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Review

Role of vinpocetine in cerebrovascular diseases

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Abstract:
A cerebrovascular accident, or stroke, is defined as the abrupt onset of a neurological deficit, which can be due to ischemia. Cerebral ischemia is caused by a reduction in blood flow that thereby decreases cerebral metabolism. Chronic cerebral hypoperfusion leads to irreversible brain damage and plays an important role in the development of certain types of dementia. Vinpocetine, chemically known as ethyl apovincaminate, is a vinca alkaloid that exhibits cerebral blood-flow enhancing and neuroprotective effects. Non-clinical and clinical studies have suggested multiple mechanisms responsible for the beneficial neuroprotective effects of vinpocetine. As no significant side effects related to vinpocetine treatment have been reported, it is considered to be safe for long-term use. This vasoactive alkaloid is widely marketed as a supplement for vasodilation and as a nootropic for the improvement of memory. The present review focuses on studies investigating the role of vinpocetine in cerebrovascular diseases.

Key words:
vinpocetine, cerebrovascular, neuroprotection, ischemia, nootropic, positron emission tomography

Abbreviations: Aβ – amyloid β-peptides, AD – Alzheimer's disease, AEDs – antiepileptic drugs, AICVD – asymptomatic ischemic cerebrovascular disorders, ATP – adenosine triphosphate, CGI – Clinical Global Impression, cGMP – cyclic guanosine monophosphate, DOPAC – 3,4-dihydroxyphenylacetic acid, DPG – 2,3-diphosphoglycerate, GABA – γ-aminobutyric acid, LC – locus coeruleus, MMSQ – mini-mental status questionnaire, NMDA – N-methyl-D-aspartic acid, PET – positron emission tomography, PSNHL – progressive sensorineural hearing loss, PTZ – pentylenetetrazole, RBC – red blood cell, rCBF – regional cerebral blood flow, ROS – reactive oxygen species, RR – relative risk, SCAG – Sandoz clinical assessment geriatric scale

Introduction

Cerebrovascular diseases include a group of brain disorders associated with cerebral vascularization. The most common disorders include ischemic stroke, hemorrhagic stroke and cerebrovascular anomalies, such as intracranial aneurysms and arteriovenous malformations. Other disorders of cerebrovascular origin include memory problems, aphasia, apraxia, motor disorders, dizziness, hearing dysfunction (tinnitus and progressive sensorineural hearing loss) and headache. As per a study conducted 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 [82]. Various clinical studies have indicated that the incidence and high mortality of cerebrovascular diseases can be prevented to a large extent. Antiplatelet therapy and carotid endarterectomy are effective for secondary stroke prevention. However, with the exception of aspirin, the medical and surgical therapies used to treat

acute ischemic stroke have very limited efficacy [3]. Thus, there is a pressing demand for the development of newer, safer and more effective drugs.

Vinpocetine is a synthetic ethyl ester of the alkaloid apovincamine, which is isolated from the leaves of *Vinca minor*, commonly known as the lesser periwinkle. The chemical name for vinpocetine is ethyl apovincaminate [35]. Since its synthesis in the late 1960s, vinpocetine has been widely used for the treatment of cerebrovascular disorders, as it has shown cerebral blood-flow enhancing and neuroprotective effects [3]. Vinpocetine has also been marketed as a nootropic agent for the improvement of memory. Other indications for vinpocetine exist in the fields of geriatry, neuropsychiatry, ophthalmology and otolaryngology [19, 53, 72]. In addition, vinpocetine has shown promising results in the treatment of tinnitus and progressive sensorineural hearing loss (PSNHL) [46, 53]. It has been used to alleviate macular degeneration, certain glaucoma-related problems and other vision disorders of vascular origin [26]. Animal studies have demonstrated its effectiveness in preventing gastric mucosal damage [43]. Some studies have reported potential uses for this compound in the treatment of kidney stones, as its application removed tumoral calcinosis in kidney dialysis patients with renal failure [41]. Vinpocetine is also being studied for the treatment of hair loss. However, for the purpose of the current review, we will only focus on the cerebrovascular and neuropsychiatric indications of this compound.

Chemistry

The active drug substance of vinpocetine is (3α,16α)-eburnamenine-14-carboxylic acid ethyl ester (Fig. 1). It is a solid, white powder with a molecular weight of 350.5 g/mol and is soluble in 100% ethanol, dimethyl sulfoxide and acetone [35].

Pharmacology

Mechanism of action

Several different mechanisms have been implicated in the action of vinpocetine. Studies have reported that vinpocetine selectively inhibits voltage-sensitive sodium (Na^+) channels, causing a dose-dependent decrease in evoked extracellular calcium (Ca^{2+}) ions in striatal nerve endings [60]. It has been shown that increases in intracellular Na^+ and Ca^{2+} concentrations are responsible for the cell damage induced by ischemia/reperfusion and the development of other acute dysfunctions, including acidosis, cytotoxic edema and glutamate excitotoxicity. Thus, the Na^+ channel-inhibiting properties of vinpocetine are thought to be responsible for its neuroprotective and anticonvulsant activities [1]. A recent study has revealed that the neuroprotective action of vinpocetine involves additional drug targets along with the neuronal peripheral-type benzodiazepine receptors (PBRs) involved in the mitochondrial transition pore complex [74]. Another mechanism responsible for the neuroprotection exhibited by vinpocetine is its marked antioxidant activity due to the scavenging of hydroxyl radicals [65]. Vinpocetine selectively inhibits Ca^{2+}-calmodulin-dependent cGMP-phosphodiesterase, thereby enhancing intracellular cGMP levels in the vascular smooth muscle leading to reduced resistance in cerebral vessels and an increase of cerebral blood flow. This property is also responsible for neuroprotection [17, 20, 78]. Recent studies have shown that vinpocetine has potent anti-inflammatory actions that are caused by a direct inhibition of the IκB kinase complex (IKK) rather than phosphodiesterase blockade. This finding indicates that the anti-inflammatory action of vinpocetine can be exploited for the treatment of cerebrovascular diseases because chronic inflammation results in endothelial dysfunction and atherosclerosis, which further enhance the risk of stroke. The anti-inflammatory role of vinpocetine, in addition to its cognitive improvement properties, makes it a potential candidate

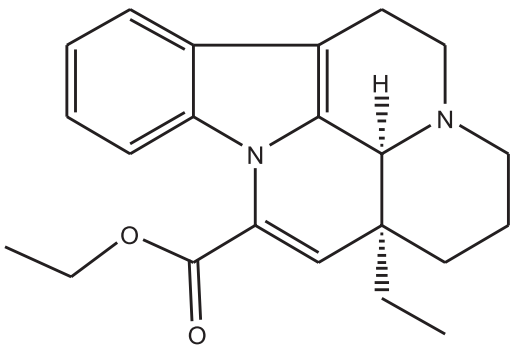

Fig. 1. Chemical structure of vinpocetine ($C_{22}H_{26}N_2O_2$)

for the treatment of neurodegenerative conditions, such as Parkinson's disease and Alzheimer's disease (AD) [25]. Studies have demonstrated that vinpocetine increases the levels of neurotransmitters involved in memory functions, namely noradrenaline, dopamine and acetylcholine [37, 58]. In addition to this, vinpocetine has been reported to increase the levels of DOPAC, the main metabolite of dopamine, in isolated striatum nerve endings [77]. Studies have also shown that vinpocetine effectively inhibits the reuptake of adenosine, an endogenous anticonvulsant and cerebral protectant [39]. In addition, vinpocetine has been reported to increase cerebral metabolism, which is responsible for the utility of this compound in the treatment of cerebral circulatory disorders, such as dementia and acute stroke. Increased cerebral metabolism is attained through enhanced cerebral flow (vasodilation), the increased consumption of glucose and oxygen in the brain, the increased production of ATP in brain cells and increased levels of neurotransmitters involved in memory, namely noradrenaline, dopamine and serotonin [29, 41]. Apart from a selective increase in cerebral blood flow, the activity of vinpocetine as an inhibitor of platelet aggregation and an activator of erythrocyte deformability lowers the viscosity of blood, thereby making this compound effective in the treatment of ischemic stroke [31]. A novel effect of vinpocetine, the locally restricted decrease of nociception, implies an inhibition of the retrograde axoplasmic transport of nerve growth factor (NGF) in peripheral nerves [7].

Pharmacokinetics

Vinpocetine is readily absorbed from the small intestine following oral administration. It undergoes extensive metabolism yielding its main metabolite, apovincaminic acid, which is absorbed from the stomach [52]. Due to this extensive metabolism, it has low bioavailability. Under fasting conditions, its absolute bioavailability is 6.7%, and the relative bioavailability under non-fasting conditions has been reported to be 60–100% higher [34, 40]. Following oral administration, vinpocetine readily enters the blood stream from the stomach and gastrointestinal tract and, consequently, passes through the blood-brain barrier and enters the brain. Vinpocetine is readily eliminated from the body, and the elimination half-life after oral administration is one to two hours. Thus, it undergoes extensive, but saturable, plasma protein binding [81, 83].

Preclinical studies for various indications

Neuroprotection against hypoxia and ischemia

As mentioned earlier, the neuroprotective activity of vinpocetine is the result of multiple pharmacological mechanisms. These include increased cerebral circulation and cerebral metabolism, a reduction in blood viscosity, the inhibition of Na^+ channels and the scavenging of hydroxyl radicals. Various studies have demonstrated the aforementioned activities and provided support for the neuroprotective potential of vinpocetine under both *in vitro* and *in vivo* conditions. The results of a study conducted by Dezsi et al. [10] confirmed the strong neuroprotective potential of vinpocetine. Vinpocetine treatment significantly decreased the infarct volume and dose-dependently inhibited prolonged or transient glutamate, and transient N-methyl-D-aspartate (NMDA) or veratridine-induced excitotoxicity. These results highlight the strong neuroprotective potential of vinpocetine and further suggest an important role for this compound in ischemic stroke therapy. In another study, vinpocetine reduced the hippocampal neuronal damage in a rat model of central ischemia from 77% to 37%. Similar results have been found in both rats and other animals in other areas of the brain [28, 38]. The neuroprotective effect of this compound has been reported in different experimental models of hypoxia/ischemia [33, 36]. Other studies have demonstrated that pre- or post-ischemic vinpocetine administration decreases hippocampal neuronal necrosis in a model of forebrain ischemia in rats [55]. Furthermore, vinpocetine inhibited adenosine reuptake, resulting in increased neuroprotection in a model of cytotoxic hypoxia in cultured chick embryo neurons [30].

Cerebral perfusion

Because cerebral perfusion plays an important role in neuroprotection against ischemic/hypoxic disorders and certain types of dementia, several studies have been evaluated the effect of vinpocetine on cerebral circulation. Various preclinical studies have shown that vinpocetine is a selective cerebral vasodilator and increases the cerebral blood flow by reducing cerebral vascular resistance without significantly altering the blood pressure or cardiac effort. A study conducted to evaluate the impact of regional volumetric cerebral

blood flow and local vascular reactivity in mild and moderate experimental craniocerebral trauma using animals with alloxan-induced diabetes and animals with isolated brain injury demonstrated that alloxan diabetes aggravated cerebral vascular disorders occurring after injury to the skull and brain. The vasoactive agent, vinpocetine, reduced the changed cerebral blood flow [56]. Similarly, another study reported an increase in the local cerebral blood flow in a rat model of forebrain ischemia [30, 55]. Two previous studies in dogs demonstrated an increase in brain perfusion due to improved cerebral blood flow and decreased cerebral vascular resistance [27, 71].

Cerebral metabolism

Studies performed in anesthetized dogs demonstrated that vinpocetine enhances the cerebral arterial-venous oxygen difference, the cerebral metabolic rate for oxygen and cerebral oxygen utilization, suggesting that vinpocetine increases the rate of cerebral metabolism [27]. Another study reported that this compound prevents the local increase in cerebral glucose utilization caused by 10-min forebrain ischemia in rats [54].

Dementia

Based on its neuroprotective mode of action, vinpocetine has been studied for the prevention and treatment of cerebrovascular diseases that predispose patients to the development of dementia. DeNoble et al. [8] demonstrated the cognition-enhancing activity of this compound in models of scopolamine- and hypoxia-induced memory impairment in rats. Following NMDA-induced neurotoxicity in a rat entorhinal cortex lesion model of dementia, both vinpocetine and cis-apovincaminic acid significantly decreased the lesion size and the region of microglia activation and effectively attenuated the behavioral deficits. These findings confirmed that vinpocetine has a marked potential in alleviating lesion-induced attention deficits and learning disabilities [44]. Chronic treatment with vinpocetine for 21 days significantly improved streptozotocin-induced learning and memory impairments in rats, reduced the oxidative-nitrosative stress, restored the levels of reduced glutathione (GSH) and reduced acetylcholinesterase activity and lactate dehydrogenase levels. These findings indicate that vinpocetine enhances spatial memory through an antioxidant mechanism, the modulation of cholinergic functions and the prevention of neuronal cell damage [9]. A recent study suggested the inhibition of slow-inactivating K^+-currents by vinpocetine as another mechanism responsible for the beneficial effects in dementia [63]. Furthermore, vinpocetine improved mitochondrial function, oxidative stress and other signs of toxicity in cells treated with β-amyloid. It has also been shown to protect against the deficits caused by scopolamine and hypoxia [5].

Convulsions

Earlier studies found that vinpocetine protects mice against convulsions induced by corazol, strychnine and thiosemicarbazide, and this anticonvulsant activity was suggested to be mediated by GABA and serotonergic mechanisms [11]. Anticonvulsive effects in electroshock- and pentylenetetrazole (PTZ)-induced convulsions in mice have also been reported [48]. An experimental study conducted to explore the anticonvulsant action of vinpocetine concluded that by blocking the tetrodotoxin-sensitive fraction of the rise in internal Na^+ induced by a convulsing agent 4-aminopyridine (4-AP), vinpocetine inhibits the concomitant rise in internal Ca^{2+}. This inhibitory effect on pre-synaptic voltage-sensitive Na^+ channels may be responsible for the *in vivo* anticonvulsant action of vinpocetine [60]. Another study conducted in primary cultures of rat cerebral cortex reported that vinpocetine is about 100-fold more efficient that phenytoin (a prototype Na^+-channel blocker) in the inhibition of veratridine-evoked cell death, thereby suggesting the blockade of voltage-gated Na^+ channels as a possible mechanism for the neuroprotective and anticonvulsant properties [32]. Recently, it was demonstrated that vinpocetine antagonizes the release of excitatory neurotransmitters triggered by Na^+ channel activation, which is hypothesized to be responsible for its anticonvulsant action, and also increases the levels of DOPAC in isolated striatum nerve endings [77]. Vinpocetine has shown higher potency and efficacy than the most widely used antiepileptic drugs (carbamazepine, phenytoin, valproate, oxcarbazepine, lamotrigine and topiramate) in inhibiting the high K^+-evoked release of [^{3}H]Glu in isolated hippocampal nerve endings. Therefore, the use of vinpocetine may reduce the adverse effects associated with higher doses of other antiepileptics (AEDs) [61]. Vinpocetine was tested in different types of kindled seizures in rats and was found to be effective in PTZ-, amygdala- and neocortically-kindled rats [57].

Brain aging and AD

In addition to the above-mentioned reasons, i.e., lack of perfusion and lack of oxygen or energy, aging also affects cognition and memory through the degeneration of neurons. Because reactive oxygen species (ROS) play an important role in the neuronal damage and death commonly seen in various neurodegenerative disorders like AD, the role of vinpocetine in oxidative stress is also being studied as a possible neuroprotective strategy. Studies conducted using *in vitro* models of oxidative stress have reported the protective effect of vinpocetine against ROS attacks. It neutralizes ROS, reduces the neurodegenerative process and delays the progression of age-related brain disorders [49]. It was also reported that vinpocetine protects PC12 cells from the inhibition in redox status induced by exposure to amyloid β-peptides (Aβ25–35 and Aβ1–40). In addition, vinpocetine was shown to protect cells from Aβ toxicity, preventing oxidative stress caused by the excessive accumulation of ROS. Thus, the study concluded that vinpocetine has neuroprotective potential that might be exploited for the treatment of AD or other neurodegenerative disorders in which oxidative stress is involved [50].

Clinical trials

Cerebrovascular disorders

As the efficacy of vinpocetine in cerebrovascular diseases became evident from animal studies, clinical studies were also performed. Despite the lack of unanimous opinion due to the paucity of clinical data, various clinical trials have confirmed the multiple underlying mechanisms responsible for the beneficial neuroprotective effects produced by vinpocetine. Positron emission tomography (PET) measurements performed in chronic ischemic stroke patients after a single-dose injection showed significant changes in regional cerebral blood flow (rCBF) and metabolism (rCMRglu). The changes were positive in the peristroke regions and the healthy brain tissue, with peaks in the basal ganglia, thalamus and occipital cortex [68]. Furthermore, the neuroprotective activity of vinpocetine makes it useful for the treatment of early stage cerebrovascular diseases, such as the asymptomatic ischemic cerebrovascular disorders (AICVD) [18]. In a pilot single-blinded randomized clinical trial, 30 patients with acute ischemic stroke were given either low-molecular weight dextran alone or in combination with vinpocetine. At the three-month follow-up, the relative risk (RR) reduction of a poor outcome was observed to be 30% (according to the modified Barthel Index) and 60% according to the modified Ranking score. In addition, no significant adverse effects were observed. Hence, this pilot study reported the efficacy and safety of vinpocetine [15]. Another study conducted in 87 patients with chronic cerebral ischemia demonstrated that vinpocetine exerts an endothelium protective effect through the partial renewal of endothelium-dependent vasodilatation and inhibition of rejection of the von Willebrand factor during an arteriovenous occlusion test. However, the recovery of a neurological deficit depends on the extent of renewal of the endothelium-dependent vasodilatation [80]. A study performed in 100 patients reported significant and relatively rapid improvements in reversible vascular diseases, such as hypertensive encephalopathy, intermittent vascular cerebral insufficiency and in the early stage or light cases of cerebral arteriosclerosis [72].

Studies performed to investigate the effect of ethyl apovincaminate on cerebral circulation showed that vinpocetine strongly reduces cerebral vascular resistance while significantly increasing the cerebral fraction of cardiac output [64]. Rheoencephalographic and psychological studies conducted in patients with cerebral vascular insufficiency found that the administration of vinpocetine resulted in the improvement of cerebral circulation. An improvement in memorizing capacity was recorded after one month of vinpocetine treatment and was associated with the alleviation or complete disappearance of symptoms [19]. Vinpocetine improved the cerebral circulation, particularly in patients with damaged cerebral vascularization [47]. Vinpocetine was found to increase the cerebral blood flow in the ischemia affected area of patients with cerebrovascular disease [73].

A ten-year long study on the use of vinpocetine in 967 patients with different cerebrovascular diseases showed that it was most effective in patients with early forms and primarily chronic forms, such as vegetovascular (neurocirculatory) dystonia, initial manifestations of brain blood supply insufficiency and circulatory encephalopathy in the first and second stages. It was also effective in ischemic brain stroke. The study concluded that vinpocetine should not be

used in either severe general cerebral hypertensive crises or in elderly or senile patients with acute cardio-cerebral or cerebro-cardiac syndrome, postinfarction cardiosclerosis and marked disorders of heart rhythm [6]. The continuous index and pulsatility index in the internal carotid artery were used as parameters for monitoring the changes in the cerebral vascular resistance after two months of vinpocetine administration in patients with cerebral circulatory disease. Vinpocetine caused a significant increase in the continuous index and a decrease in the pulsatility index, changes indicating cerebral vascular resistance decrease [42].

A study conducted to investigate the effect of parenteral or oral vinpocetine on the hemorheological parameters in patients with chronic cerebrovascular disease reported that high-dose parenteral vinpocetine significantly decreases red blood cell aggregation and plasma/whole blood viscosity compared to the initial values. In patients with additional oral treatment, plasma and whole blood viscosities were significantly lower compared to the placebo patients at three months [14]. A similar study was performed in 30 patients in the chronic phase of ischemic cerebrovascular disease to investigate the hemorheological changes following the administration of a low (30 mg/day) and high dose (increased to 70 mg/day) of intravenous vinpocetine for 7 days. It was observed that the high dose parenteral vinpocetine treatment significantly decreased the hematocrit, whole blood/plasma viscosity and red blood cell aggregation compared to the values before the treatment, while only red blood cell aggregation was improved significantly by the low dose treatment. This study advocated the use of vinpocetine in the treatment of chronic cerebrovascular diseases, confirming the beneficial rheological effect of high dose parenteral vinpocetine [69]. Another study also reported that during the administration of vinpocetine for three months, a significant improvement in red blood cell deformability was observed without adverse effect [21]. A comparative study conducted in five healthy volunteers who were given single oral doses of vinpocetine (10 mg), pentoxifylline (300 mg) and nicergoline (20 mg) reported vinpocetine as the most active drug [22]. A cochrane study designed to determine if vinpocetine treatment decreases the rate of early (within 1 month) and late (between 3 and 6 months) fatality as well as dependency when administered within two weeks of ischemic stroke onset summarized that there is no evidence to support the routine use of vinpocetine in all patients with acute ischemic stroke, thereby suggesting the need of further trials [4].

Memory and cognition

In a pilot study, the effect of vinpocetine on cerebral blood flow and mild cognitive impairment both in resting conditions or following chemical stimulus was investigated. It was found that after a 12-week long oral vinpocetine treatment, the increase of blood flow velocity in resting conditions compared to the baseline values was significant in the vascular group. In addition, there was significant improvement in cognitive functions in both groups. Therefore, it recommended the use of vinpocetine for the treatment of patients with mild cognitive impairment [79].

In an open-label pilot trial, 15 AD patients were treated with increasing doses of vinpocetine (30, 45, and 60 mg/day) for a 1-year period. Vinpocetine failed to improve cognition on psychometric testing or overall functioning as measured by the clinical global impression at any dose tested. The study concluded that vinpocetine is ineffective in improving cognitive deficits and does not slow the rate of decline in individuals with AD [75]. A Cochrane study conducted to assess the efficacy and safety of vinpocetine in the treatment of patients with cognitive impairment due to vascular disease, AD, a mixture of vascular disease and AD or other dementias found that 30 mg/day and 60 mg/day vinpocetine was beneficial, but the number of patients treated for 6 months or more was reduced. Therefore, the study remained inconclusive and advocated the need of larger studies for evaluating the use of vinpocetine for people suffering from well-defined types of cognitive impairment [70]. The efficacy and tolerance of orally administered vinpocetine was investigated in patients suffering from mild to moderate organic psychosyndromes, including primary dementia, by assessing ratings of clinical global impression, cognitive performance and measures of the quality of life, including depressive illness. Statistically significant improvements were found in favor of active treatment groups compared to placebo, and vinpocetine was also superior to placebo in ratings of the "severity of illness". This study demonstrated the usefulness and efficacy of vinpocetine in the management of patients with moderate organic psychosyndromes [23]. A study was conducted in 8 patients with Binswanger type vascular dementia to

investigate the effect of vinpocetine on hemoglobin oxygen affinity, erythrocyte 2,3-diphosphoglycerate (DPG) and adenosine triphosphate (ATP) concentrations. After the oral administration of vinpocetine, hemoglobin oxygen affinity (P50) was significantly increased and red blood cell (RBC) ATP concentrations were significantly increased, while DPG concentrations were unchanged. There was a significant positive correlation between the increase of P50 and the increase of erythrocyte ATP concentrations. Thus, vinpocetine is beneficial in the treatment of Binswanger type vascular dementia due to chronic ischemia [76].

In a double-blind clinical trial, vinpocetine was investigated for safety and efficacy in elderly patients with chronic cerebral dysfunction. Patients on vinpocetine scored consistently better in all evaluations of the effectiveness of treatment, including measurements on the Clinical Global Impression (CGI) scale, the Sandoz Clinical Assessment Geriatric (SCAG) scale and the Mini-Mental Status Questionnaire (MMSQ), and no serious side effects were observed [2]. Vinpocetine stimulates locus coeruleus (LC) neurons, which decline in number with increasing age. The reduced number and activity leads to a reduction in concentration, alertness and information processing speed and ability. Hence, vinpocetine's ability to improve the cerebral cortical activating power of the remaining LC neurons makes it a potential cognition enhancer [45]. A study reported that vinpocetine improved the memorizing capacity evaluated by psychological tests and alleviated associated symptoms [19]. A study conducted in 20 healthy females used 10, 20, or 40 mg of vinpocetine or placebo for 3-day periods in a crossover fashion. On the third day of each period, the subjects underwent a variety of psychological tests. Forty milligrams of vinpocetine significantly increased performance compared to the other groups, while no effects on other psychological parameters were found. The study remained inconclusive due to the short treatment periods, but suggested that vinpocetine can improve cognition in healthy individuals [38, 67]. Another study conducted in healthy adults also reported an improvement in reaction time and working memory after treatment with a combination of ginkgo and vinpocetine. However, this study was also inconclusive regarding whether this effect was due to ginkgo, vinpocetine or the combination [51].

Epilepsy

The effect of vinpocetine (15–45 mg/day) and its combinations with different anticonvulsants was stud-

Tab. 1. Comparative summary of different clinical studies indicating the safety and efficacy of vinpocetine

No.	Ref.	Total patients	Treatment group	Duration of study	Disease conditions	Efficacy	Safety
1.	[68]				Chronic stroke	Significant improvement in the transport of glucose (both uptake and release), increased blood flow as well as decreased blood flow velocity and increased peripheral vessel resistance.	
2.	[15]	30	15	3 months	Acute ischemic stroke	Relative risk (RR) reduction of poor outcome at 3 months of follow-up was 30% (according to the modified Barthel Index) and 60% (according to the modified Ranking score.	No significant adverse effects
3.	[75]	30	15	1 year	Alzheimer's disease	Ineffective in improving cognitive deficits	No significant side effects
4.	[2]	84	42	90 days	Chronic cerebral dysfunction	Significant efficacy	No serious side effects
5.	[12]	61	41	1 year	Convulsive syndrome in children after birth injury	Effectively prevented convulsive syndrome in children after birth injury	
6.	[62]	149		90 days	Chronic cerebrovascular insufficiency	Significant differences in scores before and after treatment	Well tolerated and safe

ied in 31 patients with different forms of epilepsy. Vinpocetine significantly decreased the frequency of attacks or led to their complete disappearance in 20 patients. The greatest effect of vinpocetine was observed in generalized tonic-clonic convulsions and when they were combined with absences. The study suggested that vinpocetine has anticonvulsive activities [13]. Another study was conducted to investigate the efficacy of vinpocetine in preventing convulsive syndrome in children after birth injury. Children were divided into two groups. A disappearance of seizures was reported in 6 patients from group I (n = 20, taking conventional therapy) and 27 patients from group II (n = 41, taking conventional therapy and vinpocetine). A follow-up with 29 children was done one year later. It was reported that in group I, convulsive paroxysms recurred in 4 patients, whereas in the group II children, no convulsive syndromes were recorded. In addition, group II children also showed a decrease in intracranial hypertension and a normalization of psychomotor development [12].

Safety pharmacology and toxicological studies

Various clinical studies have demonstrated that vinpocetine is safe for long-term use (Tab. 1). However, the safety of vinpocetine in pregnant women has not been evaluated. No significant side effects related to the treatment have been reported [2, 15, 68, 70, 75]. A multi-center prospective non-comparative program investigating the efficacy and safety of a new therapy scheme with vinpocetine in patients with chronic cerebrovascular insufficiency has concluded that the parenteral and peroral use of vinpocetine is well tolerated and has a favorable safety profile [62]. Some mild side effects include indigestion, nausea, dizziness, anxiety, facial flushing, insomnia, headache, drowsiness and dry mouth. Due to its capacity to decrease platelet aggregation, it should be used carefully with blood thinners [31, 38]. A study has reported the induction of agranulocytosis by vinpocetine [59]. An advantage of vinpocetine over other vasodilators is that it does not exhibit a "stealing effect", which is a phenomenon that involves an enhanced shifting of blood away from underperfused regions of ischemic damage, thereby further aggravating ischemic damage. The underlying mechanism responsible may be non-selective vasodilation, i.e., the opening of blood vessels in brain regions that do not suffer from reduced circulation. However, vinpocetine has no such "stealing effect". This finding may be due to its blood viscosity lowering property, which makes blood much more accessible to ischemic regions [19]. Apart from this, vinpocetine increases cerebral blood flow selectively without affecting blood pressure and systemic circulation, making it much safer than other vasodilators [64].

Drug interactions

Because vinpocetine decreases platelet aggregation, it should be avoided in patients on blood thinning medications. Vinpocetine's absolute bioavailability is 6.7% under fasting conditions, and the relative bioavailability under non-fasting conditions has been reported to be 60% to 100% higher. Therefore, the intake of food increases its bioavailability, and it should be taken along with meals [34]. A study was conducted in healthy volunteers to investigate the effect of vinpocetine on imipramine pharmacokinetics. C_{max} and t_{max} values indicated no change in the absorption of imipramine due to vinpocetine treatment [24]. Another study investigated the influence of multiple doses of vinpocetine on the steady state plasma concentrations of oxazepam in 16 healthy subjects. The results indicated a lack of influence of vinpocetine on oxazepam kinetics [66]. The influence of vinpocetine on glibenclamide steady state plasma levels was investigated in 18 patients suffering from type II diabetes and symptoms of dementia. The study reported no interference of vinpocetine with the kinetics of glibenclamide and concluded that the co-medication of vinpocetine and glibenclamide is safe [16].

Conclusions

Vinpocetine is widely used in Japan, Hungary, Germany, Poland and Russia for the treatment of cerebrovascular-related pathologies. Data obtained from clinical studies have indicated the efficacy and safety of vinpocetine as a neuroprotective, nootropic and anticonvulsant agent. However, as described above, most of the clinical studies had only a small sample size and a short duration. Hence, there is a great need for larger and longer studies to confirm the exact status of vinpocetine.

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