Epilepsy Research (2015) 113, 76—85

journal homepage: www.elsevier.com/locate/epilepsyres

Absence of Liver Toxicity in Perampanel-Treated Subjects: Pooled results from partial seizure phase III perampanel clinical studies

Antonio Laurenza[a,*], Haichen Yang[a], Betsy Williams[b], Sharon Zhou[b], Jim Ferry[a]

[a] *Eisai Neuroscience and General Medicine PCU, Eisai Inc., 155 Tice Blvd., Woodcliff Lake, NJ 07677, USA*
[b] *Eisai Medical and Scientific Affairs, Eisai Inc., 100 Tice Blvd., Woodcliff Lake, NJ 07677, USA*

Received 26 January 2015; accepted 11 March 2015
Available online 20 March 2015

KEYWORDS
Antiepileptic drugs;
Epilepsy;
Hepatic;
Liver;
Partial seizures;
Perampanel

Summary
Objective: The liver plays a major role in the metabolism and elimination of many antiepileptic drugs (AEDs), including perampanel. Some of the metabolites identified for perampanel are likely formed via reactive intermediates, which have the potential to covalently bind to protein and cause idiosyncratic toxicities, including hepatotoxicity. The approved AED perampanel is a selective, noncompetitive AMPA receptor antagonist. The safety and tolerability of perampanel have been well documented in 3 double-blind, randomized, placebo-controlled, phase III studies. Here we report the effects of perampanel on liver function in patients from the phase III studies to assess the potential for liver toxicity.
Methods: Following 6-week baseline, patients (≥12 years old) with drug-resistant partial seizures were randomized to once-daily double-blind treatment (6-week titration, 13-week maintenance) with 2, 4, 8, or 12 mg perampanel ($n = 1038$) or with placebo ($n = 442$). Clinical laboratory tests for hepatobiliary laboratory parameters were evaluated at baseline and at end of treatment. These included alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and total bilirubin. Treatment-emergent markedly abnormal values (an increase in NCI-CTC grade relative to baseline and a grade ≥2) and treatment-emergent adverse events (TEAEs) related to hepatobiliary parameters were also recorded.

Abbreviations: AE, adverse event; AED, antiepileptic drug; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; NCI-CTC, National Cancer Institute Common Toxicity Criteria; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

* Corresponding author. Tel.: +1 201 949 4157; fax: +1 201 949 4595.
E-mail addresses: Antonio_Laurenza@eisai.com (A. Laurenza), Haichen_Yang@eisai.com (H. Yang), betsy_williams@eisai.com (B. Williams), Xiaozheng_Zhou@eisai.com (S. Zhou), Jim_Ferry@eisai.com (J. Ferry).

http://dx.doi.org/10.1016/j.eplepsyres.2015.03.005

Results: Mean hepatobiliary values were within normal ranges at baseline and end of treatment for all perampanel groups and placebo. Mean changes from baseline to end of treatment were small. The incidence of markedly abnormal results was very low for perampanel and placebo. TEAEs related to hepatobiliary parameters occurred in 0.4% of perampanel patients and 0% of placebo patients. Hepatobiliary disorders included cholelithiasis ($n = 3$ in perampanel) and abnormal hepatic function ($n = 1$ in perampanel). None of the events were serious or led to perampanel discontinuation. No subject had values that met the criteria for Hy's Law.
Conclusion: Hepatobiliary laboratory data and related TEAEs were not notably different between perampanel and placebo treatment groups, and no dose-related trends were observed. Based on the laboratory results from the 3 Phase III studies, perampanel (2, 4, 8, and 12 mg) demonstrated no clinically important effects on liver function tests, indicating perampanel is an AED with a low potential for drug-induced liver toxicity.

Introduction

Approximately 2.2 million Americans are currently diagnosed with epilepsy, a chronic disease of the brain in which patients can have at least 2 unprovoked seizures occurring >24 h apart; 1 unprovoked seizure and a probability of further seizures similar to the general recurrence risk (≥60%) after two unprovoked seizures, occurring over the next 10 years; or a diagnosis of an epilepsy syndrome (Fisher et al., 2014; Institute of Medicine of the National Academies et al., 2012). Abnormal excessive or synchronous neuronal activity in the brain results in an epileptic seizure (Fisher et al., 2005). Initial treatment of epilepsy requires the therapeutic use of antiepileptic drugs (AEDs) in order to control seizures, avoid drug-induced adverse events, and maintain quality of life (Elger and Schmidt, 2008).

Many drugs, including AEDs, are metabolized and eliminated by the liver (Ahmed and Siddiqi, 2006; Hussein et al., 2013; Lee, 1995), and thus there is the potential for drug-induced liver injury/toxicity (Hussein et al., 2013). For some AEDs, such as valproic acid and felbamate, a risk of hepatotoxicity is evident and linked to the formation of reactive metabolic intermediates (Zaccara et al., 2007). Reactive intermediates have the potential of covalently binding to proteins, especially if reduced glutathione (GSH) levels become depleted, thus impairing detoxification (Ballet, 2010; Begriche et al., 2011; Evans et al., 2004; Lammert et al., 2010). This mechanism is considered to play a role in causing idiosyncratic toxicities, including hepatotoxicity (Ballet, 2010; Evans et al., 2004; Lammert et al., 2010). However, there is also evidence of a clinical daily dose threshold below 10 mg/day for which idiosyncratic toxicities are rare (Ballet, 2010; Evans et al., 2004; Nakayama et al., 2009; Uetrecht, 2001). Additionally, the metabolite of the parent drug and/or the products of oxidation can cause injury to hepatic cell components as well as the bile ducts, causing cholestasis (Lee, 1995). A number of blood tests measuring liver enzyme levels can assist in determining the health of the liver (Pratt and Kaplan, 2000). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can serve as markers of hepatocellular injury, while alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) can indicate an obstruction in the bile ducts, cholestasis, or hepatobiliary disease (Hussein et al., 2013; Pratt and Kaplan, 2000). A few AEDs are associated with drug-induced liver toxicity and require regular monitoring of liver enzymes or discontinuation of the drug (Hussein et al., 2013; Warner et al., 1998).

Perampanel is a first-in-class, orally active, noncompetitive, selective AMPA glutamate receptor antagonist approved in more than 40 countries, including the United States and in the European Union, for adjunctive treatment of partial seizures with or without secondarily generalized seizures, in patients with epilepsy aged ≥12 years (in Canada, perampanel is approved in patients aged ≥18 years) (FYCOMPA SPC, 2012; FYCOMPA Product Monograph, 2013; FYCOMPA Prescribing Information, 2014; Hanada et al., 2011; Krauss et al., 2013). The efficacy and safety of perampanel in patients with treatment-resistant partial seizures have been demonstrated in three multicenter, double-blind (DB), randomized, parallel-group, placebo-controlled, phase III studies (French et al., 2012, 2013; Krauss et al., 2012). Similar to other AEDs that are metabolized predominantly by the liver (Ahmed and Siddiqi, 2006), perampanel is extensively metabolized via CYP3A4 and CYP3A5 enzymes, with the main pathway being oxidation and subsequent glucuronidation (Rektor, 2013; Rogawski and Hanada, 2013). The potential for perampanel to result in liver toxicity was intensively assessed clinically using the data from the three Phase III studies. Here we report the comprehensive evaluation of perampanel on liver function tests undertaken to assess the potential for liver toxicity.

Methods

The three phase III studies (study 304: NCT00699972; 305: NCT00699582; 306: NCT00700310) were conducted between April 2008 and January 2011 (French et al., 2012, 2013; Krauss et al., 2012). All studies were compliant with the Helsinki Declaration, the European Medicines Agency requirements, and the US Code of Federal Regulations, as appropriate. Study protocols, amendments, and informed consents were reviewed by national regulatory authorities in each country and by independent ethics committees or institutional review boards for each site. All patients provided written informed consent before participation.

The three phase III core studies were randomized, double-blind, placebo-controlled evaluations of adjunctive