Clinical pharmacology of vigabatrin

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1 Upon oral administration vigabatrin is rapidly absorbed. Plasma elimination half-life ranges between 5 and 7 h in normal volunteers. Vigabatrin is eliminated primarily via the kidneys with about 65% of the administered dose found unchanged in the urine within 24 h. Kinetics are dose-linear within the range of usual therapeutic doses.

2 At therapeutic doses in man vigabatrin produces dose-related increases in CSF concentrations of free and total GABA, homocarnosine (the GABA-histidine dipeptide) and β -alanine. These biochemical changes are consistent with an inhibition of GABA-transaminase activity in brain.

3 Thus, with systemic availability upon oral administration and biochemical activity in the CNS, the prerequisites for potential uses of vigabatrin in neurological disorders have been demonstrated in clinical pharmacological studies.

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Introduction

Vigabatrin (γ -vinyl GABA; ($\pm$)-4-amino-hex-5-enoic acid) is an enzyme-activated irreversible inhibitor of GABA-transaminase (GABA-T) (Lippert *et al.*, 1977), the enzyme responsible for the degradation of the neurotransmitter, GABA. It is the most selective inhibitor of this enzyme available. Vigabatrin administration to rodents produces dose-dependent inhibition of brain GABA-T activities and corresponding increases in brain GABA concentrations (Jung *et al.*, 1977; Schechter *et al.*, 1977). Although low levels of GABA have been found outside the central nervous system, notably in kidney, liver, heart, pancreas and adrenal glands, it is clear that the major physiological function of GABA is as an inhibitory neurotransmitter in brain. It follows then that an inhibitor of GABA catabolism would be expected to have its major effects on CNS function and that a therapeutic target for vigabatrin would be found among those conditions characterized by neurological abnormalities. Therapeutic usefulness of vigabatrin would

depend firstly, on its systemic availability and secondly, on its ability to have the desired biochemical action on the target tissue in man. Thus, clinical pharmacological studies with vigabatrin were designed to address these two prerequisites.

Pharmacokinetics

Following oral administration of vigabatrin to normal volunteers, it is rapidly absorbed with peak plasma concentrations reached within the first 2 h (Figure 1). Thereafter, plasma concentrations decline with a mean terminal half-life between 5 and 7 h. Drug is still detectable in plasma 24 h after a single dose. Areas under the plasma concentration-time curves indicate that kinetics are dose-linear between 1 and 3 g doses. The apparent volume of distribution of vigabatrin is about 0.8 l kg^{-1} and total clearance is $1.7 \text{ ml min}^{-1} \text{ kg}^{-1}$ with renal clearance accounting for

Figure 1 Plasma concentration (means $\pm$ s.d.; $n = 10$) of vigabatrin as a function of time after oral administration of single doses of 1 g (▲), 2 g (■) or 3 g (●) to normal volunteers.

60–70% of this. Urinary excretion within the first 24 h represents 62–68% of administered vigabatrin as unchanged drug.

Enzyme-catalyzed reactions usually exhibit substrate stereospecificity. As an enzyme-activated inhibitor of GABA-T, vigabatrin must substitute for the natural substrate, GABA, for access to the enzyme-active site. Only the S(+)-enantiomer of the racemic vigabatrin exhibits the necessary steric properties and has been shown to be biochemically and pharmacologically active (Danzin & Jung, 1984; Meldrum & Murugaiah, 1983; Larsson *et al.*, 1986). The development of a stereospecific assay procedure for the enantiomers of vigabatrin in body fluids allowed the determination of their individual kinetics following vigabatrin administration to healthy volunteers (Haegle *et al.*, 1983).

At peak the plasma concentration of the R(–)-enantiomer was found to be approximately twice that of the S(+)-enantiomer, with the terminal elimination half-lives being equivalent for the two enantiomers (Haegle & Schechter, 1986). This resulted in a significantly greater area under the plasma concentration-time curve for the R(–)-enantiomer. Renal clearance of the two enantiomers was equivalent but 49% of the S(+)-enantiomer vs 65% of the R(–)-enantiomer was recovered unchanged in the urine. Comparison of the kinetics of the S(+)-enantiomer, administered either as such or as vigabatrin, demonstrated that concomitantly administered R(–)-enantiomer does not influence its kinetics.

Biochemical effects of vigabatrin on the central nervous system

As the target enzyme for vigabatrin is within the CNS and as vigabatrin acts as an irreversible inhibitor of this enzyme, blood concentrations of drug are unlikely to reflect its biochemical activity. Assuming the $t_{1/2}$ of GABA-T to be considerably longer than that of vigabatrin, then the duration of pharmacologic effect will be governed by the resynthesis rate of enzyme rather than the $t_{1/2}$ of the drug. In addition, based on its proposed mechanism of action, 1 mol of vigabatrin reacting with the active-site of 1 mol of enzyme should permanently inhibit the enzyme's activity and, once this has occurred, additional molecules of vigabatrin would not be expected to influence further the enzyme.

The most direct approach to assess the activity of vigabatrin would be to monitor its biochemical effect in the target tissue. Whereas samples of brain tissue are not readily available, CSF samples can be obtained repeatedly in the same individual with a minimal inconvenience to the subject.

Early studies failed to detect the presence of GABA in human CSF (Roberts, 1960); however, the development of more sensitive and reliable analytical techniques verified the presence of low concentrations of GABA in CSF. More recently the presence in CSF of considerably greater GABA concentrations than previously realized, in forms releasable upon hydrolysis, has become appreciated (Grove *et al.*, 1982b, 1983; Haegle *et al.*, 1987).

The validity of using measurements of CSF GABA to assess biological activity of vigabatrin in man is contingent upon the existence of some relationship between the biochemical effects of the inhibitor in brain and detectable changes in CSF. Comparison of CSF from simultaneous lumbar and suboccipital punctures in the same untreated individuals, as well as examination of successive fractions of lumbar CSF, demonstrated the presence of a rostro-caudal gradient for GABA in the CSF (Grove *et al.*, 1982a). This gradient suggests a central origin for at least some of the GABA present in CSF. In addition, analysis of the increases in GABA in brain and cisternal CSF of rats treated with vigabatrin demonstrated a linear correlation between these increases (Böhlen *et al.*, 1979). These results indicate that vigabatrin-induced changes in CSF GABA concentrations are likely to reflect similar qualitative changes in brain.

Several studies have been performed to assess the biochemical effects of vigabatrin treatment in human CSF. Because of considerable variation

Figure 2 Concentrations (means $\pm$ s.e. mean) of total GABA (■), homocarnosine (□), vigabatrin (▲), free GABA (●) and β -alanine (○) in lumbar ($n = 4-6$) and suboccipital ($n = 7-9$) cerebrospinal fluid of epileptic patients, prior to treatment, after 2 weeks of vigabatrin 1 g day⁻¹, 2 weeks of vigabatrin 2 g day⁻¹ and 2 weeks of post-treatment placebo.

in baseline CSF GABA concentrations it is considered essential to conduct such studies longitudinally, with pre-treatment values from each subject serving as control for subsequent changes in this individual. In 15 patients with various neurological conditions, oral treatment with daily oral doses of 0.5 g to 6 g vigabatrin for 3 days resulted in dose-dependent increases in lumbar CSF concentrations of free GABA, total GABA (i.e., GABA found upon hydrolysis of CSF), homocarnosine (the GABA-histidine dipeptide) and β -alanine (an alternate substrate

for GABA-T) (Grove *et al.*, 1981). In addition, CSF concentrations of unchanged vigabatrin also increased with an increase in the dose administered.

In a second study, 10 epileptic patients refractory to conventional therapy were treated with oral vigabatrin, 1 g day⁻¹ for 14 days, then 2 g day⁻¹ for 14 days followed by a 14 day placebo wash-out period (Schechter *et al.*, 1984). Suboccipital and lumbar CSF were simultaneously sampled before treatment and at the end of each treatment period. In each case, vigabatrin treat-

ment was associated with increases in concentrations of free GABA, total GABA, homocarnosine and β -alanine in CSF obtained from both sites (Figure 2). Concentrations of these substances were consistently greater in suboccipital than in lumbar CSF suggesting a central origin for the biochemical changes observed. In contrast, the concentrations of vigabatrin at each dose were greater in lumbar than in suboccipital CSF, suggesting that the drug can enter CSF by peripheral as well as cerebral routes. Following 2 weeks of placebo treatment, concentrations of free and total GABA, homocarnosine and

β -alanine had returned towards pre-treatment values.

Thus, oral administration of vigabatrin to man at doses within the therapeutic range is associated with biochemical alterations in CSF consistent with an inhibition of brain GABA-T activity. The resultant increase in brain GABA concentrations should serve as a means to test the many hypotheses advanced as to the role of GABA in brain function and would be expected to have important therapeutic consequences in selected pathological states.

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