

The Role of Adjuvant Vinpocetine Therapy in Aspirin-Treated Cerebrovascular Patients

Gergely Feher^{1,3}, Peter Csecsei¹, Judit Papp², Peter Kenyeres², Gabor Kesmarky², Miklos Rabai², Antal Tibold⁴, Kalman Toth², Laszlo Szapary¹

1 Department of Neurology, Medical School, University of Pecs, Pecs, Hungary;

2 First Department of Medicine, Division of Cardiology, Medical School, University of Pecs, Pecs, Hungary;

3 Neurology Ward, Szigetvar Hospital, University of Pecs, Pecs, Hungary;

4 Centre for Occupational Medicine, Medical School, University of Pecs, Pecs, Hungary.

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Gergely Feher MD, PhD, Centre for Occupational Medicine, Medical School, University of Pecs, Pecs, Hungary. Email: feher.gergely@pte.hu

Received: June 8, 2020

Revised: July 18, 2020

Accepted: July 22 2020

Published online: October 8, 2020

ABSTRACT

BACKGROUND: The aim of our pilot study was to investigate the endothel dysfunction, hemorheological and agonist-induced platelet aggregation changes in aspirin-treated cerebrovascular patients after parenteral vinpocetine admission (VP).

METHODS: Hemorheological parameters (hematocrit, plasma fibrinogen, whole blood viscosity, red blood cell aggregation and deformability), endothel dysfunction markers (von Willebrand factor, soluble P-selectin) and agonist-induced (collagen, epineprine, arachi-

donic acid and adenosine-diphosphate) platelet aggregation values were evaluated at baseline, 7th and 30th day.

RESULTS: Parenteral vinpocetine infusion significantly decreased von Willebrand factor levels and arachidonic acid-induced platelet aggregation values and they still remained significant after 30 days. Red blood cell deformability was significantly decreased after a month. No statistical differences among the other examined hemorheological parameters could be found.

CONCLUSION: Vinpocetine, partially by its beneficial hemorheological and endothel-dysfunction improving profile may help to overcome aspirin resistance.

Key words: Vinpocetine; Aspirin; Antiplatelet resistance; Hemorheology; Endothelial dysfunction; Stroke

© 2020 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Feher G, Csecsei P, Papp J, Kenyeres P, Kesmarky G, Rabai M, Tibold A, Toth K, Szapary L. The Role of Adjuvant Vinpocetine Therapy in Aspirin-Treated Cerebrovascular Patients. *Journal of Cardiology and Therapy* 2020; 7(1): 942-945 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/3000>

INTRODUCTION

Cerebrovascular diseases include a group of brain disorders with ischaemic and haemorrhagic of origin and are the second leading cause of death worldwide^[1]. Furthermore, these diseases are the leading cause of disability in adults^[2]. However, with the exception of systemic thrombolysis and thrombectomy in hyperacute and aspirin in acute stroke syndromes, other treatment strategies have very limited efficacy^[1].

Randomized, multicentre trials and meta analysis have shown the efficacy of aspirin in both the primary and secondary prevention of vascular diseases^[3]. Increasing number of reports about antiplatelet (and aspirin) resistance and unfavourable clinical outcome has led to a growing concern among clinicians and patients about the efficacy of aspirin treatment^[3,4].

Vinpocetine [ethylapovincaminat], is a derivative of the Vinca minor alkaloid vincamine, originally was developed in Hungary^[5].

Vinpocetine is still widely used in the treatment of various disease states of cerebrovascular origin and its mechanisms of action are under intensive research^[5]. The drug is claimed to be a neuroprotectant, increasing cerebral perfusion and oxygen extraction and has been shown to have beneficial hemorheological and antiplatelet properties^[5].

Hemorheological factors are significant determinants of the flow characteristics of blood^[6]. Several studies have proved that elevated hematocrit [Hct], plasma fibrinogen concentration, plasma and whole blood viscosity (WBV), and increased red blood cell (RBC) aggregation were independent risk factors of ischemic vascular diseases based on prevention trials^[6,7]. Interestingly, hemorheological disturbances may occur in nearly half of patients with ischemic stroke (IS)^[6,7]. Based on our previous results impaired rheological parameters have been shown to be associated with aspirin resistance^[7].

The aim of our present study was to detect the beneficial effects of adjuvant vinpocetine therapy on the hemorheological parameters, endothel dysfunction and platelet aggregation values of aspirin-treated cerebrovascular patients.

ETHICS STATEMENT

Written informed consent was obtained from all participants. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Regional Ethical Committee at the Faculty of Medicine, University of Pécs.

PATIENTS AND METHODS

Twenty ischaemic chronic cerebrovascular patients took part in our present study (mean age: 60±7 years). Inclusion and exclusion criteria have been published previously^[8].

Hemorheological and endothel dysfunction parameters, platelet aggregation values were determined at screening, before (visit 1) and after (visit 2 at day 7) parenteral admission and 30 days later (follow-up visit).

Hemorheological measurements

Blood samples were taken from the cubital vein; routine blood chemistry and hemorheological parameters – hematocrit, plasma fibrinogen level, plasma and whole blood viscosity, RBC aggregation and deformability – were determined. Methodology has been previously published^[7].

Endothel dysfunction markers

A quantitative direct enzyme immunoassay (Shield Diagnostics Ltd., U.K.) was used for the detection of von Willebrand factor (vWf) activity in human citrated plasma.

Determination of the level of sP-selectin was performed by using a sandwich ELISA procedure according to manufacturer’s instructions (Bender MedSystems, Austria). Methodology has been previously published^[9].

Platelet aggregation values

Epinephrine (adrenaline)-, adenosine diphosphate (ADP)-, arachidonic acid- and collagen-induced aggregation of platelets were analysed as in previous studies conducted by our workgroup^[7].

RESULTS

20 cerebrovascular patients took part in our study. High-dose parenteral vinpocetine infusion significantly decreased von Willebrand factor levels measuring at day 7 (1.649 ± 0.198 NU/ml vs. 1.558 ± 0.140 NU/ml, p = 0.011) and it still remained significant after a months (1.649 ± 0.198 NU/ml vs. 1.509 ± 0.126 NU/ml, p=0.001) (Table 1). Red blood cell deformability (0.563 ± 0.1 vs 0.558 ± 0.008, p=0.036) was significantly decreased at day 30 (Table 1, Figure 1). Arachidonic acid-induced platelet aggregation values were significantly decreased at day 7 (32.47 ± 7.28 % vs 21.89 ± 6.84, p < 0.05) and day 30 (and 32.47 ± 7.28% vs. 24.56 ± 7.79 p < 0.05) (Table 1, Figure 1). There were no statistical differences among the other examined hemorheological parameters.

DISCUSSION

Platelets have an important role in the development of atherothrombosis and subsequent vascular events. Therefore antiplatelet therapy is one of the cornerstones of both primary and secondary prevention.

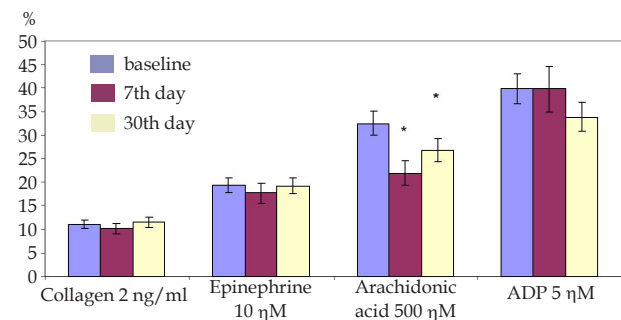


Figure 1 Changes in platelet aggregation values to agonists. *p < 0.05.

Table 1 Follow-up of the measured parameters.

	Baseline (before infusion)	7th day (after infusion)	follow-up (30th day)
Plasma fibrinogen (g/l)	3.590 ± 0.666	3.591 ± 0.834	3.605 ± 0.680
Haematocrit (%)	43.150 ± 3.815	42.667 ± 4.899	42.555 ± 4.273
Erythrocyte aggregation (%)	69.584 ± 5.137	69.043 ± 5.323	69.958 ± 5.031
Erythrocyte deformability (NU)	0.563 ± 0.010	0.562 ± 0.007	0.558 ± 0.008*
Full blood viscosity (mPa/s)	4.144 ± 0.457	4.432 ± 1.433	4.137 ± 0.642
Plasma viscosity (mPa/s)	1.254 ± 0.060	1.252 ± 0.085	1.263 ± 0.072
soluble P-selectin concentration (ng/ml)	2.515 ± 0.210	2.761 ± 0.252	2.558 ± 0.256
von-Willebrandt factor (NU/ml)	1.649 ± 0.198	1.558 ± 0.140*	1.509 ± 0.126**
Collagen 2 µg/ml (%)	11.00 ± 10.05	14.10 ± 11.72	11.47 ± 11.85
Epinephrine 10 µM (%)	19.37 ± 17.33	17.72 ± 19.38	19.21 ± 8.98
ADP 5 µM (%)	39.79 ± 12.95	39.79 ± 17.41	33.84 ± 16.56
Arachidonic acid 500 µM (%)	32.47 ± 7.28	21.89 ± 6.84*	24.56 ± 7.79*

* p < 0.05; ** p < 0.01.

Numerous patients will experience a recurrent atherothrombotic vascular event despite adequate antiplatelet therapy^[2-4].

The clinical efficacy of aspirin in decreasing vascular events has been well established in the past 30 years. Despite of its regular intake, a number of atherothrombotic events still occur, raising the possibility of resistance to aspirin^[2-4]. In recent years, a number of reports in the medical literature have shown possible relationships between residual platelet reactivity measured by different laboratory methods and unfavourable clinical outcomes^[2-4].

An exact definition of “resistance” to antiplatelet therapy on the basis of physiology does not exist^[4,11]. Our definition (using collagen and epinephrine) has been validated and shown in recent articles and has been associated with worse clinical outcome^[7,10]. On the other hand, recent European consensus papers suggest the use of arachidonic acid as the most appropriate agonist in the measurement of platelets’ response to aspirin, so we also used this agent^[11,12].

In our study, after one week of parenteral vinpocetine infusion a significant decrease of von Willebrand factor levels could be found suggesting the beneficial effects of this drug on endothel dysfunction, which plays an important role in the activation of platelets^[13]. Red blood cell deformability has also been significantly decreased at the 30th day also underlining this phenomena.

Mechanical stress provoked by inflammatory conditions (such as atherosclerosis) leads to an increase in the calcium (Ca) entry into erythrocyte leading to reduction in deformability with subsequent elevation in the blood viscosity. Based on previous results, vinpocetine inhibits sodium (Na)-dependent Ca-channels at erythrocyte membrane enhancing deformability and moreover, deformability was also linked via stimulation of cGMP pathway which has been shown to be augmented by vinpocetine^[14].

We previously showed the association between impaired hemorheological parameters and aspirin resistance^[7]. Biochemical researches have shown decreased red blood cell deformability to be associated with increased fragility with consequent adherence and ATP release, which is a potential agonist of platelet aggregation. Red blood cells with decreased deformability migrate in the center of blood flow displacing other cells (including platelets) in small vessels, enhancing their contact to the endothelial surface^[8,11]. Platelets from aspirin-resistant patients seem to be more sensitive and activable by ADP. This hypersensitivity can promote resistance to aspirin, raising the possibility of therapeutic improvement with other antiplatelet agents (especially clopidogrel)^[11]. The beneficial hemorheological profile of vinpocetine may help to overcome decreased platelets’ response to aspirin and other antiplatelet agents.

The parenteral use of vinpocetine also significantly decreased arachidonic acid-induced platelet aggregation, which is the most sensitive agonist in the measurement of platelets’ response to aspirin^[12]. In our previous work aspirin resistance was associated with unfavourable outcome in cerebrovascular patients^[10]. Although resistance to aspirin was not an independent risk factor of future vascular events, it was a phenomena of global cardiovascular risk suggesting the use of aggressive secondary prevention strategies. The use of intensive statin treatment has recently shown to overcome aspirin resistance, maybe by its pleiotrophic effects^[13,14]. On the other hand, our work is the first suggesting the beneficial effects of vinpocetine treatment of platelet aggregation values in aspirin-treated patients. Vinpocetine inhibits Ca²⁺/calmodulin-dependent phosphodiesterase (PDE) type 1^[15]. This effect would theoretically lead to an increase of cyclic AMP over cyclic GMP and may be responsible for the benefits in cerebral circulation and decreased platelet aggregation observed after vinpocetine administration^[15].

In conclusion, the short-term use of parenteral vinpocetine was associated with the improvement of endothel function, red blood cell deformability and platelets’ response to aspirin using arachidonic-acid induced aggregation. Preclinical and clinical studies suggested multiple effects of vinpocetine such as selective increase of cerebral microcirculation, reduction of plasma viscosity, increase of red blood cell deformability, increase of cerebral oxygen and glucose uptake and neuroprotection. Although the exact biochemical mechanism are still not known and under intensive research, our work suggesting the beneficial effects of vinpocetine treatment on aspirin resistance.

REFERENCES

1. Patyar S, Prakash A, Modi M, Medhi B. Role of vinpocetine in cerebrovascular diseases *Pharmacol Rep.* 2011; **63**(3): 618-28. [PMID: 21857073]; [DOI: 10.1016/s1734-1140(11)70574-6]
2. Fiolaki A, Katsanos AH, Kyritsis AP, Papadaki S, Kosmidou M, Moschonas IC, Tselepis AD, Giannopoulos S. High on treatment platelet reactivity to aspirin and clopidogrel in ischemic stroke: A systematic review and meta-analysis. *J Neurol Sci.* 2017; **376**: 112-116. [PMID: 28431593]; [DOI: 10.1016/j.jns.2017.03.010]
3. Sofi F, Marcucci R, Gori AM, Abbate R, Gensini GF. Residual platelet reactivity on aspirin therapy and recurrent cardiovascular events - a meta-analysis. *Int J Cardiol.* 2008; **128**(2): 166-71. [PMID: 18242733]; [DOI: 10.1016/j.ijcard.2007.12.010]
4. Li J, Song M, Jian Z, Guo W, Chen G, Jiang G, Wang J, Wu X, Huang L. Laboratory aspirin resistance and the risk of major adverse cardiovascular events in patients with coronary heart disease on confirmed aspirin adherence. *J Atheroscler Thromb.* 2014; **21**(3): 239-47. [PMID: 24201035]; [DOI: 10.5551/jat.19521]
5. Vas A, Gulyás B. Eburnamine derivatives and the brain. *Med Res Rev.* 2005; **25**(6): 737-57. [PMID: 16158388]; [DOI: 10.1002/med.20043]
6. Tanahashi N, Gotoh F, Tomita M, Shinohara T, Terayama Y, Mihara B, Ohta K, Nara M. Enhanced erythrocyte aggregability in occlusive cerebrovascular disease. *Stroke.* 1989; **20**(9): 1202-7. [PMID: 2475922]; [DOI: 10.1161/01.str.20.9.1202]
7. Feher G, Koltai K, Kesmarky G, Toth K. Hemorheological background of acetylsalicylic acid resistance. *Clin Hemorheol Microcirc.* 2008; **38**(3): 143-52. [PMID: 18239256. EID: 2-s2.0-43649100470]
8. Feher G, Koltai K, Kesmarky G, Horvath B, Toth K, Komoly S, Szapary L. Effect of parenteral or oral vinpocetine on the hemorheological parameters of patients with chronic cerebrovascular diseases. *Phytomedicine.* 2009; **16**(2-3): 111-7. [PMID: 19135345]; [DOI: 10.1016/j.phymed.2008.10.014]
9. Feher G, Koltai K, Alkonyi B, Papp E, Keszthelyi Z, Kesmarky G, Toth K. Clopidogrel resistance: role of body mass and concomitant medications. *Int J Cardiol.* 2007; **120**(2): 188-92. [PMID: 17169448]; [DOI: 10.1016/j.ijcard.2006.09.014]
10. Feher A, Pusch G, Harang G, Gasztonyi B, Papp E, Werling D, Menyhart M, Komaromy H, Szapary L, Feher G. Aspirin resistance in cerebrovascular patients. *Int J Cardiol.* 2011; **152**(1): 111-2. [PMID: 21794938]; [DOI: 10.1016/j.ijcard.2011.07.028]
11. Olechowski B, Ashby A, Mariathas M, Khanna V, Mahmoudi M, Curzen N. Is arachidonic acid stimulation really a test for the response to aspirin? Time to think again? *Expert Rev Cardiovasc Ther.* 2017; **15**(1): 35-46. [PMID: 27892731]; [DOI: 10.1080/14779072.2017.1266255]
12. Aradi D, Storey RF, Komócsi A, Trenk D, Gulba D, Kiss RG, Husted S, Bonello L, Sibbing D, Collet JP, Huber K; Working Group on Thrombosis of the European Society of Cardiology. Expert position paper on the role of platelet function testing in patients undergoing percutaneous coronary intervention. *Eur Heart J.* 2014; **35**(4): 209-15. [PMID: 24067509]; [DOI: 10.1093/eurheartj/eh375]

13. Tirnaksiz E, Pamukcu B, Oflaz H, Nisanci Y. Effect of high dose statin therapy on platelet function; statins reduce aspirin-resistant platelet aggregation in patients with coronary heart disease. *J Thromb Thrombolysis*. 2009; **27**: 24-28. [PMID: 17917708]; [DOI: 10.1007/s11239-007-0154-1]
14. Santos MT, Fuset MP, Ruano M, Moscardó A, Valles J. Effect of atorvastatin on platelet thromboxane A(2) synthesis in aspirin-treated patients with acute myocardial infarction. *Am J Cardiol*. 2009; **104**: 1618-1623. [PMID: 19962464]; [DOI: 10.1016/j.amjcard.2009.07.039]
15. Chiu PJ, Tetzloff G, Ahn HS, Sybertz EJ. Comparative effects of vinpocetine and 8-Br cyclic GMP on the contraction and ⁴⁵Ca-fluxes in the rabbit aorta. *Am J Hypertens* 1988; **1**: 262-268. [PMID: 2455529]; [DOI: 10.1093/ajh/1.3.262]