short communication

drug concentrations in human brain tissue samples from epileptic patients treated with felbamate

felbamate (FBM), 2-phenyl-1,3-propanediol dicarbamate, is a novel orally active and relatively nontoxic anticonvulsant that is lipophilic, sparingly soluble in water, nonionic, and, following oral administration, rapidly absorbed and distributed into the tissue of animals, including the brain (1). FBM is partly metabolized to pOHF, 2OHF, and MCF (2). Its unique profile of anticonvulsant activity has been demonstrated in laboratory animals (3-5) and in humans (6, 7). FBM is readily bioavailable in animals and humans (8). The uptake of FBM into brain and cerebrospinal fluid of adult and neonatal rats after single oral doses (9) and into brain of mice, rats, and rabbits after intracarotid injection (10) has been investigated. Both studies confirmed that FBM can rapidly and efficiently pass through the animal blood-brain barrier and, depending on the dose and the age of the animal, brain concentrations of up to 900 μM can be reached and maintained.

The objective of the study was to determine steady-state FBM brain concentrations in humans and estimate a brain/plasma partition coefficient. FBM concentrations in nine human brain samples obtained during surgery from epileptic patients on FBM therapy were determined using an HPLC assay developed for animals (11).

Materials and Methods. Brain tissue samples were obtained at the time of surgery from nine patients (A-I) undergoing surgical intervention because of uncontrolled epilepsy. The time of sample collection varied from 5 to 19 hr after the last dose of FBM.

Patient A was a 36-year-old female with complex partial seizures, receiving 3600 mg of FBM daily with carbamazepine. The brain specimen was obtained from the left amygdala/hippocampus and temporal lobe. Patient B was a 16-year-old boy with complex partial seizures with secondary generalizations, receiving 3600 mg FBM daily with phenobarbital and phenytoin prior to surgery. The brain specimen was obtained from the left frontal lobe. Patient C was a 32-year-old male with simple and complex partial seizures with secondary generalizations, receiving 3600 mg of FBM daily with carbamazepine prior to surgery. The brain specimen was obtained from the left anterior temporal lobe. Patient D was a 16-year-old girl with complex partial seizures, receiving 3600 mg FBM daily with phenobarbital and valproic acid prior to surgery. The brain specimen was obtained from the left frontal cortex. Patient E was a 13-year-old girl with complex partial seizures, receiving 1600 mg of FBM daily along with phenytoin. The brain specimen was obtained from the right frontal lobe. Patient F was a 31-year-old male with partial epilepsy and refractory tonic-clonic seizures, receiving 3600 mg of FBM daily along with phenytoin and primidone prior to surgery. The brain specimen was obtained from the right frontal lobe. Patient G was a 31-year-old male with complex partial seizures, receiving 3600 mg of FBM daily prior to surgery. The brain specimen was obtained from the right temporal lobe. Patient H was a 25-year-old male with complex partial seizures receiving 3600 mg of FBM daily along with carbamazepine prior to surgery. The brain specimen was obtained from the right temporal lobe. Patient I was a 46-year-old male with complex partial seizures receiving 3600 mg of FBM daily. The brain specimen was obtained from the left temporal lobe. Intraoperative plasma samples were also collected from patients C, F, G, H, and I.

Methods of Analysis. The brain samples, kept frozen after excision until analysis, were thawed, homogenized, and analyzed by HPLC as previously described for rat brain homogenates (11). Control rat brain homogenates were used in preparation of analyte standards for calibration because human brain control tissue was not available. An example of the separation typical for human brain homogenates is shown in fig. 1, which depicts a chromatogram of the brain homogenate from patient D. The plasma samples obtained from five patients were analyzed by a specific HPLC procedure for FBM (12) or metabolites (unpublished data).

Results and Discussion. The assay for FBM and its metabolites, originally developed for rat brain, was successfully applied to the analysis of human brain samples. No interference was encountered as determined in an analyzed brain sample homogenate from a patient not taking FBM. The concentrations of FBM and the 2OHF and MCF metabolites determined in the nine brain specimens are listed in table 1. The concentrations of the third metabolite, pOHF, were below the limit of quantitation. Only five plasma samples, taken at the time of surgery, were available from patients C, F, G, H, and I. The concentration of FBM in

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Abbreviations used are: FBM, felbamate; pOHF, 2-(4-hydroxyphenyl)-1,3-propanediol dicarbamate; 2OHF, 2-hydroxy-2-phenyl-1,3-propanediol dicarbamate; MCF, 2-phenyl-1,3-propanediol monocarbamate.

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Fig. 1. Chromatogram of brain sample homogenate obtained from patient D dosed with FBM and phenobarbital.

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these plasma samples, as well as metabolite concentrations in three plasma samples and the corresponding FBM brain/plasma concentration ratios, are also listed in Table 1. The observed FBM plasma concentrations in patients C, F, G, H, and I are in agreement with mean steady-state concentrations in patients receiving 3600 mg of FBM daily. The individual observed plasma concentration values gave a mean FBM brain/plasma partition coefficient of 0.66 ± 0.26 (see Table 1). This value indicates that the protein-unbound free fraction of FBM, determined in vitro to be ~0.76 (1), easily enters the human brain. It is also in agreement with the FBM partition coefficients determined in adults to be 0.64 and neonatal rats to be 0.83 (9), and comparable to published human brain/plasma coefficients for other lipophilic antiepileptic drugs, such as phenytoin [0.63–1.72 (13)], primidone [0.4–0.87 (14)], and carbamazepine [0.8–1.6 (15)].

Recent in vitro and in vivo animal studies have also demonstrated significant neuroprotective properties of FBM (16, 17) and suggested a mechanism for its anticonvulsant and neuroprotective properties through an interaction with the strychnine-insensitive glycine site at the N-methyl-D-aspartic acid receptor (18). The glycine site antagonists described in literature, except for HA-966, have generally poor in vivo systemic bioavailability because of their low lipophilicity and their ionic character (19).

The relatively high concentrations of FBM, ~100 µg/ml, required for in vitro neuroprotective effects in the rat (18) have been reached in vivo in rat brain (9). Data herein show that FBM levels of the same order of magnitude are also achievable in human brain due to the high lipophilicity and low protein binding of the drug. The current data does not allow any conclusions to be drawn regarding differences in distribution of FBM to various regions of the human brain. However, according to Cornford et al. (10), autoradiograms of mouse and rat brain slices showed a relatively uniform FBM distribution throughout the animal brain. This is in line with recent work published by Rambeck et al. (20) on regional brain distribution of phenobarbital and carbamazepine in human postmortem samples that showed only modest differences in distribution between various brain regions.

In addition to FBM, the presence of the 2OHF metabolite in human brain was also established but, as in the rat, the concentration of this less active metabolite is too low to be of importance. Because the more polar metabolite concentrations in human plasma are low, relative to FBM, possible enzyme induction by other antiepileptic drugs will not manifest itself in a significant decrease in FBM or increase in metabolite concentrations in the brain, but rather in a significant change in urinary FBM and metabolite concentrations.

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References


