Vigabatrin

A. Guberman

ABSTRACT: Vigabatrin (VGB) is a recently-released antiepileptic drug which works by a clearly-defined mechanism of action: inhibition of GABA transaminase leading to an elevation of brain GABA concentration. It has been proven effective, mainly as an add-on agent, in complex partial and secondarily generalized seizures in both adults and children as well as in infantile spasms in both short and long-term controlled studies. World-wide experience now includes over 150,000 patients exposed to the drug. VGB has a favorable pharmacokinetic profile since it has little protein-binding, is mainly excreted unchanged by the kidney and has a long effective half-life allowing once or twice daily dosing. It is generally well-tolerated with very few cognitive effects but may cause significant behavioral side effects such as agitation, irritability, depression or psychosis in approximately 2-4% of cases. Mild weight gain and possible exacerbation of absence and myoclonic seizures are other reported adverse effects. The role of VGB in other childhood epileptic syndromes apart from West syndrome is still being defined.

RÉSUMÉ: Le vigabatrin. Le vigabatrin (VGB) est un antiépileptique récent sur le marché, dont le mode d'action est clairement défini: il inhibe la GABA transaminase, ce qui donne lieu à une élévation de la concentration du GABA dans le cerveau. Son efficacité a été prouvée dans des études contrôlées de courte et de longue durée, principalement comme traitement d'appoint dans les crises partielles complexes et les crises secondairement généralisées, tant chez les adultes que chez les enfants, ainsi que dans le spasme infantile. 150,000 patients à travers le monde ont été exposés à ce médicament. Le VGB a un profil pharmacocinétique favorable puisqu'il se lie peu aux protéines, qu'il est excrété par le rein sans être modifié et qu'il a une longue demi-vie efficace permettant une administration une ou deux fois par jour. Il est généralement bien toléré, avec peu d'effets cognitifs, mais il peut causer des effets secondaires importants sur le comportement comme de l'agitation, de l'irritabilité, de la dépression ou une psychose dans à peu près 2 à 4% des cas. On a également rapporté une légère prise de poids et une exacerbation possible des absences et des crises myocloniques. Le rôle du VGB dans les syndromes épileptiques de l'enfance autres que le syndrome de West est en voie d'être défini.

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Mechanism of Action and Pre-clinical Studies

Several lines of evidence, both experimental and clinical, have implicated GABA, the main inhibitory neurotransmitter in the brain, as playing an important role in epilepsy.[1,2,3,4] Both clinically and experimentally, drugs which interfere with GABA action such as bicuculline and INH can induce seizures and status epilepticus and drugs which are GABAergic or enhance the action of GABA are generally antiepileptic. The GABA receptor complex has been well characterized and divided into $GABA_A$ and $GABA_B$ types, the former gating chloride channels and the latter associated with K^+ as well as Ca^{++} channels by G-protein coupling. $GABA_B$ receptors are located both pre- and post-synaptically. The receptor has a pentomeric structure with each subunit drawn from a family of subunits: alpha, beta, gamma, delta and rho and up to 16 subtypes within these families have now been sequenced and cloned.[5,6] This permits an extensive number of receptor types with regional variations in the brain. There are benzodiazepine binding sites which have been associated with the alpha and gamma subunits and additional binding sites for barbiturates, picrotoxin and neurosteroids. Some of these substances act through allosteric modification of the receptor to influence GABA binding and can increase the frequency of Cl^- channel opening (benzodiazepines) or prolong channel openings (barbiturates) thereby enhancing the hyperpolarizing/inhibitory action of GABA.

Strategies to augment the action of GABA have included: a GABA prodrug (progabide) which readily crosses the blood-brain barrier, increasing GABA synthesis (?valproate), direct stimulation of the GABA receptor (THIP), decreasing pre-synaptic and glial re-uptake of GABA (tiagabine), allosteric modifications of the GABA receptor (benzodiazepines, barbiturates) and inhibition of the GABA transaminase (GABA-T) enzyme which breaks down GABA to succinic semialdehyde.

From the Division of Neurology, Ottawa General Hospital, Ottawa.
Reprint requests to: A. Guberman, Division of Neurology, Ottawa General Hospital, 501 Smyth Rd, Ottawa, ON K1H 8L6

Among the new antiepileptic drugs, vigabatrin (VGB) is the best example of a "designer" drug with a well-defined mechanism of action. VGB was synthesized in 1973 as a GABA analogue (gamma-vinyl GABA, Figure) which serves as a "suicidal" or irreversible substrate for GABA-T. Once it binds to GABA-T, new enzyme must be resynthesized which takes approximately 5 days. Inhibition of GABA-T results in a 200-300% elevation of CNS GABA concentration which is also reflected in elevated CSF concentrations and includes GABA in the synaptic pool.[7,8] Cerebrospinal fluid GABA concentrations have also been measured in patients receiving VGB in an attempt to monitor therapeutic efficacy biochemically. Studies have demonstrated a dose-dependent two-to-threefold rise in CSF total GABA, free GABA and homocarnosine (GABA + histidine) levels without significant alterations in other neurotransmitters, amino acids or peptides.[7,9,10] Some studies have shown a correlation between the GABA levels and therapeutic response.[11,12,13] GABA-T activity can also be measured in platelets and is found to be depressed in patients receiving VGB. In a study of 16 epileptic children receiving VGB 56-88 mg/kg/d, there was a poor correlation between VGB dose and trough serum levels and no correlation between serum levels or the degree of platelet GABA-T inhibition and seizure response.[14] Recently (^{1}H) MR spectroscopy has been used to measure brain GABA, glutamate and glutamine concentrations in 7 control patients without epilepsy, 5 epilepsy patients not on VGB and in 8 epileptic patients on VGB (3-6 g/d).[15] There was a significantly higher brain concentration of GABA and lower concentration of glutamate in the group receiving VGB compared to the other two groups. The best responding patient had the highest brain GABA levels. The reduced glutamate is likely a secondary consequence of elevated GABA levels which depress glutamine synthetase activity. The possibility of biochemical monitoring of drug therapy is an attractive one and remains a strong theoretical possibility with VGB but its usefulness remains to be demonstrated. Patients' responses to VGB may depend more on the underlying pathophysiology of their epilepsy than on the reduction of GABA-T activity or GABA levels achieved. Also, the elevated GABA is in both metabolic and vesicular pools and it is only the latter which relates directly to enhanced neuronal inhibition. The preclinical profile of VGB in various models has shown efficacy in a wide variety of rodents, picrotoxin induced seizures in mice, amygdala kindled seizures, strychnine and bicuculline-induced seizures, photosensitive seizures in baboons, pilocarpine-induced status epilepticus but not in pentylenetetrazol-induced seizures.[7,16]

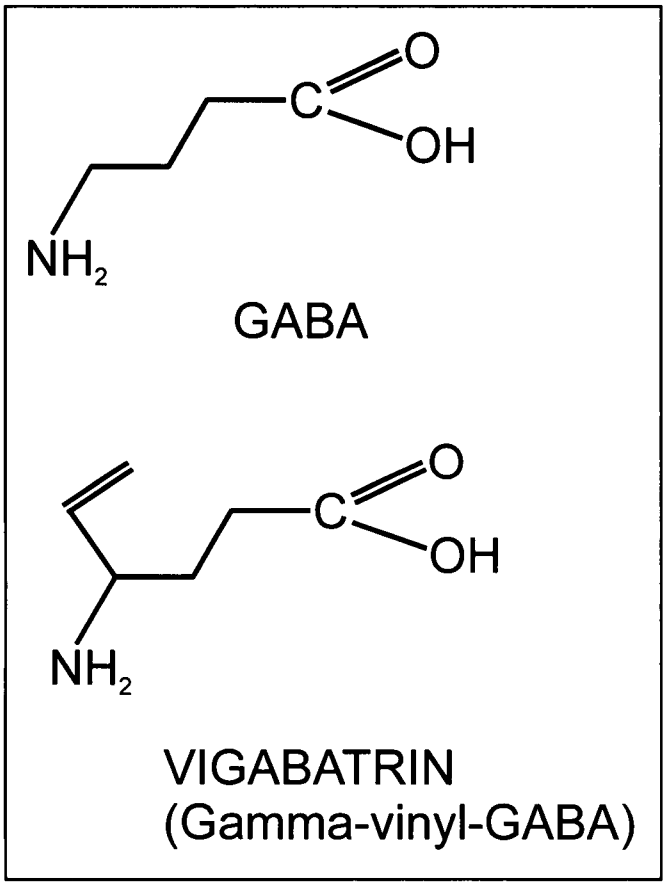

Figure 1: Structure of vigabatrin (gamma-vinyl GABA) compared to GABA

Although VGB was tested extensively shortly following its synthesis, human studies were temporarily interrupted in the U.S. due to the discovery of intramyelinic edema in rodents and dogs, but not primates, exposed to high doses of the drug over prolonged periods. This edema has been extensively studied.[16,17] It occurs particularly in the hippocampus, cerebellar white matter, visual pathways and columns of the fornix and does not appear to affect the behavior of the animal. Ultrastructurally, it produces vacuoles which split the myelin sheath at the interperiod line. It is readily detected by MRI imaging and also causes increased latency of somatosensory and visual evoked potentials. It is reversible upon discontinuation of the drug but may leave an astrocytosis. Extensive MRI, evoked potential and neuropsychological testing in humans, in some cases over several years, as well as neuropathological studies have failed to show evidence for this complication.[18,19]

A histological study of the cerebral cortex in 5 patients (who had received vigabatrin 3-4 g/d for 3-5.5 years (4 temporal lobectomy specimens and 1 autopsy) failed to show any evidence of microvacuolation.[20] Interestingly, because of the awareness of this particular neurotoxic effect in subprimates, the potential neurotoxic effects of vigabatrin in humans have been more thoroughly studied than for any other of the new antiepileptic drugs.

Pharmacokinetics

Vigabatrin has a very favorable pharmacokinetic profile with rapid and fairly high absorption, almost no protein binding and no enzyme induction (Table). Since it is largely excreted unchanged by the kidney, corrections must be made for decreases in creatinine clearance. Its short elimination half-life is not relevant to its duration of action which would be predicted to be around five days, the time necessary for re-synthesis of brain GABA-T. It has been observed, however, that sudden discontinuation of the drug, can lead to a rebound in seizures occurring within a short space of time, an unexplained effect. Single daily doses have been shown to be effective.[21]

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Table: Vigabatrin: Pharmacokinetics

Absorption	60-80%, Tmax 0.5-2 hr, linear and unaffected by food
Apparent volume of distribution	0.8 L/kg
Plasma T 1/2	5-7 hr
Protein binding	Negligible
Metabolism	0
Hepatic enzyme induction	0
Elimination	Renal 70%, first-order kinetics
Pharmacodynamic activity	5-7 days
Drug interactions	Minimal: reduces [PHT] 20%
Serum levels	Not related to efficacy

Efficacy

Over 22 controlled, single or double-blinded studies, as well as numerous open long-term studies, have now been reported from Europe and North America.[22-34] It is remarkable that the response rates (≥50% seizure reduction) are relatively uniform, about 50%, for add-on therapy in intractable adult partial epilepsy. Approximately 7% of such patients achieve a seizure-free status.[16] Vigabatrin has not been well studied in primary generalized epilepsies but does not appear to be particularly effective and may exacerbate absence attacks. Pediatric uncontrolled studies have shown only modest efficacy in the Lennox-Gastaut syndrome and a tendency to exacerbate myoclonic seizures or cause status epilepticus in some childhood cases.[35-38] Partial seizures, however, have shown response rates similar to those obtained in adults.[39,40,41] Remarkable responses have been achieved in West syndrome with a greater than 50% reduction of infantile spasms in 50-100% of patients in most studies. Chiron et al,[42] Appelton[37] and others have been able to achieve complete long-term resolution of spasms in 55-65% of patients with even higher responses in symptomatic West syndrome, especially when due to tuberous sclerosis. Vigabatrin has been successfully used as monotherapy in West syndrome and responses are usually obtained within 5 or 6 days. Vigabatrin offers an alternative choice to ACTH or valproic acid for this condition, although long-term adverse effects have not yet been well studied and controlled comparative studies have not been reported.

A recent placebo-controlled, double-blind, multicentre Canadian dose-ranging study of vigabatrin as an add-on agent in adult partial epilepsy with doses up to 4 gm per day and one year open follow-up has been reported.[43,44] Vigabatrin serum levels, MRI scans, visual and somatosensory evoked potentials and extensive mood and cognitive testing were performed. The initial double-blind study involved a 36-week treatment phase following a 12-week baseline. The intent-to-treat population included 53 patients on placebo and 58 on vigabatrin, 85% of whom were titrated up to 4 gm/d. Complex partial and secondarily generalized tonic-clonic seizures were reduced by 53%, significantly (p=0.001) greater than in the placebo group. However, secondarily generalized seizures, although reduced by 33%, were not statistically different from the reduction in the placebo group. Nine percent of patients on VGB were seizure-free compared to 4% in the placebo group. In the continuation study, only responders (≥50%) were allowed to continue after 14 weeks. By the end of the study (52 weeks) 57.7% of the 97 intent-to-treat patients had achieved a ≥50% seizure reduction, 11.3% were seizure-free and responders in the double-blind study maintained their response.

Some authors have suggested that tolerance may be seen with the drug in that up to 20% of patients may lose their response in the long-term.[30] However, several long-term studies have suggested that response is largely maintained over follow-up periods as long as 6 years.[34]

The question of whether VGB is effective in monotherapy is still being studied but some data are now available. Kalviainen et al have compared VGB monotherapy with carbamazepine in newly diagnosed mostly partial adult epilepsy in an open study.[45] There were 50 patients in each group and the mean daily doses were 50 mg/kg for vigabatrin and a dose of carbamazepine which would provide a plasma level of 35 micromol/L. After 1 year, 32% of patients in the VGB group vs 52% in the CBZ group were seizure-free. Twenty-eight percent in the VGB group and 8% in the CBZ group had acceptable seizure control. Lack of efficacy was seen in 28% of the VGB patients vs 8% on CBZ. However 28% of the CBZ group had to discontinue the drug due to side effects (15% due to skin rash) and none in the VGB group. These data suggest that VGB would be useful in monotherapy. Other controlled blinded comparative monotherapy trials are presently under way in Europe and the U.S. Tanganelli and Regestra obtained very similar results in 51 adult patients in comparing VGB 3.5g vs CBZ 1.4 g in a monotherapy trial.[46]

Adverse Effects

In virtually all studies, VGB has been remarkably well tolerated. Allergic reactions are exceedingly rare. One case of possible allergic vasculitis has been reported.[47] Dose-related neurotoxicity in the form of somnolence (sustained in up to 20%), ataxia or headache as well as moderate weight gain are the most frequent adverse events.[32,41] In the Canadian study, 12% had a weight increase vs 2% in the placebo group but the mean weight gain was only 2 kg on a dose of 4 g/d (vs 0.3 kg on placebo). However by the end of the 52 week open label continuation study, there was a mean overall weight gain of 3.7 kg.[43,44] Worsening of seizures (especially myoclonic) and possibly status epilepticus have been mentioned previously as occasional adverse effects.

The cognitive effects of VGB have been studied extensively in view of the myelin changes seen in pre-clinical studies. In a small group of patients (n=15) receiving 2 g/d as an add-on for 4 weeks, no adverse effects were seen on cognitive function or mood and there was a suggestion of increased performance on an arithmetic test.[48] In a larger (n=45) blinded add-on study, an extensive neuropsychological test battery was administered.[33] Scores on a dominant hand tapping motor task and on a visual memory task were lower in the VGB group but there were no mood differences detected. In the Canadian study, a battery of neuropsychological tests was employed with no demonstrated effect of VGB on cognitive function. However, some subscores on the mood tests tended to favor the placebo group over the VGB group.[43] Mood or cognitive impairment has generally not been found in other studies.[49,50] Patients on VGB monotherapy performed better than patients on carbamazepine when compared to baseline in four subtests of cognitive, memory and motor function.[34]

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Behavioral or psychiatric side effects of VGB have been observed although their relationship to elevation of brain GABA is unclear. Two to four percent of patients in some large studies were discontinued due to severe depression, an acute psychotic reaction or other behavioral disturbances such as agitation.[43,44,51] The cases of psychosis/psychotic depression must be viewed in the context of a baseline incidence of behavioral disturbances and psychosis in any population of severe epileptic patients. Sander, Hart and Trimble published a series of 14 cases of schizophreniform psychosis (9 patients) or delirium occurring in 210 patients on VGB for intractable epilepsy.[52] Five patients had experienced previous psychotic episodes. The psychosis appeared between 5 days and 32 weeks after initiation of VGB treatment and 10/14 cases began within 6 weeks. The dose range was 0.5-4.0 g/d except for one case following an overdose of 12 g. Four cases fit the pattern of an alternating psychosis and in another 4 there was an initial complete response of seizures followed by a flurry of seizures and transient psychosis/delirium. Postmarketing surveys in Europe and elsewhere have shown incidences of around 1%, likely related to the fact that less severe epileptic patients were involved.

In the Canadian double-blind study,[43] there were 5/58 discontinuations in the VGB group for behavioral reasons. Two were due to psychotic depression but only one definitely related to the drug. Another case was labelled "schizophrenia" and felt not to be related to the drug. The other 2 cases involved agitation, headache and insomnia and were assessed as possibly or probably related to VGB. None of the four discontinuations in the placebo group involved psychosis or depression although severe agitation was seen in one patient. In the open continuation study (n=97),[44] twelve patients had to be discontinued, all for neurological or psychiatric symptoms, 8 of whom had previously been in the placebo group. Two had psychosis/delirium and one suicidal depression felt to be related to VGB. One other patient had confusion/delirium and 2 had aggressive reactions felt to be due to other causes. In all cases, the psychiatric symptomatology has been reversible with discontinuation of the drug. Although few dispute the increased incidence of severe behavioral toxicity on VGB (2-4%), the role of CNS GABA elevation, possible secondary effects on serotonin metabolism and "forced normalization" remains to be clarified. Some of these patients have had a history of previous psychotic or depressive episodes and in such patients, VGB should be used only with caution. It is clear however that severe behavioral reactions may appear abruptly in patients without a past psychiatric history,[52,53] with low initial doses and slow titration[53] and sometimes after several months of treatment.[52] Patients starting on the drug should be forewarned to report any insomnia, agitation, confusion, irritability or changes in mood or thinking.

Some data concerning safety of VGB in pregnancy are now available from European post-marketing surveillance.[54] Of the 97 pregnancies with VGB exposure reported to May, 1995, 70 resulted in a normal baby. There were 15 abortions, 9 of which were spontaneous. A variety of malformations were seen in 12 offspring, with no particular pattern and all of the mothers were receiving polytherapy making the relationship to VGB difficult to assess. These included Siamese twins (1), underdeveloped left cerebral hemisphere (1), bilateral cleft palate (1), VSD (1) and spina bifida plus microcephaly (1). At present, no firm conclusion can be drawn concerning the teratogenicity of VGB.

Conclusion

Vigabatrin is a potent antiepileptic drug with a well-delineated mechanism of action and with proven efficacy in partial seizures and in infantile spasms. Its place in other childhood epilepsies such as the Lennox-Gastaut syndrome remains to be defined. It is generally very well tolerated, has a favorable pharmacokinetic profile and does not have significant interactions with other drugs. Doses of 3 g/d in adults and 80 mg/kg/d in children seem optimal and once daily dosing appears effective. The most noteworthy adverse effects are behavioral toxicity with severe depression or psychosis in about 2-4% of cases and a tendency to exacerbate absence and myoclonic seizures. Preliminary monotherapy data have been positive.

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