European Journal of Pharmaceutical Sciences 49 (2013) 836–844

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

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

Influence of mild and moderate liver impairment on the pharmacokinetics and metabolism of almorexant, a dual orexin receptor antagonist

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ARTICLE INFO

Article history:
Received 17 January 2013
Received in revised form 9 April 2013
Accepted 2 June 2013
Available online 11 June 2013

Keywords:
Almorexant
Hepatic impairment
Pharmacokinetics
Metabolism
Insomnia

ABSTRACT

This single-dose study aimed at investigating the effect of different degrees of hepatic impairment on the pharmacokinetics (PK), metabolism, and tolerability of almorexant, a first-in-class dual orexin receptor antagonist. Subjects with mild (Child-Pugh A, Group A, $n = 8$) and moderate (Child-Pugh B, Group B, $n = 9$) liver impairment and subjects with normal liver function (Group D_A and D_B, both $n = 9$) received a dose of 100 mg almorexant. PK parameters of almorexant and its four primary metabolites were determined. Almorexant exposure increased with severity of hepatic impairment. Geometric mean ratios (90% confidence interval) of $AUC_{0-\infty}$ were 2.8 (1.5–5.4), 7.2 (3.7–14.1), and 3.3 (1.7–6.4) comparing A vs. D_A, B vs. D_B, and B vs. A, respectively. The four metabolic pathways involved in the formation of the primary metabolites were affected in a different fashion. Geometric mean $AUC_{0-\infty}$ ratios comparing A vs. D_A were 6.9, 1.1, 1.4, and 3.6 for M3, M5, M6, and M8, respectively. Comparing B vs. D_B the corresponding figures were 7.3, 2.0, 5.4, and 1.3, respectively. Significant effects of hepatic impairment on the PK of almorexant suggested the need for dose adjustment in subjects with mild hepatic impairment and did not support its use in subjects with moderate or severe hepatic impairment.

1. Introduction

Insomnia is one of the most common central nervous system disorders. Population-based studies indicate that approximately 30% of adults in different countries report at least one symptom of insomnia (Ancoli-Israel and Roth, 1999). Modulation of sleep and wakefulness is mainly dependent of the balance between two systems, a sleep induction system via the gamma-aminobutyric acid (GABA) receptor complex and an arousal system in which orexin receptors are at the crossroad of arousal systems that promote wakefulness (Nishino, 2007; Scammell and Winrow, 2011; Richey and Krystal, 2011). The neuropeptides orexin-A and orexin-B were discovered in 1998 as the result of intensive research programs on orphan G-protein-coupled receptors (GPCRs) (Civelli et al., 2001; de Lecea et al., 1998; Sakurai et al., 1998; Stadel et al., 1997). Orexins are endogenous ligands of two GPCRs (OX_1 and OX_2 receptors). Orexin-A has equal affinity at both receptors, while orexin-B displays a 10-fold higher affinity for the OX_2 than for the OX_1 receptor (Smart et al., 1999). The orexin peptides and their receptors play a central role in the regulation of sleep-wake balance and appetite (Smart and Jerman, 2002; Lee et al., 2005; Sakurai, 2005). While the most widely applied aim is to reinforce the sleep induction system with $GABA_A$ receptor agonists, orexin receptor antagonists aim at reducing the activity of arousal systems in insomniac patients in whom a state of hyperarousal has been characterized.

Almorexant, a tetrahydroisoquinoline derivative, was the first dual orexin receptor antagonist in clinical development for primary insomnia. Almorexant remains a useful model compound for investigating the orexin system (Brisbare-Roch et al., 2007; Hoever et al., 2010, 2012). A significant proportion of insomnia patients comprise elderly subjects frequently suffering from various forms of liver disease associated with impaired hepatic function. As almorexant has a bioavailability of 11% and is mainly eliminated by hepatic metabolism (Hoch et al., 2012), impaired liver function might affect the PK of almorexant. Almorexant metabolism is mostly dependent on cytochrome P450 (CYP) 3A4 and has been shown to be inhibited by strong and moderate CYP3A4 inhibitors such as ketoconazole and diltiazem, respectively (Cruz et al., 2011, Gehin et al., 2011). Metabolism of almorexant is characterized by four primary metabolic pathways involving demethylation of methoxy groups in the 6- or 7-position of the tetrahydroisoquinoline ring to yield the isomeric phenols M3 (ACT-127980) and M8 (ACT-127979), dehydrogenation of the tetrahydroisoquinoline to the aromatic isoquinolinium ion M5 (ACT-127515), and oxidative dealkylation with loss of the phenylglycine moiety to yield M6 (ACT-078332). The

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http://dx.doi.org/10.1016/j.ejps.2013.06.002

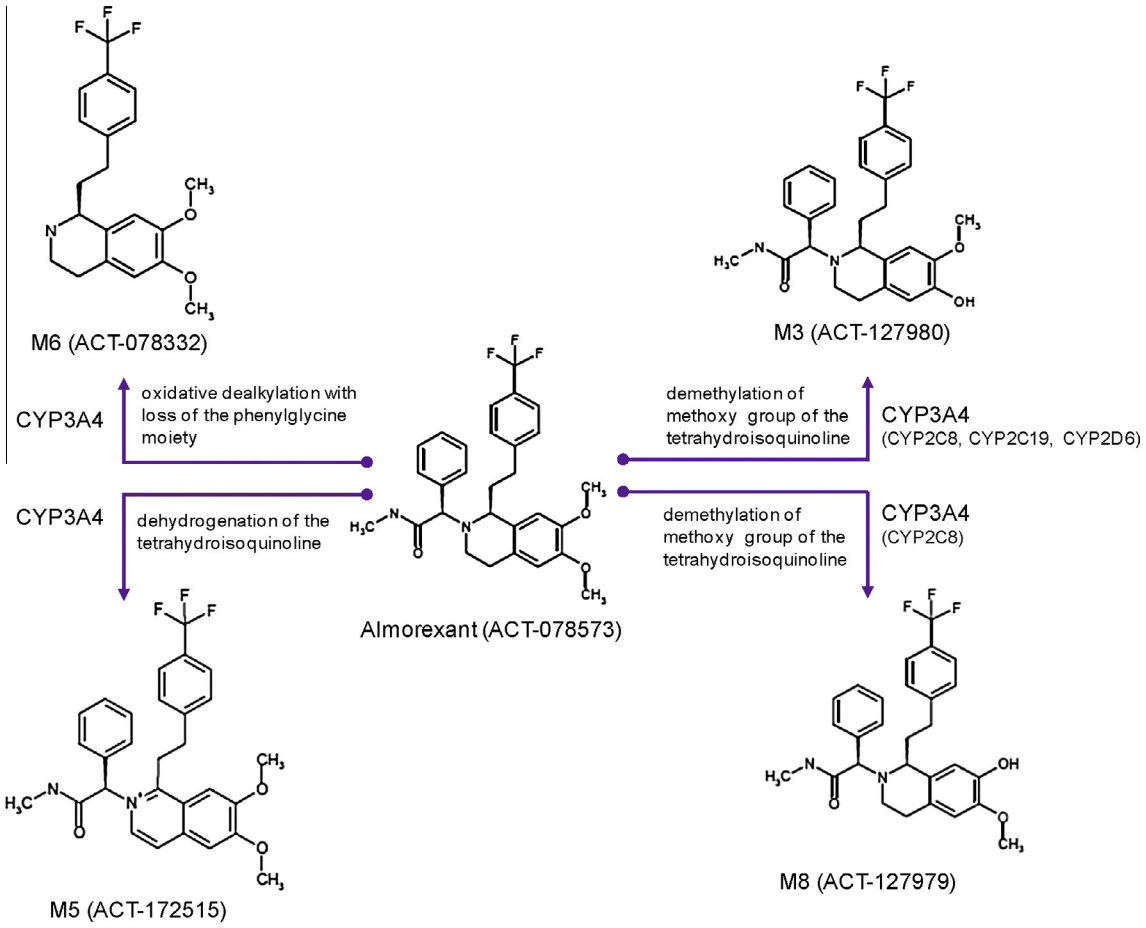

Fig. 1. Metabolic scheme for almorexant and formation of its four primary metabolites.

metabolic scheme of the formation of the primary almorexant metabolites is displayed in Fig. 1.

In vitro experiments have been conducted to explore the role of drug transporters in the disposition of almorexant and no involvement of P-gp and OATP was demonstrated (Actelion Pharmaceuticals Ltd, data on file).

The liver plays a central role in the metabolism of various drugs. Hepatic dysfunction may alter drug absorption, distribution, and elimination, as a result of reduction in absolute cell mass and in cellular enzyme content or activity (McLean and Morgan, 1991; Westphal and Brogard, 1997). Reduced hepatic blood flow in chronic hepatic disease may also decrease hepatic clearance. Biliary excretion of drugs and oxidative drug metabolism have been shown to be impaired in subjects with hepatic cirrhosis whereas conjugation of drugs often remains unaffected (McLean and Morgan, 1991; Westphal and Brogard, 1997; Morgan and McLean, 1995; Sonne, 1996).

The present study was designed to assess the effect of mild, moderate, and severe hepatic impairment on the PK and metabolism of almorexant and its primary metabolites after single oral administration of 100 mg almorexant. In addition, the tolerability and safety of almorexant were investigated.

2. Materials and methods

2.1. Subjects

Male and female subjects with normal hepatic function or mild, moderate, or severe hepatic impairment due to liver cirrhosis were eligible for this study. All study participants were enrolled from the subject database at Drug Research Center Ltd, Balatonfüred, Hungary. The accepted age range was 30–75 years (inclusive) and the body mass index (BMI) of the subjects was required to be 18–32 kg/m^2 with 50 kg being the lowest accepted body weight. This study aimed at including patients from all three Child-Pugh categories (mild, moderate, and severe) (Pugh et al., 1973) as well as control subjects with normal hepatic function (Food and Drug Administration, 2003; CHMP, 2005). Relevant assessments for encephalopathy grading (i.e., neurological examination and EEG) were carried out within 28–3 days prior to drug administration. An abdominal sonography was carried out to assess the absence or presence and grade of ascites and the absence or presence of hepatocellular carcinoma. The study population was to be allocated to 4 main groups: Group A (subjects with mild hepatic impairment, Child-Pugh A), Group B (subjects with moderate hepatic impairment, Child-Pugh B), Group C (subjects with severe hepatic impairment, Child-Pugh C), and Group D (healthy matched subjects). Group D was subdivided into subgroups D_A and D_B including matched healthy subjects of Groups A and B, respectively. Healthy subjects were matched to each subject with hepatic impairment with regard to age (±5 years difference allowed), both body weight and height (±10% difference allowed), and sex based on results obtained at screening. Selection and enrollment of each matched healthy subject was performed after the corresponding subject with hepatic impairment had completed all study procedures according to the study protocol. The minimum creatinine clearance (according to Cockroft and Gault formula) for inclusion was stratified by age and was >80 ml/min for subjects <50 years of age, >70 ml/min for subjects 50–60 years of age, and