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ScienceDirect
Pharmacology, Biochemistry and Behavior 89 (2008) 523 – 534
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
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In vivo pharmacological effects of JZP-4, a novel anticonvulsant, in models for anticonvulsant, antimania and antidepressant activity

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Received 6 August 2007; received in revised form 28 January 2008; accepted 4 February 2008
Available online 11 February 2008

Abstract

JZP-4 is a potent calcium and sodium channel blocker, which is currently being evaluated in patients as an anticonvulsant and mood stabilizer. In the current studies, JZP-4 was evaluated in a variety of animal models for anticonvulsant, antimania and antidepressant activity. In the mouse and rat maximal electroshock models, JZP-4 was slightly more potent than LTG. In the mouse pentylenetetrazole induced seizures model, JZP-4 was approximately twice as potent as lamotrigine in prolonging the time to clonus. In the mouse 6-Hz model for drug resistant or refractory epilepsy, JZP-4 had potent anticonvulsant activity at all current intensities, whereas LTG was active at only the lowest current intensity. In the mouse amphetamine-chlordiazepoxide model for antimanic effects, JZP-4, but not LTG, produced dose-related and significant effects at 3 and 10 mg/kg i.p. In the rat forced swim model of antidepressant activity, JZP-4 (30 mg/kg i.p.) produced a significant reduction in immobility and an increase in climbing behavior. LTG (30 mg/kg i.p.) produced similar effects but these effects did not achieve statistical significance. The specificity of this antidepressant response was confirmed in the rat locomotor test. In this test, JZP-4 produced dose-related and significant reductions in locomotor activity, indicating that it was not a CNS stimulant. LTG produced no significant effects in the rat locomotor test. The studies have demonstrated that JZP-4 has greater potency and efficacy than LTG in models of refractory epilepsy, antidepressant activity and antimania activity. The variance between the effects of LTG and JZP-4 may be related to the greater potency at sodium channels or the additional pharmacological actions of JZP-4 on calcium channels.

Keywords: JZP-4; Lamotrigine; Anticonvulsant; Mood stabilizer; Antidepressant; Mania; Epilepsy; Bipolar disorder

1. Introduction

Anticonvulsants are among the most widely utilized pharmacological agents for CNS disorders with applications for neurological disorders such as epilepsy, essential tremor and neuropathic pain and for psychiatric disorders such as mood stabilizers in bipolar disorder, schizophrenia and drug withdrawal (Goldsmith et al., 2003; French et al., 2004; Morley-Forster, 2006; Weisler et al., 2006). Although these compounds are used in a broad range of patients, many of these drugs have dose limiting side-effects, such as sedation, cognitive impairment, weight gain or birth defects. A few of these compounds may even have rare, but life-threatening side-effects such as serious rash, blood dyscrasias, hepatic failure or cardiac arrhythmias (Stefan and Feuerstein, 2007). To avoid some of these adverse events, many anticonvulsants have to be titrated slowly to a therapeutic level, which also implies that the patients will have minimal benefit during the initial subtherapeutic phase (Ketter et al., 2005). There remains a

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0091-3057/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2008.02.007

need for drugs that have broad spectrum efficacy and the tolerability and pharmacokinetic profiles that allow them to be dosed rapidly to achieve steady state pharmacokinetics at therapeutic doses.

Lamotrigine (LTG), one of the better tolerated anticonvulsants, is clinically useful as an anticonvulsant for the treatment of refractory partial epilepsy, generalized seizures, absence seizures and Lennox-Gastaut syndrome (Leach et al., 2002) and as a mood stabilizer in bipolar II disorder (Bowden, 1998; Shelton, 2002; Goldsmith et al., 2003). Although LTG is generally well tolerated, it has to be titrated to therapeutic doses because it can induce an immunologic hypersensitivity reaction (Ketter et al., 2005). The cause of this hypersensitivity has been linked to an arene oxide metabolite, which has been proposed to be the immunoreactive antigen (Maggs et al., 2000; Anderson, 2002; Bavdekar et al., 2004, Fig. 1). Further complicating the titration of LTG is its long (14–60 h) half-life which requires a prolonged titration period to achieve steady state serum concentrations.

JZP-4 (3-(2,3,5-trichloro-phenyl)-pyrazine-2,6-diamine) is a potent and selective sodium and calcium channel blocker (Foreman et al., submitted for publication) that is currently in clinical trials as an anticonvulsant and mood stabilizer. It has structural similarities related to LTG but has a trichlorophenyl ring rather than a dichlorophenyl ring and a pyrazine rather than a triazine ring (Fig. 1). These modifications may be responsible for its greater potency for both sodium and calcium channels and a greater selectivity for the central compared to peripheral ion channels (Foreman et al., submitted for publication). The structural characteristics of JZP-4 also change in pathways involved with the metabolism from predominately metabolism by UGT1A4 for lamotrigine to oxidation by CYP1A2 followed by glucuronidation by UGT2B15 for JZP-4. The additional chlorine on the phenyl ring also reduces the possibility of the formation of the potentially immunogenic arene oxide (Fig. 1), which may lower its risk of serious dermatological side-effects. JZP-4 also has a lower half-life compared to LTG (manuscript in preparation), making it pharmacokinetically possible to achieve therapeutic doses at steady state with a shorter titration period (Eller et al., in preparation).

The current studies focus on the comparative effects of JZP-4 in a variety of animal models for different forms of epilepsy, bipolar mania and depression. The animal models for anticonvulsant activity included are those that are considered predictive for anticonvulsant activity in generalized myoclonic seizures, generalized tonic–clonic seizures, partial seizures with secondary generalization and treatment-resistant epilepsy. The animal models for psychiatric disorders included the amphetamine-chlordiazepoxide induced hyperactivity model for antimania activity, the forced swim test for antidepressant activity and the locomotor activity evaluation that discriminates generalized stimulatory or sedative effects that can lead to false positive responses in the other behavioral models. Each of these psychopharmacological models are considered to be predictive and have been extensively validated.

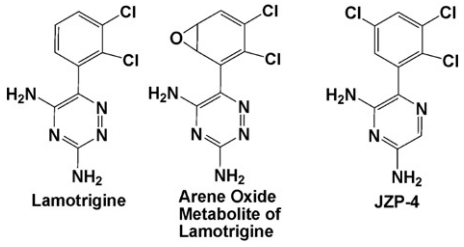

Fig. 1. Structures of lamotrigine, the arene oxide metabolite of lamotrigine and JZP-4.

2. Methods

2.1. Animals and testing vehicle

Male albino CF1 mice (18–25 g, Charles River, Portage, MI) and male albino Sprague Dawley rats (100–150 g; Simonsen, Gliroy, CA and Charles River, Raleigh, NC) were used as experimental animals in the MES, and 6 Hz tests conducted at the NINDS-Anticonvulsant Testing Center. Male C57Bl/6J mice (8 weeks of age, Jackson Laboratories, Bar Harbor, Maine) were used in the mouse amphetamine-chlordiazepoxide induced locomotor model of antimania activity conducted at Psychogenics, Inc. Young adult, male Sprague Dawley rats (approximately 150 g) from Harlan Laboratories (Indianapolis, IN) were used in the rat forced swim test for antidepressant activity and the locomotor activity tests conducted at Psychogenics, Inc. Male Lister hooded rats (280–350 g at the time of surgery) used for the kindling studies; young adult (5–8 weeks of age) EL mice used for the EL mouse studies, and male CD1 mice (25 g) used for the intravenous PTZ tests conducted at GlaxoSmithKline were obtained from the GlaxoSmithKline Rodent Breeding Unit.

All rats and mice used in the studies at Psychogenics and the NINDS-Anticonvulsant Screening Center were housed, fed and handled in a manner consistent with the recommendations in the National Research Council Publication, “Guide for the Care and Use of Laboratory Animals” and used only once. No insecticides capable of altering hepatic drug metabolism enzymes were used in the animal facilities. All animals were euthanized in accordance with the Institute of Laboratory Resources policies on the humane care of laboratory animals. The animal care and use procedures for the studies conducted at GlaxoSmithKline were in accordance with UK Home Office regulations.

For the mouse MES, PTZ and 6 Hz anticonvulsant studies and the mania studies, all test suspensions were administered either i.p. or p.o. at volumes of 0.01 ml/g body weight in a 0.5% methylcellulose suspension. For the rat MES, all test suspensions were administered at 4 ml/kg body weight in a 0.5% methylcellulose suspension. In the rat forced swim and locomotor activity studies, all suspensions were administered in volumes of 1 ml/kg. For the kindled rat studies, JZP-4 was administered p.o. in a 0.25% methylcellulose suspension at a volume of 1 ml/kg p.o.

2.2. MES test and 6 Hz test

For the MES and 6 Hz tests, a drop of anesthetic/electrolyte solution (0.5% tetracaine hydrochloride in 0.9% saline) was applied to the eyes of each animal prior to placement of the corneal electrodes. Eight animals per treatment group were used in both the mouse and rat MES studies. The doses used for the