A Risk-Benefit Assessment of Vigabatrin in the Treatment of Neurological Disorders

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Summary

Vigabatrin was designed to increase the levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) in the brain. It does this by replacing GABA as a substrate for the action of the catabolic enzyme GABA-transaminase. As a result of this inhibition, neuronal GABA levels are elevated, resulting in enhanced endogenous GABA transmission.

A number of clinical trials assessing the effect of vigabatrin in epilepsy have been completed. Vigabatrin is of proven benefit in partial seizures and secondarily generalised tonic clonic seizures, and it is licensed for use as adjunctive therapy in these conditions in several European countries. It has been shown to be effective in some epilepsy syndromes in children including West’s syndrome, infantile spasms and cryptogenic partial seizures. Its effect on primary generalised tonic clonic seizures is variable, while there is considerable evidence that it has a deleterious effect on myoclonic and absence seizures. There have been a few reports of the benefits of vigabatrin in other neurological disorders including tardive dyskinesia, degenerative ataxias and GABA metabolism disorders.

The adverse effects associated with vigabatrin are similar to those seen with other anticonvul-
sants, with a predominance of CNS effects including somnolence, fatigue, irritability, dizziness and headache. Psychiatric symptoms including depression and psychosis are seen in a small number of patients and cause the most problems. These often necessitate discontinuation of vigabatrin, which usually results in resolution of symptoms.

1. Pharmacology
1.1 Pharmacokinetics

Vigabatrin (γ-vinyl GABA) is a structural analogue of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the CNS. Vigabatrin is administered in the racemic form and exists as S(+) and R(−) enantiomers, of which only the S-form is pharmacologically active (Haegele et al. 1983; Schechter 1989). The R-enantiomer does not interfere with the S-form and does not undergo chiral inversion in vivo. Absorption of vigabatrin is rapid and complete after oral administration, and time to peak plasma concentrations is between 1 to 3 hours (Schechter 1989). There is no evidence that food delays drug absorption (Frisk-Holmberg et al. 1989). The peak plasma concentration of the active S-enantiomer is twice that of the inactive R-enantiomer (Haegele & Schechter 1986). The volume of distribution of vigabatrin is approximately 0.8 L/kg and it has negligible protein binding (Schechter 1989).

The concentrations of vigabatrin in the plasma and cerebrospinal fluid correlate poorly with its clinical effect because of its irreversible effect on GABA-transaminase (GABA-T). Plasma concentrations follow a bi-exponential decay in healthy volunteers, with an elimination half-life of 7 hours (Frisk-Holmberg et al. 1989). The renal clearance of both enantiomers is approximately 1.3 ml/min/kg, and about 60% of a single oral dose is excreted in the urine within 24 hours (Schechter 1989). After a single oral dose of 1.5g, about 50% of the S-enantiomer and 65% of the R-enantiomer are recovered from the urine (Haegele & Schechter 1986). The half-life of vigabatrin ranges between 5 and 11 hours and is similar for both enantiomers. The half-life can be prolonged in the elderly with age-related impairment of renal function (Mumford 1988). Despite its short plasma half-life, the irreversible inhibition of GABA-T results in a relatively long duration of action, and CSF GABA levels can remain elevated for as long as 120 hours after a single oral dose (Gram et al. 1989).

1.2 Pharmacodynamics

Vigabatrin was specifically designed to elevate the levels of neuronal GABA by inhibiting its catabolism by GABA-T. Vigabatrin replaces GABA as the substrate for enzymatic inactivation by GABA-T, and produces an intermediate which binds covalently to the active site, consuming both enzyme and inhibitor in an irreversible reaction (Lippert et al. 1977). Though vigabatrin is administered in the racemic form, only the S-enantiomer of vigabatrin is pharmacologically active.

Animal studies have shown that vigabatrin inhibits GABA-T activity in a concentration-dependent manner. The IC_{50} (concentrations of vigabatrin which reduce enzyme activity by 50%) was 145 μmol/L, and the S-enantiomer was responsible for this effect (Gram et al. 1989). The effect of vigabatrin on GABA-T is rapid and follows pseudo-first order kinetics. Vigabatrin has been shown to increase free and total CSF GABA levels by 2- to 4-fold when administered to patients in doses between 1 and 3 g/day (Ben-Menachem et al. 1989). When vigabatrin is withdrawn from neuronal cultures, GABA-T activity returns to pretreatment levels in 4 to 6 days - this is the time taken to synthesise new enzyme (Gram et al. 1989).

Vigabatrin is very specific in its effect on GABA-T, and apart from a minor inhibitory effect on hepatic ALT (SGPT), there is no evidence it inhibits any other enzyme (Lippert et al. 1979). The inhibition of ALT is seen at IC_{50} concentrations of 10 000 μmol/L. Vigabatrin has not been shown to affect any of the other neurotransmitters apart from an effect on the excitatory neurotransmitter, glycine. Glycine levels were significantly elevated in