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Short communication

Tiagabine in glial tumors

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Abstract

Rationale and purpose: Preliminary reports have suggested a possible 'aetiology-specific' efficacy of tiagabine (TGB) in patients with drug-resistant partial epilepsy (DRPE) related to cerebral glial tumors (GTs). This efficacy should be related to selective blocking of GAT-1 transporter by TGB. We presented our open-label, add-on TGB experience in a group of patients with GTs, compared with other symptomatic DRPEs of different aetiology. *Material and methods:* eleven patients with DRPE related to oligodendroglioma (six cases), astrocytoma (4) or multiform gliobastoma (1); 12 patients with DRPE related to a miscellanea of CNS lesions. TGB was added to previous AEDs, at dosage of 20–60 mg per die. Responders are defined by seizure frequency reduction $>50\%$ compared with baseline. *Results:* Seven patients are responders with three seizure-free (SF) in GTs group, a rate of efficacy much higher than in matching group (63.6 vs. 16.6%). Adverse events have been observed only rarely, not leading to discontinuation, in GTs group. *Conclusion:* This preliminary observation seems to confirm the high efficacy and tolerability of TGB in DRPE related to GTs.

Keywords: Tiagabine; Drug resistant epilepsy; Cerebral gliomas

1. Introduction

Tiagabine (TGB) is a new antiepileptic drug (AED), acting through the enhancement of GABA-mediated inhibition. In detail, it selectively blocks GAT-1 type of GABA transporter (Borden et al., 1994) thus inhibiting the reuptake of GABA and increasing its cerebral concentration in rodent (Fink-Jensen et al., 1992) and in human (During et al., 1992) synapses. Recent clinical studies showed a long-term efficacy of TGB in about 30% of patients with partial seizures (Loiseau, 1999; Crawford et al., 2001).

One preliminary report has suggested TGB could have a particular efficacy in epilepsy secondary to glial tumors (GTs) of the central nervous system (CNS), likely related to its specific mechanism of action (Dean et al., 1998).

In this paper, we report about the effect of TGB add-on therapy in a group of patients with drug-resistant partial epilepsy (DRPE) related to GTs.

In the attempt to demonstrate a possible 'aetiology-specific' efficacy, the data are matched with a group of symptomatic DRPEs related to a miscellanea of CNS lesions.

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2. Methods

2.1. Population

Eleven patients (6 M, 5 F; age: 10–52 years, mean: 32.5) with DRPE secondary to GTs. Clinical data of this group are summarized in Table 1. Ten patients had been submitted to surgical resection, and seven also to radiation therapy; the specific aetiology, according to WHO criteria (Kleihues et al., 1993), was: oligodendroglioma in six cases, astrocytoma in three, and multiform glioblastoma in one. Another patient, with a MRI diagnosed astrocytoma, was inoperable, because of his tumor location. Among the ten operated patients, resection had been only partial in eight of them. Epilepsy was characterized by simple (SPS) or complex partial (CPS) seizures, with secondary generalization in one case. All patients were resistant to previous therapy, with at least two seizures per month, and more than one seizure per day in five patients, during the 2-month baseline period. Epilepsy duration ranged between 1 and 20 years (mean: 7.36). TGB was added with a slow increasing schedule (5 mg every week) to previous AED regimen, at dosage of 20–60 mg per die, in three daily doses, according to clinical response and tolerability. Associated AEDs were CBZ in eight patients, PB and PHT in four, LTG in two and VGB in one. Eight patients were taking two drugs, with an average of 1.72 AED per patient.

Previous therapy remained unchanged during baseline and add-on phase.

The GTs group was matched with a small group of patients affected from DRPEs related to a miscellanea of lesional aetiologies, treated with open-label TGB add-on, and comparable protocol, in the same period of time. This group was formed by 12 patients (8 M, 4F; age: 23–60 years, mean: 35); the syndromic diagnosis was temporal lobe epilepsy in nine, and frontal (FLE), parietal and occipital lobe epilepsy in the other three patients. The specific underlying aetiology was: hyppocampal sclerosis in five, perinatal injury in three, cortical dysplasia (CD) in two, post-surgical malacia in one, and Rasmussen encephalitis (previously treated with subtotal callosotomy, too) in another one. Epilepsy was of long-duration (3–40 years, mean: 21.5) and severe in all of them, with at least five seizure per month, and more than 1 per day in three cases; associated treatment was 1–3 AEDs (mean: 1.91 per patient): CBZ in six, OXC in four, LTG and CLB in three, PB and VPA in two, PHT, TPM and FLB in one. Patients are considered reponders if the frequency of seizures decreased, in a follow-up period at least of 1 year, more than 50% of baseline, without intolerable adverse effects (AEs).

3. Results

3.1. GTs group

Seven patients (63.6%) are responders, with three (27.2%) seizure-free (SF), without difference by seizure type. Tolerability of TGB was good in all but two patients; referred AEs were nausea in one case, not leading to drop-out, and tiredness in another, not-responder, patient.

Patient 8 shifted her CPS in very frequent SPS, with disagreeable epigastric aura, so leading to drop-out. No relevant changes in plasma concentration of concomitant AEDs was noticed during add-on of TGB.

3.2. Matching group

Two patients (16.6%) are responders, without SF cases. One patient, with FLE, and another with CD, dropped-out during titration phase, due to worsening of seizure frequency and severity; another patient dropped-out, because of appearance of myoclonus. Furthermore, minor AEs (asthenia, dizziness) were reported in two non-responders patients.

4. Discussion

Value of this clinical observation is limited and it should be interpreted with criticism. The sample of patients is small, and possible confusion can be related to the natural evolution of disease. In addition, this open-label add-on treatment can

Table 1
Clinical data of GTs group

Patient	Sex, years	Kind of tumor and localization	Surgical resection (year)	Radio-therapy	Seizure type	Frequency	Add-on AEDs	TGB max dose (mg per die)	Outcome
1	M,20	Left temporal astrocytoma (low grade)	Partial (1995)	Yes	CPS, SPS	~10 per month	[GVG,PB] CBZ	60	Responder[a]
2	M,33	Left frontal oligodendroglioma (relapse)	Partial (1991)	Yes	CPS	>1 per day	[PHT] CBZ+LTG	45	Responder
3	M,36	Right frontal oligodendroglioma (low grade)	Partial (1998)	Yes	SPS	~2 per month	PB+PHT	30	Responder
4	M,49	Right frontal multiform glioblastoma	Partial (1999)	Yes	SPS, GTCS	~10 per month	PB+PHT	30	Not responder
5	M,29	Right parietal oligodendroglioma	Partial (1997)	Yes	SPS	>1 per day	CBZ	30	Responder
6	F,20	Left temporal pilocityc astrocytoma	Partial (1989)	Yes	CPS	>1 per day	CBZ+PB	45	SF
7	M,33	Left occipital oligodendroglioma	Total (1981)	No	CPS	>1 per day	[PB] CBZ+GVG	30	Not responder[a]
8	F,45	Left temporal oligodendroglioma	Partial (1996)	No	CPS	~10 per month	CBZ+LTG	30	Not responder[b]
9	M,52	Right rolandic astrocytoma	No	No	SPS	>1 per day	[CNP] PHT+PB	30	SF
10	F,31	Right temporal oligodendroglioma	Total (1989)	No	CPS	~2 per month	[PB,GPT] CBZ	30	SF
11	F,10	Left frontal astrocytoma (relapse)	Partial (1999)	Yes	CPS	~15 per month	PB+CBZ	20	Not responder

[], previous, discontinued AEDs; SPS, simple partial seizure; CPS, complex partial seizures; GTCS, secondarily generalized tonic clonic seizures; SF, seizure-free.
[a] Adverse effects.
[b] Appearance of SPS.

not be reasonably compared with double blind, randomized, placebo-controlled, fixed drug regulatory trials.

In the attempt to evidence a possible aetiology-specific efficacy, we matched the GTs group with a group of very severe epilepsy related to a variety of lesional aetiologies. However, also this comparison must be interpreted cautiously. Age of patients, type and frequency of seizures, number and type of associated AEDs are similar in both groups, but duration of epilepsy is much longer in the control than in GTs group (21.5 vs. 7.36 years). Therefore, the long duration of epilepsy could justify the very low rate of responders in the matching group.

However, despite these limitations, TGB seems to be very effective in DRPE related to cerebral GTs: about 2/3 of our patients are responders, with higher rate of efficacy compared with Literature data (Loiseau, 1999; Crawford et al., 2001); in addition, tolerability is generally good.

However, the hypothesis of a relatively specific, aetiology-related, efficacy of TGB in DRPE due to GTs should be confirmed in larger, policentric, double blind trials.

Possible role of TGB in GTs could be related to interaction of underlying pathology with its specific mechanism of action. TBG acts through the inhibition of GABA reuptake, thus increasing its concentration in brain (Fink-Jensen et al., 1992; During et al., 1992). GABA reuptake is realized by at least four different transporters (Borden, 1996; Roettger and Amara, 1999); TGB blocks mostly GAT-1, and, in a lesser extent, GAT-3 (Borden et al., 1994). In the rat, GAT-1 is predominantly localized to GABAergic neural terminals, but, at least in some cerebral regions, it is found additionally or exclusively in glia (Minelli et al., 1995); therefore, higher efficacy in GTs could simply be related to particular plenty of GAT-1 in neoplastic tissue derived from cells of glial line. However, the specific mechanism leading to epileptic seizures in patients with GTs is still debated. In particular, is not clear whether the tumor transforms the normal surrounding brain tissue into an epileptic structure, thus inducing the seizures, or if neoplastic tissue itself contains epileptogenic cells. Recent in vitro studies showed that brain slices obtained from human surgical material from oligodendroglioma can generate action potentials, so making as electrically excitable cells, at least in first days of its growth.

In other words, cells derived from glial line could transitorily acquire neuronal properties, and serving as epileptogenic substrate (Kettenmann, 1999). Obviously, data from a clinical trial are not enough to give sufficient answers in favor of an ipothesis or the other one; in vitro studies on neoplastic tissue, e.g. with patch-clamp technique, could probably offer more precise informations about TGB mechanism of action in these cell population.

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