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Evaluating the safety and efficacy of felbamate in the context of a black box warning: A single center experience

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ABSTRACT

Introduction: Felbamate was approved in 1993 to treat partial seizures with and without secondary generalization in adults and in Lennox–Gastaut Syndrome in children. Its use was later restricted when rare but fatal cases of aplastic anemia and hepatic failure were identified.
Methods: This single center analysis retrospectively evaluated the safety and efficacy of felbamate in a cohort of children, adolescents, and adults with epilepsy.
Results: A chart review identified 103 patients taking felbamate. The range of felbamate dose was 300–4500 mg (mean: 1800 ± 900 mg). The duration of therapy ranged from 1 month to 20 years (mean duration: 35 ± 45 months). Eighteen (17.5%) subjects experienced adverse events including insomnia, nausea, vomiting, decreased appetite, weight loss, gastric discomfort, diarrhea, mood and behavioral problems, high blood pressure, headache, and elevated liver enzymes. Out of these, 6 (5.9%) patients discontinued the therapy. No hepatic failure or agranulocytosis was observed. Fifty-nine (57.72%) patients achieved ≥50% reduction in seizure frequency, and 30 (29.12%) patients achieved seizure freedom.
Conclusions: These findings suggest that felbamate is safe, well tolerated, and effective in treatment of various types of epilepsy syndromes.

1. Introduction

Epilepsy is a chronic condition characterized by recurrent, unprovoked seizures requiring continued medication for long-term management. The Institute of Medicine reports that more than 150,000 cases of epilepsy are diagnosed annually in USA. It is estimated that 2.9 million Americans have epilepsy, and it is considered as the 4th most prevalent condition after migraine, stroke, and Alzheimer's disease [1,2]. Despite the introduction of over a dozen new antiepileptic drugs in the past two decades, 30% of patients may not have remission despite appropriate polypharmacy [3]. While some patients with refractory epilepsy are candidates for resective epilepsy surgery or palliative neuromodulation therapy; most patients with Lennox–Gastaut Syndrome (LGS) and generalized epilepsies as well as many with partial epilepsies must be managed with nonsurgical approaches [4].

Felbamate was the first new molecular entity approved in the United States (in 1993) since the approval of valproate. It was also the first drug to be approved specifically for the treatment of LGS. Felbamate is a unique drug which inhibits N-Methyl-D-aspartate (NMDA) channels at therapeutic concentration [5]. At higher concentration, it also modulates the GABA receptor [6].

Felbamate was approved in 1993 for partial seizures with and without secondary generalization in adults and for LGS. Over the next year since approval, felbamate was used in up to 110,000 patients [7]. In 1994, however, its use was markedly reduced after 10 cases developed fatal aplastic anemia. A "Dear Doctor" letter was sent out to 500,000 physicians [8]. It was recommended that the drug remain available only for patients with severe epilepsy for whom the benefits outweigh the risks and that changes be made to the product's labeling to reflect the newly recognized risk. Additional warning was added to the labeling after 10 patients with acute liver failure were also identified.

There have been a total of 31 cases of aplastic anemia and a total of 18 cases of hepatic failure after the drug was marketed in the US. Detailed evaluation of these 31 cases was performed by the Slone epidemiology unit of Boston University by using International Agranulocytosis and Aplastic Anemia Study (IAAAS) guidelines. It was established that only 23 cases met the criteria for aplastic anemia. Out of these 23 cases, considering some potential confounders, only 3 cases (13%) were thought to be actually associated with felbamate. Notably, only one pediatric patient was diagnosed with aplastic anemia in this series [7].

Of the 18 patients with hepatic failure, only 7 cases were considered to be actually caused by FBM [9]. A panel of three internationally recognized hepatologists found that the remaining 11 cases were complicated

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by other etiologies to account for the hepatic pathology (status epilepticus, viral hepatitis, acetaminophen use, and "shock liver").

Despite the black box warning, some epileptologists have continued to use felbamate for patients who have not adequately responded to other treatments with close monitoring of hepatic and hematologic functions. No standard protocol exists for the intensity of such monitoring, and it remains unknown if such monitoring can prevent life threatening complications of FBM use. We report our experience of the continued use of felbamate post-black box warning over the past 20 years, with the specific aim of assessing safety and efficacy of FBM when closely monitored.

2. Methods

This was a retrospective study in which chart review was done on patients who were on FBM for epilepsy from January 1995 to May 2015. The study was approved by the hospital Institutional Review Board. Several clinical databases were queried using the keywords "Felbamate", "Felbatol", and "FBM" including the outpatient electronic medical record (EPIC, in place since August 2010) and the epilepsy center surgical case conference database (all patients presenting to multidisciplinary surgical conference since 2006 onwards). A total of 271 patients who were on FBM were identified. Of these, 103 cases were identified with complete details available in their electronic medical records. For some of the older cases, extensive manual chart review was done from archived records. Information regarding demographics, etiology, seizure onset and type, epilepsy syndrome, comorbidities, clinical exam, other medications, seizure frequency, medication dosage, efficacy, adverse events, surgery, and VNS was obtained retrospectively from the medical records. Seizure frequency and types were obtained either from their history, telephonic encounters, or from diaries that patients maintained.

For descriptive and statistical analysis, SPSS version 21.00 was used. The Student's t-test was used for the statistical analysis of between group differences.

3. Results

Out of 103 patients who were assessed in this study, 54.3% were male. There were 53 (51.4%) pediatric patients (i.e., age less than 18 years). Median age at diagnosis of seizures was seven years (range: 0.01 year–61 years). Patient's demographic characteristics are summarized in Table 1. Thirteen percent of the patients had intellectual disability, 5.7% had neurobehavioral disorders, 4.8% had autism, and 1% had a mood disorder.

Fifty percent of patients had no known etiology, while the most common seizure type was generalized convulsive. Ten percent were diagnosed with LGS by the treating physician. Except for two cases, FBM was prescribed as second-line treatment in all other cases. Other antiepileptic drugs (AEDs) used in combination with FBM included valproate (33.3%) and clobazam (33.3%), followed by levetiracetam (27.5%) and lamotrigine (21%).

Baseline CBC, differential and reticulocyte count, AST, ALT, GGT, bilirubin, creatinine, and urinalysis were checked prior to starting FBM. Subsequently, liver function and CBC were monitored every 2–4 weeks for 3 months, and then every 3 months thereafter. The starting dose of FBM in children 2–14 years of age was 15 mg/kg/day in 3 divided doses; this was increased by 15 mg/kg/day increments at weekly intervals with a maximum dose of 45 mg/kg/day or 3600 mg/day (whichever was less). In children >14 years of age and in adults, the initial starting dose was 1.2 g/day administered in 3 divided doses and the dosage was increased by 1.2 g/day at weekly increments to a maximum of 3.6 g daily administered in 3 divided doses. The median dose of FBM was 1750 mg while the median blood FBM level was around 47 mcg/mL (no exact range is established, but 30–60 mcg/mL is recommended [9]). The range of FBM dose was 300–4500 mg (mean: 1800 ± 900 mg) and was similar to other studies [10–12]. The range in nonresponders (1813 ± 920 mg) was slightly higher but statistically not significant from responders (1797 ± 890 mg).

Table 1
Demographic and clinical data (N = 103).

Characteristics	n (%)
Boys	57/103 (54.3%)
Mean age of diagnosis, years (SD)	10.68 (13.19)
Epilepsy etiology	
Genetic	17 (16.5%)
Structural abnormalities	34 (33%)
Unknown	52 (50%)
Specific	
Genetic	17 (16.5%)
Neurocutaneous syndrome	8 (7.6%)
Hypoxic ischemic encephalopathy	4 (3.8%)
Traumatic brain injury	7 (6.5%)
Neoplasm	6 (5.7%)
Infection	4
Other structural	4
Stroke	1 (1%)
Other unknown	52 (50%)
Seizure type	
Generalized convulsive	65 (61.9%)
Focal onset with secondary generalization	23 (21.9%)
Focal	5 (4.2%)
Generalized absence	4 (3.8%)
Infantile spasm	2 (1.9%)
Generalized unspecified	1 (1%)
Comorbidities	
Normal	59 (69.4%)
Autism	5 (5.9%)
Mood disorders	1 (1.2%)
Neurobehavioral disorders	6 (7.1%)
Intellectual and developmental disability	14 (16.5%)
Brain surgery	16 (17.4%)
VNS	10 (12%)
Concomitant antiepileptic drug	
Levetiracetam	28 (27.5%)
Topiramate	10 (9.5%)
Valproate	35 (33.3%)
Clonazepam	15 (16.2%)
Lorazepam	7 (7.4%)
Clobazam	35 (33.3%)
Diazepam	15 (14.3%)
Rufinamide	4 (4.3%)
Zonisamide	7 (7.4%)
Perampanel	3 (2.9%)
Prednisolone	7 (6.7%)
Lacosamide	17 (16.7%)
Eslicarbazepine	7 (6.4%)
Ethosuximide	1 (0.9%)
Phenytoin	2 (1.9%)
Lamotrigine	22 (21%)
Phenobarbital	5 (4.8%)
Vigabatrin	3 (2.9%)

A summary of the FBM profile is described in Table 2. The mean seizure frequency (as obtained either from their history, telephonic encounters, or seizure diaries) before starting FBM was 35/month

Table 2
Felbamate safety and efficacy profile.

Seizure frequency before felbamate, median (SD)	10 (80)
Felbamate duration in years, median (SD) (range)	2 (4.12) (.08–20)
Seizure frequency after felbamate, median (SD)	4 (29)
>50% seizure reduction	59 (57.72%)
Felbamate dose, median	1750 mg
Blood felbamate levels, median	47
Abnormal LFT	1 (1%)
Abnormal CBC	4 (3.8%)
Adverse effects	18 (17.47%)
Discontinuation due to adverse drug effects	6 (5.9%)
Total dropouts	8 (7.8%)
Serious adverse events (liver cell failure or agranulocytosis)	0 (0%)