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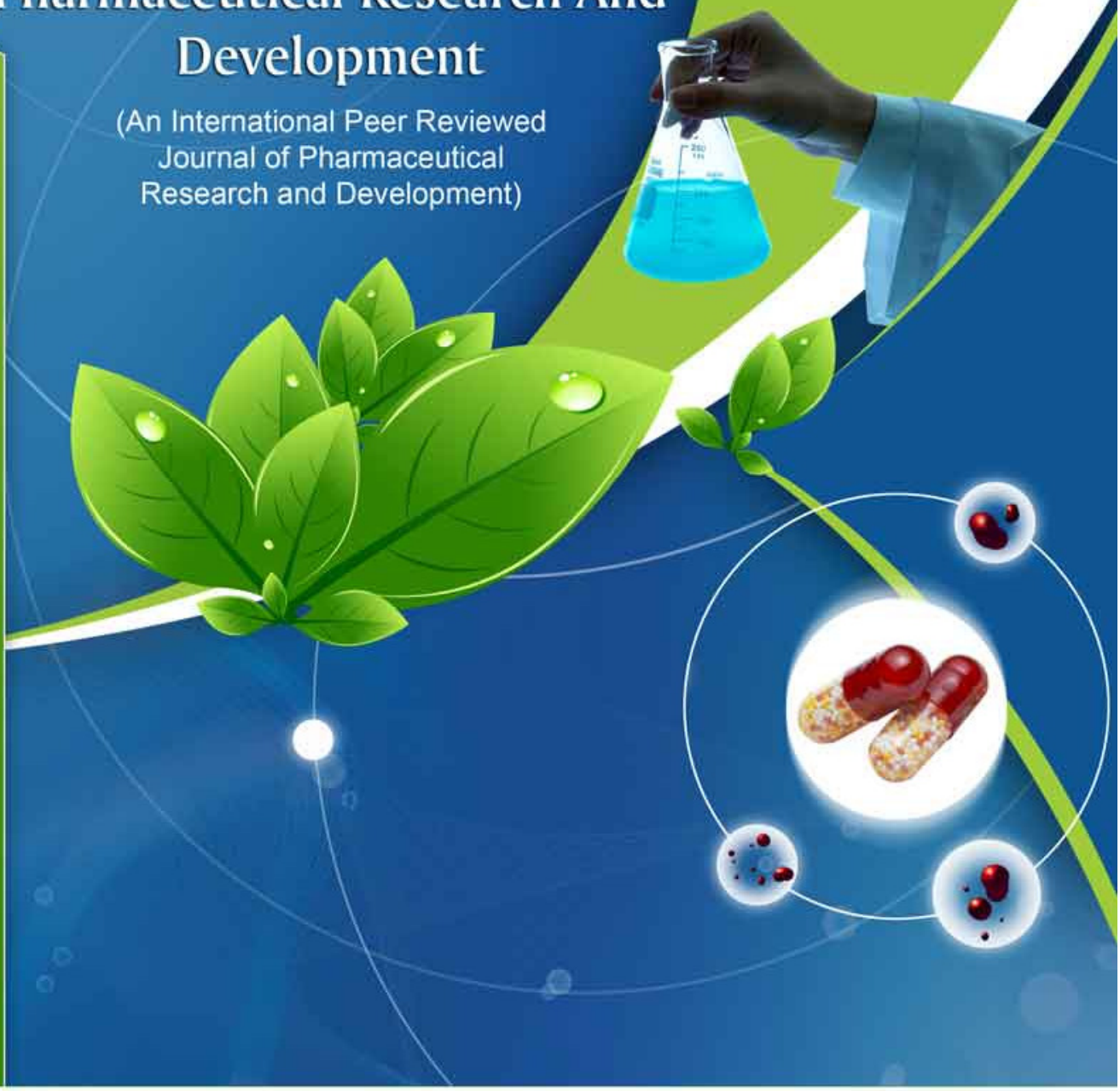

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Review Article

Vinpocetine: Hype, Hope and Hurdles towards Neuroprotection

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ABSTRACT

The in progress research studies and the current knowledge about vinpocetine strongly suggest that "the one molecule fits for many at many times" This review provides a brief overview of vinpocetine for its pharmacokinetics, pharmacodynamics, uses, adverse effects and research summary. In theory, such an ideal "Vinpocetine" preferably known as nootropic is a very effective tool used in memory enhancement. Vinpocetine is a safe and non-toxic with a marvelous range of efficient and structural benefits for superior vigour. However, considering the pharmacokinetic study and uses of Vinpocetine it is a suitable candidate to develop various dosage forms for various disorders. Vinpocetine enhances brain circulation and oxygen consumption by dilating blood vessels and reducing blood stickiness. Vinpocetine is a potent inhibitor of the voltage-dependent Na^+ channels and a selective inhibitor of the Ca^{2+}/caldmoduline-dependent phosphodiesterasethere. Both vinpocetine and its main metabolite cis-apovincaminic acid exert a neuroprotective type of action. Some hurdles may be produced due to Vinpocetine in the patients associated with Hypotension, Constipation and Seizure.

KEYWORDS:*Vinpocetine, Neuroprotection, Memory Enhancement, Nootropic, Alzheimer's Disease, Sundowning Syndrome*

INTRODUCTION

Vinpocetine is a semi-synthetic component derived from vincamine alkaloid; vincamine is present in the aerial part of *Vinca minor, Crioceras longiflorus* and seeds of *Voacanga africana* plants belong from Apocynacea family [1, 2]. Vinpocetine has been used to maintain the brain and its blood vessels by European and Japanese medical practitioners from more than two decades. Vinpocetine is approved by the European and British Pharmacopoeias [1, 2].Vinpocetine was initially discovered, developed and marketed under the trade name Cavinton® (Chemical Works of Gedeon Richter Ltd., Budapest, Hungary).

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Since its introduction to the market in 1978 the drug has been broadly used in several countries of the world [3]. It is sometimes called a nootropic, meaning cognition enhancer. Vinpocetine, as well as vincamine are used in Germany, Poland, Hungary, Japan and Mexico as pharmaceutical agents for the management of cerebrovascular and cognitive disorders. In the United States of America, Vinpocetine is available in the market as a dietary supplement [4]. The IUPAC Name of vinpocetine is Eburnamenine-14-carboxylic acid ethylester and has Molecular weight of 350.46 g/mol, molecular formula: $C_{22}H_{26}N_2O_2$ and CAS No. 42971-09-5.Chemical Structure of vinpocetine is given in figure 1 [1].The most basic investigations of vinpocetine resulted in its utilization for the treatment of cerebrovascular dysfunctions. Since then it has become a reference standard compound in the pharmacological study of cognitive deficits

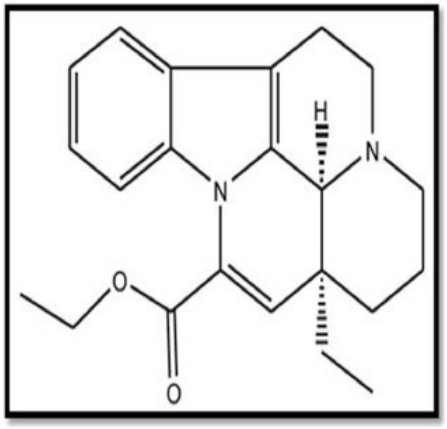

Figure 1: Structure of Vinpocetine

occurred due to hypoxia (lack of adequate oxygen) and ischemia (lack of necessary blood, which carries glucose and oxygen). Clinical data indicate that vinpocetine provides a considerable effect to the neuron. In logic, vinpocetine is a Viagra® for the brain [5]. As per a study carried out by the World Health Organization (WHO), cerebrovascular disease is the second leading cause of death worldwide. The study estimated that cerebrovascular disease (stroke) accounted for 9.6% of all deaths. Furthermore, these diseases are the leading cause of disability in adults [6]. Vinpocetine know how to dilate blood vessels, boost the brain circulation, progress in oxygen utilization, make red blood cells more workable, and inhibit aggregation of platelets. Apart vinpocetine has antioxidant action. It achieves levels peak in the bloodstream within an hour and a half after the intake [4]. Vinpocetine simply cross the blood brain barrier and enters into the brain [7]

MECHANISM OF ACTION

Vinpocetine has numerous pharmacological and biochemical performance, such as stimulating cerebral vasodilation, raising the tolerance of cerebral tissue to hypoxia and ischemic insults, anticonvulsant activity, inhibitory effects on phosphodiesterase (PDE) convalescing hematologic flow properties and inhibiting thrombocyte aggregation [8, 9]

Inhibit the Voltage-dependent Sodium (Na^+) Channel

It has been predicted that the claim of vinpocetine in ischemic stroke is secondary to its effect on voltage-dependent sodium channels in the brain. Inhibition of sodium channels in neural tissue is the primary mechanism of several different drugs reported to have properties of neuroprotective in experimental ischemia. This stroke, effectively blocking growth of sodium in neurons, reduces the damage of reperfusion injury and can be helpful in minimising the toxic effects of oxidative stress resulting from anoxia [3, 10]. Shield of neurons against a Na^+ burden is a very important factor in the neuroprotective effect of vinpocetine. The role of an intracellular Na^+ loading under hypoxic conditions has been first documented in white matter [11, 12] and has been recommended to result from non-inactivating Na^+ conductance [11, 13]. These currents have also been found in hippocampal [14] and cortical neurons [12], where blockers of Na^+ channels were able to attenuate the hypoxic injury.

Inhibition of Phosphodiesterase-1(PDE-1)

Vinpocetine may inhibit Ca^{+2}/calmodulin-dependent phosphodiesterase (PDE) type 1. This cause would hypothetically lead to an increase of cyclic AMP over cyclic GMP and may be dependable for the benefits in cerebral blood circulation and decreased platelet aggregation count observed after vinpocetine management. It has been suggested that vinpocetine non-competitively inhibits Ca^{2+}/calmodulin-dependent cGMP-PDE. These findings were confirmed by several authors [3, 15] and Vinpocetine is now considered to be a selective inhibitor of the Ca^{2+}/calmoduline-dependent PDE type 1 (PDE-1 isoenzyme) [3, 16]. Most probably, inhibition of PDE enzyme type I and increase of cAMP and cGMP level are responsible for the positive vascular effects, thus for the improvement of the cerebral circulation as well as for the effect exerted on platelets [3].

Uptake-Inhibitory Action

Vinpocetine inhibits adenosine consumption. Adenosine is known as an inhibiting neurotransmitter. Thus, particularly in hypoxia and ischemia (when the extensive declines of ATP can lead to the increase in extracellular adenosine concentration), adenosine reduces Ca^{2+} channel movement which can effect in

excitotoxic damage. At the equal time, it can inhibit excessive release of glutamate which can have an excitotoxic effect [17]. Vinpocetine blocks the sodium channel (Na^+) operation at the neuronal level, which regulates calcium channel (Ca^{2+}) operations preventing high intracellular Ca^{2+} concentrations. Minimizing neurotransmitter excitotoxicity may lead to lowering ischemic or hypoxic damage and providing cerebro-protective effects. Vinpocetine also inhibits uptake of the neurotransmitter adenosine. This reduces the Ca^{2+} channel activity preventing excitotoxic damage. It is also shown that vinpocetine's inhibition of the enzyme phosphodiesterase type I (PDE1) lessens cGMP and soothens blood vessel muscles and increases cAMP. PDE1 is dependent on calmodulin (CaM), a calcium binding protein, which is weakly inhibited by Vinpocetine. CaM is weakly inhibited by Ca^{2+}. Vinpocetine may weakly inhibit the effect of CaM on PDE1 either through inhibition of calmodulin or its effect on Ca^{2+}. CaM enhances nitric oxide's relaxation effect by increasing cGMP [3, 5].

Exhibit Antioxidant Property

Similar to Tocopherol (Vitamin E), Vinpocetine is a successful hunter of hydroxyl radicals. It has also been exposed to inhibit lipid peroxidation in synaptosomes of murine brain tissue and to guard against global anoxia and hypoxia in animals. Vinpocetine has decreased areas of neuronal necrosis in animal models up to 60 percent in experimentally-induced ischemia [3].

Other Neuroprotective Mechanisms

Vinpocetine has been exposed to defend neurons from the toxicity of glutamate and N-methyl-d-aspartate (NMDA). Vinpocetine lowers blood viscosity in patients associated with cerebrovascular disease [18], and it has major vasodilating properties [19], it decreases platelet aggregation, increases and maintains erythrocyte flexibility under oxidative stress [20] all of which are potentially helpful in cerebrovascular disease.

PHARMACOKINETIC PROFILE OF VINPOCETINE

Considering human studies, Vinpocetine is easily absorbed from the upper part of the gastrointestinal tract and its active metabolite apovincaminic acid is absorbed from the stomach. The absolute oral bioavailability of the compound is 6.7% due to a pronounced first pass metabolism [21]. Have found that food intake increased the bioavailability of Vinpocetine upto 80-90%; maximal plasma concentration (Cmax) and area under the curve (AUC) values were approximately 60–100% higher after food intake than under fasting conditions. Protein binding is about 86.6–99.99 % the rate of vinpocetine absorption from the gastrointestinal tract is rapid. Peak plasma levels are reached at about 1 hour after oral administration irrespective of dose and food intake [22]. Vinpocetine is more soluble in gastric pH (pH 1.2) than intestinal pH (pH 6.8). The half life of Vinpocetine is 1-2 hour and after 8 hour Vinpocetine is completely eliminated from the body [23].

Dose and Marketed Dosage forms

The recommended dose of Vinpocetine is 15 to 30 mg in a day. Sometimes it may extend up to 40 mg [4, 24]. The marketed dosage forms of vinpocetine given in Table I

Table I: Marketed Dosage Forms of Vinpocetine

Brand Name	*Dosage Form*
Neurovin®	10 mg Tablet
Cogvin®	5 mg Tablet
Vinpotin®	5 mg tablet and 5 mg/ml injection
Cognitol®	5 mg Tablet
Vinpocetine (SRS Pharmaceuticals)	10 /20/30 mg Vial

CLINICAL APPLICATIONS

Epilepsy

The outcome of vinpocetine (15–45 mg/day) and its combinations appreciably decreased the frequency of attacks or led to their complete vanishing from the patients. The maximum effect of vinpocetine was observed in generalized tonic-clonic convulsions and when they were combined with absences. It recommended that vinpocetine has anticonvulsive activities and showed a decrease in intracranial hypertension and a normalization of psychomotor development [6].

Chronic Cerebral Vascular Ischemia

In the chronic stroke vinpocetine has a considerable effect in rising glucose uptake and metabolism in the healthy cortical and subcortical regions of the brain, mainly in the area surrounding the region of the stroke [25]. A learn in chronic ischemic stroke, it was found that more than two weeks vinpocetine trial significantly increases the cerebral blood flow in the non-symptomatic hemisphere. Advance studies using doppler sonography and near infrared spectroscopy have shown enlarged perfusion of the middle cerebral artery in an individual associated with chronic cerebrovascular disease given a single infusion of Vinpocetine [3].

Alzheimer's and Related Dementias

Now these days in western countries many individuals of any age suffer from stress, mental disturbances and habitual life style lead to Alzheimer's disease. Vinpocetine found very effective in vascular dementia, Alzheimer's disease, Multiple-infarct dementia, long term memory loss, age related dementias produced due to the damage in neurons, short term memory loss. It improves cognitive and memory functions [1, 4, 5].

Acute Ischemic Stroke

While few studies have shown that vinpocetine has an instant vasodilating effect on cerebrovascular blood circulation, a meta-analysis of the existing studies examining short- and long term fatal outcome rates with vinpocetine was unable to assess efficacy. In the analysis of acute stroke patients (Vinpocetine was given within one to two weeks of the incident), only one study met the meta-analysis criteria. In the certain trial, three weeks after onset of i.v. vinpocetine therapy, 8 among 17 Vinpocetine patients and 12 among 16 placebo patients were determined "dependant" (unable to live without assistance), and all the patients were alive. The meta-analysis authors were unable to determine a beneficial effect of vinpocetine, but research state that considering the in vitro studies and animal data, Vinpocetine has possible to be effective in acute stroke. Correctly designed studies have not yet been conducted [2, 26].

Degenerative Senile Cerebral Dysfunction

Six randomized and controlled meta-analysis carried out in 731 patients with degenerative senile cerebral dysfunction it indicates that vinpocetine was greatly useful in the treatment of senile cerebral dysfunction. With some psychometric testing scales in addition to physical behavioral (speech and movement ability, muscular harmonization and strength, sensory-perceptual ability) the investigator were able to show a highly considerable effect of vinpocetine on both cognitive and motor functions [2, 27].

Sundowning syndrome

Most individuals suffering from Alzheimer's disease and other progressive dementias demonstrate one or more behavioral symptoms. Behavioral symptoms of dementia may occur at any time of the day, but several individuals experience behavioral symptoms mainly in the afternoon and early evening and are commonly called "sundowners". This syndrome is called as a sundowning syndrome. The behavioral symptoms in such patients usually start at around 4 p.m. And last as late as 11 p.m. In such condition Vinpocetine found to be effective to counteract behavioral dysfunction [28, 29].

Tinnitus/ Meniere's disease/ Visual Impairment

Vinpocetine has been old in the treatment of acoustic trauma with subsequent hearing loss and tinnitus. Vinpocetine has also been starting to be useful in treating Meniere's disease and in vision impairment [30].

Health benefits of Vinpocetine [31]

Aging Process

Vinpocetine can reduce the decline in the release of dopamine that usually occurs in tandem with the progression of the aging process.

Cardiovascular system

- Vinpocetine can recover blood circulation to the brain and may thereby reduces and alleviate cerebral insufficiency.
- Vinpocetine may improve the flexibility of red blood cells and may thus help to stop strokes (A reduction in the flexibility of red blood cells is coupled with an increased risk of stroke)

Nervous Systems

- Vinpocetine can increase attentiveness and alertness by recovering glucose and oxygen utilization in the brain.
- Vinpocetine can alleviate mind-set sickness due to its capability to improve body's utilization of oxygen.
- Vinpocetine may help to avoid amnesia by improving blood circulation and oxygen delivery to the brain.
- Vinpocetine may decrease confusion and depression especially where the underlying cause of depression is dementia or sundowning syndrome.
- Vinpocetine may reduce excessive fear due to cerebral insufficiency.
- Vinpocetine may alleviate travel sickness, fatigue and vertigo in many people.
- Vinpocetine possesses the antioxidant action as compared to vitamin E and it deactivates the hydroxyl free radicals present in the body.
- Vinpocetine may reduce the inflammation and irritation of the stomach (alcohol induced gastric lesions) caused by excessive alcohol intake and may also counteract the toxic effects of excessive alcohol on the brain.
- Vinpocetine found useful in management of asthma and Parkinson's disease.

VINPOCETINE: A HOPE TOWARDS FORMULATION AND DEVELOPMENT OF NOVEL DRUG DELIVERY SYSTEM

- The available dosage forms of vinpocetine in market are conventional dosage forms. To obtain maximum pharmacological activity and patient compliance it can be converted into various dosage forms.
- Bioavailability can be increased under fasting condition with Solid-lipid nanoparticles, Self Micro-emulsifing drug delivery system.
- Enhancement of solubility by different techniques e.g. Complexion, Admixture
- Bioavailability is increased with formulating a Gastroretentive dosage form e.g. Gastroretentive tablet and Microspheres.
- Due to minimal half life it is a good drug for sustain release dosage form, Buccal drug delivery system, Transadermal drug delivery system
- It can be used in pulsatile drug delivery system to treat chronological behaviour of Alzheimer's disease.
- Combination with another drug it can be used to treat various cerebral disorders e.g. bilayer or trilayer tablet.

HURDLES ASSOCIATED WITH USE OF VINPOCETINE

Vinpocetine is a smart drug having few harmless adverse reactions such as dizziness, pressure-type headache, insomnia, drowsiness, transient hypotension, nausea, transient tachycardia, dry mouth and facial flushing. Small reductions in systolic and diastolic blood pressure with long use of vinpocetine have been reported, as well as minor reductions in blood glucose level. The use of vinpocetine is only carried out by considering the patients disease history [4, 5].

Contraindications

- It is necessary to tell the doctor if the patient is pregnant or breast feeding.
- Do not consume vinpocetine if the patient has a low blood pressure.
- Do not take vinpocetine if the patient has constipation. (Complexity in bowel movement)
- Do not use vinpocetine if the patient has a seizure disorder.
- Do not use vinpocetine if a patient has liver problems.

CONCLUSION

Vinpocetine is a unique drug having lots of memory enhancing property. It is extensively used as cerebral vasodilator and has good neuroprotective action. It causes relaxation of smooth muscle, dilation of blood vessels, and improved blood flow to the brain, all of which have favourable health effects. It also imparts protection for nerve cells poor of oxygen and nutrients, and further protects those cells from oxidative stress when blood flow is restored. The supplement has its utmost proven clinical benefit in patients with chronic cerebral vascular ischemia, and evidence is growing for its potential usefulness in Alzheimer's disease, related dementias, acute stroke, and urinary incontinence. It has good pharmacokinetic and pharmacodynamic property and lots of uses so it is a potential drug to develop novel drug delivery systems. Hurdles in use of vinpocetine are in the form of side effects and adverse events. They are infrequently reported among patients taking Vinpocetine supplements. So it concludes that vinpocetine is a very effective in neuroprotection.

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