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Single dose efficacy evaluation of two partial benzodiazepine receptor agonists in photosensitive epilepsy patients: A placebo-controlled pilot study

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ABSTRACT

Benzodiazepines (BZDs) are highly effective to suppress various types of seizures; however, their clinical use is limited due to adverse effects and tolerance and dependence liability. Drugs that act only as *partial* agonists at the BZD recognition site (initially termed "BZD receptor") of the $GABA_A$ receptor chloride ionophore complex or exhibit a $GABA_A$ receptor subtype-selectivity are thought to have advantages vs. full agonists such as diazepam and most other clinically used BZDs in that such compounds have less adverse effects and reduced or absent tolerance and dependence liability. One of such compounds, abecarnil, has been clinically evaluated as a novel anxiolytic drug, but, despite its potent preclinical anti-seizure activity, it has not yet been evaluated in patients with epilepsy. In the present proof-of-concept study, we performed a within-subject placebo-controlled, single oral dose study of abecarnil in patients with photosensitive epilepsy. Flumazenil, which is generally considered a BZD receptor antagonist, but has slight partial agonistic properties, was used for comparison. In total, 12 patients were enrolled in this study. Abecarnil, 5 or 10 mg, completely abolished the photo-paroxysmal EEG response, while flumazenil, 30, 60 or 100 mg, was less effective. The anti-epileptic effect of abecarnil was significantly different from both placebo and flumazenil. Sedative adverse effects were observed after abecarnil but not flumazenil. The study substantiates previous pre-clinical experiments that abecarnil exerts pronounced anti-seizure activity. Epilepsy is often associated with anxiety, so that the anxiolytic activity of abecarnil would be an added advantage when using this compound in epilepsy patients.

Introduction

Benzodiazepines (BZDs) are widely used for difficult-to-treat seizures and as rescue therapy (acute repetitive seizures, status epilepticus) (Prasad et al., 2014; McKee and Abou-Khalil, 2015). Their prophylactic and therapeutic use is, however, limited due to adverse effects such as sedation, motor incoordination, alcohol potentiation, impairment of cognitive function and withdrawal seizures (Riss et al., 2008). Furthermore, long-term treatment is associated with loss of efficacy (tolerance) and development of physical and psychological dependence and addiction, so that BZDs such as diazepam and clonazepam are only of limited use in the long-term treatment of epilepsy (Löscher and Schmidt, 2006).

BZDs act as positive allosteric modulators of the inhibitory neurotransmitter GABA by binding to a high-affinity, saturable, and stereoselective recognition site (initially termed "BZD receptor") of the $GABA_A$ receptor chloride ionophore complex, leading to increased chloride channel opening frequency, increased chloride influx, and, consequently, to increased membrane

Abbreviations: AED, antiepileptic drug; BZD, benzodiazepine; IPS, intermittent photic stimulation; PoC, proof-of-concept; PPR, photo-paroxysmal EEG response; SPR, standardised photoparoxysmal response.

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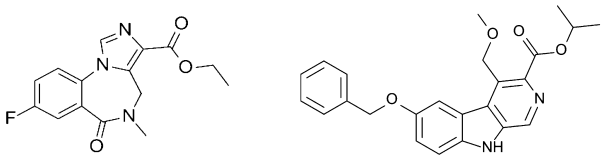

Flumazenil
(Ro 15-1788;
ethyl 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4*H*-benzo[*f*]imidazo[1,5-*a*][1,4]diazepine-3-carboxylate)

Abecarnil
(ZK 112,119;
propan-2-yl 4-(methoxymethyl)-6-(phenylmethoxy) -9*H*-pyrido[5,4-b]indole-3-carboxylate)

Fig. 1. Chemical structures of the benzodiazepine flumazenil and the β-carboline abecarnil.

hyperpolarization (Rogawski and Löscher, 2004). One of the early concepts to resolve the problem of tolerance and dependence liability of BZD receptor ligands was to develop partial agonists for this site (Haefely, 1988a; Stephens and Sarter, 1988; Haefely et al., 1990, 1992; Costa and Guidotti, 1996). Initial compounds thus developed were either based on the BZD structure, e.g., bretazenil and imidazenil, or the β-carboline structure, e.g., abecarnil (Fig. 1). Compared to the traditional BZDs, such as diazepam, which act as full agonists at the BZD site of the $GABA_A$ receptor, partial agonist were shown to exert less sedative adverse effects and were not associated with tolerance and dependence during chronic administration in animal models. The main goal behind such compounds was to develop anxioselective anxiolytics, i.e., compounds with the rapid and robust anti-anxiety effects of a BZD but without the side effects (Stephens et al., 1993; Skolnick, 2012); one of us (W.L.) became particularly interested in using the advantages of partial BZD agonists also for treatment of epilepsy (Löscher et al., 1990; Löscher, 1993). Indeed, the partial BZD receptor agonist abecarnil, a β-carboline derivative developed by Schering in Berlin, Germany, in the 1980s, exhibited promising anti-seizure efficacy in various animal models of seizures and epilepsy, high tolerability, and reduced or absent tolerance or dependence liability during initial studies in rodents, dogs, and monkeys (Löscher et al., 1990; Turski et al., 1990; Sannerud et al., 1992). However, at the time of development, epilepsy was not considered a primary indication for abecarnil, but the drug underwent clinical trials in patients with generalized anxiety, and further development was halted in the mid-1990s because of lack of advantages vs. traditional BZDs (Skolnick, 2012). In the present pilot study, we evaluated whether abecarnil inhibits the photo-paroxysmal EEG response (PPR) in patients with photosensitive epilepsy. For comparison, we used flumazenil (Fig. 1), a BZD that is generally considered a BZD receptor antagonist, but has slight partial agonistic properties (Haefely and Polc, 1986; Haefely, 1988b), which may explain the anti-seizure effects of this drug observed previously in patients with epilepsy (Scollo-Lavizzari, 1984, 1988).

Material and methods

For both abecarnil and flumazenil, similar design and methodology were used. Both studies were performed in the same hospital one after another and within a total timeframe of 4 years.

Design

The trial design was a single-center, single-blind, within subject placebo-controlled, single oral dose study of the drug under investigation (Phase IIa). Female and male adult epilepsy patients (18–60 yr of age and otherwise healthy) were eligible if they had shown generalized epileptiform EEG reactions on intermittent photic stimulation (IPS), consistently and reliably during prior EEG assessments and at 2 separate flash frequencies as absolute minimum. Two AEDs at most, excluding ethosuximide and benzodiazepines, were allowed during the three day-trials for their safety and to maintain steady state.

Patients were considered as healthy volunteers when participating in these early phase PoC trials. After informed consent and complete physical/neurological examination, laboratory screening and pregnancy tests if applicable, patients were admitted for three days to the EEG-ward. Concomitant AEDs were taken as before and no other restrictions were imposed, except reduction in visual stimulation by watching television.

Subjects received a single dose of matched placebo on the morning of Day 1, a single dose of investigational drug on the morning of Day 2, and a second single dose of placebo again on the morning of Day 3. IPS EEG sessions with determination of photosensitivity ranges were performed at predose and at hourly and two hourly intervals up to a minimum 6 h post dose on Days 1, 2 and 3. In several patients IPS EEG sessions continued two hourly up to 10 or 12 h after dosing on Day 2. In the flumazenil trial, additional IPS sessions took place at 0.5 h and/or 1.5 h post dose. Timings at Day 1, 2 and 3 were kept the same.

The trial design was adaptive: depending on the results per two patients (efficacy and side-effects) doses of the experimental drugs were either increased or decreased until abolishment of PPR was achieved without significant side-effects. Dose selection was based on previous studies with abecarnil in patients with generalized anxiety disorder (Lydiard et al., 1997; Pollack et al., 1997; Small and Bystritsky, 1997; Rickels et al., 2000) and with flumazenil in patients with epilepsy (Scollo-Lavizzari, 1988).

For safety reasons vital signs (standing and supine blood pressure, pulse rate) were recorded at screening, at pre-dose and 2 h post-dose on Days 1, 2 and 3. Furthermore, a neurological examination was performed at screening and at 2 h post-dose on Days 1, 2, and 3.

Photic stimulation procedure

Methodology

The international 10:20 system of electrode placement was used to record EEGs. Intermittent photic stimulation (IPS) was performed using the *Grass PS 33 plus* stimulator (round Xenon lamp giving flashes of 10 μs duration, 1 Joule/flash, diameter 14 cm). Patients sat at a distance of 30 cm from the photic simulator and were asked to look at the center of the lamp. Ambient lighting was minimized (c. 50 lx), yet sufficient to facilitate observation of the patient whilst controlling ocular fixation on the centre of the lamp.

Separate trains of flashes of 4–6 s' duration were used at fourteen different frequencies (at maximum—see later for explanation): 2, 6, 8, 10, 12, 15, 18, 20, 23, 25, 30, 40, 50, and 60 Hz. Flash trains were separated by a pause of at least 5–7 s.

IPS was used to assess the lowest (starting at, and increasing from 2 Hz) and highest (starting at, and decreasing from 60 Hz) frequencies evoking a generalized PPR. At screening, these ranges were assessed in three distinct eye conditions, in the same sequence for all patients: eye-closure, eyes-closed and eyes-open. The most provocative eye condition was then chosen for the three day trial. To discriminate between spontaneous and IPS-evoked discharges, the EEG was initially recorded without IPS for at least 2.5 min with eyes open and another 2.5 min with eyes closed. All tracings were re-analyzed retrospectively.

Photosensitivity range

Each threshold flash frequency was assessed at each timepoint commencing at 2 Hz. As soon as generalised epileptiform activity appeared, the stimulation for that particular frequency was