

Vinpocetine

Ethyl apovincamate (Vinpocetine) is a vincamine derivative has been used in the clinical practice for over 25 years for the treatment of cerebrovascular disorders and related symptoms. The effects of vinpocetine on cerebral blood flow, brain metabolism, memory functions, and its neuroprotective action have been confirmed in the past years in numerous animal experiments and human studies.

Pharmacological properties

Vinpocetine exerts a brain neuroprotective effect by a combined action on cerebral circulation, brain metabolism, and rheological properties of the blood. Early experiments showed an improvement of the cerebral circulation and oxygen utilization without changes in systemic circulation, cerebral protection in conditions of hypoxia/ischaemia, cognition-enhancing and anticonvulsant activity, and improvement of rheological properties of the blood. Later studies confirmed the above effects and clearly demonstrated a direct neuroprotective action at a cellular level.

Cerebral circulation

- Increases brain perfusion by improvement of cerebral blood flow and decrease of the cerebral vascular resistance in dogs. (Karpati and Szporny, 1976; Szmolenszky and Torok, 1976);
- Increases the cerebral capillary flow rate in dogs (Szmolenszky and Torok, 1976)
- Improves total cerebral blood flow in normal conditions and in hypoxic hypoxia in dogs (Bencsáth et al., 1976).

Brain metabolism

- Enhances the cerebral metabolic rate of oxygen in dogs (Karpati and Szporny, 1976)
- Prevents the local cerebral glucose utilization increase, caused by forebrain ischaemia of 10-min duration in rats (Rischke and Krieglstein, 1990).

Neuroprotective action in conditions of hypoxia/ischaemia

- Increases latency to ischemic convulsion in a dose-related manner In a rat model of cerebral ischaemia (bilateral carotid artery occlusion). After 5 days administration (25 mg/kg/day) increases survival time (King and Narcavage, 1986).
- Demonstrates a pronounced protective effect against hypoxia and ischaemia in several animal models (Lamar et al., 1988).
- Increases the local CBF in a model of rat forebrain ischaemia of 10-min duration after 1 h of recirculation (Rischke and Krieglstein, 1991), and at the 7th day after the ischaemia (Rischke and Krieglstein, 1990).
- Increases the neuroprotective effect of adenosine in a model of cytotoxic hypoxia in cultured chick embryo neurons (Krieglstein and Rischke, 1991).
- Reduces the hippocampal neuronal necrosis after pre- or post-ischemic administration in a model of forebrain ischaemia in rats (Rischke and Krieglstein, 1991).
- Exerts a pronounced brain protective effect in doses 5, 10 and 20 mg/kg in different experimental models of hypoxia/ischaemia (Maslarova and Nikolov, 1999). The effect was similar to nicergoline and weaker than the effect of piracetam.

Biochemical mechanisms

- Vinpocetine showed weaker calcium antagonistic properties in comparison with the effects of flunarizine, verapamil, diltiazem

and nimodipine in isolated rabbit basilar and splenic artery (Lamar et al., 1988).

- In binding experiments on rat brain cortical membranes vinpocetine showed properties of a quisqualate/AMPA antagonist of some specificity and selectivity (Kiss et al., 1991).
- Using primary cultures of rat cerebral cortex Lakics et al. (1995) showed that the blockade of voltage-gated sodium channels is a possible mechanism of action for the neuroprotective and anticonvulsant properties of vinpocetine.
- Antioxidant and ROS (reactive oxygen species) scavenging action in conditions in which ROS are excessively generated such as oxidative stress, hypoxia/reoxygenation, ischaemia/reperfusion (Stolc, 1999).
- In vitro studies demonstrated the effect of vinpocetine on Ca²⁺-calmodulin dependent cGMP-PDE, voltage-operated Ca²⁺ channels, glutamate receptors and voltage-dependent neuronal Na⁺ channels (Bonoczka et al., 2000).

Other effects

- Increases myocardial and renal capillary flow rate in dogs (Szmolenszky and Torok, 1976).
- Anticonvulsive effect in electroshock and pentylenetetrazole-induced convulsions in mice (Palosi and Szporny, 1976)
- Cognition-enhancing activity in models of scopolamine-induced and hypoxia-induced memory impairment in rats (DeNoble et al., 1986)

Clinical efficacy

Cerebrovascular disease

Szobor and Klein (1976) studied the effectiveness of vinpocetine in 100 patients with neurovascular diseases distributed in two groups. Forty six patients were given combined treatment (i.m. and oral) vinpocetine in daily dose 10-30 mg; 54 patients were treated with oral vinpocetine 30-45 mg daily. Vinpocetine caused significant improvement in the reversible vascular diseases such as hypertensive encephalopathy, intermittent vascular cerebral insufficiency and cerebral arteriosclerosis.

Solti et al. (1976) demonstrated in 10 patients with cerebrovascular diseases that vinpocetine (10 mg i.v. drop infusion within 4-6 min) reduced cerebral vascular resistance and increased cerebral fraction of cardiac output without effect on systemic circulation.

Hajiev and Yancheva (1976) studied the effect of vinpocetine on the rheoencephalogram in 50 patients with ischemic disturbances of cerebral circulation. The drug was administered in a single i.v. dose of 10 mg and orally three times daily 5 mg for a month. Vinpocetine caused an increase of cerebral circulation demonstrated by an improvement of the rheoencephalographic parameters, especially tga 1 (tangent of the angle of inclination of slow systolic filling), which reflected changes in the small blood vessels. Blood flow increased most markedly in the gray matter.

Orosz et al., (1976) studied the effect of vinpocetine after i.v. administration on cerebral circulation in neurosurgical patients by use of H₂ clearance technique and serial carotid angiography. Vinpocetine improved the cerebral circulation, particularly in patients with damaged cerebral vascularisation. Vinpocetine was found to increase the cerebral blood flow in the ischaemia affected area of patients with cerebrovascular disease (Tamaki et al., 1985).

Burtsev et al. (1992) summarized 10-years experience of the use of vinpocetine in 967 patients with different cerebrovascular diseases. Better effect was found in patients with early forms and primarily chronic forms: neurocirculatory dystonia, initial manifestation of

cerebral blood flow insufficiency, circulatory encephalopathy. In ischemic stroke the improvement of cerebral symptoms was more rapid in the patients with normal blood pressure.

Using Doppler ultrasonic technique Miyazaki (1995) examined the changes in the cerebral vascular resistance after 2-months administration of vinpocetine in patients with cerebral circulatory disease. Continuous index and pulsatility index in the internal carotid artery were used as parameters for monitoring the changes in the cerebral vascular resistance. Vinpocetine caused a significant increase of the continuous index and a decrease of the pulsatility index, changes indicating cerebral vascular resistance decrease.

Szakall et al., (1998) studied the effect of vinpocetine on the cerebral glucose metabolism of chronic stroke patients by the use of positron emission tomography. Single-dose of intravenous vinpocetine improved significantly the transport of glucose through the blood-brain barrier in the whole brain, the entire contralateral hemisphere, and in the brain tissue around the infarct area of the affected hemisphere.

Gulyas et al. (2001) studied the effect of a single-dose i.v. infusion of vinpocetine on the cerebral blood flow (CBF) and glucose metabolism of post-stroke patients. Regional and global cerebral metabolic rates of glucose, transcranial Doppler and single photon emission tomography measurements were performed. Although the single-dose of vinpocetine did not affect significantly the regional or global metabolic rates of glucose, the glucose transport was significantly improved in the whole brain, in the contralateral hemisphere and in the peri-infarct area of the affected hemisphere. A slightly increased cerebral blood flow was observed in the contralateral hemisphere and a decreased flow was found in the affected hemisphere.

Feigin et al. (2001) studied the efficacy and safety of vinpocetine in acute ischemic stroke. Thirty patients with computed tomography verified diagnoses were enrolled in this pilot study. The patients were

randomly allocated to receive either low-molecular weight dextran alone or in combination with vinpocetine. The results showed that the National Institute of Health Stroke Scale score was marginally significantly better in the vinpocetine treated group at the end of the 3 months follow-up period.

Rheological properties of the blood

Hayakawa (1992) studied the effect of vinpocetine on the deformability of erythrocytes in patients with chronic ischemic cerebrovascular disease. Vinpocetine led to a significant improvement of the red blood cell deformability after 3 months administration. Akopov and Gabrielian (1992) studied the effect of vinpocetine in comparison with the aspirin, nifedipine, and dipyridamole on platelet aggregability in patients with atherosclerosis. The drugs studied reduced platelet aggregability when aggregation was induced by ADP, adrenaline, or collagen. It inhibits platelet aggregation and adhesion in patients with cerebrovascular disorders (Itoh, 1982).

Memory functions

Using the psychological tests “10 words” and Wechsler’s fifth subtest Hajiev and Yancheva (1976) investigated the effect of vinpocetine (one month oral administration) on memorizing capacity of 50 patients with ischemic disturbances of cerebral circulation. Vinpocetine improved considerably the memory functions in most of the patients.

Szobor and Klein (1976) have found that vinpocetine (30-40 mg daily) improved memory functions and attention in 46 out of 60 patients with neurovascular diseases, using psychodiagnostic tests (free association, figural Bourdon, Ranschburg-Ziechen test). Balestreri et al. (1987) studied the effect of vinpocetine in a double blind clinical trial on 42 elderly patients with chronic cerebral dysfunction. The patients received 10 mg vinpocetine three times daily for 30 days then 5 mg for 60 days. Vinpocetine caused

improvement of the memory functions of the patients as measured by the Clinical Global Impression scale, the Sandoz Clinical Assessment-Geriatric scale and the Mini-Mental Status Questionnaire.

Bhatti and Hindmarch (1987) studied the effect of pre-treatment with vinpocetine (40 mg) on flunitrazepam-induced impairment of memory in 8 normal volunteers. Treatment with vinpocetine led to improvements in short-term memory.

Hindmarch et al. (1991) studied the efficacy and tolerability of orally administered vinpocetine in patients with mild to moderate organic psychosyndromes including primary dementia. In the conditions of a placebo-controlled, randomized double-blind, multicentre trial 203 patients have been distributed in groups to receive daily 30 mg vinpocetine, 60 mg vinpocetine, or placebo for 16 weeks. Statistically significant improvements were found in vinpocetine groups in comparison with placebo in the clinical global impression and cognitive performance.

Other effects

Ribari et al. (1976) found a significant improvement of speech-audiograms of patients with sensorineural impairments of hearing after administration of 15 mg vinpocetine daily for 1-5 months. Kahán and Oláh (1976) demonstrated that vinpocetine (20 mg in drop infusion or 10 mg i.v. three times daily) improved considerably the visual acuities in 100 arteriosclerotic patients. Improvement was most pronounced in occlusions and retinopathies associated with atherosclerosis of the central retinal artery.

Dutov et al. (1986) studied the effect of vinpocetine 15-45 mg daily and a combination of vinpocetine with different anticonvulsants in different forms of epilepsy. In 20 of the 31 patients studied vinpocetine either significantly decreased the frequency of the attacks or abolished them. Most pronounced effect was observed in generalized tonic-clonic convulsions especially when combined with

absences. The clinical improvement not always correlated with EEG normalization. The mechanism of the anticonvulsive action of vinpocetine might be explained by normalization of the cerebral blood flow, by its antihypoxic action, or by a presence of own anticonvulsive properties.

Kis (1990) investigated the effect of vinpocetine when applied in addition to the standard hormone replacement therapy on 40 postmenopausal women. Vinpocetine significantly improved the effects of the hormone replacement therapy, and the author recommends such a combination therapy for alleviation of the menopausal complaints in postmenopausal women.

Tolerability

Numerous clinical studies indicated that vinpocetine is safe during long-term administration. No serious side effects related to the treatment have been found (Balestreri et al., 1987; Kis, 1990; Feigin et al., 2001).

Szobor and Klein, (1976) established that vinpocetine (10-30 mg daily at combined oral and i.m. administration, or 30-45 mg daily orally) did not change laboratory tests, blood pictures, blood sugar, liver functions, did not cumulate and did not produce allergic symptoms). There are few reports about side effects of vinpocetine after i.v. administration. Some patients had a passing sensation of warmth after injection of the drug (Orosz et al., 1976; Hajiev and Yancheva, 1976; Ribári et al., 1976)

Why Do People Use Vinpocetine

Stroke and vascular dementia

Vinpocetine is thought to increase blood circulation in the brain, which may explain why some preliminary studies suggest that it may

reduce brain impairment and dementia after an ischemic stroke. Although promising, well-designed human studies are needed.

Alzheimer's disease

Vinpocetine is also being explored as a complementary treatment for people with Alzheimer's disease. It's thought to enhance the brain's use of oxygen, protect brain cells against damage, and increase blood flow to the brain by inhibiting an enzyme called phosphodiesterase. Although preliminary studies on the use of vinpocetine for Alzheimer's disease showed promise, a critical review of previously published studies found that the evidence as a whole was too weak to rely on, due to limitations in the design of the studies.

Tinnitus

Studies suggest that vinpocetine may help with tinnitus after trauma to the ear.

To boost brain function

Vinpocetine is marketed in North America as a supplement that can boost memory and brain function in healthy people, but there is no real evidence yet that it can help.

Side Effects and Safety Concerns

Side effects of vinpocetine may include indigestion, nausea, dizziness, anxiety, facial flushing, insomnia, headache, drowsiness and dry mouth. Vinpocetine may also cause a temporary drop in blood pressure.

Vinpocetine should not be taken by pregnant or nursing women. The safety of vinpocetine in people with liver or kidney damage is not known. People with bleeding disorders, low blood pressure or seizure disorders should not use vinpocetine. It also should not be used two weeks before or after a surgical or dental procedure.

There is one case report of agranulocytosis associated with the use of vinpocetine.

Possible Drug Interactions

Vinpocetine should not be taken by people who are taking drugs or herbs that “thin” the blood (anti-clotting or anti-platelet medications), such as aspirin, clopidogrel, ticlopidine, pentoxifylline, vitamin E, garlic or ginkgo. It should not be used with Coumadin (warfarin).

Vinpocetine, ethyl(13aS, 13bS)-13a-ethyl-2,3,5,6,13a,13b-hexahydro-1H-indolo(3,2,1-de) pyrido-(3,2,1-ij)(1,5)naphthyridine-12-carboxylate, which was synthesized in 1984, is used for patients with cerebral circulatory diseases as a cerebral vasodilator. It has the property of reducing cerebral vascular tone while increasing total peripheral vascular resistance (Miyazaki, 1995). In human studies, it has been suggested that vinpocetine was reported to increase cerebral blood flow in previously ischaemic cerebral regions (Tamaki et al, 1985), to decrease platelet aggregability, in patients after transient ischaemic attack or stroke and to increase erythrocyte deformability in patients after ischaemic stroke (Hayakawa 1992). In addition, it is known to facilitate the transmembrane glucose transport, resulting in increased glucose uptake and release, and thus the extraction of glucose, predominantly in brain tissue spared by stroke (Szakall et al, 1998).

Vinpocetine has also been shown to block voltagegated Na⁺ channels in rat cortical neurons, helping to provide neuroprotective and anticonvulsant effects. Furthermore, vinpocetine is used as a cyclic nucleotide phosphodiesterase inhibitor (Fisher et al, 1998). Based on the results of pharmacologic studies and data from animal experiments, vinpocetine was recommended for use and has been administered to patients with stroke in several countries in Europe and in Japan. It is also useful for the management of patients with moderate organic psychosyndromes including primary dementia. No fatal adverse effects have been reported so far linked to vinpocetine.

Vinpocetine: Cognitive Enhancers Role Expands to Incontinence and Epilepsy

The periwinkle has long been an established part of summer gardens. But research has revealed that this flower is more than just a pretty addition to landscaping. Studies have indicated that vinpocetine, a natural substance derived from vincamine, an extract of the periwinkle, may support cognitive health, alleviate some of the symptoms of urinary incontinence, and, when administered intravenously in animals, alleviate some of the negative effects that occur in epilepsy.

Early experiments with vinpocetine indicated it has five main mechanisms of action. It can selectively enhance brain circulation and the brain's use of oxygen without significantly altering circulation throughout the body. Vinpocetine also increases the brain's tolerance toward hypoxia (oxygen deficiency) and ischemia (obstructed blood flow) and acts as an anticonvulsant. In addition, it inhibits the enzyme phosphodiesterase (PDE)-1, which breaks down adenosine monophosphate, an important nucleotide that the body makes from the cellular energy molecule known as adenosine triphosphate (ATP). Finally, vinpocetine stops blood cells from sticking together. Later studies confirmed the above effects and pinpointed other mechanism of actions of vinpocetine (including its ability to act as a sodium channel blocker).

Cognitive Support

Many vinpocetine studies have focused on its potential ability to enhance brain function. Vinpocetine increases blood circulation and metabolism in the brain, which may be why vinpocetine reduced the loss of neurons due to decreased blood flow in animal studies.

In three studies of older adults with memory problems associated with poor brain circulation or dementia-related disease, vinpocetine

treated subjects experienced significantly more improvement than placebo-treated subjects on global cognitive tests reflecting attention, concentration, and memory.

In one study, the efficacy and tolerance of orally administered vinpocetine was investigated in patients suffering from mild to moderate organic psychological syndromes, including primary dementia. In the placebo-controlled, randomized, double-blind trial, 203 patients received daily for 16 weeks either 10 mgs of vinpocetine three times per day, 20 mgs of vinpocetine three times per day, or a placebo three times per day. On both the lower and higher doses, the patients treated with vinpocetine experienced statistically significant improvements in cognitive performance compared to the placebo groups. Vinpocetine was also superior to placebo in improving ratings of the $\frac{1}{2}$ severity of illness. There were no clinically relevant side-effects reported and the frequencies of adverse events between patients treated with vinpocetine and placebo were comparable.

Urinary Incontinence

Although vinpocetine is best known for the part it plays in cognitive support, researchers also have unearthed another potential role for this substance; urinary incontinence. The standard drugs available for incontinence and low compliance bladder are limited by a low clinical efficacy and significant side effects. Previous in vitro studies indicated that the enzyme known as phosphodiesterase (PDE)-1 (which breaks down adenosine monophosphate) may be involved in the regulation of contractility in the bladder's layer of muscle. Due to this connection, researchers decided to investigate the effect of vinpocetine, a PDE-1 inhibitor, in people who did not respond to standard drug therapy and who had been told that surgery is needed to correct the problem.

The 19 subjects (10 women and nine men, average age 56) were given 5 mg per day of vinpocetine for two weeks, then 10 mg per day for another two weeks. In 11 subjects (57.9 percent) clinical symptoms

and/or the holding and storage of urine were improved. In eight subjects, there was a marked improvement after vinpocetine treatment. In three of the subjects, there was a slight improvement after treatment. The other eight subjects did not respond to vinpocetine. Although the researchers called the initial data preliminary, they pointed out that this study represents the first evidence that a phosphodiesterase (PDE)-1 enzyme inhibitor such as vinpocetine may be a novel approach to the treatment of lower urinary tract disorders.

Vinpocetine appears to be more effective in what is known as urge incontinence because it relaxes or desensitizes the bladder, whereas other agents that stimulate and strengthen the pelvic floor are more effective for stress incontinence. Urge incontinence is when an individual experiences involuntary passage of urine occurring soon after a strong sense of urgency to void. Stress incontinence is the inability to prevent escape of small amounts of urine during laughing, coughing, sneezing or lifting.

Epilepsy

Vinpocetine also has been investigated for its potential role in epilepsy. One group of researchers induced convulsions in guinea pigs by using an agent called 4-aminopyridine (4-AP). The researchers injected the animals with vinpocetine and then observed its effects. Vinpocetine inhibited the undesirable electroencephalogram (EEG) changes induced by 4-AP. In addition, it prevented the hearing loss that usually accompanies 4-AP administration. The researchers concluded, Vinpocetine could be a promising alternative for the treatment of epilepsy.