

## Vinpocetin Overview

Vinpocetine is a chemical derived from vincamine, a constituent found in the leaves of common periwinkle plant, *Vinca minor*. Vinpocetine is used in about 35 countries in the treatment of stroke and vascular dementia. Its action is to dilate blood vessels to enhance blood flow to specific regions of the brain as well as to reduce damage from free radicals by improving oxygen utilization. In Europe, vinpocetine is marketed as a drug called Cavinton for the treatment of various cerebral insufficiency conditions. It improves cerebral metabolism (glucose and oxygen uptake), increases ATP concentration, and selectively increases blood flow to the brain (without lowering blood flow to other parts of the body); and reduces blood clotting by making red blood cells more pliable and inhibiting platelet aggregation. Vinpocetin is also known as a memory enhancer; a treatment for Alzheimer's disease; a treatment for stroke; it improves circulation (especially to the brain); and it is a powerful antioxidant.

Research studies on vinpocetine have shown that it enhances overall brain function and cognitive ability in people recovering from stroke, Alzheimer's disease, and age-related declines in memory. It provides significant improvements in cognitive function in patients suffering from mild to moderate dementia and in stroke patients, it significantly improved the transport of glucose (both uptake and release) in the brain and especially in the brain tissue around the area damaged by stroke. These changes appeared to be related to increased blood in the entire region in and around the area of damage. Thousands of patients with different cerebrovascular diseases have shown improvement (75-85% of patients) on measures of cognitive function with the use Cavinton in Europe, over the past 10-20 years.

**Dosage:** Typical dosage recommendations for vinpocetine are 5-10mg, taken 2-3 times per day with meals (to increase absorption and reduce gastrointestinal discomfort).

**Side Effects:** Side effects of vinpocetine are quite rare, typically minor and disappear with discontinuance of consumption. Rarely, side effects such as gastrointestinal upset; low blood pressure (hypotension), dry mouth, insomnia, headaches and heart palpitations (rapid heart beat) have been reported.

(Source: [www.supplementwatch.com](http://www.supplementwatch.com))

## Research Overview

1. Treats early stages of cerebrovascular disease
2. Provides neuroprotection in those with high risk of ischemic stroke
3. Stabilizes cerebrovascular disorders
4. Effective treatment for central nervous system degenerative disorders in elderly people
5. Improves brain blood flow
6. Improves coronary, intestinal and renal blood flow
7. Improves short-term memory capacity
8. Reduces cerebral vascular resistance
9. Effective vasodilator
10. May be of benefit in Alzheimer's disease treatment
11. May reduce risk of retinal damage associated with hepatitis B infection
12. May have gastroprotective properties
13. May be a quisqualate antagonist
14. Improves glucose metabolism in the brain
15. Improves space motion sickness
16. May be a treatment for Meniere's disease

Vinpocetin Abstracts (38)

Neuroprotection 1. Ideggyogy Sz. 2003 May 20;56(5-6):166-72. Asymptomatic ischemic cerebrovascular disorders and neuroprotection with vinpocetine. Hadjiev D. University Hospital of Neurology and Psychiatry, St. Naum Compl. Javorov, B-1504 Bulgaria, Sofia, bl. 21. A. dimiter\_hadjiev@hotmail.com

The asymptomatic ischemic cerebrovascular disorders (AICVD) is an early manifestation of cerebrovascular disease. It is also known as latent insufficiency of the cerebrovascular circulation or as asymptomatic cerebrovascular disorders. Recently, the term subclinical disease, detected noninvasively, has been introduced by American Heart Association. The diagnosis is based on the following criteria: evidence of vascular risk factors; episodic nonspecific complaints without any focal cerebral symptoms; mild cognitive deficit, detected by neuropsychological tests; carotid ultrasonography often shows intimal-medial thickening, atherosclerotic plaques and carotid stenosis; CT and MRI occasionally reveal silent cerebral infarctions, white matter hyperintensities or cerebral atrophy; regional hypoperfusion above the ischemic threshold is also seen by rCBF measurements. Treatment of the AICVD, modifying the vascular risk factors and using neuroprotective agents, should be the cornerstone of primary prevention of ischemic stroke and cognitive decline, caused by cerebrovascular disorders. Vinpocetine has been found to interfere with various stages of the ischemic cascade: ATP depletion, activation of voltage-sensitive Na(+)- and Ca(++)-channels, glutamate and free radicals release. The inhibition of the voltage-sensitive Na(+)-channels appears to be especially relevant to the neuroprotective effect of vinpocetine. Pronounced antioxidant activity of the drug could also contribute to the neuroprotection. PET studies in primates and man showed that <sup>11</sup>C labelled vinpocetine passes the blood-brain barrier rapidly. Heterogeneous brain distribution of the compound was observed mainly in the thalamus, basal ganglia, occipital, parietal and temporal cortex, regions which are closely related to the cognitive functions. PET studies in chronic ischemic stroke patients revealed favourable effects of vinpocetine on rCBF and glucose metabolism in the thalamus, basal ganglia and primary visual cortex. It seems, vinpocetine, affecting the multiple mechanisms of the AICVD, could be of benefit for the treatment in this early stage of cerebrovascular disease. Vinpocetine may also become a new therapeutic approach to prophylactic neuroprotection in patients at high risk of ischemic stroke.

2. Vinpocetin protects against excitotoxic cell death in primary cultures of rat cerebral cortex Erdo S.L.; Nin sheng C.; Wolff J.R.; Kiss B. Laboratory of Neurochemistry, Department of Anatomy, Georg August University, 36 Kreuzberggring, D 3400 Gottingen Germany, Federal Republic of EUR. J. PHARMACOL. (Netherlands), 1990, 187/3 (551 553)

The protective effect of vinpocetin, a drug clinically useful in brain hypoxia/ischemia, was examined in vitro on cerebrocortical cultures treated with glutamate and related excitotoxins. The extent of cell death was quantified by measuring lactic dehydrogenase activity released from damaged cells into the culture medium. Vinpocetin partially protected the cortical cells against cell death induced by N methyl D aspartate, quisqualate and kainate, indicating that the drug exerts a direct protective action on cerebrocortical cells bearing excitatory amino acid receptors.

#### Cerebrovascular insufficiency/disease

3. Orv Hetil. 2001 Feb 25;142(8):383-9. [The use of vinpocetine in chronic disorders caused by cerebral hypoperfusion] [Article in Hungarian] Horvath S. Pest Megyei Onkormanyzat Flor Ferenc Korhaza, Kistarcsa, Neurologiai Osztaly.

The clinical signs and symptoms of so-called "cerebrovascular insufficiency" or "cerebral vascular dysfunction" have the characteristics of those of chronic cerebral hypoperfusion. The clinical features of chronic cerebral hypoperfusion often show the symptoms of cognitive impairment and organic psychosyndromes. Cerebral hypoperfusion could be found in dementias of different origin (subcortical arteriosclerotic leucoencephalopathy [Binswanger], vascular dementia, Alzheimer's disease, etc.). Pathological changes caused by chronic cerebral hypoperfusion often confined only to the white matter (demyelisation, glial activation, damage of oligodendroglial cells, as well as scattered cell death). Each therapy has an influence on the biochemical and pathophysiological alterations caused by chronic cerebral hypoperfusion can be used with reason in these disorders. The mechanism of action of vinpocetine is interfering on many aspects with the biochemical and pathophysiological processes attributable to chronic cerebral hypoperfusion, independently of the original alteration responsible for hypoperfusion. This fact might give an explanation on the beneficial effect of vinpocetine on clinical signs and symptoms of chronic cerebrovascular insufficiency.

4. Ten years of experience gained with the use of cavinton in cerebrovascular diseases Burtsev E.M.; Savkov V.S.; Shprakh V.V.; Burtsev M.E. USSR ZH. NEVROPATOL. PSIKHIATR. IM. S. S. KORSAKOVA (USSR), 1992, 92/1 (56 60)

Cavinton was used for 10 years in 967 patients with different cerebrovascular diseases. The highest effect was seen in patients with early forms and primarily chronic forms: vegetovascular (neurocirculatory) dystonia, initial manifestations of brain blood supply insufficiency, dyscirculatory encephalopathy in the first and second stages. Improvement of the subjective status and a decrease of the intensity of vestibulocerebellar disorders were recorded by the end of the treatment in 75 85% of such patients. In ischemic brain stroke, regress of general cerebral and focal symptoms was more rapid and significant in the adequate reaction type of cerebral hemodynamics to cavinton administration (a rise of pulse blood content of the brain and a reduction of the vascular tone according to the REG data) and was less noticeable in the hypertonic and, in particular, in the hypotonic type. Cavinton should not

be used in severe general cerebral hypertensive crises, as well as in elderly or senile patients with acute cardiocerebral or cerebrocardial syndrome, postinfarction cardioisclerosis, marked disorders of heart rhythm.

5. Cavinton in the prevention of the convulsive syndrome in children with a history of birth trauma Dutov A.A.; Goltvanitsa G.A.; Volkova V.A.; Sukhanova O.N.; Lavrishcheva T.G.; Petrov A.P. Tsentral'naja NI Laboratorija Chitinskogo Meditsinskogo Instituta, Chita USSR ZH. NEVROPATOL. PSIKHIATR. IM. S. S. KORSAKOVA (USSR), 1991, 91/8 (21 22)

The authors studied the efficacy of cavinton as an agent helpful in preventing neurologic disorders in the newborn with hypoxic ischemic encephalopathy due to intracranial birth trauma. The short term results of the treatment were elucidated in 61 children. In group I including 20 persons given conventional therapy, the disappearance of seizures was recorded in 6 patients; out of 41 children (group II) given additionally cavinton, in 27. Twenty nine children were followed up for a year. In group I, convulsive paroxysms recurred in 4 patients, whereas in the group II children, no convulsive syndrome was recorded on the follow up. The group II children also showed a decrease of the phenomena of intracranial hypertension and normalization of the psychomotor development. The preventive effect of cavinton seen in children with a history of birth trauma may be accounted for by its capacity of normalizing cerebrovascular disorders and by its own anticonvulsive properties.

6. A double blind placebo controlled evaluation of the safety and efficacy of vinpocetine in the treatment of patients with chronic vascular senile cerebral dysfunction Balestreri R.; Fontana L.; Astengo F. Department of Internal Medicine, University of Genoa, Genoa ITALY J. AM. GERIATR. SOC. (USA), 1987, 35/5 (425 430)

In a double blind clinical trial, vinpocetine, a synthetic ethyl ester of apovincamine, was shown to effect significant improvement in elderly patients with chronic cerebral dysfunction. Forty two patients received 10 mg vinpocetine three times a day (tid) for 30 days, then 5 mg tid for 60 days. Matching placebo tablets were given to another 42 patients for the 90 day trial period. Patients on vinpocetine scored consistently better in all evaluation 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). There were no serious side effects related to the treatment drug.

7. A double blind clinical trial of vinpocetine in the treatment of cerebral insufficiency of vascular and degenerative origin Manconi E.; Binaghi F.; Pitzus F. Department of Internal Medicine, University of Cagliari, Cagliari ITALY CURR. THER. RES., CLIN. EXP. (USA), 1986, 40/4 (702 709)

We used vinpocetine, a synthetic ethyl ester of apovincamine, to treat 22 elderly patients with central nervous system degenerative disorders, in a double blind clinical trial. Patients received 10 mg vinpocetine TID for 30 days, then 5 mg TID for 60 days. Another 18 elderly patients were given matching placebo tablets for the 90 day trial. Vinpocetine treated patients scored consistently better in all evaluations of the effectiveness of treatment, including measurements on the Clinical Global Impressions (CGI) and Sandoz Clinical Assessment Geriatric (SCAG) scales, and the Mini Mental Status Questionnaire. According to CGI assessments, severity of illness decreased in 73% of the patients in the vinpocetine group at day 30 and 77% at day 90, and improvement was seen in 77% and 87% of the patients at days 30 and 90, respectively. Patients also showed statistically significant improvement for all SCAG items but one, at days 30 and 90. The physician rated the improvement in 59% of the vinpocetine treated patients as 'good' to 'excellent'. No serious side effects were related to the treatment drug.

8. Cerebral regulation and cerebral regulators ZEREBRALE REGULATION ZEREBRALE REGULATOREN Braun P. Med. Abt., Krankenh. Robert Karoly Korut, Budapest HUNGARY THER. HUNG. (HUNGARY), 1980, 28/3 (103 110)

The epidemiology and pathogenic mechanisms of disorders due to cerebral ischemia are described and the therapeutic use of Vinca minor alkaloids is reviewed with reference to their indications in neuropsychiatry, otology and ophthalmology. The literature on Devincan and Cavinton is reviewed. Devincan exerts a mild hypotensive action, while Cavinton improves the circulation and the oxygen consumption of the brain cells, a valuable effect in the treatment of cerebrovascular disease of ischemic etiology (one of its main indications).

9. Comparative study of the effect of ethyl apovincamate and xantinol nicotinate in cerebrovascular diseases; immediate drug effects on the concentrations of carbohydrate metabolites and electrolytes in blood and CSF Vamosi B.; Molnar L.; Demeter J.; Tury F. Dept. Neurol. Psychiat., Univ. Debrecen Med. Sch., Debrecen HUNGARY ARZNEIMITTEL FORSCH. (GERMANY, WEST), 1976, 26/10A (1980 1984)

Randomly selected 34 cerebrovascular patients were treated with ethyl apovincamate (RGH 4405, Cavinton) and 109 with xantinol nicotinate. The effects of drugs given in slow i.v. infusions on the concentration of carbohydrate metabolites and electrolytes in serum and CSF were observed. Cavinton improved the paresis in 60.6% of patients while xantinol nicotinate did so only in 47.1%. On the basis of the biochemical changes, it can be concluded that Cavinton enhances both the glycolytic and the oxidative glucose breakdown in CNS.

10. Rheoencephalographic and psychological studies with ethyl apovincamate in cerebral vascular insufficiency Hadjiev D.;

The effect of ethyl apovincamate (RGH 4405, Cavinton) on the rheoencephalogram and memory functions was studied in 50 patients with ischaemic 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. Improvement of cerebral circulation was observed after i.v. and oral medication. Blood flow was most markedly increased in the gray matter. The effect on arterial pressure was negligible. Improvement of memorizing capacity evaluated by psychological tests was recorded after one month of Cavinton treatment, associated with alleviation or complete disappearance of symptoms. No side effects attributable to the drug were observed. It is pointed out that Cavinton is indicated in the treatment of ischaemic disorders of the cerebral circulation, particularly in chronic insufficiency.

11. Effect of ethyl apovincamate on the cerebral circulation; studies in patients with obliterative cerebral arterial disease Solti F.; Iskum M.; Czako E. Dept. Vasc. Heart Surg., Semmelweis Med. Univ., Budapest HUNGARY ARZNEIMITTEL FORSCH. (GERMANY, WEST), 1976, 26/10A (1945 1947)

The effect of ethyl apovincamate (RGH 4405, Cavinton) on the cerebral and systemic circulations has been studied in detail in ten cases of cerebrovascular disease. 10 mg doses of Cavinton were given as infusion within 4 6 min; circulatory tests were carried out prior to administration of the drug and 3 6 min after. The principal results showed the following: On Cavinton cerebral vascular resistance was strongly reduced, while cerebral fraction of cardiac output significantly increased. On acute effect of the drug arterial mean pressure slightly decreased but cerebral blood flow nevertheless increased in general. Total vascular resistance also decreased but this decrease was less marked than that registered in cerebral vascular resistance.

12. Ideggyogy Sz. 2003 May 20;56(5-6):166-72.

Asymptomatic ischemic cerebrovascular disorders and neuroprotection with vinpocetine.

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The asymptomatic ischemic cerebrovascular disorders (AICVD) is an early manifestation of cerebrovascular disease. It is also known as latent insufficiency of the cerebrovascular circulation or as asymptomatic cerebrovascular disorders. Recently, the term subclinical disease, detected noninvasively, has been introduced by American Heart Association. The diagnosis is based on the following criteria: evidence of vascular risk factors; episodic nonspecific complaints without any focal cerebral symptoms; mild cognitive deficit, detected by neuropsychological tests; carotid ultrasonography often shows intimal-medial thickening, atherosclerotic plaques and carotid stenosis; CT and MRI occasionally reveal silent cerebral infarctions, white matter hyperintensities or cerebral atrophy; regional hypoperfusion above the ischemic threshold is also seen by rCBF measurements. Treatment of the AICVD, modifying the vascular risk factors and using neuroprotective agents, should be the cornerstone of primary prevention of ischemic stroke and cognitive decline, caused by cerebrovascular disorders. Vinpocetine has been found to interfere with various stages of the ischemic cascade: ATP depletion, activation of voltage-sensitive Na(+)- and Ca(++)-channels, glutamate and free radicals release. The inhibition of the voltage-sensitive Na(+)-channels appears to be especially relevant to the neuroprotective effect of vinpocetine. Pronounced antioxidant activity of the drug could also contribute to the neuroprotection. PET studies in primates and man showed that <sup>11</sup>C labelled vinpocetine passes the blood-brain barrier rapidly. Heterogeneous brain distribution of the compound was observed mainly in the thalamus, basal ganglia, occipital, parietal and temporal cortex, regions which are closely related to the cognitive functions. PET studies in chronic ischemic stroke patients revealed favourable effects of vinpocetine on rCBF and glucose metabolism in the thalamus, basal ganglia and primary visual cortex. It seems, vinpocetine, affecting the multiple mechanisms of the AICVD, could be of benefit for the treatment in this early stage of cerebrovascular disease. Vinpocetine may also become a new therapeutic approach to prophylactic neuroprotection in patients at high risk of ischemic stroke.

Cognitive dysfunction

13. Altern Med Rev. 1999 Jun;4(3):144-61. A review of nutrients and botanicals in the integrative management of cognitive dysfunction. Kidd PM.

Dementias and other severe cognitive dysfunction states pose a daunting challenge to existing medical management strategies. An integrative, early intervention approach seems warranted. Whereas, allopathic treatment options are highly limited, nutritional and botanical therapies are available which have proven degrees of efficacy and generally favorable benefit-to-risk profiles. This review covers five such therapies: phosphatidylserine (PS), acetyl-L-carnitine (ALC), vinpocetine, Ginkgo biloba extract (GbE), and Bacopa monniera (Bacopa). PS is a phospholipid enriched in the brain, validated through double-blind trials for improving memory, learning, concentration, word recall, and mood in middle-aged and elderly subjects with dementia or age-related cognitive decline.

PS has an excellent benefit-to-risk profile. ALC is an energizer and metabolic cofactor which also benefits various cognitive functions in the middle-aged and elderly, but with a slightly less favorable benefit-to-risk profile. Vinpocetine, found in the lesser periwinkle *Vinca minor*, is an excellent vasodilator and cerebral metabolic enhancer with proven benefits for vascular-based cognitive dysfunction. Two meta-analyses of GbE demonstrate the best preparations offer limited benefits for vascular insufficiencies and even more limited benefits for Alzheimer's, while "commodity" GbE products offer little benefit, if any at all. GbE (and probably also vinpocetine) is incompatible with blood-thinning drugs. Bacopa is an Ayurvedic botanical with apparent anti-anxiety, anti-fatigue, and memory-strengthening effects. These five substances offer interesting contributions to a personalized approach for restoring cognitive function, perhaps eventually in conjunction with the judicious application of growth factors.

#### Vasodilator

14. *Circulation*. 2001 Nov 6;104(19):2338-43. Upregulation of phosphodiesterase 1A1 expression is associated with the development of nitrate tolerance. Kim D, Rybalkin SD, Pi X, Wang Y, Zhang C, Munzel T, Beavo JA, Berk BC, Yan C. Department of Medicine, University of Rochester, Rochester, NY, USA.

**BACKGROUND:** The efficacy of nitroglycerin (NTG) as a vasodilator is limited by tolerance, which develops shortly after treatment begins. In vascular smooth muscle cells (VSMCs), NTG is denitrated to form nitric oxide (NO), which activates guanylyl cyclase and generates cGMP. cGMP plays a key role in nitrate-induced vasodilation by reducing intracellular Ca(2+) concentration. Therefore, one possible mechanism for development of nitrate tolerance would be increased activity of the cGMP phosphodiesterase (PDE), which decreases cGMP levels. **METHODS AND RESULTS:** To test this hypothesis, rats were made tolerant by continuous infusion of NTG for 3 days (10 microgram kg(-1). min(-1) SC) with an osmotic pump. Analysis of PDE activities showed an increased function of Ca(2+)/calmodulin (CaM)-stimulated PDE (PDE1A1), which preferentially hydrolyzes cGMP after NTG treatment. Western blot analysis for the Ca(2+)/CaM-stimulated PDE revealed that PDE1A1 was increased 2.3-fold in NTG-tolerant rat aortas. Increased PDE1A1 was due to mRNA upregulation as measured by relative quantitative reverse transcription-polymerase chain reaction. The PDE1-specific inhibitor vinpocetine partially restored the sensitivity of the tolerant vasculature to subsequent NTG exposure. In cultured rat aortic VSMCs, angiotensin II (Ang II) increased PDE1A1 activity, and vinpocetine blocked the effect of Ang II on decrease in cGMP accumulation. **CONCLUSIONS:** Induction of PDE1A1 in nitrate-tolerant vessels may be one mechanism by which NO/cGMP-mediated vasodilation is desensitized and Ca(2+)-mediated vasoconstriction is supersensitized. Inhibiting PDE1A1 expression and/or activity could be a novel therapeutic approach to limit nitrate tolerance.

15. Mechanism of vasodilative action of cavinton on brain vessels Plotnikov M.B.; Kotov A.N. Kafedra Farmakologii, Tomskogo Meditsinskogo Instituta, Tomsk USSR FARMAKOL. TOKSIKOL. (USSR), 1983, 46/6 (36 39)

Experiments on human middle cerebral and cat internal maxillary arteries have shown high vasodilative activity of cavinton. The mechanism of the vasodilative action of the drug involves inhibition of the ingress of extracellular calcium via electrogenic and chemosensitive channels, suppression of calcium mobilization from the intracellular depot with depolarization of the membranes of vascular smooth cells and a decrease in phosphodiesterase activity.

16. Cavinton, a new cerebral vasodilator Solti F. *Inst. Gefasschir., Semmelweis Med. Univ., Budapest HUNGARY THER. HUNG.* (HUNGARY), 1979, 27/1 (15 16)

Vincamine, an alkaloid isolated from *Vinca minor*, exerts not only a moderate antihypertensive effect but also increases the cerebral blood flow c.q. significantly decreases resistance of cerebral vessels. The substance is a potent cerebral vasodilator which gives particularly good results in disorders of the cerebral circulation in which hypertension is present. It proved possible by chemical alteration of the vincamine molecule to synthesize a number of derivatives. Among these, cavinton proved to be the apovincamine acid ethylester with the most intensive action. Experiments in animals showed that cavinton increases the cerebral blood flow without significantly altering the blood pressure or cardiac effort.

17. Study on the vasodilator effects of ethyl apovincamate in neurosurgical patients Fenyves Gy.; Tarjanyi J.; Ladvanszky Cs. II Dept. Surg., Med. Univ. Szeged HUNGARY ARZNEIMITTEL FORSCH. (GERMANY, WEST), 1976, 26/10A (1956 1962)

Studies have been performed in a series of 44 neurosurgical cases. The patients were subjected to detailed neurological examination and EEG after admission and before being discharged. The effect of ethyl apovincamate (RGH 4405, Cavinton) on cortical electric activity was investigated after the administration of 10 mg i.v. Cavinton. In cases on long term courses of three times daily 5 mg Cavinton in tablets, control EEG was performed one and two mth, resp., after the start of medication. The state of vessels of the eye ground was also checked. In cerebral angiography attention was concentrated on width of the vascular lumen and visualization of Cavinton effect on vessels which on account of narrowing or spasm had not filled up with contrast medium prior to Cavinton. During angiography the patients were given i.v. 10 mg Cavinton diluted to 10 ml with physiological saline. In the cases where investigations failed to reveal any change requiring neurosurgical intervention and insufficient cerebral circulation had to be held responsible for the patient's condition, 3 times 10 mg Cavinton i.v. was administered daily as long as the patient was at our Department. After having been discharged these patients took 3 times daily 5 mg Cavinton in tablets. Duration of the course of oral

Cavinton depended on the degree of improvement in the patient's condition. Cavinton was used with success in cases where cerebral circulation was damaged for functional or organic reasons. Allergic hypersensitivity did not occur in any of the cases, either on single doses or long term use of parenteral or oral Cavinton.

18. General and cerebral haemodynamic activity of ethyl apovincamate Karpati E.; Szporny L. Dept. Pharmacol., Chem. Works Gedeon Richter Ltd, Budapest HUNGARY ARZNEIMITTEL FORSCH. (GERMANY, WEST), 1976, 26/10A (1908 1912)

Systemic and cerebral haemodynamic effects of ethyl apovincamate (RGH 4405, Cavinton), a new compound, have been investigated in anaesthetized dogs. The compound was administered i.v. and produced an increase in the cerebral blood flow accompanied by a decrease in cerebral vascular resistance which persisted for 15 min. The effective dose was 0.2-0.5 mg/kg. Mean arterial blood pressure, total peripheral resistance and cardiac work were decreased, heart rate and cardiac output were increased. Cerebral metabolic rate of oxygen was enhanced. It is assumed that the compound has a direct effect on cerebral metabolism. RGH 4405 has a weak antiarrhythmic and coronary dilating activity. Its effect on smooth muscle is more marked than that of papaverine. RGH 4405 appears to be a potent cerebral vasodilator enhancing cerebral metabolism.

#### Cerebral ischemia

19. Calcium antagonist activity of vinpocetine and vincamine in several models of cerebral ischaemia Lamar J.-C.; Poignet H.; Beaughard M.; Dureng G. Department of Pharmacology, Riom Laboratories-Cerm, F-63203 Riom Cedex France

DRUG DEV. RES. (USA), 1988, 14/3 4 (297 304)

The potency and selectivity (i.e., the central vs. peripheral vascular smooth muscle activity) of the calcium antagonist (CA) effects of vinpocetine and vincamine have been compared with those of the standard CAs: flunarizine, verapamil, diltiazem, and nimodipine in rabbit basilar and splenic artery preparations. The cerebral antiischemic activity of these substances also was evaluated in five well documented in vivo models, i.e., hypobaric and normobaric hypoxia, global cerebral ischemia to MgCl<sub>2</sub>, cytotoxic anoxia with KCN, and cerebral edema induced by triethyl tin. Both vinpocetine and vincamine possess only weak CA activity, the potency order being: nimodipine > diltiazem > flunarizine = verapamil > vinpocetine > vincamine, with vinpocetine and flunarizine, in contrast to other compounds, showing a clear, 6 to 13 fold selectivity for cerebral vascular smooth muscle. In the in vivo models, vinpocetine and flunarizine, together with vincamine, proved most active and had a larger spectrum of activity than the other CAs. These results suggest that the cerebrally selective CA effects of vinpocetine are at most only partly responsible for the effects of this compound in the in vivo models of cerebral ischemia.

20. Study on the anti-hypoxic effect of some drugs used in the pharmacotherapy of cerebrovascular disease.

Milanova D, Nikolov R, Nikolova M.

Methods Find Exp Clin Pharmacol. 1983 Nov;5(9):607-12.

The anti-hypoxic effect of some agents used in the pharmacotherapy of cerebrovascular disease was studied using the following methods: incomplete ischemia by bilateral carotid ligation in rats, anoxic hypoxia by inhalation of argon in mice, and hemic hypoxia induced by injection of sodium nitrite (120 mg/kg s.c.) in rats. The following drugs were studied: piracetam, orotic acid, centrophenoquine, pentobarbital, vincamine, vinpocetine, cinnarizine, aligeron, xanthinol nicotinate and papaverine. The most pronounced anti-hypoxic effect was shown primarily with the metabolic acting drugs, such as orotic acid, centrophenoquine, piracetam and pentobarbital, followed by the preparations with combined metabolic and vasoactive properties (vincamine and vinpocetine). The predominantly vasoactive drugs were less effective in anoxic hypoxia, but showed more pronounced effect in incomplete ischemia.

#### Mechanism of action

21. On the mechanism of action of vinpocetine Kiss B.; Karpati E. Farmakologiai Kutató Központ, Richter Gedeon Vegyeszeti Gyár Rt., Pf. 27, H 1475 Budapest Hungary Acta Pharmaceutica Hungarica (Hungary), 1996, 66/5 (213 224)

Cavinton was introduced into the clinical practice some twenty years ago in Hungary for the treatment of cerebrovascular disorders and related symptoms. Since then, its active ingredient, vinpocetine, beside its therapeutical utilization, has become a reference compound in the pharmacological research of cognitive deficits caused by hypoxia and ischaemia as well as in the cellular and biochemical investigations related to cyclic nucleotides. In this review a survey is given on the experimental data obtained with vinpocetine and an attempt is made to outline the drug's mechanism of action. Early experiments with vinpocetine indicated five main pharmacological and biochemical actions: (1) selective enhancement of the brain circulation and oxygen utilization without significant alteration in parameters of systemic circulation, (2) increased tolerance of the brain toward hypoxia and ischemia, (3) anticonvulsant activity, (4) inhibitory effect on phosphodiesterase (PDE) enzyme and (5) improvement of theological properties of

the blood and inhibition of aggregation of thrombocytes. Later studies in various laboratories confirmed the above effects and clearly demonstrated that vinpocetine offers significant and direct neuroprotection both under in vitro and in vivo conditions. Evidence has been obtained that neuroprotective action vinpocetine is related to the inhibition of operation of voltage dependent neuronal Na<sup>+</sup> channels, indirect inhibition of some molecular cascades initiated by the rise of intracellular Ca<sup>2+</sup> levels and, to a lesser extent, inhibition of adenosine reuptake. Vinpocetine has been shown to be selective inhibitor of Ca<sup>2+</sup> calmodulin dependent cGMP PDE. It is assumed that this inhibition enhances intracellular a GMP levels in the vascular smooth muscle leading to reduced resistance of cerebral vessels and increase of cerebral flow. This effect might also beneficially contribute to the neuroprotective action.

22. Biochemical effects of ethyl apovincamate Rosdy B.; Balazs M.; Szporny L. Dept. Pharmacol., Chem. Works Gedeon Richter Ltd, Budapest HUNGARY ARZNEIMITTEL FORSCH. (GERMANY, WEST), 1976, 26/10A (1923 1926)

Some cerebrobiochemical effects of a new cerebrovasodilatory agent, ethyl apovincamate (RGH 4405, Cavinton) were studied. Changes of biogenic amines, 5 hydroxyindole acetic acid (5 HIAA) levels, serotonin (5 HT) turnover rate, and the effect on 3',5' cyclic nucleotide phosphodiesterase (PDE; E.C. 3.1.4.c) activity, isolated from different tissues, were determined. Lasting increase of cerebral 5 HIAA level was observed after treatment with the compound, 5 HT levels were transiently enhanced 2 hr following i.p. treatment. At later periods (4 6 hr) after treatment catecholamine levels were significantly raised. 5 HT turnover was practically uninfluenced by the compound. Activities of PDE preparations isolated from cerebral tissues were markedly inhibited. Various hypotheses are suggested in order to explain the biochemical mechanism of action of the compound.

## Learning

23. Nootropic drugs have different effects on kindling induced learning deficits in rats Becker A.; Grecksch G. Otto von Guericke University, Faculty of Medicine, Inst. Pharmacology and Toxicology, Leipziger Str, 44, 39120 Magdeburg Germany Pharmacological Research (United Kingdom), 1995, 32/3 (115 122)

Kindling represents an accepted model of human epileptogenesis. Furthermore, it has been demonstrated that kindled rats show a diminished learning performance in an active avoidance task. In our study we administered different nootropic drugs to kindled rats to test their effects on learning a two way active avoidance task in the shuttle box. Kindling was induced by repeated intraperitoneal injections of 45 mg kg<sup>-1</sup> pentylenetetrazol (PTZ) once every 48 h. The substances vinpocetine (0.1 and 1.0 mg kg<sup>-1</sup>), methylglucamin orotate (225 and 450 mg kg<sup>-1</sup>), piracetam (100 mg kg<sup>-1</sup>), and meclofenoxate (100 mg kg<sup>-1</sup>) were administered during kindling development and after kindling completion prior to each session in the learning experiment. The nootropic drugs had little if any effect on severity of seizures. Concerning their effect on learning the substances each acted in a specific manner. Methylglucamin orotate enhanced the learning deficit induced by kindling. Meclofenoxate injected prior to the kindling stimulation was ineffective, whereas administration prior to the learning test improved the learning performance effectively. A complementary action was shown in experiments with vinpocetine. Only piracetam prevented the occurrence of kindling induced learning deficits regardless the administration schedule.

24. Effect of vinpocetine on noradrenergic neurons in rat locus coeruleus Gaal L.; Molnar P. Department of Biochemistry, Pharmacological Research Centre, Chemical Works of Gedeon Richter Ltd., P.O. Box 27, H 1475 Budapest Hungary EUR. J. PHARMACOL. (Netherlands), 1990, 187/3 (537 539)

Conventional extracellular single unit recordings were used to investigate the effect of vinpocetine on locus coeruleus noradrenergic neurons in chloral hydrate anesthetized rats. Vinpocetine produced a significant and dose dependent increase in the firing rate of locus coeruleus neurons (ED<sub>30</sub> = 0.75 mg/kg i.v.) up to 1 mg/kg i.v., followed by a complete blockade of spiking activity at doses higher than this. The effective dose range was in very good agreement with the dose range corresponding to the memory enhancing effects of the compound. Our results supplied direct electrophysiological evidence that vinpocetine increases the activity of ascending noradrenergic pathways. This effect can be related to the cognitive enhancing characteristics of the compound.

25. Comparison of the effects of vinpocetine, vincamine, and nicergoline on the normal and hypoxia damaged learning process in spontaneously hypertensive rats Groo D.; Palosi E.; Szporny L. Chemical Works of Gedeon Richter Ltd., Pharmacological Research Centre, H 1475 Budapest Hungary DRUG DEV. RES. (USA), 1988, 15/1 (75 85)

Vinpocetine (Cavinton (R)), vincamine, and nicergoline (Sermion (R)) were evaluated for the ability to protect cognitive function of spontaneously hypertensive rats from the damaging effect of hypoxia. Normobaric hypoxia (6% oxygen) was applied during the acquisition of a two way active avoidance task (3 sessions, 50 trials/session). Hypoxia decreased the percentage of conditioned avoidance responses by 50% on day 3. Vinpocetine (1.25 10 mg/kg) administered orally 60 min prior to the daily sessions did not significantly improve learning in normoxic conditions; however, it prevented hypoxia induced learning deficit (1.25 mg/kg peak effect dose). The dose response relationship for the compounds is an inverted U shaped curve. Vincamine (2.5 20 mg/kg p.o.) did not facilitate learning under normoxic conditions, but afforded protection against hypoxia at the 20 mg/kg dose. Nicergoline (2.5 20 mg/kg p.o.) did not increase acquisition of the normoxic avoidance response, and it also showed a moderate antihypoxic effect. Vinpocetine, and to a lesser degree vincamine and nicergoline drugs useful in the therapy of cognitive disturbances following

cerebral ischemic hypoxic states proved effective in the prevention of a hypoxia induced learning deficit.

26. *Int Clin Psychopharmacol.* 1987 Oct;2(4):325-31.

Vinpocetine effects on cognitive impairments produced by flunitrazepam.

Bhatti JZ, Hindmarch I.

Human Psychopharmacology Research Unit, University of Leeds, U.K.

The effects of pre-treatment with vinpocetine 40 mg, on flunitrazepam-induced impairment of memory, were studied in 8 normal volunteers. Tests of Critical Flicker Fusion Threshold, a Sternberg Memory Scanning Task, along with subjective ratings of drug action were used. Drug effects were found to be modest. Treatment with vinpocetine was associated with improvements in short-term memory processes.

Retina 27. Clinical and immunological signs of retinal involvement and potentialities of its drug correction in patients with chronic diffuse viral diseases of the liver and in Australian antigen carriers Slepova O.S.; Kushnir V.N.; Zaitseva N.S.; Titarenko Z.D.; Dumbra V.A. Mosk. NI Institut Glaznykh Boleznj, Minzdravmedproma Rossii, Moskva Russian Federation *Vestnik Oftalmologii* (Russian Federation), 1994, 110/4 (27 29)

A total of 133 subjects aged 15 to 55 were followed up, the main group (n = 87), patients with chronic diffuse diseases of the liver caused by hepatitis B virus, and two reference groups, 26 patients with uveitis and 20 normal subjects, 13 and 4 subjects of each group, respectively, were Australian antigen (HBsAg) carriers. Functional disorders of the retina were detected in 93.2% of group 1 patients, as well as intensified local (tears) and total system (blood) autoimmune reactions to tissue specific retinal S antigen (mol.mass 48 kD). An increased detection rate of antibodies to S antigen and its higher titers were found in healthy virus carriers as compared to HBsAg seronegative donors. These data may be regarded as evidence of an increased risk of uveoretinal pathology in subjects infected with hepatitis B virus, this being confirmed by a higher incidence (50%) of latent virus carriership in the group of patients with uveoretinitis. Stabilizing effect of cavinton in functional changes of the retina was revealed, this recommending this drug for combined therapy of patients with chronic diffuse diseases of the liver and for prevention of ocular diseases. The majority of the examinees in whom retinal abnormalities were found being young, the authors draw attention to the social aspect of the problem.

#### Absorption

28. Study on the absorption of vinpocetine and apovincaminic acid Pudleiner P.; Vereczkey L. Chemical Works of Gedeon Richter Ltd, PO Box 27, 1475 Budapest 10 Hungary EUR. *J. DRUG METAB. PHARMACOKINET.* (Switzerland), 1993, 18/4 (317 321)

The absorption of vinpocetine (Cavinton) and apovincaminic acid, compounds showing a marked difference in their physico chemical properties, was studied in rats in in situ loop experiments by using radiolabelled compounds. In the case of apovincaminic acid, the investigations also involved the estimation of the portion of radioactivity excreted in urine and faeces after i.v. and p.o. administration of the compound. According to our results, it can be concluded that both vinpocetine and apovincaminic acid are absorbed from the gastrointestinal tract apovincaminic acid mainly from the stomach, while vinpocetine is absorbed from the small intestine.

Gastroprotective 29. Protective action of vinpocetine against experimentally induced gastric damage in rats Nosalova V.; Machova J.; Babulova A. Institute of Pharmacology, Slovak Academy of Sciences, Dubravska cesta 9, 84216 Bratislava Slovak Republic *ARZNEIM. FORSCH. DRUG RES.* (Germany), 1993, 43/9 (981 985)

The efficacy of vinpocetine (CAS 42971 09 5) to prevent gastric mucosal damage induced by several noxious agents and its antisecretory effect were studied in rats. Vinpocetine administered orally or intraperitoneally inhibited the development of gastric lesions induced by 96% ethanol in a dose dependent way. The highest protective activity was observed when vinpocetine was given intraperitoneally 30 min before ethanol, and its effect was still significant when administered 120 min before ethanol exposure. Oral administration of vincamine also displayed gastroprotective action in this model. Pretreatment with indometacin counteracted the protective action of vinpocetine against ethanol induced damage, suggesting the involvement of a prostaglandin mediated mechanism. The protective effect of vinpocetine was compared with that of prostaglandin E2, sucralfate, and tripotassium dicitrate bismuthate. The antiulcer activity of vinpocetine was demonstrated also in gastric injury induced by phenylbutazone and in chronic gastric ulcer induced by acetic acid. Histamine stimulated gastric acid secretion in pylorus ligated rats was partially inhibited by vinpocetine administered intraduodenally. The activity of vinpocetine established in these experiments is indicative of its potential clinical value as a gastroprotective agent.

Quisqualate/AMPA antagonist

30. Vinpocetine preferentially antagonizes quisqualate/AMPA receptor responses: Evidence from release and ligand binding studies Kiss B.; Cai N. S.; Erdo S.L. Laboratory of Cellular and Molecular Pharmacology, Gedeon Richter Ltd., P.O. Box 27, H 1475 Budapest Hungary EUR. J. PHARMACOL. (Netherlands), 1991, 209/1 (109 112)

The effect of vinpocetine on excitatory amino acid receptors was examined in the rat brain by two different biochemical approaches. In release experiments with striatal slices, vinpocetine reduced the efflux of dopamine and acetylcholine evoked by glutamate, quisqualate and N methyl D aspartate (NMDA), but not that evoked by kainate. In binding experiments with cortical membranes, vinpocetine reduced the binding of (3H)2 amino 3 3 hydroxy s methylisoxazole 4 yl propionic acid ((3H)AMPA), a quisqualate partial agonist, in an incomplete manner, but failed to influence the binding of (3H)kainate and (3H)3 (2 carboxypyperazine 4 yl) p ropyl 1 phosphonic acid ((3H)CPP), an NMDA agonist. These findings suggest that vinpocetine is a quisqualate/AMPA antagonist of some specificity and selectivity.

Microcirculation 31. Microcirculation, rheological properties of blood and their correction in ischemic disorders of cerebral circulation Veselsky I.Sh.; Sanik A.V. Kafedra Nervnykh Boleznej Poltavskogo Meditsinskogo Stomatologicheskogo Instituta, Poltava Ukrainian SSR ZH. NEVROPATOL. PSIKHIATR. IM. S. S. KORSAKOVA (USSR), 1991, 91/11 (67 70)

A study was made of microcirculation using bulbar biomicroscopy and of the aggregation properties of platelets in 94 patients with initial manifestations of cerebral circulatory failure and dyscirculatory encephalopathy before and after the treatment with vasoactive drugs and actovegin. It has been recorded that the impairment of hemomicrocirculation progresses with the rise of the disease stage, being more pronounced in patients with vegetovascular crises. To correct microcirculatory disorders and the rheological properties of blood, the authors provide evidence for administering cavinton, euphylline and nicotinic acid combined with actovegin.

32. Effect of ethyl apovincamate on the cerebral circulation; serial angiography and regional cerebral circulation studies in neurosurgical patients Orosz E.; Deak Gy.; Benoist Gy. Nat. Sci. Inst. Neurosurg., Budapest HUNGARY ARZNEIMITTEL FORSCH. (GERMANY, WEST), 1976, 26/10A (1951 1956)

The effect of ethyl apovincamate (RGH 4405, Cavinton) on the cerebral circulation has been studied with two methods in a series of neurosurgical patients. Regional circulation was studied with the Hsub 2 clearance method in five patients in whom deep electrodes were lodged in various cerebral structures with stereotactic surgery performed for the underlying disease. In connection with serial angiography of 25 patients 10 mg Cavinton was injected i.v.; circulation time of the contrast medium, arterial circulation time, changes of normal and pathological filling were appraised. Registered 15 min after administration, regional circulation showed significant increase, but slight increase was demonstrable in every structure investigated. The change was more marked in two elderly patients over 60 years. In eight cases of serial angiography marked difference was seen in filling by normal and pathological vessels on Cavinton effect; arterial circulation time changed in three cases, contrast medium circulation time did in any of the cases. The most marked changes occurred in three cases of cerebral vascular disease. In two cases of glioma vascularization of the tumour was visualized by Cavinton.

33. Effect of ethyl apovincamate on cerebral circulation of dogs under normal conditions and in arterial hypoxia Bencsath P.; Debreczeni L.; Takacs L. II Dept. Med., Semmelweis Univ. Med. Sch., Budapest HUNGARY ARZNEIMITTEL FORSCH. (GERMANY, WEST), 1976, 26/10A (1920 1923)

Effects of 1, 2 and 4 mg/kg i.v. doses of ethyl apovincamate (RGH 4405, Cavinton) on cerebral blood flow, determined in the internal carotid and vertebral artery, were studied in anaesthetized dogs under 21, 16 and 11% Osub 2 inhalation. Total cerebral blood flow was increased by 4 mg/kg Cavinton under normal Osub 2 and between 100 and 200 mmHg perfusion pressures, while 2 mg/kg doses were effective under hypoxia. Similar phenomena were observed in the carotid and vertebral flow, separately. Arterial hypoxia seems to potentiate the effect of Cavinton on cerebral blood flow.

Glucose utilization 34. Effect of ethyl apovincamate on the utilization of 14C glucoses by rat brain in vitro Matkovics B.; Szabo L.; Kiss B.; Szpornyi L. Biological Isotope Laboratory, 'Atilla Jozsef' University, Kozepfasor 52, H 6726 Szeged Hungary ARZNEIM. FORSCH. DRUG RES. (Germany, Federal Republic of), 1991, 41/2 (107 108)

The effect of the presence of 500 microg ethyl epovincamate (Cavinton (R)) on the aerobic metabolism of 14C labelled glucoses was studied in vitro. The drug tested increased the metabolism of (1 14C) D glucose first of all, which indicated a significant activation of pentose phosphate shunt.

35. Cerebral effects of a single dose of intravenous vinpocetine in chronic stroke patients: a PET study.

Szakall S, Boros I, Balkay L, Emri M, Fekete I, Kerényi L, Lehel S, Marian T, Molnar T, Varga J, Galuska L, Tron L, Bereczki D, Csiba L, Gulyas B. PET Centre, Debrecen University Medical School, Hungary.

J Neuroimaging. 1998 Oct;8(4):197-204.

The effects of vinpocetine (Cavinton) on the cerebral glucose metabolism of chronic stroke patients are studied with positron emission tomography. The regional and global cerebral metabolic rates of glucose (CMRglu) and the kinetic constants related to them are quantified before and after single-dose intravenous vinpocetine treatment. These measurements are completed with transcranial Doppler sonography and single photon emission computed tomography to explore the possible mechanisms underlying the resulting changes in glucose uptake and metabolism in the brain. The authors' findings indicate that a single-dose vinpocetine treatment, although it does not affect significantly the regional or global metabolic rates of glucose, improves significantly the transport of glucose (both uptake and release) through the blood-brain barrier in the whole brain, the entire contralateral hemisphere, and in the brain tissue around the infarct area of the symptomatic hemisphere. These changes are in accord with increased blood flow in the entire contralateral hemisphere as well as decreased blood flow velocity and increased peripheral vessel resistance in the entire symptomatic hemisphere.

Space motion sickness 36. Experimental assessment of selected antimotion drugs Matsnev E.I.; Bodo D. Institute of Biomedical Problems, 123007 Moscow USSR AVIAT. SPACE ENVIRON. MED. (USA), 1984, 55/4 (281 286)

Space motion sickness (SMS) has been a perplexing problem in both the Soviet and U.S. manned space programs. Both the sensory conflict theory (neuronal signal mismatch) and the cephalad fluid shift concept explain the mechanism. This paper reviews the mechanism of action of various drugs that primarily affect brain blood flow or brain metabolism. In particular, Cavinton (apovincamic acid ethyl ester) has been used successfully in offsetting SMS in experimental test subjects.

Cardiac output 37. Effect of oral pretreatment with ethyl apovincamate on the cardiac output and nutritive blood flow of various organs in rats Debreczeni L.; Takacs L. II Dept. Med., Semmelweis Univ. Med. Sch., Budapest HUNGARY ARZNEIMITTEL FORSCH. (GERMANY, WEST), 1976, 26/10A (1912 1917)

Effects of ethyl apovincamate (RGH 4405, Cavinton), administered repeatedly p.o. in doses of 0.5 1.5 4.5 mg/100 g body weight for 5 days, on cardiac output and organ fractions of cardiac output were studied in rats anesthetized with sodium pentobarbital by Evans blue dilution and the isotope fractionation technique of Sapirstein. Cardiac output, cerebral, coronary, renal, intestinal and dermal blood flow was increased by 18 42% after 4.5 mg/100 g Cavinton, while blood pressure was unaltered. Total peripheral resistance, cerebral, coronary, dermal resistance and that of the carcass decreased significantly. Organ fractions of the cardiac output were not significantly altered after treatment.

#### Meniere's disease

38. Vestn Otorinolaringol. 1980 May-Jun;(3):18-22. [Prospects of using cavinton for treating Meniere's disease] [Article in Russian] Nikolaev MP, Konstantinova ZD, Mertsalova ON, Sheremet AS.

Cavinton, a new drug made by Gedeon Richter, was used for the treatment of 20 patients with Meniere's disease and frequent attacks of vertigo according to the following scheme: 4 ml (20 mg) in 5-20 ml of physiological saline was injected intravenously daily for up to 10 days, then 2 ml (10 mg) intramuscularly twice a day for 20 days, and then 1 ml (5 mg) three times a day for 10 to 20 days. As a result the attacks were arrested in all patients. In 15 cases vertigo disappeared, tinnitus aurium diminished, and static imbalance was eliminated. In 10 patients who had monthly attacks of the disease before treatment, the remission persisted for up to 6 months. Cavinton is believed to be effective enough and thus promising for the treatment of Meniere's disease with frequent attacks of vertigo.

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