Gabapentin raises human brain GABA within thirty minutes

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Introduction. Gabapentin is a recently introduced antiepileptic drug [1]. Gabapentin is now widely prescribed for the management of neuropathic pain [2]. Designed to mimic GABA, its mechanism of action remains elusive [3]. Daily use of gabapentin is associated with above normal occipital lobe GABA in those patients whose seizure control improved [4, 5]. Vigabatrin is one of the most potent of the newer antiepileptic drugs [6]. It is designed to irreversibly inhibit the main enzyme which metabolizes GABA, GABA-transaminase. The first dose of vigabatrin increases brain GABA within one hour and levels remain elevated for several days [7, 8]. The currents experiments were designed to measure the initial brain GABA response to gabapentin in patients with refractory complex partial seizures. The rise in brain GABA in response to gabapentin is compared with the response measured after the first dose of vigabatrin in a similar group of patients [8].

Methods. Studies were done with a 2.1 Tesla Oxford Magnet Technologies (OMT)1 meter bore magnet equipped with a modified Bruker AVANCE spectrometer and OMT shielded gradients and power supplies. The back of the head rested on an 8 cm distributed capacitance radio-frequency surface coil tuned to the ^1H NMR frequency of 89.43 MHz. From the scout image a 3.0x1.5x3.0 cm (14 cm^3) volume in the occipital cortex was chosen for NMR measurements. Homonuclear editing of the 3.0 ppm C4-GABA and the 3.4 ppm C4-pyrrolidinone resonances were performed using the J-editing pulse sequence described previously [9, 10]. Brain GABA measurements were corrected for co-edited signals from homocarnosine and macromolecules [9, 10].

Six patients (two men) with refractory complex partial seizures were enrolled to measure the effects of gabapentin on brain GABA metabolism. Other medications included carbamazepine, primidone, or phenytoin. The first gabapentin dose was 1200 mg as capsules.The Yale Human Investigations Committee approved the studies.

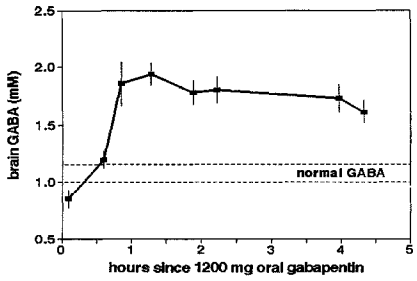

Figure 1 shows serial mean brain GABA measurements with standard error bars after the first dose of gabapentin.

Results and Discussion. The first, 1200 mg dose of gabapentin increased brain GABA within 30 minutes of oral administration (Figure 1). Brain GABA increased by 1.3 mM (se 0.2, n 6) within one hour. The increase was maintained for at least five hours. Brain GABA increased at a linear rate of 3.1 mM/hour (se 0.7, n 6).

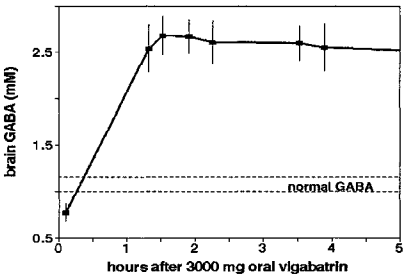

Figure 2 shows serial mean brain GABA measurements with standard error bars after the first dose of vigabatrin [8]. Brain GABA increased by 1.8 mM (se 0.3, n 6) within 90 minutes. GABA initially increased at a linear rate of 1.5 mM/hour (se 0.1, n 6).

Not unexpectedly, vigabatrin increased GABA 40% more than gabapentin. However, gabapentin increased GABA at twice the rate of the response to vigabatrin. These observations suggest that gabapentin stimulates GABA synthesis rather than slows catabolism as vigabatrin does.

A single dose of 1200 mg of gabapentin was well tolerated by our patients. One patient developed a mild ataxia which resolved within hours and did not recur with daily dosing. Our experience with patients is similar to the experience in healthy subjects given 1200 mg gabapentin [11]. The rapid rise in brain GABA presumably offers enhanced seizure protection within one hour of ingestion. Therefore, gabapentin could be used to stop flurries of seizures on an as needed basis. It should have fewer cognitive side-effects than the oral or rectal benzodiazepines currently used for this purpose.

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