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Pharmacodynamics of remifentanil. Induced intracranial spike activity in mesial temporal lobe epilepsy

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ABSTRACT

Patients with medically refractory epilepsy may benefit from resective epilepsy surgery. However even the best centers experience surgical failures. It is therefore important to find techniques that may aid in neurosurgical planning of epileptic focus resection. Recordings of electrical brain activity with EEG during seizures reveal abnormal cortical hypersynchronization. Between seizures the EEG often shows interictal depolarizing phenomena such as spikes reflecting an irritable focus of the brain.

In the present study we investigated the effect of intravenous remifentanil on the spike activity in the temporal neocortex and hippocampus. We examined 65 patients with mesial temporal lobe epilepsy during surgery, prior to resection. We used a 20-lead grid on the cortex and a 4-lead strip in the lateral ventricle on the hippocampus. At least two 3-min periods of ECoG were recorded – before and after remifentanil injection. In a number of patients we examined the effect of repeated injections in order to estimate the dose-response curve.

We describe a significant effect of remifentanil on the average spike activity with an increment from 16 spikes per minute at baseline to 36 spikes per minute after remifentanil injection ($p < 0.0001$). The increase in spike activity was typically seen after 40–50 s. When mu-receptors were antagonized with a preceding injection of naloxone, spike activity increased 25% in response to remifentanil as opposed to 80% when remifentanil was preceded by placebo. In only seven out of 59 patients did the injection of remifentanil change the topographic location of the spike focus. Typically administration of remifentanil led to a focus of increased spike count. Activity in other areas was suppressed making the focus stand out from the background.

Our observation that remifentanil potentiates spike activity is in agreement with previous findings from smaller studies. Furthermore, we were able to describe the pharmacodynamics of the remifentanil effect on spike activity. Peri-operative provocation with remifentanil may play a future role in guiding neurosurgical intervention during epilepsy resection surgery.

1. Introduction

Recordings of electrical brain activity with EEG during epileptic seizures reveal abnormal cortical hypersynchronization. Between seizures the EEG often shows interictal depolarizing phenomena such as spikes generated by assemblies of hyperexcitable neurons. When interictal spikes appear in a part of cortex it is considered an irritative zone. Seizures arise from the seizure onset zone. Often

Abbreviations: EEG, electroencephalography; ECT, electro-convulsive therapy; ECoG, electrocorticography; MTS, mesial temporal sclerosis; TLE, temporal lobe epilepsy.

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these zones are in close spatial proximity (de Curtis and Avanzini, 2001).

While the unprovoked epileptic seizures are the main problem for most epilepsy patients, epileptic seizures may also be provoked by a number of factors in patients as well as in normal individuals. The provoking factors include physical, chemical and pharmaceutical interference with brain networks. It is often assumed that provoked and unprovoked seizures in patients share the same brain networks, however this is not always the case (Kjaer et al., 2010).

Remifentanil is a short acting selective mu-opioid agonist mainly used for reducing pain during general anesthesia. Additionally remifentanil has been shown to be proconvulsive, i.e. increasing the likelihood of developing epileptic seizures (Akcaboy et al., 2005). The proconvulsive effect of remifentanil is utilized in ECT to treat severe neuropsychiatric conditions such as stupor and depression. It is thought that part of the effect of the transcranial electrical stimulation is the induction of seizures. Thus induction of seizures is a measure of effect and many centers supplement anesthesia with remifentanil for ECT. A number of mechanisms are thought to contribute to the proconvulsive effect including shifts of ions, destabilization of cortex and delay of inhibition circuits (Zuleta-Alarcon et al., 2014).

Patients with medically intractable focal epilepsy benefit from surgical resection of the epileptic focus (Englot et al., 2015; Yuan et al., 2012). During surgery, administration of remifentanil may help to localize the epileptic focus. A previous study observed an increase in spike activity after remifentanil administration in 92% of patients with MTLE (Gronlykke et al., 2008), suggesting that remifentanil could enhance spike activity in the epileptogenic zone and perhaps reveal hidden epileptogenic tissue. In this study we have looked into the pharmacodynamics of remifentanil induced spike activity.

2. Methods

Patients with medically refractory epilepsy in the Danish epilepsy surgery program were included from 2008 to 2011. All patients in the epilepsy surgery program were offered inclusion independent of focus localization. Patients received oral and written information at the presurgical anesthesiologist visit. Everyone was given a three day period to consider if they were willing to participate. If so a written consent was given. Due to the large variation in presentation, recording topography and pathology, we subsequently decided to limit the scope of this manuscript to patients with TLE and MTS. Patients with dual pathology were not included. The patients included towards the end of the study participated in the investigation arms for tachyphylaxis and dose-response examination. The study was approved by the local ethics committee (H-B-2008-017).

Anesthesia was induced with propofol 2 mg/kg as a bolus injection. Cisatracurium 0.1 mg/kg was administered to facilitate intubation. Anesthesia was maintained with sevoflurane 2–3%, resembling a MAC value of approximately 1.5, depending on pulse and blood pressure. Local anesthesia of approximately 10 ml of bupivacaine 5 mg/ml was given in the skin corresponding to the pin holes from the 4-pin head holder and the planned cutaneous incision.

The head was positioned and fixed in a Zugitta 4-pin head holder. A 4 × 3 cm antero-basal craniotomy was performed over the relevant temporal lobe. Before any cortical resection was performed a 4-electrode strip (Adtech) was placed in the lateral ventricle through an 1½ cm linear opening anterior in the superior temporal sulcus, covering the anterior 3 cm of the hippocampus and a 4 × 5 electrode grid (Adtech) was placed on the lateral and inferior aspects of the temporal lobe according to Fig. 1. Electrodes

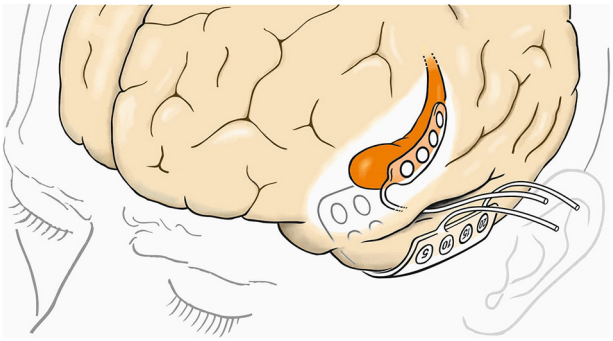

Fig. 1. Intraoperative electrocorticography (ECoG) recordings performed with a 4-lead strip on the intraventricular hippocampus and with a 20-lead grid on the anterior inferior temporal and lateral neocortex.

were connected to the Cadwell EEG (tm) recording system (Cadwell Laboratories Inc, Kennewick, WA, USA, version 2.02). Data were sampled at 256 Hz.

The sevoflurane anesthesia was lifted to an end-tidal concentration of 0.8–1.0%. A few minutes after the end-tidal concentration had stabilized the ECoG was recorded first for 3 min as baseline. Subsequently remifentanil was injected and after a 30 s delay another 3 min recording was performed. In a few patients the administration of remifentanil was associated with a drop in blood pressure that was corrected with ephedrine. End-Tidal Carbon Dioxide partial pressure (ETCO2) was maintained in the interval 4.0–4.5 kPa throughout the registration. After the recordings the electrodes were removed and the resection was performed. The resection was guided by the result of the recordings.

In 48 patients remifentanil was administered as a single standard bolus 4 μg/kg and the ECoG-recordings were performed as described above. In one patient the initial dose of 4 μg/kg was repeated after 4 min to check for tachyphylaxis. In four patients a dose-response relationship was estimated by administering 1/3 of the standard dose, followed after 4 min by administration of 2/3 of the standard dose and then after another 4 min by the standard dose of 4 μg/kg. Twelve patients underwent a randomized double blind placebo controlled test. In this test baseline recording was followed by injection of a test drug. The test drug was either 1 ml of normal saline or 1 ml of naloxone corresponding to 0.4 mg. The dose of naloxone was equivalent to the dose of remifentanil on a molar basis. A nurse who was not in the operating room filled the test syringe after instructions in a drawn envelope. Thus the investigators were blinded to whether naloxone or placebo was administered. Four minutes after test injection all twelve patients were given a standard dose of remifentanil, 4 μg/kg.

We quantified the spike activity in two 3 min periods before and after administration of remifentanil. The first 30 s after administration of remifentanil was not quantified to allow for drug distribution. Each 3 min period was saved in a separate anonymized file. Spike activity was quantified manually by a board certified clinical neurophysiologist (TWK) reviewing all 10-s segments using a common average reference montage. The reviewer was blinded to the presence/absence of remifentanil. If a spike occurred in several channels simultaneously it was only counted once in the channel where it had the highest amplitude. Spike estimates were summed across channels every 10 s to get an estimate of the spike dynamics and across time for each channel to evaluate the topographical distribution of activity.

3. Results

Sixty-five patients (41% females, age 1–57 yrs (median 34yrs)) were included. Ten of these patients have been reported previ-