Effect of analgesics and sedatives on the occurrence of spreading depolarizations accompanying acute brain injury

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Spreading depolarizations are waves of mass neuronal and glial depolarization that propagate across the injured human cortex. They can occur with depression of neuronal activity as spreading depressions or isoelectric spreading depolarizations on a background of absent or minimal electroencephalogram activity. Spreading depolarizations are characterized by the loss of neuronal ion homeostasis and are believed to damage functional neurons, leading to neuronal necrosis or neurological degeneration and poor outcome. Analgesics and sedatives influence activity-dependent neuronal ion homeostasis and therefore represent potential modulators of spreading depolarizations. In this exploratory retrospective international multicentre analysis, we investigated the influence of midazolam, propofol, fentanyl, sufentanil, ketamine and morphine on the occurrence of spreading depolarizations in 115 brain-injured patients. A surface electrode strip was placed on the cortex, and continuous electrocorticographical recordings were obtained. We used multivariable binary logistic regression to quantify associations between the investigated drugs and the hours of electrocorticographical recordings with and without spreading depolarizations or clusters of spreading depolarizations. We found that administration of ketamine was associated with a reduction of spreading depolarizations and spreading depolarization clusters (P < 0.05). Midazolam anaesthesia, in contrast, was associated with an increased number of spreading depolarization clusters (P < 0.05). By using a univariate odds ratio analysis, we also found a significant
association between ketamine administration and reduced occurrence of isoelectric spreading depolarizations in patients suffering from traumatic brain injury, subarachnoid haemorrhage and malignant hemispheric stroke ($P < 0.05$). Our findings suggest that ketamine—or another N-methyl-D-aspartate receptor antagonist—may represent a viable treatment for patients at risk for spreading depolarizations. This hypothesis will be tested in a prospective study.

**Keywords:** spreading depolarization; isoelectric spreading; depolarization; ketamine; midazolam

**Abbreviations:** COSBID = cooperative study of brain injury depolarizations; NMDA = N-methyl-D-aspartic acid

### Introduction

Spreading depolarizations are characterized by the abrupt, near-complete breakdown of ion gradients across cellular membranes, the sustained depolarization of neurons and glia, loss of brain electrical activity and neuronal swelling. This term describes the full spectrum of such cortical waves, from terminal depolarizations, characteristic of severe anoxia and ischaemia, to the short-lasting depolarizations assumed to underlie migraine aura (Strong et al., 2002; Dreier et al., 2006; Dreier, 2011). Electrocorticographically, spreading depolarizations are characterized by a large and slow potential change (Canals et al., 2005). When neuronal metabolism is largely intact before the onset of spreading depolarizations, it leads to a depression of neuronal activity (Strong et al., 2002), because the accompanying sustained neuronal depolarization lies above the inactivation threshold for action potential-generating ion channels (Karger et al., 2002). On the other hand, when neuronal metabolism is disturbed before spreading depolarization onset, neuronal activity has already ceased and spreading depolarizations cannot trigger a further depression of activity. Under these conditions, spreading depolarizations are termed as isoelectric spreading depolarizations to distinguish them from spreading depressions (Hartings et al., 2011). Temporally clustered spreading depolarizations are associated with the development of new infarcts after aneurysmal subarachnoid haemorrhage and with poorer outcome after subarachnoid haemorrhage and traumatic brain injury (Dreier et al., 2006; Dreier, 2011; Hartings et al., 2011). Moreover, they are frequently observed in malignant hemispheric stroke (Dohmen et al., 2008). Thus, the occurrence of isoelectric spreading depolarizations is probably associated with a poorer prognosis than the occurrence of spreading depressions (Fabricius et al., 2006; Hartings et al., 2012).

Whether spreading depolarizations can be modulated pharmacologically in the human brain is largely unknown (Lauritzen et al., 2011; Dreier, 2011). However, our preliminary findings suggest that large doses of analgesic and sedative drugs—such as are administered on intensive care units—may influence the occurrence of spreading depolarizations (Sakowitz et al., 2009). Interestingly, most recordings of spreading depolarizations are made under the influence of such analgesic and sedative drugs. These include enhancers of γ-aminobutyric acid (GABA) receptor action such as benzodiazepines and barbiturates, opioid receptor agonists and the N-methyl-D-aspartate (NMDA) receptor blocker, ketamine. These drugs target receptors that regulate neuronal activity and synaptic transmission and may thereby alter susceptibility to and course of spreading depolarizations (Somjen, 2001).

Although the occurrence of spreading depolarizations may presumably be modulated by a broad range of molecular and physical entities, we chose in this study to focus solely on the influence mediated by a selected set of drugs commonly employed on intensive care units. The goal of our analyses was to identify the possible drug candidates for reducing the occurrence of spreading depolarizations in patients following acute brain injury.

### Materials and methods

We received 115 sets of patient data from seven member centres of the international multicentre observational study group, Cooperative Study of Brain Injury Depolarizations (COSBID) (www.cosbid.org), in Europe and USA (Cologne, Cincinnati, Berlin, Heidelberg, London, Richmond and Pittsburgh). All procedures were carried out in accordance with ethical standards and were approved by local research ethics committees. After a decision for surgery (craniotomy) was made, patient or guardian consent was obtained according to the Declaration of Helsinki. For the analyses presented here, we collected prospective data including gender, age, disease group, time of ictus, time(s) of spreading depolarization events and outcome 6 months after surgery, which was quantified using the extended Glasgow Outcome Scale. These data belong to the COSBID basic data set and were obtained from the secure COSBID online database (www.swinklink.com/caboodle). In addition, all participating centres provided patient sedation logs. Because some centres recorded drug dose data in bedside patient charts by clock-hour, the highest resolution for our analysis was 1 h. Administered analgesics and sedatives included midazolam, fentanyl, propofol, sufentanil, remifentanil, ketamine, propofol, γ-hydroxybutyric acid, morphine and clonidine. One centre also reported 17 bolus administrations of oxycodone. We focused on those drugs for which the total hours of electrocorticographic recordings exceeded 1000: midazolam, fentanyl, sufentanil, ketamine, propofol and morphine (Table 1). Flunitrazepam (80 h, $n = 2$ patients), thiopental (222 h, $n = 13$), remifentanil (200 h, $n = 9$), γ-hydroxybutyric acid (57 h, $n = 2$) and clonidine (180 h, $n = 17$) were not further investigated in this study. To normalize drug doses for further comparison, four quartiles were defined: $1 = <25\%$, $2 = 25\%$ quartile to below median, $3 = $median to $<75\%$ and $4 = \geq75\%$ (Table 1).

Electrocorticographic recordings were initiated immediately after each craniotomy and placement of the subdural electrode strip, and on average 37 h ($\pm41$ h) after the initial stroke or trauma. In these data, we found that both the total number of recorded hours and the number of recorded hours with spreading depolarizations peaked on the third day after ictus (Fig. 1B). The time courses for drug administration, however, were different from both the distribution of total recorded hours and the recorded hours with spreading depolarizations
and also different for each individual drug under study. For example, although the number of recorded hours reached a peak 3 days after ictus (Fig. 1B), morphine administration peaked at 2 days after ictus, whereas ketamine administration did not reach a peak until 7 days after ictus (Fig. 1B).

The occurrence of multiple spreading depolarizations in close temporal proximity is typically referred to as a cluster. However, neither the precise number of spreading depolarizations within a cluster nor their frequency are yet defined. For this study, we defined a cluster as the smallest number of non-randomly distributed spreading depolarizations that could be temporally associated with a certainty of at least 99%. For all recorded hours in all patients, the probability that a spreading depolarization occurred in any given hour of recording was calculated as \((1850/15445) = 0.120 = 12.0\%\). It suggests that the probability for two spreading depolarizations to occur within the same hour or within two consecutive hours of recording was \((1850/15445)^2 = 0.014 = 1.4\%\) and that the probability that a sequence of at least three spreading depolarizations occurred within three consecutive hours of recording was \((1850/15445)^3 = 0.002 = 0.2\%\). Accordingly, the occurrence of at least three spreading depolarizations within three or fewer consecutive recording hours was considered to be a cluster.

Of the 115 data sets, 98 were complete (85%), 10 lacked an extended Glasgow Outcome Scale score, and the time of ictus was not indicated or unknown for eight data sets. For analysis of isoelectric spreading depolarizations, only data sets from patients with at least one isoelectric spreading depolarization were included.

Table 1 Investigated drugs with more than 1000 h of electrocorticographic recordings

<table>
<thead>
<tr>
<th>Investigated drug</th>
<th>Recorded hours</th>
<th>Patients (n)</th>
<th>Median drug dose and quartiles (mg)</th>
<th>25%</th>
<th>Median</th>
<th>75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>5608</td>
<td>61</td>
<td>14.4 22.3 36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>5459</td>
<td>71</td>
<td>0.1 0.15 0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>3397</td>
<td>81</td>
<td>100 150 200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufentanil</td>
<td>1456</td>
<td>14</td>
<td>0.03 0.06 0.105</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>2168</td>
<td>26</td>
<td>125 200 300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>1646</td>
<td>30</td>
<td>6 8 10</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Mean ± standard deviation, unless otherwise indicated. Outcome was assessed using an extended Glasgow Outcome Scale ranging from 1 (dead) to 8 (upper good recovery); ECoG = electrocorticography.

Table 2 Patient characteristics overview

<table>
<thead>
<tr>
<th>Patients</th>
<th>n = 115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>46 (40)</td>
</tr>
<tr>
<td>Age (years) range 18–79</td>
<td>49.6 (±15)</td>
</tr>
<tr>
<td>Extended Glasgow Outcome Scale (n = 105)</td>
<td>3 (1.5–5.5), median (25–75% percentile)</td>
</tr>
<tr>
<td>Recorded ECoG hours and sedation logs</td>
<td>117.6 (±59.9)</td>
</tr>
<tr>
<td>Spreading depolarizations (n = 76)</td>
<td>24.3 (±27.7)</td>
</tr>
<tr>
<td>Recorded hours with spreading depolarizations (n = 76)</td>
<td>17.6 (±18.2)</td>
</tr>
<tr>
<td>Clustered spreading depolarizations (n = 47)</td>
<td>13.9 (±13.5)</td>
</tr>
<tr>
<td>Isoelectric spreading depolarizations (n = 13)</td>
<td>9.77 (±13.6)</td>
</tr>
</tbody>
</table>

Results

Surgical procedures in our group of patients were performed to treat traumatic brain injury, relieve compression after malignant hemispheric stroke, clip aneurysms and remove blood clots resulting from subarachnoid haemorrhage and intracerebral haemorrhage (Tables 2 and 3). Electrocorticographic recordings were obtained during postsurgical observation on the intensive care unit from a surface electrode strip placed on the cortex during each surgical procedure. We observed spreading depolarizations

Figure 1 Recorded hours and administrations of sedatives and analgesics. (A) Total recorded hours of all patients and all observed spreading depolarizations (SDs). (B) The number of hours recorded for each drug depends on day of observation.
in 76 of 115 patients (66%). In our primary statistical analysis, frequencies of spreading depolarizations with and without administration of ketamine were analysed. More specifically, we compared paired relative frequencies of hours with spreading depolarizations with and without ketamine in individual patients. We found that ketamine reduced the occurrence of spreading depolarizations (paired t-test \( P < 0.05, n = 26 \) patients). When evaluated using the same approach, no other drugs exhibited such differences (Fig. 2A). Binary multivariable logistic regression was used to investigate additional associations between drug administration and spreading depolarization occurrence. For this analysis, the drug dosage of 115 patients was normalized in quartiles (Table 1). All drugs for which \( >1000 \) h of electrocorticographic recordings were available were included in the model and were significantly associated with spreading depolarization occurrence (omnibus-test for \( \chi^2 \); \( P < 0.05 \)). The odds ratio for each of the six drugs was also determined (Table 4). According to these calculations, only ketamine administration was significantly associated with reduced occurrence of spreading depolarizations (\( P < 0.05 \)). Because choice of the analgesic and sedative drugs seemed to be influenced by the time passed since ictus, we evaluated spreading depolarization events and drug administration with respect to time (Fig. 1A and B). This analysis revealed that the reduction in

### Table 3  Spreading depolarizations by type of brain injury

<table>
<thead>
<tr>
<th>Disease group</th>
<th>Patients with spreading depolarizations (% incidence)</th>
<th>Mean spreading depolarizations frequency (SD/h ± standard deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic brain injury</td>
<td>32 (53)</td>
<td>0.10 (±0.2)</td>
</tr>
<tr>
<td>SAH/ICH (n = 31)</td>
<td>24 (77)</td>
<td>0.10 (±0.1)</td>
</tr>
<tr>
<td>MHS (n = 24)</td>
<td>21 (88)</td>
<td>0.11 (±0.1)</td>
</tr>
</tbody>
</table>

ICH = intracerebral haemorrhage; MHS = malignant hemispheric stroke; SAH = subarachnoid haemorrhage; SD/h = spreading depolarizations per hour.

**Figure 2** Ketamine markedly decreases the incidence of cortical spreading depolarizations in acutely brain-injured patients. (A) Ketamine administration within the individual patient reduced spreading depolarizations (SDs). Within-patient analysis of spreading depolarizations per hour of electrocorticographic recordings under drug influence and without analgesic or sedative drugs (\( n \) = number of included patients). (B) The inhibitory effect of ketamine on spreading depolarization occurrence is consistent across days and therefore independent of time since ictus. (C) Doses of ketamine were negatively correlated with spreading depolarization frequency. (D) Isoelectric spreading depolarization occurrence is influenced by analgesics and sedatives in a drug-dependent manner. *Significant at \( P < 0.05 \).
spreading depolarization occurrence during hours recorded with ketamine was not associated with any of the total recorded hours, the total recorded hours with spreading depolarizations or the time after ictus (Fig. 2B). To further evaluate a dose–response relationship, all given doses of ketamine were correlated with their spreading depolarization frequencies. A significant linear association was found between ketamine dose and spreading depolarization frequency (Fig. 2C). On the basis of the fact that this study was fully observational, and none of the drugs were given with the intention to treat spreading depolarizations, our preliminary outcome analysis (data not shown) must be viewed with caution. Patients with high spreading depolarization per hour frequencies displayed a trend towards bad outcome (Spearman $r = -0.2$; $P < 0.1$, $n = 105$ patients); however, although ketamine reduces spreading depolarization per hour frequencies (Fig. 2C), increasing doses of ketamine were correlated with poorer extended Glasgow Outcome Scale after 6 months (Spearman $r = -0.4$; $P < 0.001$, $n = 105$ patients).

The best logistic regression model to predict the influence of analgesic and sedative drugs on clusters of spreading depolarizations was chosen by the backward stepwise elimination technique. This analysis revealed a significant positive association between midazolam administration and cluster occurrence and a significant negative association between ketamine administration and cluster occurrence (Table 4). Propofol was also negatively associated with cluster occurrence, although not to the same extent as ketamine (Table 4).

Isoelectric spreading depolarizations are believed to represent a subtype of spreading depolarizations that occur in either ischaemic or immediately peri-ischaemic tissue, the ischaemic part of which being at risk for cell death with permanent loss of neuronal function (Oliveira-Ferreira et al., 2010). Of 1340 total hours of recording, 127 hours with isoelectric spreading depolarization events in 13 patients were observed. Unfortunately, these data are too limited to allow the use of a multivariate statistical model for analysis. However, calculations of univariate, patient-independent odds ratios revealed a significant decrease in the probability of isoelectric spreading depolarizations for most drugs (Fig. 2D).

Because the injured brain has general mechanisms of reaction and repair such as oedema, swelling and neuronal reorganization, it seemed reasonable to evaluate the overall occurrence of spreading depolarizations following different kinds of brain insult, such as traumatic brain injury, malignant hemispheric stroke, subarachnoid haemorrhage and intracerebral haemorrhage. However, it remains possible that the observed effect of ketamine and other drugs on spreading depolarizations could be limited to one or a few specific types of brain injury. Indeed, we found that spreading depolarization occurrence within the different disease entities showed different responses to drug treatment. Still, the relatively small number of patients per disease group limited the power of our analysis. This was reflected by the large variability within the recorded data. Within recordings from patients with traumatic brain injury, we found a peak of recorded hours with and without drug at Day 2 after ictus. The recordings from patients with subarachnoid haemorrhage and intracerebral haemorrhage peaked on Day 4 after ictus, and most recordings after malignant hemispheric stroke were made on Day 5 after ictus (Fig. 3A). The recording time from patients with malignant hemispheric stroke without influence of one of the investigated drugs was low. Only a total of 268 recorded hours between Days 1 and 8 were obtained without analgesia or sedation (Fig. 3B), and none of these contained spreading depolarizations. On the basis of the number of spreading depolarizations observed following malignant hemispheric stroke under the influence of analgesics and sedatives, we would have expected to observe at least one spreading depolarization in 11 hours of recordings without drugs. Nonetheless, we attribute this surprising observation to be an artefactual consequence of the small number of recorded hours without drug influence. In the subarachnoid haemorrhage/intracerebral haemorrhage and traumatic brain injury disease groups, we found that for most days after ictus, the number of spreading depolarizations/hour recorded under analgesics and sedatives are well below that observed for recordings made without sedation (Fig. 3B). The effect of ketamine on spreading depolarization occurrence was sustained for all disease groups (Fig. 3C). Other drugs also seemed to influence spreading depolarization occurrence in this subgroup analysis. Because these results are based on relatively low patient numbers, however, their value is limited.

**Discussion**

The most conspicuous finding of this analysis was a strong and sustained suppression of spreading depolarizations by ketamine. Specifically, administration of ketamine was found to be inversely correlated with the occurrence of spreading depolarizations,

**Table 4 Multivariate analysis of investigated analgesics and sedatives in 115 patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Odds ratio for spreading depolarization occurrence (95% CI)</th>
<th>P-value</th>
<th>Odds ratio for cluster occurrence (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>1.28 (0.93–1.75)</td>
<td>0.13</td>
<td>1.35 (1–1.81)</td>
<td>0.048</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.97 (0.68–1.38)</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>0.89 (0.68–1.16)</td>
<td>0.38</td>
<td>0.68 (0.49–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>1.06 (0.64–1.76)</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.38 (0.18–0.79)</td>
<td>0.01</td>
<td>0.2 (0.06–0.64)</td>
<td>0.01</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.93 (0.65–1.3)</td>
<td>0.67</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drugs were included in the model using the enter method. Relative risk for the occurrence of spreading depolarizations and spreading depolarization clusters are shown for dose ranges of each drug in quartiles. For cluster analysis, the table includes stepwise backward selected drugs.
clusters of spreading depolarizations, and isoelectric spreading depolarizations. This effect was observed for all disease-specific subgroups and was persistent across all days after the initial event of brain injury.

To date only two patients with traumatic brain injury and aneurysmal subarachnoid haemorrhage were reported in whom spreading depolarizations were abolised under the influence of the non-competitive NMDA receptor antagonist ketamine (Sakowitz et al., 2009). Another patient with aneurysmal subarachnoid haemorrhage displayed a cluster of spreading depolarizations under a lower dose of ketamine, developed severe delayed ischaemic strokes and died (Dreier et al., 2009). These heterogeneous findings may reflect a situation, recognized from animal experiments, that deleterious conditions induce spreading depolarization as they shift the balance of ion fluxes across neuron cell membranes towards a net positive inward flux, whereas protective drugs such as NMDA receptor antagonists have the opposite effect. If the deleterious condition is stronger than the NMDA receptor antagonist, spreading depolarization will occur despite the presence of the drug in the region exposed to the deleterious condition (Hernández-Cáceres et al., 1987; Aitken et al., 1988); nevertheless, the NMDA receptor antagonist may be sufficient to block the spread of spreading depolarization into the healthier peri-ischaemic tissue. Spreading depolarizations may have beneficial effects in the peri-ischaemic tissue where they could have preconditioning effects or promote plasticity and regeneration (Nakamura et al., 2010; Dreier, 2011).

Theoretically, this suggests the risk that spreading depolarizations will be unaffected by an underdosed NMDA receptor antagonist in regions where they lead to damage but will be abolished where they could be beneficial. However, in this study, we found a strong and sustained effect on spreading depolarizations. In addition, an effect on isoelectric spreading depolarizations was observed. Isolelectric spreading depolarizations occur immediately not only in the peri-ischaemic tissue but also in the ischaemic zone where spreading depolarizations are deleterious (Oliveira-Ferreira et al., 2010; Hartings et al., 2011a). Consistent with the notion that isoelectric spreading depolarizations carry a particular risk, it has been recently found that they were associated with a worse outcome after traumatic brain injury (Hartings et al., 2011b). So far, clinical evidence regarding neurological recovery after ketamine administration is limited. Ketamine has been shown to increase cerebral perfusion pressure and might therefore increase neuronal survival (Kolenda et al., 1996; Albanese et al., 1997). However, an improved outcome has not been reported (Roberts et al., 2011). Underdosing of the drug and adverse effects were possibly responsible for the failure of NMDA receptor antagonists in a number of clinical studies on

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**Figure 3** Analgesics and sedatives influence the relative probability of spreading depolarization (SDs) occurrence after traumatic brain injury (TBI), subarachnoid haemorrhage (SAH) and malignant hemispheric stroke (MHS). (A) The hours of electrocorticographic recordings obtained after acute brain injury were highly variable and depended on the type of brain injury. (B) Rates of spreading depolarization occurrence for all recorded hours and for all hours recorded without the investigated drugs. (C) Analgesic and sedative drugs changed the relative probability of spreading depolarization occurrence in a disease- and drug-specific manner. *Significant at $P < 0.05$.

noDrug = none of the drugs were used; All = all recording hours are included.
stroke and brain trauma (Lees et al., 2000; Sacco et al., 2001; Ikonomidou and Turski, 2002). Despite this failure, ketamine is still associated with a powerful neuroprotective potential (Hudetz and Pagel, 2010). Neuronomonitoring of spreading depolarizations may offer the chance for real-time detection of the advent of ischaemic complications in patients with subarachnoid haemorrhage or traumatic brain injury. This could allow early targeted treatment for those patients who benefit from such therapy, whereas drug treatment with unnecessary side effects is avoided in those patients who do not develop the complication (Hartings et al., 2012). Thus, it may be worthwhile to retest the potential neuroprotective effect of an NMDA receptor antagonist such as ketamine in patients in whom depolarizations are detected.

On a cellular level, spreading depolarizations reflect a breakdown of ion homeostasis in neurons and glia (Hopwood et al., 2005). Although functioning and viable glia are believed to be beneficial for neuronal survival, they seem not to be critical for the generation of spreading depolarizations (Largo et al., 1996). Spreading depolarization may result either from acute hyperexcitability with increased influx of cations, or from disturbance of Na+ /K+-ATPase activity with decreased outflux of cations. Thus, spreading depolarization starts when net cation fluxes of sodium and calcium turn inwards, being no longer compensated by the outward flux produced by Na+ /K+-ATPase activity (Kager et al., 2002). Ischaemia is an important mechanism underlying reduced Na+ /K+-ATPase activity as ATP is no longer able to drive the pump. Cation influx across the neuronal membrane is triggered by neuronal activity and by second messengers and ligands. Anaesthetics and sedative drugs primarily target receptors on neuronal cells that influence ion homeostasis and neuronal excitability. Ketamine, for instance, binds to the NMDA receptor, and during glutamatergic synaptic transmission, it decreases its open probability—and therewith the total sodium influx into a cell. Indeed, the use of non-competitive NMDA receptor antagonists is considered one of the most promising strategies for suppression of spreading depolarizations (Iijima et al., 1992; Obrenovitch and Zilkha, 1996). The first experimental evidence to this effect was obtained in animal experiments and was attributed specifically to NMDA receptor blockade (Marrannes et al., 1988). Human brain slices obtained after neurosurgical resection for epilepsy likewise showed diminished spreading depolarizations after treatment with antagonists of the NMDA receptor (Avoli et al., 1991; Gorji et al., 2001).

Our analyses suggest that other commonly used intensive care unit drugs exert little to no influence on the occurrence of spreading depolarizations. Besides ketamine, midazolam displayed a possible influence on spreading depolarizations and was associated with increased numbers of spreading depolarization clusters. Midazolam, like all benzodiazepines, enhances GABAergic activity and leads to neuronal hyperpolarization. This reduction in neuronal excitability should theoretically lead to less spreading depolarizations and cannot be responsible for increased clusters of spreading depolarizations. But there are other possible explanations for this observation. Midazolam and ketamine have opposite effects on brain energy consumption, and brain metabolism plays a crucial role in generation and propagation of spreading depolarizations. Specifically, the reduction of cerebral metabolic rate under the influence of midazolam is magnitudes greater than that measured during normal brain inactivity without the influence of sedatives (Alkire et al., 1999; Shulman et al., 2009). Ketamine has been shown to increase energy consumption of the brain (Dawson et al., 1971; Långström et al., 2003). In contrast with the effect of ketamine on brain metabolism and spreading depolarization clusters, midazolam might induce clusters of spreading depolarizations along with the reduction of brain energy utilization. These findings suggest that GABAergically mediated metabolic depression could potentially aggravate the failure of energy-dependent ion pumps and therefore increase generation and propagation of spreading depolarization clusters.

The analysis of spreading depolarization frequency (spreading depolarization per hour) with and without each drug was used as a straightforward approach. Using continuous spreading depolarization per hour data, we analysed spreading depolarization occurrence with and without anaesthetic or sedative drugs (Fig. 2A). With respect to drug dosage, we analysed hours with spreading depolarizations including hours with one or more spreading depolarization. To resolve the important occurrence of multiple spreading depolarizations within close proximity, clusters of three or more spreading depolarizations were further analysed (Feuerstein et al., 2010). Patients in this retrospective study received no standard dose or standard drug regimen. Thus, changes in drug dosage and in sedative or opioid were common during recordings, even in a single patient. In addition, spreading depolarizations are rare events and do not even occur in all patients. Taken together, the variability of the available data and the number of patients included limited the power of our analysis. Furthermore, neuroprotective properties of ketamine could not be characterized in our patients. A part of this may be due to the fact that sedative use per se is correlated with the extent of the initial brain injury, i.e. patients with severe brain tissue injury are more likely to require sedation during neurointensive care treatment. We were nonetheless surprised by this result given that ketamine reduced spreading depolarization frequency, and a reduced spreading depolarization frequency was generally associated with a better outcome.

In this observational study, we proposed that a cluster of spreading depolarizations should be defined as the occurrence of three or more spreading depolarizations within 3 h. It is reasonable to distinguish isolated spreading depolarizations from temporally clustered spreading depolarizations as the latter are likely to be more harmful to brain tissue (Dreier et al., 2006; Bosche et al., 2010). Future investigations may provide a better indication of what number and frequency of clustered spreading depolarizations compromise metabolism critically and result in irreversible damage to functional brain tissue. Data presented here suggest, however, that a cluster must consist of at least three spreading depolarizations within close temporal proximity, as the observation of any fewer or more widely distributed spreading depolarizations in a cluster may be merely coincidental.

Conclusion

Analgesic and sedative drugs had a significant impact on the occurrence of spreading depolarizations. In particular, ketamine
markedly decreased the probability for cortical spreading depolarizations to occur. This finding suggests that spreading depolarizations can be modulated in humans and are therefore valuable targets for neuroprotective therapy that might even exceed the action of ketamine. Prospective clinical studies with neuromonitoring of spreading depolarizations are needed to verify both the effects of ketamine on spreading depolarization occurrence and to examine its benefits for acutely brain-injured patients.

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