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ANNUAL MEETING OF BIOSCIENCE SOCIETIES 2021

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RESPONSIBLE EDITORS
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period of growth between 10 and 19 years extended to 21 years. The prevalence of primary, clinical (CHT) and especially subclinical (SHT) hypothyroidism in children-adolescent is less than 2% with a low incidence of hyperthyroidism (HyT). These pathologies have a profound impact on growth, maturation, pubertal development, adult height and have been linked to pro-atherogenic metabolic abnormalities. **OBJECTIVE.** Study the frequency of thyroid dysfunction in adolescents treated in a public institution. **MATERIALS AND METHODS.** We evaluated 134 adolescents of both sexes who attended the laboratory for 6 months. The demographic and hormonal data were collected from the Laboratory Informatic System. Serum thyrotrophin (TSH) and free thyroxine (FT4) were dosed by chemiluminescence in ARCHITECT. Results are expressed as mean (X) \pm standard error of mean (SEM), ranges, parametric t-test, significance $p < 0.05$ (GraphPadPRISM 8.0.1). Stages of adolescence (age) Middle Adolescence (MA): 14 to 16, Late (LA): 17 to 21; SHT, CHT and HyT according to consensus. **RESULTS.** The group included 34 MA and 100 LA, 81% female and 19% male. In MA males 35% vs 13% in LA, were similar distribution of female between groups. TSH (μ IU /mL) and FT4 (ng/dL) in MA 3.36 ± 0.33 (0.89 to 8.10) and 0.99 ± 0.09 (0.88 to 1.19), in LA 3.65 ± 0.006 (0.006 to 77.91) and 1.05 ± 0.11 (0.85 to 1.41) respectively. The frequency of thyroid dysfunction was 16.2%: SHT 13.5% (5% MA, 8.5% LA), CHT 0.7% (male LA), HyT 2.0% (Graves Basedow, subclinical hyperthyroidism). The female-male ratio was MA 5/2 and LA 15/1. **CONCLUSION.** In our group, the frequency of hypothyroidism was higher than the prevalence reported in the literature, respecting the patterns by sex. Our results support the intervention of the endocrinologist for diagnosis, follow-up and eventual treatment in the suspected illness and/or TSH level altered.

FARMACOCINÉTICA

81. (124) COMPARACIÓN DE LA FARMACOCINÉTICA DE AMPICILINA SÓDICA EN LLAMAS (*Lama glama*) ADMINISTRADA POR VÍA INTRAMUSCULAR EN DIFERENTES SITIOS DE APLICACIÓN

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Las enfermedades infecciosas en la llama (*Lama glama*) repercuten negativamente en la producción y en la preservación de las especies silvestres. La ampicilina es un antibiótico betalactámico activo contra las bacterias que producen las enfermedades más comunes en el ámbito veterinario. Existen pocos productos aprobados para su uso en llamas y la mayoría de los tratamientos antibacterianos se aplican empíricamente y extrapolando de otras especies emparentadas (ovejas, cabras, vacas), siendo escasos los estudios farmacocinéticos de antibióticos en camélidos. Tanto la formulación como la vía de administración pueden modificar el perfil farmacocinético y con ello la eficacia clínica. El objetivo del presente trabajo fue comparar la farmacocinética de la ampicilina sódica administrada por vía intramuscular (im) en dos sitios de aplicación, músculo semitendinoso (ST) y músculos sublumbares (SL), en llamas.

Las concentraciones plasmáticas se determinaron mediante el método microbiológico, utilizando *Bacillus subtilis* ATCC 6633 como microorganismo patrón. La curva fue validada en plasma para linearidad ($r^2: 0.99$), exactitud (>90%) y precisión (6.33%) para concentraciones entre 100 y 0,09 μ g/ml. Los resultados fueron analizados utilizando Graph Pad Prism, Excel y WinNonlin. Los límites de cuantificación y de detección del método fueron de 0,09 μ g/ml. Los parámetros farmacocinéticos fueron: $C_{\text{máx}}$: 35.89 ± 9.31 y 26.69 ± 14.21 ; $T_{\text{máx}}$: 0.19 ± 0.07 y 0.62 ± 0.47 ; $t_{1/2}$: 0.66 ± 0.14 y 1.24 ± 0.38 y TMR_{inf} : 0.68 ± 0.09 y 1.38 ± 0.31 ; $T > CIM$ para 0.5μ g/ml: 3.51 ± 0.31 y 5.58 ± 1.26 , para la administración en ST y SL, respectivamente. Se encontraron diferencias significativas en $t_{1/2}$, TMR_{inf} , y $T > CIM$ relacionadas con el sitio de aplicación, siendo mayores los valores para la aplicación en SL. Sin embargo, no se requiere realizar modificaciones en la posología para la ampicilina sódica cuando se ad-

ministra a dosis de 20 mg/kg por vía im cada 6 u 8 h cuando los microorganismos presenten CIM 0.5μ g/ml.

82. (287) SUSTAINED TREATMENT WITH FENBENDAZOLE INDUCES CYTOCHROME P450 ENZYME ACTIVITIES IN SWINE

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The anthelmintic fenbendazole (FBZ), a benzimidazole (BZD) drug, is used to control gastrointestinal parasites in swine production. This compound is commercially available as a powder to be mixed with food for oral administration in pigs for 7-10 days. BZD-containing drugs possess the ability to significantly induce certain cytochrome P450 (CYP) isozymes in different species, particularly those belonging to the CYP1A family. This work aimed to evaluate *in vitro* the effect FBZ sustained administration on CYP1A-dependent enzyme activities in pig liver. Eleven (11) piglets were divided in two groups: five (5) animals remained untreated and used as controls; six (6) animals were treated with a FBZ commercial powder mixed with food. The drug concentration in food was 0.01% and animals were fed *ad libitum* for 10 days. Animals were euthanized for preparation of liver microsomes. Two CYP 1A-dependent enzyme activities, namely 7-ethoxresorufin O-deethylase (EROD) and methoxyresorufin O-demethylase (MROD) were assayed in a spectrofluorometer. FBZ and its S-oxygenated metabolites, oxfendazole (OFZ) and fenbendazole sulphone (FBZSO₂), were detected in the systemic circulation of treated piglets. Mean plasma AUCs (μ g.day/mL) were 0.28 ± 0.08 (FBZ), 4.10 ± 0.58 (OFZ) and 4.56 ± 1.01 (FBZSO₂). The parent drug FBZ represented around the 46% ($4.66 \pm 1.59 \mu$ g/g) of the total anthelmintic molecules in the liver, followed by OFZ ($3.11 \pm 1.06 \mu$ g/g, 31%) and the inactive FBZSO₂ ($2.30 \pm 0.99 \mu$ g/mL, 23%). In liver microsomes from treated animals, both EROD and MROD enzyme activities increased 24.5-fold ($p=0.003$) and 17.2-fold ($p=0.0006$), respectively. The sustained administration of FBZ caused the induction of the CYP1A-dependent metabolism in pig liver. This fact may affect the metabolic fate of FBZ itself but also of other foreign compounds such as aflatoxin B1 present in certain pig foodstuffs.

83. (429) EFFECT OF DIFFERENT ORGAPHOSPHATES ON THE HEPATIC OXIDATIVE METABOLISM BY MIXED FUNCTION OXIDASES IN CATTLE.

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Organophosphates (OPs) are widely used for crop protection in agriculture and for the control of ectoparasites in animal husbandry. The sustained use of these chemical compounds increases the risk of environmental contamination and/or alteration of different physiological cellular functions in farm animals. A number of OPs are substrates of hepatic mixed function oxidases, such as those belonging to the cytochrome P450 (CYP) and flavin-containing monooxygenase (FMO) families of enzymes. In addition, these xenobiotics may also affect enzyme function by induction or inhibition of their catalytic activities. This work aimed to evaluate *in vitro* the effect of the following OPs: chlorpyrifos (CPF), ethion (ETN), diazinon (DZN) and dichlorvos (DCV) on CYP- and FMO-dependent enzyme activities in cattle liver. Bovine ($n=4$) liver microsomes were incubated (10 min at 37°C in aerobiosis) in the absence (control assays) and in presence of each OP compound under study at 1, 10 and 100 μ M (final concentrations). Five CYP- or FMO-dependent catalytic activities were assayed by spectrofluorimetric or HPLC methods: 7-ethoxyresorufin O-deethylase (EROD, for CYP1A1), methoxyresorufin O-demethylase (MROD, for CYP1A2), benzyloxyresorufin O-debenzylase (BROD, for CYP2B), testosterone 6-beta hydroxylase (for CYP3A) and benzydamine N-oxidase (for FMO). Only the CYP3A-dependent hepatic metabolism was significantly affected by the presence of

ETN and DZN. ETN, at 10 μ M and 100 μ M, inhibited ($p<0.01$) testosterone 6-beta hydroxylase activity (76% and 81%, respectively) in cattle liver microsomes. Similar results were obtained in presence of equimolar concentrations of DZN (74% and 93% at 10 μ M and 100 μ M, respectively; $p<0.01$). Both ETN and DZN would potentially interfere with the pattern of the hepatic metabolism of relevant CYP3A substrates pharmacologically relevant in bovine medicine, such as tiamulin, macrolide antibiotics and the ionophore monensin.

84. (448) MEROPENEN INHIBITS THE CYTOCHROME P450 (CYP) 3A-DEPENDENT BIOTRANSFORMATION OF THE IMMUNOSUPPRESSIVE TACROLIMUS IN HUMAN LIVER MICROSOMES.

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Tacrolimus (TAC), a immunosuppressive drug used in solid organ transplantation, is metabolized by CYP3A4 and 3A5. The simultaneous administration of TAC and meropenem (MEP) in pediatric kidney transplant patients may lead to a significant increase in plasma concentrations of TAC. We hypothesized that this negative pharmacokinetic interaction is due to the inhibition of the CYP3A4-mediated biotransformation of TAC by MEP, particularly in those individuals lacking the expression of CYP3A5. The aim of this study was to evaluate *in vitro* the potential metabolic interaction between TAC and MEP. Human liver microsomes were prepared with discard liver samples obtained from healthy donors ($n=2$) and individuals subjected to tumor resection ($n=2$). The specific CYP3A-dependent enzyme activity, testosterone 6-beta hydroxylase, was assayed in the absence (control) and in presence of TAC (5 and 20 μ M), MEP (10 μ M) and the combinations of TAC and MEP. TAC, incubated at 5 and 20 μ M, inhibited ($p<0.05$) the CYP3A-mediated 6-beta hydroxylation of testosterone (18±13% and 51±16%, respectively). This finding may confirm the high affinity of CYP3A4 for TAC. MEP, at 10 μ M, did not affect this enzyme reaction. After co-incubations of TAC and MEP, testosterone 6-beta hydroxylase activities resembled those observed when TAC was incubated alone. In control assays, rates of TAC metabolism were 30±20 and 120±40 pmol/min.mg of microsomal protein, respectively. MEP, at 10 μ M, significantly inhibited ($p<0.05$) the hepatic biotransformation of TAC; rates (pmol/min.mg) of TAC metabolism (at 5 and 20 μ M) were 20±10 (43±24% inhibition) and 70±50 (49±23% inhibition), respectively. These preliminary results show a metabolic interaction between TAC and MRP on CYP3A-dependent metabolism in human liver. The enhancement of the systemic availability of TAC observed *in vivo* in the co-administration with MEP would be due to the inhibition of the CYP3A4-dependent biotransformation of the immunosuppressive drug.

Farmacognosia - Farmacobotánica

85. (091) ANTIANGIOGENIC ACTIVITY OF THE ALKALOID SKIMMIANINE ISOLATED FROM ZANTHOXYLUM COCO.

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The term angiogenesis refers to the development of new blood vessels from the preexisting vasculature. Under physiological conditions, this process is strictly regulated being focal and self-limited in time. Nevertheless, imbalances between the biochemical signals that regulate angiogenesis may occur, resulting in a chronic neovascularization that takes part in a large number of diseases including neoplastic transformation, rheumatoid arthritis, psoriasis, and different ocular conditions. In this context, the development of new agents capable of downregulating pathological angiogenesis become relevant in the field of drug discovery.

The flora from Argentina stands out among the different sources of new bioactive molecules. In previous studies conducted by our research team, the ethanol extract of *Zanthoxylum coco* showed a remarkable antiangiogenic effect. Therefore, this species was submitted to the bioassay guided isolation of its active principle. This process involved the alternation of different chromatographic techniques with the evaluation of the antiangiogenic activity in terms of the tube formation assay. One compound identified by diverse spectroscopic techniques as the alkaloid skimmianine was isolated. This molecule significantly inhibited tube formation even at 12.5 mg/mL. HPLC analysis showed that this compound is one of the major constituents of the ethanol extract of *Z. coco*. No toxic effect against peripheral blood mononuclear cells, used as model of normal cells, was observed. Additionally, the compound did not affect the integrity of the erythrocyte membrane. Pharmacokinetic and drug-likeness parameters were evaluated by SwissADMET online tool.

The obtained results support the potential of the flora from Argentina as a source of new small molecules capable of downregulating neovascularization and position this naturally occurring alkaloid as a promising lead for the development of new analogs with improved antiangiogenic activity.

86. (194) INHIBITION OF LIPID PEROXIDATION BY CANNABIS SATIVA AND LARREA DIVARICATA EXTRACTS AND THEIR COMBINATION

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Oxidative stress, through lipid peroxidation, affects central nervous system altering cognitive functioning during epilepsy. *Cannabis sativa* L. (Cannabaceae) is a medicinal plant used as anticonvulsant, being cannabidiol (CBD) its main anticonvulsant agent. *Larrea divaricata* Cav. (Zygophyllaceae) is an autochthonous plant with antioxidant activity. The aim of this work was to study the synergistic effect of an ethanolic extract of *C. sativa* (CSR) and an aqueous extract of *L. divaricata* (LE) on inhibition of lipid peroxidation to improve the therapeutic outcomes. The participation of CBD and nordihydroguaiaretic acid (NDGA) was evaluated.

CBD and NDGA were identified and quantified by HPLC-UV. Antioxidant activity was determined in an egg yolk phospholipid peroxidation model. A combination index (CI) was calculated to investigate the interaction between extracts. Results were expressed as inhibitory concentration 50 (IC50) or as mean g% p/p ± SEM of two or three assays made in triplicate.

Quantification of CBD: 23.1 g% p/p. Quantification of NDGA: 1.56 g% p/p. Inhibition of lipid peroxidation: IC50 drugs alone: CSR: 30.5±3.0 μ g/ml; LE: 630.95 ± 63 μ g/ml; CBD: 10.2±1 μ g/ml. IC50 of better combinations: CSR + LE 500 μ g/ml: 2.45±0.1 μ g/ml ($p<0.0001$); CBD+ LE 500 μ g/ml: 2.18 ± 0.2 μ g/ml ($p<0.0001$). CI of better combinations: CSR 10 μ g/ml/LE 500 μ g/ml: 0.16 (strong synergism); CSR 3 μ g/ml/LE 500 μ g/ml: 0.36 (significative synergism).

Conclusions: CSR and LE presented inhibitory activity. CBD was involved in CSR activity. NDGA showed a very low activity. The association of extracts showed strong, significative or weak synergism