group versus I group (by 232.2% and 310.5% accordingly). All investigated drugs decreased these indices in a varying degree. eNOS expression was significantly less in diabetic group by 70.8% ($p < 0.05$). All the drugs (especially pramiracetam) increased its level in a varying degree (table 1).

Conclusion: Course administration of neuroprotective drugs piracetam, pramiracetam and Ginkgo biloba extract in conditions of experimental alloxan diabetes was established to promote reduction of endothelial dysfunction indices and to inhibit platelet aggregation. Pramiracetam possesses the most positive endotheliotropic and antiaggregative properties.

References

[1] Potenza, M.A., Gagliardi, S., Nacci, C., 2009 Endothelial dysfunction in diabetes: from mechanisms to therapeutic targets. Curr. Med. Chem. 16, 94–112.

P.1.c.054 Genotype–phenotype correlations between the CYPC19 polymorphism and pharmacokinetic parameters in Romanian epileptic patients

A.D. Buzoianu[1]*, I.C. Bocsan[1], C. Maier[2], A.P. Trifa[3], F.C. Militaru[1], L. Perju Dumbrava[4], Z.Z. Major[1]. *[1]University of Medicine and Pharmacy Cluj-Napoca, Dept of Pharmacology, Cluj-Napoca, Romania; [2]University of Medicine and Pharmacy Cluj-Napoca, Dept of Drug Analysing, Cluj-Napoca, Romania; [3]University of Medicine and Pharmacy Cluj-Napoca, Dept of Genetics, Cluj-Napoca, Romania; [4]University of Medicine and Pharmacy Cluj-Napoca, Dept of Neurology, Cluj-Napoca, Romania*

Introduction: The polymorphisms of the genes involved in the metabolism of AEDs can potentially modify the activity of the coded enzymes. The CYP2C9 and CYP2C19 genes belong to the P450 (CYP) enzymatic system, being involved in the metabolism of the main AEDs. Valproic acid/Sodium valproate (VPA) is an AED with a broad spectrum, and it is extensively metabolized in the liver, the enzymes of the P450 system being involved in the process [1]. The polymorphism of the CYP2C9 and CYP2C19 isoenzymes represent a potentially determinant factor in the alteration of some drug's metabolism [2]. There are relatively few studies investigating the influence of the CYP2C9 and CYP2C19 polymorphisms over VPA pharmacokinetics.

Aim of the study: The aim of the study was to evaluate the influence of genetic status on the metabolism of valproic acid (VPA) and the correlation between the genotype and the plasma levels of it.

Materials and Method: 80 patients with a mean age of 39.25±1.59 years, either with idiopathic or secondary epilepsy, evaluated in the Neurology Clinic of Cluj-Napoca, Romania were included into the study. Steady state plasma concentration of VPA were determined using the GC/FID technique to all patients under a stable treatment for at least a month. We considered therapeutic level of VPA between 50–100 μg/mL. According to steady-state plasma concentration of VPA the patients were divided into three groups: patients with subtherapeutic (<50 μg/mL), supratherapeutic (>100 μg/mL) or normal (50–100 μg/mL) therapeutic levels. Genotyping was conducted using DNA extracted from lymphocytes of peripheral blood. Using the PCR-RFLP method for each patient we have determined allelic variant CYP2C19*2 and CYP2C19*3. We correlated the plasmatic level of VPA with CYP2C9 and CYP2C19 polymorphisms. The statistical evaluation was performed, using a Chi-square test, with a significance at $p < 0.05$, with SPSS version 17.

Results: 58.25% were female patients and 43.75 male patients, sex ration F:M = 1.33. 60% of the patients presented idiopathic epilepsy, while 40% of them had a secondary form of the disease. The mean plasmatic level of VPA was 71.18±30.87 μg/mL 62% of the patients had therapeutic level of VPA, while 20% had sub-therapeutic and 18% of the patients supra-therapeutic level of it. 22.5% of the patients were heterozygous for CYP2C9*2, and 1.25% were homozygous, while 21.25% of the patients were heterozygous for CYP2C9*3. None of the patients were homozygous for CYP2C9*. Regarding CYP2C19*2 16.25% of the patients were heterozygous and 7.5% of them homozygous. The polymorphism of CYP2C19*3 was absent. There were no significant correlation between the presence of CYP2C9*2 ($p = 0.9$) and CYP2C9*3 ($p = 0.52$) polymorphism and the plasma concentrations of VPA. The same observation was noticed in case of CYP2C19*2 polymorphisms ($p = 0.77$).

Conclusions: The different allelic expression of CYP2C9 and CYP2C19 have no statistically significant influence on plasmatic level of VPA.

References

[1] Lan Tan, Jin-Tai Yu, Yan-Ping Sun, Jiang-Rong Ou, Jing-Hui Song, Yang Yu, 2010. The influence of cytochrome oxidase CYP2A6, CYP2B6, and CYP2C9 polymorphisms on the plasma concentrations of valproic acid in epileptic patients. Clinical Neurology and Neurosurgery; 112: 320–323.

[2] Kirchheiner J, Brockmöller J, 2005. Clinical consequences of cytochrome P450 CYP2C9 polymorphisms. Clin Pharmacol Ther; 77: 1–16.

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P.1.c.055 Metadoxine: a novel 5HT-2B receptor antagonist with a possible therapeutic role in treating ADHD

Y. Daniely[1]*, D. Reich[1], D. Megiddo[1], I. Manor[2]. *[1]Alcobra Ltd., R&D, Tel Aviv, Israel; [2]Geha Mental Health Hospital, ADHD clinic, Petach Tikva, Israel*

Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate), an ion-pair salt of pyridoxine and pyrrolidone carboxylate, is approved in some countries for use in the treatment of acute and chronic alcohol intoxication and for treatment of related chronic liver diseases. In a preliminary clinical trial, Metadoxine demonstrated improvements in cognitive performance in alcohol impaired individuals, as demonstrated by results obtained from the Test of Variables of Attention (T.O.V.A), a computerized test of attention. Therefore, a subsequent 40-person adult (32.1+6.9 yrs) study was conducted in Geha Medical Center in ADHD diagnosed subjects, in which all participants were dosed with a single1400 mg dose of Extended-Release Metadoxine. A cognitive improvement in a T.O.V.A. test (mean score increase of –4.9 to a mean on of –1.8, SE=2.1, $p < 0.001$) was seen suggesting that Metadoxine could indeed improve ADHD symptoms. Pre-clinical (in vitro and in vivo) studies were conducted in order to elucidate the mechanism of action of Metadoxine in cognitive function.

Data obtained from a panel of in vitro receptor binding assays suggest that Metadoxine affects the Serotonin receptor family; in an agonist radioligand assay, it was shown that Metadoxine binds

to the 5HT-$_2$B receptor, pertaining to the 5-HT$_2$ receptor subfamily. In an ex vivo functional isolated organ bioassay performed subsequently, it was additionally found that the compound binds to 5HT-$_2$B in an antagonistic manner.

In the open field test performed on normal SD rats, animals treated with an equivalent clinical dose of Metadoxine showed accelerated habituation [demonstrated by reduction in distance (396.2±49.1 cm in the treatment group vs. 547.7±61.2 cm in the vehicle, p = 0.06) and rearing parameters (5.2±1.3 episodes in treatment group vs. 9.2±1.2, p = 0.03)] in response to novelty compared to the vehicle treated group. This reduction in exploration and rearing time may be an indication of an anxiolytic effect of Metadoxine, pointing to an effect on the serotonergic system in vivo. In the water maze test performed on the same rats, an improvement of almost 20% in latency in finding the platform was observed in the Metadoxine treated group (38.8±6.2 in 1st trial compared to 31.3±5 secs in 2nd trial), compared to the vehicle group (34.2±7.0 in 1st trial compared to 34.9±8.1secs in 2nd trial, p = 0.61, 0.70 for 1st and 2nd trial comparisons, respectively), in which there was an increase in latency to find the platform of almost 2%. Although these results were not statistically significant due to a small sample size, an evident trend was seen supporting a possible effect of Metadoxine on the cholinergic system.

These findings lead us to propose that Metadoxine may play a therapeutic role in ADHD through serotonergic and cholinergic pathways, and act as a potential novel non-stimulant therapeutic. New studies are currently underway in order to further elucidate Metadoxine's mechanism of action and role in cognitive function improvement.

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P.1.c.056 Serum brain-derived neurotrophic factor levels increase with the improvement of neuropsychiatric manifestations in systemic lupus

P. Louzada-Junior[1] *, L.M. Faleiros[1], R. Oliveira[1], E.A. Donadi[1], C.M. Del-Ben[2], E.R. Frota[3], D.H. Rodrigues[4], A.L. Teixeira[5].

[1]School of Medicine of Ribeirão Preto of University of São Paulo, Clinical Immunology, Ribeirão Preto, Brazil; [2]School of Medicine of Ribeirão Pretoof University of São Paulo, Psychiatry, Ribeirão Preto, Brazil; [3]School of Medicine of Federal University of Minas Gerais, Neurology, Belo Horizonte, Brazil; [4]Federal University of Minas Gerais, Institute of Biological Sciences, Belo Horizonte, Brazil; [5]School of Medicine of Federal University of Minas Gerais, Internal Medicine, Belo Horizonte, Brazil

Introduction: Brain-derived neurotrophic factor (BDNF) is an important mediator of neuronal development, survival, and function. In addition, BDNF modulate and regulate immune functions. BDNF is associated with the pathogenesis of several neuropsychiatric diseases [1] but there are few studies [2] evolving systemic lupus erythematosus (SLE). Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of antibodies against various cell components leading to a spectrum of clinical findings ranging from lesions confined to the skin to multisystem organ involvement [3]. Between 10% and 70% of SLE patients exhibit central nervous system involvement, which is associated with inflammatory features in the brain.

Objective: To investigate if the serum BDNF levels were associated with disease activity in SLE patients with neuropsychiatric (NPS) and no-neuropsychiatric (no-NPS) manifestations.

Methods: A total of 141 SLE subjects were evaluated: 72 patients presenting NPS-SLE (42 with active disease), and 71 patients with no-NPS-SLE (27 with active disease). NPS-LES patients presented psychosis (n = 22), major depression (n = 12), seizures (n = 11), stroke (n = 10), vasculitis (n = 4), panic disorder (n = 3), transverse myelitis (2), peripheral neuropathy (n = 2), corea (n = 10), and aseptic meningitis (n = 1). All patients were diagnosed according to criteria set by the American College of Rheumatology. Lupus activity was assessed using the disease activity index (SLEDAI), being active SLE defined with SLEDAI >5, and inactive SLE with SLEDAI < 2. We also evaluated 36 out of 42 patients with active SLENPS in two different moments: one with active disease and other six months after the improvement of neuropsychiatric symptoms (inactive state). All blood samples were collected in the morning, and the plasma was separated and frozen at-70ºC until BDNF assessment. BDNF was measured by sandwich ELISA according to the protocol provided by the manufacturer (R&D Systems, USA). Parametric analysis was performed using the ANOVA test or paired t-test for comparison of unpaired and paired data, respectively. The p value was set at 0.05.

Results: Serum BDNF levels were significantly reduced in active NPS-SLE (mean+SE = 2.87+0.23 ng/mL) when compared with inactive NPS-SLE (mean+SE = 4.39+0.33 ng/mL, p < 0.0001). We observed similar findings in active no-NPS-SLE (mean+SE = 2.25+0.28 ng/mL) when compared with inactive no-NPS-SLE (mean+SE = 2.25+0.69, p < 0.0001). When we analyzed 36 active SLENPS patients during NPS manifestation and after six months, we observed an increased in serum BDNF levels in parallel with the improvement of neuropsychiatric symptoms (mean+SE = 2.89+0.24 ng/mL versus mean+SE = 4.01+0.30 ng/mL, p < 0.05).

Conclusions: Serum BDNF levels were reduced in active SLE, irrespective of neuropsychiatric manifestations. In addition, serum BDNF levels increased in parallel with the improvement of neuropsychiatric symptoms, suggesting that BDNF could be a biological marker for SLE disease activity

References

[1] Frota ER, et al. 2009 Increased plasma levels of brain derived neurotrophic factor (BDNF) after multiple sclerosis relapse. Neurosci Lett 460, 130–132.

[2] Ikenouchi-Sugita A, et al. 2010 Serum brain-derived neurotrophic factor levels as a novel biological marker for the activities of psychiatric symptoms in systemic lupus erythematosus. World J Biol Psychiatry 11, 121–128.

[3] Magalhães MB, et al. 2007 Lymphocytotoxic antibodies in systemic lupus erythematosus are associated with disease activity irrespective of the presence of neuropsychiatric manifestations. Scand J Rheumatol. 36, 442–447.

P.1.c.057 Characterisation of behavioural, neurochemical and histological alterations promoted by bilateral intranigral rotenone administration

C.G. Moreira[1], D. Ariza[1], P.A. Dombrowski[1], P. Sabioni[1], M. Bortolanza[1], C. Da Cunha[1], M.M.S. Lima[1], J.K. Barbiero[1], M.A.B.F. Vital[1] *. *[1]Universidade Federal do Paraná, Pharmacology, Curitiba, Brazil*

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by the loss of midbrain dopamine neurons and Lewy body inclusions affecting 5% of the population