11. Clinical Pharmacology, Pharmacokinetics, Pharmacogenomics and Preclinical Toxicology

11.001 Analysis of the postnatal development of mice offspring exposed to yellow fever vaccine during intrauterine life. Marianno P, Costa GA, Salles MJS UEL – Biological Sciences

Introduction: The most effective method to prevent yellow fever is the vaccine developed with live attenuated virus strain 17D.The hypothetical risk of transplacental infection and the observation that fetuses are susceptible to 17D virus neuroinvasion, lead to non-recommendation of the use of the vaccine during pregnancy by WHO. Objectives: This study aimed at evaluating the physical and reflexological development in the offspring of mice exposed to the vaccine during the 5th, 10th and 15th days of gestation. **Methods:** Swiss mice were divided into 6 experimental groups, 3 control groups (C) and 3 treated groups (GD). Each group was composed by 10 animals. The female mice of the treatment groups received a dose of 2.0 log 10 PFU of yellow fever vaccine subcutaneously the 5^{th} (GD5) or 10^{th} (GD10) or at 15^{th} (GD15) days of pregnancy. The control groups received water for injection in the same experimental design. The birth occurred naturally and soon an assessment neonatal was done to verify the presence or absence of visible malformations. The pups were analyzed until the 30th day of their postnatal life regarding weight and body development, besides reflexological, physical and sexual development. The Reflexological development was evaluated using parameters reflecting the straightening posture, negative geotaxia, adult walking and grip strength. The physical parameters analyzed were ramifications of the ears, teeth eruption, hair appearance, eyes opening, ear canal opening, and measurement of anogenital distance. The testicular descent, the nipples appearance and the vaginal opening were part of the sexual evaluation. **Results:** None of the parameters analyzed showed changes statistically significant among the six experimental groups. **Discussion:** Based on the results we can conclude that the yellow fever vaccine, when administered on the 5^{th}, 10^{th} and 15^{th} days of pregnancy, does not cause changes to the physical, reflexological and sexual development of mice offspring. **References:** SILVA, F.C. Effects of yellow fever vaccination gestation in mice. Master's degree - Institute of Biomedical Sciences,University of São Paulo, 2009. MONATH, T.P Yellow fever: an update. Lancet Infect. Dis., V.1, p.11, 2001. **Financial Agency and acknowledgments:** CNPq e Instituto Biomanguinhos- Fundação Oswaldo Cruz. **License number of the Animal Ethics Committee:** registered and approved by the Ethics Committee on Animal Use State University of Londrina under the number 01/11.

11.002 Evaluation of therapeutic association's effect on digoxin pharmacokinetics. Souza FC, Baptista TM, Neri JS, Scaramello CBV UFF – Farmacologia Experimental

Introduction: Knowledge of drugs' pharmacokinetic (PK) parameters in different patients is essential for safe therapeutics regimens establishment. Digoxin (DIG) is used in heart failure (HF) and constitutes an insecure drug due to its narrow therapeutic range-TR (Einarson. Can J Hosp Pharm. 42:63, 1989; Bressler & Bahl. Mayo Clin Proc. 78:1564, 2003). A retrospective study conducted by our group at Instituto Nacional de Cardiologia (INC) showed that 647 patients were admitted to the HF ward along 2009-2010 and 194 of these individuals have used DIG. As unexpected, the digitalis plasma concentration (C_p) was measured in less than 50% of these patients (n=80); 53% (n=42) of these patients with registered C_p had this value outside the TR. This study also showed that patients' profile associated with increased risk of toxicity includes males (79%), aged between 21-60 years-old (76%), HF NYHA-functional class-FC III (65%), presenting comorbidities such as renal failure (33%) and drug interactions, like carvedilol (55%) and omeprazole (48%). So the aim of this work was to evaluate the effect of these therapeutic associations on digoxin PK. **Methods:** The project was approved by the Ethics Committee on Human Research of the INC (N° 0306/07-12-10). Male patients, aged between 21-60 years-old, HF NYHA-functional class-FC III, who have signed an informed consent, were stratified into two layers: I. Patients taking DIG without (G1; n=3) and with carvedilol (G2; n=5); II. Patients taking DIG without (G3; n=10) and with omeprazole (G4; n=7). Blood samples were collected at different times over 24h after oral administration of DIG. Measurement of digitalis C_p was performed using immuno-chemiluminescence method. (LLOQ=0.3ng/mL; precision≤10%). Graphical representation, calculation of PK parameters and statistical analysis were proceeded using Graph Pad Prism 5.0 (GraphPad Prism Software Inc., San Diego,CA). Data were presented as mean and standard error of the mean (SEM), analyzed by Student's *t* test and considered statistically different if $P<0.05$(*). **Results:** Carvedilol association changed some PK parameters of digoxin such as C_p after 24h of digitalis administration and CL/F (G1: AUC_{0-24} = 17.60 ± 2.09 ng.h/mL, C_{max} = 1.05 ± 0.074ng/mL, T_{max} = 3.67 ± 2.19h; CL/F = 0.237 ± 0,071L/h/Kg; C_{p24h} = 0,57/ G2: AUC_{0-24} = 26.68 ± 3.31 ng.h/mL, C_{max} = 1.40 ± 0.12 ng/mL, T_{max} = 2.00 ± 0.55h; CL/F = 0.074* ± 0.019 L/h/Kg; C_{p24h} = 1,09*). However, omeprazole association did not change digoxin PK parameters (G3: AUC_{0-24} = 25.52 ± 2.87ng.h/mL, C_{max} = 1.38 ± 0.15ng/mL, T_{max} = 2.83 ± 0.92h; CL/F = 0.11 ± 0.03L/h/Kg / G4: AUC_{0-24} = 20.39 ± 2.93ng.h/mL, C_{max} = 1.21 ± 0.15ng/mL, T_{max} = 1.57 ± 0.20h; CL/F = 0.17 ± 0,04 L/h/Kg). **Discussion**: According to our data, it is possible to allege that just carvedilol affects digoxin pharmacokinetics. Despite beta blocker data, this work suggests that drug interactions influence on digoxin PK appears to be better estimated by mathematical models developed from data of experimental PK studies. **Financial Support:** FAPERJ, CAPES, Proppi/UFF.

11.003 A novel *in vivo* model for evaluation of vaginal permeability test applied to fenticonazole. Campos RM[1], Pissinatti L[1], Rojas-Moscoso JA[1], Chen LS[2], Porto M[1], Gagliano TJD[3], de Nucci G[1] [1]Unicamp – Pharmacology, [2]Galeno Research Unit, [3]IBCCF-UFRJ

Introduction: To date, there are only in vitro model to evaluate vaginal permeability (van Eyk&van der Bijl., 2005**.)** Permeability is a dynamic process, involving a great deal of blood perfusion of the tissues involved and, therefore, is poorly mimicked *in vitro.* Due to the presence of blood vessels networks in the submucosa space and few interference of the estrous cycle in the epithelium, we propose the well known rabbit model for evaluation of vaginal toxicity as a animal model to also evaluate vaginal drug permeability (Costin et al., 2011). **Method:** Fenticonazole nitrate (Fentizol® or test formulation) was administered by vaginal route during eight days consecutive and plasma levels of fenticonazole were quantified by high performance liquid chromatography coupled to electrospray tanden mass spectometry. After sacrifice, were performed macroscopic and histopatology analyze.The protocol in the present study was approved by the Ethics Committee for research of the State University of Campinas (protocol: 2997-1). **Results:** The mean data of the area under the curve were 595.± 226ng.h/mL for Fentizol®, 637±129 ng.h/mL for the test formulation (F-test) for the first 4 hours after administration (unpaired t test Vs test formulation ;p= 0.88) and 967±179 ng.h/mL for Fentizol® and 1556±425 ng.h/mL for F-test during 8th day of treatment (unpaired t test Vs F-test ;p= 0.27). There were no differences between the groups in relation to maximum concentration achieved and great changes in the organ tract morphology. **Discussion:** The model is easy to perform, allows evaluation of fenticonazole vaginal permeability. The method suggested is useful to determine drug safety for vaginal formulations, evaluating the presence of side effects and toxic sign. **Sources of Research Support**: This study was supported by CNPq/Brazil

11.004 Simvastatin treatment increases nitrite levels in obese women: **Modulation by T-786 polymorphism of NOS3**. Andrade V[1], Sertorio J[2], Fernandes K[1], Sandrim V[1] [1]IEP-SCBH, [2]Unicamp – Farmacologia

Introduction*:* Evidences indicate an impairment of nitric oxide (NO) pathway in obesity. Statins presents pleiotropic effects independently of cholesterol-lowering, including increasing of eNOS expression and antioxidant effects. **Methods***:* We evaluated the simvastatin treatment by 45 days on circulating nitrite (NO marker) and TBARS-MDA levels in obese women without comorbidities (N=33). Also, we verified the effect of $T^{-786}C$ (genotyped by RFLP) polymorphism located in *eNOS* on the modulation of simvastatin treatment. The license number of the Human Ethics Committees was 070/2011 SCBH.*Results:* Simvastatin treatment increased and reduced significantly the plasma nitrite and TBARS-MDA levels (42%; P=0.0008 and 58%, P=0.0069, respectively). We observed increased levels of nitrite in both groups of genotypes, however, the raise in C-allele carrier was 60% comparing with 44% in TT. **Discussion***:* our results demonstrated a restore of nitrite levels in obese women treated with simvastatin which is modulated by T-786C polymorphism. **Financial Support***:* This study was funded by the Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG-Brazil), Fundação de Amparo a Pesquisa do Estado de São Paulo (FAPESP-Brazil), the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

11.005 Robotic simulation used to optimization of teaching applied pharmacology to medicine. Fagundes Junior LH[1], Aguiar ARA[2], Suassuna FAB[1], Câmara PRS[1] [1]UnP – Medicina, [2]UnP – Enfermagem

Introduction: The task-based teaching (TBT) is a method in which the students are first confronted with a problem and sequentially subjected to a process of seeking grants for their resolution, thus rescuing the student's previous knowledge. Medical robots helps train medical students minimizing stress and preparing for a large variety of emergency situations, reducing this way the percentage of errors in the emergency room. **Methods**: Medical robots were used to help medical students to minimizing stress and preparing for a large variety of emergency situations, reducing this way the percentage of errors in the emergency room. **Results and Discussion**: In the present study, we noted that the use of active learning methodology, i.e., application and discussion of clinical cases with the subsequent debriefing, enabled the student an improvement of his experiences and practice skills. After the completion of each scenario, many discussions were created about which is the better pharmacological and clinical conduct to follow for each clinical case. This enabled a better understanding by students, about which is the best pharmacological therapy applied in each clinical case, minimizing this way, the possible errors of conduct and prescription, without leaving the ethical context and favoring a most solid professional training. 1-Ziv A et al. Simulation-based medical education: an ethical imperative. Acad Med 78(8):783, 2003. 2- Mennin S, et. al. Position paper on problem-based learning. Educ Health 16(1):98, 2003. 3- Beasley, RA. Medical Robots: Current Systems and Research Directions. J. Robotics, 2012. Financial Support and acknowledgements: Universidade Potiguar (UNP)

11.006 Evaluation of ozonized sunflower oil in skin healing in rats. Figueiredo M, Miara LC, Anater A, Ribeiro DR, Rodrigues Filho JG, Michelotto Junior PV, Farias MR, Pimpão CT
FCAV-PUCPR – Animal Science

Introduction: The veterinary dermatology is one of the fastest growing specialties in veterinary medicine because skin diseases or skin diseases are the major causes in the clinical care of small animals around the world. Despite major advances seen in recent decades not only in understanding the various factors and phenomena involved in the process of tissue repair, but simultaneously with the growing research and discovery of new resources and technologies to intervene in it, there is much to be discovered. So far the official medicine has not yet recognized the topical use of O_3 and derivatives in therapy, because few clinical studies have not been published in magazines and newspapers. **Objective:** To evaluate the healing power of ozonized sunflower oil in skin lesions in rats through macroscopic aspect and check the microbiota of skin lesions. **Methods:** A total of 100 female Wistar rats from the vivarium of PUCPR (CEUA/PUCPR n°650) were used. A piece of skin (2x1cm) was removed from the back of the animals. The animals were divided equal into 5 groups (n=20), for the treatment of surgical injury: CG 1 - NaCl 0.9%, CG2 - NaCl 0.9% + sunflower oil; O_3G (90) - NaCl 0.9% + ozonized sunflower oil (90g/L – pH2); O_3G (60) - NaCl 0.9% + ozonized sunflower oil (60 g/L – pH4); GG - NaCl 0.9% + ointment gentamicin (5 mg/g). The lesions were daily evaluated in relation to pain and healing. Samples were collected for culture (5 animals/group; n=60) on day: +1, +4 and +7 treatment. In every 7 days, 5 animals/group were euthanized for histological examination of the skin. **Results:** In the evaluation of parameters related to pain, there no were significant differences ($p>0.05$). The macroscopic examination of the lesion showed a better evolution of healing into group $O_3G(90)$ and group $O_3G(60)$ ($p<0.05$) compared to the other. The gentamicin group showed the worst results related to healing ($p<0.05$). 57.3% of the animals were positive for *Staphylococcus aureus*, *Staphylococcus pseudintermedius* 34.6% and 8% for *Staphylococcus sp*. (coagulase negative). Histological evaluation showed a lower degree collagen ($p<0.05$) in GG and a higher degree of mononuclear cells ($p<0.05$). **Discussion:** Animals treated with ozonized sunflower oil obtained good and rapid healing, but there was an intense inflammatory reaction in the early days of treatment group O_3G (90), probably due to the acidic pH of the ozonated oil. The animals treated with gentamicin ointment had delayed healing, despite the infection was absent. **Conclusion:** Considering the data obtained, the group $O_3G(60)$ showed the best results regarding the healing. **Keywords:** Healing; Sunflower Oil; Ozone;

11.007 Pharmacokinetics profile of thalidomide on the doses 200 mg and 400 mg in healthy male volunteers. Sales LC[1], Leite ALAS[1], Nascimento DF[1], Kerr LRFS[2], Costa IF[1], Freire LM[1], Rocha MBS[1], Pontes AV[1], Frota Bezerra FA[1], Moraes MO[1], Moraes MEA[1] [1]UFC – Fisiologia e Farmacologia, [2]UFC – Saúde Comunitária

Introduction: The aim of the study was to evaluate the pharmacokinetic profile of the two different doses of Thalidomide (200 and 400mg), through determining pharmacokinetics parameters related to absorption, distribution and elimination in healthy male volunteers whereas there is no pharmacokinetic data available concerning the Brazilian formulation of Thalidomide. **Methods:** Fifty-four healthy male volunteers aged between 18 and 50 years and BMI between 19-30 kg/m^2 were selected for the study after assessment of their health status by clinical evaluation (physical examination, ECG) and the following laboratory tests: blood glucose, urea, creatinine, AST, ALT, alkaline phosphatase, total bilirubin, albumin and total protein, triglyceride, total cholesterol, hemoglobin, hematocrit, total and differential white cell counts and routine urinalysis. All subjects were negative for HIV, HCV and HBV (except for serological scar). All subjects gave written informed consent and the Ethics Committee of the Federal University of Ceará approved the clinical protocol (Protocol n° 50/09). The study was conducted in accordance with the provisions of the Declaration of Helsinki (1964), Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996) and Edinburgh (2000) revisions. A single oral dose, open-label, 2-period crossover, randomized study was conducted. The volunteers received 200mg or 400mg of thalidomide with a seven days washout period. Plasma was obtained over a 36h interval. The thalidomide concentrations were analyzed by combined reversed phase liquid chromatography and tandem mass spectrometry (LC-MS-MS) with positive ion electrospray ionization using selected daughter ion monitoring (MRM). **Results and Discussions:** The method validation investigated the parameters recommended for the bioanalytical methods and yielded good results with limit of quantification of 20ng/mL. The chromatographic separation was obtained within 3 min, and the response was linear in the concentration range of 0.05-5000 ng/mL (r^2= 0.9985).The pharmacokinetic data (mean ± standard deviation) obtained from the formulations containing thalidomide 200mg and 400mg were 12663.54 ± 23056.11 2123.99 and 3437.08ng * h/mL for AUC_{0-36}, 13282.84 ± 2065.91 and 26292.67 ± 4187.85ng * h/mL for $AUC_{0-\infty}$, 861.58 ± 187.30 and 1131.63 ± 266.93ng/mL for $C_{máx}$, 4.52 ± 1.53 and 6.88 ± 4.71h to $T_{máx}$, 6.89 ± 1.44 and 11.01 ± 4.36h to t1/2, 0.10 ± 0.02 and 0.07 ± 0.03 1/h for Ke, respectively. The comparison between pharmacokinetic parameters, at doses of 200 and 400mg, presented proportional curves. When comparing the pharmacokinetic parameters of this study and those found in studies of TEO et al., 1999, NOORMOHAMED et al., 1999 and PAGANOTTO, 2002 it was observed that the FUNED formulation presents smaller and slower absorption than the others. **Financial support:** CNPq, InCB, MS-RNPC-UNIFAC-HM, FINEP.

11.008 Influence of food on bioavailability of venlafaxine administered in extended release capsules. Freire LM, Rocha MBS, Leite ALAS, Nascimento DF, Pontes AV, Sales LC, Sena KS, Costa IF, Lopes BB, Frota Bezerra FA, Moraes MO, Moraes MEA UFC – Fisiologia e Farmacologia

Introduction: Venlafaxine (VLX) is a antidepressant drug bicyclic derivated of phenethylamine that act inhibiting the serotonin´s, noradrenalin's and dopamine´s reuptake.The aim was to evaluate the influence of food in the bioavailability of two formulations of venlafaxine extended-release capsules in healthy volunteers. **Methods:** 36 healthy volunteers of both sexes aged between 18 and 50 years and BMI between 19-30 kg/m^2 were selected for the study after assessment of their health status by clinical evaluation and hematological, biochemical and routine urinalysis parameters. All subjects were negative for HIV, HCV and HBV (except for serological scar). All subjects gave written informed consent and the Ethics Committee of the Federal University of Ceará approved the clinical protocol (Protocol n° 20/11). The study was conducted in accordance with the provisions of the Declaration of Helsinki (1964) and its revisions. The study was open, randomized, crossover clinical trial was consisted of four periods, two sequences, in which healthy adult volunteers received 01 extended-release capsule of VLX 75mg of test formulation and another of reference formulation in each distinct period under fasting or fed conditions, with an interval of seven days. 24 Blood samples were collected at predetermined times. VLX concentrations were determined through a HPLC-MS/MS method. **Results and Discussions:** The food did not influence the VLX bioavailability when the 90 percent of confidence interval for the geometric ratio between fed and fasted treatment was contained in the equivalence limits of 80-125% for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$ and C_{max} when compared to administration of the drug in fasting condition. Adverse events were monitored during the study. Thirty-three subjects ended the study, 51.5% were male (17 men) and were 48.5% female (16 women). The mean age was 28.2 years ± 8.6 years, mean weight was 66 kg ± 11.1 kg, mean height was 160 cm ± 0.1 cm and the mean body mass index (BMI) was 24.4 kg/m^2 ± 3.0 kg/m^2. The most frequent adverse events were: headache representing 32.4%, drowsiness with 16.2% and nausea with 14.7% of all events. There was no significant difference in the frequency of occurrence in the groups (reference and test) related to the fasting or fed state. Regarding the pharmacokinetic parameters, in the statistical comparison, no difference was found in the $AUC_{0\text{-}t}$ and the $AUC_{0\text{-}inf}$ in the fasted versus fed conditions in the reference and test formulation groups. The T_{max} was lower and the C_{max} higher in both fed groups and the $T_{1/2}$ was lower in the fed state in the test formulation. The confidence interval for all parameters required to evaluate the effect of food on the bioavailability of the reference and test formulations were within the range of 80-125%. Regarding the bioequivalence of drugs, both formulations in fed and fasted state were within the established range (80-125%). Although the food did change some pharmacokinetic parameters, feeding did not influence the bioavailability of VLX in both reference and test formulations. The studied capsules of VLX extended-release (test and reference products) showed similar bioavailability when administered a single oral dose of 75mg to healthy adult volunteers, fasting and fed and, thus, were considered bioequivalent to the rate and extent of absorption. **Financial support:** CAPES, CNPq, FUNCAP, InCB; MS-RNPC-UNIFAC-HM.

11.009 Inosine via adenosine receptors prevents MeHg-induced motor impairment: behavioral and biochemical aspects. Macedo-Junior SJ[1], Cerutti ML[2], Nascimento DB[3], Farina M[4], Santos ARS[2], Cardozo AM[5] [1]UFSC – Farmacologia, [2]UFSC – Ciências Fisiológicas, [3]UFSM – Química, [4]UFSC – Bioquímica, [5]UFSC – Patologia

Introduction: Methylmercury (MeHg) have been speculated as environmental contaminant involved in neurological deficit in both animals and humans. The present study aimed to evaluate the protective effect of inosine, an endogenous purine with recognized neuroprotective activity, against MeHg exposure in mice, using behavioral and biochemical tests. **Methods:** Were used male Swiss mice. Animals were exposed to 40 mg MeHg/L in drink water during 15 days. During this period, liquid ingestion was monitored every 3 days. Initially, animals received inosine intraperitoneally (i.p.) at doses of 3, 10, 30 or 100mg/kg, once a day during 15 consecutive days. On the 15th day, they were submitted to the rotarod test to evaluate locomotor activity and coordination, after which were sacrificed by decapitation and the cerebellum were collected for subsequent measurement of BDNF levels by ELISA; Na^+K^+ATPase activity; and mercury contents by atomic absorption spectrometry using cold vapor technique. In another set of experiments, in order to assess a possible mechanism by which inosine was promoting its effects, animals received inosine (10mg/kg, i.p.) or a mixture of inosine (10mg/kg) and caffeine (3mg/kg), by i.p. route, once a day during 15 consecutive days. Next, it was performed rotarod test and tested for hind limb clasping phenomenon. Experimental procedures were approved by CEUA/UFSC 00745. **Results:** The results of the present study demonstrate that liquid consumptions did not differ between groups, while MeHg exposure induced motor impairment (34.4% of control). Furthermore, inosine (10mg/kg, i.p.) partially protected against MeHg-induced motor impairment (76.0% of control) and completely, when tested in face of the hind limb clasping phenomenon. Caffeine (3mg/kg, i.p.) co-administered with inosine (10mg/kg, i.p.) completely prevented inosine protective effect in rotarod test and partially in the hind limb clasping phenomenon. In the biochemical tests, MeHg promoted an increase in BDNF levels in cerebellum, which was prevented by inosine (10mg/kg, i.p.; I=38.0±14%). In addition, MeHg exposure decreased Na^+K^+ATPase activity (65±10% of control), which was not prevented by inosine. Interestingly, inosine (10mg/kg, i.p.) *per se* reduced Na^+K^+ATPase activity (86±1% of control). Finally, MeHg exposure increased mercury content in cerebellum, which was not prevented by inosine. **Discussion:** According to the results presented here, inosine (10mg/kg, i.p.) was able to prevent MeHg induced motor impairment, dyskinetic posture and BDNF increased levels in cerebellum. Its effect seems to involve adenosine receptors, since its co-administration with caffeine, a non-selective adenosine receptors antagonist, abolished inosine effects. On the other hand, inosine did not prevent MeHg-induced Na^+K^+ATPase activity decreased. Surprisingly, inosine *per se* reduced Na^+K^+ATPase activity due to a mechanism so far unknown. **Financial support:** CAPES.

11.010 Haematological responses in *Rhamdia quelen* sedated with propofol. Gressler L[1], Spall S[2], Sutili F[1], da Costa S[3], Parodi T[1], Baldisserotto B[1] [1]UFSM – Fisiologia e Farmacologia, [2]UFSM – Farmácia Industrial, [3]CESNORS-UFSM – Zootecnia,

Introduction: Propofol has been described as capable of decreasing ventilatory drive as well as cardiac output and contractility in mammals[1]. This study aimed at evaluating the effects of propofol on *Rhamdiaquelen* haematological parameters. **Methods:** *Rhamdia quelen* (*n* = 90; 91.44 ± 1.98 g; 20.66 ± 0.15 cm) were acquired from a fish farm in Santa Maria and housed at LAFIPE-UFSM. Acclimation (7 days) was performed in 250 l tanks in a semi-static system with aerated water at 21.5 ± 0.08 ºC, pH 7.45 ± 0.13 and dissolved oxygen 8.04 ± 0.26 mg l^{-1}. Fish were subjected to one of the following concentrations of propofol: 0, 0.4 or 0.8 mg l^{-1}. Each treatment was further divided into an exposure time of 1, 6 and 12 h (short, medium and long transport times respectively). For every concentration/time combination, 10 fish were tested (2 replicates of 5 fish each). Fish were transferred to trial tanks and kept under the experimental conditions for the assigned period. Once exposure time had elapsed, fish were individually removed from the tanks and a 2 ml blood sample was taken from the caudal peduncle with heparinized sterile syringes. Haematocrit (ht) was measured in microcapillary tubes centrifuged at 10000 Xg for 10 min and read with a card reader. RBC count was determined with a Neubauer haemocytometer[2]. Haemoglobin (hb) was assayed by the cyanmethaemoglobin method using a spectrophotometer[3]. MCV, MCH and MCHC were also calculated[4]. Registration at the Ethics Committee on Animal Experimentation of UFSM: 67/2012. **Results:** At 0.4 mg l^{-1} propofol the ht was lower at 6 compared to 12 h while at 0.8 mg l^{-1} propofol the ht was lower at 1 h than at the remaining times. The level of ht was lower at 0.4 than at 0 and 0.8 mg l^{-1} propofol in fish exposed for 6 h. The concentration of hb was significantly greater within 6 h of exposure to the highest concentration of the anaesthetic. Statistical evidence did not identify any effect on RBC, MCV, MCH or MCHC. **Discussion:** The reduction in ht may have been an adaptive response without major physiological significance especially because RBC number remained unchanged[5]. The most prominent changes were observed in hb content. The values found for hb at 0.8 mg l^{-1} propofol after 6 h exposure may indicate that in this group there was a transient requirement for increased blood oxygen-carrying capacity, achieved by the movement of water from primary to secondary circulation systems, thus increasing the content of hb[6]. The capacitance response is a rapid means of preserving oxygen delivery to tissues under hypoxic challenge, which in this case was mostly likely a result of the reduced gill ventilation during anesthesia, as previously related[7,8]. **References:** [1]Pagel, P. S. Anesthesiol. 78, 100; [2]Tavares-Dias, M. (2002). Cienc. Rural 32, 693; [3]Brow, B. (1976). Hematology: Principles and procedures, 2nd edn. Philadelphia, PA: Lea and Febiger; [4]Wintrobe, M. (1934). Folia Haematol. 51, 32; [5]Franklin, C. (1993). J. Exp. Biol. 174, 381; [6]Wells, R. (1990). J. Exp. Biol. 150, 461; [7]Molinero, A. Comp. Biochem. Physiol. 3, 405; [8]Sudagara, M. J. Aquac. Feed Sc. Nut. 1, 1. **Financial support:** FAPERGS/PRONEX, Capes, CNPq.

11.011 Evaluation of the plasma kinetics and biodistribution of association of paclitaxel with a cholesterol-rich nanoemulsion in *Cebus apella*. Feio DCA[1], Oliveira NCL[1], Morikawa AT, Muniz JAPC, Burbano RMR, Maranhão RC, Lima PD [1]UFPA

Introduction: The treatment of cancer is usually performed with a combination of multiple anticancer agents. However, this combination chemotherapy can be harmful by the addition of toxicity of each drug used. One of the strategies to reduce toxicity is to associate the drugs delivery systems able to target drugs to the site of action. The lipid nanoemulsions (LDE) may be used as carriers of paclitaxel (PTX), and other drugs to reduce toxicity and increase their therapeutic action. The aim of the study was to evaluate the plasma kinetics and biodistribution of paclitaxel association with cholesterol-rich nanoemulsion in *Cebus apella*. **Methods:** The study was approved by the UFPA Animal Ethics Committee (CEPAE/ BIO008-11). We used 4 adults male *Cebus apella* with a mean weight of 3.750 Kg, kept in captivity in the Centro Nacional de Primatas (CENP). About 500 µL of LDE-Paclitaxel oleate (LDE-OPTX) labeled with [^{3}H]-free cholesterol was injected intravenously. For 24 hours blood samples were collected at time intervals predetermined and after this period the major internal organs were removed for determination of the decay curve, the fractional clearance rate (FCR), in min-1, calculation of kinetic parameters (k) and the biodistribution of the nanoemulsion. The lipids were extracted following the method of FOLCH and radioactivity was measured with a liquid scintillation spectrometer. **Results:** The plasma kinetics presented a decay with no statistical difference between the animals in values of (expressed as mean ± SD) FCR (0.0564±0.0052), k1,0 non-specific removal of LDE (0.7429±0.2275), k1,2 LDE transformed by the acquisition of apolipoproteins (1.0833±0.3389) and K2,0 is LDE removed from the plasma compartment for the extravascular space (0.0346±0.0119). The decay curve profile showed bioexponential with a rapid initial decay followed by a slower decay. Already the biodistribution analysis showed an accumulation of LDE-OPTX mainly in the liver, spleen, adrenal and bone marrow. **Discussion:** This study analyzed the pharmacokinetic profile of plasma clearance and biodistribution of LDE-OPTX in *Cebus apella*, and demonstrated characteristic decay of radiotracers in a similar way when compared to studies with LDL and LDE. The inclination of the curve revealed that the first 60 min presented a rapid decay, suggesting its distribution among tissues, decreasing the amount of circulating nanoemulsion. Biodistribution, according pharmacokinetic parameters analyzed, showed an accumulation of radioactivity in the organs that express higher amounts of LDL receptors, especially the liver, the main organ related to lipid metabolism, confirming uptake via the LDL receptor. **Financial Agencies:** CNPq, CAPES, CENP, FAPESP and FAPESPA

11.012 Pharmacokinetic evaluation of sulfamethoxazole + trimethoprim in rats as a tool for predictive bioequivalence / bioavailability studies in humans. Hoffmann FI[1], Pritsch MC[1], Postali M[1], Santos MB[1], Manfio JL[1], de Lima TCM[2] [1]Biocinese – Biopharmaceutical Studies, [2]UFSC

Introduction: Differences related to physic-chemical characteristics of the drug, formulations components and manufacturing processes can lead to problems in drug bioavailability (1); (2). With this assumption, and the need for more specific tests prior to implementation of relative bioavailability / bioequivalence studies in humans an animal model was developed to outatively predict or not the bioequivalence of formulations developed before testing in humans. The study aimed to evaluate the pharmacokinetic profiles of Sulfamethoxazole (SMZ) + Trimethoprim (TMP) formulations administered to Wistar rats and compare with previously obtained data in studies of relative bioavailability / bioequivalence in healthy volunteers. **Methods:** 48 *Wistar* rats were divided in two groups (SMZ+TMT tablet and suspension). Each group received a single dose of the formulations by oral gavage. To perform the pharmacokinetic evaluation blood samples of 0,4 mL were collected in pre-determined times. An analytical method was developed for the quantification of the analytes and internal standard (Guaifenesine) by High Performance Liquid Cromathograpy (HPLC). The statistical analysis was performed using WinNolin® software. All procedures were approved and conducted in agreement with the Animal Ethics Committee under the number 23080.023789/2010-80/CEUA/UFSC. **Results:** The analytical method was validated and linearity of the method was demonstrated by the following coefficients (SMZ r^2 = 0.998754; TMP r^2 = 0.997136). The linearity range for SMZ was 500-40000 ng/mL and for TMP 50-1500 ng/mL. The SMZ suspension pharmacokinetic parameters in rats were: the peak of maximum concentration (Tmax) = 1.33 h for the reference and 1.50 h for the test product. The maximum concentration (Cmax) of SMZ in rats was 57979.02 ng/mL (reference) and 46360.10 ng/mL (test). For SMZ tablet in rats Tmax was 1.83 h (test and reference) and Cmax was 125681.02 ng/mL (reference) and 109536.20 ng/mL (test). The TMP suspension Tmax was 1.56 (reference) 1.58 h (test) and the Cmax were 768.29 ng/mL (reference) 633.82 ng/mL (test). For TMP tablets the results were Tmax 2.68 h (reference) and 2.10 (test) and Cmax 612.22 ng/mL (reference) and 702.92 (test). The rats pharmacokinetic parameters (Tmax, Cmax, Kel, T1/2, AUC) were compared to human previous results. **Discussion:** It was observed that the results were more consistent for the suspension formulation, being possible to correlate the drugs profile in rats and humans. For the tablets, there was some relationship between values; however, limitations of the animal model did not allow a complete correlation with the results found in humans. The findings of the study allow assessments of individual pharmacokinetic behavior for each formulation tested, contributing to identify problems and solve them prior to submission of official drug bioavailability / bioequivalence studies in humans. **Financial Support**: Biocinese – Biopharmaceutical Studies Center. **References**: (1) CHEN, M.L.; et al. *Pharmaceutical Research*, 24:73–80, 2007; (2) ELIOPOULOS, H et al., *Clinical Cancer Research*, 14:3683–3688, 2008.

11.013 Preclinical toxicology studies of LASSBIO-788, a potential antiatherogenic compound, on the male rat reproductive tract. Alfradique VAP[1], Motta NAV[1], Kummerle AE[2], Barreiro EJ[2], Brito FCF[1], Ribas JAS[1], Marostica E[1] [1]UFF – Physiology and Pharmacology, [2]UFRJ – LASSBio

Introduction: Atherosclerosis is closely associated with inflammatory and immune responses, besides to promote the activation of platelet aggregation and increase of oxidative stress. The development of drugs that combine anti-inflammatory, antiplatelet, antioxidant and lipid lowering properties are important for the treatment of this pathological condition. The compound LASSBio-788 is a thienyacylhhydrazone derivative that has a potencial antiatherogenic effect with antiplatelet, anti-inflammatory, vasodilatory, anti-oxidants and lipidic lowering *in vitro* properties (Brito et al, Eur. J. Pharmacol, 5, 2010; Motta, 2011). For this reason it is considered a potential candidate drug for the treatment of atherosclerosis. Therefore it is important to evaluate the toxic effects caused by the drug on the tissues, such as the reproductive tract. Thus, the aim of this study is evaluate the possible toxicological effects in the rat testis and male gamete treated with LASBio-788. **Methods:** Male Wistar rats (150-200g) (CEPA/UFF 0116/09) were separated in three groups (n=3/group): CO-fed with commercial ration; AT-fed with hypercholesterolemic diet; AT+788 - fed with hypercholesterolemic diet, treated with LASSBio-788 (100µmol/kg ip) for 15 days. After 45 days of experiment, the animals were anesthetized and testes from different experimental groups were removed, weighed and processed for morphmetric analyze (seminiferous tubules diameter and seminiferous epithelial high) using the program-NIS Elements Advanced Research. In addition, spermatogenic lineage cells (spermatogonia, spermatocyte and round spermatid) and Sertoli cells were also counted and spermatic evaluation (progressive motility, membrane integrity and sperm number) was done using sperm from epididymis cauda. **Results:** The values are mean±SEM. The diameter (CO:247.41±1.48; AT:248.37±2.63; AT+788: 267.14±1.82 μ) and tubular epithelium (CO: 82.02±1.30; AT: 44.70±0.93; AT+788: 61.3±2,31 μ) were different among the groups. In addition, the count of spermatogonia (CO: 28.25± 0,56, AT:28.42±0.47, AT+788:24.79±0.45), spermatocytes (CO: 48.15±0,84; AT: 46,73±0.86), AT+788: 42.90±0.87), but not the round spermatids (CO: 101.03±1.76; AT: 97.28±1.76; AT+788: 96.0±1.71) were lower in AT+788. Spermatic parameters were lower in AT and AT+788 groups when compared to CO. The treatment with LASSBio788 recovers only partially the progressive motility. **Discussion:** Our preliminary results showed that administration of LASSBio-788, a potential antiatherogenic compound, did not cause any harmful effect on the spermatogenic process and testicular parenchyma structure, however it was not able to recover the harmful effect of hypercholesterolemia on male gamete. **Supported by:** CAPES, CNPq, FAPERJ, PROPPi/UFF.

11.014 Evaluation of safety of cyclosporin used in dogs. Anater A, Ribeiro DR, Rebello AP, Solomon S, Souza Netto A, Farias MR, Pimpão CT FCAV-PUCPR

Introduction: Ciclosporin (CS) is an immunosuppressive drug isolated from fungi and despite its clinical efficacy, their systemic use is associated with various side effects. Currently has been indicated for the treatment of atopic dermatitis canina. This study was approved by the Ethics Committee of the Pontifical Catholic University of Paraná under number 588. **Objective:** To evaluate the safety of cyclosporine (CS) in healthy dogs. **Methods:** 12 rats were selected and randomly divided into two groups, CS5 (5mg/kg/SID) and CS10 (10mg/kg/SID) orally for 60 days. The dose was calculated as though the CS test was formulated in capsules 25 and 50 mg / kg doses were adjusted upward. Clinical evaluations were performed by the system, bi-evaluating all physiological parameters (weight, mucous membranes, skin and appendages, pulse, state of hydration, capillary refill time, heart rate and respiratory rate), in addition to evaluation of the respiratory system, cardio-circulatory linfohematopoiético, digestive and genito-urinary tract. We collected blood samples (blood count, alkaline phosphatase, ALT, AST, potassium ion, sodium ion, ionized calcium, phosphorus, urea and creatinine, total protein and albumin) and urine (urinalysis) on days D0, D +15, D + 30, D 45 and D 60 after the start of the test. The data were analyzed using the Kruskal-Wallis test followed by Dunn's test for comparison within groups and between groups we used the Mann-Whitney test. **Results:** CS was well tolerated by the animals (CS5 and 10) and there was no difficulty in its administration. Clinical symptoms related side effects were observed in 33% of animals in CS5 showed sporadic episodes of vomiting for two days, which involuted spontaneously. There was no change evident cutaneous (pharmacodermias), cardiovascular, respiratory, gastroenteric, liver, and urinary or neurological. In the group CS5 was realized an increase in hematocrit values and alanine aminotransferase and decreases in the level of eosinophils ($p < 0.01$). In the CS10 group observed changes in the values of alanine aminotransferase and alkaline phosphatase, and a decrease in the amounts of calcium and potassium ion ($p < .01$). However, all figures in both groups remained within the reference values. Some values eritograma and WBC showed small oscillations in relation to the reference values, but are not important clinical relevance. There was no difference between the other parameters analyzed. **Discussion:** CS overdoses cause emesis forced two hours after ingestion may occur transient hepatotoxicity and nephrotoxicity. In the present study, no significant side effects in the digestive system of dogs of groups 2, only two animals had episodes of vomiting that involuted without it being necessary to stop treatment. Considering ALT, ALP and ions, the dogs showed no clinical evidence of side effects, which may be explained by the fact that these values are maintained within the physiological parameter. **Conclusion:** The CS used in these concentrations is safe for use during the 60 days left to the discretion of the veterinarian to determine the optimal dose for the patient's need.