Detection of an epileptic mirror focus after oral application of clonidine

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We report detection of an epileptic mirror focus approximately 2 h after administration of oral clonidine 150 µg in a patient with an intractable complex partial seizure disorder. The specific epileptic activity was documented by electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings. The case illustrates a possible role of clonidine in facilitating specific discharges.

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In patients with refractory epilepsy, precise delineation of the epileptogenic focus is the prerequisite for successful surgical therapy. To this end, pharmacological provocation of specific epileptic electric discharges may be required during presurgical evaluation. A variety of anaesthetics have proconvulsive properties and methohexital is often selected as an activating agent during presurgical and intraoperative evaluation of epileptic foci. There are several anaesthetic protocols concerning the dose of this barbiturate, but few data on sedative premedication before this type of ‘evaluative anaesthesia’.1 2 As benzodiazepines have anti-rather than proconvulsive effects, we have chosen the alpha-2 agonist clonidine for this purpose.3 We report detection of a mirror focus after orally administered clonidine in a patient during presurgical evaluation.

Case report

A 25-yr-old woman (weight 48 kg, height 159 cm) with an intractable complex partial seizure disorder was admitted for focus evaluation with respect to the possibility of future surgical treatment. Her medical history included excision of a right frontolateral hamartoma which had caused one tonic–clonic seizure at 14 yr of age. After this surgery, she developed symptomatic epilepsy with complex partial seizures generalizing to tonic–clonic seizures. Medical attempts to control the seizures included various anticonvulsant regimens. At the time of admission she suffered from three to four seizures per week, despite adequate serum concentrations of carbamazepine (10.3 mg ml–1). Otherwise, physical and neurological status was unremarkable, in addition to ECG and blood chemistry, with the exception of a leucocyte count of 3700 ml–1. MR imaging of the brain revealed the situation after resection of a tumour in the right frontal lobe.

On days 2–5 after admission, the patient underwent long-term video EEG monitoring. In order to facilitate the occurrence of seizures and epileptic discharges, the anticonvulsant medication was reduced by half and serum concentrations of carbamazepine were obtained daily. During this 4-day observation period, the patient had five complex partial seizures. According to clinical symptoms, the origin was suspected in the right frontal lobe, but because of muscular artefacts, not even lateralization of the focus could be obtained from EEG recordings. As interictal EEG showed little specific epileptic activity, diagnostic focus activation using a methohexitol test was carried out, according to a procedure approved by the Local Medical Ethics Committee. The design included simultaneous recordings of 10/20 EEG and bi-hemispheric magnetoencephalography (MEG). MEG is a novel non-invasive technique to assess brain magnetic activity generated by neuronal current sources, with one of its major applications being source localization of specific epileptic discharges. MEG was recorded with a dual sensor, 74-channel biomagnetic system (Magnes II, BTI, San Diego, CA, USA). The test was performed in a magnetically shielded room under supervision of an anaesthetist. Offline MEG analysis included source localization of conspicuous signals, according to the model of a dipole in a homogeneous conducting sphere. The resulting dipole locations were displayed in the corresponding magnetic resonance images (MRI), based on co-registration of MEG and MRI data (Magnetic Source Imaging, MSI). The common spatial reference system originated from fiducial landmarks on the head.

Twenty-four hours before the test, baseline spontaneous
activity was recorded for 10 min. On the day of the test, approximately 90 min before commencement of recordings, the patient was given clonidine 150 µg orally, and an indwelling venous cannula was inserted. The investigation consisted of a 20-min recording period, with administration of methohexital i.v. after the first 10 min. Throughout the test, arterial pressure, heart rate and transcutaneous oxygen saturation were monitored continuously; oxygen was supplied via a face mask. The patient’s heart rate was 55 beat min⁻¹, arterial pressure 100/50 mm Hg and oxygen saturation 100%. After the procedure, the patient was monitored for 3 h in the recovery room.

In spite of the rare occurrence of interictal epileptic discharges during the 4 days of video EEG monitoring, which had led to the decision to perform methohexital spike provocation, baseline recordings showed several spikes. Surprisingly, however, the maximum spike frequency was found in the 10-min recordings before application of methohexital, rather than during anaesthesia. Moreover, during the interval before administration of methohexital, the patient fell asleep, and on recovery had two complex partial seizures of approximately 10 s duration, characterized by spatial confusion and movement of the left hand. Whereas both interictal spikes and the majority of ictal activity yielded dipole locations in the right frontal lobe next to the resection cavity, additional ictal epileptic discharges were found in the left hemispheric recordings. The resulting dipole source represented a mirror image of the suspected site in the contralateral frontal lobe (Fig. 1). An increase in interictal discharges, sleep and occurrence of seizures, and source location indicating a mirror focus occurred during the period when the effect of oral clonidine was likely to be maximal.

Discussion
The barbiturates thiopental and methohexital are used mainly for diagnostic activation of epileptic discharges. It is striking that the majority of reports do not include recommendations for premedication. This is probably because benzodiazepines, most commonly used to relieve anxiety and induce sedation, suppress EEG activity and therefore are unsuitable for the activation test.

In our study, we used clonidine, a centrally acting alpha-2 adrenoceptor agonist, as premedication. Clonidine was introduced into anaesthetic practice for its anxiolytic, analgesic and sedative effects. In our patient, EEG and MEG recordings after administration of clonidine revealed focal epileptic activity, with spreading to the contralateral brain region (mirror focus). The assumption that these epileptic discharges were related to clonidine is based on two considerations: first, increase in specific epileptic activity was recorded approximately 2 h after administration of clonidine, the time of the peak effect of the drug; and second,
clonidine (in common with other alpha-2 adrenoceptor agonists) attenuates central noradrenergic transmission by depletion of norepinephrine in different brain regions, especially in the locus coeruleus. There is considerable evidence that central catecholamines play an important role in the control of convulsions induced either by electric shock or drugs. It has been shown that reduction in brain norepinephrine content decreases seizure thresholds in a variety of experimental procedures. In a recent article, Mirski and colleagues demonstrated a dose-dependent proconvulsant action of the alpha-2 agonist dexmedetomidine in epileptic rats. Although interactions between central norepinephrine disturbances and seizure susceptibility are not fully understood, there is some evidence that norepinephrine may act as an anticonvulsant via augmentation of inhibitory GABA effects.

In our patient, clonidine may have potentiated spontaneous epileptic discharges, a hypothesis supported by several experimental observations in rats. Jando and colleagues reported that clonidine induced spike and wave patterns only in rats with spontaneous high voltage spike and wave spindles. As a possible mechanism, they also discussed brain depletion of norepinephrine after clonidine. Based on these experiments, it may be hypothesized that patients with spontaneous epileptic discharges are more sensitive to clonidine because of pre-existing depletion of norepinephrine in certain brain regions.

In contrast, several studies in experimental animals indicated that the effects of clonidine change according to dose. Some have found an anticonvulsant effect of low-dose clonidine, whereas high doses decreased seizure thresholds. Interestingly, seizures are described as side effects after overdose of clonidine in humans. Moreover, in a double-blind, randomized study comparing clonidine with chlorpromazine in the treatment of alcohol withdrawal, seizures occurred only in the clonidine group. In a recent review on the pharmacological management of alcohol withdrawal, clonidine monotherapy was not recommended because conclusive studies of its effect on seizures and delirium are lacking.

Our patient fell asleep during recordings, an effect most probably related to the action of clonidine. It is well known that sedation or induction of sleep can enhance epileptic discharges; it is used deliberately to localize epileptogenic foci with the aid of barbiturates. Although the mechanism responsible for focus activation during sleep onset is not fully understood, one could speculate that clonidine may have increased epileptic discharges via its sedative properties.

We conclude that clonidine may have played a role in facilitating specific discharges and seizure activity. Further studies are required to elucidate this effect.

References

1. Gumpert J, Paul R. Activation of the electroencephalogram with intravenous Brietal (methohexitone): the findings in 100 cases. J Neurol Neurosurg Psychiatry 1971; 34: 466–8