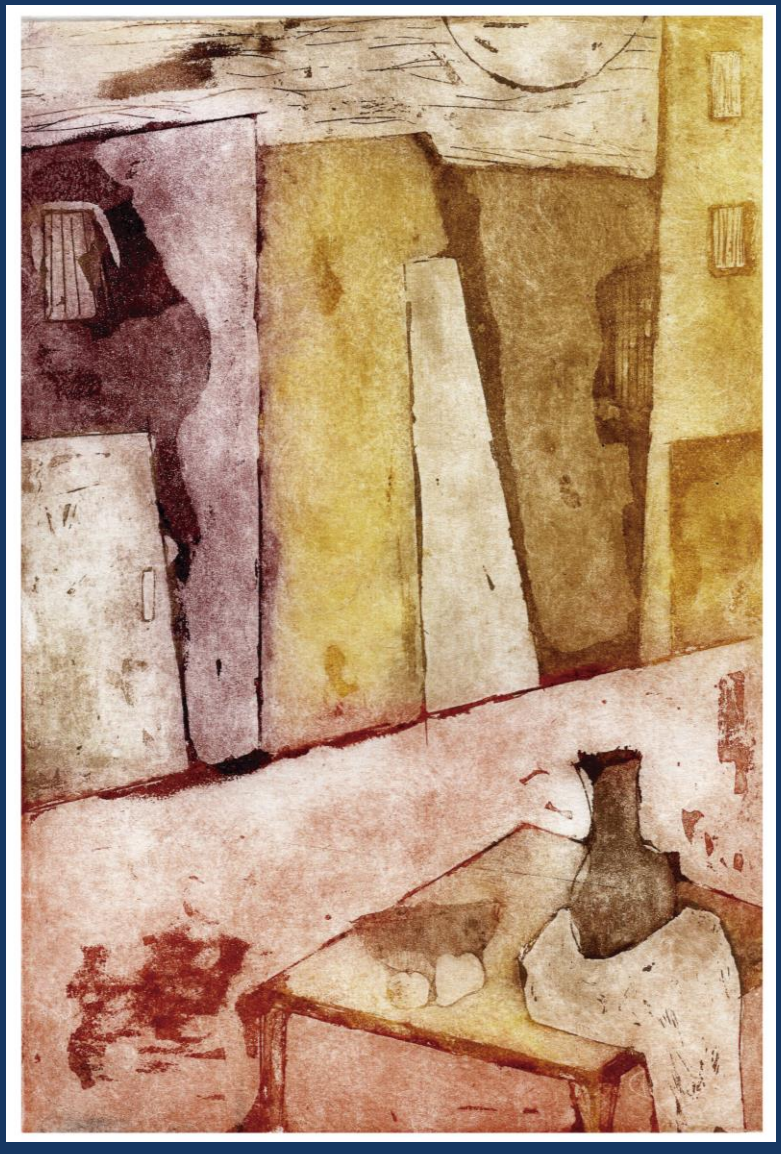
2019

medicina

BUENOS AIRES VOL. 79 Supl. IV - 2019

80° Aniversario



MEDICINA

Volumen 79, Supl. IV, págs. 1-338

medicina

BUENOS AIRES, VOL. 79 Supl. IV - 2019

COMITÉ DE REDACCIÓN

MIEMBROS EMÉRITOS

La Tapa (*Ver* pág. 4)
Atardecer en la tarde
Antonella Ricagni

MEDICINA (Buenos Aires) – Revista bimestral – ISSN 0025-7680 (Impresa) – ISSN 1669-9106 (En línea)

REVISTA BIMESTRAL
Registro de la Propiedad Intelectual N° 02683675
Personería Jurídica N° C-7497
Publicación de la Fundación Revista Medicina (Buenos Aires)
Propietario de la publicación: Fundación Revista Medicina
Queda hecho el depósito que establece la Ley 11723

Publicada con el apoyo del Ministerio de Ciencia, Tecnología e Innovación Productiva.
MEDICINA no tiene propósitos comerciales. El objeto de su creación ha sido propender al adelanto de la medicina argentina.
Los beneficios que pudieran obtenerse serán aplicados exclusivamente a este fin.
Aparece en *MEDLINE (PubMed), ISI-THOMSON REUTERS (Journal Citation Report, Current Contents, Biological Abstracts, Biosis, Life Sciences), CABI (Global Health), ELSEVIER (Scopus, Embase, Excerpta Medica), SciELO, LATINDEX, BVS* (Biblioteca Virtual en Salud), *DOAJ, Google Scholar y Google Books.*
Incluida en el Núcleo Básico de Revistas Científicas Argentinas del CONICET.

Directores Responsables:
Basilio A. Kotsias, Eduardo L. De Vito, Isabel Narvaiz Kantor, Guillermo B. Semeniuk

Secretaría de Redacción: Ethel Di Vita, Instituto de Investigaciones Médicas Alfredo Lanari, Combatientes de Malvinas 3150, 1427 Buenos Aires, Argentina
Tel. 5287-3827 Int. 73919 y 4523-6619
e-mail: revmedbuenosaires@gmail.com – http//: www.medicinabuenosaires.com

Vol. 79, Supl. IV, Noviembre 2019

UNIDAD DE TRATAMIENTOS INNOVADORES, SERVICIO MEDICINA DE PRECISIÓN, HOSPITAL DE PEDIATRÍA GARRAHAN (1); SERVICIO DE PATOLOGÍA, HOSPITAL DE PEDIATRÍA GARRAHAN (2); SERVICIO DE HEMATO-ONCOLOGÍA, HOSPITAL DE PEDIATRÍA GARRAHAN (3); SERVICIO DE OFTALMOLOGÍA, HOSPITAL DE PEDIATRÍA GARRAHAN (4); DEPARTAMENTO DE HEMATOLOGÍA Y ONCOLOGÍA PEDIÁTRICA, HOSPITAL SANT JOAN DE DEU (5); SERVICIO DE MEDICINA DE PRECISIÓN, HOSPITAL DE PEDIATRÍA GARRAHAN (6)

Patients with metastatic retinoblastoma receive an empirical and aggressive chemotherapy treatment but they still have a fatal outcome. Considering this malignancy like an unmet medical need, new therapies or alternative drugs are necessary. We were previously successful in identifying FDA approved drugs with cytotoxicity effect in a cell line derived from tumor dissemination in the lymph node using High-Throughput Screening. Now, we aimed to identify and evaluate drug combinations with a synergistic effect between active drugs previously selected using a homemade decision algorithm. We evaluated carboplatin-CB, vincristine-VC, panobinostat-PN and bortezomib-BT in a 3x2 concentration matrix at the IC10, IC25 and IC50 (drug concentration that inhibits 10, 25 or 50 % of cell proliferation) to determine the most promising combinations. To confirm the activity of the selected combinations, we evaluated the dose-response curves of the combination and compared the IC50s to those calculated for individual drugs according to the combination index (CompuSyn). Mean (range) IC50s for CB, PN, BT, and VC was 95.6 µM (94.2-97.6), 67.2 nM (74.2-47.7), 5.2 nM (5.2-3.2), and 62.6 nM (56.7-68.5), respectively. The IC50s for CB and PN combined with PN at the IC25 and BT at the IC50 were 70 µM and 8.2 mM, respectively. Both combinations presented a combination index <1 meaning a synergistic effect. In this study we managed to develop a rational design of drug selection to evaluate cytotoxic activity in preclinical models and identified two drug combinations with synergistic effects in a primary cell line derived from a patient with metastatic retinoblastoma. Synergistic effect was observed between CB-PN and PN-BT in vitro. These results are the first step for an upcoming evaluation in an animal tumor model.

0189 - P-GP MODULATING EFFECT OF THE PENTACYCLIC TRITERPENOID BETULIN, ISOLATED FROM LIGARIA CUNEIFOLIA, IN MULTIDRUG RESISTANT LEUKEMIC CELLS.

Jerónimo LAIOLO | Mariana Belen JORAY | María Cecilia CARPINELLA

INSTITUTO DE INVESTIGACIONES EN RECURSOS NATURALES Y SUSTENTABILIDAD JOSE SANCHEZ LABRADOR S.J.

Multidrug resistant (MDR) constitutes nowadays one of the major obstacle in cancer therapy, being the efflux of drugs by P-glycoprotein (P-gp) a predominant factor. Plants are recognized as a rich source of metabolites with structural diversity being an invaluable starting point for drug discovery. With the aim of finding promising compounds to modulate MDR phenotype mediated by P-gp, 120 native and naturalized plants collected in the hills of Córdoba, Argentina, were screened on K562 human myelogenous leukemia cell line and its MDR counterpart Lucena 1. Ligaria cuneifolia was one of the most active and thus it was subjected to bioguided isolation to separate the active principle responsible for its activity. This process yielded the triterpenoid betulin (1). Intracellular doxorubicin (DOX) accumulation was determined, at non-cytotoxic concentrations determined by MTT, using flow cytometry. Fluorescence intensity radio (FIR) was calculated as the ratio between the fluorescence intensity of each cell line treated and the fluorescence intensity of its respective solvent control. The activity was confirmed by the MTT reversal assay. Compound 1 increased the accumulation of DOX at a minimum effective concentration (MEC) of 1.56 µM (FIR 1.09 ± 0.04) and increased DOX cytotoxicity by a factor of 3.83 ± 0.26 at 12.5 µM and 1.29 ± 0.08 at 0.39 µM showing no differences with respect to the same concentrations of verapamil, used as positive control ($p \geq 0.05$). Compound 1 showed no effect at the MEC on K562 cells. This is the first report regarding compound 1 as an inhibitor of the efflux mediated by P-gp. This triterpenoid could arise as scaffold to obtain novel P-gp inhibitors to use in combination with anticancer drugs for the improvement of leukemia therapies.

0190 - STUDY OF THE ANTIANGIOGENIC EFFECT OF A TERTHIOPHENE ISOLATED FROM TAGETES MINUTA.

María Candelaria LLORENS DE LOS RÍOS(1) | Priscila Ailin LANZA CASTRONUOVO(2) | Cecilia Luján BARBIERI(2) | Macarena FUNES CHABAN(3) | Domingo Mariano VERA(2) | Gastón SORIA(1) | María Cecilia CARPINELLA(3) | **Mariana Belen JORAY** (3)

CIBICI-CONICET. FACULTAD DE CIENCIAS QUÍMICAS. UNIVERSIDAD NACIONAL DE CÓRDOBA. (1); INBIOTEC-CONICET, FACULTAD DE CIENCIAS EXACTAS Y NATURALES. UNIVERSIDAD NACIONAL DE MAR DEL PLATA. (2); IRNASUS-CONICET. FACULTAD DE CIENCIAS QUÍMICAS. UNIVERSIDAD CATÓLICA DE CÓRDOBA. (3)

Angiogenesis is an essential mechanism involved in biological processes such as reproduction, development and wound healing. Imbalances between the factors that regulate angiogenesis have been linked to different diseases that affect human health. Despite the great progress achieved in antiangiogenic therapy, its limited efficacy, severe adverse effects and the development of resistance demands the continuous development of novel therapeutic agents to overcome these obstacles. In this context plant-derived metabolites continue to play a highly significant role in drug discovery. From a screening performed in our laboratory, the ethanol extract of Tagetes minuta arose as a potent antiangiogenic agent. This effect was evaluated by the tube formation assay using bovine aortic endothelial cells (BAEC). Through bio-guided chemical fractionation three compounds identified as: 5´-methyl-5-(4-hydroxybut-1-ynyl)-2,2´-bithiophene (1), 5-(4-hydroxybut-1-ynyl)-2,2´-bithiophene (2) and alfa-terthienylmethanol (3) were obtained. Among these, compound 3 showed a potent antiangiogenic activity (IC50 = 2.69 µM). The influence of 3 over cell proliferation and cell invasion induced by the vascular endothelial growth factor (VEGF) was evaluated. While no effect was observed in the MTT proliferation assays, 3D transwell experiments demonstrated that compound 3 efficiently blocked cell invasion. Additionally, molecular docking experiments showed that 3 overlaps with the tyrosine kinase inhibitor sorafenib (a potent antioangiogenic agent) at the catalytic cleft of VEGF receptor 2 interacting with key aminoacids such as Glu885, Phe1047 and Cys919, extending over Val916 into the adjacent allosteric hydrophobic back pocket resembling a type II inhibition. These studies contribute to position 3 as a potential candidate to be used in antiangiogenic therapy itself or as a lead compound for the development of analogues with improved activity.

0375 - COMPARATIVE XENOBIOTIC BIOTRANSFORMATION IN PRECISSION-CUT LIVER SLICES FROM SWINE AND CATTLE

María Victoria MIRÓ | Paula VIVIANI | Juan HERRERA | Laura MATÉ | Carlos LANUSSE | Adrian LIFSCHITZ | Guillermo VIRKEL

CIVETAN (CONICET-CICPBA-UNCPBA), FACULTAD DE CIENCIAS VETERINARIAS, UNCPBA, TANDIL

Species differences in the pattern of metabolism of foreign compounds is a key issue for veterinary practitioners. Comparative studies on the in vitro hepatic metabolism of xenobiotics among different farm animals requires the use of consistent and robust methodologies. The aim of the current work was to validate the technique of precision-cut liver slices (LSs) for comparative studies on xenobiotic metabolism in swine and cattle. Swine (n= 3) and bovine (n= 6) liver samples were obtained from local abattoirs. LSs

(around 20 mg wet weight) were produced by operating a Brendel-Vitron™ tissue slicer filled with oxygenated ice-cold Krebs buffer. LSs were cultured (up to 6 h) in Williams' Medium E at 37 °C under a humidified atmosphere (95% O_2: 5% CO_2). Tissue viability was assessed by histopathology and the measurement of intracellular reduced (GSH) and oxidized (GSSG) glutathione. The assayed enzyme activities were: benzydamine N-oxidase (BZ N-ox, flavin-containing monooxygenase), ethoxyresorufin O-deethylase (EROD, cytochrome P450 1A1) and methoxyresorufin O-demethylase (MROD, cytochrome P450 1A2). The S-oxidation of the anthelmintic drugs albendazole (ABZ) and fenbendazole (FBZ) was also assessed. HPLC analysis was performed and the rates of appearance of the metabolites in the incubation medium were calculated. Similar BZ N-ox and EROD activities were observed in both species. Conversely, MROD was 2.6-fold higher ($p<0.05$) in swine (12 ± 9 pmol/h) compared to cattle (4.6 ± 2.5 pmol/h). The S-oxidation of ABZ was 1.5-fold higher ($p<0.05$) in swine (3.3 ± 0.7 nmol/h) compared to cattle (2.2 ± 0.5 nmol/h), but the opposite occurred for FBZ S-oxidation. In both species, as observed in other in vitro systems like liver microsomes, ABZ S-oxidation resulted 5-fold (cattle) and 13-fold (swine) higher ($p<0.05$) compared to FBZ S-oxidation. The work described here shows that LSs are a useful tool to obtain relevant information on species-specific differences in xenobiotic metabolism.

0493 - GA-RXODE METHOD, A NEW PROCEDURE WITH SEVERAL USES IN PHARMACOMETRICS

Mikhail MOROZOV | **Eduardo NUSKE** | Héctor Alejandro SERRA

PRIMERA CÁTEDRA DE FARMACOLOGÍA, FACULTAD DE MEDICINA, UBA

Background: In the "Big Data era" it seems paradoxical that few drugs have a complete and available set of pharmacometric data. Combining two R written routines, "Genetics Algorithms" (GA) and "Running simulations from Ordinary Differential Equations based models" (RxODE), we have developed a procedure to improve those data from the available ones. The aim of present work was to describe and validate GA-RxODE method, an informatic instrument running in any computer, capable to optimize raw data in general. We have applied the method on pharmacokinetic (PK) raw data of clarithromycin sustained release formulation study and validated it by population PK modelling in SAEMIX, an R written non-linear mixed effects algorithm. Applying GA-RxODE we have obtained a final construct called token data or sim(ulated)-data. From reconstructed sim-data concentration-time curves of clarithromycin we have generated several population PK models: Complete Model (CM) including the original number of determinations (11) as the clarithromycin study, and Partial Models (PMs) containing 4 to 10 determinations. We have expressed the values as median (interquartile range) and used one- or two-way ANOVA to analyze them. The uncorrected-to-zero correlation between variances (raw concentration and the corresponding sim-data) exhibited a slope of 0.6026 ± 0.087; r^2= 0.842; $p<0.001$, indicating sim-data maintained the original structure with less variability. In addition, Cmax analysis, CM= 1.91 (1.54-2.28) mg/l vs PM with only 4 values= 1.73 (1.41-2.04) mg/l, was non-significant indicating a good agreement between models. Conclusions: By optimizing raw data, maintaining their structure and reducing their variability, the derived sim-data can be suitable to any further PK analysis. Furthermore, the procedure can be considered valid because the CM was non-different from PMs. This places GA-RxODE method as a proper tool to be applied in Pharmacometrics.

0635 - POPULATION PHARMACOKINETIC MODELING OF PYRIMETHAMINE (PYR) DURING THE TREATMENT OF CONGENITAL TOXOPLASMOSIS IN PEDIATRICS.

Ulises FLEITAS (1) | Maria Elena MARSON(1) | Jaime ALTCHEH(1) | Carlos PEREZ(2) | Anabela PROSPITTI(3) | Guillermo MOSCATELLI(2) | Samanta MORONI(4) | Guido MASTRANTONIO(1) | Facundo GARCIA BOURNISSEN(2)

FACULTAD DE CIENCIAS EXACTAS, UNLP - UPL, CICPBA - CONICET (1); HOSPITAL DE NIÑOS RICARDO GUTIERREZ - CONICET (2); UPL-COMISION DE INVESTIGACIONES CIENTÍFICAS DE LA PROVINCIA DE BUENOS AIRES (3); HOSPITAL DE NIÑOS "RICARDO GUTIERREZ" (4)

Infection with Toxoplasma gondii, is one of the most widespread zoonoses in the world. Particularly risky is congenital form (CT) with a global risk of transmission by this route of about 40 %, reaching 90 % in the last month of pregnancy. Children with CT receive treatment, usually PYR and sulfadiazine, to prevent morbidity. The current therapy in pediatric patients is protocolized, but due to the absence of pediatric formulations the drugs are prepared in the hospital pharmacy in the form of syrup and at the moment, pharmacological parameters of these drugs have not been corroborated in patients, especially PYR. The objective of this study was to evaluate the pharmacokinetics of PYR in the treatment of pediatric toxoplasmosis, from a population approach (Pop-PK). The study was approved by the institutional ethics committee of the HNRG, including the informed consent for the use of the samples. Residual blood samples (taken for routine clinical procedures) were obtained from 12 pediatric patients undergoing treatment with PYR (0.77-2.7 mg/kg/day), and followed-up in the Parasitology service of the Ricardo Gutiérrez Children's Hospital (HNRG). PYR was quantified on 60 serum samples by high performance reverse chromatography coupled to tandem mass spectrometry (Shimadzu Nexera and Sciex qTrap6500). For the analysis of Pop-PK and the evaluation of pharmacokinetic models, Monolix® was used. Akaike´s information criteria and Bayesian information criteria were selected as statistical criteria for the selection of the best model. The results obtained in the Pop-PK modeling proposed a one-compartmental (Vp= 1.05 L) model with first-order absorption (Kap= 0.843 h^{-1}) and linear elimination (Kep= 0.00531 h^{-1}), with weight-dependent distribution volume (β= 0.349 L/Kg). Other more complex models did not result in an improvement in fit and were discarded. Pharmacokinetic studies reported for PYR that differ in populations, set of drugs used and treatment times, propose similar results when comparing Ka and Ke for the pediatric population, but were found to be significantly different from those evaluated for the adult population.

0742 - DIFLOXACIN PLASMA PHARMACOKINETICS, TISSUE DISPOSITION AND WITHDRAWAL PERIOD IN BROILERS

Bernardo SOBRECASAS(1) | Natalia URZÙA(1) | Jimena MESSINA(1) | Marìa TONINI(1) | Guillermo PRIETO(1) | Marìa Emilia ERRECALDE(1) | Carlos LUDERS(2) | Rosendo LIBOÀ(1) | **Carlos ERRECALDE** (1)

UNIVERSIDAD NACIONAL DE RÍO CUARTO (1); UNIVERSIDAD CATÒLICA DE TEMUCO (2)

Difloxacin (DFX) is a fluoroquinolone used only in domestic animals that develops bactericidal actions by selective blocking of the DNA-gyrase enzyme in G+, G- and mycoplasma microorganisms. The background of DFX in mammals indicates high tissue distribution. This study seeks to establish in broiler chickens, if plasma and tissue levels are equivalent and establish a withdrawal period (Pr) in different tissues. Chickens (n= 70) Cobb line, approximately 45 days old and 1.9 ± 0.2 kg weight, randomly selected from a stock of 1200 birds. 14 batches of 5 animals each were formed, who received an oral single dose of 20 mg/kg of DFX after fasting for 12 and 3 hours before and after application, respectively. Subsequently, each batch was sacrificed at pre-established times, samples of blood, by exanguination, and tissue samples were obtained until 120 hours post application. DFX was quantified by HPLC using C18 column, mobile phase consisting of water, acetonitrile and triethylamine (790: 200: 10 v/v/v) adjusted to pH 3.0 and fluorometer reading set at 295 nm excitation and 490 nm emission. In plasma and each tissue, DFX concentration averages by time were analyzed with the non-compartimental pharmacokinetic software PK Solution. Pr was