamine is a dissociative anesthetic inducing dose-related unconsciousness and analgesia without classical anesthesia. Undesired side effects are mainly related to its psychomimetic properties. It is a racemic mixture in which the clinically used, optically pure S(+)-enantiomer is twice as potent as the R(-)-enantiomer. It also binds weakly to opioid receptors and inhibits uptake of catecholamines by central sympathetic nerve endings. Ketamine dilates cerebral arteries and bronchioles. A positive inotropic effect on myocardium results in increased cardiac output (limiting its use in patients with coronary artery disease, however). The use of ketamine has been controversial in patients with increased intracranial pressure. More recent clinical evidence, however, suggests that the S(+)-enantiomer can be used safely in ventilated patients who are adequately sedated with an additional classical anesthetic. In patients with familial hemiplegic migraine, ketamine is able to stop aura symptoms (presumably a manifestation of SD).8

We demonstrate 2 cases with an inhibitory effect of ketamine on SD in humans. In absence of hemodynamic changes, this effect is likely mediated by NMDAR blockade.2,3 However, it remains elusive whether inhibition of these SDs was neuroprotective. Experimental evidence suggests that only the fraction of SDs in normal or mildly energy-depleted tissue is blocked by NMDAR antagonists, whereas they are both increasingly intractable and deleterious in severely compromised tissue.9,10 However, in both cases, the prolonged ECoG depression before ketamine administration suggests that the recording was performed in a penumbral area with some degree of energy compromise.5 The recovery from the depolarization block of ECoG activity after ketamine administration possibly indicates a metabolic improvement in this area. To further elucidate whether “injurious” types of SD are inhibited by ketamine and whether this conveys neuroprotection, an interventional trial of ketamine should be considered in selected patients with acute neuronal injury in whom SDs are detected using ECoG.

Acknowledgments
Contributions by the medical and nursing staff of the neurosurgical intensive care units of Heidelberg and Berlin are gratefully acknowledged.

Sources of Funding
O.W.S. received grant support through “ZNS—Hannelore Kohl Stiftung” (#2004006) and the Medical Faculty of the University of Heidelberg (“Young Investigator Award”). J.P.D. was supported by the Wilhelm Sander Foundation (2002.028.1), Deutsche Forschungsgemeinschaft (SFB-507A1, DFG DR 323/3-1, 323/5-1), BMBF Berlin Neuroimaging Center (01GI9902/4)Center for Stroke Research (01 EO 0801), and Kompetenznetz Schlaganfall.

Disclosures
None.

References


Preliminary Evidence That Ketamine Inhibits Spreading Depolarizations in Acute Human Brain Injury

Oliver W. Sakowitz, Karl L. Kiening, Kara L. Krajewski, Asita S. Sarrafzadeh, Martin Fabricius, Anthony J. Strong, Andreas W. Unterberg and Jens P. Dreier

Stroke. 2009;40:e519-e522; originally published online June 11, 2009; doi: 10.1161/STROKEAHA.109.549303

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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/40/8/e519

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/