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SHORT COMMUNICATION

Effects of subdural application of lidocaine in patients with focal epilepsy

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KEYWORDS Lidocaine; Transmeningeal; Focal; Epilepsy **Summary** Antiepileptic drug (AED) delivery directly into the neocortex has recently been shown to be able to both prevent and terminate focal seizures in rats. The present clinical experiment aimed to test the local effects of lidocaine delivered onto the pia mater adjacent to epileptogenic zones in human patients. Administration of lidocaine resulted in a marked diminishment of spike counts on all patients, with a decremental effect of lidocaine on the faster frequency elements of individual spikes and overall testing epochs. The direct cortical application of lidocaine appears to affect local epileptogenic activity in human patients with intractable focal epilepsy.

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1. Introduction

The transmeningeal application of antiepileptic drug (AED) directly to the brain neocortex has recently begun to be explored for the treatment of refractory partial epilepsies (Ludvig et al., 2006; John et al., 2007). Drug delivery through the meninges has been shown to both prevent and terminate focal seizures in rats, as demonstrated by the epidural application of diazepam (DZP) markedly reducing the amount of electroencephalographic (EEG) spiking in rat models (Eder et al., 1997), and intracortically infused GABA by reducing motor seizures in amygdala kindled rats (Fukuda et al.,

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1987). Based on these observations, and on recent histological evidence that water-soluble small molecules diffuse into the neocortex through the cerebral meninges (Ludvig et al., 2008), the delivery of AEDs transmeningeally *in situ* to terminate or prevent seizures in humans appears to be a feasible concept.

Specifically, this experiment aimed to test the hypothesis that focal administration of a channel blocker in humans can have similar effects to those observed in animals. During these experiments, we tested the local effects of lidocaine delivered onto the pia mater overlying EEG spiking activity. Lidocaine is a local anesthetic with a number of distinct cellular effects, including inhibition of the calcium-activated potassium channel and voltage-gated sodium channel. It has been demonstrated to have multiple inhibitory effects in the central nervous system (CNS) in animal models, with lidocaine administration increas-

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ing the current threshold to depolarization and decreasing action potential amplitude in single pyramidal cells isolated from rat hippocampus (Butterworth et al., 1993). We have also shown that intrahippocampal microdialysis with lidocaine suppresses hippocampal neuronal firing in freely moving rats (Ludvig et al., 1994). In addition, there appeared to be a concentration-dependent effect on current threshold in the above study, which was also found in sciatic nerve experiments in the frog and rat (Bokesch et al., 1986). Lidocaine also produces severe impairment of auditory brain-stem responses (ABR) in rat models (Schmidt et al., 1990), thereby demonstrating its inhibitory effects on neuronal transmission. As it is water soluble, it was technically feasible to directly infuse lidocaine solutions onto the pial surface. The following study is an initial demonstration of the effects of direct lidocaine application on local spiking characteristics in humans, intended as a proof of concept for future experiments related to transmeningeal focal AED administration.

2. Methods

2.1. EEG recordings

Consent from the IRB was obtained for the intraoperative use of lidocaine. Three patients undergoing resection for intractable focal epilepsy were examined using intraoperative electrocorticography (ECoG, sampled at 256 Hz, using a band-pass of 0.1-70 Hz and application of a 60 Hz notch filter), recorded using a Nicolet Biomedical EEG system (Viasys Healthcare, Inc.). Either a 4×4 electrode grid or multiple four contact electrode strips (5 mm electrode diameter) were placed directly over the region of the resection zone, which was determined by previous intracranial EEG recordings. After the recording of a 5 min baseline ECoG control epoch, a Gelfoam[®]



Figure 1 Patient spike counts (left) and corresponding FFT plots determined over 5-min epochs prior to lidocaine application (red), and with application of 0.2% (green) and 0.4% (violet) solutions, in patients 1–3. Lidocaine administration appeared to diminish spike numbers at both concentrations in each patient, with a markedly pronounced spike reduction noted in patient 1. The FFT frequency scale is expressed on the *x*-axis, and the total power at a given frequency expressed as a percentage is visualized on the *y*-axis. Note the decrement of power after lidocaine administration in patients 1 and 2. Please note the difference in scale in the spike count of patient 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)



Figure 2 Wavelet analysis of averaged spikes from patient 1, prior to lidocaine administration (a), after 0.2% solution application (b), and after 0.4% solution application (c). Spikes were isolated, and aligned according to their amplitude maxima. The maximal frequency can be seen as the region of highest power on the spectrogram, and also expressed numerically on the figure.

square $(1 \text{ cm} \times 1 \text{ cm})$ was immersed in 0.2% lidocaine solution (1 cc of 2% lidocaine dissolved in 9 cc saline) for 30 s, and applied to the maximal area of spiking by placing the Gelfoam underneath and between the electrodes followed by 5 min of recording. Following the first recording, we increased the dose to 0.4% lidocaine solution using an identical protocol as above with 5 min recording period. Finally, the Gelfoam was removed and the area of cortex irrigated with 38 C saline for 1 min followed by a 5 min of EEG recording using the same electrodes.

2.2. Patients

Patient 1 is a 30-year-old right-handed male with a history of refractory seizures originating from the right frontal region, without an appreciable lesion noted. Frequent epileptiform spikes and sharp waves were noted during intracranial monitoring with subdural electrodes, and the patient underwent corticography-assisted resection of this region.

Patient 2 is a 26-year-old left-handed male with a history of developmental delay and seizures starting at 1 month of age. He continued to have refractory seizures despite corpus callosotomy at age 14. Intracranial monitoring revealed very frequent spike and wave discharges occurring in 10 s runs and partial seizures originating from the left frontal lobe.

Patient 3 is a 38-year-old right-handed female with a history of a right temporo-parietal arteriovenous malformation (AVM), who developed seizures 2 years following a hemorrhage of her AVM with subsequent resection. Intracranial monitoring revealed a persistent spiking focus in the superior parietal lobe, around the region of postoperative encephalomalacia. During monitoring, she developed a complex partial seizure which evolved into status epilepticus, originating from the temporal lobe border of encephalomalacia.

2.3. EEG and spike analysis

A single EEG channel was identified from each patient to represent the areas of most active spiking. Spikes from each epoch were identified based on morphology and temporal features (<50 ms spike duration), and counted for each patient. Wavelet analysis (Mallat, 1989; Torrence and Compo, 1998) was employed to perform spike signal analysis. As opposed to Fourier analysis, which separates freguent bands within a defined epoch, the wavelet transform (WT) decomposes the signal in both frequency and time. This can provide additional instantaneous frequency information at the peak of each spike, and not only during a longer fixed time interval. Morlet wavelets were chosen for the analysis of individual spike curves, between the frequencies of 2–50 Hz, sampled every 0.5 Hz. Wavelet analysis was performed on 10 randomly selected spikes from each epoch of patient 1 (who was the only patient who had a sufficient number of spikes for analysis), and averaged. Average wavelet spectrograms were obtained by superimposing the wavelet frequency decompositions in spectrogram form for individual spikes, with their temporal location aligned at their maxima. Local maxima on the cross-section of the spectrogram at the time of the spike were used to identify the dominant instantaneous frequency of each spike, and these maxima were averaged. Fast Fourier Transforms (FFTs) were then performed on each 5 min epoch from each patient to identify changes in power among frequency bands between 0 and 50 Hz.

3. Results

Administration of lidocaine resulted in a gradual diminishment of spike counts on all patients, with an almost 20-fold decrement for patient 1 (Fig. 1). FFT analysis revealed a decrease of power over frequencies between 5 and 20 Hz after lidocaine administration in patients 1 and 2, with relative increases in the frequencies under 5 Hz (Fig. 2). FFT analysis on patient 3 did not yield similar results, which may have been related to increased electrical noise present on this recording. In patient 1, averaged wavelet analysis revealed a decrement of the maximal frequency peak after each lidocaine administration (7.3 Hz prior to lidocaine, 6.1 Hz with 0.2% solution, and 5.7 Hz with 0.4% solution), again suggesting a decremental effect of lidocaine on the faster frequency elements of individual spikes (Fig. 2).

4. Discussion

The above experiments demonstrate that lidocaine, delivered directly on the pia mater adherent to underlying epileptogenic cortex, suppresses cortical EEG spiking. This phenomenon was observed in all examined patients. As the generation of an interictal spike on ECoG appears to be correlated with the synchronized production of action potentials from multiple neuronal generators within the epileptogenic cortex, lidocaine may be interfering with this synchronization process by raising depolarization thresholds in these cell populations. The attenuation of spiking may be a direct reflection of the pharmacological effects of lidocaine; for instance, the resultant sodium channel blockade on pyramidal cell dendrites can reduce the excitatory post-synaptic potentials (EPSP) and paroxysmal depolarizing shifts (PDS) necessary for the production of action poten-

tial trains that underlie spike production. These effects, possibly in combination with sodium channel blockades on subcortical and cortical axons carrying excitatory inputs to pyramidal cells, may result in disordered and temporally spread out action potentials, which could potentially cause spikes with diminished amplitude or complete absence of spikes on ECoG. The suppression of faster frequencies with increased lidocaine concentration as displayed by FFT may be due to dendritic and axonal sodium channel inhibition in pyramidal cells, resulting in a diminished capacity of neuronal populations to produce synchronized high frequency activity. Lidocaine may also have an inhibitory effect on GABAergic interneurons, which appear to be related to the production of gamma-frequency cortical activity (Buzsaki et al., 1995; Fisahn et al., 1998; Ylinen et al., 1995), and high frequency field oscillations (Buzsaki et al., 1992). This may play a further role in interfering with neuronal synchronization.

These preliminary experiments appear to demonstrate the effectiveness of pial administration of AED, namely lidocaine, on spiking activity within the human epileptogenic zone. These results suggest that transmeningeal application of a current channel blocker such as lidocaine or similar drugs could be effective in the reduction of epileptogenic activity, and perhaps seizures in human subjects. These initial protocols did not accurately control for specific lidocaine concentrations, as the Gelfoam® was immersed in lidocaine solution and placed on the cortical surface without accurate control of how much drug is delivered into the cortex. However, these shortcomings are limited by the observation of a direct correlation between spiking rate reductions and lidocaine concentrations, by the use of a consistent lidocaine concentration and by incorporating an internal control via the washout period. Future experiments are currently underway to confirm this effect using more stringent controls for lidocaine concentration, and washout periods following each lidocaine solution administration. These results suggest that localized cortical infusion of drugs should be further explored for treatment of focal seizures.

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