Session 11 − **Clinical Pharmacology, Pharmacokinetics, Pharmacogenomics and Preclinical Toxicology**

11. **001**

The proper use of self medication and risks and consequences in the health area of universities. Naime ACA, Reis LM, Garcia JAD, Soares EA, Loyola YCS UNIFENAS − Farmácia

Introduction: The self medication is defined as the consumptions of medications without the medical orientation following the impulses or other influences being the usual practice not only in Brazil but in other countries. It is a common practice among university students who make use of self medication to reach through a drug intellectual improvement and the attainment of a better evening rest. As all medications are not entirely harmless to the organism, the incidence of not desirable effects do increase every day. Among the observed problems with the self medications the most important thing is the maskering or the impediment of a correct diagnostic of a great illness. It can affect negatively any pathologic process in the patient and provoke interaction of great importance resulting in secondary effects and risks not accepted therapeutically. The present study had objectives: Determine self medication prevalence in the group and principal causes that lead to self medication, what drugs were more consumed and the effects they can cause. **Methods:** All methods were in accord with the established norms by the Committee of Ethic and Research from the University of Alfenas (Report 55/2009). They were interviewed 180 academic students through questionnaires from Dental and Pharmacy Courses from the universities of Alfenas, MG, Brazil in the year 2009. **Results and Discussion:** The results were expressed in percent frequency for each question in the descriptive analyses. In what it refers to frequency of self medication, only 4% did not self medicate and 63% of the interviewed consumed medication without orientation what demonstrated negligent attitude as to the use of drugs. Fifty three of all the students got information from persons not capacitated and only 33% tried special instructions meaning that student of health area are under the influence of friends and family members, according to many studies. The most utilized medications were the analgesics and anti-inflammatory 53% anti-acids 17% and antithermics 16%. The anti-inflammatory not steroids were potent rs of synthesis blockers of prostaglandins that could offer serious risks to the health of consumers. The use of medication is interrupted in 76% of the cases when the symptoms of the illness are ended. The students related that they knew of the risks of self-medication (98%) and that they knew the responsibility to make clear to patients about the incorrect use of medications (100%). It is necessary to point out the importance of their responsibility to society once it is theirs the responsibility to reduce this practice though the orientation of self medication and consequently, the reduction of the number of health hazards this can cause.

11.002

A functional matrix metalloproteinase (MMP)-9 polymorphism modifies plasma MMP-9 levels in subjects environmentally exposed to mercury. Jacob Ferreira ALB[1], Barbosa Jr F[2], Gerlach RF[3], Tanus-Santos JE[4] [1]FCM-UNICAMP − Farmacologia, [2]FCFRP-USP − Toxicologia, [3]FORP−USP − Morfologia, [4]FMRP-USP − Farmacologia

Introduction: Mercury (Hg) exposure causes health problems, including cardiovascular diseases. Although the mechanisms are not precisely defined, metalloproteinases (MMPs) may be involved. Increased expression and activities of MMPs are demonstrated in several pathological conditions, and recent studies have demonstrated that circulating levels of MMPs could be used as a blood-borne biomarker for cardiovascular risk. The gene encoding MMP-9 presents genetic polymorphisms which affect the expression and activity level of this enzyme. Two polymorphisms in the promoter region [C-1562T and (CA)n] are functionally relevant and are implicated in several diseases. We investigated the association between circulating levels of MMP-9 and its endogenous inhibitor (TIMP)-1 with circulating levels of Hg in individuals exposed to Hg in the Brazilian Amazon (N=266), and whether these MMP-9 polymorphisms affect circulating net MMP-9 activity in persons exposed to mercury. **Methods:** We analyzed the concentrations of plasma Hg by inductively coupled plasma-mass spectrometry (ICP-MS). MMP-9 and TIMP-1 levels were measured in plasma samples by zymography and ELISA, respectively. Genomic DNA was extracted from blood, and genotypes for the C–1562T and the microsatellite (CA)n polymorphisms were determined. The relationship between plasma Hg concentrations and MMP-9 levels, as well as the relationship between MMP-9 genotypes and MMP-9 levels, were examined using multivariate regression models. RESULTS: No relationship was found between Hg in plasma and MMP-9 (β=0.041630; p=0.2371). However, plasma Hg levels were negatively associated with TIMP-1 levels (β=-22.89477; p=0.0350), and thereby with increasing MMP-9/TIMP-1 ratios (β=0.000296; p=0.0408), thus indicating a positive association between plasma Hg and circulating net MMP-9 activity. The polymorphisms of MMP-9 were not related to net MMP-9 activity when all subjects were analyzed together. However, when we divided the population into tertiles of plasma Hg concentrations, the polymorphism (CA)n affected MMP-9 concentrations and MMP-9/TIMP-1 ratio in people with lower levels of Hg (p=0.0175 and p=0.0545, respectively). MMP-9 levels were higher in persons with genotypes including alleles with more than 21 CA repeats (H alleles) (β=0.107561; p=0.0115) and lower in those whose genotype including alleles with less than 21 CA repeats (L alleles) (β=-0.165174; p=0.0065). Conversely, this polymorphism had no effects in persons with intermediate or high plasma Hg level. No association was found between the C-1562T polymorphism and MMP-9 levels in the three groups. **Discussion:** These findings show that the (CA)n polymorphism of MMP-9 affects net MMP-9 activity. The increase in MMP-9 levels could increase the risk of developing cardiovascular diseases in persons exposed to Hg, especially those with the HH genotype. Approval was obtained from Ethics Committee of the University of São Paulo at Ribeirão Preto. Protocol number CEP/FCFRP #71. **Financial support** by: FAPESP, CNPq.

11.003

Endothelial nitric oxide synthase gene haplotypes affect nitrite levels in black subjects. Metzger IF[1], Ishizawa MH[1], Rios-Santos F[2], Carvalho WA[3], Tanus-Santos JE[1] [1]FMRP-USP − Farmacologia, [2]UESC − Saúde, [3]HSR − Patologia Clínica e Toxicologia

Introduction: The Nitric Oxide (NO) plays an important role in cardiovascular homeostase. However, some studies found differences on nitric oxide biodisponibility between the ethnics groups. There are differences in haplotypes frequencies distribution between black and white individuals. The eNOS haplotype “C 4b Glu” was associated with lower plasma NOx and Nitrite concentrations in health white subjects, features which remain unknown in black population. **Methods:** In this way, we sought to verify the effect of eNOS haplotype on Nitrite levels in 198 black healthy subjects (males, non-smokers, 18-60 years of age, and not taking any medication). The distribution of haplotypes involving three relevant eNOS polymorphisms (T-786C in the promoter region; b/a in intron 4, and Glu298Asp in exon 7) was compared with low and high circulating nitrite levels (plasma, RBC and whole blood) in these subjects. Genomic DNA was isolated in order to determine the genotypes. The T-786C and the Glu298Asp polymorphisms were determined by Taqman® Allele Discrimination assay and the Intron 4 by PCR and fragment separation by electrophoresis. To assess NO formation, the plasma concentrations of nitrite were determined using an ozone-based chemiluminescence assay and an enzyme immunoassay. Haplotypes were inferred using the PHASE 2. 1 program. **Results and Discussion:** No significant differences were found in age, body mass index, systolic and diastolic arterial blood pressure, heart rate or nitrite among the genotype groups for the three polymorphisms studied here (all $p>0.05$). The subjects were divided, according to the observed nitrite levels in group L (low) and H (high). The observed nitrite levels in group L and H were, respectively: Plasma - 37.7+7.4 nM and 463. 0+159.8 nM; RBC - 204.9+71.6 nM and 1085. 0+390.2 nM; and Whole Blood – 94.9+24.9 nM and 860.5+256.3 nM. Interestingly, as in white healthy individuals, the “C 4b Glu” haplotype was associated with lower nitrite plasma concentrations (p corrected for multiple <0.0063). The estimated frequency of “C 4b Glu” haplotype was 11.2% in Plasma and 12.4 % in whole blood in group L while was 0% in group H in both. No other significant differences were found in the frequencies of the remaining haplotypes. These findings suggest that eNOS gene variants combined within a specific haplotype modulate NO formation independently of race. (Project Approved by Research Ethics Committee of São Rafael Hospital -Salvador-BA, Project number 04/06) Apoio Financeiro: FAPESP, CNPq and Capes

11.004

Interethnic diversity of NAT2 polymorphisms in Brazilian admixed populations. Talbot J[1], Magno LA[1], Santana CVN[1], Souza SMB[1], Melo PRS[1], Corrêa RX[1], Di Pietro G[2], Rios-Santos F[2] [1]DCB-UESC, [2]DCS-UESC

Introduction: N-acetyltransferase type 2 (NAT2) is a phase II metabolizing enzyme that plays a key role in bioactivation of aromatic and heterocyclic amines. Its relevance in drug metabolism and disease susceptibility remains a central theme for pharmacogenetic research, mainly because of its variability among human populations due to genetic single nucleotide polymorphisms (SNPs). In fact, the evolutionary and ethnic-specific SNPs on the NAT2 gene remains a focus for the potential of personalized drug therapy and disease markers discoveries. Despite wide characterization of NAT2 SNPs frequencies in established ethnic groups, few data is available in a highly admixed population. In this context, the five common NAT2 SNPs were investigated in population composed of Afro-Brazilians, Whites and Amerindians in northeast of Brazil. Thus, we sought to determine whether NAT2 polymorphisms distributions are different among these three ethnic groups. **Methods:** PCR-RFLP assay was used to detect in 183 healthy individuals (CEP-UESC: 041/06) five different NAT2 SNPs: G191A (rs1801279), C481T (rs1799929), G590A (rs1799930), A803G (rs1208) and G857A (rs1799931). Individual marker analyses were performed using qui-square tests and for evaluation of the ethnic influences on the polymorphism frequency multiple logistic regression analysis, pairwise linkage disequilibrium (LD) and genetic associations were used. **Results:** Overall, there were no statistically significant differences in the distribution of NAT2 polymorphisms evaluated when compared Afro-Brazilian and White groups. Even the 191A allele frequency, relatively common in African-descendents, was not different between the Afro-Brazilian and White groups. However, allelic and genotypic frequencies of 590A and 857A SNPs were significantly overrepresented in our Amerindian group than in the Afro-Brazilian or White groups. Interestingly, we found some haplotypes in Amerindians not found in the others groups. Five slow acetylator haplotypes were found, which were higher in Amerindians (44.9%) than Afro-Brazilians and Whites (22.9% and 25.8%, respectively). **Discussion:** Under these circumstances, our observations provide support that the ethnic admixture might contribute to a particular NAT2 genetic diversity and offer new insights for the investigation of possible new NAT2 gene-environment effects (drug disposition and diseases risk) in the admixed populations. **Financial support**: FAPESB, CNPq and UESC

11.005

Pharmacokinetic evaluation of the anticancer candidate LaSOM 65 in rats. Torres B[1], Uchoa FDT[2], Canto RFS[1], Crestani A[3], Russowsky D[4], Eifler-Lima VL[1], Dalla Costa T[1] [1]UFRGS − Ciências Farmacêuticas, [2]FF-UFRGS – Medica-mentos, [3]FF-UFRGS − Síntese Orgânica Medicinal, [4]UFRGS − Química

Introduction: Dihydropyrimidinones are a class of compounds reported as prototypes for drug development aiming anticancer therapy1,2. From this group, the compound ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-carboxylate (LaSOM 65) showed a good anticancer activity by inhibiting Sarcoma 180 growth in mice and glioma cells in vitro (data not published). In this context, the aim of this study was to investigate the pre-clinical pharmacokinetics of LaSOM 65 in rats after intravenous (i. v.) and oral (p. o.) administration. **Methods:** The animal experiments were approved by UFRGS Ethics in Research Committee (Protocol 2008196). LaSOM 65 pharmacokinetic evaluation was conducted using three groups of animals. One group (n = 7) received a single i. v. bolus dose of the drug (1 mg/kg) injected into the lateral tail vein. The second and the third groups received a single dose of 10 mg/kg (n = 8) or 30 mg/kg (n = 6) of LaSOM 65 by oral gavage. At scheduled times (0.08, 0.25, 0.33, 0.5, 1, 1.5, 3, 4.5 and 6 h) after i. v. administration, 200 µl of blood was withdrawn via lateral tail vein puncture into heparinized centrifuge tubes. The same procedure was carried out after p. o. administration with blood sampling at 0.25, 0.5, 0.75, 1.5, 3, 4.5, 6, 8, 10 and 12 h. Plasma was separated by centrifugation at 6800×g, 4 °C for 10 min and stored at −20 ºC until analysis. Plasma samples (100 µL) were deproteinized with acetonitrile (1:2), vortexed (10 sec) and centrifuged (12. 000 rpm, 10 min). A 50 µL aliquot of the supernatant was analyzed for drug quantification by a previously validated HPLC/UV method. Briefly, the chromatography was performed on a C18 column (Nova Pak®, 15cm) with isocratic elution of acetonitrile:water (45:55, v/v) at a flow of 0.8 mL/min and detection at 303 nm. From the plasma profiles obtained, individual pharmacokinetic parameters were estimated by compartmental and non-compartmental approaches. **Results and Discussion:** The pharmacokinetic plasma profile of LaSOM 65 after i. v. dosing exhibited a rapid distribution phase followed by a slower elimination phase, compatible with a two compartment open model. The total clearances (0.82 ± 0.12 L/h/kg; 0.81 ± 0.09 L/h/kg and 0.94 ± 0.41 L/h/kg), the volumes of distribution (1.76 ± 0.33 L/kg, 1.74 ± 0.39 L/kg, 2.92 ± 1. 04 L/kg), and the terminal half-lives (1.7 ± 0.39 h; 1.48 ± 0.26 h and 2.33 ± 0.83 h) were statistically similar after i. v and p. o. dosing (10 and 30 mg/kg), respectively (α = 0.05). The oral bioavailability was 58.6% for the 10 mg/kg oral dosing and 49.2% for the 30 mg/kg, indicating that the absorption process is dose-dependent. The absorption rate constant for the 10 mg/kg oral dosing (0.43 ± 0.11 h-1) was statistically higher than that observed for the 30 mg/kg dosing (0.26 ± 0.04 h-1) corroborating the bioavailability findings. References: 1Kappe, C. O. Eur. J. Med. Chem.35, 1043, 2000.2DeSimone, R. W. Comb. Chem. High Throughput Screen.7, 473, 2004 **Acknowledgments:** The authors thank INCT-if (CNPq/Brazil) and CNPq (Universal 477657/2008-7) for **Financial support** and postgraduate scholarship (566201/2008)

11.006

Pharmacoepidemiological evaluation of analgesic use for children and adolescents from a public school. Alves DS[1], Lacerda JSJ[1], Matias TC[1], Borlini PG[1], Brito BG[1], Almeida JM[1], Beijamini V[2] [1]UFES − Ciências da Saúde, [2]UFES − Ciências Farmacêuticas

Introduction: Analgesics such as acetylsalicylic acid, acetaminophen and dipyrone are among the best-selling drugs worldwide and are frequently used in children and adolescents. The choice of analgesic depends greatly on the profile of adverse effects. Acetylsalicylic acid should not be used to treat acute febrile viral illness in children. Although no causal link has been proven, data from case-control and historic cohort studies demonstrate an association between aspirin use and Reye syndrome. Also, this analgesic should not be used in patients with dengue due to the risk of bleeding complications. The aim of this study was to evaluate the use of analgesics among students EEEFM Santo Antonio, in São Mateus / ES, as well as the knowledge that these students have about the restrictions on the use of certain medications, especially in terms concerns or suspected cases of dengue and other viral diseases. **Methods:** We conducted a cross-sectional study with an anonymously questionnaire about pharmacoepidemiological profile analgesic use. We evaluated the following socio-demographic indicators regarding gender, age, grade, the siblings, profession and education of the mother. The pharmacoepidemiological profile was drawn: reference to the use of analgesics in the last 15 days, identification of analgesic used, and indication of use (prescription or self-medication); analgesic drug which should not be used in cases of dengue. The study was approved by the Research Ethical Committee from CEUNES/UFES (number protocol 12/2009). **Results and Discussion:** Most of the students who participated in the survey are female, live with their parents, have average household income of up to two minimum wages and mothers who attended only elementary school. Approximately 60% of students responded that used analgesics during the 15 days preceding the survey. Of that group, 41% referred the use of analgesic dipyrone and 32.7% used acetaminophen. The main motivation for such use was headache. Most students reported that they used analgesics for self-medication or referred by a doctor or other indication of a relative/friend/neighbor. Finally, regarding the question on which analgesics should not be used in case of dengue, 16.9% of students reported acetaminophen, 27.5% reported dipyrone and 30.6% scored acetylsalicylic acid. The results showed that this population does a few use of acetylsalicylic acid. Self-medication in younger children using such drugs as dipyrone suggested inappropriate drug use and potential risks. This should be closely monitored and warrants an education program for families. **Financial support**: FAPES

11.007

Imbalanced matrix metalloproteinases levels in women with polycystic ovary. Gomes VA[1], Jacob Ferreira ALB[2], Belo VA[2], Vieira, CS[3], Fernandes JBF[3], Soares GM[3], Ferriani R[3], Tanus-Santos JE[4] [1]FCM-UNICAMP, [2]FCM-UNICAMP − Farmacologia, [3]FMRP-USP − Ginecologia e Obstetrícia, [4]FMRP-USP − Farmacologia

Introduction: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age. PCOS is associated with metabolic abnormalities that predispose to increase risk of cardiovascular disease. Elevated activity of matrix metalloproteinases (MMPs) has been implicated in numerous pathological processes including atherosclerosis, cardiovascular disease and ovarian dysfunction. Our objective was to investigate plasma MMPs and tissue inhibitors of metalloproteinase (TIMPs) levels in PCOS women. The study protocol was approved by HCRP-USP Ethics Committee (number 15811/2005). **Methods:** We studied 94 PCOS women and 68 healthy women (controls). MMP-2 plasma levels were determined by zymography and MMP-9, MMP-8, TIMP-1, and TIMP-2 plasma levels were determined by ELISA. **Results:** We found no differences in MMP-2, TIMP-1, MMP-8 and MMP-8/TIMP-1 ratios plasma levels between groups (all $P>0.05$). Women with PCOS women had lower TIMP-2 (185. 0 ± 4.9) compared with controls (206. 1 ± 6.8; $P <0.05$). However, patients with PCOS have higher plasma MMP-2/TIMP-2 ratios (5.9 ± 0.022 vs 5.52 ± 0.024; $P<0.05$), MMP-9 (177.7 ± 11.51 vs 144. 1 ± 9.2, $P<0.05$) and MMP-9/TIMP-1 (0.23 ± 0.017 vs 0.19 ± 0.015, $P<0.05$) than control healthy women. **Discussion:** The elevated MMP-9 and the reduced TIMP-2 concentrations in plasma from women with PCOS show imbalanced MMPs levels in these patients. These findings may help to explain the increased cardiovascular risk usually found in such patients, and suggest that MMPs inhibitors may be useful in this condition. **Financial support**: CAPES

11.008

Histological changes in different tissues of non-pregnant and pregnant rats and their fetuses treated with statins. Oliveira LP, Ikeda CM, Maciel LIS, Pereira DA, Ferreira TMI, Melo R, Braga-Vilela AS UNIFENAS − Ciências Biomédicas

Introduction: Statins are widely used substances in the treatment of hypercholesterolemia and there are few studies about the potential teratogenic effect. Despite being highly effective drugs have several adverse effects being the most severe hepatotoxicity and myopathy. The aim of this research is to verify the occurrence of possible tissue changes in non-pregnant and pregnant rats treated with simvastatin and atorvastatin. **Methods:** Virgin rats were used from the animal colony of UNIFAL-MG. The animals were placed to mate overnight. The 1st day of pregnancy was confirmed by the presence of sperm in the vaginal smear. Pregnant rats (n=5 per dose) were then treated with simvastatin (Group PS- 0,3mg/Kg and 1,1mg/Kg), and atorvastatin (Group PA- 0,3mg/Kg and 1,1mg/Kg) daily and orally from the 9th day to the 19th day of pregnancy. On the 20th day of pregnancy, the rats were sacrificed for collection of fetuses and target tissues. Also non-pregnant female rats (n=5 per dose) treated with simvastatin (Group NS- 0,3mg/Kg and 1,1mg/Kg), and atorvastatin (Group NA- 0,3mg/Kg and 1,1mg/Kg) daily and orally for ten days. The control groups (untreated) were: non-pregnant (CN) and pregnant (CP) rats (n=5). On the 11th day the rats were sacrificed for collection of target tissues. It was performed fixation and paraffin embedding. The tissue sections were made with 6µm thickness and staining by hematoxylin-eosin, Picrosirius and Verhöeff. Karyometry and Chalkley test of tissues were done. The data were subjected to statistical analysis with the Wilcoxon-Mann-Whitney. **Results and Discussion:** Fetuses and placentas of all treated groups were underweight when compared with fetuses in the control group. Fetuses in the group treated with atorvastatin (PA-1,1) were observed an apparent reduction in the amount of collagen in skin and elastic fibers in abdominal aortic wall. Lesions were detected in ventricular myocardial fibers of pregnant rats treated with statins (PA-0,3; PS-0,3 and PA-1,1). The Wilcoxon - Mann - Whitney test revealed significant differences on nuclear volumes of smooth muscle cells of the intestine of pregnant rats those between the CP, PS-1,1 and PA-0,3. When compared to the pregnant rats, we observed a reduction in nuclear volume of bladder smooth muscle cells that was statistically significant in all treated groups compared with CP. The Karyometry showed that pregnant rats presented nuclear volumes of tissues more similar to the CP when compared to non-pregnant rats that did not present data as similar to the CN. Analysis of intestinal smooth muscle tissue by Chalkley test from non-pregnant rats showed an increase of interstitium in relation to the nucleus and cytoplasm in the treated groups compared to CN. Conclusions: The data suggest that treatment with statins in rats caused alterations in connective tissue and muscle tissue of pregnant and non-pregnant rats. The synthetic activity of cells in different fetal and maternal tissues was modified. Pregnant rats showed karyometric data similar to the control group of pregnant rats (CP), indicating a possible protective effect of pregnancy in relation to tissue changes detected. License numbers of authorization from the ethics committee of animal: 168/2008; 190/2008 **Financial support**: Fapemig, PROBIC/ UNIFAL-MG

11.009

Influence of isotretinoin in liver transaminases and triglycerides plasma levels. Vieira AS[1], Beijamini V[2], Melchiors, AC[1] [1]UFES − Ciências da Saúde, [2]UFES − Ciências Farmacêuticas

Introduction: Acne is a chronic inflammatory condition that develops in the pilosebaceous follicle. The most part of population in the world have any grade of acne. This pathology does not present major risk to healthy individuals, but it can affect the emotional state of them. The use of oral isotretinoin has been the best medication for severe acne. Isotretinoin's mechanism of action is not completely defined. It is known that the drug reduces the activity, size and sebum production of sebaceous gland. However, one obstacle to the use of this drug are its side effects, such as the mucocutaneous, ocular, musculoskeletal, lipid and hepatic effects, in addition to its teratogenicity. Therefore, during the treatment with isotretinoin, it is necessary the monitoring of triglycerides and transaminases plasma levels. Thus, the aim of the study was to evaluate the profile of changes in the concentration of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and triglycerides levels in patients who used isotretinoin and acquired this drug in Regional Pharmacy of Exceptional Medicines in São Mateus/ES. **Methods:** Exploratory observational longitudinal study, conducted in São Mateus/ES. It was used a data collection instrument completed after the observation of the clinical record of each patient. The sample comprised all patients from exceptional drugs pharmacy in São Mateus/ES and underwent a treatment with oral isotretinoin from January to December of 2009. Were excluded patients whose medical records did not show any results of treatment monitoring. Statistical analysis was performed with SPSS software v. 12. 0 for Windows. The study was approved by research ethics committee of the Centro Universitário Norte do Espírito Santo/UFES (n. 056/2009). **Results and Discussion:** The sample consisted of 70 patients considering a population of 130 patients, with significance level of 95% and an 8% error. Of the 70 patients, 39 (55.7%) were females and 31 (44.3%) males. The average age of the studied population was 22.2 years (range 13 to 42 years-old). The average age of women (23.9 years) was higher than the average age of men (20.1), $p < 0.05$. Statistical analysis of the values of triglycerides, AST and ALT before and after 3 months or more of treatment with oral isotretinoin, for each patient, showed that there is a statistically significant difference within the levels of triglycerides (87. 0 ± 48,2 versus 105.3 ± 48.8; $p<0.01$), AST (20.4 ± 6.3 versus 24.4 ± 11.9; $p<0.05$) and ALT (18.2 ± 8.3 versus 23.3 ± 20.0; $p<0.05$). Furthermore, from patients who started treatment with oral isotretinoin with normal triglycerides, 11% had their values increased above normal values (>150mg/dL). Similarly, 8.6% and 7.3% had values of AST and ALT (>40mg/dL), respectively, increased above normal values. The results showed that the use of oral isotretinoin for the acne treatment can lead to changes in the levels of triglycerides, ALT and AST, raising the risk of the patient acquire cardiovascular and hepatic disease. There is, therefore, a relevant issue in monitoring patients taking oral isotretinoin for the treatment of acne.

11.010

Matrix metalloproteinase 9 gene polymorphisms affect left ventricular hypertrophy in hypertensive patients. Lacchini R[1], Jacob Ferreira ALB[2], Luizon MR[1], Coeli FB[3], Izidoro-Toledo TC[1], Gasparini G[4], Ferreira-Sae MC[4], Schreiber R[4], Nadruz Filho W[5], Tanus-Santos JE[1] [1]FMRP-USP − Farmacologia, [2]FCM-UNICAMP − Farmacologia, [3]FMRP-USP − Endocrinologia, [4]FCM-UNICAMP − Patologia, [5]FCM-UNICAMP − Clínica Médica

Introduction: Hypertension is one of the most important issues in health care system nowadays1. The progression of disease leads to cardiovascular remodeling process, which is characterized by increase in wall thickness of arterial vessels, end organ damage, cardiac hypertrophy, and other hazardous effects. Together, all this effects are responsible for the high morbidity and mortality of hypertensive disease. Matrix metalloproteinases (MMP) are structurally related, zinc dependent, enzymes that degrade several components of extracellular matrix 2. Among several other MMPs, MMP-2 and MMP-9 are involved in cardiac remodeling 3 and may be related to progression of cardiac hypertrophy4. Our objective is to examine whether matrix metalloproteinase (MMP)-9 genetic polymorphisms are associated with hypertension and whether they influence left ventricular (LV) remodeling in hypertensive patients. **Methods:** 173 hypertensive patients and 137 age, race and gender matched healthy controls were enrolled. Heart echocardiography was performed in all patients and the following MMP-9 genetic polymorphisms were analyzed: C-1562T (rs3918242), -90 (CA)14-24 (rs2234681) and Q279R (rs17576). This study was approved by Human Research Ethics Committee of FCM-UNICAMP (process number: 181/2005). Fisher´s exact test was used to compare genotype and allele frequencies between groups. Haplo. stats analysis was used to assess whether MMP-9 haplotypes are associated with hypertension. Linear regression analysis was performed to assess whether MMP-9 haplotypes affect LV mass index (LVMI) and other echocardiography parameters. **Results:** MMP-9 -90 (CA)14-24 “HH” genotype (H allele defined by number of CA repeats ≥ 21) was associated with hypertension (P=0.0085; OR=2.321, 95% confidence interval=1.250 to 4.309). While three MMP-9 haplotypes (C-L-Q, C-H-Q, and T-H-R) protect against LV remodeling (all P<0.03), one MMP-9 haplotype (T-H-Q, P<0.0001) apparently has detrimental effects on LVMI in hypertensive patients. **Discussion:** Our results indicate that genetic polymorphisms in MMP-9 gene may modify the susceptibility of hypertensive patients to LV remodeling. Further studies are necessary to examine whether these polymorphisms affect the incidence of clinical events in hypertensive patients. 1 - Chobanian, A. V. , et al. , Hypertension, 42, 1206-52, 2003.2 - Nagase, H. , et al. , J Biol Chem, 274, 21491-4, 1999.3 - Polyakova, V. , et al. , J Am Coll Cardiol, 44, 1609-18, 2004.4 - Ahmed, S. H. , et al. , Circulation, 113, 2089-96, 2006.

11.011

Endothelial nitric oxide synthase (ENOS) haplotypes associated with aura in women with migraine. Gonçalves FM[1], Oliveira AM[2], Speciali JG[3], Izidoro-Toledo TC[4], Silva PS[1], Dach F[3], Tanus-Santos JE[4] [1]UNICAMP − Farmacologia, [2]USP − Farmacologia, [3]FMRP − Neurologia, [4]FMRP-USP − Farmacologia

Introduction: Migraine, especially migraine with aura, has been associated with risk of cardiovascular disease, mostly ischemic stroke. Despite the pathophysiology of migraine not fully elucidated, there is strong evidence that nitric oxide (NO) is critically involved in cerebral vasodilatation and pain of migraine. In this regard, clinically relevant polymorphisms in the gene encoding endothelial nitric oxide syntase (eNOS) affect NO formation and may have an impact on migraine susceptibility. Objective: The aim of this study was investigate whether genetic polymorphisms and haplotypes in the eNOS gene (rs2070744, intron 4, rs1799983, rs3918226 and rs743506) are associated with migraine susceptibility. **Methods:** We studied 117 healthy women without migraine, 134 women without aura (MWA) and 44 women with aura (MA). This study was approved by the Ethics Committee at Faculty of Medicine of Ribeirao Preto (n.6120/2007), University of Sao Paulo, Brazil. Genotypes were determined by PCR followed by fragment separation by electrophoresis for intron 4 and by real-time polymerase chain reaction for the others polymorphisms. We compared the distribution of eNOS genotypes, alleles and haplotypes in the study groups. **Results:** There was remarkable disparity in the distribution of genotypes for two (rs1799983 and rs743506) polymorphisms among the groups studied. The TT (rs1799983) and GG (rs743506) genotypes were more common in patients with migraine than in control group ($P<0.05$). Importantly, both the haplotype including the variants “C a Glu C G” and the haplotype including the variants “C b Glu C G” was more frequent in MA than MWA group (both $P<0.0016$). Conclusions: Our findings suggest that eNOS haplotypes “C a Glu C G” and “C b Glu C G” may be associated with increase susceptibility to migraine with aura in women with migraine. However, further studies examining the possible interactions of eNOS haplotypes with environmental factors and other genetic markers involved in the development of migraine are warranted. **Acknowledgments:** This study was supported by Fundação de Amparo à Pesquisa do Estado de Sao Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenadoria de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

11.012

Efficacy evaluation of the therapeutic protocols used to treatment of TMDR patients in a respiratory diseases reference centre, in Salvador, Bahia, Brazil. Pitanga QML[1], Santos CBS[1], Pitta LB[1], Pinheiro CG[1], Carvalho JSM.[2], Carvalho FLDQ[1] [1]UNEB − Ciências da Vida, [2]UNIJORGE − Saúde

Introduction: Tuberculosis is a millenary disease still related to deaths, specially caused by the onset of multidrug-resistant strains. For this reason, it has been much discussed and the worry is associated to the possibility of public dissemination and the difficulty to establish therapeutic protocol with efficacy and efficiency in order to combat the tuberculosis in Brazil as in the world. This work aims evaluating efficacy of the protocols used to treatment of tuberculosis multidrug-resistant patients (TMDR) in a respiratory diseases reference centre, in Salvador-Bahia, Brazil. **Methods:** This study is based on the data obtained from the medical records of 71 patients with 18 years old minimum hospitalized in the Octávio Mangabeira Reference Hospital (OMRH), in the period between 2004 and 2009 with TMDR diagnostic. This study was approved by the Ethics Committee of the Bahia State University (UNEB), protocol n. 0603090088013, as well as by the OMRH Center for Research Pneumology. **Results and Discussion:** After collecting the data, it was possible to design the multidrug-resistance profile from the hospitalized patients during the period of study. It was observed a variance among the first line medicines that are determined by the Brazilian Ministry of Health: Rifampicin (95%), Isoniazid (90%), Ethambutol (46%), Estreptomycin (42%), Ethionamide (24%), and Pyrazinamide (16%). From the total 71 patients records studied, 33 (46%) used the therapeutic protocol currently defined by the Ministry of Health to TMDR (Amikacin, Terizidone, Ofloxacin, Ethambutol, and Pyrazinamide), while 38 (53,5%) were submitted to individual protocols, in which the drugs were added or substituted according to the patient response. When the end of therapy was compared between these two groups (first line versus individual), the cure rates were higher to those that received the individual treatment (23,3%) than those that used the Ministry of Health first line drugs (12,5%). This work has not finished, but the preliminary results suggest that the individual TMDR treatment is more effective to reach the cure than the first line Ministry protocol. Such study can contribute to guide therapeutic options as well as help to design public strategies to control the problem in Brazil. **Financial support**: FAPESB.

11.013

Quantification of cyproheptadine in human plasma by high-performance liquid chromatography coupled to electrospray tandem mass spectrometry in a bioequivalence study. Arruda AMM[1], Mendes GD[1], Chen LS[2], Nucci G[1] [1]FCM-UNICAMP − Farmacologia/FCM, [2]Galeno Research Unit − Bioequivalence

A rapid, sensitive and specific method to quantify cyproheptadine in human plasma using amitriptyline as internal standard (IS) is described. The study was approved by the Research Ethics Committee of the Medical Faculty of UNICAMP (number 478/2009). The analyte and the IS were extracted from plasma by liquid-liquid extraction using a diethyl-ether/dichloromethane (70/30; v/v). After removing and drying the organic phase, the extracts were reconstituted with a fixed volume of acetonitrile/water (50/50; v/v) + 0.1% of acetic acid. The extracts were analyzed by high performance liquid chromatography coupled to electrospray tandem mass spectrometry (HPLC-MS-MS). Chromatography was performed isocratically in an Alltech Prevail C18 5 µm analytical column, (150 mm x 4.6 mm I. D.). The method had a chromatographic run time of 3.8 min and a linear calibration curve ranging from 0.05 to 10 ng/ml (r2 > 0.997200). The limit of quantification was 0.05 ng/ml. This HPLC-MS/MS procedure was used to assess the bioequivalence of cyproheptadine in two cyproheptadine + cobamamide (4 mg + 1 mg) tablet formulations (Cobactin® [cyproheptadine + cobamamide] test formulation supplied from Zambon Laboratórios Farmacêuticos Ltda and Cobavital® from Solvay Farma (standard reference formulation). A single 4 mg + 1 mg [cyproheptadine + cobamamide] dose of each formulation was administered to healthy volunteers and the study was conducted using an open, randomized, two-period crossover design with a 1-week washout interval. Since the 90% CI for Cmax and AUCs ratios were all within the 80-125% interval proposed by the US Food and Drug Administration, it was concluded that the cyproheptadine test formulation (Cobactin®) is bioequivalent to the Cobavital® for both the rate and the extent of absorption. Thanks to FAPESP for **Financial support**.

11.014

Multi-drug resistance tuberculosis: association between comorbidities, drug resistance and treatment. Santos CBS[1], Pitanga QML[1], Pitta, LB[2], Pinheiro CG[2], Carvalho JSM[2], Carvalho FLDQ[1] [1]UNEB − Ciências da Vida, [2]UNIJORGE − Saúde

Introduction: Tuberculosis is one of the most important bacterial diseases of impact to public health. Even being a serious disease, cure is almost always possible specially in the new cases, if the therapeutic protocol is correctly followed. The irregular treatment is correlated to fails to achieve the cure, and it leads to drugs resistance induction. For these reasons, this work aimed to study the factors associated to the multi-drug resistance onset and its relationship to the socioeconomic aspects, co-morbidities, drug resistance, and the effective treatment of these resistant strains patients (TBMR) in a public reference center to respiratory diseases in Salvador-Bahia, Brazil. **Methods:** This study was based on the data obtained from the medical records of 71 patients with 18 years old minimum hospitalized in the Otávio Mangabeira Reference Hospital (OMRH), the public reference center to respiratory diseases, in the period between 2004 and 2009 with TBMR diagnostic. This study was approved by the Ethics Committee of the Bahia State University (UNEB), protocol n. 0603090088013, as well as by the OMRH Center for Research Pneumology. **Results and Discussion:** The data obtained revealed that most of the TBMR patients were the masculine gender, 40-49 years old of age, HIV negative, low schooling level and the maximum of one salary fee. Most of these patients records informed that they had abandoned previous treatment, 60,2% were alcohol users, 47,9% had consumed tobacco, and 15% had used illicit drugs. Only 5,4% had HIV positive diagnostic. When the reasons for the final of the treatment were evaluated, we observed that death, abandon the treatment or even soliciting to leave the hospital were present in 50% of the HIV positive patients and in 36,3% of illicit drug users. Among all 71 patients, 2,7% developed resistance to one drug; 31,5 % to two drugs; 17,8% resisted to three drugs; 17,8% to four drugs and 13,6% to five or more drugs. It wasn't observed any unfavorable final of treatment to the group of one drug resistant patients, but the highest percentages were observed in the three drug resistance group (38,4%) and in the five or more resistance group (40%). Our data suggest that factors such as HIV seropositive, tobacco or illicit drugs consumption, and abandonment of prior therapy affect in an important manner the development of resistance to treatment, especially in the presence of use of three or more drugs. **Financial support**: FAPESB.

11.015

Specific matrix metalloproteinase-9 (MMP-9) genotype and haplotype in obese children and adolescents. Belo VA[1], Souza-Costa DC[2], Carneiro PC[3], Lanna CM[4], Izidoro-Toledo TC[3], Gerlach RF[5], Tanus-Santos JE[3] [1]UNICAMP − Farmacologia, [2]UFJF − Farmacologia, [3]FMRP-USP − Farmacologia, [4]UFJF − Fisiologia, [5]FORP-USP − Morfologia

Background: Matrix metalloproteinase-9 (MMP-9) has been implicated in the atherosclerotic process and in pathogenesis of cardiovascular risk factors as obesity. Two functional polymorphisms -90 CAn and R279Q of MMP-9 gene have been associated with several diseases. We investigated whether these polymorphisms isolated or combined in haplotypes affect the circulating levels of MMP-9 in obese and healthy children and adolescents. **Methods:** We studied 123 obese children and adolescents and 167 healthy children and adolescents. Genomic DNA was extracted from whole blood and genotypes for -90 CAn and R279Q polymorphisms were determined. MMP-9 levels were measured in plasma samples by ELISA. **Results:** We found no differences in total MMP-9 levels between groups ($p>0.05$). We found no significant difference in the genotype and allelic distribution for the two polymorphisms when obese children and adolescents were compared with control group ($p>0.05$). There was significant influence of MMP-9 genotypes on plasma MMP-9 levels in obese group, we found that the GG genotype was associated with higher plasma MMP-9 concentrations ($p<0.05$). Moreover, we found no significant differences in the distributions of haplotypes frequencies ($p>0.05$). We analyzed the contribution of the different haplotypes on MMP-9 plasma concentrations. Interestingly, we found that the “H A” haplotype in obese group was associated with lower plasma MMP-9 concentrations when compared with “H G” and “L G” haplotypes ($p<0.05$). Conclusion: Our findings showed that the GG genotype was associated to higher MMP-9 plasma levels, however the “H A” haplotype was associated with lower MMP-9 plasma levels in obese group. These findings suggest that genotypes and haplotypes of MMP-9 gene are linked with significant plasma MMP-9 variations in obese children and adolescents and may contribute with higher cardiovascular risk in the obesity.

11.016

Adverse reactions to chemotherapy for breast cancer: influence of clinical and histopathologic variables. Índio-do-Brasil V[1], Telles C[1], Vianna-Jorge R[2], Koifman S[3]
[1]INCa − Farmacologia, [2]UFRJ − Farmacologia Básica e Clínica, [3]ENSP-FIOCRUZ − Saúde Pública e Meio Ambiente

Introduction: The CAF protocol (cyclophosphamide, doxorubicin and 5-fluorouracil) for breast cancer chemotherapy has improved efficacy, with lower risk of recurrence, but causes several adverse drug reactions (ADRs), which can lead to low quality of life, hospitalization for treatment of life-threatening conditions and increased risk of death. The ADRs show great interindividual variability and the search for prognostic factors is a goal towards personalized medicine. The objective of the present work was to characterize the prevalence and the relative risk of ADRs to CAF protocol and to evaluate which clinical and/or histopathologic variables are associated with the occurrence of moderate to severe toxicity. **Methods:** The study population consisted of a prospective cohort of Brazilian women with first diagnosis of unilateral non-metastatic breast cancer with clinical indication for adjuvant chemotherapy. The study protocol (129/08) was approved by the Ethics Committee of INCA and all participants signed a written informed consent. Recruitment was initiated in march/2009 and an active search for 27 possible ADRs was based on interviews, conducted at each chemotherapy cycle, and on consults to medical files. The interview was semi-structured and the ADRs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 2. 0.The prevalence of each ADR was characterized by the frequency of patients with new or increased degree of toxicity after the first cycle of chemotherapy. The relative risk was calculated for each ADR based on the frequency of patients with events of any grade (1 to 4) before and after the first cycle of chemotherapy. The association between ADRs and clinical or histopathological variables was evaluated by the odds ratio (OR) of moderate to severe events (grades 2 to 4) in relation to the absence or to mild events (grades 0 to 1). **Results:** The results involved data from 140 patients (among 442 recruited), who completed the first cycle of the CAF protocol until february/2010.The ADRs with more than 10% prevalence and significantly increased risk associated to the CAF protocol were: alopecia (93.6%; $p < 0.0001$), nausea [57.9%; RR: 16.2 (IC95% 6.77 – 38.76)], constipation [52.9%; RR: 3. 1 (IC95% 2. 07 – 4,58)], fatigue [47. 1%; RR: 22. 0 (IC95% 7. 08 – 68.31)]; anorexia [40.0%; RR: 14. 0 (IC95% 5.22 – 37.56)], muscular weakness [33.6%; RR: 7.8 (IC95% 3.46 – 17.73)], dyspepsia [29.3%; RR: 2.7 (IC95% 1.59 – 4.70)], emesis [23.6%; RR: 11. 0 (IC95% 3,45 – 35,04)], nail change [22. 1%, RR: 3.4 (IC95% 1.70 – 6.97)], neutropenia [20.0%; RR: 9.3 (IC95% 2.90 – 29.99)], abdominal pain [17.9%; RR: 3.6 (IC95% 1.60 – 7.99)], diarrhea (15. 0%, $p < 0.0001$), leucopenia [14.3%; RR: 6.7 (IC95% 2. 03 – 21.93)], prurience [13.6%, RR: 2.4 (IC95% 1. 08 – 5.24)], cystitis [12.9%; RR: 4.5 (IC95% 1.56 – 12.96)]. The only clinical variable apparently associated with the risk of ADRs was the postmenopausal status, which increased the chance of moderate to severe neutropenia in relation to premenopausal women (OR = 3.72; IC95% 1. 11 – 13.71). This increased risk does not seem to be dependent on age, which had no independent effect on the risk of moderate to severe neutropenia (OR = 1. 14; IC95% 0.46 - 2.89). Conclusions: The diversity and high prevalence of ADRs to the CAF protocol is in accordance with literature data. The strategy of active search enabled the determination of the relative risk of the treatment and can be useful to identify clinical variables with prognostic value. Further analyses are warranted to evaluate if the menopausal status can be used as a prognostic factor for neutropenia. **Financial support**: MS/FAF, CNPQ, FAPERJ.

11.017

Evaluation of the toxicity of the ethanolic extract of *Gracilaria ferox* J. Agardh (Gracilariaceae) leaves. Almeida CLF, Falcão HS, Montenegro CA, Lima GRM, Ramirez RRA, Souza MFV, Batista LM LTF-DCF-UFPB

Introdution: *Greville* gender (Gracilariales, Rhodophyta) is a macro algae group with 150 species. The Gracilaria species have high importance for industrial and biotechnological of world economy (KAIN, J. M. ; Journal of Applied Phycology, v.7, p.269, 1995). This gender of algae too is interesting for pharmaceutical industry because show important bioactive metabolites such as the first compound with antibiotic activity, acrylic acid (GLICKMAN, M.; Hidrobiology, v. 151-152, p.31, 1987), and the eicosanoids which are derivate of the metabolizing of C20 polyunsaturated fatty acids by oxidative pathways originate mainly arachidonic acid and eicosapentaenoic acids, precursors of prostaglandins (GLOMBITZA, K. W. ; Hoppe, v. 1, p.303, 1979). The aim of this study was to investigate the toxicity of extracts obtained from leaves of G. ferox (GF-EEtOH). **Methods:** In the study of acute oral toxicity, single dose of 2000 mg/kg was administered GF-EEtOH (1mL/100g) in a group of twelve mices (males and females) after 12 h. The animals that received vehicle (saline 0,9%) served as controls. After treatment, the parameters of behavior were observed, as effects stimulants, depressants, for 30, 60, 90, 120, 180, 240 minutes, 24h, 48h and 72h (ALMEIDA et al. ; Rev. Bras. Science Farmacia, v.80, p.72, 1999). Food and water consumption were evaluated in within 14 days. At the end of the period the number of survivors was recorded to determine the LD50 was estimated body weight of mice, followed the animals were sacrificed and organs (heart, lung, liver, kidney and spleen) were weighed. Macroscopic changes in organs of mice were evaluated. The experimental protocols were approved by the Institutional Committee for Ethics in Animal Research of LTF/UFPB registered under 0608/09. RESULTS AND **DISCUSSION:** When evaluating the weight of organs was not observed any significant change in the control groups of males, the onset (30.62 ± 3.919) at the end (32.76 ± 3.639) of the experiment. Likewise, with females (early: 32. 14 ± 2.985; end: 34. 14 ± 2. 014). In the case of the treated groups did not change in males (early: 30.23 ± 3.925; end: 33. 12 ± 3.535) while for the females was no significant difference in the treated group (32.65 ± 4.612 *) in relation the control (39.55 ± 4. 182). In evaluating the water consumption was not observed any changes in the male control group (10.17 + 1.403) compared to the treated group (9. 054 + 1.610). In the case of females, there was a reduction in water consumption in the treated group (6.518 ± 1.317 ***) compared to control (9. 167 + 1.403). Likewise, occurred with ingestion of feed, which in the case of males showed no significant difference in the treated group (7.635 + 1. 158) compared with controls (7. 163 + 1. 132) and in the case of females, there was some difference between the control (6.518 ± 1.317 ***) and treated (6. 004 + 1. 015 **). In macroscopic bodies, no changes in color, texture, shape and size of organs from treated animals. Given the conditions of evaluation, we concluded that EEtOH ferox G. showed low toxicity. **Financial support**: CAPES/CNPq/LTF/UFPB

11.018

Adverse reactions to chemotherapy for breast cancer and impact of genetic polymorphisms. Martins CL[1], Índio-do-Brasil V[1], Telles C[1], Vianna-Jorge R[2], Koifman S[3] [1]INCa − Farmacologia, [2]UFRJ − Farmacologia Básica e Clínica [3]ENSP-FIOCRUZ – Saúde Pública e Meio Ambiente

Introduction: The current standard chemotherapy protocol for breast cancer consists of 3 cycles of FAC (5-fluorouracil, doxorubicin and cyclophosphamide) followed by 3 cycles of docetaxel alone or in combination with trastuzumab. This protocol has shown benefits in efficacy, with lower risk of recurrence, but did not improve safety, causing several adverse reactions, which can lead to low quality of life, hospitalization for treatment of life-threatening conditions and increased risk of death. The occurrence of adverse reactions shows great interindividual variability and the search for prognostic factors is a goal towards personalized medicine. The objective of the present work was to characterize the incidence of adverse reactions in a Brazilian cohort of breast cancer patients and to evaluate the impact of genetic polymorphisms in drug-metabolizing enzymes or in molecular targets for drug action on the risk of severe toxicity. **Methods:** The study population consisted of a prospective cohort of Brazilian women with first diagnosis of unilateral non-metastatic breast cancer with clinical indication for adjuvant chemotherapy. The study protocol (# 129/08) was approved by the Ethics Committee of INCA and all participants signed a written informed consent. Recruitment was initiated in march/2009 and an active search for adverse reactions was based on interviews, conducted at each chemotherapy cycle, and on consults to medical files. The interview was semi-structured and the adverse reactions were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3. 0.The polymorphisms CYP3A5*3 and ERBB2 Ile655Val were characterized by PCR-RFLP or real time-PCR using DNA from peripheral blood cells. The incidence of adverse reactions was characterized by the number of events of any toxicity (grades 1 to 4) in relation to the total number of valid observations. The impact of polymorphisms on the risk of severe adverse reactions was evaluated by the odds ratio (OR) of severe events (grades 3 or 4) in relation to the absence or to mild or moderate events (grades 0 to 2). **Results:** The results involved data from 140 patients (among 442 recruited), who completed the first cycle of chemotherapy with FAC until february/2010, consisting of 4411 observations. Among these 140 patients, 70 also completed the first cycle of docetaxel (8 of which used trastuzumab), leading to 2146 observations. The global incidence of adverse events at any degree was 20% (95%CI = 19%–21%) for FAC and 32% (95%CI = 30%–34%), for docetaxel/trastuzumab, and the global incidence of severe adverse reactions was 3% (95%CI = 2,5%–5,0%) for FAC and 6% (95%CI = 5,0%–7,0%) for docetaxel/trastuzumab, indicating that docetaxel/trastuzumab is more toxic than FAC (Pearson P < 0.0001). The polymorphisms CYP3A5*3 and ERBB2 Ile655Val did not affect the global incidence of adverse reactions at any degree for either protocol, but ERBB2 Ile655Val increased the risk of severe adverse reactions with docetaxel/trastuzumab (OR = 1.76, 95%CI = 1. 05–2.92). Conclusion: Preliminary results suggest that polymorphism ERBB2 Ile655Val might be useful as a prognostic factor of severe toxicity to docetaxel/trastuzumab. **Financial support**: MS/FAF, CNPQ, FAPERJ.

11.019

Pre-clinical pharmacokinetic study of LASSBio-468: a new achiral thalidomide analogue. Kaiser M[1], Haas SE[2], Azeredo FJ[2], Torres B[2], Brum Junior L[2], Uchôa FDT[1], Contri, RV[2], Lima LM[3], Barreiro EJ[3], Dalla Costa T[2] [1]UFRGS − Medicamentos, [2]UFRGS − Ciências Farmacêuticas, [3]UFRJ − LASSBio

Introduction: Acute respiratory distress syndrome is characterized by inflammation of the lung parenchyma leading to increased pulmonary arterial pressure, reduction of the ratio of arterial oxygen pressure and concomitant systemic release of inflammatory mediators1. Thalidomide has been used to treat different inflammatory diseases, showing reduction of the expression and half-life of the TNF-a, a primary cytokine mediator of inflammation. However, because of the serious adverse effects reported to the use of this drug, new strategies are being developed using thalidomide as prototype for the design of new compounds with greater anti-TNF-a selective activity and less toxicity2. LASSBio-468, a synthetic compound without any chiral center, is an important cytokine inhibitor with attractive immunopharmacological profile. This new lead compound, active in TNF-a production and NO down modulation represents a new non-terathogenic candidate to be used in the in therapy of TNF-a-associated diseases such as rheumatoid arthritis, Crohn´s disease and septic shock syndrome3. In this context, this study aimed to investigate the pre-clinical pharmacokinetics (PK) of LASSBio-468 in rodents. **Methods:** PK studies were approved by UFRGS Ethics in Research Committee (2007794). LASSBio-468 was administered intravenously (i. v.) and intraperitoneally (i. p) to Wistar rats (250-350 g) at 10 mg/kg (6 mg/mL) and 50 mg/kg (30 mg/mL) doses respectively, as a drug suspension prepared with 1% Tween® 80 and 10% DMSO in saline solution (n = 8/group). Blood samples were collected from the lateral tail vein at pre-determined time points and plasma samples were frozen for posterior drug quantification by HPLC-UV method previously validated. PK parameters were determined using non-compartmental (Excel®) and compartmental (Scientist®) analysis. Pharmacokinetic parameters were compared by ANOVA (a = 0.05). **Results and Discussion:** LASSBio-468 presented three different slopes after i. v. dosing, characteristic of the three-compartment model. The mean distribution rate micro-constants k12 (11.6 ± 1.9 h-1) and k13 (7.5 ± 1.8 h-1) after i. v. administration suggest a high and broad biodistribution among different tissues of the shallow and deep peripheral compartments which is corroborated by the high volume of distribution of the prototype (7.3 ± 3.5 L/kg). The total clearance determined was 3.3 ± 0.8 L/h/kg and a half-life of 3.6 ± 0.5. The bioavailability after i. p. dose was 15% and the pharmacokinetic profile was adequately modeled by one-compartment open model. After LASSBio-468 i. p. dosing, peak plasma concentration of 0.33 ± 0.08 µg/mL was observed at 1.5 ± 0.6 h. Comparing the pharmacokinetic results between modeled i. v. and i. p. routes, there was no statistically significant differences between the evaluated parameters, except for a smaller area under the curve (AUC0-∞) and a greater mean residence time (MRT) after i. p. dosing ($p < 0.05$). Conclusion: LASSBio-468 shows a large biodistribution, a short half-life and a small i. p. bioavailability. The PK of other routes of administration is under investigation. References: 1WHO, 2004.2Lima, L. M. , Bio. & Med. Chem. , 10: 3067, 2002.3Alexandre-Moreira, M. S. , Inter. Immuno.5: 485, 2005 **Acknowledgments: Financial support** from INCT-INOFAR/CNPq (Project 383195/2009-8)

11.020

Assessment of the pharmaceutical equivalence of captopril and propranolol hydrochloride tablets sold in the popular pharmacy program in Brazil. Pontes AV, Pimenta Costa CS, Nascimento DF, Leite ALAS, Capistrano Júnior VL, Rocha MBS, Moraes RA, Frota Bezerra FA, Moraes MEA, Moraes MO UFC − Fisiologia e Farmacologia

Introduction: The pharmaceutical equivalence between two medicines is based on the confirmation that both contain the same active drug on the same dosage and dosage form, which is assessed by in vitro tests. In Brazil, the National Health Surveillance Agency defines that allopathic medicines can be registered in three categories: innovator, generic and similar drugs. The actual legislation determines that to register new generic and similar medicines it is necessary to prove its pharmaceutical equivalence and bioequivalence with a reference drug. Products registered before 2003 have until 2014 to present these equivalence results. The Popular Pharmacy Program in Brazil is a new strategy of pharmaceutical assistance of the Health System with the purpose to facilitate the population's access to medicines considered basic and essential, lowering the price impact of these medicines in the family budgets. The objective of this study was to assess the pharmaceutical equivalence of captopril 25 mg and propranolol hydrochloride 40 mg tablets sold in the Popular Pharmacy Program in Brazil, comparing them to a reference and generic drug, debating the importance of the quality of drugs for the public health. **Methods:** Physical and physicochemical tests such as identification, weight variation, disintegration, hardness, friability, purity, dosage, content uniformity, and dissolution profile, were performed according to the Brazilian Pharmacopeia 4th edition. The dissolution profiles were compared by the Dissolution Efficiency (DE) method. The research project and the experimental protocol were submitted to the Research Ethics Committee of the Federal University of Ceará, which approved the protocol of nº 116/10. **Results and Discussion:** The results showed a low hardness of propranolol hydrochloride tablets originated from the Popular Pharmacy Program. The dissolution profiles analyzed by analysis of variance (ANOVA) and Tukey test demonstrated significant differences between the dissolution profiles of both drugs originated from the Popular Pharmacy Program and their respective reference and generic drugs ($p<0,001$). The extension of the active drug dissolved from the Popular Pharmacy medicine was significantly lower than the dissolution from the reference and generic drugs ($P < 0,001$) for both captopril and propranolol hydrochloride. Even though captopril would fulfill the requirements of the National Health Surveillance Agency to be considered equivalent, it was not approved on the dissolution efficiency test. Therefore, the assessed tablets originated from the Popular Pharmacy Program in Brazil were not considered pharmaceutical equivalents when compared to their respective reference and generic drugs. **FINANCIAL SUPPORT**: CNPq, CAPES, FUNCAP, FINEP, MS-RNPC-UNIFAC-HM, Instituto Claude Bernard.

11.021

Reduction of nitric oxide levels after intervention with sitagliptin in type 2 diabetic patients. Capistrano Júnior VL[1], Tagliapietra JI[1], Oliveira JC[1], Pimenta Costa CS[1], Souza MHLP[1], Montenegro Jr RM[2], Leite ALAS[1], Frota Bezerra FA[1], Vale OC[1], Moraes MEA[1] [1]UFC − Fisiologia e Farmacologia, [2]HU-UFC − Endocrinologia e Metabologia

Introduction: Nitric oxide (NO) is synthesized in endothelial cells from the amino acid L-arginine by the action of an enzyme called nitric oxide synthase (NOS), which is presented in three forms: neuronal nitric oxide synthase (nNOS), constitutive and present in neurons and pancreatic β cells; induced nitric oxide synthase (iNOS), stimulated by cytokines and lipopolysaccharide in the endothelium and vascular smooth muscle; and endothelial nitric oxide synthase (eNOS), a constitutive NOS that produces NO in the vascular endothelium under basal conditions. NO is considered a potent vasodilator and has been implicated in the pathophysiology of type 2 diabetes mellitus (T2DM). Hyperglycemia contributes to arterial wall stress and to an increase in the endothelial dysfunction. However, the production of NO in T2DM, especially in the vascular endothelium, has been generating controversial results. Endothelial dysfunction has been associated with a decrease in NO production, reducing vasodilation, and with an increase in its production, followed by its neutralization by superoxide and by iNOS stimulation. Studies have shown a decrease in NO levels in diabetics treated with sulfonylurea and reduced levels of eNOS and iNOS with pioglitazone. The aim of this study was to analyze the levels of NO before and after an intervention with sitagliptin. **Methods:** Interventional, prospective and open study with 41 recently diagnosed (< 6 months) T2DM patients, who were submitted to anthropometric, blood pressure (BP) and metabolic evaluations, including the dosage of NO, before and after the use of sitagliptin 100 mg/day, for a period of three months. The research project, the experimental protocol and the term of free and informed consent were submitted to the Research Ethics Committee of the Federal University of Ceará, which approved the protocol of nº 189/07. RESULTS AND **DISCUSSION:** Among the evaluated patients, 28 were women and 13 men, mean age was of 53.2 ± 9.43 years, 100% were obese, 100% had dyslipidemia and 50% were hypertensive. After treatment, there was an improvement in anthropometric indices, BP and all laboratory parameters with emphasis on fasting glucose (pre: 174.43 ± 67. 18 and post: 129. 07 ± 29. 19 mg / dL), A1c (pre: 8.76 ± 2.68 and post: 6.64 ± 1. 11%) and NO (pre: 85.21 ± 44. 02 and post: 39.91 ± 20.99 mM) all P <0.0001. The results suggest that the initial increase of NO could be an effort to compensate for its possible inactivation through reactive oxygen species reaction, which would be increased because of the effect of oxidative stress and changes of inflammatory cytokines that may have stimulated the iNOS activity. Intervention with sitagliptin, even for a short period, promoted a metabolic control in these patients, with an improvement of the pro-inflammatory status, which probably brought an impact on the enzyme activity and reduced the levels of NO. **Financial support**: CNPq, CAPES, FUNCAP, FINEP, MS-RNPC-UNIFAC-HM, Instituto Claude Bernard.

11.022

Learning and teaching pharmacology: a case study in Rio de Janeiro, Brazil. Fidalgo-Neto AA, Lopes RM, Alves LA IOC-FIOCRUZ − Comunicação Celular

Introduction: Medical students are expected to learn a significant amount of information in their graduation. Since the understanding of pharmacology and pharmacotherapeutics demands the knowledge of nearly 20,000 currently utilized therapeutic agents (3), its inclusion in medical curriculum increases the quantity of information needed to apprehend. In addition, pharmacology is more than a distinct subject in medical education, it is capable to integrate basic and clinical sciences. Unfortunately, to teach basic pharmacological concepts is an arduous process, and many students find it difficult to relate it to practice and clinical experience (4). The literature has pointed out the need to review teaching practices at pharmacology education (5,6,7,8,9). In addition, clinical errors have become a huge global problem (10), with a significant number of these errors concerning to usage of drugs. This study aimed to describe nowadays pharmacology education practices in Rio de Janeiro states' Medical schools and their educational strategies. **Methods:** All medical schools in Rio de Janeiro were invited to participate. Fourteen pharmacology teachers filled out a structured survey with four sets of questions allowing the analysis of: 1. Staff characteristics, 2. Pharmacology content/general organization, 3. Teacher's perceptions and concepts 4. Common practices/resources used by each medical school. **Results:** Our results showed the numbers of teachers with higher qualification were not equally distributed among the schools and only a few of them also research as well as teaching. The overall curricula compositions of the fourteen medical schools were similar. In regard to practices and resources, we found out that the most common pedagogical resource used was the multimedia projector. In addition, the medical schools' libraries do not provide enough textbooks. Conclusion: In general, the Brazilian common practices involving teaching and learning pharmacology could be improved. More active pedagogical strategies as well as use of technological resources could to be implemented in order to adequacy teaching medical global demands. **References**: 1. Scheindlin, S. Modern Drug Discovery4:87(2001) 2. Sousa, A. T. (1981) 3. Franson, K. L. et al. J. Vis. Commun. Med.30:156(2007) 4. Lymn, Joanne et al. BMC Nursing7:2(2008) 5. British Pharmacological Society et al. Trends Pharmacol. Sci27:130(2006) 6. Kwan, Chiu YinNaunyn-Schmiedeberg´s Archives of Pharmacology366:10(2002) 7. Faingold, C. L. et al. Naunyn Schmiedebergs Arch. Pharmacol.366:18(2002) 8. Kwan, C. Y. Acta Pharmacol. Sin.25:1186(2004) 9. Hughes, I. Nippon Yakurigaku Zasshi122:411(2003) 10.Wheeler, S. J. et al. Anaesthesia60:257(2005) Funding: IOC-FIOCRUZ. Ethical approval: 044/2009 (IPEC-FIOCRUZ)

11.023

Plasma levels of matrix metalloproteinases -8 and -9 and their endogenous inhibitors TIMP-1 and TIMP-2 in untreated hypertensive patients. Fontana V[1], Silva PS[2], Belo VA[2], Biagi C[3], Tanus-Santos JE[1] [1]FMRP-USP − Farmacologia, [2]FCM-UNICAMP − Farmacologia, [3]Santa Casa de Araçatuba − Cardiologia

Introduction: Hypertension is a chronic disease that affects 1 billion individuals in the world, and is responsible for 7 million deaths per year[1]. The vascular remodeling in hypertension entails changes in vessels structure, that contribute to cardiovascular complications of hypertension[2]. Matrix metalloproteinases (MMPs) are zinc-dependent proteolytic enzymes that degrade extracellular matrix proteins[3]. An imbalance between MMPs and their endogenous inhibitors, the tissue inhibitors of MMPs (TIMPs), has been implicated in the pathological changes in the vessel wall[3]. The aim of this study was to evaluate plasma levels of MMP-8, MMP-9, TIMP-1 and TIMP-2 in stage I or II untreated hypertensive patients. **Methods:** Approval for the use of human subjects was obtained from the institutional review board at the Faculty of Medicine of Ribeirão Preto, University of São Paulo (nº 9237/2009), and subjects gave informed consent. We determined the plasma levels of the MMP-9 92KDa by gelatin zymography (22 normotensive individuals and 29 untreated hypertensive patients) and MMP-8, MMP-9, TIMP-1 and TIMP-2 by ELISA (12 normotensive individuals and 12 untreated hypertensive patients). **Results:** Plasma MMP-9 activity, measured by gel zymography, reveals no significant difference between normotensive (0.69±0.10 arbitrary units) and hypertensive patients (0.96±0.11 arbitrary units) (p=0,10). In the ELISA assays, we found no significant difference between the groups in MMP-9 levels (62,2±4,2 ng/mL in normotensive; 80,3±10,4 ng/mL in hypertensive group; p=0,12); MMP-8 levels (367,9±64,2 ng/mL in normotensive; 559,9±129,5 ng/mL in hypertensive group; p=0,31); TIMP-1 levels (334,3±13,2 ng/mL in normotensive; 358,2±11,7 ng/mL in hypertensive group; p=0,19), neither TIMP-2 levels (187,6±7,2 ng/mL in normotensive; 181,9±16,7 ng/mL in hypertensive group; p=0,76). **Discussion:** No differences in MMPs and TIMPs plasma levels in hypertensive and normotensive individuals was observed in this preliminary study. Further analysis are going on, including larger number of patients, to corroborate our results and clarify the role of MMPs and TIMPs in hypertension. References: 1. Chobanian AV, Hypertension 42, 1206, 2003.2. Intengan HD, Hypertension 38, 581, 2001.3. Raffetto JD, Biochem Pharmacol 75, 346, 2008. Supported by: CAPES,CNPQ and FAPESP.

11.024

Efficacy and safety of the *Mentha crispa* in the treatment of trichomonas infections: a randomized, open and parallel study. Pimenta Costa CS, Cavalcanti PP, Cunha GH, Pontes AV, Fechine FV, Oliveira JC, Andrade WS, Moraes RA, Camarão GC, Moraes MEA UFC − Fisiologia e Farmacologia

Introduction: *Trichomonas vaginalis* is a flagellate protozoan that infects the urogenital tract of men and women. According to WHO estimatives, in 2005, the global incidence of cases of trichomonas infections were approximately 250 millions, being 24.5 millions of these cases in Europe. The *Mentha crispa* (Lamiaceae) is a hybrid plant originating from the cross between *Mentha spicata* L. and *Mentha suaveolens* Ehrh. The leaves and stems of *Mentha crispa* are widely used in traditional medicine for its antiparasitics property. The aim of the present study was to investigate the therapeutic efficacy and safety of the *Mentha crispa* in the treatment of trichomonas infections. The *Mentha crispa* has been widely used as antiparasitic but its efficacy has yet to be proven in humans with *Trichomonas vaginalis*. **Methods:** Randomized, open and parallel clinical trial performed in the Unit of Clinical Pharmacology, Ceara, Brazil. The study consisted of three phases, pre-treatment, treatment and post-treatment. There were two treatment groups, *Mentha crispa* (24 mg) and Secnidazole (2000 mg), both in the formulation of tablets and in single dose. Primary endpoint for the evaluation of the effectiveness of *Mentha crispa* was absence of the protozoan (*Trichomonas vaginalis*) in vaginal fluid by diagnostic test. Secondary endpoints were the improvement of clinical complaints: vaginal discharge, unpleasant odor, genital burning, dysuria, dyspareunia, pelvic pain and itching. The research project, the experimental protocol and the term of free and informed consent were submitted to the Research Ethics Committee of the Federal University of Ceara, which approved the protocol of nº 267/08. **Results and Discussion:** Of the 77 patients with trichomonas infections initially evaluated, only 60 met the inclusion criteria, all of them were female. Thirty patients were randomized to receive *Mentha crispa* and 30 to receive Secnidazole. In the pre-treatment, *Mentha crispa* and Secnidazole groups showed statistically similar in age, body mass index, diastolic and systolic blood pressure. After treatment the proportion of patients without *Trichomonas vaginalis* in secnidazole group was 96.67% and in the *Mentha crispa* group was 90.00%, no difference was found between groups (P = 0.6120). There was improvement of vaginal discharge, unpleasant odor, genital burning, dysuria, dyspareunia, pelvic pain and itching in the patients of the two groups of treatment, without statistically significant difference between them (P = 0, 4583). Adverse effects were significantly higher (P = 0.0006) in the Secnidazole group (66.67%) that in the *Mentha crispa* group (20.00%), occurring mainly nausea and metallic taste with statistically significant difference between the treatment groups (P <0.001). No signs of toxicity were observed during treatment. This study concluded that *Mentha crispa* is effective and safe when used orally at a single dose of 24mg, representing an alternative for treatment in patients with trichomonas infections. **Financial support**: CNPq, CAPES, FUNCAP, FINEP, MS-RNPC-UNIFAC-HM, Instituto Claude Bernard.

11.025

Effects of sitagliptin on visual alterations diagnosed by visual evoked potential in type 2 diabetic patients. Capistrano Júnior, VL[1], Tagliapietra JI[1], Pontes AV[1], Cunha GH[1], Rocha MBS.[1], Frota Bezerra FA[1], Vale OC[1], Fernandes VO[2], Montenegro Jr RM[2], Moraes MEA[1] [1]UFC − Fisiologia e Farmacologia, [2]HU-UFC − Endocrinologia e Diabetes, [4]HU-UFC − Endocrinologia e Metabologia

Introduction: In diabetes mellitus (DM), visual impairment seems to result from vascular disease and metabolic alterations. Thus, the visual impairment is not restricted to the retina, it can also affect the optic nerve and visual pathway, as in the ischemic optic neuropathy. The visual evoked potential (VEP) is able to detect pathologies involving the optical pathways and visual cortex and so can be used as a complementary diagnostic method for subclinical diabetic retinopathy and in the evaluation of other visual nerve conduction pathways, and can be directly or indirectly related to changes in glycemic control. The aim of this study was to evaluate the effect of metabolic control in the results of VEP exams in patients with type 2 diabetes mellitus (T2DM) before and after treatment with sitagliptin. **Methods:** Interventional, prospective and open study with asymptomatic and recently diagnosed (< 6 months) T2DM patients, who were submitted to physical, metabolic fasting evaluations and also after a feeding stimulus of 566 kcal. Sequential blood samples were collected during three hours for glucose, insulin and glucagon, active GLP-1 and total GIP and VEP was also evaluated. After these assessments, patients received sitagliptin 100 mg/day for three months, followed by the completion of the same protocol after this period. The research project, the experimental protocol and the term of free and informed consent were submitted to the Research Ethics Committee of the Federal University of Ceara, which approved the protocol of nº 189/07. RESULTS AND **DISCUSSION:** 20 patients were evaluated: 68.29% were women. Over 60% had between 41-60 years old (53.24 + 9.43 years), no significant differences in ages between genders (P = 0.356). 51.22% of the patients were hypertensive. 100% were obese. After treatment, an improvement was observed in all anthropometric and laboratory parameters, specially fasting glucose (pre: 174.43 ± 67. 18 mg/dL and post: 129. 07 ± 29. 19 mg/dL) and A1c (pre: 8.76 ± 2.68 and post: 6.64 ± 1. 11%), all with P <0.0001. Also, there was an increase in the concentration of the AUC of active GLP-1 (P = 0.003), a decrease of the AUC of total GIP (P = 0.001). It was verified that there were changes in latencies of VEP in the pre-treatment when compared to reference values of the laboratory. Comparing the exams pre and post-treatment, we observed a reduction of latencies of N75, P100 and N120 at the end of the study and statistically significant correlations between biochemical and electroneurophysiological parameters (fasting C-peptide (p = 0.008), total cholesterol (p = 0.045), AST (p = 0.010), A1C (p = 0.007)). In conclusion, there was clinical, metabolic and visual nerve conduction pathways improvement in patients treated with sitagliptin. **FINANCIAL SUPPORT**: CNPq, CAPES, FUNCAP, FINEP, MS-RNPC-UNIFAC-HM, Instituto Claude Bernard.

11.026

NAT2, GSTT1 and GSTM1 genotypes and predisposition to adverse drug reaction (ADR) in tuberculosis patients. Costa GNO[1], Santana CVN[2], Konstantinovas C[1], Magno LA[3], Bastos-Rodrigues L[3], Miranda DM[4], Romano-Silva M[3], Marco LAC[5], Di Pietro G[1], Rios-Santos F[1] [1]LAFEM-UESC − Ciências da Saúde, [2]LAFEM-UESC − Ciências Biológicas, [3]UFMG − Saúde Mental, [4]UFMG − Pediatria, [5]UFMG − Cirurgia

Introduction: Genetically determined differences in metabolism capacity have proved to be important determinants of both the effectiveness of therapeutic response and the development of adverse drug reactions and toxicity during drug treatment. In this regard, tuberculosis treatment is long and requires the use of multidrug therapy that lasts from six months to a year. Isoniazid (INH) represented a breakthrough in the treatment of tuberculosis due to its power of lethality under the M. tuberculosis, low cost and effectiveness at low concentrations, when compared to others drugs. But it is a drug liable to many adverse reactions, which are related to the metabolites generated in its metabolic pathway. In this study we investigated the influence of NAT2 and GSTs enzymes in adverse drugs reaction in INH-treated patients with tuberculosis. **Methods:** Interview, written informed consent and review of medical records were obtained from each patient included in this study (CEP 098/2007). A total of 129 Brazilian patients with tuberculosis were included in the study. The NAT2 gene was analyzed by direct sequencing and the GSTT1 and GSTM1 genes by multiplex-PCR. The acetylator phenotype was confirmed by INH determination by HPLC and Cmax measurements based on random samples. ADRs were investigated by clinical follow up and complementary laboratory exams. Differences in allele, genotype, haplotype, and haplotype combination distribution between the groups were examined by qui-square test. The results obtained were analyzed through the univariate analysis and multiple logistic regression using SPSS v. 10.Determination of NAT2 acetylation phenotype from genotype data was performed by NAT2PRED software. Phenotypes status were compared with GraphPad Prism software. **Results and Discussion:** No hepatotoxicity was detected by measuring levels of transaminases and bilirubin, but there were a significant increase in transaminases after 30 days of treatment. The females were more susceptible to ADRs, as well as maintaining the smoking habit during early treatment. Gastrointestinal disorders (38. 1%) were the more frequent ADRs. Regarding the acetylation phenotype, we found significant differences between fast and slow acetylators (p-value = 0.039). No association between GSTT1 and GSTM1 genotypes and ADRs was found. The most frequent NAT2 genotype was NAT2*5/*5 (20.9%), which contributed with 37.6% of alleles. There was association between slow acetylators and ADRs occurrence (OR = 2.7, CI 95%, p-value = 0.03), even after multivariate analysis. In conclusion, slow acetylator genotype for NAT2 was a significant susceptibility risk factor for antituberculosis ADRs. **Financial support**: FAPESB, CAPES, UESC and INCT de Medicina Molecular.

11.027

Sulfadiazine determination in human plasma by high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC-MS-MS): application to pharmacokinetic study. Nascimento DF, Oliveira JC, Pimenta Costa CS, Rocha MBS., Moraes RA, Cunha GH, Magalhães MS, Uchoa CRA, Moraes MO, Moraes MEA UFC − Fisiologia e Farmacologia

Introduction: Sulfadiazine inhibits the enzyme dihydrofolic acid synthetase (DHF) which is required for synthesis of tetrahydrofolic acid (THF), purines and DNA. The aim of the present study was to develop and validate a liquid chromatography (LC) method for the determination of sulfadiazine in human plasma supporting a pharmacokinetic and bioequivalence study. **Methods:** Sulfadiazine and sulfamethoxazole (internal standard) were extracted from plasma by protein precipitation using acetonitrile as solvent and separated on a Genesis C18 (100 x 2. 1mm) maintained at 35 ºC, with methanol: water (35:65 v/v) + 0.5% Formic acid as mobile phase. The flow rate was 250 µL/min and the detection was carried out by mass spectrometry. The bioequivalence study was an open, randomized, two period crossover design with a one week washout interval between the doses. Twenty four healthy volunteers aged between 18 and 50 years and within mass body index between 19 and 30 were selected by clinical evaluation and laboratory tests. The clinical protocol was approved by the local Ethic Committee (Protocol n° 156/08) and the volunteers given written informed agreement to participate in the study. During each period, a single oral dose of sulfadiazine (1 tablet-500 mg) was given after an overnight fast of at least 10 hours, and the blood samples were collected up to 48 hours post dosing. **Results and Discussion:** The method validation investigated the parameters recommended for the bioanalytical methods and yielded good results with limit of quantification of 0.05µg/mL. The chromatographic separation was obtained within 3 min, and the response was linear in the concentration range of 0.05-25 µg/mL (r2= 0.9999). The mean extraction recoveries were 88% for sulfadiazine and 92% for sulfamethoxazole. The intra-day precision for the quality controls low (QCL), middle (QCM) and high (QCH) were respectively 2. 1, 1.5 and 1.7%. The inter-day precision for QCL, QCM and QCH were respectively: 7.2% and 5. 0 and 6.3%. The intra-day accuracy for QCL, QCM and QCH were103.9, 101. 0 and 101.4% respectively. The results of the inter-day accuracy QCL, QCM and QCH were respectively and 103.8, 101.4, 95.9% respectively. The proposed method was successfully applied for the bioequivalence study of two tablet formulations (test and reference) of sulfadiazine 500 mg after single oral dose administration to 24 healthy volunteers. The geometric means ratios of Cmax, AUC(0-t) and AUC(0-inf) were 94.96, 95.93 and 98.49% with 90% confidence intervals of 88. 01–102.45%, 91.44-100.65% and 91. 53-105.97% respectively. Since the 90% CI for Cmax, AUC(0-t) and AUC(0-inf) were within 80-125% interval proposed by ANVISA and FDA, it was concluded that the two formulations of sulfadiazine were bioequivalents, according to rate and extent of absorption. **Financial support**: CNPq, InCB, MS-RNPC-UNIFAC-HM, FINEP.

11.028

Susceptible NOS3 (endothelial nitric oxide synthase) gene haplotypes in hypertension and resistant hypertension. Luizon MR[1], Sandrim VC[2], Izidoro-Toledo TC[1], Coelho EB[3], Tanus-Santos JE[1] [1]FMRP-USP − Farmacologia, [2]Santa Casa de Belo Horizonte, [3]FMRP-USP − Clínica Médica

Introduction: Haplotypes, i. e. combinations of genetic polymorphisms, in the endothelial nitric oxide synthase (NOS3) gene have been previously associated with hypertension (Sandrim et al. Atherosclerosis 186(2):428, 2006). These haplotypes were formed by two functional SNPs (T-786C in the promoter region-rs2070744, and Glu298Asp in exon 7-rs1799983-G/T) and a variable number of tandem repeats in intron 4 (b/a). However, polymorphisms not previously investigated at NOS3 gene may contribute to the associations reported. Here we have evaluated the association of extended NOS3 haplotypes with hypertension and resistant hypertension. **Methods:** Our case-control study was approved by the Ethics Research Committee of FMRP/USP (HCRP no. 11760/2007). The four tagging SNPs (rs3918226-C/T, rs3918188-A/C, rs743506-A/G, and rs7830-A/C) were selected according to the SeattleSNPs GVS database (Minor Allele Frequency, MAF > 0.10) in order to capture the majority (> 60%) of variability across the whole NOS3 gene, including the promoter, coding region, and 5´ and 3´ untranslated regions. Hypertensives (81 whites and 53 blacks) and normotensives (83 whites and 43 blacks) were evaluated, as well as 33 patients with resistant hypertension. Since significant interethnic differences exist in the distribution of NOS3 polymorphisms (Marroni et al. Nitric Oxide 12(3):177, 2005; Luizon et al. DNA Cell Biol.28(7):329, 2009) we first carried an analysis including black and white individuals, and then another one that took into consideration only white individuals (63% of the whole sample). Haplotype frequencies were estimated by the Haplo. stats package. The function haplo. score was used to compute haplotype-specific score statistics to test for association (Schaid et al. Am J Hum Genet.70(2):425, 2002), with the value of $P < 0.05$ to be statistically significant. **Results and Discussion:** The haplotype "CCbGCGA" was more common in normotensives than hypertensives, both when considered the whole sample (3% vs. zero, respectively; p=0.05) and only white individuals (6% vs. zero, respectively; p=0.007). In addition, the haplotype "TCbGAGC" was more commonly found in the whole sample of hypertensives than in the normotensives (8% vs. zero, respectively; p=0.02). Interestingly, the same haplotype was more common in white hypertensives than in white normotensives, and in the group of resistant hypertension than in hypertensives, but these comparative frequencies were found to lack statistical significance. These results suggest one eNOS haplotype associated with a protective effect against hypertension despite of the ethnic label, and one eNOS haplotype conferring susceptibility to hypertension. **Financial Agency**: FAPESP (BP. PD 2007/55908-6)

11.030

New educational strategies to improve pharmacology teaching: a interdisciplinary approach. Fidalgo-Neto AA, Lopes RM, Alves LA[2] IOC-FIOCRUZ Laboratório de Comunicação Celular

Introduction: The primary objective in learning pharmacology in the biological and health curriculum would be to motivate students to learn the general pharmacological and therapeutic principles for effective management of diseases(1). In addition, pharmacology is an interdisciplinary subject, able to integrate basic and clinical sciences. Unfortunately, to teach pharmacological basic concepts is an arduous process and many students find it difficult to correlate it to practice and clinical experience (2). The literature has pointed out the need to review teaching practices at pharmacology education (3,1,4,5,6). As the development of biomedical technology is advancing with unprecedented speed, teaching and learning of pharmacological sciences in the medical curriculum would need a novel, effective and holistic approach to motivate students to reach the essential objectives of subject. This study aimed to use educational pharmacology software to teach specific contents of pharmacology curriculum and then evaluate the student performance. Method: Eighty students, all of biological and health areas, at the end of their courses perform a test with questions covering drug absorption, drug membrane transport, pK concept and related issues. At the end of the test, the students were divided in 3 groups and participated of a lecture using the Drug Absorption Module of Pharmavirtua software (creative_commons_licensed) with 3 different pharmacology professors. At the end of this new step, the students performed the same test and their performances were compared before and after of the use of the software. Furthermore, the students responded a survey to evaluate the quality perception and other organizational characteristics of the software, different of the specific test content performed. The grades were statistically analyzed by paired t test ($p<0.05$) performed using GraphPadPrism v5. 00 **Results:** All students' evaluation was positive in regard to design, learning motivation and general organization and content of the software. In addition, the students' grades showed a consistent trend of improvement. The overall dispersion of the data (before and after) showed a significant decrease. Despite of the absolute grades were low, we could demonstrate a slight improvement in overall grades. The test performed before the use of the software showed a grade (mean ± SD) of 4.58±1.80 and that obtained after the use of the software (mean ± SD) was 5.27±1.55 ($p<0.001$). Conclusion: In general, the literature shows no improvement in overall students' performance, when software or other informational technologies are used (7,8,9). However, our data suggest that there is a slight improvement in overall grades as well as the potential contribution related to motivational aspects of learning when lectures were performed using the Pharmavirtua Software. **References**: 1. Kwan, Chiu YinNaunyn-Schmiedeberg´s Archives of Pharmacology366:10(2002) 2. Lymn, Joanne et al. BMC Nursing7:2(2008) 3. British Pharmacological Society et al. Trends Pharmacol. Sci27:130(2006) 4. Faingold, C. L. et al. Naunyn Schmiedebergs Arch. Pharmacol.366:18(2002) 5. Kwan, C. Y. Acta Pharmacol. Sin.25:1186(2004) 6. Hughes, I. Nippon Yakurigaku Zasshi122:411(2003) 7. Davis, J. et al. BMC. Med Educ7:23(2007) 8. Dagdilelis, Vassilios et al. Computers & Education40:307(2003) 9. Dwyer, Tom et al. Educ. Soc. Campinas 28:1303(2007) **Funding**: IOC-FIOCRUZ. Ethical approval: 044/2009 (IPEC-FIOCRUZ)

11.031

Interference of matrix metalloproteinase (MMP)-9 genotypes and haplotypes in the responsiveness to antihypertensive therapy of patients with preeclampsia or gestational hypertension. Palei ACT[1], Sandrim VC[2], Cavalli RC[3], Gerlach RF[4], Tanus-Santos JE[5] [1]FCM − UNICAMP − Farmacologia, [2]Santa Casa de Belo Horizonte − Farmacologia, [3]FMRP-USP − Ginecologia e Obstetrícia, [4]FORP-USP − Morfologia, [5]FMRP-USP − Farmacologia

Introduction: Matrix Metalloproteinases (MMPs) are endopeptidases that break down extracellular matrix macromolecules. Several members of this enzyme family, especially MMP-9, are present at the fetal-maternal interface and an imbalance in MMPs levels may affect placentation. Some studies have shown that a microsatellite (CA repeats)13-25 and a single nucleotide polymorphism (SNP: C-1562T) localized in the promoter region of MMP-9 gene can alter gene expression and consequently MMP-9 activity. We have found that C-1562T polymorphism is associated only with gestational hypertension. Now we examined whether MMP-9 polymorphisms affect the therapeutic responses of women with gestational hypertension (GH) or preeclampsia (PE). **Methods:** We studied 146 pregnants with GH (blood pressure ≥ 140/90 mmHg after 20 weeks of gestation) and 158 pregnants with PE (hypertension gestational plus proteinuria > 0.3 g/L in 24 h), who were stratified as responsive or nonresponsive to antihypertensive therapy defined as: methyldopa 1000-1500 mg/day followed by nifedipine 40-60 mg/day and/or hydralazine 5-30 mg/day, which were added in case of lack of response to methyldopa, according to clinical and laboratorial parameters of therapeutic responsiveness. Genomic DNA was extracted from whole blood and genotyping for CAn and C-1562T polymorphisms were done by polymerase chain reaction without and with restriction (PCR-RFLP), respectively. Haplotypes frequencies were inferred using the program PHASE version 2. This study was approved by the local Ethics Review Board (CEP HCRP n° 4682/2006). **Results:** Alleles for the CAn polymorphism were grouped as 14 or lower CA repeats (L) and 21 or higher CA repeats (H). The genotype and allele frequencies were not different in responsive and nonresponsive GH patients (58% H and 42% L versus 60% H and 40% L). Similar frequencies were found in responsive and nonresponsive PE to therapy (54% H and 46% L versus 63% H and 37% L). However, significant differences were found for the C-1562T polymorphism in GH patients (85% C and 15% T versus 71% C and 29% T in responsive and nonresponsive groups, respectively; p=0.002), although no differences were found in the PE group (85% C and 15% T versus 89% C and 11% T). Genotypes distributions followed Hardy-Weinberg equilibrium. No differences were found in MMP-9 haplotype distributions when responsive and nonresponsive HP or PE were compared (44% HC, 14% HT and 42% LC versus 33% HC, 28% HT and 40% LC in HP; 40% HC, 14% HT and 46% LC versus 52% HC, 11% HT and 37% LC in PE). Conclusion: Our results suggest that the C-1562T polymorphism affects the responsiveness to antihypertensive therapy of gestational hypertension. The lack of such associations in preeclampsia is consistent with the notion that different pathophysiological mechanisms are involved in these hypertensive disorders of pregnancy. **Financial support**: FAPESP e CNPq.

11.032

Comorbidities and medication use in elderly women with vestibular disorders. Prezotto AO, Paulino CA, Onishi ET UNIBAN

Background: Balance or vestibular disorders are common among the elderly and may be associated with various comorbidities, requiring the use of various drugs and therapeutic measures such as vestibular rehabilitation. Some drug classes are known for their toxicity on the labyrinth, such as antiinflammatory drugs, diuretics, appetite suppressants, contraceptives, some antibiotics and others. Thus, this study evaluated the presence of comorbidities and medication use among elderly women with balance and hearing disorders (vestibular disorders). **Methods:** The study population consisted of 18 women aged 60-84 years old, evaluated in the Laboratory of Rehabilitation and Social Inclusion of the Bandeirante University of São Paulo. The study design was retrospective, without risks to health or integrity of the participants, performed only after Ethics Committee approval (Protocol 251/08). To collect data we used the medical records of elderly patients, consisting health information necessary for the study. **Results:** Assessing vestibular symptoms and age groups, with the highest prevalence were observed: dizziness in the range 71-75 years (33%); dizziness in the ranges 71-75 and 60-65 years (both 28%); tinnitus and hearing impairment in the range 71-75 years (28%), and hearing loss in the range 71-75 and 60-65 years (both 6%). Regarding the amount of drugs was observed using up more than 6 concurrent medications and only an elderly did not report medication use; the most prevalent was the use of three drugs in the age group between 71-75 years (17%) and 4-5 medicines in the range 66-70 years (both 11%). The most common pharmacological groups have been reported: antihypertensives (44%), diuretics (33%) and the hormone levothyroxine to hypothyroidism treatment (28%). Among antihypertensive drugs, the most common were enalapril and losartan, and among diuretics, hydrochlorothiazide. It should be noted that many elderly reported the concurrent use of more than one drug. **Discussion:** The vestibular dysfunctions are most relevant among the elderly; in this moment of life, dizziness is the most prevalent symptom, especially in individuals over 75 years. These results agree with data showing that the dizziness was the most prevalent symptom, especially among the elderly aged 71-75 years, which may suggest a higher risk of falls, followed or not by fractures and other consequences. Dizziness may be associated with hearing symptoms such as tinnitus and hearing loss also observed in this study. Moreover, dizziness reported here is a common form of dizziness. In addition, the presence of comorbidities such as hypertension and hypothyroidism and drug therapy for its control may be associated with vestibular symptoms. In fact, the side effects of some medications, or their interactions, may promote the onset of otoneurological symptoms and even the occurrence of falls, particularly in the elderly. This impairment of body balance may limit daily activities and reduce quality of life of elderly with vestibular diseases. **Financial support**: UNIBAN.

11.033

Serum cortisol and IL-10 levels increase in chronic renal failure patients with cognitive deficit. Degaspari D[1], Stein G[2], Munhoz CD[1], Martins JPB[2], Ribeiro Junior E[2], Sá Lima L[1], Tzanno-Martins CB[1], Scavone C[1], Kawamoto EM[1] [1]ICB-USP − Farmacologia, [2]CEHUS-CINE

Introduction: Chronic renal failure (CRF) is a condition described as an extended and irreversible alteration of renal function1. The relationship between CRF and cognitive deficit has been recently described, and the cognitive dysfunction level seems to be directly associated to the stage of renal failure2. Also, it has been shown that inflammation could be present in neurodegenerative disorders3,4. The objective of this study was to evaluate the role of pro and anti-inflammatory cytokines in CRF patients in hemodialysis with or without cognitive deficit. **Methods:** This study was submitted and approved by the National Committee of Ethics in Human Being Researches –CONEP (897/CEP June 04, 2009. ICB - USP). Thirty six CRF patients (40-50 years old) in hemodialysis were submitted to cognition test through Modified Mini Exam of Mental State (3MS) and Kidney Disease Quality of Life (KDQOL). Blood was collected before and after hemodialysis procedure. Serum was used to analyze IL-6, IL-10, TNF-α and cortisol levels by ELISA test. Data were analyzed by one-way ANOVA, followed by Newman-Keuls post-test. $p \leq 0,05$ was considered statistically significant. RESULTS: Forty percent of patients subject to 3MS and KDQOL showed mild and moderate cognitive decline non-diagnosed previously. We observed that IL-6 (control = 7. 1 ± 0.4 pg/ml) and TNF-α (control = 14.4 ± 4.8 pg/ml) levels were increased in CRF patients (IL-6 = 227.8 ± 92. 1 pg/ml and TNF-α = 53.7 ± 9.4 pg/ml) without cognitive decline before hemodialysis and TNF-α levels were also increased in CRF patients without cognitive decline (TNF-α = 30,2 ± 4.4 pg/ml) after hemodialysis, whereas IL-10 (control = 7.4 ± 2.4 pg/ml) and cortisol (control = 0.16 ± 0.03 mg/dl) levels were increased in CRF patients with cognitive decline before (IL-10 = 22.6 ±8.5 pg/ml; cortisol = 0.32 ± 0.03 mg/dl) and after (IL-10 = 32.4 ± 9. 1 pg/ml and cortisol = 0.28 ± 0.04 mg/dl) hemodialysis. **DISCUSSION:** Our results suggest that CRF patients in hemodialysis show changes in proinflammatory cytokines levels, regardless the cognitive pattern, and IL-10 and cortisol serum levels increase in patients with cognitive decline could be a response from the body against an inflammation state. REFERENCES 1. Madero, M. et al. , Dis. Sem. Dial, 21, 29-37, 2008.2. Murray, A. M. , Adv. Chron. Kidney Dis. , 15 (2), 123-132, 2008.3. Munhoz et al. , Eur. J. PHarmacol, 2: 3-4, 2005.4. Cunninghan, C. et al. , Biol. Psychiatry, 65, 304-312, 2009. **Financial Support**: FAPESP, CNPq and CINE.

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Changes in cardiovascular and biochemical parameters produced by chronic treatment with celecoxib in normotensive rats. Figueiredo LF, Baracho NCV FMIT

Introduction and objective: Nonsteroidal anti-inflammatory drugs are widely used in medical practice for its analgesic, antipyretic and antiinflammatory. There are two isoforms of cyclooxygenase, COX-1 and physiological action of COX-2 inflammatory action, the latter being the main target of anti-inflammatories. The aim of present study were evaluate the changes in cardiovascular and biochemical parameters produced by chronic treatment with celecoxib in normotensive rats. Material and **Methods:** This study was approved by the Research Ethics Committee of the Faculty of Medicine of Itajubá under protocol 018/08 and received financial support from FAPEMIG. Twenty male Wistar rats 200-300 g were used, and were allocated into two groups: 1) control, 2) celecoxib . The normotensive Wistar rats, received, for a period of 90 days, the following treatments orally (gavage): 1) control group (n = 10), which received distilled water, 2) celecoxib group (n = 10), which received 200 mg / kg celecoxib Animals were kept in plastic cages during the 12 weeks with food and water *ad libitum* and subjected to light and dark cycle of 12 hours. MAP was measured once a week by tail plethismography. At the end of the experiment, under anesthesia, blood samples were collected for glucose, urea, creatinine, total cholesterol, triglycerides, total protein, albumin, uric acid, calcium and magnesium dosages. **Results:** Treatment with celecoxib produced a significant increase in mean arterial pressure (MAP) from the third week of treatment compared to the control group ($p < 0.01$). The increase in MAP produced by celecoxib was maintained throughout the experimental period ($p < 0.01$). When compared to day zero of the group treated with celecoxib with 90 days of this same group, we observed a significant increase in MAP of animals. Regarding biochemical parameters, treatment with celecoxib produced a significant increase of serum glucose when compared with controls ($p < 0.05$). Moreover, this treatment produced highly significant reduction in serum albumin ($p = 0.001$) and significantly reduced serum total protein ($p < 0.05$) compared to controls. The others biochemical parameters did not change significantly with treatment with celecoxib ($p > 0.05$). **Discussion:** The data indicate that the chronic treatment with celecoxib would produce important increase in MAP and important changes in plasma levels of glucose, albumin and total protein. The mechanisms involved in these effects did not knowledge and will be investigated by our research group. 1-Brooks P. Am J Med. 1998; 104(suppl. 1): 43S-51S.2-Ekman EF, Fiechtner JJ, Levy S, Fort JG. Am J Orthop 2002 31:445-51.3-Hippisley-Cox J, Coupland C. BMJ 2005 330:1366.