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Selective serotonin reuptake inhibitors prolong seizures – Preliminary results from an observational study

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ABSTRACT

Objective: Selective serotonin reuptake inhibitors (SSRIs) are often used in the treatment of depressive disorders in patients with epilepsy. Pro- and anti-convulsive effects of SSRIs are discussed controversially. The aim of this study was to investigate a possible impact of SSRIs-treatment on duration of EEG and clinical features in epilepsy patients.
Methods: We studied video-EEG data from 162 patients with focal epilepsies between January 2006 and March 2008 using a case–control study design. Eleven patients with 19 complex focal seizures (CFSs) and 16 secondary generalized tonic-clonic seizures (sGTCSs) treated with SSRIs (SSRIs+) were matched to 13 patients without SSRIs-treatment (SSRIs−). We compared duration of ictal EEG in CFSs and sGTCSs, duration of convulsions in sGTCSs and duration of postictal EEG suppression after sGTCSs in SSRIs+ and SSRIs− patients.
Results: Ictal EEG duration of both, CFSs and sGTCSs, was significantly longer in SSRIs+ patients than in SSRIs− patients ($p = 0.004$ and $p = 0.015$, respectively). No significant difference was found between convulsive phase duration of sGTCSs as well as duration of postictal EEG suppression after sGTCSs in both groups.
Conclusion: Seizures last significantly longer in patients with epilepsy and SSRIs as co-medication. A causative role of SSRIs in ictal activity has to be explored in prospective studies.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs), the newer generation of antidepressants, are widely used in the treatment of depressive and anxiety disorders [1]. Pro-convulsive as well as anti-convulsive properties of SSRIs are still discussed controversially.

Anticonvulsant effects of SSRIs have been demonstrated in animal studies [2] and open clinical trials with fluoxetine in limited samples of patients with unsatisfactory seizure control showed favorable effect of these drugs on seizure activity [3]. Furthermore, SSRIs seem to reduce severity of ictal hypoxemia in patients with focal epilepsies [4]. However, proconvulsive effects of SSRIs have been described in humans, but mainly in overdose [5].

The aim of this study was to investigate a possible impact of a co-existing SSRIs treatment on electrographic and clinical seizure duration in a cohort of patients undergoing presurgical assessment. Therefore we used a case–control design in which we compared the duration of ictal EEG, convulsive phase and duration of postictal EEG suppression in seizures of patients with focal epilepsies with SSRIs (SSRIs+) compared to matched controls without SSRIs-treatment (SSRIs−).

2. Materials and methods

We reviewed 162 consecutive patients with focal epilepsies who were admitted to the video-EEG monitoring unit of the Epilepsy Service and EEG Laboratory at the Medical University Innsbruck, Department of Neurology, Austria, between January 2006 and March 2008 for presurgical or diagnostic procedure. Nineteen complex focal seizures (CFSs) and 16 secondary generalized tonic-clonic

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seizures (sGTCSs) in 11 SSRIs+ patients were detected as case-seizures. Control-seizures (19 CFSs, 16 sGTCSs) of 13 patients were matched to the same seizure type of case-seizures according to sex, age (±5 years), etiology of epilepsy (symptomatic/structural or metabolic; cryptogenic/unknown) and type of recording (surface or intracranial EEG).

We matched seizures of the same seizure type, as seizure duration differs for various seizure types [6] and tolerated therefore different seizure onset regions (frontal, temporal etc.).

Seizures were matched in order of their occurrence during monitoring sessions, e.g. a case-seizure occurring as first recorded seizure during monitoring session was matched to a control-seizure also occurring as first recorded seizure during video-EEG monitoring, a third case-seizure was matched to a control-seizure, which also occurred as third seizure during monitoring and so on. The maximum accepted time difference between seizure occurrences in case–control pairs was 48 h.

Withdrawal of antiepileptic drugs was started in all patients on the first day of monitoring session. We compared duration of ictal EEG in CFSs and sGTCSs (electrographic seizure duration), duration of convulsions in sGTCSs and duration of postictal EEG suppression after sGTCSs in SSRIs+ and SSRIs− patients: Duration of ictal EEG was defined as time between earliest sustained local or regional onset of ictal EEG pattern and the end of ictal discharge. We considered head version or vocalization as onset of generalization in sGTCSs. The duration of convulsive phase was defined as time between onset of generalization and last clonic movement. Postictal suppression of EEG after sGTCSs was calculated as period after the end of ictal discharges with an amplitude below 10 μV by visual analysis. Seizures with duration longer than 5 min were classified as status epilepticus (SE). Compliance with SSRI therapy was based on history and documented during video-EEG monitoring on video.

Nonparametric matched paired statistical analysis was employed (Wilcoxon signed ranks test). All calculations were performed with statistical software SPSS 12.0 (Chicago, IL).

3. Results

Eleven patients treated with SSRIs (7 M, mean age 32.8 ± 10 years) and 13 patients without SSRI treatment during video-EEG monitoring (9 M, mean 32.9 ± 10.1 years) were enrolled in the study. In SSRI+ patients, 8 had symptomatic (structural/metabolic) epilepsies and 3 cryptogenic (unknown etiology) epilepsies. In SSRI− patients, 9 had symptomatic (structural/metabolic) and 4 patients cryptogenic (unknown) etiology. In both groups, one patient underwent invasive recording with an intracranial EEG (SSRIs+: 10 surface EEG, SSRIs−: 12 surface EEG). The final analysis was performed in 35 case–control seizure pairs (19 CFSs and 16 sGTCSs).

For clinical characteristics of case- and control-seizures see Table 1. Ictal EEG of SSRIs+ patients lasted significantly longer (median 132 s, range 27–1850), than in SSRIs− controls (median 85 s; range 22–168; $p < 0.001$, Fig. 1). The SD has still been significantly different even when extreme values from the SSRI+ group were removed. In the SSRI+ group, 12 episodes of SE occurred, but no one in the SSRI− group.

Separate analysis of seizure types also showed significant difference. Thus, ictal EEG of sGTCSs/convulsive SE in SSRIs+ patients

Table 1
Clinical characteristics of 35 case–control seizure pairs.

No. of case–control Sz Pairs	Patient no.	Gender	Age	Etiology	MR-finding	Lobe	Sz type	Type of Rec.	SSRI-treatment	SSRI (dose; mg)
1	1/1	W/W	20/20	C/C	Normal/Normal	T/T	sGTCS/sGTCS	Surface/Surface	+/−	Citalopram (20)/-
2	2/2	M/M	29/34	S/S	Cavernoma/Gliosis	F/MF	CFS/CFS	Surface/Surface	+/−	Paroxetin (20)/-
3	2/2	M/M	29/34	S/S	Cavernoma/Gliosis	F/MF	CFS/CFS	Surface/Surface	+/−	Paroxetin (20)/-
4	2/2	M/M	29/34	S/S	Cavernoma/Gliosis	F/MF	sGTCS/sGTCS	Surface/Surface	+/−	Paroxetin (20)/-
5	2/3	M/M	29/25	S/S	Cavernoma/PMG	F/T	sGTCS/sGTCS	Surface/Surface	+/−	Paroxetin (20)/-
6	2/3	M/M	29/25	S/S	Cavernoma/PMG	F/T	sGTCS/sGTCS	Surface/Surface	+/−	Paroxetin (20)/-
7	3/4	M/M	18/20	S/S	Hamartoma/FCD	Indef./T	CFS/CFS	Surface/Surface	+/−	Sertralin (50)/-
8	3/4	M/M	18/20	S/S	Hamartoma/FCD	Indef./T	CFS/CFS	Surface/Surface	+/−	Sertralin (50)/-
9	3/4	M/M	18/20	S/S	Hamartoma/FCD	Indef./T	CFS/CFS	Surface/Surface	+/−	Sertralin (50)/-
10	3/4	M/M	18/20	S/S	Hamartoma/FCD	Indef./T	CFS/CFS	Surface/Surface	+/−	Sertralin (50)/-
11	3/4	M/M	18/20	S/S	Hamartoma/FCD	Indef./T	CFS/CFS	Surface/Surface	+/−	Sertralin (50)/-
12	4/5	W/W	34/32	S/S	Ulegyria/Heterotopia	MF/Indef.	sGTCS/sGTCS	Surface/Surface	+/−	Citalopram (20)/-
13	4/5	W/W	34/32	S/S	Ulegyria/Heterotopia	MF/Indef.	sGTCS/sGTCS	Surface/Surface	+/−	Citalopram (20)/-
14	4/5	W/W	34/32	S/S	Ulegyria/Heterotopia	MF/Indef.	sGTCS/sGTCS	Surface/Surface	+/−	Citalopram (20)/-
15	5/6	M/M	30/29	S/S	Normal/HS	T/T	sGTCS/sGTCS	Surface/Surface	+/−	Citalopam (20)/-
16	5/6	M/M	30/29	S/S	Normal/HS	T/T	sGTCS/sGTCS	Surface/Surface	+/−	Citalopam (20)/-
17	5/6	M/M	30/29	S/S	Normal/HS	T/T	sGTCS/sGTCS	Surface/Surface	+/−	Citalopam (20)/-
18	6/7	M/M	38/33	S/S	Gliosis/Gliosis	F/F	sGTCS/sGTCS	Surface/Surface	+/−	Sertralin (50)/-
19	7/8	M/M	53/58	S/S	Gliosis/Astrocytoma	F/T	CFS/CFS	Surface/Surface	+/−	Escitalopram (10)/-
20	7/8	M/M	53/58	S/S	Gliosis/Astrocytoma	F/T	CFS/CFS	Surface/Surface	+/−	Escitalopram (10)/-
21	7/8	M/M	53/58	S/S	Gliosis/Astrocytoma	F/T	sGTCS/sGTCS	Surface/Surface	+/−	Escitalopram (10)/-
22	8/9	M/M	25/29	C/C	Normal/Normal	T/T	sGTCS/sGTCS	Surface/Surface	+/−	Escitalopram (10)/-
23	8/9	M/M	25/29	C/C	Normal/Normal	T/T	sGTCS/sGTCS	Surface/Surface	+/−	Escitalopram (10)/-
24	9/10	M/M	41/44	S/S	HS/FCD	T/T	CFS/CFS	Surface/Surface	+/−	Citalopram (10)/-
25	9/10	M/M	41/44	S/S	HS/FCD	T/T	CFS/CFS	Surface/Surface	+/−	Citalopram (10)/-
26	9/10	M/M	41/44	S/S	HS/FCD	T/T	CFS/CFS	Surface/Surface	+/−	Citalopram (10)/-
27	9/10	M/M	41/44	S/S	HS/FCD	T/T	CFS/CFS	Surface/Surface	+/−	Citalopram (10)/-
28	9/10	M/M	41/44	S/S	HS/FCD	T/T	CFS/CFS	Surface/Surface	+/−	Citalopram (10)/-
29	10/11	W/W	38/39	S/S	HS/HS	T/T	CFS/CFS	Surface/Surface	+/−	Escitalopram (10)/-
30	10/11	W/W	38/39	S/S	HS/HS	T/T	CFS/CFS	Surface/Surface	+/−	Escitalopram (10)/-
31	10/11	W/W	38/39	S/S	HS/HS	T/T	CFS/CFS	Surface/Surface	+/−	Escitalopram (10)/-
32	11/12	W/W	35/30	C/C	Normal/Normal	T/T	CFS/CFS	Surface/Surface	+/−	Escitalopram (10)/-
33	11/12	W/W	35/30	C/C	Normal/Normal	T/T	CFS/CFS	Surface/Surface	+/−	Escitalopram (10)/-
34	5/13	M/M	31/35	C/C	Normal/Normal	F/F	sGTCS/sGTCS	Intracr./Intracr.	+/−	Citalopram (10)/-
35	5/13	M/M	31/35	C/C	Normal/Normal	F/F	sGTCS/sGTCS	Intracr./Intracr.	+/−	Citalopram (10)/-

C: cryptogenic; CFS: complex focal seizure; F: frontal; FCD: focal cortical dysplasia; HS: hippocampal scerlosis; Indef.: Indefinable; Intracr.: Intracranial; M: man; MF: multifocal; no.: number; PMG: polymicrogyria; Rec.: Recording; S: symptomatic; sGTCS: secondary generalized tonic clonic seizure; Sz: seizure; T: temporal; W: woman.