Drug and Alcohol Dependence 188 (2018) 295–303

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Full length article

TV-1380 attenuates cocaine-induced changes in cardiodynamic parameters in monkeys and reduces the formation of cocaethylene

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ARTICLE INFO

Keywords:
Addiction
Butycholinesterase
Cardiac troponin I
Cocaethylene
Cocaine
TV-1380

ABSTRACT

Background: TV-1380 is a rationally mutated, human BChE fused to human serum albumin that has high hydrolytic enzymatic activity against cocaine and as well as an extended elimination half-life.
Objective: The present studies examined the safety of TV-1380 and its protective effect when given to monkeys alone or concomitantly with cocaine and ethanol.
Methods: A set of studies was conducted in monkeys with TV-1380. The parameters tested included telemetric assessment of cardiovascular parameters, clinical pathology, plasma analysis of cardiac troponin I, ex-vivo analyses of cocaethylene and PK analysis of serum concentrations of TV-1380, cocaine and its metabolites, and histopathological examinations.
Results: TV-1380 treatment in monkeys was well tolerated. TV-1380 pretreatment prior to cocaine significantly attenuated the cardiac effects of cocaine and reduced cocaine-induced elevations in serum cardiac troponin I. TV-1380 changed the metabolic fate of cocaine resulting in decreased exposure to benzoylecgonine, while increasing the exposure to ecgonine methyl ester in plasma.TV-1380 reduced the plasma levels of the toxic metabolite cocaethylene formed after co-administration of ethanol and cocaine.
Conclusion: The results of this study demonstrate that TV-1380 not only accelerates the elimination of cocaine, but also protects the treated animal from the cardiac effects of cocaine, and inhibits the formation of the toxic cocaethylene metabolite when cocaine is given together with ethanol, supporting further clinical development of modified BChE products as possible treatments for cocaine abuse.

1. Introduction

Cocaine use impacted the lives of 18 million people in 2014, as reported by the United Nations Office on Drugs and Crime in 2016 (UNODC, 2016). In addition to the known hazards of cocaine use and abuse, cocaine can cause cardiovascular pathologies, including myocardial infarction, heart failure, arrhythmias, aortic dissection, and endocarditis (Rezkalla and Kloner, 2007; Stankowski et al., 2015).

Presently, there are no approved pharmaceuticals to treat cocaine addiction (Shorter et al., 2015). A potential approach to treatment of cocaine addiction is the administration of rational, mutagenic, hydrolytic enzymes that can accelerate cocaine metabolism (Sun et al., 2002). Butyrylcholinesterase (BChE) is the main endogenous enzyme that hydrolyses cocaine to its inactive metabolites, ecgonine methyl ester and benzoic acid in plasma (Xie et al., 1999; Inaba et al., 1978). Carboxylesterase-1 (CE1) is active in the liver and hydrolyzes cocaine to produce benzoylecgonine and methanol. Oxidative enzymes in the liver can also metabolize cocaine to produce norcocaine, which can be further metabolized by BChE hydrolysis to norecogonine methyl ester (Fig. 1). Cocaine elimination can be enhanced by using exogenously added BChE. This treatment is well tolerated (Morishima et al., 1999). However, because its half-life is short and it has low catalytic activity on cocaine, endogenous BChE was not developed as a treatment for cocaine addiction. TV-1380 (AlbuBChE/Albu-CocH), was developed as a quadruple mutant form of human BChE (A199S/S287G/A328W/Y332G) with approximately 1000x fold higher hydrolytic activity (Pan et al., 2005) against cocaine than BChE, and a longer half-life due to its fusion at its carboxy- terminus with recombinant human serum albumin (HAS; Schlindler et al., 2013; Gao et al., 2008).

Clinical trials for TV-1380 as a treatment for cocaine dependence and overdose were initiated when pretreatment with TV-1380 was found to accelerate cocaine metabolism in monkeys (Schlindler et al., 2013), attenuate the toxic effects of cocaine, prevent convulsions, and prevent priming-induced relapse to cocaine use in rats (Brimijoin et al., 2008). In 2016, the clinical development of TV-1380 was halted after a phase II clinical trial did not result in an enhanced rate of abstinence

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https://doi.org/10.1016/j.drugalcdep.2018.01.033
Received 27 October 2017; Received in revised form 21 December 2017; Accepted 11 January 2018
Available online 26 March 2018
0376-8716/

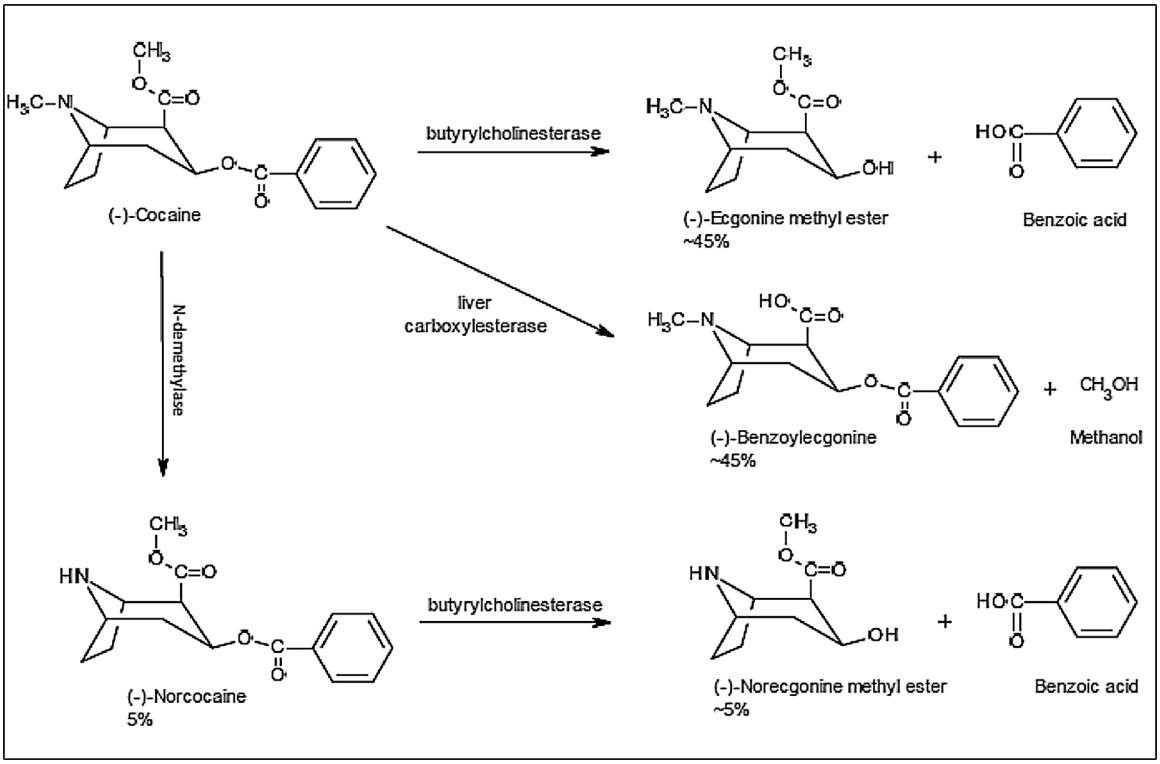

Fig. 1. Metabolic pathways for cocaine elimination in humans. With permission from Xie et al. (1999). Molecular Pharmacology 55, 83–91.

among the treated users (Gilgun-Sherki et al., 2016).

Part of the development program of TV-1380 involved assessing its safety in monkeys, and in the course of these studies, it found that TV-1380 may have benefits as a treatment to reduce the cardiotoxic effects that can occur with cocaine abuse, in particular when it is consumed in combination with alcohol.

Thus, the studies described herein are investigations of the potential of TV-1380 to reduce cocaine-induced changes of cardiodynamic parameters. First, we measured cardiac safety parameters in treated cynomolgus monkeys and the blood concentrations of cocaine and its metabolites in the presence or absence of TV-1380. Secondly, we investigated the interaction with ethanol, since a vast majority of cocaine users consume cocaine in combination with alcohol (European Monitoring Centre for Drugs and Drug Addiction, 2009) because of a more intense feeling of 'high' beyond that perceived with either drug alone (Pennings et al., 2002). Alcohol is known to react with cocaine to produce cocaethylene, an active cytotoxic metabolite (Julien et al., 2011) that is implicated in the cardiotoxicity of cocaine (Wilson et al., 2001; McCance-Katz et al., 1998). Cocaethylene has a similar psychoactive effect as cocaine, but is associated with liver damage, seizures and the risk of immediate death is known to be 18–25 times higher than with cocaine alone (Andrews, 1997). To address this complication, we have tested the effect of TV-1380 on the generation of cocaethylene in monkeys treated with cocaine and ethanol.

2. Materials and methods

2.1. Animal husbandry

The animal studies complied with Good Laboratory Practice (GLP) and were carried out at AVANZA (Gaithersburg, MD, USA) and MPI Research, Inc. (Mattawan, MI, USA) laboratories in cynomolgus monkeys (Macaca fascicularis), originally supplied by Harlan or Alpha Genesis at the age range of 3–8 years old. The animals had unrestricted access to water and were fed a daily amount of diet (Lab Diet) supplemented with fresh fruits, vegetables, and other enrichment foods. All animals were housed in a humidity-and temperature-controlled room. The animal care facilities were fully accredited by AAALAC International and all experiments were approved by the Institutional Animal Care and Use Committee (IACUC). Male monkeys were housed individually, and female monkeys were pair-housed in stainless steel double-sized cages.

2.2. Study designs

2.2.1. Subchronic toxicology study in monkeys

Twenty male and twenty female sexually mature cynomolgus monkeys were divided into four groups, a control group (n = 6/gender) that received the vehicle (formulation buffer) and three groups that received TV-1380; 10 mg/kg (n = 4/gender), 20 mg/kg (n = 4/gender) and 50 mg/kg (n = 6/gender). Animals were administered the formulations twice weekly for 13 weeks (26 doses) via two bolus intramuscular (IM) injections. In the high dose and control groups, 2 animals per sex were maintained for an off treatment/recovery period of 4 weeks. All animals were observed for morbidity, mortality, clinical signs, clinical pathology evaluation, body weights, food and water consumption. At termination, necropsy examinations were performed.

2.2.2. Cardiovascular and respiratory safety study

Six male and six female animals with implanted telemetrized units were assigned to 4 treatment groups. Group 1 (n = 3/gender) animals were injected twice with the vehicle (formulation buffer), once on Day −8 to measure baseline cardiovascular and ECG parameters, and once on Day −4 to measure baseline respiration parameters. On day 1 of the study, TV-1380 was administered IM at a dose level of 15 mg/kg and cardiovascular and ECG parameters were assessed. Treatment with TV-1380 was repeated on Day 4 and respiration endpoints were followed (Table 1). The second phase of the study started after Group 1 was completed. Group 2 (n = 3/gender) monkeys were used to test the interaction of TV-1380 and cocaine. Baseline of the cardiovascular parameters was established at Day −4. On Day 1, animals were treated with vehicle and with cocaine alone at 1 mg/kg by IV injection. On Day