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Carphedon at the Crossroads: A Dangerous Drug or a Promising Psychopharmaceutical?

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Abstract

Carphedon is a phenyl derivative of the nootropic drug piracetam (Nootropil) and is effective in increasing physical endurance and cold resistance and is used for amnesia treatment. It was developed in Russia as a stimulant to keep astronauts awake on long missions, and occasionally used in Russia as a nootropic prescription for various types of neurological disease. It became well known a couple years ago when a leading nootropic supplier in California started selling it on the Internet as a supplement and a bunch of athletes got kicked out of the Olympics for illegal using it. Carphedon was found to activate the operant behavior more powerfully, to remove psychodepressant effects of diazepam, to inhibit post-rotational nystagmus, and to prevent the development of retrograde amnesia. Unlike piracetam, carphedon exhibits a specific anticonvulsant action. When given in high doses, produces psychodepressant effects. It is also claimed to increase physical stamina and provide improved tolerance to cold. As a result, it appears on the lists of banned substances issued by the World Anti-Doping Agency.

Keywords: Carphedon; Phenotropil; 2-(4-Phenyl-2-Oxopyrrolidin-1-Yl)Acetamide; Nootropic; Stimulant

Introduction

Carphedon (carphedone, fonturacetam, phenotropyl, 4-phenylpiracetam) was synthesized in 1990 by Russian chemists as a combination of two drugs - nootropic piracetam and amphetamine stimulant. It was developed as a medicine that improves the physical and psychological ability of astronauts to work at different stages of space travel. It was assumed that it could combine the properties of both groups of drugs not only in chemical but also in pharmacological terms. That is, it will have a beneficial effect on the psyche while improving cognitive brain function. An ideal combination of medicine that would certainly find its place in the military, astronautics and wherever a person is exposed to great physical and/or mental stress. Indeed, carphedon has been shown to increase physical performance, resistance to cold, and is useful as a drug in amnesia. The usefulness of carphedon as a medicine that helps astronauts to cope with problems in a weightless state has also aroused the interest of experts in civil medicine. In 2005, carphedon was launched on the Russian market as a new drug called Phenotropil [1,2].

Chemistry

Carphedon, 2-oxo-4-phenyl-1-pyrrrolidine acetamide, $C_{12}H_{14}N_2O_2$, mol. wt. 218.25, CAS Number 77472-70-9, is a liquid compound having a density of 1.22 g / cm^3 with a refractive index of 1.579 and boiling point 486.4° C at 760 mm Hg. Carphedon is a phenyl-derivative of piracetam (Nootropil) and also an amphetamine derivative. Part of its structure is identical to piracetam, part with amphetamine (Figure 1). Carphedone is a chiral compound existing in two stereoisomers, R and S. In medical practice it is used as a racemate.

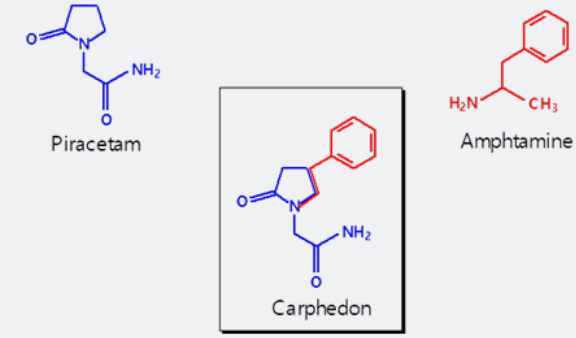

Figure 1: Chemical structures of carphedon, piracetam and amphetamine. The carphedon molecule is formed by the "superposition" of the piracetam molecule with the amphetamine molecule.

Pharmacology

Carphedone can be considered pharmacologically nootropic, stimulant and adaptogen. As a substance with the nootropic effect of piracetam, it opens up new possibilities in the treatment of CNS diseases [3]. Phenotropil contains racemic carphedone, but its stereoisomers do not have completely identical pharmacological properties [4].

Pharmacokinetics

Carphedon is rapidly absorbed from the GIT and rapidly distributed to tissues. Its bioavailability in humans after p.o. administration is 100%. Maximum blood concentration is reached after 1 hour, half-life is 3 to 5 hours. It easily crosses the blood-brain barrier [3,5]. Carphedon is not metabolised in the body and is excreted unchanged - 40% in urine and 60% in bile and sweat [6]. In urine, carphedone can be quantitated by capillary gas chromatography with NP-detector [7] or mass spectrometer [8], so its abuse as doping can be easily controlled [9] .

Pharmacodynamics

Carphedon is primarily a nootropic drug [10]. It activates brain integration activities, improves memory, facilitates learning, increases the speed of information transfer between hemispheres of the brain, increases concentration on mental work, and increases resistance to brain hypoxia and poisons [11]. It has antiamnestic and anticonvulsant effects, acts anxiolytically, and induces good mood [3,5,12]. It also acts as an anorectic, beneficially affects brain metabolic processes and improves blood circulation in the ischemic areas of the brain [1] and enhances the body's energy potential by improving glucose utilization [3]. In the rat model, carfedone at 100mg / kg (i.p.) was found to suppress the effect of scopolamine on cholinergic receptors, affect the density changes of dopaminergic and benzodiazepine receptors, and abolish its amnestic effect [13].

The stimulating effect of carphedon is evident in improving motor skills, increasing physical capacity for work and resistance to stress and fatigue [14]. The psychostimulant effect is to improve concentration on mental work and to improve mood [12]. Carphedone also has a slightly analgesic effect and increases the pain threshold [6].

The adaptogenic effect of carphedone results in increased resistance to stress under conditions of excessive mental and physical activity, fatigue, hypokinesia and low temperature immobilization. Peoples used carphedon claim that they have increased visual acuity and expanded their field of vision [3]. Carphedon has no effect on respiration or cardiovascular system. It stimulates the production of antibodies in response to antigen, increases immunity, but does not alter the skin's allergic inflammatory response to foreign proteins. Carhedon does not induce dependence, tolerance and withdrawal syndrome [15].

Stereoselective Pharmacodynamics

All previously published works on carphedon were performed with the racemate of this drug. It has only recently been published [16] that the differences exist in the biological effects of both stereoisomers. The aim of the study was to compare stereoselective pharmacological activities of the R- and S-enantiomers of carphedon in various behavioral tests. Racemic carphedone served as a control. The amount of drug in the brain was measured by high performance liquid chromatography and tandem mass spectrometry (HPLC / MS / MS).

Significant increases in spontaneous motor activity (open-field test) were observed following single administration of R-carphedon at 10 and 50mg / kg and S-carphedon at 50mg / kg. In the forced swimming test, the R-carphedon showed an antidepressant effect at doses of 50 and 100mg / kg and S-carphedone only at a higher dose, i.e. 100mg / kg. R-carphedon had a significantly better effect in the passive avoidance test already at 1mg / kg, whereas S-carphedon was ineffective in this test up to 100mg / kg. Behavioral tests have shown that both carphedon enantiomers have an antidepressant effect and an ability to increase motor activity, but only R-carphedon improves memory, although the brain concentration of both enantiomers was the same. These results may be important for the clinical use of optically pure carphedone isomers [4].

Recently, it was shown that S-carphedon is a selective dopamine transporter (DAT) inhibitor that does not influence norepinephrine (NE) or serotonin (5-HT) receptors. S-Carphedon reduces the plasma glucose and leptin concentration and decreases hyperglycemia in a glucose tolerance test in both the mice and the rats. S-Carphedon did not influence locomotor activity in the obese Zucker rats or in the WD-fed mice. The results demonstrate that this compound reduces body weight gain and improves adaptation to hyperglycemia without stimulating locomotor activity. S-Carphedon could be potentially useful for treating obesity in patients with metabolic syndrome with fewer adverse health consequences compared to other anorectic agents [16].

Toxicology

The acute toxicity of carphedon is low, the median lethal dose (LD50) for mouse at p.o. administration is 1100mg / kg [17], a lethal dose for humans is estimated at 800mg / kg. The substance has no mutagenic, teratogenic or carcinogenic effects. Carphedon administration to rats at 50mg / kg for two weeks resulted in increased ovarian weight and increased pregnancy index, but did not affect either pregnancy or embryo development [18].

Clinics

Carphedon has been or is being tested and recommended as a medicament in seven of indications such as:

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a) CNS diseases of various etiology, especially in connection with vascular diseases and disorders of brain metabolism, intoxication, impaired mental function, decreased motor activity [2,3].

b) Prevention and therapy of stroke [19,20].

c) Neurotic disorders, neurocirculatory asthenia, flaccidity, increased fatigue, decreased psychomotor activity, attention deficit disorder, memory impairment [12,21,22].

d) Epilepsy [23-27].

e) Learning Disorders, Mild to Moderate Depression, Psychoorganic Syndrome, Mental Disorders, Apathetic Abuse Syndrome [1].

f) Prevention of hypoxia, increased stress resistance, correction of the functional state of the organism in extreme conditions by professionals to prevent the development of fatigue and improve mental and physical ability to work, correction of daily biorhythms [3,28,29].

g) Chronic alcoholism [30].

Contraindication

Contraindication is individual intolerance and allergy to pyrrolidine group drugs, pregnancy and breastfeeding. There is not enough clinical research data. It is also not recommended to prescribe carfedon to children because there is no data on their use in childhood. Caution should be exercised when administering carphedone to patients with severe organic liver and kidney damage, severe hypertension, and people with atherosclerosis. It should not be given to those who have a history of panic attacks or acute psychotic conditions, especially psychomotor agitation.

Side Effects

Insomnia, psychomotor restlessness, hyperemia of the skin, feeling warm, increasing blood pressure. The effects of carphedone can be potentiated by drugs that stimulate the CNS, antidepressants and nootropics.

Carphedon as Prohibited Doping

Even before carphedon was marketed as a nootropic with a similar effect to piracetam, it aroused the interest of athletes, especially athletes, as a new type of doping [31,32]. For the first time, carphedon discovered doping control of athletes at the Athletics World Championships in Athens in 1997 [33] and in 1998 the International Olympic Committee included it in the Prohibited List [34]. The World Anti-Doping Agency (WADA) leads it as a stimulant drug [35]. As an illicit doping, carphedon was first demonstrated in athletes at the 6th World Championships in Athletics, Athens 1997 [33,36]. Anti-doping analysis of about 100,000 urine samples from 2000 to 2009 by the World Anti-Doping Agency's Italian Anti-Doping Laboratory showed 1.0 to 1.8% of positive findings. The most common were cannabinoids (0.2 - 0.4%), cocaine (0.1%) and stimulants - amphetamines, ephedrine, but also caffeine [37]. Carphedon is particularly popular among Russian athletes [38] and several have suffered from its use [39]. Among other things, the 2002 Olympic Biathlon Champion Olga Pylevová and the Russian cyclist Sergei Šilov [40].

Conclusion

Carphedon is classified by its pharmacological profile between nootropics and stimulants. Preclinical and partly clinical research has suggested that carphedon opens up new possibilities in the treatment of CNS diseases, but the results of clinical trials are not complete and not always entirely convincing. Carphedon abuse as doping and its inclusion in the Prohibited List limits its availability to official medicine and prevents it from being tested on humans again.

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