Oral Abstracts

SESSION PLÉNIÈRE: METABOLISMES, DU GÈNE AU PATIENT

Contribution of bone to whole-body metabolic regulation
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Bone is the only tissue of the vertebrate body that contains a cell type, the osteoclast, whose only function is to destroy the host tissue. This does not occur at random but rather in the context of a well ordered physiological process called bone modeling during childhood and remodeling during adulthood. We hypothesized that this process requires a daily delivery of a large amount of energy to bone cells; a large body of clinical observations supports this hypothesis. Testing this hypothesis led us to reveal the bone endocrine nature of bone and to identify osteocalcin as an osteoblast-derived hormone affecting multiple aspects of energy metabolism. We will review during this lecture the functions and mode of action of osteocalcin and address its overall importance in the control of whole body glucose homeostasis.

Futur developments in personalized human obesity management: is systemic medicine usefull?
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Abstract not available:

SESSION 1: GS MIXTE RESPIRATION

Bitter taste receptors in the lung: a new pharmacological target?
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Bitter taste receptors (TAS2Rs) are known for long for their role in taste as sensors of the presence of toxic compounds in foods, but their unexpected expression in airways epithelium and smooth muscle cells or in peripheral blood leucocytes has been recently documented. This family of GPCRs includes about 25 members in humans and each subtype has a variable selectivity towards bitter compounds, some of them being restrictedly selective to a unique molecule and others responding to a wider range. More than a hundred molecules such as chloroquine, caffeine, strychnine, colchicine or erythromycin have thus been described as TAS2R agonists while TAS2R19, 41, 42, 45 and 60 are considered as orphans since no agonist has been identified.
In the airways, the initial observation by Desphandes et al. (2010) described the relaxation of pre-contracted mouse trachea following exposure to chloroquine, denatonium, quinine or saccharine, which was suggested to be even more pronounced that the relaxation obtained with the reference relaxing agents β2 - adrenoreceptor agonists. Interestingly, an original intracellular signaling pathway in the response of airway smooth muscle cells to bitter-taste receptor agonists was proposed, involving the G-protein βγ subunit and leading to a localized increase in intracellular calcium, which in turn causes membrane hyperpolarisation through an activation of large conductance potassium channels (BK Ca). In addition to these results in cell cultures or airways preparations, inhaled bitter tastants were shown effective in decreasing airway resistance in ovalbumin-sensitized mice, but very little is known in humans to date. However, transcriptome analysis revealed upregulation of TAS2R signaling in peripheral blood leucocytes from patients with severe asthma, as well as a correlation between clinical markers of asthma severity and TAS2R expression.
Overall, these works suggest that bitter taste receptors may constitute a new pharmacological target for obstructive lung diseases such as asthma and COPD. We will address the role of bitter taste receptors in respiratory pharmacology, with a special focus on results obtained in human tissues.

01-01
Neural substrates of ventilatory chaos in humans
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Objectives: Biological systems exhibit nonlinear deterministic dynamics that can be chaotic, either at a cellular, organ or system levels. Human ventilation exhibits chaotic behavior, as well*. Direct evidences that ventilatory complexity is linked to the activity of the respiratory neural centers are still lacking in humans.
Methods: In 25 healthy subjects and 25 patients with chronic obstructive pulmonary disease (COPD), we evaluate airway flow chaos (noise titration, largest Lyapunov exponent and correlation dimension). Brainstem respiratory centers are located with cerebral functional magnetic resonance imaging (fMRI) in the ventro-lateral (VL) medulla (PreBötzinger complex) and the VL pons (parafacial group). Neural activity of the centers is studied through the low frequency of amplitude oscillations (LFAO) of fMRI signal of the selected brainstem regions of interest. It is a validated index of fMRI neural activation.
Results: COPD patients display a higher level of airway flow complexity as compared with healthy subjects. In controls and COPD patients ventilatory complexity correlates with the activity of the respiratory neural centers. During spontaneous breathing in controls, inspiratory chaos is tightly linked with the LFAO of the ventro-lateral (VL) medulla ($R^2 = 0.75$, $P = 0.01$) while in COPD patients, expiratory chaos correlates with LFAO of the VL pons ($R^2 = 0.4$, $P = 0.03$). External inspiratory resistive overload inhibits brainstem fMRI signal while significantly decreasing the resulting airway flow complexity in parallel in both populations.
Conclusions: We present the first study showing that airway flow complexity is strongly depending on the activity of the respiratory central pattern generators assess with fMRI. COPD patients have a high neural ventilatory drive due to chronically enhance respiratory load. We show in patients, at rest and during an increase load, a high level of airway flow complexity that translates the altered high activity of the brainstem respiratory centers. These findings may be involved in the onset of respiratory failure when the neural network becomes inefficient to sustain respiratory overload.
References:
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Mangin L., et al. *Am. J. Physiol.* (2009) **296**(4) R1088–R1097.
Mangin L., et al. *PLoS One* (2011) **6**(1) e16297.
Fundings: PHRC, BQR Paris 7, Fond de dotation Recherche Respiratoire
Keywords: respiratory neural network-chaos-breathing-fMRI-COPD.

01-02
Optoelectronic plethysmography in suspected and diagnosed unilateral diaphragm weakness
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Objective: The objective was to determine whether optoelectronic plethysmography (OEP) can detect asymmetrical ventilation related to unilateral or asymmetrical diaphragmatic weakness, suggesting usefulness as a diagnostic tool.
Material and methods: Thirteen patients with suspected asymmetrical diaphragmatic dysfunction based on dyspnea and hemidiaphragm elevation on the chest radiograph were studied, as well as three patients with maltase acid deficiency (a cause of symmetrical diaphragmatic weakness). The transdiaphragmatic pressure response to unilateral magnetic stimulation ($latPdi_{Tw}$) and the diaphragm compound muscle action potentials (CMAPs) elicited by transcutaneous electrical stimulation of each phrenic nerve. Chest wall kinematics was studied in the supine position using a motion analysis system (Motion Analysis®, Santa Rosa, USA) during spirometric tidal volume (VT) and inspiratory capacity (IC) measurement with a Vmax 229 Sensormedics System (Yorba Linda, USA). Fifty-two reflective markers were placed over the anterior chest wall from the clavicles to the pubic bone. To compute volumes, chest wall surface area was calculated from a triangular mesh created by connecting the nodes represented by the reflective markers, and we used standard algorithms to obtain the total chest cavity volume and volume changes in each thoracoabdominal compartment. Then, each compartment was separated into two sides (affected side and other side). Because in 12 healthy controls, we found that the inspired volume measured on one side during VT or IC measurement was never >55% or smaller than 45% of the total inspired volume values above or below these limits were taken to indicate unilateral or asymmetrical diaphragm dysfunction.
Results: The CMAPs and $latPdi_{Tw}$ showed unilateral or predominantly unilateral diaphragmatic dysfunction in nine of the 13 patients. By OEP, the affected side contributed <45% of the inspiratory capacity in each of these nine patients, whereas no asymmetry was noted in the other four patients or in the three patients with maltase acid deficiency. All patients preferred OEP over CMAP or $latPdi_{Tw}$.
Discussion: OEP detected asymmetric ventilation in all patients diagnosed with diaphragm weakness and in no patients without this diagnosis. Thus, OEP is an effective noninvasive alternative that is preferred by the patients over CMAP response and latPdiTw.
Keywords: plethysmography; chest wall; diaphragm; phrenic nerve.

01-03
NGF contributes to medial and intimal remodelling of pulmonary arteries in experimental pulmonary hypertension: receptors and signalling pathways involved
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Introduction: We have previously shown that expression of the nerve growth factor NGF is increased in pulmonary hypertension (PH), with NGF playing a role in various PH pathophysiological aspects. We have here studied whether NGF is involved in medial and intimal remodelling of pulmonary arteries in vivo in PH rat models. Receptors and signalling pathways involved in NGF-induced proliferation of human pulmonary arterial smooth muscle (PASMC) and endothelial cells (PAEC) in vitro were also investigated.
Methods: Experimental PH in the rat was induced either by a single injection of monocrotaline (MCT, day (D1, 60 mg/kg), or after 28 days of chronic hypoxia (CH, 0.5 atm). Anti-NGF blocking antibodies (10 μg/kg ip) were administered as a preventive treatment at D0-2-7 for MCT or at D1-8-15-22 for CH. Antibodies

04-03

Increased production of free radicals: a new pathogenic role for mitochondria in inflammatory myopathies?

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Introduction: Non-immunological mechanisms are emerging players in the pathophysiology of inflammatory myopathies (IM) (Henriques-Pons et al. 2009). Surprisingly, oxidative stress in the muscle of IM patients has not been explored. H2O2, which is mainly produced by NADPH oxidase, xanthine oxidase and mitochondrial respiratory chain, can play a direct toxic effect on muscle functioning (Westerblad 2011) and act as a chemokine for inflammatory cells (Niethammer et al. 2009). We determined whether H2O2 level is increased in muscle of IM patients and investigated whether mitochondria participate in H2O2 production.

Methods: Five patients with IM were included in this study. Five patients suffering from myalgia, but without muscle pathology, were used as controls. Samples from deltoid muscle were obtained at the time of muscle biopsy performed for diagnosis purpose. The production of H2O2 was recorded in the presence of different substrates increasing the activity of the mitochondrial respiratory chain using spectrofluorometry (Amplex red).

Results: Average age was comparable in both groups (IM: 44.4 ± 13.2 years; controls: 44.2 ± 10.7 years). The sex ratio was ¼ in both groups.

Without mitochondrial substrates, H2O2 production was similar in both groups (IM: 1.94 ± 1.44 pmol/min/mg; controls: 1.21 ± 0.75 pmol/min/mg, $P = 0.55$). After addition of glutamate and malate, H2O2 production was higher in IM group (5.55 ± 3.45 vs. 1.06 ± 1.03 pmol/min/mg, $P < 0.04$). Similar results were obtained with succinate (11.5 ± 5.22 vs. 2.54 ± 2.26 pmol/min/mg $P < 0.04$) and ADP (7.38 ± 6.84 vs. 0.52 ± 0.21 pmol/min/mg $P < 0.04$) (Figure 1).

Discussion – Conclusion: These results are the first data available on oxidative stress production in muscle of IM patients. Very interestingly, increased H2O2 production was higher in IM patients as compared with controls only in the presence of mitochondrial substrates. This suggests a key role for respiratory chains complexes in H2O2 production during IM. Whether mitochondria from muscle fibers or inflammatory cells (or both) are involved in this process require further investigations.

References:

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2. Westerblad et al. *Antioxid Redox Signal.* (2011) **15** 2487–2499.
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Keywords: Inflammatory myopathies; oxidative stress; mitochondria.

04-04

Protective effect of *Eucalyptus globulus* against acetaminophen induced liver damage in male rat

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Under our experimental conditions, acetaminophen poisoning resulted in an oxidative stress evidenced by a significant increase of lipids peroxidation level in hepatic tissues, hyperglycaemia and deccreased levels of total cholesterol and triglycerides, and transaminases activities in blood. Previous administration of *Eucalyptus globulus* extract was found to alleviate this damages.

Experimental design: Rats were divided into four batches: (C) was the control group; (P) was a group of rats treated with acetaminophen (300 mg/kg); (P) was a group of rats given *Eucalyptus globulus* extract (20 g/100 mL) during 4 weeks; (PE) was a group treated by *Eucalyptus globulus* then injected by acetaminophen (300 mg/kg). After 4 weeks, animals from each group were rapidly sacrificed.

Biochemical assays: Level of lipids peroxidation was measured as thiobarbituric acid reactive substances (TBARS), according to The total (Cu-Zn and Mn) superoxide-dismutase (SOD) activity was determined by measuring its ability to inhibit the photoreduction of nitroblue tetrazolium (NBT) . One unit of SOD represents the amount inhibiting the photoreduction of NBT by 50%. The activity was expressed as units/mg protein, at 25°C. Glutathione-peroxidase (GPX) activity was expressed as µmoles of GSH oxidized/min/g protein. The level of glycaemia, cholesterol, triglycerides, and transaminases in serum were determined by kit methods (Spinreact).

Results: TBARS levels in hepatic tissue were increased in acetaminophen treated rats as compared to controls. Administration of *Eucalyptus globulus* significantly reduced these TBARS levels. Activities of enzymes that protect against oxidative stresses, SOD, CAT and GPX were found to be respectively reduced in liver of acetaminophen treated rats, as compared to controls. These changes, revealing a failing defence against an oxidative stress, were largely corrected in animals treated by *Eucalyptus globulus* extract. Acetaminophen treatment induced severe liver damages evidenced in serum by a significant increase of hepaic enzymes. When acetaminophen treated rats were also treated with *Eucalyptus globulus* extract, all theses biomarkers were restored.

References:

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2. Clement Y.N., Williams A.F. Protection against paracetamol-induced hepatic injury by prazosin pre-treatment in CD-1 mice. *Mutat. Res.* **579** (2005) 182–188.

Keywords: acetaminophen *Eucalyptus globulus*, hyperglycaemia.

04-05

Metabolic syndrome and urinary lithiasis

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Objectives: Closer the links between these two pathologies that have alarmingly propagated into the entire world without exception by assessing the epidemiological parameters.

Patients and methods: An epidemiological investigation was conducted in the city of Sidi Bel Abbes (Algeria). Our study was performed on patient files at the Endocrinology Service during 3 years [(12/2006–11/2007)(12/2007/11/2008) (12/2008–11/2009)].

The methodology of the statistical analysis was based in two axes: 1- Descriptive statistics (Prevalence & Incidence) and 2- Analytic statistics (Exposed /Non Exposed: relative risk).

Results and discussion: The epidemiological study of 600 files shows that the prevalence of Metabolic Syndrome (MS) [NCEP ATP III, 2002] is 42.66% which is 1.7 times higher among women compared to men and the prevalence of Urinary Lithiasis (UL) in the general population is 6.16% whereas in those with MS is 11.32%. We also noted an increase in the incidence of MS and its risk factors parallel to that of the UL. For 2006–2007: MS (43.47%), UL on all population (3.91%), UL on those with MS (0.3%). For 2007–2008: MS (39.25%), UL on all population (6.07%), UL on those with MS (13.09%). For 2008–2009: MS (46.15%), UL on all population (9.61%), UL on those with MS (20.83%). The results show also that the RR is >1 among patients who have the MS than those unscathed and this proves that MS is a risk factor of UL.

Keywords: Metabolic Syndrome, Urinary Lithiasis, Risk Factor, Epidemiology, Prevalence, Incidence.

SESSION 5: A3P COMMUNICATIONS LIBRES

Management of bleeding in patients taking new oral anticoagulant treatment

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Bleeding is the major complication of oral anticoagulation therapy and is yet the most frequent of major adverse drugs events in terms of morbidity and mortality. Vitamine K antagonists (VKA) were the only oral anticoagulants for decades and are yet the widely prescribed. In recent years, new oral anticoagulants (NOACs) that selectively inhibit either thrombin (dabigatran etexilate) or factor Xa (rivaroxaban, apixaban) have been marketed. They differ in many respects and especially in pharmacokinetics but all have the advantage of having a wide therapeutic range without requiring regular monitoring. To date, clinical studies show that the incidence of spontaneous bleeding with NOACs is comparable to that of established anticoagulants. However, unlike vitamin K antagonists, there are currently no clinically available antidotes or approved reversal agents for NOACs. For rivaroxaban, a specific decoy is under evaluation (FXa-GLAless), whereas, for dabigatran, the Company is developing a specific selective antidote.

Attempts have been made to restore normal coagulation after NOACs using compounds such as recombinant activated factor VII (rFVIIa), prothrombin complex concentrate (PCC), or FEIBA (factor eight inhibitor bypassing activity). Dabigatran has the additional option of removal from the blood system via dialysis. Emergency dialysis can remove about 60% of the dabigatran concentration in 4 h.

However very limited pre-clinical data and even less clinical evidence are available on the usefulness of these methods for the emergency management of critical bleedings. So, only weak propositions can be currently performed for management of bleeding events with NOACs in clinical practice, based on old established measures that are the same for all anticoagulant treatments and on some more specific but no validated options.

05-01

Increase in the rate of spontaneous adverse drug reaction notification and improvement of pharmacologic quality analysis in a department of infectious diseases using an electronic medical record: NADIS®

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Background: Adverse Drug Reactions (ADRs) are commonly under-reported. NADISO is an electronic medical record (EMR) for Human Immunodeficiency Virus (HIV) infected subjects seeking care in french public hospitals. An automatic warning, informing the physician of each new Adverse Drug Reactions (ADRs) associated with Anti-Retroviral Drugs (ARDs) leading to discontinuation, has recently been added in NADIS®.

Material and methods: The aim of this study was to measure the quality and the benefit of NADIS® in the Regional Pharmacovigilance Center of Nantes. ADRs reported via NADIS® pharmacovigilance tool were collected during 21 months (from January 2011, start date of NADIS® pharmacovigilance tool utilization, to October 2012). Each effect was sent to the Regional Center. After sorting the data according to System Organ Class (SOC), the rate of ADRs with each drug was calculated. Severity, evolution, and patient characteristics were also notified and analysed.

Results: Eighty-eight cases were retained for analysis, and observed in 81 HIV-infected patients. In comparison with a 21 months long lasting period before NADIS® pharmacovigilance tool utilization (from April 2009 to December 2010), an increase of 60% in collected cases was observed. The mean age of patients was 44 years (SD: 14; min: 18; max: 82), with a sex ratio of 1.79 (M/F). Seven (7.9 %) ADRs were recorded as serious, leading to hospitalisation, or being life threatening. The outcome of thirty-nine (44.3%) ADRs were favourable after drug dis-

continuation. Renal and urinary (19.3%), gastro-intestinal (14.8%), nervous system and psychiatric (15.1%), skin and subcutaneous tissue (10.2%), metabolism and nutrition (10.2%) disorders were the most frequently described ADRs. Regimens including Nucleoside Reverse Transcriptase Inhibitor combined with Non Nucleoside Reverse Transcriptase Inhibitors or with Protease Inhibitors have been associated with ADRs in 36.4% and 43.2% of cases, respectively.
Discussion/Conclusion: Since the availability of NADIS® pharmacovigilance tool, a significant increase in spontaneous notifications has been observed limiting the under-reporting rate. Pharmacologists and Physicians collaboration associated with suitable information collect via NADIS® can contribute to improve the quality of pharmacologic analysis and the medical following of each report, in order to carry on the benefit/risk ratio regimens.
Keywords: Pharmacovigilance, Electronic medical record, Anti-retroviral drugs, Adverse Drug Reactions.

05-02
Adverse drug reactions and off-label drug prescription in paediatric outpatients: a survey among general practitioners in south western France
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Aim: To study the association between off-label drug prescription and Adverse Drug Reaction (ADR) occurrence in a sample of paediatric outpatients managed by general practitioners
Methods: A prospective pharmacovigilance survey on paediatric drug prescribing was implemented in a sample of general practitioners from 46 practices in Midi-Pyrénées area (South western France). All consecutive patients aged 0–16 were included. Characteristics of the patients (age, gender, weight), main reasons for consulting, and drug prescribed (including strength, route and indication) were collected. Incidence and characteristics of ADRs occurring within 10 days after the date of consult and identified by the GP were recorded. Off-label prescription was defined as prescribing outside the specifications of the Summary of Products Characteristics. Unlicensed drugs were those with no valid marketing authorization.
Results: Among the 2313 visits included from March 8, 2011 to July 31, 2011, 1960 involved at least one prescribed drug with a total of 4888 drugs prescribed. Mean age was 5.59 (SD 4.49), with a sex ratio of 1.06. Among the 1960 children receiving at least one prescription, 37.6 % (n = 737) were exposed to at least one off-label prescribing, and 6.7% (n = 132) to at least one unlicensed drug. Off-label prescribing involved an unapproved indication in 56.4% of the cases (n = 416), a lower dosage than specified in 26.5% (n = 195), a higher dosage than specified in 19.5% (n = 144), age not labeled in 7.2% (n = 53), incorrect route of administration in 3.5% (n = 26), and contraindication in 0.3 % (n = 2). A total of 23 ADRs were reported, giving an incidence of 1.0% in the population study and of 1.5% in patients exposed to at least one off-label prescription. None of the ADRs was considered as 'serious', and all were reported to the pharmacovigilance center. ADRs occurrence was not found to be significantly related to off-label drug prescribing.
Discussion: Despite the numerous initiatives implemented since 2005 for promoting rational medicines use in children, the magnitude of off-label prescription in outpatient paediatric practice remains high (around 35% to 40%). By contrast with the findings of a previous study conducted more than 10 years ago [1], we did not found any increased ADR risk related to off-label prescribing.
Reference:
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Keywords: Adverse drug reactions, Off-label drug use/prescription, Paediatric outpatients, Pharmacovigilance.

05-03
Azathioprine and breastfeeding: long-term follow-up
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Objective: Although a number of reports indicate that azathioprine can be safely used during lactation, data on long-term follow-up of breastfed babies are still limited. Our aim was to report the biological and long-term clinical follow-up of breastfed infants from azathioprine-treated mothers.
Methods: All azathioprine-treated mothers who contacted Lyon Pharmacovigilance Center before initiating breastfeeding, and finally opted to breastfeed their baby for at least 1 month during treatment were included. The follow-up was performed through regular telephone interviews of the mother and/or her pediatrician. The data collected for the breastfed infants included results of the blood cell counts (usually at birth and after 2–3 weeks of breastfeeding), and data on growth and general health.
Results: Twenty-nine women (30 newborns) receiving azathioprine 50–175 mg/day were included. Eleven babies were born prematurely (27–36 weeks), including one set of twins. Breastfeeding duration ranged from 1 to 17 months (median: 3.5 months). Blood cell counts performed at birth in 16 newborns evidenced a decrease in white cell count in 3, which further normalized despite breastfeeding continuation, suggesting this might be the consequence of in utero exposure to azathioprine. Among the 20 babies who had late blood cell counts, only one presented with asymptomatic neutropenia on day 15, but azathioprine metabolites below the limit of quantification. Neutropenia fluctuated from 0.5 to 1 G/L during the 1.5-month period of breastfeeding, persisted for 15 days after breastfeeding discontinuation, and completely resolved 3.5 months later. No other causes were found. Several episodes of non serious winter infections were noted later at the age of 6–12 months. No unexpected adverse outcome was observed among the 29 other babies followed up until the age of 1.5–30 months (median: 9.5 months) and nine experienced common infectious episodes.
Discussion: Except one debatable case of asymptomatic neutropenia, no biological or clinical consequences of maternal azathioprine treatment were observed in breastfed babies, even after long-term follow-up, or in premature newborn. Although these results are reassuring, infant blood cell counting should be systematically proposed 10–15 days after breastfeeding initiation.
Keywords: Azathioprine, Breastfeeding, Long-term follow-up.

05-04
Evolution and characteristics of pristinamycin-induced adverse effects: analysis from the French National Pharmacovigilance database
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Pristinamycin is the mixture of pristinamycin IA (group B streptogramin) and pristinamycin IB (macrolide), active on staphylococci and streptococci. It is available in France for over 30 years. Following the observations in our hospital of adverse effects (AE) unusual for their severity and/or onset delay, our objective was to evaluate pristinamycin-induced AE, qualitatively and quantitatively, along the time, from the French National Pharmacovigilance database.
Methods: An analysis from the database was performed since 1999, counting the number of severe and non severe AE, skin and non-skin AE, with pristinamycin suspected. A more precise analysis compared all the severe AE notified in 2004–2005–2006 to those in 2009–2010–2011. Sails volume was kindly provided by ANSM. Some cases were reclassified as DRESS syndrome when Kardaun score was found ≥ 3.
Results: The number of AE, around 125/year, sharply increased in 2007–2008, to reach 180/year thereafter. The ratio of severe/non severe AE increased from a mean of 1.1 before 2007 to 1.8 after 2007. The number of non-severe AE was stable, as well as the proportion of skin AE (severe and not severe) (68.8 % of total AE).
Comparison of severe AE between the two groups of 3 years indicated that the number of digestive AE, hematological AE, bullous dermatitis, DRESS, vascular purpura, and other skin reactions, had practically doubled whereas sails volume increased by 35 %. Their median delay of onset was shorter in the second period, with a statistically significant difference reached for type I reactions (2 vs. 0.5 h). Characteristics of age and sex remained similar. In 11 cases of bullous reactions (including Lyell syndrome) and 23 cases of DRESS, 1 or 2 days only separated pristinamycin introduction to the reaction onset.
Discussion: Characteristics of some severe AE are not presently indicated in the summary of product characteristics: mainly cytopenias, and DRESS syndrome with the possibility of very unusual short delay of occurrence. The increase number of hypersensitivity reactions together with the short time of onset for DRESS and bullous dermatitis suggest that the population has been sensitized to pristinamycin. A food origin for this sensitization cannot be excluded.
Keywords: pristinamycin, severe adverse reactions, French pharmacovigilance database.

SESSION 6: PHARMACO CLINIQUE

06-01
Pharmacological treatment in type II diabetes and evidence based medicine
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Recently ADA and EASD published a position statement in the management of hyperglycaemia in type II diabetes (T2D), without questioning the 'treat to target' dogma, proposing 'individualized' HbA1C targets depending on history of diabetes, contra-indications and co-morbid conditions. But how strong is the evidence for an intensive strategy compared with a less stringent standard? A meta-analysis of 13 trials compared the effect of intensive vs. standard treatment in T2D on both microvascular and cardiovascular complications. Intensified treatment did not reduce all-cause or cardiovascular mortality; a reduction in the risk of non-fatal myocardial infarction and microalbuminuria was observed, but these reductions were not anymore significant when high quality studies only were considered. The risk of severe hypoglycemia was more than twofold increased, leaving the benefit-risk ratio uncertain.
Here we further investigated on the same data the relationship between HbA1c decrease and clinical outcomes as log(OR) in a meta-regression with random effect model. On average, the decrease in HbA1c was associated with a non-significant increase in mortality (seven studies), cardiovascular mortality (eight studies), and stroke (seven studies). It did not display statistically significant relation with the decrease in the risk of myocardial infarction (six studies) and heart failure (eight studies). The relations between HbA1c and the risk of photocoagulation (three studies), visual loss (three studies), worsening of renal failure or doubling of plasma creatinin (four studies), neuropathy and peripheral vascular disease (six studies for both) were also inconclusive.
This systematic review did not show significant association between HbA1c reduction and any clinical benefit. The efficacy of glucose lowering treatments has been seriously challenged by meta-analyses, these drugs should be used cautiously to avoid acute metabolic accidents, e.g. hypoglycemia, and major hyperglycemia. The prevention of cardiovascular complications should first rely upon ACE inhibitors and statins that present a much higher level of evidence in that

Results: A time-dependent increase of all the abovementioned analytes was observed during global ischemia. A fast recovery to basal values was observed during reperfusion period. Comparatively to the basal value (before ischemia), the higher increase was observed with NAADP after 40 min of ischemia (0.8 vs. 0.03 μM, $P < 0.001$), followed by UTP (1.5 vs. 0.08 μM, $P < 0.05$), NAD (0.35 vs.0.03 μM), cADP-ribose (0.06 vs. 0.006 μM), and adenosine (2 vs. 0.23 μM, $P < 0.05$). The increase of NAADP metabolite, NAAD, was non-significant (0.1 vs. 0.02 μM).
Conclusion: We confirm that UTP and adenosine are released during ischemia. To the best of our knowledge, this is the first report of a significant increase in extracellular concentrations of NAD and its metabolites such as NAADP and cADP-ribose during heart ischemia. These metabolites could be involved in endogenous cardioprotective mechanisms.
Peart J and Headrick JP, Am J Physiol (2000).
Keywords: interstitial beta-NAD, NAADP and cADP-ribose, cardiac ischemia, microdialysis

25-08
Chicoric acid is an anti-oxidant molecule stimulating AMP Kinase, PGC-1alpha expression and mitochondrial activity in a model of skeletal muscular cells
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Introduction: It was suggested that food anti-oxidants may prevent insulin resistance and development of oxidative stress associated with metabolic diseases. In particular, caffeic acid and its derivatives, chorogenic and chicoric acids, were described as having anti-diabetic properties, although their mechanism is not completely understood. In the present work, we used the L6 cell line model of skeletal muscle to explore the mechanism of chicoric acid (CA) by determining its effects on oxidative stress, michondrial activity, AMP-activated kinase (AMPK) and insulin pathways.
Material and methods: Protein and mRNA expressions were determined by Western blotting and qPCR, respectively. Reactive oxigen species (ROS) were quantified using the 2',7-dichlorofluorescein probe and cellular glucose uptake determined using 2-deoxy-D-glucose[^{3}H].
Results: In differenciated L6 myotubes, CA was shown to be a ROS scavenger, both in basal and oxidative stress conditions. CA increased the activities of anti-oxidant defense system enzymes glutathion peroxydase and superoxyde dismutase (SOD). CA protected mitochondria against oxidative damages by increasing MnSOD expression. CA also increased the activity of complex II and the expression of PGC-1α, a transcriptional co-activator involved in the regulation of anti-oxidant enzyme expression and mitochondrial biogenesis. CA also stimulated AMPK/ACC and inhibited insulin-stimulated Akt/mTOR pathways without any significant change in glucose uptake.
Conclusion: CA possesses anti-oxydant properties, both through its capacity to neutralize ROS and increase anti-oxidant enzymatic defense systems. CA also stimulates mitochondrial biogenesis and protects mitochondria against oxidative damages, along with increasing the mitochondrial capacity to oxidize fatty acids by stimulation of AMPK and increase of complex II activity. Those results suggest that the potential of chicoric acid to prevent or treat metabolic syndrome-related pathologies deserves to be further studied.
Keywords: Free Radicals, Mitochondria, Chicoric acid, myotubes, anti-oxidant, AMPK

25-09
Anodal iontophoresis of a soluble guanylate cyclase activator induces a sustained increase in skin blood flow in rats
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Introduction: The treatment of systemic sclerosis-related digital ulcers is still a therapeutic challenge. While the only effective drugs are prostacyclin analogues, their current use is limited by frequent vasodilation-related adverse reactions. Iontophoresis is a non-invasive method permitting local drug-delivery, which may allow reaching high concentrations of drugs into the dermis while limiting their systemic effects. The objectives of this study were: 1/ to screen whether iontophoretically-administered non-prostanoid IP agonists and soluble guanylate cyclase (sGC) activators increase skin blood flow in rats; 2/ to test different drug concentrations and protocols, and 3/ the safety of candidates.
Methods: Three sGC activators (A-350619, SIN-1 and CFM 1571) and two non-prostanoid IP agonists (MRE-269 and BMY 45778) were selected on their physicochemical properties. In experiment 1 drugs were delivered by cathodal or anodal iontophoresis onto the hindquarters of anaesthesized rats ($n = 8$ for each drug) and skin blood flow was quantified using laser Doppler imaging. Experiment 2 aimed at comparing the effect of three different concentrations of the candidates selected in experiment 1; tolerance was also assessed by recording blood pressure continuously, and by histopathologic examination of full-thickness skin biopsies. We finally aimed at optimizing drug delivery by comparing continous vs. sequential iontophoresis protocols (experiment 3).
Results: Anodal iontophoresis of A-350619 (7.54 mM) induced a significant and sustained increase in cutaneous blood flow ($P = 0.008$, vs. NaCl). The other drugs we tested exhibited poor or no effect. We observed a concentration-dependent vasodilation when delivering A-350619 through iontophoresis ($P < 0.001$, Jonckheere-Terpstra trend test). Finally, tolerance was good for A-350619, with no evidence of skin damage, no significant effect on systemic blood pressure and no cutaneous resistance change.
Conclusions: Anodal iontophoresis of A-350619, a sGC activator, increases cutaneous blood flow with good local tolerance while other tested drugs exhibited poor or no effect. Iontophoresis of sGC activators should be investigated as a new local therapy for digital ulcerations in patients with scleroderma.
Keywords: iontophoresis; soluble guanylate cyclase; prostacyclin; non-prostanoid prostacyclin receptor; microcirculation

25-10
Structure and activation mechanism of G-protein-coupled receptors: role of the proline residues in helices 2 and 5
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Objectives: Class A G-Protein-coupled receptors (GPCRs) constitute a large family of transmembrane receptors. Helical distortions play a major role in the overall fold and in the activation mechanism of these receptors. Most distortions are related to the presence of conserved proline residues. However, in helices TM2 and TM5, the presence of proline is not mandatory and the correlated mutation of these proline residues is observed in several GPCR sub-families. In addition, the position of the TM2 proline is variable (2.58–2.60). We are interested in the role of the TM2 and TM5 proline residues in the folding and activation mechanism of GPCRs.
Methods: We selected two receptors, the vasopressin receptor 2 (V2R) and the thyrotropin receptor (TSHR), as prototypes of receptors with and without proline, respectively, in both TM2 and TM5. By site-directed mutagenesis, we engineered TSHR mutants with proline residues at different positions in TM2 and/or at position 5.50 in TM5. We also engineered V2R mutants without proline in TM2 and /or TM5 and with proline at different positions in TM2. We studied the influence of these mutations on the receptor folding, membrane expression and activation of the cAMP pathway.
Results: Most mutations in either TSHR or V2R impair the folding and the translocation to the plasma membrane of the receptors. In particular, mutations in both helices are very disruptive. However, a few single mutations are tolerated and the corresponding mutants are able to activate the cAMP pathway with decreased EC50.
Discussion: Our experimental results enlighten the importance of the presence (or absence) of the TM2 and TM5 proline residues in the activation mechanism of specific GPCR sub-families. Coupled to molecular modeling, our study will help understand the specific features of each receptor in relation with their proline pattern to improve drug design.
Keywords: receptor, GPCR, proline, helix, activation mechanism

25-11
New targets of endocrine disruptors: example of FSH receptor
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Research in the field of endocrine disruptors (ED) has tremendously expanded during the last years. In humans, ED was associated with sexual development abnormalities (genital malformation, precocious puberty). Regarding the mechanisms of action of ED, most of the published studies have focused on their interferences with nuclear receptor signalization and/or with alterations in hormone synthesis. However, these target systems and axis partly depend on G protein coupled receptors (GPCRs) that are involved in numerous physiologic and physiopathologic processes. In this context, we hypothesized that the GPCRs should be regarded as putative targets for ED. Initially we focused on the impact of ED on the FSH (Follicle-Stimulating Hormone) receptor (FSHR) activity. Molecules (pesticide, bisphenol A, phthalates, and heavy metals) are tested solo or in combination, to mimic multiple expositions in vivo, on stably transfected cell lines overexpressing the human FSHR. The effect of ED on FSHR activity is assessed by cyclic AMP measurement by biosensor kit. The majority of pollutants tested potentiate the maximal response of FSHR. Thus, the maximal response is increased 1.5-fold with 10^{-4} M Mono Butyl Phthalate or 1.3-fold with 10^{-8} M bisphenol A. However, DiEthylHexyl Phthalate do not impact the FSH dose-response in contrast to their metabolites such as 10^{-5} M Mono EthylHexyl Phthalate, that rise 2.3-fold the maximal response. Moreover, we observed a synergic effect between ED and heavy metal. We now, try to determine the ED action mechanisms and more particularly their impact on internalization, desensitization or the recycling process of receptor.
Keywords: Endocrine-disruptors; G protein coupled receptor; FSH receptor

SESSION 26: PHARMACO ET GROSSESSE

26-01
Drug-induced adverse reactions via breastfeeding: a study in the French Pharmacovigilance Database
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Introduction: It is well established that most of drugs were excreted into breast milk and thus also available to the infant. The effects on the infant, of many drugs taken by the mother are unknown.
Objective: To describe Adverse Drug Reactions (ADRs) registered in the French Pharmacovigilance Database.
Method: All spontaneous reports of ADRs in breastfed infants recorded by the 31 French Regional Pharmacovigilance centres in the National Pharmacovigilance database were investigated.
Results: Between January 1985 and June 2011, 174 ADRs in breastfed infant were notified to the French network of PharmacoVigilance. Median age was 49.0 ± 66.7 days. Mean weight (3863.9 ±1326.9 g) and length (49.4 ±3.0 cm) of infants were lower than in the French general population. The most

often reported ADRs were nervous system disorders (28.6%), followed by gastrointestinal disorders (20.3%) and skin and subcutaneous tissue disorders (6.5%). Sixty-five (37.4%) ADRs were considered as serious. Most frequently suspected drugs were nervous system drugs, mainly antiepileptics, benzodiazepines and opioid analgesics. Drugs more often suspected in serious ADRS were dextropropoxyphene (respiratory distress, apnea…), ketoprofene (renal and digestive adverse effects…), lamotrigine, hydroxyzine and clonazepam.
Conclusion: Some drug classes such as opioids and antiepileptics drugs, NSAIDs and benzodiazepines, which produced adverse effects in the infant, should be used, when necessary, with great care
Keywords: Adverse Drug Reaction, Pharmacovigilance, Breastfeeding, drugs

26-02
Veinotonics in pregnancy: a comparative study in the EFEMERIS database

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Introduction: There is few published data about possible effects of veinotonics in pregnant women. However, many French women use these medications during their pregnancy.
Objective: The present study investigates potential adverse drug reactions of veinotonics in pregnancy.
Method: EFEMERIS is a database including prescribed and dispensed reimbursed drugs during pregnancy (data from Caisse Primaire d'Assurance Maladie of Haute-Garonne) and outcomes (data from Maternal and Infant Protection Service and from Antenatal diagnostic Centre). Women who delivered from July 1st 2004 to September 30th 2008 in Haute-Garonne (time period when veinotonics were still reimbursed) and were registered in the French Health Insurance Service have been included into the EFEMERIS database. We compared pregnancy outcomes and newborn health between women exposed to veinotonics during pregnancy and unexposed women. Malformations were classified according to Eurocat classification.
Results: 9,671 (25.7%) newborns exposed *in utero* to veinotonics were compared with 27 982 controls (non exposed newborns). The most widely used veinotonics were hesperidin, diosmin and troxerutin. The mean age of the mothers was 31.2 ± 4.8 years in the exposed group and 30.0 ± 5.1 in the control group ($P < 10^{-4}$). The mean number of drugs taken during pregnancy was higher in the exposed group (13.4 ± 8 vs. 9.4 ± 7; $P < 10^{-4}$). Pregnancies led to 98.2% vs. 93.4% of live-births, 0.2% vs. 0.2% of postnatal deaths and 1.6% vs. 6.4% of pregnancy termination (miscarriage, ectopic pregnancy, medical termination, intra uterine death) in exposed and non exposed groups respectively. In the group of newborns whose mother had a prescription of veinotonics during organogenesis, 42 out of 1,360 (3.1%) had a malformation vs. 790 (3.0%) in the control group ($P = 0.6$). The rate of neonatal pathologies was higher in the control group (5.8 vs. 6.4, $P = 0.04$).
Conclusion: We found no increased risk of adverse pregnancy outcome including neonatal pathology and congenital malformation among women exposed to veinotonics compared with unexposed pregnant women.
Keywords: EFEMERIS, veinotonics, pregnancy, pharmacoepidemiology

26-03
Pregnancy outcome in women exposed to dopamine agonists during pregnancy: a study in EFEMERIS database

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Objective: Dopamine agonist drugs can be prescribed for several indications like hyperprolactinemia or Parkinson's disease. Prevalence of these diseases is low during pregnancy. Thus, very little is known on the possible effect of dopaminergic agonists on embryo-fetal development. The aim was to describe pregnancy outcomes in women exposed to prescription of dopamine agonists in EFEMERIS, a cohort of French pregnant women.
Method: An 'exposed-non exposed' study was conducted in EFEMERIS cohort (database including prescribed and dispensed drugs during pregnancy and outcomes). The present study concerns the 57 408 mother-outcomes pairs included in EFEMERIS database between 2004 and 2010. Women who received at least one dispensation of a dopamine agonist drug during pregnancy were considered as exposed to dopamine agonist drugs and classified in the 'exposed group'. They were individually matched to 2 'unexposed' women. We compared adverse foetal outcomes in the two groups using conditional logistic regressions.
Results: One hundred and eighty-three women (0.3%) had a dispensation of at least one dopamine agonist during pregnancy. Bromocriptine was the most-prescribed drug (more than half of the exposed women) followed by cabergoline (20%) and quinagolide (10%). Most of the indications (67%) were for hyperprolactinemia. 75% of dopamine agonist prescriptions were performed during the first trimester of pregnancy. Prescriptions strongly decreased during the second trimester (8.8%). There was no difference between the two groups concerning pregnancy history and demographic data. Women exposed to a dopamine agonist received more prescriptions of other active substances during pregnancy than the unexposed group. After adjustment for potential confounders, the risks of pregnancy termination and preterm birth were significantly increased after exposure to dopamine agonist drug during pregnancy with respectively a prevalence odds ratio of 3.7 (95% CI 1.8, 7.4) and 2.7 (95% CI 1.04, 7.0). The prevalence of birth defect and low birthweight was not statistically different between the two groups. No difference in psychomotor development at 9 and 24 months of babies was observed.
Discussion: The results of this study suggest that fetal exposure to dopamine agonist drugs may increase the risk of adverse fetal outcomes. Due to limited enrolment, further studies are needed for better evaluation of these risks.
Keywords: Pregnancy, prescriptions, dopamine agonist, outcome, pharmacoepidemiology

26-04
Pregnancy outcomes after maternal use of azathioprine: a French cohort Study

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Although azathioprine is considered relatively safe during pregnancy, it remains listed as a category « D » drug by the FDA.
Objectives: Our main purpose was to examine the rate of malformations and spontaneous abortions in women treated with azathioprine during the first trimester of pregnancy. Prematurity and low birth weight in infants exposed to azathioprine during the third trimester were also analysed.
Study design: In this multicenter prospective study, pregnant women exposed to azathioprine during the 1st trimester were included after request for risk assessment. Each patient was matched with one disease-paired control that used other immunosuppressant than azathioprine for similar indications (excepting mycophenolate mofetil). The primary endpoint was to evaluate the incidence of major malformations.
Results: One hundred and twenty four pregnant women exposed to azathioprine during the 1st trimester of pregnancy were included. The rates of spontaneous abortions did not differ between the 2 groups (4.9 vs. 3.6%, $P = 0.7$). The rate of all birth defects was 7.2% in the azathioprine group vs. 5.4% in the other immunosuppressant group [RR = 1.36 (0.4–4.2)]. The rate of major malformations was slightly higher in the azathioprine group (5/97 or 5.2%) compared to disease-matched controls (2/110 or 1.8%) but did not significantly differ between groups RR 2.96 [0.5–15.6]. Two of the 5 major birth defects from the azathioprine group were observed in women also exposed to tacrolimus for organ transplantation. Birth weight (3225 g vs. 3279 g), gestational age at delivery (37.7 vs. 38 w), and preterm deliveries (22.6% vs. 21.4%) were comparable between both groups.
Conclusions: Azathioprine exposure during organogenesis does not appear to increase the risk of major malformations but larger studies are needed to confirm this observation. Exposure throughout pregnancy was not associated with an increased risk of low birth weight or preterm delivery.
Keywords: Azathioprine, pregnancy, prospective study

26-05
Pregnancy outcome in women exposed to aripiprazole during the embryonic period: a prospective multicentric cohort

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Objectives: Aripiprazole, an atypical antipsychotic, is not recommended during pregnancy because of teratogenicity suggested in animal studies and the paucity of clinical data. The main objective of our study was to evaluate whether aripiprazole exposure during the embryonic period was associated with an increased risk of major malformations. Secondary objectives were to evaluate the risks of miscarriage, prematurity, fetal growth retardation and maternal complications and to describe possible neonatal adverse effects.
Methods: We conducted a multicenter cohort study using data prospectively collected by the French Regional Pharmacovigilance Centres participing to the Terappel program and the Centre de Référence sur les Agents Tératogènes (CRAT) between 2004 and 2011. 'Exposed patients' were pregnant women exposed to aripiprazole during embryogenesis, i.e. 4–10 weeks after the last menstrual period (exclusion of patients co-exposed to known teratogenic agent). 'Unexposed patients' were pregnant women without exposure or exposed to non-teratogenic agent during embryonic period. Each 'exposed patient' was matched with two 'unexposed patients' for age (±2 years) and gestational age at call (±2 weeks).
Results: Eighty-six patients were included in the exposed group and 172 in the unexposed group. Compared to unexposed patients, exposure to aripiprazole was not associated with a significant increased risk of major malformations (OR = 2.30; 95%CI= 0.32–16.69) or miscarriage (OR = 1.66; 95%CI=0.63–4.38) or gestational diabetes (OR = 1.15; 95%CI=0.33–4.04); but was associated with a significant increased risk of prematurity (OR = 2.57; 95%CI=1.06–6.27) and fetal growth retardation (OR = 2.97; 95%CI=1.23–7.16). Among the 19 newborns exposed to aripiprazole near delivery, there were one case of withdrawal syndrome with pulmonary hypertension and respiratory distress and one case of amniotic fluid aspiration pneumonia.
Conclusion: Our study suggests that aripiprazole is not associated with a major teratogenic risk. These preliminary results support the reassuring limited published data, but must be confirmed by more powerful studies.
Keywords: aripiprazole, pregnancy, malformations