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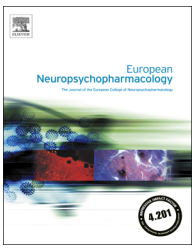

Effects of biperiden on the treatment of cocaine/crack addiction: A randomised, double-blind, placebo-controlled trial

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Abstract
Cocaine use affects approximately 13.4 million people, or 0.3% of the world's population between 15 and 64 years of age. Several authors have described drug addiction as a disease of the brain reward system. Given that the cholinergic system impacts reward mechanisms and drug self-administration, acetylcholine (ACh) might play an important role in the cocaine addiction process. We evaluated the efficacy of biperiden (a cholinergic antagonist) in reducing craving and the amount used, and in increasing compliance with treatment for cocaine/crack addiction. It was a study double-blind, randomised, placebo-controlled, 8-week trial of 111 cocaine or crack addicted male patients between 18 and 50 years old. Two groups were compared: placebo ($n=55$) or biperiden ($n=56$) combined with weekly sessions of brief group cognitive-behavioural therapy. The efficacy of treatment was evaluated according to the patients' compliance and several instruments: the Minnesota Cocaine Craving Scale, the Beck Depression and Anxiety Scales and a questionnaire assessing the amount of drug used. All of the patients attended weekly sessions for two months. We analysed the data considering the patients' intention to treat based on our last observation. Of the 56 patients in the biperiden group, 24 completed the treatment (42.8%) compared with only 11 patients in the placebo group (20%), which was a significant difference ($p=0.009$). Compliance with treatment was 118% higher in the biperiden group, which was also the group that presented a statistically significant reduction in the amount of cocaine/crack use ($p<0.001$). There was statistically

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significant difference between the craving score in the biperiden group. Pharmacological blockade of the cholinergic system with biperiden is a promising alternative to treat cocaine/crack addiction, helping patients to reduce the amount used and improving compliance with psychotherapy treatment.

1. Introduction

Cocaine use affects approximately 13.4 million people, or 0.3% of the world's population between 15 and 64 years of age. Addiction to that substance is a public health issue worldwide, characterised by relapses, several health problems and psychosocial complications (EMCDDA, 2012; UNODC, 2012). Till date, there is no effective treatment to address this problem.

On the other hand, there has been a growing body of preclinical evidence in recent years showing that the cholinergic system plays an important role in cocaine addiction onset and its maintenance and aspects of reward, learning and memory (Adinoff et al., 2010; Williams and Adinoff, 2008).

Several studies have shown that cocaine-related reward effects are mediated by M5 muscarinic receptors in the tegmental area (Fink-Jensen et al., 2003; Thomsen et al., 2005; Yeomans et al., 2001). Additionally, M4 receptors influence dopaminergic neurotransmission regulation. Schmidt et al. (2011) demonstrated that knockout mice lacking those receptors presented an increase in cocaine self-administration. In addition to directly inhibiting dopamine reuptake, cocaine acts on M1 and M2 receptors (Flynn et al., 1992).

Itzhak and Martin (2000) showed, in an animal model, that the administration of scopolamine (an anticholinergic substance) changed the cocaine-conditioned place preference, an effect that is not observed with the administration of only scopolamine. Our studies revealed that biperiden (an irreversible antagonist of muscarinic receptors) reduced both the expression of cocaine-conditioned place preference in mice and memory consolidation in this animal model (Ramos et al., 2012; Zacarias et al., 2012). Biperiden is a white powder chemically known as 3-piperidin-1-phenyl-1-bicycloheptenyl -1-propanol, an anticholinergic agent which acts predominantly in the central nervous system. It has a prominent central blocking effect on M1 receptors, being prescribed for the treatment of the side effects of neuroleptics and other drugs that block dopamine receptors (Penttilä et al., 2005).

Clinical studies in humans proved that muscarinic acetylcholine receptor (mAChR) M2 gene (CHRM2) polymorphism is involved in a phenotype that is predictive of substance use disorders (Dick et al., 2008). Adinoff et al. (2010) reported that regional cerebral blood flow (rCBF) in the limbic regions of cocaine-addicted individuals was altered after the administration of both physostigmine (a cholinergic agonist) and scopolamine (a muscarinic antagonist) compared with rCBF in the control group. The nicotinic cholinergic receptors have also been the target of researchers. A double-blind placebo controlled study with varenicline (an alpha4beta2 partial agonist) that lasted nine weeks showed a significantly greater decrease in the rates of cocaine reward when compared with the placebo group (Plebani et al., 2012). Therefore, there appears to be evidence of a certain degree of participation of the cholinergic system in cocaine addiction.

The cholinergic system projects into several brain areas and regulate cognitive, affective and behavioural functions (Williams and Adinoff, 2008). The limbic and paralimbic regions contain intense cholinergic innervation and are supposed to be the most relevant to the process of addiction (Bonson et al., 2002; Goldstein and Volkow, 2002). These cholinergic interactions with the reward circuit might interfere with the learning and memory processes, which are related to relapse and craving (Hoebel et al., 2007; Mark et al., 2011; See et al., 2003).

The present study evaluated the efficacy of biperiden (a muscarinic antagonist) in reducing consumption and craving and in improving compliance with the psychotherapeutic treatment of cocaine/crack-addicted individuals.

2. Experimental procedures

2.1. Patients and trial design

This study was a randomised, double-blind, placebo-controlled trial. In total, 56 male patients received daily oral doses of biperiden capsules (6 mg divided into three doses), whereas 55 other patients, also male, received placebo (under the same regimen as biperiden). The total sample, therefore, comprised 111 patients. The patients reported to the research centre weekly to be evaluated and to receive capsules for the next days, ensuring that they were actually using the substances involved in the study. Additionally, all 111 patients were instructed to undergo group psychotherapy by means of a brief intervention at the same centre (Marques and Formigoni, 2001). In Figure 1 we have the flow chart describing the randomisation process and the follow-up.

The inclusion criteria were as follows: cocaine or crack dependence, according to the DSM-IV (APA, 1994); an age between 18 and 55 years old; male gender; not using psychoactive medication; not presenting other psychiatric disorders; and not presenting criteria for other drug dependence, except tobacco.

The patients answered the Minnesota Cocaine Craving Scale (Halikas et al., 1991) and the Beck Scales for Anxiety and Depression (Beck et al., 1961; Beck et al., 1988).The patients also answered a questionnaire on cocaine/crack use, which consists of 10 items that evaluate the pattern of drug use, involving aspects such as the amount and frequency. They used a calendar to remember the amount of their daily use in the month prior to each of their four appointments. The quantification of drug consumption was based on the number of capsules/packets of cocaine or of crack stones (a single dose of which is equivalent to one gram) considering the use in the month prior to the interview. For the analysis, we added the amount used during the three months of the study.

The Committee of Ethics in Research of UNIFESP approved the project (number 1777/10). The study was also registered, with