El material que se presenta a continuación proviene de los datos proporcionados por la OAIC (Oficina de Apoyo a la Investigación Clínica de nuestro Hospital).

Abstracts de publicaciones internacionales ISI 2011

DEPARTAMENTO CARDIOVASCULAR

BASIC CLIN PHARMACOL TOXICOL. 2011 APR;108(4):256-62.

ANTIOXIDANT THERAPY REDUCES OXIDATIVE AND INFLAMMATORY TISSUE DAMAGE IN PATIENTS SUBJECTED TO CARDIAC SURGERY WITH EXTRACORPOREAL CIRCULATION.

Castillo R, Rodrigo R, Perez F, Cereceda M, Asenjo R, Zamorano J, Navarrete R, Villalabeitia E, Sanz J, Baeza C, Aguayo R.

Ischaemia reperfusion injury is a pathophysiological event that occurs after cardiac surgery with extracorporeal circulation. This clinical event has been associated with the induction of oxidative and inflammatory damage in atrial tissue. Here, we tested whether combined omega 3 polyunsaturated fatty acids (n-3 PUFA)-antioxidant vitamin protocol therapy reduces oxidative and inflammatory cardiac tissue damage. This trial assigned 95 either-sex patients to supplementation with n-3 PUFA (2 g/day), or matching placebo groups, 7 days before on-pump surgery. Antioxidant vitamins C (1 g/day) and E (400 IU/day) or placebo were added from 2 days before surgery until discharge. Blood and atrial tissue samples were obtained during the intervention. Reduced/oxidized glutathione (GSH/GSSG) ratio, malondialdehyde (MDA) and protein carbonylation were determined in atrial tissue. Leucocyte count and high-sensitivity C-reactive protein (hs-CRP) in blood plus nuclear factor (NF)-κappaB activation in atrial tissue served for inflammation assessment. Lipid peroxidation and protein carbonylation were 27.5 and 24% lower in supplemented patients ($p < 0.01$). GSH/GSSG ratio was 38.1% higher in supplemented patients compared with placebo ($p < 0.01$). Leucocyte count and serum hs-CRP levels were markedly lower throughout the protocol in supplemented patients ($p < 0.01$). Atrial tissue NF-κB DNA activation in supplemented patients was 22.5% lower than that in placebo patients ($p < 0.05$). The combined n-3 PUFA-antioxidant vitamin protocol therapy here proposed reduced the oxidative stress and inflammation biomarkers, in patients undergoing on-pump cardiac surgery.

PHARMACOL BIOCHEM BEHAV. 2011 NOV;100(1):125-9.

ANTINOCICEPTION INDUCED BY ATORVASTATIN IN DIFFERENT PAIN MODELS.

Garcia GG, Miranda HF, Noriega V, Sierralta F, Olavarría L, Zepeda RJ, Prieto JC.

Atorvastatin is a statin that inhibits the 3-hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase. Several landmark clinical trials have demonstrated the beneficial effects of statin therapy for primary and secondary prevention of cardiovascular disease. It is assumed that the beneficial effects of statin therapy are entirely due to cholesterol reduction. Statins have an additional activity (pleiotropic effect) that has been associated to their anti-inflammatory effects. The aim of the present study was to assess the antinociceptive activity of atorvastatin in five animal pain models. The daily administration of 3-100mg/kg of atorvastatin by oral gavage induced a significant dose-dependent antinociception in the writhing, tail-flick, orofacial formalin and formalin hind paw tests. However, this antinociceptive activity of atorvastatin was detectable only at high concentrations in the hot plate assay. The data obtained in the present study demonstrates the effect of atorvastatin to reduce nociception and inflammation in different animal pain models.

BASIC CLIN PHARMACOL TOXICOL. 2011 DEC;109(6):438-42.

ANTINOCICEPTION AND ANTI-INFLAMMATION INDUCED BY SIMVASTATIN IN ALGESIOMETRIC ASSAYS IN MICE.

Miranda HF, Noriega V, Olavarria L, Zepeda RJ, Sierralta F, Prieto JC.

Statins, belonging to a well-known drug class used for lowering cholesterol through competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, also have other pleiotropic properties, such as anti-inflammatory action. The purpose of this study was to evaluate the antinociceptive and anti-inflammatory effects of simvastatin in five models of nociceptive behaviour. Oral gavage administration of simvastatin induced a dose-dependent inhibition of nociception for 1 day in the acetic acid writhing (ED(50) = 5.59 ± 0.07), tail-flick (ED(50) = 112.96 ± 8.00), hot-plate (ED(50) = 134.87 ± 2.20), formalin hind paw (ED(50) = 19.86 ± 1.12 in phase I and 23.30 ± 2.05 in phase II) and orofacial formalin (ED(50) = 5.54 ± 2.74 in phase I and 11.48 ± 1.88 in phase II) tests. However, after 3 days, the values were in the acetic acid writhing (ED(50) = 6.14 ± 0.51), tail-flick (ED(50) = 154 ± 8.88), hot-plate (ED(50) = 136.14 ± 2.94), formalin hind paw (ED(50) = 15.93 ± 0.42 in phase I and 17.10 ± 1.80 in phase II) and orofacial formalin (ED(50) = 6.79 ± 0.66 in phase I and 5.80 ± 1.49 in phase II) tests. This study demonstrated the antinociceptive and anti-inflammatory activities of simvastatin in five models of tonic or phasic pain. These actions seem to be related to the inhibition of cytokine and prostanoid release and stimulation of nitric oxide synthesis. A possible clinical role of simvastatin could be related to the potentially beneficial effects in the neuropathic pain, and by their pleiotropic properties, they could play a clinical role in anti-inflammatory disease.

PHARMACOL REP. 2011;63(2):433-40.

SYNERGISM BETWEEN DEXKETOPROFEN AND MELOXICAM IN AN OROFACIAL FORMALIN TEST WAS NOT MODIFIED BY OPIOID ANTAGONISTS.

Gonzalez C, Zegpi C, Noriega V, Prieto JC, Miranda HF.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs for the management of acute and chronic pain. The role of the opioid system in the synergism between NSAIDs is not well characterized. Mice were injected with a 5% formalin solution (20 μl) into the upper right lip to perform an orofacial formalin test. The isobolographic method was used to determine the interaction between dexketoprofen, which is the (S)-(+) enantiomer of ketoprofen, and meloxicam co-administration. Additionally, the non-selective, opioid antagonist naltrexone, the selective κ opioid receptor (DOP) antagonist naltrindole and the selective κ opioid receptor (KOP) antagonist norbinaltorphimine were used to assess the opioid effects on this interaction. Intraperitoneal administration of dexketoprofen or meloxicam induced dose-dependent antinociception with different phase I and phase II potencies in the orofacial formalin test. Meloxicam displayed similar potencies (ED(50)) in phase I (7.20 mg/kg) and phase II (8.60 mg/kg). Dexketoprofen was more potent in phase I (19.96 mg/kg) than in phase II (50.90 mg/kg). The interactions between dexketoprofen and meloxicam were synergistic in both phases. This was determined based on the fixed ratios (1:1) of their ED(50) values, which were determined by isobolographic analysis. Furthermore, this antinociceptive activity does not seem to be modulated by opioid receptor blockers because they did not induce changes in the nature of this interaction. This finding may be relevant with regards to NSAID multi-modal analgesia where an opioid antagonist must be used.

N ENGL J MED. 2011 NOV 13.

THROMBIN-RECEPTOR ANTAGONIST VORAPAXAR IN ACUTE CORONARY SYNDROMES.

Tricoci P, Huang Z, Held C, Moliterno DJ, Armstrong PW, Van de Werf F, White HD, Aylward PE, Wallentin L, Chen E, Lokhnygina Y, Pei J, Leonardi S, Rorick TL, Kilian AM, Jennings LH, Ambrosio G, Bode C, Cequier A, Cornel JH, Diaz R, Erkan A, Huber K, Hudson MP, Jiang L, Jukema JW, Lewis BS, Lincoff AM, Montalescot G, Nicolau JC, Ogawa H, Pfisterer M, Prieto JC, Ruzyllo W, Sinnaeve PR, Storey RF, Valgimigli M, Whellan DJ, Widimsky P, Strony J, Harrington RA, Mahaffey KW; TRACER Investigators.

BACKGROUND: Vorapaxar is a new oral protease-activated-receptor 1 (PAR-1) antagonist that inhibits thrombin-induced platelet activation. METHODS: In this multinational, double-blind, randomized trial, we compared vorapaxar with placebo in 12,944 patients who had acute coronary syndromes without ST-segment elevation. The primary end point was a composite of death from cardiovascular causes, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization. RESULTS: Follow-up in the trial was terminated early after a safety review. After a median follow-up of 502 days (interquartile range, 349 to 667), the primary end point occurred in 1031 of 6473 patients receiving vorapaxar versus 1102 of 6471 patients receiving placebo (Kaplan-Meier 2-year rate, 18.5% vs. 19.9%; hazard ratio, 0.92; 95% confidence

interval [CI], 0.85 to 1.01; P=0.07). A composite of death from cardiovascular causes, myocardial infarction, or stroke occurred in 822 patients in the vorapaxar group versus 910 in the placebo group (14.7% and 16.4%, respectively; hazard ratio, 0.89; 95% CI, 0.81 to 0.98; P=0.02). Rates of moderate and severe bleeding were 7.2% in the vorapaxar group and 5.2% in the placebo group (hazard ratio, 1.35; 95% CI, 1.16 to 1.58; P<0.001). Intracranial hemorrhage rates were 1.1% and 0.2%, respectively (hazard ratio, 3.39; 95% CI, 1.78 to 6.45; P<0.001). Rates of nonhemorrhagic adverse events were similar in the two groups. CONCLUSIONS: In patients with acute coronary syndromes, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite end point but significantly increased the risk of major bleeding, including intracranial hemorrhage. (Funded by Merck; TRACER ClinicalTrials.gov number, NCT00527943.).

DEPARTAMENTO DE DERMATOLOGÍA

J EUR ACAD DERMATOL VENEREOL. 2011 MAY 30.

FINGER RETRONYCHIAS DETECTED EARLY BY 3D ULTRASOUND EXAMINATION.

Wortsman X, Calderon P, Baran R.

BACKGROUND: A new pattern of ingrown nail, called retronychia is involved in the posterior translation of the whole nail unit producing paronychia. OBJECTIVE: To demonstrate an unusual case of paronychia that affected three of the fingers on the right hand. METHODS: We used 3D ultrasound to study the whole nail unit in the fingers of both the affected (right) and non affected (left) hand. RESULTS: Backward motion of the nail unit with decreased distance between the origin of the nail plates and the distal interphalangeal joint was clearly demonstrated by 3D ultrasound in the affected fingers. CONCLUSION: 3D ultrasound provides non invasive and more understandable information about the physiopathological changes in retronychia.

DEPARTAMENTO DE MEDICINA

ENDOCRINOLOGÍA

GYNECOL ONCOL. 2011 APR;121(1):13-23.

TYROSINE KINASE A RECEPTOR (TRKA): A POTENTIAL MARKER IN EPITHELIAL OVARIAN CANCER.

Tapia V, Gabler F, Muñoz M, Yazigi R, Paredes A, Selman A, Vega M, Romero C.

OBJECTIVES: To evaluate the role of trkA receptor as a potential tumor marker in serous epithelial ovarian cancer and its relationship with the angiogenic factors expression as vascular endothelial growth factor (VEGF) and nerve growth factor (NGF). Additionally, to examine whether NGF and VEGF secreted by epithelial ovarian cancer (EOC) explants and from epithelial ovarian cancer cell line (A2780) are involved in the process of angiogenesis, such as cellular proliferation, migration and differentiation of the human endothelial cell line (EA.hy926). METHODS: The mRNA levels of VEGF, NGF and trkA receptors were measured using PCR in 60 ovarian samples. Cellular localization and semi-quantitative estimation of VEGF, NGF, total trkA and p-trkA was performed using IHC in epithelial cells. NGF, total trkA and p-trkA protein were also evaluated in endothelial cells from the same tissues. Human endothelial cell line EA.hy926 was cultured with conditioned media obtained from both EOC explants and from the A2780 cell line, with or without NGF stimulus. RESULTS: Significantly higher levels of NGF, total trkA and p-trkA protein expressions were observed in epithelial and endothelial cells in poorly differentiated EOC versus normal ovary. Interestingly, the p-trkA receptor expression level showed the most significant difference and its presence was only found in borderline tumor and EOC samples indicating the importance of trkA receptor in EOC as a potential tumor marker. A significant increase in proliferation, migration and differentiation of EA.hy926 cells was observed with NGF, and this effect was significantly reverted when NGF was immuno-blocked and when a trkA inhibitor was used, showing that NGF is an important angiogenic factor in EOC by activating its trkA receptor. CONCLUSION: These results indicate that p-trkA may be considered as a new potential tumor marker in EOC, and that NGF may also act as a direct angiogenic factor in EOC.

PSYCHIATRY RES. 2011 DEC 30;190(2-3):372-4.

INCREASE IN C-REACTIVE PROTEIN AND LIPIDS IN ADOLESCENTS WITH PSYCHIATRIC DISEASE.

Rojas P, Villar M, Gonzalez A, Poblete C, Funez F, Tong A, Liberman C.

Eighteen adolescent patients with severe psychiatric disorders were compared with healthy, eutrophics adolescents for the presence of inflammation and cardiovascular risk factors. We found significant differences in high-sensitivity C-reactive protein, total cholesterol, and triglycerides. Our results show, evidence of an inflammatory status and a deleterious lipid profile, in a very early state of psychiatric disease.

BIOL RES 44:181-188, 2011

PROPYLTHIOURACIL-INDUCED HYPOTHYROIDISM DELAYS APOPTOSIS DURING THE FIRST WAVE OF SPERMATOGENESIS

Doris Silva, Carlos Lizama, Verónica Tapia and Ricardo D. Moreno,

Mammalian germ cell apoptosis plays a key role in controlling the correct number of germ cells supported by Sertoli cells during the first wave of spermatogenesis in mammalian puberty. However, little is known about hormonal factors that could influence the rate of germ cell apoptosis during puberty or adulthood. In this work we evaluate germ cell apoptosis under hypothyroidism induced by goitrogen propylthiouracil (PTU) during the first wave of spermatogenesis. Neonatally administered PTU promoted a delay in the differentiation of Sertoli cells as evaluated by the expression of clusterin using immunohistochemistry and RT-PCR. Clusterin had different expression levels in control and PTU-treated animals, but under both conditions the highest levels were found in 35-day-old rats. In addition, clusterin displayed a cytoplasmic localization in control testes, but appeared located in the nucleus in PTU-treated animals. The wave of apoptosis (determined by caspase activity and quantification of apoptotic cells) characteristic of the first round of spermatogenesis was delayed by at least 10 days in these animals. The expression levels of proapoptotic genes like BAX or BAD were different between control and PTU-treated rats; although in both groups the highest level was found at the same age (days). Thus our results indicate that the characteristic pubertal apoptotic wave during rat spermatogenesis is delayed in neonatal hypothyroid rats.

GASTROENTEROLOGÍA

ANN HEPATOL. 2011 JAN-MAR;10(1):93-8.

ACUTE AND FULMINANT HEPATITIS INDUCED BY FLUTAMIDE: CASE SERIES REPORT AND REVIEW OF THE LITERATURE

Brahm J, Brahm M, Segovia R, Latorre R, Zapata R, Poniachik J, Buckel E, Contreras L.

Flutamide is a non-steroidal anti-androgenic drug, commonly used in the treatment of advanced prostate cancer, acne and hirsutism. This drug may induce various degrees of liver injury, including acute liver failure (ALF), with further need for liver transplantation. Here, we present a report of 10 consecutive patients seen in a period of 14 years, with acute liver toxicity induced by flutamide (in most cases severe hepatotoxicity): 3 men and 7 women, with a mean age of 75 and 29 years old, respectively. All men received flutamide as treatment of advanced prostate carcinoma and they developed hepatotoxicity without ALF, and three months after withdrawal of the drug, they recovered completely. In contrast, in 7 young female with liver toxicity caused by flutamide as treatment of various hyperandrogenic conditions (acne and hirsutism), ALF was observed in 5 patients, all of them requiring urgent liver transplantation, with excellent outcome and survival in 4 of them. Based on the above, we believe that flutamide treatment should be preferentially avoided in young female patients with benign pathologies, or if it is used, patients should be warned of its potential severe complications. Also, serial liver tests should be closely monitored and, in case of elevations, the drug should be immediately withdrawn.

WORLD J GASTROENTEROL. 2011 AUG 21;17(31):3636-9.

IL28B POLYMORPHISMS ASSOCIATED WITH THERAPY RESPONSE IN CHILEAN CHRONIC HEPATITIS C PATIENTS.

Venegas M, Villanueva RA, González K, Brahm J.

AIM: To analyze the association of three IL28B single nucleotide polymorphisms with response to therapy in Chilean patients infected with hepatitis C virus (HCV). METHODS: We studied two groups of patients with chronic HCV infection (genotype 1), under standard combined treatment with pegylated interferon plus ribavirin. One group consisted of 50 patients with

sustained virological response, whereas the second group consisted of 49 null responders. In order to analyze the IL28B single nucleotide polymorphisms rs12979860, rs12980275 and rs8099917, samples were used for polymerase chain reaction amplification, and the genotyping was performed by restriction fragment length polymorphism. RESULTS: The IL28B rs12979860 CC, rs12980275 AA and rs8099917 TT genotypes were much more frequently found in patients with sustained virological response compared to null responders (38%, 44% and 50% vs 2%, 8.2% and 8.2%, respectively). These differences were highly significant in all three cases (P < 0.0001). CONCLUSION: The three IL28B polymorphisms studied are strongly associated with sustained virological response to therapy in Chilean patients with chronic HCV (genotype 1).

J MED VIROL. 2011 SEP;83(9):1530-6.

PHYLOGENETIC ANALYSIS OF HEPATITIS B VIRUS GENOTYPE F COMPLETE GENOME SEQUENCES FROM CHILEAN PATIENTS WITH CHRONIC INFECTION.

Venegas M, Alvarado-Mora MV, Villanueva RA, Rebello Pinho JR, Carrilho FJ, Locarnini S, Yuen L, Brahm J.

Molecular epidemiological data concerning the hepatitis B virus (HBV) in Chile are not known completely. Since the HBV genotype F is the most prevalent in the country, the goal of this study was to obtain full HBV genome sequences from patients infected chronically in order to determine their subgenotypes and the occurrence of resistance-associated mutations. Twenty-one serum samples from antiviral drug-naive patients with chronic hepatitis B were subjected to full-length PCR amplification, and both strands of the whole genomes were fully sequenced. Phylogenetic analyses were performed along with reference sequences available from GenBank (n = 290). The sequences were aligned using Clustal X and edited in the SE-AL software. Bayesian phylogenetic analyses were conducted by Markov Chain Monte Carlo simulations (MCMC) for 10 million generations in order to obtain the substitution tree using BEAST. The sequences were also analyzed for the presence of primary drug resistance mutations using CodonCode Aligner Software. The phylogenetic analyses indicated that all sequences were found to be the HBV subgenotype F1b, clustered into four different groups, suggesting that diverse lineages of this subgenotype may be circulating within this population of Chilean patients.

WORLD J GASTROENTEROL. 2011 MAY 7;17(17):2181-90.

SOLUBLE ST2: A NEW AND PROMISING ACTIVITY MARKER IN ULCERATIVE COLITIS.

Díaz-Jiménez D, Núñez LE, Beltrán CJ, Candia E, Suazo C, Alvarez-Lobos M, González MJ, Hermoso MA, Quera R.

AIM: To correlate circulating soluble ST2 (sST2) levels with the severity of ulcerative colitis (UC) and serum levels of pro-inflammatory cytokines, and to demonstrate the predictive power of sST2 levels for differentiation between active and inactive UC. METHODS: We recruited 153 patients: 82 with UC, 26 with Crohn's disease (CD) and 43 disease controls [non-inflammatory bowel disease (IBD)]. Subjects were excluded if they had diagnosis of asthma, autoimmune diseases or hypertension. The serum levels of sST2 and pro-inflammatory cytokines [pg/mL; median (25th-75th)] as well as clinical features, endoscopic and histological features, were subjected to analyses. The sST2 performance for discrimination between active and inactive UC, non-IBD and healthy controls (HC) was determined with regard to sensitivity and specificity, and Spearman's rank correlation coefficient (r). To validate the method, the area under the curve (AUC) of receiver-operator characteristic (ROC) was determined (AUC, 95% CI) and the total ST2 content of the colonic mucosa in UC patients was correlated with circulating levels of sST2. RESULTS: The serum sST2 value was significantly higher in patients with active [235.80 (90.65-367.90) pg/mL] rather than inactive UC [33.19 (20.04-65.32) pg/mL], based on clinical, endoscopic and histopathological characteristics, as well as compared with non-IBD and HC (P < 0.001). The median level of sST2 in CD patients was 54.17 (35.02-122.0) pg/mL, significantly higher than that of the HC group only (P < 0.01). The cutoff was set at 74.87 pg/mL to compare active with inactive UC in a multicenter cohort of patients. Values of sensitivity, specificity, and ability to correctly classify UC, according to activity, were 83.33%, 83.33% and 83.33%, respectively. The AUC of the ROC curve to assess the ability of this molecule to discriminate between active vs inactive UC was 0.92 (0.86-0.97, P < 0.0001). The serum levels of sST2 in patients with UC significantly correlated with endoscopic and histopathological scores (r = 0.76 and r = 0.67, P < 0.0001, respectively), and with the pro-inflammatory cytokine, tumor necrosis factor-α (r = 0.69 and r = 0.61, respectively, P < 0.0001). Interestingly, we found a direct correlation between total intestinal ST2 content and serum levels of sST2, adjusted to endoscopic activity score in patients with mild (r = 0.44, P = 0.004), moderate (r = 0.59, P = 0.002) and severe disease (r = 0.82, P = 0.002). Only patients with inactive UC showed no significant correlation (r = 0.45, P = 0.267). CONCLUSION: sST2 levels correlated with disease severity and inflammatory cytokines, are able to differentiate active from inactive UC and might have a role as a biomarker.

GENÉTICA

AM J MED GENET A. 2011 OCT;155A(10):2552-5.

TWO SISTERS RESEMBLING GORLIN-CHAUDHRY-MOSS SYNDROME.

Aravena T, Passalacqua C, Pizarro O, Aracena M.

The Gorlin-Chaudhry-Moss syndrome (GCMS), was describe initially by Gorlin et al. [Gorlin et al. (1960)] in two sisters with craniosynostosis, hypertrichosis, hypoplastic labia majora, dental defects, eye anomalies, patent ductus arteriosus, and normal intelligence. Two other sporadic instances have been documented. Here, we report on two sisters with a condition with some similarities to GCMS as well as some differences, which could represent either previously unreported variability in GCMS, or it may represent a novel disorder.

AM J MED GENET A. 2011 AUG;155A(8):2015-7.

A PIGMENTARY SKIN DEFECT IS A NEW FINDING IN MARSHALL-SMITH SYNDROME.

Passalacqua C, Melo C, Martín LM, Rojas F, Sanz P, Taucher SC, Aranibar L.

Marshall-Smith Syndrome (OMIM 602535) was described initially by Marshall in two infants with a syndrome characterized by accelerated skeletal maturation, failure to thrive, and dysmorphic facial features. We report a new patient with clinical features of Marshall-Smith syndrome with additional findings such as hyperpigmented lines on trunk and the four extremities.

INMUNOLOGÍA

CLIN CANCER RES. 2011 APR 15;17(8):2474-83.

HEAT-SHOCK INDUCTION OF TUMOR-DERIVED DANGER SIGNALS MEDIATES RAPID MONOCYTE DIFFERENTIATION INTO CLINICALLY EFFECTIVE DENDRITIC CELLS.

Aguilera R, Saffie C, Tittarelli A, González FE, Ramírez M, Reyes D, Pereda C, Hevia D, García T, Salazar L, Ferreira A, Hermoso M, Mendoza-Naranjo A, Ferrada C, Garrido P, López MN, Salazar-Onfray F.

PURPOSE: This study characterizes, biologically and clinically, a novel type of dendritic cells (DC) produced in the short term and called tumor antigen-presenting cells (TAPCells). In particular, we identified factors present in a lysate derived from heat-shocked allogeneic melanoma cells (TRIMEL) that are associated with TAPCells' enhanced capability to induce CD8(+) T-cell responses in vitro and in vaccinated melanoma patients. EXPERIMENTAL DESIGN: First, extensive phenotypic and functional characterization of TAPCells was performed, followed by vaccination of 45 melanoma patients with four doses of TAPCells over a period of 2 months. Specific delayed-type hypersensitivity (DTH) reaction was analyzed posttreatment and correlated with overall survival rates. Furthermore, heat-shock (HS)-induced factors present in TRIMEL and their effects on DC activation were identified and studied. RESULTS: TRIMEL induced a committed, mature, DC-like phenotype in TAPCells and effectively activated melanoma-specific CD4(+) and CD8(+) T cells. Clinically, 64% of vaccinated patients showed positive DTH reaction against TRIMEL, and this was associated with improved overall survival. HS treatment of tumor cells increased calreticulin (CRT) plasma membrane translocation and induced the release of high-mobility group box 1 proteins (HMGB1). Both CRT and HMGB1 mobilization were associated with enhanced TAPCells' maturation and antigen (Ag) cross-presentation, respectively. DTH infiltration analysis revealed the presence of CD8(+)/CD45RO(+) T cells, thus confirming TAPCells' ability to cross-present Ags in vivo. CONCLUSIONS: Our results indicate that lysates derived from heat-shocked tumor cells are an optimal source of tumor-associated Ags, which are crucial for the generation of DCs with improved Ag cross-presentation capacity and clinically effective immunogenicity.

MEDICINA NUCLEAR

PLATELETS. 2011;22(8):596-601.

PLATELET ACTIVATION IN CHRONIC COCAINE USERS: EFFECT OF SHORT TERM ABSTINENCE.

Pereira J, Sáez CG, Pallavicini J, Panes O, Pereira-Flores K, Cabreras MJ, Massardo T, Mezzano D.

Cocaine abuse increases the risk of cardiac and cerebrovascular events, such as myocardial infarction and ischemic stroke. The underlying mechanisms leading to these complications are not fully understood although intravascular thrombus formation has been observed. The aim of this study was to investigate the existence of platelet activation and the effect of short-term abstinence in

chronic cocaine consumers. We studied 23 cocaine dependent individuals (aged 20-54 years) who met DSM-IV criteria for cocaine dependence and 20 controls. Samples were obtained at baseline, within 72h of last drug exposure and after 4 weeks of controlled abstinence. Monocyte-platelet aggregates (MPA) were measured by flow cytometry. Plasma levels of soluble CD40L (sCD40L), Neutrophil-Activating Peptide-2 (NAP-2) and regulated on activation normal T cells expressed and secreted (RANTES) were determined by ELISA. Levels of MPA, sCD40L, NAP-2 and RANTES were significantly higher (all $p < 0.05$) in cocaine addicts compared to controls at baseline. All the parameters returned to values similar to the control group after 4-weeks' abstinence. Levels of sCD40L and RANTES were associated with an index of intensity of drug consumption ($p < 0.02$). Our results demonstrate that cocaine use induces platelet activation which is a prominent finding after recent consumption. The persistence over time of this condition may contribute not only to acute thrombotic complications but also to the development of early-onset atherosclerotic process observed in cocaine abusers.

THROMB RES. 2011 OCT;128(4):E18-23.

INCREASED NUMBER OF CIRCULATING ENDOTHELIAL CELLS AND PLASMA MARKERS OF ENDOTHELIAL DAMAGE IN CHRONIC COCAINE USERS.

Sáez CG, Olivares P, Pallavicini J, Panes O, Moreno N, Massardo T, Mezzano D, Pereira J.

BACKGROUND: Cocaine use has been related with the development of accelerated atherosclerosis and with an increased risk of cardiac and cerebrovascular events, such as myocardial infarction, sudden cardiac death, and ischemic stroke. The underlying mechanisms leading to these complications are not fully understood, although thrombus formation and altered vascular function are prominent findings. OBJECTIVES: Our aim was to evaluate markers of endothelial dysfunction in chronic cocaine consumers before and after drug withdrawal. PATIENTS/METHODS: We determined circulating endothelial cells (CECs) and plasma levels of stromal cell-derived factor-1 (SDF-1), monocyte chemotactic protein-1(MCP-1), soluble intracellular adhesion molecule (sICAM), high-sensitivity C reactive protein (hsCRP) and endothelin-1(ET-1), in DSM-IV cocaine addicts at baseline and after one month of cocaine abstinence. RESULTS: Cocaine users showed a strikingly higher numbers of CEC (62.35 ± 18.4 vs 8.25 ± 13.8 CEC/mL) and significantly elevated plasma levels for all the markers evaluated as compared to the control group. After cocaine withdrawal, patients improved SDF-1, ET-1, hsCRP and sICAM levels. However, CEC number and MCP-1 plasma levels remained significantly elevated. All the results were adjusted for blood levels of cholesterol and triglycerides and for smoking habit. CONCLUSIONS: Our results demonstrated that chronic cocaine consumption alters several functions of the endothelium towards a pro-thrombotic condition and that some of those functions remain abnormal even after short-term drug withdrawal. These observations support the notion that endothelial dysfunction may play a key role in the pathogenesis of ischemic vascular disease observed in cocaine abusers.

ANN TROP MED PARASITOL. 2011 MAR;105(2):123-8.

THE INVESTIGATION OF CONGENITAL INFECTION BY TRYPANOSOMA CRUZI IN AN ENDEMIC AREA OF CHILE: THREE PROTOCOLS EXPLORED IN A PILOT PROJECT.

Zulantay I, Corral G, Guzman MC, Aldunate F, Guerra W, Cruz I, Araya A, Tapia V, Marquez F, Muñoz C, Apt W.

Given the increasing travel of pregnant women from areas were Trypanosoma cruzi is endemic, the congenital transmission of the parasite has become a global public-health problem. In a recent pilot study, which ran in Chile from 2006 to 2010, three strategies for exploring and managing T. cruzi-infected mothers and their infected or uninfected neonates were investigated. Any protocols applied to the investigation of such mother-and-child pairs need to include the detection of infection in pregnant women, the detection of infection, if any, in the children born to the women, the appropriate treatment of the infected neonates, and the serological-parasitological follow-up of all of the neonates until their medical discharge.

REUMATOLOGÍA

CLIN RHEUMATOL. 2011 MAR;30(3):391-5.

THE PRESENCE OF ANTI-CITRULLINATED PROTEIN ANTIBODIES (ACPA) DOES NOT AFFECT THE CLINICAL RESPONSE TO ADALIMUMAB IN A GROUP OF RA PATIENTS WITH THE TUMOR NECROSIS FACTOR (TNF) A-308 G/G PROMOTER POLYMORPHISM.

Soto L, Sabugo F, Catalan D, Wurmann P, Cermenatti T, Gatica H, Aravena O, Salazar L, Aguillón JC, Cuchacovich M.

The introduction of antitumor necrosis factor (TNF) agents has improved the outcome for many patients with rheumatoid

arthritis (RA). To date, the only replicated genetic predictor of anti-TNF response is the -308 G > A single-nucleotide polymorphism in the TNF promoter region. The presence of the -308 TNF G/G genotype appears to be a marker of good response to anti-TNF treatment. Anti-citrullinated protein antibodies (ACPA) have been linked with erosive disease, and have been established as the single most reliable prognostic factor in clinical practice. To test the hypothesis that the ACPA status may affect the -308 G/G patients rate of response to TNF blockade, we prospectively investigated a group of 52 RA patients with the -308 G/G genotype who were ACPA (+) or ACPA (-). All patients were treated with adalimumab, and the clinical response was studied using the Disease Activity Score in 28 joints (DAS28) at 24 weeks of treatment. Over 85% of patients were DAS28 responders in both groups. No significant differences were found between patients from both groups, according to the DAS28 criteria of response at week 24 (p = 0.79). In conclusion, our findings suggest that the ACPA status does not affect the clinical response to anti-TNF therapy in -308 TNF G/G patients.

RHEUMATOLOGY (OXFORD). 2011 SEP;50(9):1665-71.

EFFECTS OF METHOTREXATE ON THE EXPRESSION OF THE TRANSLATIONAL ISOFORMS OF GLUCOCORTICOID RECEPTORS A AND B: CORRELATION WITH METHOTREXATE EFFICACY IN RHEUMATOID ARTHRITIS PATIENTS.

Gatica H, Aliste M, Guerrero J, Goecke IA.

OBJECTIVES: To test the effect of MTX on the expression of glucocorticoid receptor (GR) α and β isoforms AB, C and D in peripheral blood mononuclear cells (PBMCs) in culture, from newly diagnosed RA patients and to evaluate whether the test results correlate with patients' subsequent response to MTX treatment. METHODS: Twenty patients with early active RA were enrolled. Patients who had previously received any DMARD or cytotoxic agent, or who had received CSs in the 6 months before enrolment were excluded. PBMCs from all patients were obtained and cultured in the presence and absence of MTX (10(-4), 10(-6) and 10(-8) M). The expression of GR isoforms was evaluated by western blot. After blood samples were taken, patients entered a 24-week study receiving MTX, diclofenac and prednisone (10 mg/day). At Week 24, the ACR core set of disease activity measures was calculated and a correlation between the MTX effect on patients' PBMC GR expression in vitro and the ACR response was evaluated. RESULTS: MTX 10(-6) M in the culture medium induced the expression of the PBMC isoform AB of GRα (P = 0.009). Other GR isoforms were unaffected. The magnitude of the induced expression correlated with the ACR response to treatment at Week 24 of therapy (r = 0.92, P = 0.00003). CONCLUSION: MTX in vitro induces greater expression of GRαAB isoform in PBMC from RA patients who later respond to MTX treatment than in non-responding patients. This may have clinical applications for predicting MTX efficacy in RA patients.

IMMUNOBIOLOGY. 2011 DEC;216(12):1256-63.

ANTI-TNF THERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS DECREASES TH1 AND TH17 CELL POPULATIONS AND EXPANDS IFN-Γ-PRODUCING NK CELL AND REGULATORY T CELL SUBSETS.

Aravena O, Pesce B, Soto L, Orrego N, Sabugo F, Wurmann P, Molina MC, Alfaro J, Cuchacovich M, Aguillón JC, Catalán D.

The aim of this work was to study the effect of anti-TNF treatment on CD4+ Th1, Th17 and regulatory T cells (Tregs), together with CD8+ T cells and NK cells from rheumatoid arthritis (RA) patients. For this purpose, 18 RA patients received adalimumab during 16weeks and their peripheral blood lymphocytes were assessed by flow cytometry at the beginning and at the end of the study. We found that the proportion of Th17 cells was directly correlated with Th1 cells, but inversely correlated with IFN-γ-producing NK cells. A decrease was observed in Th1, Th17 cells and IFN-γ-producing CD8+ T cells by anti-TNF therapy. Conversely, the proportion of Tregs increased, as did the percentage of IFN-γ-producing NK cells. We postulate that a rise in IFN-γ production due to recovery of NK cells' function, together with expanded Tregs, contribute to decrease the Th17 response in anti-TNF-treated RA patients.

RHEUMATOL INT. 2011 JUL 19.

WEAK CD4+ T-CELL RESPONSES TO CITRULLINATED VIMENTIN IN RHEUMATOID ARTHRITIS PATIENTS CARRYING HLA-DR9 ALLELES.

Catalán D, Aravena O, Zúñiga R, Silva N, Escobar A, Sabugo F, Wurmann P, Soto L, González R, Alfaro J, Larrondo M, Cuchacovich M, Aguillón JC.

Citrullinated vimentin (cVIM) is one of the antigens specifically targeted by anti-citrullinated protein antibodies (ACPA) in rheumatoid arthritis (RA) patients. The association between ACPA and certain HLA-DRB1 alleles, those coding for the shared epitope (SE), suggests that this response could be T-cell mediated. HLA-DR9 alleles, which do not code for the SE, have

recently been associated with ACPA (+) RA. The objective of this work was to study CD4+ T cell responses to cVIM in RA patients and healthy controls carrying HLA-DR9 alleles. Fourteen RA patients and ten healthy controls previously genotyped for HLA-DRB1 were studied for the presence of serum anti-cVIM antibodies by Western blot and ELISA. Peripheral blood mononuclear cells were stimulated with native vimentin and cVIM, and CD4+ T cells proliferation was assessed by flow cytometry. Citrulline-specific CD4+ T cells proliferation was found not only in RA patients but also in healthy controls. Although most patients carrying HLA-DR9 alleles present anti-cVIM antibodies, HLA-DR9 alleles were associated with weaker cVIM-driven CD4+ T-cell responses among RA patients. These results suggest that HLA-DR9 alleles could exert a protective effect on the recognition of cVIM epitopes by CD4+ T cells. In this context, other citrullinated proteins may break T and B cell tolerance, with cVIM only acting as a cross-reactive target for ACPA.

DEPARTAMENTO DE CIRUGÍA

OBES SURG. 2011 SEP;21(9):1319-22.

LATE MARGINAL ULCERS AFTER GASTRIC BYPASS FOR MORBID OBESITY. CLINICAL AND ENDOSCOPIC FINDINGS AND RESPONSE TO TREATMENT.

Csendes A, Torres J, Burgos AM.

Marginal ulcer (MU) is an occasional complication after gastric bypass which can occur early or late after surgery. In this study, we evaluated the incidence, clinical presentation, and endoscopic behavior of patients with late MU. Five hundred fifty morbidly obese patients were evaluated prospectively performing an endoscopic study 1-8 years after surgery. They were submitted either to laparotomic (n = 392) or laparoscopic (n = 158) approach. Six patients (1%) presented late MU 12 to 84 months after surgery. Four patients had single ulcer, while two patients had multiple ulcers. All were treated with proton pump inhibitors (PPIs). Several endoscopic evaluations were performed in each patient showing healing and no recurrence of the ulcer. Late MU occurs in a small proportion (1%) of patients submitted to gastric bypass. It can be single or multiple. Medical treatment with PPIs achieves healing at a mean time of 7 months. Several endoscopic evaluations should be performed in these patients in order to demonstrate healing of the ulcer and no recurrence.

ARCH OTOLARYNGOL HEAD NECK SURG. 2011 AUG;137(8):806-12.

CURRENT STRATEGIES IN RECONSTRUCTION OF MAXILLECTOMY DEFECTS.

Andrades P, Militsakh O, Hanasono MM, Rieger J, Rosenthal EL.

OBJECTIVE: To outline a contemporary review of defect classification and reconstructive options. DESIGN: Review article. SETTING: Tertiary care referral centers. RESULTS: Although prosthetic rehabilitation remains the standard of care in many institutions, the discomfort of wearing, removing, and cleaning a prosthesis; the inability to retain a prosthesis in large defects; and the frequent need for readjustments often limit the value of this cost-effective and successful method of restoring speech and mastication. However, flap reconstruction offers an option for many, although there is no agreement as to which techniques should be used for optimal reconstruction. Flap reconstruction also involves a longer recovery time with increased risk of surgical complications, has higher costs associated with the procedure, and requires access to a highly experienced surgeon. CONCLUSION: The surgeon and reconstructive team must make individualized decisions based on the extent of the maxillectomy defect (eg, the resection of the infraorbital rim, the extent of palate excision, skin compromise) and the need for radiation therapy.

OBES SURG. 2011 AUG;21(8):1232-7.

GASTRIC LEAK AFTER SLEEVE GASTRECTOMY: ANALYSIS OF ITS MANAGEMENT.

de Aretxabala X, Leon J, Wiedmaier G, Turu I, Ovalle C, Maluenda F, Gonzalez C, Humphrey J, Hurtado M, Benavides C.

BACKGROUND: Bariatric surgery is increasingly being performed and sleeve gastrectomy (SG) has proved to be effective and safe. Among its complications, leaks are the most serious and life threatening. METHODS: The focus of the study is nine patients who underwent a SG and developed a gastric leak after surgery. Our data were obtained from the clinical charts of the patients and through interviews with the surgeon who performed the index surgery. RESULTS: Eight patients underwent SG at outside institutions while one was operated at Clinica Alemana. Three patients developed symptoms within 5 days

after surgery, while the rest were diagnosed after 10 days from the surgery. A CT scan was the method used to confirm the diagnosis in all patients. The three patients who had a leak detected during the immediate postoperative period underwent laparoscopic reoperation. Among the rest of the patients, percutaneous drainage was employed in one patient as the primary procedure while the other underwent surgical drainage. An esophageal endoluminal stent was employed in four patients. The leak closed in all patients with the healing time ranging from 21 to 240 days. CONCLUSIONS: Diagnosis of a leak after a SG required a greater index of suspicion in order to perform an early diagnosis. Sepsis control and nutritional support are the cornerstones of this treatment. Evolution is characterized by longer periods of time that are necessary in order to wait until the leak closes. Management must be tailored to each patient.

INT SURG. 2011 APR-JUN;96(2):95-103.

LAPAROSCOPIC SURGICAL TREATMENT FOR PATIENTS WITH SHORT- AND LONG-SEGMENT BARRETT'S ESOPHAGUS: WHICH TECHNIQUE IN WHICH PATIENT?

Braghetto I, Korn O, Valladares H, Debandi A, Díaz JC, Brunet L.

Laparoscopic antireflux surgery is very successful in patients with short-segment Barrett's esophagus (BE), but in patients with long-segment BE, the results remain in discussion. In these patients, during the open era of surgery, we performed acid suppression + duodenal diversion procedures added to the antireflux procedure (fundoplication + vagotomy + antrectomy + Roux-en-Y gastrojejunostomy) to obtain better results at long-term follow-up. The aim of this prospective study is to present the results of 3 to 5 years' follow-up in patients with short-segment and long-segment or complicated BE (ulcer or stricture) who underwent fundoplication or the acid suppression-duodenal diversion technique, both performed by a laparoscopic approach. One hundred eight patients with histologically confirmed BE were included: 58 patients with short-segment BE, and 50 with long-segment BE, 28 of whom had complications associated with severe erosive esophagitis, ulcer, or stricture. After surgery, among patients treated with fundoplication with cardia calibration, endoscopic erosive esophagitis was observed in 6.9% of patients with short-segment BE, while 50% of patients with long-segment BE presented with positive acid reflux, persistence of endoscopic esophagitis with intestinal metaplasia, and progression to dysplasia (in 5% of cases; P = 0.000). On the contrary, after acid suppression-duodenal diversion surgery in patients with long-segment BE, more than 95.6% presented with successful results regarding recurrent symptoms and endoscopic regression of esophagitis. Regression of intestinal metaplasia to the cardiac mucosa was observed in 56.9% of patients with short-segment BE who underwent fundoplication and in 61% of those with long-segment BE treated with the acid suppression-duodenal diversion procedure. Patients with long-segment BE who experienced fundoplication alone presented no regression of intestinal metaplasia; on the contrary, progression to dysplasia was observed in 1 case (P = 0.049). Patients with short-segment BE can be successfully treated with fundoplication, but for patients with long-segment BE, we suggest performance of fundoplication plus an acid suppression-duodenal diversion procedure.

OBES SURG. 2011 MAY;21(5):561-8.

TRACE ELEMENT STATUS AND INFLAMMATION PARAMETERS AFTER 6 MONTHS OF ROUX-EN-Y GASTRIC BYPASS.

Rojas P, Carrasco F, Codoceo J, Inostroza J, Basfi-fer K, Papapietro K, Csendes A, Rojas J, Pizarro F, Olivares M, Ruz M.

BACKGROUND: Knowledge about the practical consequences of the nutritional status of Fe, Zn, and Cu and inflammation in obesity is limited. The objective of this study was to evaluate changes on trace element status and their potential associations with selected inflammation parameters in patients after Roux-en-Y gastric bypass (RYGBP). METHODS: Sixty-three women (mean age, 36.9 ± 9.2 years, body mass index, 43.8 ± 4.3 kg/m^2) were evaluated at baseline and 6 months after RYGBP. Anthropometric (weight, waist circumference), body composition (fat mass and fat-free mass), dietary (nutrient intakes), and metabolic and inflammation (glucose, insulin, HOMA-IR, adiponectin, HDL-cholesterol, LDL-cholesterol, triglycerides, hs-CRP, leukocytes, polymorphonuclear neutrophils (PMN)) parameters were determined in addition to selected indices of Fe, Zn, and Cu status. RESULTS: All but one (HDL-cholesterol) metabolic and inflammation parameters had significant differences when compared before and after RYGBP. Hemoglobin, serum ferritin, the size of the rapidly exchangeable zinc pool, and plasma copper decreased after RYGBP. Plasma and hair zinc, as well as zinc protoporphyrin increased. The change in Hb was significantly associated ($p < 0.05$) to the change in leukocytes ($r = 0.33$) and adiponectin ($r = -0.44$). Zinc protoporphyrin change was associated to the change in PMN ($r = 0.32$) and HDL-cholesterol ($r = -0.29$). No other associations between the changes of the rest of Fe, Zn, and Cu parameters with the changes of any of the metabolic and inflammation parameters

were observed. CONCLUSION: RYGBP produced significant weight and fat mass losses, with improvement of metabolic and inflammation parameters. Iron, zinc, and copper status were impaired after the surgery.

ANN N Y ACAD SCI. 2011 SEP;1232:175-95.

BARRETT'S ESOPHAGUS: SURGICAL TREATMENTS.

Parise P, Rosati R, Savarino E, Locatelli A, Ceolin M, Dua KS, Tatum RP, Braghetto I, Gyawali CP, Hejazi RA, McCallum RW, Sarosiek I, Bonavina L, Wassenaar EB, Pellegrini CA, Jacobson BC, Canon CL, Badaloni A, del Genio G.

The following on surgical treatments for Barrett's esophagus includes commentaries on the indications for antireflux surgery after medical treatment; the effects of the various procedures on the lower esophageal sphincter; the role of impaired esophageal motility and delayed gastric emptying in the choice of the surgical procedure; indications for associated highly selective vagotomy, duodenal switch, and gastric electrical stimulation; therapeutic strategies for detection and treatment of shortened esophagus; the role of antireflux surgery on the regression of metaplastic mucosa and the risk of malignant progression; the detection of asymptomatic reflux brfore bariatric surgery; the role of non-GERD symptoms on the results of surgery; and the indications of Collis gastroplasty and choice of the type of fundoplication.

AM J CLIN NUTR. 2011 OCT;94(4):1004-11.

ZINC ABSORPTION AND ZINC STATUS ARE REDUCED AFTER ROUX-EN-Y GASTRIC BYPASS: A RANDOMIZED STUDY USING 2 SUPPLEMENTS.

Ruz M, Carrasco F, Rojas P, Codoceo J, Inostroza J, Basfi-fer K, Csendes A, Papapietro K, Pizarro F, Olivares M, Sian L, Westcott JL, Miller LV, Hambidge KM, Krebs NF.

BACKGROUND: Micronutrient deficiencies are common in patients undergoing gastric bypass. The effect of this type of surgery on zinc absorption and zinc status is not well known. OBJECTIVE: The objective was to evaluate the effects of Roux-en-Y gastric bypass (RYGBP) on zinc status and zinc absorption at different stages after surgery. We hypothesized that zinc status would be significantly impaired after surgery and that this impairment would be less severe in subjects receiving increased supplemental zinc. We also hypothesized that zinc absorption would be lower after surgery. DESIGN: Anthropometric and body-composition variables and dietary and biochemical indexes of zinc status and zinc absorption were determined in 67 severe and morbidly obese women [mean (±SD) age: 36.9 ± 9.8 y; BMI (in kg/m(2)): 45.2 ± 4.7] who underwent RYGBP. The subjects were randomly assigned to 1 of 2 vitamin-mineral supplementation groups. Measurements were made before and 6, 12, and 18 mo after surgery. Fifty-six subjects completed the 18-mo follow-up. RESULTS: Mean plasma zinc, erythrocyte membrane alkaline phosphatase activity, and the size of the rapidly exchangeable zinc pool decreased after RYGBP. Percentage zinc absorption decreased significantly from 32.3% to 13.6% at 6 mo after RYGBP and to 21% at 18 mo after surgery. No effect of supplement type was observed. CONCLUSIONS: Zinc status is impaired after RYGBP, despite the finding that dietary plus supplemental zinc doubled recommended zinc intakes in healthy persons. Zinc absorption capacity is significantly reduced soon after RYGBP, with no major changes until 18 mo after surgery.

DEPARTAMENTO DE NEUROLOGÍA Y NEUROCIRUGÍA

J GERONTOL A BIOL SCI MED SCI. 2011 JUL;66(7):732-40.

AGE-DEPENDENT INCREASES IN APOPTOSIS/NECROSIS RATIOS IN HUMAN LYMPHOCYTES EXPOSED TO OXIDATIVE STRESS.

Behrens MI, Silva M, Schmied A, Salech F, Manzur H, Rebolledo R, Bull R, Torres V, Henriquez M, Quest AF.

Unlike apoptosis, mechanisms leading to necrosis are less well understood. Moreover, changes in necrosis as a function of age have not been studied in human lymphocytes. H(2)O(2)-induced death of peripheral lymphocytes (56 healthy donors, 24-95 years) was evaluated by flow cytometry and propidium iodide staining, caspase activation, DNA laddering, and electron microscopy. H(2)O(2)-induced stress was associated with high levels of necrosis in young individuals (≤30 years), whereas progressively enhanced apoptotic death was observed in older donors, without changes in overall lymphocyte survival. Thus, apoptosis/necrosis ratios were inverted in young versus elderly (≥65 years) donors. Death was not accompanied by increased caspase activity and, accordingly, unaffected by caspase inhibition; however, it was almost completely prevented

by poly ADP ribose polymerase inhibition. In summary, aging was associated with changes in the apoptosis/necrosis ratios, rather than susceptibility per se to H(2)O(2)-induced death, which was caspase independent but poly ADP ribose polymerase dependent. Understanding this switch in death modes may aid in understanding age-related disorders.

ACTA NEUROCHIR SUPPL. 2011;108:251-4.

PERCUTANEOUS BALLOON COMPRESSION OF THE GASSERIAN GANGLION FOR THE TREATMENT OF TRIGEMINAL NEURALGIA: PERSONAL EXPERIENCE OF 206 PATIENTS.

Baabor MG, Perez-Limonte L.

In a retrospective study of 206 patients diagnosed with trigeminal neuralgia (TN), we examined the results of percutaneous balloon compression (PBC) of the Gasserian ganglion performed by the same surgeon from September 1991 to November 2005. In these patients, 230 procedures were done. All patients had clinical follow-up for a minimum of 3 years while being evaluated for any recurrence of the symptoms. Initial pain relief was complete in 214 operated patients (93%) while in 16 operated patients (7%) it was not. From those, nine patients had another PBC performed immediately with eight of them becoming pain free while the remaining seven patients opted for medical treatment. From that last group, we found that six patients ended up experiencing resolution of their symptoms. In total, only 2 patients (1%) from the original 206 did not improve initially, while 99% had an excellent response. After a 3-year follow-up, only 35 patients (15%) had developed recurrent symptoms. In the majority of cases, the recurrence occurred between 2 and 3 year intervals (16 patients). There was no mortality. The low cost, low morbidity, low recurrence rate and high positive results make this procedure a valid option in the treatment of trigeminal neuralgia refractory to medical treatment.

NEUROCHIR SUPPL. 2011;108:97-101.

AUTOMATED NUCLEOTOMY AND NUCLEOLYSIS WITH OZONE.

Baabor MG, Vázquez PF, Sánchez JA.

Lumbar and radicular pain due to HNP has been described since 1934. It is thought that the pain is caused by compression and by other local chemical mediators that are present in the area of interaction between the root and the disc.With the objective of treating patients suffering from this syndrome and with a percutaneous minimally invasive approach, we designed a mixed technique: percutaneous automated nucleotomy plus nucleolysis and periradicular infiltration with ozone.A retrospective study of 105 patients was conducted, including 60 men and 45 women with an average age of 43 years. All patients were treated with that technique between November 2006 and August 2008. Clinical follow-up of 15.2 months was provided by telephone, utilizing a modified Mac Nab scale. The results were as follows: 60% excellent, 22.8% good (82.8% success), 9.6% acceptable, 7.6% poor. From the eight patients that reported poor results, five were considered to have recurrent symptoms (4.8%), because they had initially shown a period of significant improvement post operatively. Morbidity was manifested by transient pain and muscle spasms in the post operative area (2.8%).We conclude that this new mixed technique, compared to automated percutaneous nucleotomy alone, may be more widely utilized by broadening the indications, with acceptable results.

NEUROSCI LETT. 2011 MAR 3;490(3):170-4.

HEMATOMA SIZE AS MAJOR MODULATOR OF THE CELLULAR IMMUNE SYSTEM AFTER EXPERIMENTAL INTRACEREBRAL HEMORRHAGE.

Illanes S, Liesz A, Sun L, Dalpke A, Zorn M, Veltkamp R.

Inflammatory cascades are increasingly recognized as an important pathophysiological mechanism in intracerebral hemorrhage (ICH). In contrast, the effect of ICH on the systemic immune system has barely been investigated. We examined the effects of different hematoma volumes on immune cell subpopulations in experimental murine ICH. In C57BL/6 mice, ICH was induced by striatal injection of autologous blood (10, 30 or 50 µL). Control animals received the respective sham operation. Three days after ICH induction, differential blood leukocyte counting was performed. Lymphocyte subpopulations were further characterized by flow cytometry in blood, spleen, lymph node and thymus. Infectious complications were studied using microbiological cultures of blood and lungs. Only after large ICH a marked decrease of leukocyte counts and most lymphocyte subsets was observed in all organs. Despite this general leukocytopenia, a significant, up to 10-fold increase, was detected in the monocyte population after extensive hemorrhage. After moderate ICH induction, only specific lymphocyte subpopulations were differentially affected. Mature thymic cells

were unaffected while immature CD4+CD8+ cells were depleted by over 90% after large ICH. A significant proportion of mice with extensive ICH (36.4%) developed spontaneous pneumonia and/or bacteremia while none of the sham operated mice had infectious complications. The ICH size determines the extent of systemic immunomodulation. Large ICH predisposes animals to infections.

PRENAT DIAGN. 2011 NOV;31(11):1082-5.

FREE FETAL DNA LEVELS IN PATIENTS AT RISK OF PRETERM LABOUR.

Illanes S, Gomez R, Fornes R, Figueroa-Diesel H, Schepeler M, Searovic P, Serra R, Perez A, Nien JK.

OBJECTIVES: Our main goals were to evaluate the capability of ffDNA to increase the accuracy in prediction of preterm labour by cervical length and to explore potential mechanisms of disease associated with this pathology. METHODS: Fifty-six women, with male fetus, with cervical length assessment at between 22 and 24 weeks were included in the study and divided in 1) Short cervix (<15 mm) delivered at term (T = 20); 2) Short cervix delivered before 37 weeks (PT = 14); and 3) Patients who delivered at term with normal cervical length (N = 22). Maternal plasma samples were collected between 22 and 24 weeks of gestational age. PCR using primers against DYS14 gene were used to quantified ffDNA in plasma samples. Statistical analysis was done using ANOVA test and spearman´s correlation. RESULTS: The median gestational age at delivery for short cervix groups was 26 + 1 for PT and 39 + 3 for T. The control group delivered at a median gestational age of 39 + 6 weeks. ffDNA was detectable in all cases. There was no significant difference between the 3 groups. Similarly, no significant correlation was observed between ffDNA and gestational age at delivery (r = -0.23; p = 0.07). CONCLUSIONS: ffDNA does not increase the accuracy of short cervix at between 22 and 24 weeks for the prediction of preterm labour.

NEUROEPIDEMIOLOGY. 2011;37(1):45-51.

SOCIOECONOMIC AND CARDIOVASCULAR VARIABLES EXPLAINING REGIONAL VARIATIONS IN STROKE MORTALITY IN CHILE: AN ECOLOGICAL STUDY.

Lavados PM, Díaz V, Jadue L, Olavarría VV, Cárcamo DA, Delgado I.

BACKGROUND: Regional differences in stroke mortality rates have been described in Chile. These could be related to the distribution of cardiovascular risk factors, the quality of medical care or socioeconomic status influencing incidence or case fatality rates. Our objective was to investigate variables explaining the variability in stroke mortality rates in the different regions of Chile. METHODS: Adjusted stroke mortality rates in different regions were calculated for the year 2003. Variables were added from three sources: the National Death Certificate Database, the National Socioeconomic Characterization Survey and the National Health Survey. A logistic regression model was used to investigate regions, demographic variables and socioeconomic variables associated with the risk of death from stroke. A linear regression model was used to study the association of socioeconomic variables and cardiovascular risk factors with the standardized mortality rate by region and the contribution of these to the variability. RESULTS: A twofold increase was found in adjusted stroke mortality rates among regions. Greater risk was associated with older age, female gender and residence in regions V, VII, VIII and IX. Sixty-two percent of the regional variability rate was explained by the combined prevalence of poverty (34%), diabetes (17%), sedentarism (8%) and overweight (3%). CONCLUSION: The risk of death from stroke in Chile is associated with age, sex and living in four specific regions of the country. The majority of the increased risk in these regions is explained by the prevalence of poverty, diabetes, a sedentary lifestyle and overweight.

PARKINSONISM RELAT DISORD. 2011 SEP;17(8):629-31.

LRRK2 P.Q1111H SUBSTITUTION AND PARKINSON'S DISEASE IN LATIN AMERICA.

Mata IF, Wilhoite GJ, Yearout D, Bacon JA, Cornejo-Olivas M, Mazzetti P, Marca V, Ortega O, Acosta O, Cosentino C, Torres L, Medina AC, Perez-Pastene C, Díaz-Grez F, Vilariño-Güell C, **Venegas P**, Miranda M, Trujillo-Godoy O, Layson L, Avello R, Dieguez E, Raggio V, Micheli F, Perandones C, Alvarez V, Segura-Aguilar J, Farrer MJ, Zabetian CP, Ross OA.

Mutations in the LRRK2 gene are the most common genetic cause of Parkinson's disease, with frequencies displaying a high degree of population-specificity. Although more than 100 coding substitutions have been identified, only seven have been proven to be highly penetrant pathogenic mutations. Studies however are lacking in non-white populations. Recently, Lrrk2 p.Q1111H (rs78365431) was identified in two affected Hispanic brothers and absent in 386 non-Hispanic white healthy controls. We therefore screened this variant in 1460 individuals (1150 PD patients and 310 healthy controls) from 4 Latin American countries (Peru, Chile, Uruguay and Argentina). In our case-control series from Peru and Chile we observed an increased frequency of Lrrk2 p.Q1111H

in patients (7.9%) compared to controls (5.4%) although the difference did not reach significance (OR 1.38; p = 0.10). In addition, the frequency of Lrrk2 p.Q1111H varied greatly between populations and further screening in a set of pure Amerindian and pure Spanish controls suggested that this variant likely originated in an Amerindian population. Further studies in other Latin American populations are warranted to assess its role as a risk factor for Parkinson's disease. Screening in Parkinson's disease patients from under-represented populations will increase our understanding of the role of LRRK2 variants in disease risk worldwide.

STROKE. 2011 DEC;42(12):3594-9.

HEMOSTATIC THERAPY IN EXPERIMENTAL INTRACEREBRAL HEMORRHAGE ASSOCIATED WITH THE DIRECT THROMBIN INHIBITOR DABIGATRAN.

Zhou W, Schwarting S, **Illanes S**, Liesz A, Middelhoff M, Zorn M, Bendszus M, Heiland S, van Ryn J, Veltkamp R.

BACKGROUND AND PURPOSE: Dabigatran-etexilate (DE) recently has been approved for stroke prevention in atrial fibrillation. However, lack of effective antagonists represents a major concern in the event of intracerebral hemorrhage (ICH). The aims of the present study were to establish a murine model of ICH associated with dabigatran, and to test the efficacy of different hemostatic factors in preventing hematoma growth. METHODS: In C57BL/6 mice receiving DE (4.5 or 9.0 mg/kg), in vivo and in vitro coagulation assays and dabigatran plasma levels were measured repeatedly. Thirty minutes after inducing ICH by striatal collagenase injection, mice received an intravenous injection of saline, prothrombin complex concentrate (PCC; 100 U/kg), murine fresh-frozen plasma (200 μL), or recombinant human factor VIIa (8.0 mg/kg). ICH volume was quantified on brain cryosections 24 hours later. RESULTS: DE substantially prolonged tail vein bleeding time and ecarin clotting time for 4 hours corresponding to dabigatran plasma levels. Intracerebral hematoma expansion was observed mainly during the first 3 hours on serial T2* MRI. Anticoagulation with high doses of DE increased the hematoma volume significantly. PCC and, less consistently, fresh-frozen plasma prevented excess hematoma expansion caused by DE, whereas recombinant human factor VIIa was ineffective. Prevention of hematoma growth and reversal of tail vein bleeding time by PCC were dose-dependent. CONCLUSIONS: The study provides strong evidence that PCC and, less consistently, fresh-frozen plasma prevent excess intracerebral hematoma expansion in a murine ICH model associated with dabigatran. The efficacy and safety of this strategy must be further evaluated in clinical studies.

PARKINSONISM RELAT DISORD. 2011 NOV 18.

MOTOR PATHWAY EXCITABILITY IN ATP13A2 MUTATION CARRIERS: A TRANSCRANIAL MAGNETIC STIMULATION STUDY.

Zittel S, Kroeger J, van der Vegt JP, Siebner HR, Brüggemann N, Ramirez A, Behrens MI, Gerloff C, Bäumer T, Klein C, Münchau A.

OBJECTIVE: To describe excitability of motor pathways in Kufor-Rakeb syndrome (PARK9), an autosomal recessive nigro-striatal-pallidal-pyramidal neurodegeneration caused by a mutation in the ATP13A2 gene, using transcranial magnetic stimulation (TMS). METHODS: Five members of a Chilean family with an ATP13A2 mutation (one affected mutation carrier (MC) with a compound heterozygous mutation, 4 asymptomatic MC with a single heterozygous mutation) and 11 healthy subjects without mutations were studied. We measured motor evoked potentials (MEP), the contralateral silent period (cSP), short interval intracortical inhibition (SICI), intracortical facilitation (ICF), short latency afferent inhibition (SAI) as markers of intracortical intrahemispheric inhibition/facilitation and the ipsilateral silent period (iSP) and paired-pulse interhemispheric inhibition (IHI) to probe interhemispheric motor interactions. RESULTS: CSP duration was increased in the symptomatic ATP13A2 MC. The iSP measurements revealed increased interhemispheric inhibition in both the compound heterozygous and the heterozygous MC. CONCLUSION: A compound heterozygous mutation in the ATP13A2 gene is associated with increased intracortical inhibition. In addition, some aspects of interhemispheric inhibition are increased in the presence of a single ATP13A2 mutation.

DEPARTAMENTO DE OBSTETRICIA Y GINECOLOGÍA

GYNECOL OBSTET INVEST. 2011;72(3):152-6.

FIRST-TRIMESTER ADIPONECTIN AND SUBSEQUENT DEVELOPMENT OF PREECLAMPSIA OR FETAL GROWTH RESTRICTION.

Valdés ER, Lattes KA, Muñoz HS, Barja PY, Papapietro KV.

Background/Aims: The evidence regarding the utility of assessing first-trimester adiponectin (ApN) serum levels in early prediction of preeclampsia (PE) and fetal growth restriction (FGR) is contradictory. This study aims to determine the role of maternal serum

ApN levels as an early predictor of PE and FGR. Methods: A prospective case-control study among a pregnant population who attended their 11- to 14-week ultrasound scan at the University of Chile's Clinical Hospital's Fetal Medicine Unit. We included patients who developed PE or FGR (10 cases per group) and 35 healthy controls. We determined ApN levels in blood samples from these 55 patients using a commercial ELISA kit and assessed the relationship of ApN levels with variables like development of PE, FGR, weight at birth and maternal BMI. Results: There were no significant differences among first-trimester ApN serum levels in the groups. Average concentrations were 8, 6.8 and 10.8 ng/ml for the control, PE and FGR groups, respectively. Conclusion: In our study, maternal serum ApN levels were not useful in predicting subsequent development of PE and FGR. However, maternal serum ApN concentration adjusted by BMI was significantly higher during the first trimester in women who later developed FGR.

DEPARTAMENTO DE OFTALMOLOGÍA

MOL VIS. 2011;17:1929-39.

C.194 A>C (Q65P) MUTATION IN THE LMX1B GENE IN PATIENTS WITH NAIL-PATELLA SYNDROME ASSOCIATED WITH GLAUCOMA.

Romero P, Sanhueza F, Lopez P, Reyes L, Herrera L.

PURPOSE: To report the clinical, ophthalmic, extraophthalmic, and genetic characteristics of nail-patella syndrome (NPS) in a Chilean family and to investigate the expressivity of open angle glaucoma (OAG) and ocular hypertension (OHT) in the family members. METHODS: Five family members affected with NPS and two unaffected members underwent a complete ophthalmologic examination, including computerized visual field, optical coherence tomography (OCT) of the optic disc and ultrasound pachymetry. Renal function was assessed by urinalysis and blood tests. Orthopedic evaluations were also performed, including radiological studies of the wrist, elbow and hip joints. Genomic DNA was extracted from peripheral leukocytes of the five affected and two unaffected family members. Exons 2-6 of the LIM homeobox transcription factor 1-beta (LMX1B) gene were screened for mutations by DNA sequencing of the proband. We also screened for mutations in exon 2 by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) of the other participants and 91 blood donors. RESULTS: Five living family members from three generations were positively diagnosed with NPS, three of them with varying degrees of OAG and one with OHT. Retinal nerve fiber layer (RNFL) thickness measured by spectral domain OCT was below normal values in three individuals. All subjects evaluated had normal nephrologic function. Orthopedic, clinical, and radiological alterations were compatible with NPS. Screening for mutations in exons 2- 6 of LMX1B showed a heterozygous missense mutation c.194 A>C changing glutamine to proline within exon 2 in codon 65 (Q65P) of the coding sequence. This mutation was present in all NPS subjects and absent in the unaffected family members and in 91 Chilean blood donors. CONCLUSIONS: This is the first report of c.194 A>C mutation in LMX1B in a Chilean family with NPS and the second worldwide. The phenotype associated with this mutation is variable within the family, although we noted a close connection between the presence of the c.194 A>C mutation and the presence of OHT or OAG and probably also with an early onset of OHT in patients with NPS. All subjects older than 21 years had either OHT or OAG. We also suggest that the LMX1B mutation may be related to affective disorders.

DEPARTAMENTO DE ORTOPEDIA Y TRAUMATOLOGÍA

SPINE (PHILA PA 1976). 2011 MAY 20;36(12):945-50.

HARMS C1-C2 INSTRUMENTATION TECHNIQUE: ANATOMO-SURGICAL GUIDE.

Schulz R, Macchiavello N, Fernández E, Carredano X, Garrido O, Diaz J, Melcher RP.

STUDY DESIGN: Anatomic study. OBJECTIVE: To measure C1 and C2 critical areas related to the screws trajectory, according to Harms technique, in Latin specimens. To investigate vertebral's artery course in cadavers. SUMMARY OF BACKGROUND DATA: To our knowledge there are no studies addressing vertebral surface measurements for screw placement, according to Harms C1-C2 instrumentation technique, nor cadaveric measurements of the trajectory of the vertebral artery in Latin specimens. METHODS: C1 and C2 specimens were measured. C1 measurements: height, width, anteroposterior diameter (intraosseus screw length) and convergence in the axial plane of the lateral mass; length from the posterior border of the posterior C1 arch to the anterior cortex of the articular mass (total screw length). C2 measurements: width, height, convergence

and sagittal inclination of the pars interarticularis. Direction of the trajectory of the vertebral artery in the suboccipital region in fresh cadavers. RESULTS: C1: left mass width 14.20 mm, right: 14.32 mm; left intraosseus screw length: 17.17 mm, right 16.9 mm; left total length of the screw: 27.14 mm, right: 26.72 mm; left mass height: 10.22 mm, right: 10.29 mm. Right mass convergence: 24.68°, left: 22.44°. C2: width: left 8.75 mm, right: 8.53 mm; height: left 10 mm, right 9.81 mm; convergence: left 42.15°, right: 38.98°; sagittal inclination: left 35.50°, right 33.07°. Vertebral artery's medial border is between 13 and 22 mm from the middle line of C1 posterior arch. CONCLUSION: Convergence and inclination of the pars are slightly greater than the suggested by Harms. Individual and/or racial variations must be considered. There is enough space for safe placement of a 3.5 mm screw in the lateral masses of C1 and through the pars of C2. Dissecting the superior face of the posterior arch of C1 laterally more than 10 mm from the posterior tubercule could injure the vertebral artery.

DEPARTAMENTO DE OTORRINOLARINGOLOGÍA

J ASSOC RES OTOLARYNGOL. 2011 JUN;12(3):317-27.

EFFECTS OF ELECTRICAL STIMULATION OF OLIVOCOCHLEAR FIBERS IN COCHLEAR POTENTIALS IN THE CHINCHILLA.

Elgueda D, Delano PH, Robles L.

The mammalian cochlea has two types of sensory cells; inner hair cells, which receive auditory-nerve afferent innervation, and outer hair cells, innervated by efferent axons of the medial olivocochlear (MOC) system. The role of the MOC system in hearing is still controversial. Recently, by recording cochlear potentials in behaving chinchillas, we suggested that one of the possible functions of the efferent system is to reduce cochlear sensitivity during attention to other sensory modalities (Delano et al. in J Neurosci 27:4146-4153, 2007). However, in spite of these compelling results, the physiological effects of electrical MOC activation on cochlear potentials have not been described in detail in chinchillas. The main objective of the present work was to describe these efferent effects in the chinchilla, comparing them with those in other species and in behavioral experiments. We activated the MOC efferent axons in chinchillas with sectioned middle-ear muscles by applying current pulses at the fourth-ventricle floor. Auditory-nerve compound action potentials (CAP) and cochlear microphonics (CM) were acquired in response to clicks and tones of several frequencies, using a round-window electrode. Electrical efferent stimulation produced CAP amplitude suppressions reaching up to 11 dB. They were higher for low to moderate sound levels. Additionally, CM amplitude increments were found, the largest (≤ 2.5 dB) for low intensity tones. CAP suppression was present at all stimulus frequencies, but was greatest for 2 kHz. CM increments were highest for low-frequency tones, and almost absent at high frequencies. We conclude that the effect obtained in chinchilla is similar to but smaller than that observed in cats, and that the effects seen in awake chinchillas, albeit different in magnitude, are consistent with the activation of efferent fibers.

DEPARTAMENTO DE PSIQUIATRÍA Y SALUD MENTAL

BMC PSYCHIATRY. 2011 FEB 15;11:29.

P300 AMPLITUDE IS INSENSITIVE TO WORKING MEMORY LOAD IN SCHIZOPHRENIA.

Gaspar PA, Ruiz S, Zamorano F, Altayó M, Pérez C, Bosman CA, Aboitiz F.

BACKGROUND: Working memory (WM) tasks usually elicit a P300 ERP component, whose amplitude decreases with increasing WM load. So far, this effect has not been studied in schizophrenics (SZs), a group that is considered to have an aberrant brain connectivity and impairments in WM capacity. The aim of this study was to determine the dependency of the P300 component on WM load in a sample of SZ subjects. METHODS: We recorded 26 subjects (13 SZ patients and their matched controls) with an 80-channel electroencephalogram. Subjects performed an N-back task, a WM paradigm that manipulates the number of items to be stored in memory. RESULTS: In healthy subjects, P300 amplitude was highest in the low WM load condition, and lowest in both the attentional control condition and the high WM load condition. In contrast, SZs evidenced low P300 amplitude in all conditions. A significant between group difference in P300 amplitude was evidenced only at the low WM load condition (1 -back), being smaller in SZs. CONCLUSIONS: SZ subjects display a lower than normal P300 amplitude, which does not vary as a function of memory load. These results are consistent with a general impairment in WM capacity in these patients.

ACTAS ESPAÑOLAS DE PSIQUIATRÍA. 2010 DIC;38(6):358-364.

TRASTORNOS DEL SUEÑO EN LA POBLACIÓN ADULTA DE SANTIAGO DE CHILE Y SU ASOCIACIÓN CON TRASTORNOS PSIQUIÁTRICOS COMUNES.

R. Fritsch Montero; P. Lahsen Martínez; R. Romeo Gómez; R. Araya Baltra.

Introduction. Sleep disorders are a frequent problem and they are a usual reason of primary care consultation, because they cause a significant deterioration in the quality of life. Insomnia is the most common sleep disorder and it has a total prevalence in adults estimated of 19.1%, of whom 85% are chronic insomnia, which in turn is closely related to psychiatric disorders and even more it has been described as a depressive episode marker. Aims. To characterize the Santiago adult population suffering from sleep disorders and analyze their statistical association with common mental disorders. Methodology. It corresponds to a secondary analysis of the survey "Common Mental Disorders in Santiago". A cross-sectional survey that used as a sampling frame the adult population of Santiago aged between 16 to 64 years was carried out. A structured interview covering sociodemographic factors and the Revised Clinical Interview Schedule (CIS-R) to measure emotional symptoms, were applied. Results. 3867 people representative of the adult population were evaluated (52.3% women, 47.7% men). The prevalence of sleep disorders was 26.3%. Sociodemographic risk factors, statistically significants, were detected like female gender, unemployed seeking employment, the presence of a common mental disorder, alcohol and drugs consumption in the last month, among others. Conclusions: There is a high prevalence of sleep disorders among the population of Santiago; this is closely associated to female gender, social disadvantages and potently to the presence of a common mental disorder.

TRIALS. 2011 FEB 19;12:49.

SCHOOL-BASED INTERVENTION TO IMPROVE THE MENTAL HEALTH OF LOW-INCOME, SECONDARY SCHOOL STUDENTS IN SANTIAGO, CHILE (YPSA): STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL.

Araya R, Montgomery AA, Fritsch R, Gunnell D, Stallard P, Noble S, Martinez V, Barroilhet S, Vohringer P, Guajardo V, Cova F, Gaete J, Gomez A, Rojas G.

BACKGROUND: Depression is common and can have devastating effects on the life of adolescents. Psychological interventions are the first-line for treating or preventing depression among adolescents. This proposal aims to evaluate a school-based, universal psychological intervention to reduce depressive symptoms among student's aged 13-14 attending municipal state secondary schools in Santiago, Chile. STUDY DESIGN: This is a cluster randomised controlled trial with schools as the main clusters. We compared this intervention with a control group in a study involving 22 schools, 66 classes and approximately 2,600 students. Students in the active schools attended 11 weekly and 3 booster sessions of an intervention based on cognitive-behavioural models. The control schools received their usual but enhanced counselling sessions currently included in their curriculum. Mean depression scores and indicators of levels of functioning were assessed at 3 and 12 months after the completion of the intervention in order to assess the effectiveness of the intervention. Direct and indirect costs were measured in both groups to assess the cost-effectiveness of this intervention. DISCUSSION: As far as we are aware this is the first cluster randomised controlled trial of a school intervention for depression among adolescents outside the Western world.

PSYCHIATRY RES. 2011 SEP 30;189(2):239-45.

SERUM BRAIN-DERIVED NEUROTROPHIC FACTOR AND GLUCOCORTICOID RECEPTOR LEVELS IN LYMPHOCYTES AS MARKERS OF ANTIDEPRESSANT RESPONSE IN MAJOR DEPRESSIVE PATIENTS: A PILOT STUDY.

Rojas PS, Fritsch R, Rojas RA, Jara P, Fiedler JL.

Depressive patients often have altered cortisol secretion, an effect that likely derives from impaired activity of the glucocorticoid receptor (GR), the main regulator of the hypothalamus-pituitary-adrenal (HPA) axis. Glucocorticoids reduce the levels of brain-derived neurotrophic factor (BDNF), a downstream target of antidepressants. Antidepressants promote the transcriptional activity of cyclic adenosine monophosphate (cAMP) response element binding protein (CREB), a regulator of BDNF expression. To identify potential biomarkers for the onset of antidepressant action in depressive patients, GR and phospho-CREB (pCREB) levels in lymphocytes and serum BDNF levels were repeatedly measured during the course of antidepressant treatment. Thirty-four depressed outpatients (10 male and 24 female) were treated with venlafaxine (75mg/day), and individuals exhibiting a 50% reduction in their baseline 17-Item Hamilton Depression Rating Scale score by the 6th week of treatment were considered responders. Responders showed an early improvement in parallel with a rise in BDNF levels during the first two weeks of

treatment. Non-responders showed increased GR levels by the third week and reduced serum BDNF by the sixth week of treatment. In contrast, venlafaxine did not affect levels of pCREB. We conclude that levels of BDNF in serum and GR levels in lymphocytes may represent biomarkers that could be used to predict responses to venlafaxine treatment.

CURR ALZHEIMER RES. 2011 SEP;8(6):652-8.

MOLECULAR TARGETS IN THE RATIONAL DESIGN OF AD SPECIFIC PET TRACERS: TAU OR AMYLOID AGGREGATES?

Rojo LE, Gaspar PA, Maccioni RB.

A major limitation in finding therapeutic solutions for Alzheimer's disease (AD) has been the lack of a reliable method for early diagnosis of this devastating disease. Besides the development of biomarkers in biological fluids of patients, the search for a pathology-specific neuroimaging tools is critical at the present stage in which almost 30 million people suffer this disease worldwide. Several interesting approaches have been developed, however their clinical impact has been low. One of the difficulties has been to find the proper molecular tracers to specifically tag pathognomonic lesions in AD brain, including not only amyloid aggregates but also filaments of the modified microtubule-associated protein tau. In this review, we analyze the evidence towards developing pathology-specific diagnostic tools for AD. We analyze the current evidence and clinical implications of new imaging technologies for AD, and how tau hypothesis and the amyloid cascade hypothesis will impact on these scientific efforts in the near future.

ACTA NEUROL SCAND. 2011 JUL 28

INCIDENCE OF MULTIPLE SCLEROSIS IN CHILE. A HOSPITAL REGISTRY STUDY.

Díaz V, Barahona J, Antinao J, Quezada R, Delgado I, Silva C, Guiloff RJ.

Objective. to study the incidence of MS in Chile by examining the hospitalizations across all geographical regions of the country and to examine whether there is a correlation between these rates and the latitude or ultraviolet radiation. Methods – This is a descriptive study examining the national registry of hospitalizations because of MS (code G35 in ICD-10) from January 1, 2001, to December 31, 2006. Incidence rates were calculated by gender and geographical region and standardized to the world population estimated for 2010. Results – A total of 6857 hospitalizations were analyzed. There were 935 individuals; 63.9% were women. The mean incidence rate for 2002–2006 period was 0,90 (95% CI: 0.75–1.05). The annualized incidence rates for regions from North to South were as follows: I Tarapaca 0.54 (95% CI: 0.0–1.21), II Antofagasta 0,93 (0.10–1.75), III Atacama 1.07 (0.0–2.31), IV Coquimbo 0.63 (0.01–1.24), V Valparaiso 0.83 (0.38–1.27), VI O'Higgins 0.72 (0.14–1.30), VII Maule 0.52 (0.06–0.98), VIII BIO BIO 0.81 (0.41–1.21), IX Araucanía 0.43 (0.0–0.86), X Los Lagos 0.91 (0.35–1.46), XI Aysen 0.99 (0.0–2.98), XII Magallanes 3.54 (0.57–6.51), and XIII Metropolitana 1.10 (0.84–1.36). There were no significant correlations between hospitalization rates and latitude, except for region XII. UV radiation levels showed significant differences only for region XII. Conclusion – There is a moderate risk of MS in Chile. The southernmost region showed significantly higher incidence rates than those in the rest of the country (a cluster zone). We did not find any correlation between incidence rates and latitude or UV radiation.

OAIC

IMMUNOBIOLOGY. 2011 OCT;216(10):1117-26.

A SYNTHETIC PEPTIDE HOMOLOGOUS TO IL-10 FUNCTIONAL DOMAIN INDUCES MONOCYTE DIFFERENTIATION TO TGF–B+ TOLEROGENIC DENDRITIC CELLS.

López MN, Pesce B, Kurte M, Pérez C, Segal G, Roa J, Aguillón JC, Mendoza-Naranjo A, Gesser B, Larsen C, Villablanca A, Choudhury A, Kiessling R, Salazar-Onfray F.

We have previously demonstrated that IT9302, a nonameric peptide homologous to the C-terminal domain of human IL-10, mimics several effects of the cytokine including down-regulation of the antigen presentation machinery and increased sensitivity of tumor cells to NK-mediated lysis. In the present report, we have explored a potential therapeutic utility for IT9302 related to the ex vivo production of tolerogenic dendritic cells (DCs). Our results indicate that IT9302 impedes human monocyte response to differentiation factors and reduces antigen presentation and co-stimulatory capacity by DCs. Additionally, peptide-treated DCs show impaired capacity to stimulate T-cell proliferation and IFN-γ production. IT9302 exerts its effect through mechanisms, in part, distinct from IL-10, involving STAT3 inactivation and NF-κB intracellular pathway. IT9302-treated DCs display

increased expression of membrane-associated TGF-β, linked to a more effective induction of foxp3+ regulatory T cells. These results illustrate for the first time that a short synthetic peptide can promote monocytes differentiation to tolerogenic DCs with therapeutic potential for the treatment of autoimmune and transplantation-related immunopathologic disease.

J IMMUNOL. 2011 SEP 15;187(6):3121-32.

FUNCTIONAL GAP JUNCTIONS ACCUMULATE AT THE IMMUNOLOGICAL SYNAPSE AND CONTRIBUTE TO T CELL ACTIVATION.

Mendoza-Naranjo A, Bouma G, Pereda C, Ramírez M, Webb KF, Tittarelli A, López MN, Kalergis AM, Thrasher AJ, Becker DL, Salazar-Onfray F.

Gap junction (GJ) mediates intercellular communication through linked hemichannels from each of two adjacent cells. Using human and mouse models, we show that connexin 43 (Cx43), the main GJ protein in the immune system, was recruited to the immunological synapse during T cell priming as both GJs and stand-alone hemichannels. Cx43 accumulation at the synapse was Ag specific and time dependent, and required an intact actin cytoskeleton. Fluorescence recovery after photobleaching and Cx43-specific inhibitors were used to prove that intercellular communication between T cells and dendritic cells is bidirectional and specifically mediated by Cx43. Moreover, this intercellular cross talk contributed to T cell activation as silencing of Cx43 with an antisense or inhibition of GJ docking impaired intracellular Ca(2+) responses and cytokine release by T cells. These findings identify Cx43 as an important functional component of the immunological synapse and reveal a crucial role for GJs and hemichannels as coordinators of the dendritic cell-T cell signaling machinery that regulates T cell activation.

UNIDAD DE PACIENTES CRÍTICOS

ANN HEPATOL. 2011 JAN-MAR;10(1):99-102.

THALIDOMIDE FOR THE TREATMENT OF METASTATIC HEPATIC EPITHELIOID HEMANGIOENDOTHELIOMA: A CASE REPORT WITH A LONG TERM FOLLOW-UP.

Salech F, Valderrama S, Nervi B, Rodriguez JC, Oksenberg D, Koch A, Smok G, Duarte I, Pérez-Ayuso RM, Jarufe N, Martínez J, Soza A, Arrese M, Riquelme A.

Hepatic epithelioid hemangioendothelioma (HEH) is an unusual, low-grade malignant vascular tumor of the liver. Here we describe a case of a 40-year-old woman who presented with abdominal pain in the upper right quadrant and giant hepatomegaly, in which imaging studies and a fine-needle liver biopsy confirmed the presence of a large EHE with an isolated lung metastasis. After balancing all possible therapeutic modalities the patient was treated conservatively with thalidomide (300 mg/day). The drug was well tolerated with minimal toxicity and the patient continues on therapy 109 months after treatment was started with no disease progression. Current therapeutic options for HEH are discussed in light of the clinical case with particular emphasis on anti-angiogenic therapies.

MINERVA ANESTESIOL. 2011 MAY;77(5):510-21.

SYSTEMATIC APPROACH FOR SEVERE RESPIRATORY FAILURE DUE TO NOVEL A (H1N1) INFLUENZA.

Cornejo R, Tobar E, Díaz G, Romero C, Llanos O, Gálvez LR, Zamorano A, Fábrega L, Neira W, Arellano D, Repetto C, Aedo D, Díaz JC, González R.

AIM: In April 2009, a novel influenza A (H1N1) virus appeared in Mexico. It rapidly acquired the characteristics of a pandemic disease. Our objective is to present a case series of mechanically ventilated patients with severe influenza, treated with a systematic approach. METHODS: Prospective, observational, single-center study in a University Hospital. A (H1N1) virus was confirmed by rRT-PCR. In this report, we only considered patients that required mechanical ventilation (MV). All patients received antibiotics, steroids and oseltamivir from the time of admission. The main strategies incorporated in the systematic approach were a lung-protective strategy, PEEP adjusted for each patient, protocol-guided sedoanalgesia, restrictive fluid management, weaning protocol, and prolonged prone ventilation and extracorporeal membrane oxygenation (ECMO) as rescue therapies. RESULTS: We studied 19 patients: age 41 ± 13 years old, APACHE II 16 ± 7 and SOFA 8 ± 4. All patients presented PaO2/FiO2 ≤ 200 before connection to MV. Their worst values within the first 24 hours for oxygenation index, PaO2/FiO2, and PaCO2 on MV were 21.8 ± 13, 98 ± 39, and 48 ± 16 mmHg, respectively. Sixteen patients achieved ARDS; three exhibited acute lung injury

criteria. Ten required a prone position, and two required ECMO (one patient required both therapies). Time on MV was 16 ± 13 days. Length of stay in the ICU and in hospital was 18 ± 12 and 28 ± 17 days, respectively. Mortality was 21%. CONCLUSION: Severe hypoxemia and a high rate of rescue therapies were observed among our patients. Nevertheless, mortality was lower than previously reported in comparable populations, which may be related to the management by a critical care team and the use of a systematic approach for ventilatory and non-ventilatory therapeutic strategies.

INT J ANTIMICROB AGENTS. 2011 AUG;38(2):146-51.

HIGHER THAN RECOMMENDED AMIKACIN LOADING DOSES ACHIEVE PHARMACOKINETIC TARGETS WITHOUT ASSOCIATED TOXICITY.

Gálvez R, Luengo C, Cornejo R, Kosche J, Romero C, Tobar E, Illanes V, Llanos O, Castro J.

Antibiotic therapy improves the outcome of severe sepsis and septic shock, however pharmacokinetic properties are altered in this scenario. Amikacin (AMK) is an option to treat community or nosocomial infections, although standard doses might be insufficient in critically ill patients. The aim of this study was to evaluate two AMK dosage regimens in comparison with standard therapy with regard to efficacy in achieving adequate plasma levels as well as safety. In total, 99 patients with severe sepsis or septic shock were randomised to different AMK dose protocols: Group 1, 25 mg/kg/day; Group 2, 30 mg/kg/day; and Group 3, historical standard dose (15 mg/kg/day). Peak plasma concentrations at 1 h (C(max)) were determined. Pharmacokinetics was determined and renal function was monitored to evaluate toxicity. Groups were compared using bilateral T-test. Demographic characteristics of the three groups were comparable. AMK C(max) values were 57.4±9.8, 72.1±18.4 and 35.2±9.4 μg/mL, respectively (P<0.001 between Groups 1 and 2 versus Group 3, and P<0.01 between Group 1 versus Group 2). A C(max)>60 μg/mL was reached by 39%, 76% and 0% of patients in Groups 1, 2 and 3, respectively (P<0.001) and creatinine clearance at Day 28 was 95.6±47.4, 89.7±26.6 and 56.4±18.4 mL/min, respectively. In conclusion, a 30 mg/kg daily dose of AMK presents significantly higher C(max) compared with the other groups, with 76% of patients reaching recommended peak plasma levels with no association with higher nephrotoxicity. Standard doses are insufficient in critically ill patients to reach the recommended C(max).

J CRIT CARE. 2011 AUG;26(4):435.E9-14.

PERSISTENT SEPSIS-INDUCED HYPOTENSION WITHOUT HYPERLACTATEMIA: IS IT REALLY SEPTIC SHOCK?

Hernandez G, Castro R, Romero C, de la Hoz C, Angulo D, Aranguiz I, Larrondo J, Bujes A, Bruhn A.

PURPOSE: The prognostic value of hyperlactatemia in septic shock is unquestionable. However, as current definitions do not include hyperlactatemia as a mandatory criterion, some hypotensive patients may be diagnosed as having septic shock despite exhibiting normolactatemia. The significance of persistent sepsis-induced hypotension without hyperlactatemia is unclear. Is it really septic shock? Our aim was to determine differences in outcome between patients diagnosed as having septic shock but exhibiting normal vs elevated lactate levels during evolution. We also explored the potential implications of including hyperlactatemia as an obligatory diagnostic criterion. METHODS: We performed retrospective analyses on a cohort of 302 septic shock patients. RESULTS: When we divided patients according to the presence of hyperlactatemia, 34% evolved without hyperlactatemia and exhibited a very low mortality risk (7.7% compared with 42.9% of those with hyperlactatemia). These patients also presented less severe organ dysfunctions and higher central venous O(2) saturation values, and required lower norepinephrine doses. The potential inclusion of hyperlactatemia in septic shock definition would reduce incidence in 34% but increase absolute mortality risk in 11%. CONCLUSIONS: Persistent sepsis-induced hypotension without hyperlactatemia may not constitute a real septic shock. Our results support the need to review the current definition of septic shock. Hyperlactatemia could represent an objective parameter worth to be explored as a potential diagnostic criterion for septic shock.

J CRIT CARE. 2011 JUL 26.

EVOLUTION OF PERIPHERAL VS METABOLIC PERFUSION PARAMETERS DURING SEPTIC SHOCK RESUSCITATION. A CLINICAL-PHYSIOLOGIC STUDY.

Hernandez G, Pedreros C, Veas E, Bruhn A, Romero C, Rovegno M, Neira R, Bravo S, Castro R, Kattan E, Ince C.

PURPOSE: Perfusion assessment during septic shock resuscitation is difficult and usually complex determinations. Capillary refill time (CRT) and central-to-toe temperature difference (Tc-toe) have been proposed as objective reproducible

parameters to evaluate peripheral perfusion. The comparative evolution of peripheral vs metabolic perfusion parameters in septic shock resuscitation has not been studied. We conducted a prospective observational clinical-physiologic study to address this subject. METHODS: Patients with sepsis-related circulatory dysfunction were resuscitated according to a standard local algorithm. Perfusion assessment included serial determinations of metabolic (central venous O(2) saturation [Scvo(2)] and central venous to arterial Pco(2) gradient [P(cv-a)co(2)]) and peripheral perfusion parameters (CRT and Tc-toe, among others). Successful resuscitation was defined as a normal plasma lactate at 24 hours. RESULTS: Forty-one patients were included. The presence of normal values for both CRT and Tc-toe considered together at 6 hours was independently associated with a successful resuscitation (P = .02), as compared with the behavior of metabolic parameters. Capillary refill time was the first parameter to be significantly normalized. CONCLUSION: Early recovery of peripheral perfusion anticipates a successful resuscitation compared with traditional metabolic parameters in septic shock patients. Our findings support the inclusion of serial peripheral perfusion assessment in multimodal monitoring strategies for septic shock resuscitation.

SERVICIO ANATOMÍA PATOLÓGICA

ASIAN J ANDROL. 2011 MAY;13(3):476-80.

ALTERED EXPRESSION PATTERNS OF SYNDECAN-1 AND -2 PREDICT BIOCHEMICAL RECURRENCE IN PROSTATE CANCER.

Ledezma R, Cifuentes F, Gallegos I, Fullá J, Ossandon E, Castellon EA, Contreras HR.

The clinical features of prostate cancer do not provide an accurate determination of patients undergoing biochemical relapse and are therefore not suitable as indicators of prognosis for recurrence. New molecular markers are needed for proper pre-treatment risk stratification of patients. Our aim was to assess the value of altered expression of syndecan-1 and -2 as a marker for predicting biochemical relapse in patients with clinically localized prostate cancer treated by radical prostatectomy. The expression of syndecan-1 and -2 was examined by immunohistochemical staining in a series of 60 paraffin-embedded tissue samples from patients with localized prostate cancer. Ten specimens from patients with benign prostatic hyperplasia were used as non-malignant controls. Semiquantitative analysis was performed to evaluate the staining patterns. To investigate the prognostic value, Kaplan-Meier survival curves were performed and compared by a log-rank test. In benign samples, syndecan-1 was expressed in basal and secretory epithelial cells with basolateral membrane localisation, whereas syndecan-2 was expressed preferentially in basal cells. In prostate cancer samples, the expression patterns of both syndecans shifted to granular-cytoplasmic localisation. Survival analysis showed a significant difference ($P < 0.05$) between normal and altered expression of syndecan-1 and -2 in free prostate-specific antigen recurrence survival curves. These data suggest that the expression of syndecan-1 and -2 can be used as a prognostic marker for patients with clinically localized prostate cancer, improving the prostate-specific antigen recurrence risk stratification.

J AM ACAD DERMATOL. 2011 NOV;65(5):942-8.

ACTIVITY ASSESSMENT IN MORPHEA USING COLOR DOPPLER ULTRASOUND.

Wortsman X, Wortsman J, Sazunic I, Carreño L.

BACKGROUND: Morphea (circumcripted cutaneous scleroderma) can be difficult to assess for lesion activity. Because variable-frequency ultrasound with color Doppler provides details of skin morphology and function, it may help in the categorization of morphea. OBJECTIVE: We sought to evaluate color Doppler ultrasound as a probing tool for assessing activity in morphea lesions. METHODS: Consecutive patients with cutaneous morphea referred by dermatologists were studied with color Doppler ultrasound, and the assessment of lesion activity was compared with histologic findings. Normal skin controls were obtained by performing ultrasound scans of healthy subjects or of unaffected areas of the patients themselves. Measurements included cutaneous layer thickness, relative echogenicity, and blood flow with peak systolic velocity. Ultrasound sensitivity and specificity were determined for each phase of morphea activity and the results correlated with histology. RESULTS: Fifty-one patients had a total of 104 morphea lesions. Of the lesions, 20% were active, 22% were atrophic, and 58% were inactive. Five of the patients had the Parry-Romberg syndrome with ipsilateral parotid gland inflammatory involvement, and one had an asymptomatic but sonographically active morphea lesion. Sensitivity and

specificity for ultrasound diagnosis were 100% and 98.8%, respectively. The most accurate sonographic signs of lesion activity were increased subcutaneous tissue echogenicity and increased cutaneous blood flow (sensitivity and specificity 100% and 100% for each one). LIMITATIONS: Ultrasound cannot define lesions less than 0.1-mm deep. CONCLUSIONS: The morphologic and functional data obtained noninvasively and in real time with color Doppler ultrasound provide new insight into the pathogenesis of morphea. The technique represents a useful counterpart to histologic examination for the assessment of lesion activity.

SERVICIO DE UROLOGÍA

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POSTOPERATIVE MORBIDITY OF TUBELESS VERSUS CONVENTIONAL PERCUTANEOUS NEPHROLITHOTOMY: A PROSPECTIVE COMPARATIVE STUDY.

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Percutaneous Nephrolithotomy (PNL) is an established technique for the treatment of renal calculi. Some reports have challenged the need for a nephrostomy tube at the end of the procedure, arguing that it accounts for a longer hospital stay and increased postoperative pain. During the last years, several series have addressed the feasibility and safety of tubeless PNL, where a double-J ureteral stent is left in place after the end of intervention instead of a nephrostomy tube. The aim of our study was to compare conventional versus tubeless PNL in terms of postoperative morbidity. Eighty-five patients who underwent PNL at a single center met the inclusion criteria (complete intraoperative stone clearance, no evidence of active intraoperative bleeding, single percutaneous access, and operative time shorter than 2 h) and were randomized at the end of the procedure to have placed either a nephrostomy tube (group 1) or a double-J ureteral stent (group 2). Outcomes assessed were postoperative pain, bleeding complications, leakage complications, and length of hospital stay. The patients in the tubeless group had a shorter hospital stay (3.7 vs. 5.8 days; $P < 0.001$), and less postoperative pain at postoperative days 2 and 3 ($P < 0.001$). No significant difference in bleeding or leakage complications was observed. This study supports the feasibility and safety of tubeless PNL in a selected group of the patients, suggesting some intraoperative criteria to be considered when performing it. However, further controlled studies will have to determine its impact on stone-free rates prior to be considered the standard technique in these selected cases.

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DAX-1 AND DAX-1A EXPRESSION IN HUMAN TESTICULAR TISSUES WITH PRIMARY SPERMATOGENIC FAILURE.

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DAX-1 [dosage-sensitive sex reversal-adrenal hypoplasia congenital (AHC) critical region on the X chromosome gene 1; NR0B1] is an orphan nuclear receptor that acts as a transcriptional repressor in adrenal/gonadal development, steroidogenesis and probably spermatogenesis. An alternatively spliced form called DAX-1A (NR0B1A) has been described in several tissues including the testis, and in vitro studies have shown an inhibitory effect on DAX-1 transcriptional function. We aimed to study the mRNA and protein expression of DAX-1 in testicular tissues of 65 men with primary spermatogenic failure [complete Sertoli cell only syndrome (SCOS), focal SCOS, maturation arrest and mixed atrophy] compared with 33 controls with normal spermatogenesis. As a novel finding, we observed intense immunostaining, not only in the nucleus of Sertoli cells, but also in pachytene spermatocytes and round spermatids. The quantitative mRNA expression of DAX-1 and DAX-1A was similar between cases and controls and was not associated with the levels of gonadotrophins and steroids. Moreover, DAX-I transcript expression level was ~750-fold higher than DAX-1A, and there was a strong positive correlation between them ($r = 0.52$; $P< 0.001$). We conclude that, in addition to Sertoli cells, DAX-1/DAX-1A is expressed in germ cells from spermatogonia to round spermatids. Besides, the similar mRNA expression of DAX-I and DAX-IA in testicular tissues from cases and controls does not support the involvement of DAX-1 in the etiology of primary spermatogenic failure. Finally, the low level of expression of the alternative transcriptional variant DAX-1A would not support its putative inhibitory function in vivo.

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CHEMOTHERAPY SENSITIVITY RECOVERY OF PROSTATE CANCER CELLS BY FUNCTIONAL INHIBITION AND KNOCK DOWN OF MULTIDRUG RESISTANCE PROTEINS.

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BACKGROUND: In several cancer types, expression of multidrug resistance (MDR) proteins has been associated with lack of chemotherapy response. In advanced prostate cancer (PCa) the use of chemotherapy is mainly palliative due to its high resistance. Previously, we described that MDR phenotype in PCa could be related with high basal and drug-induced expression of MDR proteins P-Glycoprotein (P-Gp), MRP1, and LRP. METHODS: Using primary cell cultures from PCa patients, we evaluated the effect of function and expression inhibition of P-Gp, MRP1, and LRP, on cell survival after chemotherapy exposure. Cells were treated with specific MDR protein substrates (docetaxel and mitoxantrone for P-Gp, methotrexate for MRP1 and cisplatin for LRP) and pharmacological inhibitors (cyclosporine A, genistein and 3-aminobenzamide), and cell survival was evaluated trough 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and cell cycle analysis. MRP1 activity was evaluated by FACS using the specific inhibitor MK571. Cells were transfected with MDR proteins siRNAs and treated with the corresponding substrates. RESULTS: PCa cell resistance to MDR protein substrates was partially reversed, decreasing cell survival in around 20%, by treating primary cell cultures with specific pharmacological inhibitors. PCa cells transfected with siRNAs against MDR proteins decreased cell survival when treated with the corresponding drugs. Docetaxel was the most effective chemotherapeutic drug to induce cell death and decrease survival. CONCLUSION: Low chemotherapy response in PCa could be explained, in part, by over-expression of functional MDR proteins. Expression and function of these proteins should be evaluated to enhance efficacy of docetaxel-based therapies of patients with hormone-resistant PCa.

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ANALYSIS OF SIX SINGLE NUCLEOTIDE POLYMORPHISMS IN THE ANDROGEN RECEPTOR GENE IN CHILEAN PATIENTS WITH PRIMARY SPERMATOGENIC FAILURE

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Androgens are essential for spermatogenesis. It has been postulated that androgen activity is modulated directly or indirectly by genetic variability in the androgen receptor gene sequence, including CAG/GGN polymorphisms and single nucleotide polymorphisms (SNPs). In this study, the frequency of six SNPs, which constitute a haplotype in the androgen receptor sequence, was determined by enzyme restriction assays and allele-specific polymerase chain reactions in 117 secretory azo/oligozoospermic men (93 idiopathic and 24 ex-cryptorchidic) and in 121 controls with normal spermatogenesis (42 obstructive and 79 normozoospermic men), whose hormonal measurements and length of CAG/GGN polymorphisms were previously determined. The frequency of these six SNPs was not different between cases and controls. A total of ten haplotypes (HAP1-10) formed by these six SNPs were found, and one of these haplotypes was observed with high frequency in the total population (HAP1= 83.2%; $P<0.001$, Chi square test). The frequency of the ten haplotypes was not different between cases and controls, except for HAP5, which was only detected in one patient with a history of bilateral cryptorchidism ($P=0.014$, Bonferroni test). On the other hand, no associations were found between the haplotypes studied and shorter or longer CAG or GGN polymorphisms. Interestingly, we found that the CAG 21 allele, which was previously correlated with an increased risk of idiopathic spermatogenic impairment, was more frequently found among the less common haplotypes that have higher FSH serum levels. In summary, we did not find an increased frequency of particular haplotypes in infertile men with idiopathic spermatogenic impairment compared to control men; however, we found that the CAG 21 allele, which appears to be associated with male infertility, is observed at a significantly higher proportion among the less common AR haplotypes.