Seizure 2003; **12:** 316–318
doi:10.1016/S1059–1311(02)00315-1

SHORT COMMUNICATION

The anticonvulsant effect of citalopram as an indirect evidence of serotonergic impairment in human epileptogenesis

E. FAVALE, D. AUDENINO, L. COCITO & C. ALBANO

Department of Neurological Sciences and Vision, University of Genoa, Genoa, Italy

Correspondence to: Professor Claudio Albano, MD, Dipartimento di Scienze Neurologiche e della Visione dell'Università di Genova, Via Antonio De Toni, 5, I-16132 Genova, Italy. *E-mail*: albano@neurologia.unige.it

Some evidence would indicate that a serotonergic deficit may be involved in epileptogenesis. A preliminary trial of citalopram, a selective inhibitor of serotonin reuptake, was carried out. Citalopram 20 mg/day was given to 11 non-depressed patients with poorly controlled epilepsy as an add on treatment with an open label design for 8–10 months. The median seizure frequency dropped by 55.6% in the whole group, with nine patients improving by at least 50%. No adverse reactions occurred with the exception of mild drowsiness. There were no changes of post-treatment as compared to pre-treatment AED serum concentrations. Although controlled studies are required to confirm the anticonvulsant effect of citalopram, these findings may be regarded as an indirect evidence of serotonergic impairment in human epileptogenesis.

Key words: epileptogenesis; 5-HTP; allopregnanolone.

INTRODUCTION

Some evidence would indicate that a serotonergic deficit may be involved in epileptogenesis. An antiepileptic effect of 5-hydroxy-tryptophane (5-HTP), the precursor of serotonin (5-HT), has been shown in the experimental animal[1], and the plasma level of 5-HTP is lower in epileptics than in controls[2]. Furthermore, fluoxetine, a selective inhibitor of serotonin uptake, showed anticonvulsant effect both in the experimental animal[3] and in man[4].

Fluoxetine however has also other CNS effects, such as an inhibition of central nicotinic ACh receptors[5] and a stimulatory effect on allopregnanolone production[6], which might partly account for its antiepileptic action. Citalopram is more selective than fluoxetine in blocking the serotonin reuptake[7], and we set out to investigate whether also this agent exerts any anticonvulsant efficacy in patients with epilepsy.

METHODS AND PATIENTS

Following informed consent, 11 epileptic patients (nine women and two men, mean age 40.9 years±15.4 SD) with unsatisfactory control of seizures (at least two seizures per month) entered this study. Demographic and clinical details of individual patients are indicated in Table 1. All patients suffered from cryptogenic complex partial seizures, and some had secondary generalisation. Two patients were in monotherapy and nine were in polytherapy. Drug regimen had not been changed for at least 2 months, and serum concentrations of antiepileptic drugs (AEDs) were within the therapeutic range. No patient was clinically depressed (Hamilton Depression Rating Scale score was lower than 10), or had a family history of depression. All patients received citalopram 20 mg in a single daily administration as an add-on therapy for 8–10 months.

1059–1311/03/$35.00

Table 1: Summary of demographic and clinical details of patients.

Subject	Sex	Age	Illness duration (years)	Seizure type	Average monthly seizure frequency		Seizure frequency reduction (%)	Concomitant AED	Plasma levels (mcg/ml)		Duration of treatment (months)
					Before treatment	After treatment			Before therapy	After therapy	
1	M	19	2	Secondary generalised	2	0.75	62.5	Carbamazepine	8.1	7.9	8
2	F	60	35	Partial complex	9	4	55.6	Carbamazepine	4.0	3.9	9
3	F	36	20	Generalized and partial complex	4	2	50	Carbamazepine	4.2	4.5	9
								Phenobarbital	14.5	15.1	
4	F	37	29	Partial complex	60	3	95	Barbexaclone	18.1[a]	17.9[a]	10
								Topiramate	n.a.	n.a.	
5	F	41	30	Partial complex	3	0	100	Phenobarbital	19.1	18.3	9
								Carbamazepine	6.3	6.0	
6	F	29	14	Partial complex	8	4	50	Carbamazepine	5.7	5.8	8
								Topiramate	n.a.	n.a.	
								Phenobarbital	23.6	22.2	
7	M	45	38	Partial complex	60	30	50	Carbamazepine	5.0	5.2	9
								Topiramate	n.a	n.a	
8	F	67	27	Secondary generalised	4	3	25	Phenobarbital	24.1	24.2	8
								Phenytoin	13.8	14.0	
9	F	18	3	Secondary generalised	3	0.6	80	Valproate	60.2	62.2	10
								Barbexaclone	28.5[a]	33.1[a]	
10	F	48	41	Partial complex	60	4	93.3	Phenobarbital	20.1	22.3	9
								Carbamazepine	6.4	6.7	
11	F	50	10	Partial complex	8	4.5	43.7	Valproate	94.8	92.1	10
								Topiramate	n.a.	n.a	

n.a. = not available.
[a] Assessed as plasma levels of phenobarbital.

Clinical chemistry and serum concentrations of concomitant AEDs were assessed just before starting the trial and after 1 month of treatment with citalopram. EEG was recorded before and at least once during the study.

RESULTS

The results are summarised in Table 1. Baseline seizure frequency was the average monthly number of seizures during the 6 months preceding the trial, and post-treatment seizure frequency was the average monthly number of seizures while receiving citalopram. Percent changes of post-treatment frequency with respect to baseline were analysed by descriptive and non-parametric statistics.

During the treatment with citalopram there was a mean reduction of seizure frequency by 64.1% (median reduction = 55.6%). One patient (N. 4) with a history of daily seizures was almost free from seizures for the whole treatment period. On the whole, four patients improved by more than 75%, five patients by at least 50%, two patients by less than 50%. Nine patients experienced mild drowsiness in the first 2–3 days of treatment but no major adverse reactions were reported. No changes of clinical chemistry, AED serum concentrations and EEG were observed in the course of treatment.

DISCUSSION

The results indicate that citalopram may be useful in epileptic patients not only as a treatment for concomitant depression, but also for the amelioration of epilepsy itself. The association between depression and epilepsy has been known since antiquity, and interictal depression occurs at some time in up to two-thirds of patients, especially those with severe and/or frequent seizures[8]. The importance of treating depressive illness in patients with epilepsy has been emphasised, and antidepressants are usually necessary[8]. However, the reported incidence of seizures occurring with antidepressants has ranged from 0.1 to 4%[9]. The higher incidence is often related to higher antidepressant dosages in smaller population samples whereas large scale data sets, for example with imipramine, have shown an incidence of 0.3–0.6%[9]. Tricyclic antidepressants have the highest epileptogenic effect, but a proconvulsant effect has also been reported for trazodone[10,11] and bupropion[12]. The availability of drugs effective on depression with no harmful effect on epilepsy would obviously be of a practical importance. The administration of citalopram as add-on therapy has replicated the results already obtained with fluoxetine, by decreasing the seizure frequency in patients with poorly controlled epilepsy[4]. This effect is unlikely to depend on control of depression or anxiety, because no patient was clinically depressed. Since citalopram is a more selective inhibitor of serotonin reuptake, this result is a further, though indirect, evidence of a serotonergic impairment as a possible mechanism of epilepsy. Although controlled studies are required to validate this hypothesis, the antiepileptic action of both citalopram and fluoxetine would indicate that an anticonvulsant effect can be obtained not only by affecting the GABA and glutamate systems[13], but also by potentiating serotonergic activity.

REFERENCES

1. Scudder, C. L., Karczmar, A. G., Everett, G. M., Gibson, J. E. and Rifkin, M. Brain catecholamines and serotonin levels in various strains and genera of mice and a possible interpretation for the correlation of amine levels with electroshock latency and behaviour. *International Journal of Neuropharmacology* 1966; **5**: 343–351.
2. Lunardi, G., Mainardi, P., Rubino, V. *et al*. Tryptophan and epilepsy. In: *Recent Advances in Tryptophan Research* (Eds G. Allegri Filippini and V. L. Costa). New York and London, Plenum Press, 1995: pp. 101–102.
3. Pasini, A., Tortorella, A. and Gale, K. Anticonvulsant effect of intranigral fluoxetine. *Brain Research* 1992; **593**: 287–290.
4. Favale, E., Rubino, V., Mainardi, P., Lunardi, G. and Albano, C. Anticonvulsant effect of fluoxetine in humans. *Neurology* 1995; **45**: 1926–1927.
5. Garcia-Colunga, J., Awad, J. N. and Miledi, R. Blockage of muscle and neuronal nicotinic acetylcholine receptors by fluoxetine (Prozac). *Proceedings of the National Academy of Sciences of the United States of America* 1997; **94**: 2041–2044.
6. Uzunov, D. P., Cooper, T. B., Costa, E. and Guidotti, A. Fluoxetine-elicited changes in brain neurosteroid content measured by negative ion mass fragmentography. *Proceedings of the National Academy of Sciences of the United States of America* 1996; **93**: 12599–12604.
7. Hyttel, J. Pharmacological characterization of selective serotonin reuptake inhibitors (SSRIs). *International Clinical Psychopharmacology* 1994; **9** (Suppl. 1): 19–26.
8. Lambert, M. V. and Robertson, M. M. Depression in epilepsy: etiology, phenomenology, and treatment. *Epilepsia* 1999; **40** (Suppl. 10): S21–S47.
9. Rosenstein, D. L., Nelson, J. C. and Jacobs, S. C. Seizures associated with antidepressants: a review. *Journal of Clinical Psychiatry* 1993; **54**: 289–299.
10. Lanes, T. and Ravaris, C. L. Prolonged ECT seizure duration in a patient taking trazodone [letter]. *American Journal of Psychiatry* 1993; **150**: 525.
11. Kaufman, K. R. and Kaufman, E. R. Psychotropic management of seizure duration during electroconvulsive therapy: trazodone, a case report. *Irish Journal of Psychological Medicine* 1992; **9**: 50–51.
12. Pesola, G. R. and Avasarala, J. Bupropion seizure proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department. *Journal of Emergency Medicine* 2002; **22**: 235–239.
13. Bradford, H. F. Glutamate, GABA and epilepsy. *Progress in Neurobiology* 1995; **47**: 477–511.