THE IMPACT OF CYP4F2 POLYMORPHISM ON THE SAFETY PROFILE AND REGIME DOSING OF PHENIDION IN PATIENTS WITH VALVULAR ATRIAL FIBRILLATION

V.S. Shakhidzhanova1; D.A. Sychev1,2; R.E. Kaz kov1,3; N.D. Grishenko1; Y.Y. Palamarchuk1; A.V. Kossovskaya1; and A.Y. Tretyakov3

1I.M. Sechenov First Moscow State Medical University, Ministry of Health of Russia Federation, Moscow, Russia; 2Russian Medical Academy of Postgraduate Education, Ministry of Health of Russia Federation, Moscow, Russia; 3Federal State Institution “Scientific Centre of Medical Products Expertise”, Moscow, Russia; and 4Belgorod National Research University, medical faculty, Belgorod, Russia

Introduction: In the reason of FDA prohibition in using of “new” oral anticoagulants, vitamin K antagonists have become uncontested drugs to the patients with valvular atrial fibrillation. The derivatives of indandion, as fluindione and phenidion, can be used in the case of intolerance and coumarins resistance. The role of the main genetic factors in individual sensitivity to coumarin’s anticoagulants is well known. But the influence of gen’s polymorphism CYP4F2 on the safety profile and regimen dosing of phenidion haven’t been studied yet.

Materials and Methods: Forty-two patients (20 male and 22 female), aged 27 to 80 years, valvular AF, were studied. The using of coumarin anticoagulants was impossible in all of them. All patients received phenidion in the dose of 30 to 130 mg daily with a target international normalized ratio (INR) of 2.0 to 3.0. Genotyping for polymorphism’s marker V433M gen CYP4F2 were designed using the PCR and RFLP (restriction fragment length polymorphism). Statistics were performed by Fisher’s exact tests.

Results: Genotype CC was found in 26 patients (62%), genotype CT in 16 patients (38%), genotype TT wasn’t found at all. In the CC group (n = 26) high dose of phenidion (>90 mg) was needed only in 2 patients (8%), versus 6 patients (37.5%) in the CT group (n = 16), P = 0.04 (significant statistically). In the CC group bleedings were found in 4 patients (9%) and in 1 patient (7%) in CT group, P = 0.63. In the CC group INR increased >3.0 in 3 patients (8%). In the CT group nobody had INR >3.0 (P = 0.5).

Conclusion: The patients with genotype CT (polymorphism V433M gen CYP4F2) are usually needed in high dose of phenidion (>90 mg) to achieve target INR of 2.0 to 3.0. There was not found out the influence of gen CYP4F2 polymorphism on the developing of bleedings and excessive hypocoagulation.

ASSOCIATION OF IMMUNE RESPONSE PARAMETERS WITH EARLY VIROLOGICAL RESPONSE IN HCV PATIENTS TREATED WITH PEGYLATED CONSENSUS INTERFERON

Y.H. Ding; H. Zhang; H. Chen; X.J. Li; Q. Zhang; C.J. Liu; L.Z. Yang; Q.M. Li; and J.Q. Niu

Phase I Clinical Research Center, The First Hospital of Jilin University, Jilin, China

Background or Introduction: The aim of the study was to test antiviral activity of pegylated consensus interferon (PEG-CIFN) in adults with HCV infection and to determine the relationship between immune response markers and virological response.

Material and Methods: Thirty naive HCV patients were injected subcutaneously with PEG-CIFN once per week for 12 weeks. Serum HCV RNA levels was measured by a COBAS Taqman HCV Test system. Serum cytokines and chemokines, IL-12p40, IL-12p70, MIG, MIP, IP-10, MCP-1 and TNF were analyzed by Luminex® assays at baseline, 4, 8 and 12 weeks. Fibrosis stages were determined by fibroscan.

Results: The HCV RNA levels in the serum were markedly decreased after therapy. Thirty percent of HCV patients had rapid virological responses (RVR), and 66.7% (16/30) had early virologic responses. The mean log HCV RNA values were 6.43, 1.37, 1.03, and 1.0 IU/mL at 0, 4, 8, and 12 weeks, respectively, in the EVR group and 6.65, 4.21, 2.98, and 3.1 IU/mL, respectively, in the non-EVR group. HCV RNA values were less at the EVR group compared to non-EVR group after treatment, P < 0.05. IL-4, IP-10, and MIP-1b levels were lower, and G-CSF levels were higher in EVR group than in the non-EVR group (P < 0.05). Fibrosis stage did not change after treatment. Correlation coefficient of HCV RNA values with IP-10 and MIP-1b were 0.82 and 0.81, respectively, in the EVR group (P < 0.05). IP-10 and MIP-1b levels were associated with aminotransferase (ALT and AST) levels. Baseline IP-10 levels less than 435 pg/mL predicted RVR at 4 weeks and less than 465 pg/mL predicted EVR at 12 weeks.

Conclusions: PEG-CIFN was well tolerated and effective at inhibiting HCV RNA. PEG-CIFN may increase or decrease levels of immune markers. IFN treatment is associated with changes in markers of immune activation in chronic HCV viral infections.

RESVERATROL AND FENOFRIBRATE AMELIORATE FRUCTOSE-INDUCED NASH IN RATS BY MODULATION OF LIVER AND ADIPOSE TISSUE EXPRESSION OF GENES

E.A. Abd El-Haleim; A.K. Bahgat; and S. Samira

Faculty of Pharmacy, Cairo University, Cairo, Egypt

Background: The intake of high-fructose beverages has been increased. The present study evaluates the effect of a polyphenol (resveratrol), alone or in combination with fenofibrate, on fructose-induced metabolic abnormalities in rats. A number genes known to be critically involved in lipid metabolism was investigated. Understanding the molecular basis of a disease could shed light onto the beneficial therapeutic effects of drugs.

Material and Methods: Giving a fructose-enriched diet (HFD) to rats for 12 weeks was used as a model for inducing hepatic dyslipidemia and insulin resistance. Fenofibrate (FENO) (100 mg/kg), resveratrol (RES) (70 mg/kg) and combined treatment (FENO+RES) (half the doses) were given orally from the 9th week till the end of experimental period. Body weight, oral glucose tolerance test (OGTT), liver index, insulin resistance (HOMA), serum and liver triglycerides (TGs), oxidative stress (liver MDA, GSH and SOD), serum AST/ALT ratio and TNF-α were measured. Additionally, hepatic gene expression of suppressor of cytokine signaling -3 (SOCS-3), sterol regulatory element binding protein-1c (SREBP-1c), fatty acid synthase (FAS), malonyl CoA decarboxylase (MCD), transforming growth factor-β1 (TGF-β1) and adipose tissue gene expression of leptin and adiponectin was evaluated.

Results: Rats fed HFD showed impairment of glucose tolerance, insulin resistance, oxidative stress, and dyslipidemia. As for gene expression, there was a change in favour of dyslipidemia and NASH development. Thus, in the liver, FAS, SOCS-3, SREBP-1c, and TGF-β1 were upregulated while MCD was downregulated. In adipose tissue, leptin and adiponectin genes were unbalanced. All treatment regimens showed effective reversal in the observed divergences contributing to hepatic steatosis and insulin resistance.

Conclusions: When resveratrol is given with half the dose of fenofibrate, the combination improved NASH-related fructose-induced disturbances and gene expression similar to a full dose of fenofibrate possibly due to attenuating the elevated transcription factors besides antioxidant activity by resveratrol.
THE FREQUENCY OF CYP2C19 GENETIC POLYMORPHISMS IN RUSSIAN PATIENTS WITH PEPTIC ULCER TREATED WITH PROTON PUMP INHIBITORS

N.P. Denisenko1,2; D.A. Sychev1,2; Zh.M. Sizova3; A.V. Grachev3; and K.A. Velikolug1

1Russian Medical Academy of Post-Graduate Education, Moscow, Russia; 2I.M. Sechenov First Moscow State Medical University, Moscow, Russia; 3Shanghai Tenth People’s Hospital, Tongji University, Shanghai, China; and 4Out-patient department No. 51 branch 3, Moscow, Russia

Introduction: Proton pump inhibitors, which are widely used as acid-inhibitory agents for the treatment of peptic ulcer, are mainly metabolized by CYP2C19 isoenzyme of cytochrome P450 (CYP2C19). CYP2C19 has genetic polymorphisms, associated with extensive, poor, intermediate or ultrarapid metabolism of proton pump inhibitors. Genetic polymorphism of CYP2C19 could be of clinical concern in the treatment of peptic ulcer with proton pump inhibitors.

The aim of the study – to investigate the frequencies of CYP2C19*2, CYP2C19*3 and CYP2C19*17 alleles and genotypes in Russian patients with peptic ulcer.

Materials and Methods: The study involved 971 patients with peptic ulcer from the European part of Russia (Moscow), 428 male (44%) and 543 female (56%). The mean age was 44.6 ± 11.9 years (range 15–88 y). DNA isolated from blood samples was used for the analysis of CYP2C19 genetic polymorphisms (CYP2C19*2, *3, *17 alleles) by real-time polymerase chain reaction.

Results: Regarding CYP2C19 genotype, 317 patients (32.65%) out of 971 were CYP2C19*1/*1 carriers classified as extensive metabolizers. Three hundred eighty-six (39.75%) with CYP2C19*1/*17 were ultrarapid metabolizers. Two hundred fifty-one people (25.85%) were intermediate metabolizers with CYP2C19*1/*2, CYP2C19*2/*17, CYP2C19*1/*3, CYP2C19*3/*17 genotypes. Seventeen patients (1.75%) with CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3 genotypes were poor metabolizers. The allele frequencies were the following: CYP2C19*2 = 0.140, CYP2C19*3 = 0.006, CYP2C19*17 = 0.274.

Conclusion: There is a high frequency of CYP2C19 genotypes associated with modified response on proton pump inhibitors in Russian patients with peptic ulcer. Genotyping for CYP2C19 polymorphisms is suggested to be a useful tool for personalized dosing of proton pump inhibitors.

FENOFIBRATE IMPROVES THE IMPAIRED ENDOTHELIAL PROGENITOR CELL FUNCTION THROUGH DeregULATING NALP3 INFLAMMAsome ACTIVITY IN DIABETIC MICE

Y.-P. Deng1; T. Zhao2; F. Huang1; M. Ni1; D.-J. Li3; G.-J. Jiang1; and E.-M. Shen1

1Zhejiang Xiaoshan Hospital, Hangzhou, Zhejiang, China; 2Second Military University, Shanghai, China; and 3Shanghai Tenth People’s Hospital, Tongji University, Shanghai, China

Background and Purpose: Impaired wound healing is a common complication of diabetes and is the leading cause of lower extremity amputation. Treatment with fenofibrate was associated with a lower risk of amputations, particularly minor amputations without known large- vessel disease, probably through nonlipid mechanisms. The current study aimed to test our hypothesis that fenofibrate improves angiogenesis and restore endothelial progenitor cell (EPC) function via deregulating NALP3 inflammasome activity in streptozotocin (STZ)-induced diabetic mice.

Material and Methods: Male C57Bl/6 mice were randomly divided into 3 groups: control, STZ-induced diabetic group and fenofibrate treated diabetic group (100 mg/kg/d intraperitoneally for 2 wk). Wound closure was assessed by wound area and CD31 positive capillaries. Both the migration and tube formation capacities of EPCs were measured. Intracellular NO and O2- levels were determined. Activity of NALP3 inflammasome in EPCs was assessed by measuring NALP3, ASC, caspase-1 and TXNIP expression.

Results: Compared with the untreated diabetic mice, wound closure and capillary densities were significantly increased in fenofibrate treated group. Fenofibrate treatment restored EPCs function, and increased NO production, decreased O2- level in EPCs of diabetic mice. Furthermore, fenofibrate deregulated the activity of NALP3 inflammasome by reducing NALP3, ASC, caspase-1, TXNIP expression in EPCs of diabetic mice. In vitro, fenofibrate improved high glucose induced EPCs dysfunction and deregulated NALP3 inflammasome activity.

Conclusion: Fenofibrate could accelerate wound healing in diabetic mice, which at least in part was mediated by improving the impaired EPCs function through deregulating NALP3 inflammasome activity.