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Felbamate in Epilepsy Therapy
Evaluating the Risks

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Contents

Abstract

Felbamate demonstrates a unique therapeutic profile and often results in seizure control when other agents fail. Its use has been associated with risks for aplastic anaemia and hepatic failure. A number of confounding factors makes the actual incidence rate for each adverse effect difficult to determine. However, certain risk factors are common in reported cases. In order to minimise the risk, at the present time, it is necessary to rely on the clinical profile of the patients reporting these adverse effects.

The patient reporting aplastic anaemia is usually female, Caucasian, and an adult. The dose did not appear to be a factor and the time to onset of aplastic anaemia was less than 1 year for all patients. Concomitant medications and diseases may play an important role. Patients with reported aplastic anaemia generally had a history of a serious allergy or toxicity to other anticonvulsants and/or

a background of having had a cytopenia due to other anticonvulsants, and a diagnosis or serological evidence of concomitant immune disorder.

The demographics associated with hepatic failure are less well defined. Patients were also predominantly female, were equally divided among adult and paediatric patients, and had a broad range of time to presentation of hepatotoxicity following felbamate therapy. Concomitant medications again play an important role with, in this case, valproic acid (sodium valproate), phenytoin and carbamazepine being the most frequent. In 50% of the population, hepatic failure was not felt to be due to felbamate but associated with confounding factors including status epilepticus, paracetamol (acetaminophen) toxicity, hepatitis and shock liver.

Initial research has failed to provide a diagnostic indicator. However, work on a potential intermediate felbamate metabolite has suggested the formation of a reactive aldehyde whose end products have been detected in the urine of felbamate treated patients. Until these data are confirmed, the medical history, clinical picture, and laboratory testing, should be used to identify patients at risk.

The risks for toxicity with felbamate should be evaluated before starting treatment. In addition, liver function tests and complete blood count (CBC) prior to therapy and at clinically rational intervals should be conducted. Patients must be educated in the likely prodromal symptoms of potential marrow/liver toxicity.

Felbamate is too valuable an anticonvulsant to be relegated to the therapeutic scrap heap. With monitoring, patient education, and continued research to further elucidate risk factors, felbamate can be a viable therapeutic agent for patients with epilepsy.

1. Initial Place of Felbamate in Epilepsy Therapy

Traditional and innovative study designs were employed to demonstrate the efficacy of felbamate.[1-7] Traditional studies included placebo-controlled, double blind add-on studies or active-controlled studies. Double-blind studies indicated the efficacy of felbamate in Lennox-Gastaut syndrome[7] and complex partial seizures.[3-5] Add-on studies and studies in which other anticonvulsants were gradually tapered with increasing felbamate dosage, indicated that felbamate was effective as an adjunct and as monotherapy.[5,6] The analysis of controlled, clinical trials indicated a statistically and clinically significant difference from placebo in the percentage of patients experiencing a >50% reduction in seizure frequency.

In innovative studies, patients whose anticonvulsant therapy had failed to control their epilepsy and were being evaluated for epilepsy surgery were given the opportunity to undergo dose reduction/discontinuation of the original anticonvulsant accompanied by felbamate as the replacement.[1-3] Felbamate dose was increased from 1600 mg/day to 3600 mg/day. A statistically significant reduction in seizures ($p = 0.002$) compared with placebo was observed in these patients who were diagnosed with therapy-resistant partial seizures.

2. Clinical Perspectives on Reported Adverse Effects

Felbamate was introduced in the US in August 1993 and represented the first new anticonvulsant approved in almost 20 years (lamotrigine and gabapentin were approved shortly thereafter). Felbamate was later approved throughout most of continental Europe, South Africa and portions of Asia and South America for the treatment of Lennox-Gastaut syndrome and/or refractory partial onset seizures. It distinguished itself as being effective in patients refractory to other medications.[1-7] The uniqueness of felbamate includes a

broad spectrum control of multiple seizure types and a relative lack of CNS depressant effects often associated with many other anticonvulsants. Adverse events associated with its use consisted of mainly gastrointestinal disturbances, headache, anorexia and insomnia with better tolerance observed when felbamate was administered as monotherapy.[8,9] Extensive preclinical data provided no evidence of hepatotoxicity or haematological toxicity with either short term or long term administration. Available clinical experience in the US in support of approval as well as European trials, likewise, provided no evidence of haematological or hepatotoxic activity.

After approval in the US for epilepsy therapy, felbamate prescriptions rose in subsequent months. Following reports of aplastic anaemia and hepatic failure approximately 1 year later, the use of felbamate was severely curtailed.[10] Felbamate is now recommended only in those patients whose epilepsy has responded inadequately to other anticonvulsants and whose epilepsy is so severe that a substantial risk of aplastic anaemia and/or liver failure is deemed an acceptable risk in light of the benefits that are conferred by its use.

Many patients who clearly benefited from the drug were withdrawn from treatment and many physicians have abandoned use of the drug. Several years following the 'Dear Doctor' letter regarding aplastic anaemia, a survey of 8800 neurologists (909 responded) showed that 14 155 of their felbamate-treated patients were discontinued from the drug. Of these patients who had withdrawn from felbamate therapy, seizure control was worse in 40.3% and quality of life assessment indicated 40.6% were worse off following felbamate discontinuation.[10] Aside from the quality of life issues, often forgotten is the increased risk of seizures, status epilepticus, serious injury and sudden unexplained death in epilepsy (SUDEP), when anticonvulsants are abruptly withdrawn or medication regimens are altered rapidly.[11-13]

2.1 Aplastic Anaemia

In August 1994, Wallace Laboratories issued a 'Dear Doctor' letter regarding the possibility of aplastic anaemia associated with felbamate use. 33 cases of aplastic anaemia were eventually reported in the US and the use of felbamate was restricted to patients based on a risk benefit evaluation. The demographics of the patients reported to have aplastic anaemia are summarised in table I. Patients were predominately female (67%), Caucasian (94%), adults (mean age 42.5 years), receiving a mean felbamate dose of 3129 mg/day (range 800 to 5400 mg/day) and the mean time to onset was 173 days (range 23 to 339 days). The incidence of aplastic anaemia attributed to felbamate using all 33 reported cases was estimated at 300 per million patients treated.

Evaluation of the demographic characteristics and patient history revealed several features which appeared regularly and which may profile the at patient who is at risk. Aside from being predominantly female (analysis of US prescribing data suggests a 1 to 1 male to female ratio), 30 of the 33 patients had prior anticonvulsant exposure (91%). 17 (52%) had a prior history of anticonvulsant allergy or toxicity (especially rash), 14 had a history of prior cytopenia (42%) and 11 (33%) had evidence of immune disease (table II). Previous anticonvulsant exposure and those demonstrating allergic responses to conventional therapy may not be surprising since refractory patients would be more likely to receive a new anticonvulsant medication. There is currently little epidemiological data in patients not developing aplastic anaemia to compare with those who did. Whether those pa-

Table I. Demographics of 33 patients reported to have aplastic anaemia associated with felbamate therapy

Mean age in years (range)	42.5 (13-75)
Gender	67% female 33% male
Race	94% Caucasian 6% Black
Felbamate dosage in mg/day (range)	3129 (800-5400)
Mean duration of therapy in days (range)	173 (23-339)

tients with prior serious anticonvulsant allergy/toxicity, immune disorder, and prior history of cytopenia are truly at risk remains to be determined. It is also important to consider the 4 patients who developed aplastic anaemia and had none of the above risk factors[14] and to consider the fact that aplastic anaemia is still a relatively rare and not well understood condition.

On review of the first 31 reports received by the Slone Epidemiology Unit of Boston University using the International Agranulocytosis and Aplastic Anemia Study (IAAAS) guidelines, only 23 cases (74%) met the criteria for aplastic anaemia.[14] Of these, felbamate was judged to be the only plausible cause (unlikely confounding factors) in 3 cases (13%), confounded but considered a likely possible cause in 11 cases and there was at least another plausible cause in another 9 patients. In the worst case (using all 23 cases defined as aplastic anaemia) the estimated incidence is 209 cases per million. In the best case scenario (i.e. the 3 cases with unlikely confounding factors), the incidence was as low as 27 per million patients treated. This is opposed to an incidence of 2 to 2.5 per million in the general population. Since there is not an adequate database on the actual incidence of aplastic anaemia in the epilepsy patient population, a background incidence is hard to establish. It is generally accepted that it may be higher than in the general population. In general, the true risk of idiopathic aplastic anaemia for many drugs displays a wide range of suspected incidence, partially due to the rare nature of the condition and uncertainty as to the actual number of exposed patients.

Table II. Profile of the patient 'at risk' of felbamate-related aplastic anaemia

Potential risk factor	Percentage of patients (n = 33)[a]
Age >17 years old	97
Female gender	67
Concomitant medications	79
Concomitant anticonvulsants	55
History significant anticonvulsant toxicity/allergy	52
History of prior cytopenia	42
History of immune disease	33

a Analysis includes all reported cases to date, regardless of definitive diagnosis of aplastic anaemia.

A review of the demographic profile of patients with reported aplastic anaemia suggests that there may be a patient profile to aid in evaluating the individual patient at risk. Available data suggest the 'at risk' patient appears to be a middle-age female with a clinical history of a previous cytopenia (particularly thrombocytopenia) and evidence of underlying immunological disorder [lupus, arthritis or elevated antinuclear antibodies (ANA)] and a significant history of prior anticonvulsant allergy. Noteworthy is the fact that there has been only 1 paediatric patient diagnosed with aplastic anaemia. However, the 13-year-old post-puberal girl with a history of mental retardation, had a pre-felbamate diagnosis of systemic lupus erythematosus. Individual case reports regarding 2 of the 33 patients have been previously published.[15-16] Thrombocytopenia associated with felbamate has also been reported.[17]

2.2 Hepatotoxicity

Eighteen cases of hepatic failure were reported in patients receiving felbamate therapy. The age, gender, duration of therapy, dose of felbamate and concomitant medications are shown in table III. Evaluation of all 18 patients indicated that 78% were female, 50% were 17 or older, and the mean time to presentation was 217 days (25 to 939 days). Of the patients, 16 were receiving other anticonvulsants. Using all reported cases of hepatic failure the estimated incidence would be 164 per million patients treated.

Three internationally recognised hepatologists, independently and jointly met to review data on the 18 reported cases of liver failure worldwide. Of the reported cases, they concluded that only 7 had a likely connection with felbamate (table III). Other cases were complicated by status epilepticus, viral hepatitis, shock liver, and paracetamol (acetaminophen) toxicity. The age range for those with likely relationship to felbamate was 5 to 56 years old and 6 of the 7 patients were female. Using a numerator of 7, the incidence of hepatic failure would be es-

Table III. Individuals reporting hepatic failure during felbamate administration: patient demographics and hepatologists determination of relationship to felbamate treatment

Classification	Age (y)	Felbamate dosage (mg/day)	Gender	Time to presentation (days)	Concomitant medications
Likely relationship (n = 7)	56	1200	F	179	Primidone, nadolol, iron supplement, amoxapine, conjugated estrogens
	12	1800	F	181	Phenobarbital (phenobarbitone), phenytoin
	44	3600	F	138	Carbamazepine, conjugated estrogens
	35	1800	F	62	Carbamazepine
	39	Unknown	F	154	Carbamazepine
	5	34 mg/kg	M	112	Phenytoin
	61	3600	F	25	Metoprolol, nifedipine
Unlikely relationship[a] (n = 9)	35	2400	F	25	Paracetamol (acetaminophen), valproic acid (sodium valproate), haloperidol, amitriptyline, phenobarbital
	29	3000	F	302	Phenytoin, valproate semisodium (divalproex sodium)
	40	1600	F	Unknown	Phenytoin, valproate semisodium (divalproex sodium)
	7	2400	M	214	Acetazolamide
	4	Unknown	M	272	Valproic acid, phenobarbital
	3	60 mg/kg	F	140	Phenytoin
	15	3600	M	184	Phenytoin, levothyroxine, erythromycin, vitamin D
	12	72 mg/kg	F	Unknown	Carbamazepine, amoxicillin
	4	240	F	939	Valproic acid, clonazepam, levothyroxine, amoxicillin, zinc, selenium
Undetermined relationship (n = 2)	3	Unknown	F	Unknown	Diazepam, lorazepam, phenytoin, phenobarbital, valproic acid
	45	2400	F	324	None reported

a Criteria used for the unlikely relationship to felbamate were shock liver, status epilepticus, pre-existing liver disease, viral disease (hepatitis), and paracetamol toxicity.

F = female; **M** = male.

timated at 64 per million patients treated. In general, with the limited number of incidents of hepatotoxicity reported to be related to felbamate, a profile of a potential 'at risk' patient and the true incidence of hepatotoxicity can not be formulated. A case report detailing 1 patient has been previously published.[18]

The remainder of this article will briefly review felbamate metabolism, potential mechanisms involved in other drugs implicated in aplastic anaemia or hepatotoxicity, and the current state of knowledge in evaluating the patient for felbamate therapy.

3. Felbamate Disposition in Humans

Critical to discussions of possible factors contributing to the occurrence of aplastic anaemia and/or hepatic failure, is an understanding of the metabolism of felbamate in humans. Some 30 years ago, the discovery that patients could be classified as fast or slow acetylators explained the then puzzling cases of isoniazid toxicity. Racial differences in the frequency of genetic defects in hepatic cytochrome P450 isoforms have been used to explain the differences in phenytoin pharmacokinetics in American and Japanese patients with epilepsy.[19] Relatively recently, the reason for paracetamol hepatotoxicity was clarified by research into the metabolism of the drug under certain conditions. With overdose or in situations where these microsomal pathways have been induced, acetaminophen metabolism takes a different route and N-acetyl-p-benzoquinonimine is formed.[20] This aberrant metabolism, which occurs on induction of specific hepatic isoforms or with saturation of glucuronidation pathways (overdose) contributes to paraceta-

mol hepatotoxicity. Thus, an understanding of metabolism can lead to safer use of a compound and even the development of antidotes useful in overdose, and the potential for avoiding toxicity.

Clinical studies with felbamate indicate the drug is not extensively metabolised. After the administration of a single, radiolabelled dose of felbamate 1000mg, 99% of the label is recoverable in the 24-hour urine.[21] Unchanged felbamate represented 47% of the radioactive material.[21] The 2-hydroxy felbamate (4 to 6%), p-hydroxy felbamate (6 to 14%) and the monocarbamate derivative (2 to 3%), as well as felbamate conjugates and polar metabolites represent the majority of metabolites found in urine.[22] A propionic acid derivative (fig. 1) has also been identified in urine (approximately 12%) as a metabolite.

In humans, felbamate is well absorbed orally and the peak plasma concentration is achieved in 3 to 5 hours. Linear pharmacokinetics following doses of felbamate 100 to 6000 mg/day were observed.[24,25] Felbamate has a volume of distribution of 0.8 L/kg. Increased clearance of felbamate has been reported in children[26] and paediatric beagle dogs.[27] The total amount of felbamate hydroxylated was found to be higher in very young dogs. Although the ratio of the 2 hydroxylated metabolites was similar in young and adult beagle dogs, the sum of both hydroxy metabolite amounts formed was 1.5 times higher in the paediatric dogs. The relevance of this observation to aplastic anaemia in adult humans has not been established.

Single dose [^{14}C]felbamate administered to rats also indicated that >95% of the dose was excreted within 48 hours. Following a single 100 mg/kg dose of [^{14}C]felbamate to rats, the percentage of the dose found in femoral bone marrow at 4, 8, 24 and 48 hours after administration were 0.013, 0.008, 0.0001, and 0.0005%, respectively.[28] Analysis of the radiolabelled material in the liver indicated that at 4, 8, 24 and 48 hours after administration, only 2.50, 1.17, 0.056, and 0.025% of the dose was found in this organ, respectively. The half-lives for the disappearance of radiolabelled material in both tissues were comparable to the plasma half-life. Therefore, it is unlikely that felbamate or its metabolites accumulate in hepatic or skeletal tissue. At least 1 other drug implicated in aplastic anaemia, the H_2 receptor antagonist metiamide, has been shown to accumulate in bone.[29]

Additional putative felbamate intermediate metabolites have been described in felbamate-treated patients and in *in vitro* studies[23,30,31] since the reports of aplastic anaemia and hepatotoxicity. It would seem unlikely that a stable, highly reactive species such as an epoxide is formed. Thus far, evidence of an epoxide has not been forthcoming. The aromatic anticonvulsants phenytoin, carbamazepine and phenobarbital (phenobarbitone) all have a carbonyl group β to the phenyl ring. Felbamate, on the other hand, has a carbonyl group γ to the phenyl ring and is separated by an ester oxygen. This should hypothetically reduce epoxide formation. Thompson et al.[30,31] propose a reactive intermediate of the monocarbamate metabolite of felbamate (atropaldehyde) based on mercapturic acid derivatives found in the urine of felbamate-treated patients.

In vitro studies[32,33] in which felbamate was added to human liver microsomes, noted that felbamate inhibited the cytochrome P450 isoenzyme CYP2C19 at concentrations of 225 μmol/L (54 μg/ml). This concentration is well within the range of plasma concentrations found in patients treated with felbamate (50 to 100 μg/ml[34,35]). No inhibition of CYP2D6, CYP3A4, CYP2E1, CYP1A2, or CYP2A6 was observed at concentrations up to 238 μg/ml. *In vitro* work suggests that felbamate metabolism to the 2-hydroxy- and p-hydroxy-felbamate metabolites may be partly mediated by CYP3A4 and CYP2E1. Inhibitors of CYP2E1 (chlorzoxazone) and CYP3A4 (troleandomycin) decreased felbamate metabolite formation in human liver microsomal preparations.[36] Clinically, however, drug interaction trials where felbamate was coadministered with the CYP3A4 inhibitor erythromycin failed to indicate any change in felbamate or erythromycin pharmacokinetic parameter estimates.[37] Further, felbamate coadministered with ethinyl estradiol and gestodene (CYP3A4 sub-

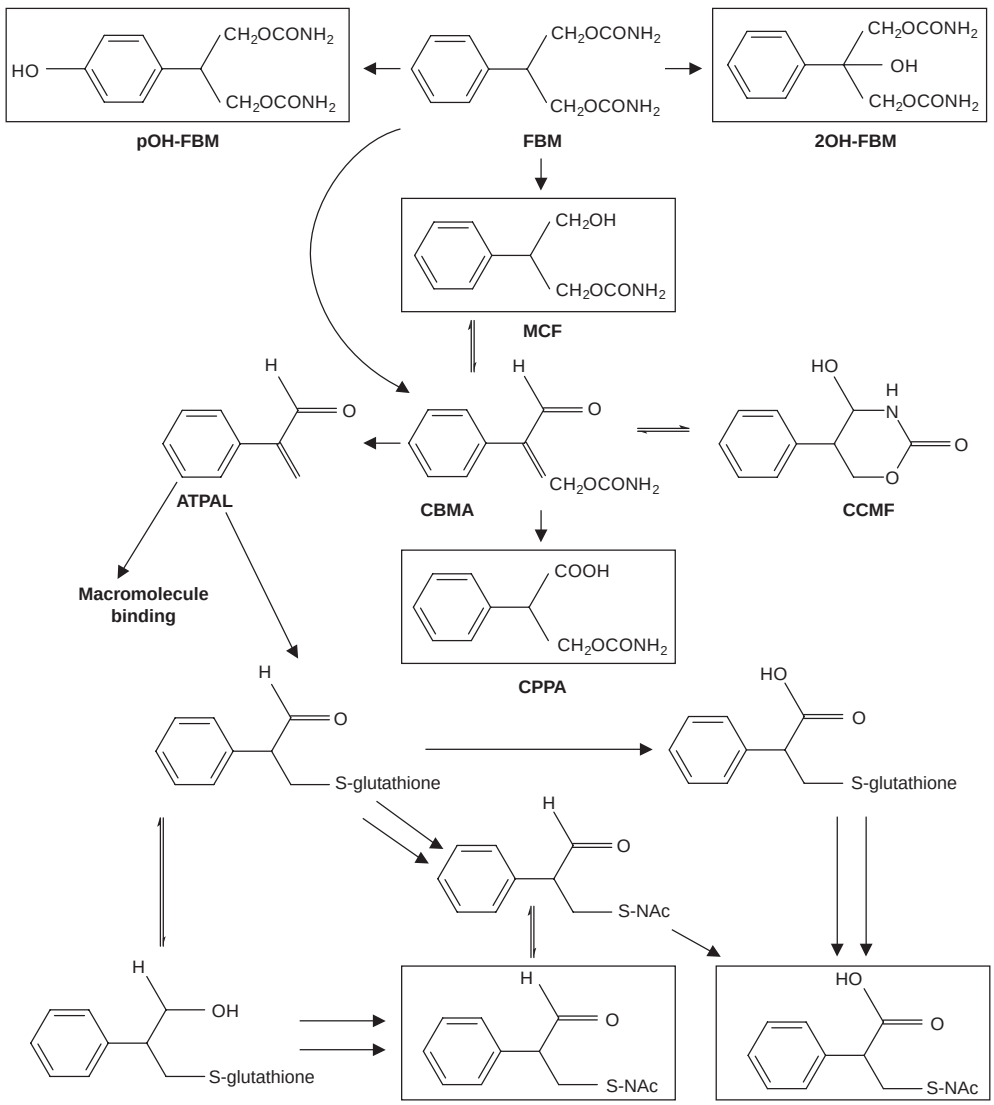

Fig. 1. The hypothesised intermediatory metabolism of felbamate. Structures included in boxes are known, identifiable felbamate metabolites in humans (from Kapetanovic et al.,[23] with permission). **ATPAL** = atropaldehyde (2-phenylpropenal); **CCMF** = 4-hydroxy-5-phenyltetrahydro-1,3-oxazin-2-one; **CMMA** = 3-carbamoyl-2-phenylproprionaldehyde; **CPPA** = 3-carbamoyl-2-phenylproprionic acid; **FBM** = felbamate; 2-(4-hydroxyphenyl)-1,3-propanediol dicarbamate; **MCF** = 2-phenyl-1,3-propanediol monocarbamate.

strates) led to a 42% decrease in gestodene area under the plasma concentration curve (AUC) and a 13% decrease in estradiol AUC.[38] Felbamate clearly did not inhibit the metabolism of these compounds and may have actually induced CYP3A4 leading to lower AUC values.

Felbamate is also known to induce the hepatic metabolism of some other anticonvulsants, such as the conversion of carbamazepine to the 10,11-epoxide.[39-41] Conversely, felbamate clearance can be increased by concomitant phenytoin, carbamazepine and phenobarbital administration.[40-44]

These drugs are known to induce hepatic microsomal enzymes. The relative changes in felbamate metabolites following the coadministration of drugs known to alter felbamate clearance has not been examined.

4. Potential Mechanisms of Aplastic Anaemia and Hepatotoxicity: Other Therapeutic Agents

4.1 Aplastic Anaemia

The aetiology of aplastic anaemia is not well understood. In an analysis of aplastic anaemia incidence rates from Thailand, Israel and Europe only 13% of the patients had been exposed to a drug generally associated with aplastic anaemia. The remaining 87% of patients had no drug exposure upon diagnosis.[45] Potential mechanisms involved in drug-induced aplastic anaemia have been extensively reviewed elsewhere.[46-51] Idiosyncratic aplastic anaemia is unpredictable, does not appear to be dose related, often has a delayed onset and spontaneous recovery is rare. Like other idiopathic drug reactions, there is evidence that both a toxic effect of the parent drug or an intermediate/metabolite and/or an immune system mediated toxicity may be responsible for the aplasia. Clinical reports suggestive of direct cytotoxicity and immune-type reactions to anticonvulsants have been described.[29,48,52,53] Interestingly enough, Shear and Spielberg[54] indicate that patients with a hypersensitivity to one anticonvulsant (particularly the aromatic anticonvulsants, phenytoin and carbamazepine) generally were at an increased risk of developing similar reactions to other drugs.

There is some evidence of a genetic predisposition to aplastic anaemia since a predisposition to chloramphenicol bone marrow damage had been shown by the occurrence of aplastic anaemia in identical twins.[55] Similar support comes from studies in which cells harvested from the fathers of patients with aplastic anaemia showed sensitivity a sensitivity to chloramphenicol that was similar the cells from the patient *in vitro*.[51]

Other proposed mechanisms of aplastic anaemia have included the possibility that a cytotoxic compound could be formed (absent or minimal in normal individuals) and circulate to the bone marrow. Along the same lines, the inability to inactivate a potentially toxic metabolite has been described with carbamazepine[46] and deferiprone.[56] A cytotoxic chloramphenicol metabolite formed by gastrointestinal bacteria in some individuals has also been proposed.[57]

Macrophages have some oxidative activity including epoxide hydrolase and myeloperoxidase. It is noteworthy that the arene oxide metabolites of drugs with high incidence rates of hepatotoxicity and/or aplastic anaemia are generally more toxic to lymphocytes than drugs with low incidence rates.[58] Sensitised T cells have often been reported as potential suspects in autoimmune disorders and xenobiotic-induced (parent or reactive intermediate) allergic responses.[59] Direct evidence of T cell mediated suppressor effects on colony forming units has been suggested.[49,60] Considering that immune suppression and immunoglobulins, which suppress the activity of T cells, are potential treatments for aplastic anaemia only strengthens the argument.

4.2 Hepatic Failure

Mechanisms involved in idiopathic hepatic failure are extensively reviewed elsewhere.[52,61-63] Drugs may have direct toxic effects (benzene), intrinsic toxicity (reactive metabolites, free radicals) or induce an immunological response (cytotoxicity or inflammation). None of the marketed anticonvulsants appears to be directly hepatotoxic. Patients with anticonvulsant-induced hepatotoxicity may have an immune-mediated response (prodromal symptoms of rash, fever and eosinophilia) or toxicity related to idiosyncratic metabolism or the failure to detoxify reactive intermediates.

The aromatic anticonvulsants are metabolised to highly reactive epoxide intermediates. These electrophilic compounds, under normal circumstances, have a limited ability to cause cellular damage due to the endogenous glutathione path-

ways and other oxidative control systems in the cell. In some individuals or in some circumstances, the detoxification mechanisms might be overwhelmed (perhaps genetically impaired). It is speculated that valproic acid hepatotoxicity is mediated by a toxic metabolite (4-en-valproate) and its synthesis is favoured when, for whatever reason, valproate metabolism is shifted from β-oxidation to ω-oxidation.[48,64-66]

Gerson et al.[46] demonstrated that an epoxide hydrolase inhibitor added to phenytoin pretreated lymphocytes significantly shifted the dose response curve to the left, e.g. lower phenytoin doses now produced cell death. This strongly suggests that detoxification of a phenytoin metabolite was crucial to cell culture survival.

Immune-mediated hepatotoxicity has also been proposed for the aromatic anticonvulsants. Patients with drug related toxicity have been reported with autoantibodies directed toward the endoplasmic reticulum of the liver.[61] In addition, the genetics of drug metabolism and oxidative defense are felt to play a strong role in the genesis of anticonvulsant-induced hepatotoxicity. Dietary deficiencies of trace metals such as copper, zinc and selenium, important modulators of glutathione activity, are also felt to be responsible in some instances.[67,68]

5. Felbamate: Avenues of Exploration

5.1 Alternative Biotransformation

It has been proposed[23,30,31] that an alternative felbamate metabolic pathway which includes the formation of 3-carbamoyl-2-phenylprionaldehyde as a potential reactive intermediate, is active in felbamate biotransformation (fig. 1). *In vitro*, the aldehyde was rapidly eliminated to form 2-phenylpropenal and could be cyclised to form 4-hydroxy-5-phenyltetrahydro-1,3-oxazin-2-one. 2-Phenylpropenal (atropaldehyde) is electrophilic and was rapidly conjugated with glutathione.

The formation of atropaldehyde *in vivo* was examined in both rats and humans and identified by end product mercapturic acid formation. Following felbamate administration, reduced and oxidised mercapturic acids, suggestive of atropaldehyde formation were identified in rat and human urine.[31]

Confirmation of atropaldehyde formation was performed *in vitro* in human liver tissue. Aldehyde intermediates were trapped as oxime derivatives and assayed by gas chromatography-mass spectrometry.[23] One hypothesis is that felbamate toxicity may be correlated with the amount of atropaldehyde formed. Thus far, the ratio of urine 3-carbamoyl-2-phenylproprionic acid (CPPA) to mercapturates has been 2.2 to 1. Data from 1 individual suggests that glutathione converts the atropaldehyde to mercapturic acid.[69] The patient, while being administered paracetamol, had a higher ratio of CPPA to mercapturic acid. The ratio was greater than 3 standard deviations away from 30 patients not taking the analgesic.[69] The authors suggest these outliers may hold potential means of monitoring patients on felbamate therapy.

Recently, a patient who was withdrawn from felbamate therapy because of a developing neutropenia, was found to have an acid carbamate to mercapturic acids ratio of 19.4 in urine that was collected approximately 96 hours after cessation of felbamate therapy (T. Macdonald, personal communication).

While an identifiable reactive intermediate metabolite is intriguing, many questions still remain unanswered. For example, carbamazepine and phenytoin have speculated and demonstrable reactive epoxide intermediates yet, like felbamate, the development of aplastic anaemia is limited to only select patients. Perhaps the answer to the question may be derived from work with other drugs associated with aplastic anaemia and hepatotoxicity where altered biotransformation, a reduced ability to detoxify, and/or an immune-type response to an intermediate/metabolite have all been implicated.

5.2 Free Radicals

Free radicals are highly reactive and it seems unlikely that they are transported to distant tissues and must be generated *in situ*. Nevertheless, a pilot

study sought to determine if patients developing aplastic anaemia during felbamate treatment demonstrated deficiencies in free radical scavenging activity following recovery.

Patients with a history of felbamate-associated aplastic anaemia had significantly lower ($p < 0.05$) erythrocyte glutathione peroxidase level. Superoxide dismutase and glutathione reductase and transferase levels were also lower in the aplastic anaemia group but the difference was not statistically significant compared with felbamate patients without aplastic anaemia and healthy controls. There were no group differences in other enzymes or in selenium, copper or zinc concentrations.[70] Carbamazepine, phenytoin and valproic acid have also been reported to have deleterious effects on antioxidant systems in some patients.[65,66] The precise meaning of these findings requires further research.

5.3 *In Vitro* Study of Possible Bioactivation and Cytotoxicity

The hypothesis that felbamate or one of its metabolites could be bioactivated to a cytotoxic metabolite was tested by Leeder.[71] Felbamate and its known metabolites were incubated *in vitro* with human lymphoblastoid cell lines transfected with human CYP1A2, CYP2E1 and CYP3A4. A control cell line (cH01) transfected with vector only, possesses constitutive CYP1A1 activity.

The metabolites 2-hydroxy-2-phenyl-1,3-propanediol dicarbamate and 2-phenyl-1,3-propanediol monocarbamate were not cytotoxic to any cell line. The metabolite 3-carbamoyloxy-2-phenylproprionic acid was not toxic in the control cell line but concentration dependent cytotoxicity was noted with the h1A2v2 and h2E1/OR cell lines (20 to 25% at 2 mmol/L). The metabolite 2-(p-hydroxyphenyl)-1,3-propanediol dicarbamate was not toxic in the control cell lines (<15% at 2 mmol/L). The same toxicity was noted with 1 mmol of the compound in the h2E1v2 cells and little toxicity was noted in the h3A4/OR cell line. There was no evidence that a cytotoxic metabolite could be generated by CYP1A2, CYP2E1 or CYP3A4.

5.4 Evaluation of Possible Metabolic Activation by Human Neutrophils

Drugs associated with a high incidence of agranulocytosis are often oxidised to chemically reactive metabolites in activated human neutrophils by hypochlorous acid (HOCl), the major oxidant produced in these cells.[72-74] In a study conducted by Uetrecht,[75] radiolabelled felbamate was added to activated neutrophils and incubated for 45 minutes. After extensive washing, radioactivity was determined and compared with control cells (not activated). In addition, the myeloperoxidase/hydrogen peroxidase system of neutrophils was used to look for covalent binding of a felbamate reaction product to protein. [^{14}C]Felbamate was oxidised with HOCl and any reactive metabolite trapped by glutathione.

The data indicate that the oxidation of felbamate by neutrophils or HOCl was very slow. No covalent binding or glutathione adduct comparable with that noted with other drugs with known blood forming element toxicity was observed.

5.5 Analyses of Epoxide Hydrolase Gene Polymorphism

Evidence that epoxide hydrolase may be important in phenytoin toxicity stems from the fact that increased phenytoin-induced cultured lymphocyte death occurs when the enzyme is inhibited.[58] In recent years, patients with a genetic predisposition to low epoxide hydrolase activity have been identified.[76] To examine whether the enzyme might be involved in felbamate toxicity, patients receiving felbamate and reporting aplastic anaemia were examined for point mutation of the epoxide hydrolase gene. Preliminary data from healthy individuals and those with aplastic anaemia indicates the groups could not be distinguished from one another (D. Grant, personal communication).

Although convincing *in vitro* evidence suggests epoxide hydrolase activity detoxifies aromatic anticonvulsants, a previous study using the same analysis techniques in 26 patients with phenobarbital, phenytoin or carbamazepine toxicity like-

wise found no genetic point mutations which would predispose patients to adverse reactions.[76]

5.6 Influence on Erythroid Cell Cultures

Patients with genetic or drug induced bone marrow failure have increased levels of fetal haemoglobin, characteristic fetal patterns of remaining red blood cell enzymes and decreased levels of erythroid progenitor cells called burst forming units-erythroid (BFU-E). Alter and Perhach[77] examined *in vitro* and *in vivo* markers of haematopoiesis in felbamate-treated patients.

Paediatric patients treated with felbamate (n = 56 with 22 receiving monotherapy), had blood analysed [complete blood count (CBC), fetal haemoglobin]. There was no significant change in CBC or other haematological parameters in felbamate-treated patients. Increased fetal haemoglobin levels were noted in 2 patients but both were receiving adjunctive therapy.

Patients with aplastic anaemia generally have decreased BFU-Es. *In vitro* studies have included the incubation of BFU-E cultures with up to 100 μg/ml of felbamate and up to 10 μg/ml of the 4 known felbamate metabolites. Felbamate and its metabolites had little inhibitory effects on BFU-E.

5.7 Felbatol® Patient Registry

The Felbatol® Patient Registry was instituted in August 1997. Its purpose is 2-fold. The first is to provide a central data collection site for patients prescribed felbamate in order to build a database and the second is to gather data on human leucocyte antigen (HLA) and tumour necrosis factor (TNF) profiles which might be useful in establishing 'risk' or 'protective' factors. When a patient is prescribed felbamate and entered into the registry, that patient is followed to determine whether any of the factors previously defined can be used to identify patients 'at risk'. The Felbatol® Patient Registry has collected demographic data and performed HLA phenotyping for approximately 120 patients who were new patients or patients who continued receiving felbamate after the 'Dear Doctor' letter, or who restarted felbamate because of poor seizure control with other medications. Since no cases of aplastic anaemia or hepatotoxicity have been reported since the inception of the registry, no conclusions can be made regarding a possible susceptible phenotype.

To date, 8 patients with previously reported aplastic anaemia have been phenotyped. This is too few to draw definitive conclusions. HLA phenotypes associated with other instances of drug toxicity have previously been reviewed.[78] HLA phenotyping in patients with idiosyncratic reactions has had positive associations in gold and penicillamine toxicity and in hydralazine-induced lupus. These associations do not, however, predict absolute individual susceptibility. Only 73% of the hydralazine-induced lupus group were HLA-DR4. Clearly, other factors may be operative including possible combinations of HLA subtypes.

6. Clinical Safety Monitoring

6.1 Routine Haematological Laboratory Tests

Aside from their cost and inconvenience, frequent CBC and differential blood counts in patients being treated with anticonvulsants may not provide any advance warning of impending aplastic anaemia or agranulocytosis. Transient leucopenia has been reported in up to 12% of patients treated with carbamazepine, while the incidence of aplastic anaemia is rare and estimated at 4 to 39 per million patients treated.[79,80] Camfield et al.[81] performed routine blood/urine tests to evaluate haematological, liver and renal function in 198 children treated with phenobarbital, phenytoin, carbamazepine or valproic acid and performed the same tests in 662 adults receiving carbamazepine, phenytoin, phenobarbital or primidone. The authors concluded that routine screening was not cost effective, potentially led to unnecessary actions (repeat tests) and, on occasion, to the cessation of beneficial therapy.

On review, it was clear that the cost of monitoring far exceeded the cost of treating an occurence. Hart and Easton[80] estimated that when prescrib-

ing carbamazepine to a patient with epilepsy, the cost of the drug was $248 and the cost of laboratory fees to undertake testing recommended in the product labelling was $US730 (1975 dollars).

Continued counselling of patients and their families for an awareness of potential adverse events may be more effective than routine laboratory analysis.[78] In a large epidemiological study of 508 patients with aplastic anaemia, symptoms of anaemia (pallor, fatigue, and dyspnea) were the first clinical signs in 88% of the patients. Bleeding tendencies (bruising, bleeding gums, petechiae, unusual bleeding) were reported in 82% and fever/infection reported in 45% of the patients prior to the confirmation of aplastic anaemia by laboratory methods.[45]

6.2 Review of the Predictive Value of Liver Function Tests

Nearly all of the most commonly used anticonvulsants (carbamazepine, valproic acid and phenytoin) are associated with a spectrum of hepatic effects ranging from asymptomatic transient elevations in liver function tests to instances of fatal hepatotoxicity. Perhaps the most studied of these drugs is valproic acid since, shortly after its introduction as monotherapy and adjunct therapy, instances of hepatotoxicity were reported in children under 2 years of age with an incidence rate as high as 1 in 600 patients treated.[47,82-84]

Two types of anticonvulsant-induced hepatotoxic reaction have been noted. The first, believed to be immune-mediated, had a prodrome of fever, rash and eosinophilia while the second type (idiosyncratic) was preceded by nausea, vomiting, lethargy, drowsiness, jaundice and coma. In valproic acid–induced hepatotoxicity, these prodromal symptoms often preceded the elevation of liver function tests. In fact, it was demonstrated that monitoring of ALT and AST levels provided near normal values in many patients until the symptoms were well advanced. Nausea, vomiting and anorexia were the most frequently reported initial symptoms in 82% of patients with valproic acid–induced hepatotoxicity and lethargy, drowsiness and coma described in 40%.[79] In addition, other authors suggest increases in seizure frequency may herald some change in hepatic function.[82-84]

It has been proposed that initial screening laboratory tests be performed and followed with testing at regular intervals. Absolute timing of laboratory testing is impossible to forecast. Available data do not suggest that early detection of laboratory abnormalities in asymptomatic patients alters the outcome of hepatic failure. More importantly, patients or their caregivers should be educated as to the possible prodromal symptoms associated with hepatotoxicity.[77]

7. Conclusions and Recommendations

A number of therapeutically important drugs are associated with a risk of aplastic anaemia and hepatotoxicity.[49,61] The identification of risk factors and an understanding of the mechanism by which toxic effects are manifested, would be the ideal situation. Historically, valproic acid was marketed without the knowledge of its propensity to induce potentially fatal hepatotoxicity and early reports of these incidents severely curtailed the use of this anticonvulsant. The identification of the risk factors (age, developmental delay and multiple anticonvulsant therapy) for hepatotoxicity allowed an increased use of valproic acid with a lesser incidence of fatal consequences.

Felbamate is an anticonvulsant with demonstrated beneficial effects in patients with epilepsy that is refractory to other anticonvulsants. Even in this difficult population, felbamate produced statistically and clinically significant reductions in seizure incidence as both monotherapy and as adjunct therapy.[1-9,85] Prior to identification of the risk of hepatotoxicity and aplastic anaemia, the therapeutic index was quite high and with gradual titration of doses, felbamate is generally well tolerated. It is much too valuable a drug to discard.[10]

Laboratory tests designed to identify the potential ‘at risk’ patients are under evaluation. The most promising of which appears to be a simple ratio of 2 metabolites found in the urine. It is currently known that no point mutations in the epoxide

hydrolase gene were observed in patients with aplastic anaemia and neutrophils exposed to felbamate-HOCl treatment fail to yield a reactive metabolite. There is no evidence to support a CYP generated cytotoxic metabolite in human cells. No evidence of significant changes in CBCs or other haematopoietic effects of felbamate could be detected in felbamate-treated patients and there was no evidence that felbamate or its known metabolites affects the activity of erythroid progenitor cells (BFU-Es) *in vitro*. The ability of patients with aplastic anaemia to scavenge free radicals appears to be reduced but it is uncertain what the activity was prior to felbamate. Further work into the significance of the possible reactive aldehyde intermediate continues at present. It is not surprising that the majority of studies have been negative due to fundamental uncertainty about the cause of aplastic anaemia.

At the current time the 'at risk' patient for aplastic anaemia is most likely a Caucasian female with a history of serious anticonvulsant toxicity/allergy, a history of immune disorder and/or prior cytopenia and who has been taking felbamate for less than one year. Continued education of the patient regarding the possible prodromal symptoms of aplastic anaemia or hepatotoxicity and reporting these symptoms immediately is necessary for ongoing felbamate therapy. Laboratory testing not prompted by symptoms will generally not aid in the reversibility of haematological or hepatic abnormalities. Rational laboratory testing and discontinuing use of the drug if no clinically significant benefit is observed after 3 to 6 months may also aid in reducing risk or help to identify abnormalities earlier.

Further research will ultimately identify the 'at risk' patient regardless of whether the eventual mechanism for felbamate-induced aplastic anaemia/hepatotoxicity is immunological, intrinsic, genetic, related to a toxic intermediate, or the inability to detoxify felbamate or a metabolite. When this occurs, felbamate will be able to take its rightful place as one of the more useful anticonvulsants.

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