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SHORT COMMUNICATION

Effects of subdural application of lidocaine in patients with focal epilepsy

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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.,

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., *in press*), 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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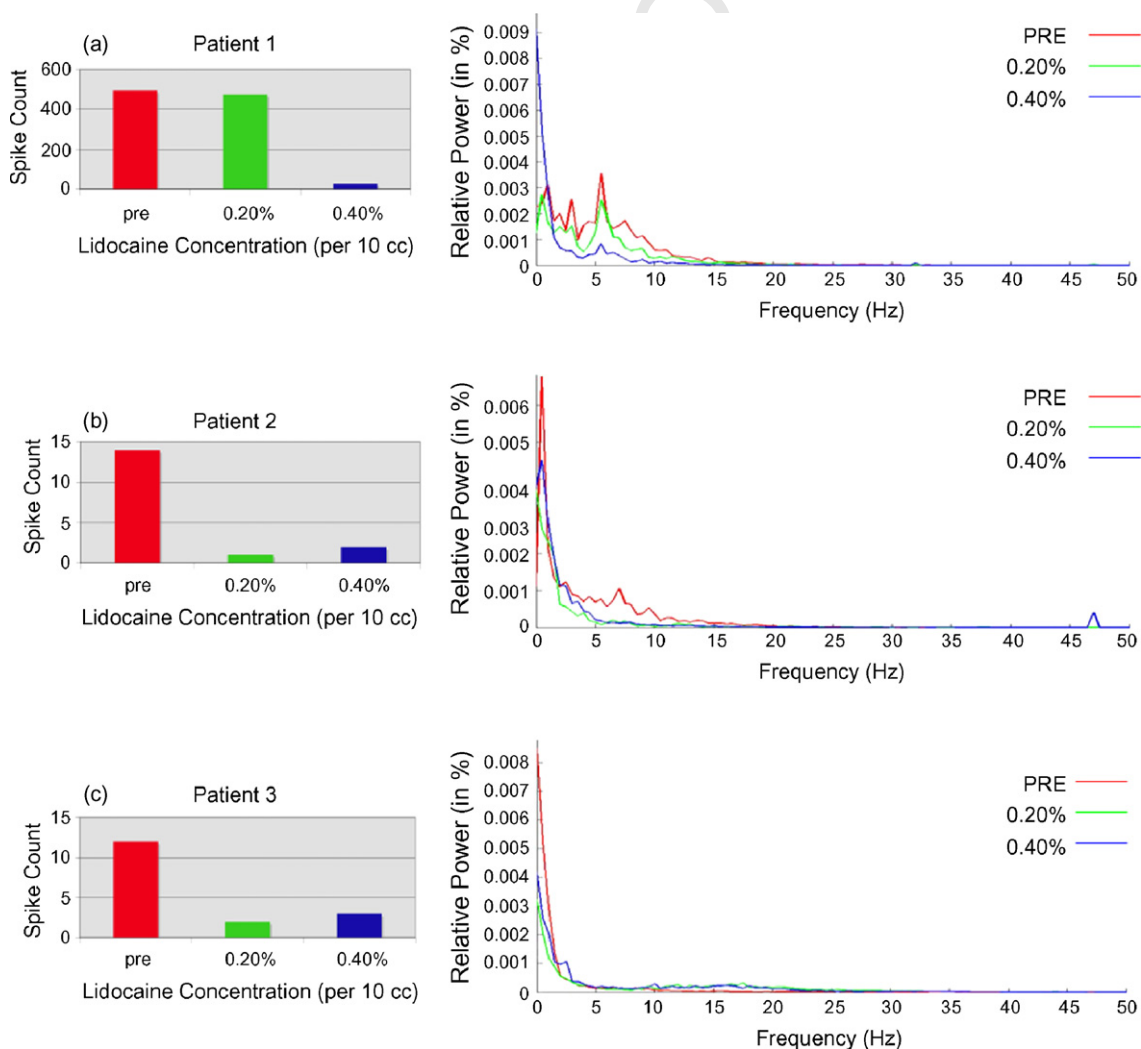
ing the current threshold to depolarization and decreasing action potential amplitude in single pyramidal cells isolated from rat hippocampus (Butterworth et al., 1993). We have also shown that intrahippocampal microdialysis with lidocaine suppresses hippocampal neuronal firing in freely moving rats (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®



Q5 **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. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

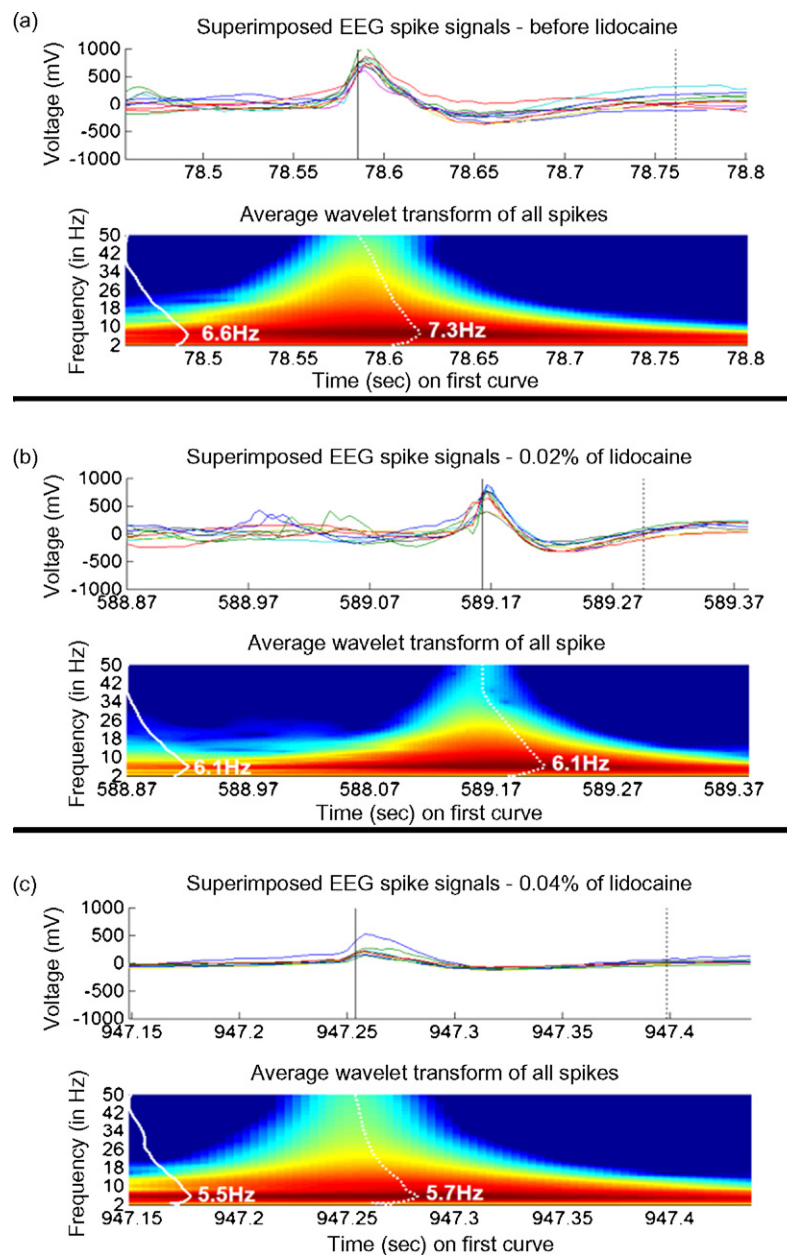


Figure 2 Wavelet analysis of averaged spikes from patient 1, prior to lidocaine administration (a), after 0.2% solution application (b), and after 0.4% solution application (c). Spikes were isolated, and aligned according to their amplitude maxima. The maximal frequency can be seen as the region of highest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

60 square (1 cm × 1 cm) was immersed in 0.2% lidocaine solution (1 cc
61 of 2% lidocaine dissolved in 9 cc saline) for 30 s, and applied to the
62 maximal area of spiking by placing the Gelfoam underneath and
63 between the electrodes followed by 5 min of recording. Following
64 the first recording, we increased the dose to 0.4% lidocaine solution
65 using an identical protocol as above with 5 min recording period.
66 Finally, the Gelfoam was removed and the area of cortex irrigated
67 with 38 C saline for 1 min followed by a 5 min of EEG recording using
68 the same electrodes.

69 2.2. Patients

70 Patient 1 is a 30-year-old right-handed male with a history of refrac-
71 tory seizures originating from the right frontal region, without an
72 appreciable lesion noted. Frequent epileptiform spikes and sharp

73 waves were noted during intracranial monitoring with subdural elec-
74 trodes, and the patient underwent corticography-assisted resection
75 of this region.

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

82 Patient 3 is a 38-year-old right-handed female with a history of
83 a right temporo-parietal arteriovenous malformation (AVM), who
84 developed seizures 2 years following a hemorrhage of her AVM with
85 subsequent resection. Intracranial monitoring revealed a persistent
86 spiking focus in the superior parietal lobe, around the region of post-
87 operative encephalomalacia. During monitoring, she developed a

88 complex partial seizure which evolved into status epilepticus, orig-
89 inating from the temporal lobe border of encephalomalacia.

90 2.3. EEG and spike analysis

91 A single EEG channel was identified from each patient to repre-
92 sent the areas of most active spiking. Spikes from each epoch were
93 identified based on morphology and temporal features (<50 ms spike
94 duration), and counted for each patient. Wavelet analysis (Mallat,
95 1989; Torrence and Compo, 1998) was employed to perform spike
96 signal analysis. As opposed to Fourier analysis, which separates fre-
97 quent bands within a defined epoch, the wavelet transform (WT)
98 decomposes the signal in both frequency and time. This can pro-
99 vide additional instantaneous frequency information at the peak of
100 each spike, and not only during a longer fixed time interval. Mor-
101 let wavelets were chosen for the analysis of individual spike curves,
102 between the frequencies of 2–50 Hz, sampled every 0.5 Hz. Wavelet
103 analysis was performed on 10 randomly selected spikes from each
104 epoch of patient 1 (who was the only patient who had a sufficient
105 number of spikes for analysis), and averaged. Average wavelet spec-
106 trograms were obtained by superimposing the wavelet frequency
107 decompositions in spectrogram form for individual spikes, with their
108 temporal location aligned at their maxima. Local maxima on the
109 cross-section of the spectrogram at the time of the spike were used
110 to identify the dominant instantaneous frequency of each spike, and
111 these maxima were averaged. Fast Fourier Transforms (FFTs) were
112 then performed on each 5 min epoch from each patient to identify
113 changes in power among frequency bands between 0 and 50 Hz.

114 3. Results

115 Administration of lidocaine resulted in a gradual diminish-
116 ment of spike counts on all patients, with an almost 20-fold
117 decrement for patient 1 (Fig. 1). FFT analysis revealed a
118 decrease of power over frequencies between 5 and 20 Hz
119 after lidocaine administration in patients 1 and 2, with rela-
120 tive increases in the frequencies under 5 Hz (Fig. 2). FFT
121 analysis on patient 3 did not yield similar results, which
122 may have been related to increased electrical noise present
123 on this recording. In patient 1, averaged wavelet analysis
124 revealed a decrement of the maximal frequency peak after
125 each lidocaine administration (7.3 Hz prior to lidocaine,
126 6.1 Hz with 0.2% solution, and 5.7 Hz with 0.4% solution),
127 again suggesting a decremental effect of lidocaine on the
128 Q3 faster frequency elements of individual spikes (Fig. 2).

129 4. Discussion

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

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

163 These preliminary experiments appear to demonstrate
164 the effectiveness of pial administration of AED, namely lido-
165 caine, on spiking activity within the human epileptogenic
166 zone. These results suggest that transmeningeal application
167 of a current channel blocker such as lidocaine or similar
168 drugs could be effective in the reduction of epileptogenic
169 activity, and perhaps seizures in human subjects. These
170 initial protocols did not accurately control for specific lido-
171 caine concentrations, as the Gelfoam® was immersed in
172 lidocaine solution and placed on the cortical surface with-
173 out accurate control of how much drug is delivered into
174 the cortex. However, these shortcomings are limited by the
175 observation of a direct correlation between spiking rate
176 reductions and lidocaine concentrations, by the use of a
177 consistent lidocaine concentration and by incorporating an
178 internal control via the washout period. Future experiments
179 are currently underway to confirm this effect using more
180 stringent controls for lidocaine concentration, and washout
181 periods following each lidocaine solution administration.
182 These results suggest that localized cortical infusion of drugs
183 should be further explored for treatment of focal seizures.

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185 All authors confirm that we have read the Journal's position
186 on issues involved in ethical publication and affirm that this
187 report is consistent with those guidelines. No conflicts of
188 interest related to this project were reported by any of the
189 contributing authors, and all authors are aware and approve
190 of the contents of this submission.

191 References

- 192 Bokesch, P.M., Post, C., Strichartz, G., 1986. Structure-activity
193 relationship of lidocaine homologs producing tonic and
194 frequency-dependent impulse blockade in nerve. *J. Pharmacol.*
195 *Exp. Ther.* 237, 773–781.
196 Buzsaki, G., Horvath, Z., Urioste, R., Hetke, J., Wise, K., 1992.
197 High-frequency network oscillation in the hippocampus. *Science*
198 256, 1025–1027.
199 Buzsaki, G., Penttonen, M., Bragin, A., Nadasdy, Z., Chrobak, J.J.,
200 1995. Possible physiological role of the perforant path-CA1 pro-
201 jection. *Hippocampus* 5, 141–146.

- 202 Butterworth, J., Cole, L., Marlow, G., 1993. Inhibition of brain cell
203 excitability by lidocaine, QX314, and tetrodotoxin: a mechanism
204 for analgesia from infused local anesthetics? *Acta Anaesthesiol.*
205 *Scand.* 37, 516–523. 225
- 206 Eder, H.G., Jones, D.B., Fisher, R.S., 1997. Local perfusion of
207 diazepam attenuates interictal and ictal events in the bicu-
208 culline model of epilepsy in rats. *Epilepsia* 38, 516–521. 226
- 209 Fisahn, A., Pike, F.G., Buhl, E.H., Paulsen, O., 1998. Cholinergic
210 induction of network oscillations at 40 Hz in the hippocampus in
211 vitro. *Nature* 394, 186–189. 227
- 212 Fukuda, H., Brailowsky, S., Menini, C., Silva-Barrat, C., Riche, D.,
213 Naquet, R., 1987. Anticonvulsant effect of intracortical, chronic
214 infusion of GABA in kindled rats: focal seizures upon withdrawal.
215 *Exp. Neurol.* 98, 120–129. 228
- 216 John, J.E., Baptiste, S.L., Sheffield, L.G., von Gizycki, H.,
217 Kuzniecky, R.I., Devinsky, O., Ludvig, N., 2007. Transmeningeal
218 delivery of GABA to control neocortical seizures in rats. *Epilepsy*
219 *Res.* 75, 10–17. 229
- 220 Ludvig, N., Kuzniecky, R.I., Baptiste, S.L., John, J.E., von Gizy-
221 cki, H., Doyle, W.K., Devinsky, O., 2006. Epidural pentobarbital
222 delivery can prevent locally induced neocortical seizures in rats:
223 the prospect of transmeningeal pharmacotherapy for intractable
224 focal epilepsy. *Epilepsia* 47, 1792–1802. 230
- Ludvig, N., Potter, P., Fox, S.E., 1994. Simultaneous single cell
recording and microdialysis within the same brain site in freely
behaving rats: a novel neurobiological method. *J. Neurosci.*
Meth. 55, 31–40. 231
- Ludvig, N., Sheffield, LG, Tang, HM, Baptiste, SL, Devinsky, O,
Kuzniecky, RI. Histological evidence for drug diffusion across
the cerebral meninges into the neocortex in rats. *Brain Res.*,
in press. Q4 232
- Mallat, S.G., 1989. A theory for multiresolution signal decompo-
sition: the wavelet representation. *IEEE Trans. PAMI* 11 (7),
674–693. 233
- Schmidt, S.H., Anniko, M., Hellstrom, S., 1990. Electrophysiolog-
ical effects of the clinically used local anesthetics lidocaine,
lidocaine-prilocaine and phenol on the rat's inner ear. *Eur. Arch.*
Otorhinolaryngol. 248, 87–94. 234
- Torrence, C., Compo, G.P., 1998. A practical guide to wavelet anal-
ysis. *Bull. Am. Meteorol. Soc.* 79, 61–78. 235
- Ylinen, A., Bragin, A., Nadasdy, Z., Jando, G., Szabo, I., Sik,
A., Buzsaki, G., 1995. Sharp wave-associated high-frequency
oscillation (200 Hz) in the intact hippocampus: network and
intracellular mechanisms. *J. Neurosci.* 15, 30–46. 236

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