S3.1

Study on the regularity between CYP3A5/3A4 polymorphism in medication of tacrolimus after renal transplantation

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Aim: To investigate the regularity between the genetic, ungenetic factors of patients and the medication of FK506 in renal transplantation recipients in the first 3 month post-transplantaton, and determine the appropriate dosage of FK506 in patients with different phenotypes at different stage after transplantation. **Methods:** 113 renal transplantation patients were involved in this study, and the blood samples of each patient were collected. The dose (D), C_0 of FK506, the weight, drug co-administration, and the relevant clinical index were detected and recorded at 3, 5, 7, 14 d and 1, 2, 3 month. The recipients were grouped according to different gene phenotypes which was involved in each regression equation, and the C_0/D of FK506 in different groups was compared. **Results:** The polymorphism of CYP3A5*3 plays a leading role in individual administration of FK506, and the C_0/D of FK506 asends with time. Although it was more significant when these two genes were considered together, CYP3A5 can be individually investigated for the determination of the initial dose of FK506. The initial dose of quick metabolizers was approximately 2 times to slow metabolic patients. **Conclusion:** The polymorphism of CYP3A5*3 is the most important reason for the individual diference of the FK506 C_0/D. The initial dose of quick metabolizers was approximately 2 times to slow metabolic patients.

Keywords: renal transplantation; FK506; stepwise multiple regression; CYP3A5*3; CYP3A4*18B; genetic polymorphism

S3.2

A positive association of the tissue kallikerin gene A2233C polymorphism with blood pressure response to benazepril

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Aim: The association of the human tissue kallikerin (hKLK1) gene A2233C polymorphism with blood pressure (BP) response to benazepril in hypertensive induviduals (hypertesnives) was investigated. **Methods:** A total of 331 hypertensives were recruited and treated with benazepril (10 mg daily, oral dosing) for 15 days. Before and after administration of drug, systolic BP (SBP) and diastolic BP (DBP) of all hypertensives were measured. Forearm venous blood samples were collected and genomic DNA was extracted. The hKLK1 A2233→C polymorphism was genotyped by PCR-RFLP. The hypertensives, whose SBP/DBP <140/90 mmHg or ΔBP (the baseline BP minus the post-treatment BP)/baseline BP ≥15% after Benazepril treatment, were defined as good responders, otherwise as poor responders. **Results:** Chi-square analysis showed that the hypertensives with AC genotype had a higher proportion in SBP (60.3% *vs* 42.0%, χ^2=10.05, *P*=0.007) and DBP (57.7% *vs* 43.6%, χ^2=6.71, *P*=0.035), respectively, to benazepril medication in good responders than in poor responders. Logistic regression analysis indicated that the hypertensives with AC genotype were more sensitive to the benazepril therapy in SBP (OR=2.35, 95% CI: 1.15–4.82, *P*=0.019) and DBP (OR=1.91, 95% CI: 1.04–3.52, *P*=0.037), as compared with those hypertensives with AA genotype. **Conclusion:** The A2233C polymorphism of the gene may be a marker of evaluation of hypertensives' responses to ACEIs, and the hypertensives with AC genotype were more sensitive to the benazepril therapy.

Keywords: ACEIs; benazepril; hKLK1 gene; hypertension; SNP

S3.3

Genotype and haplotype association of *PON1* with susceptibility to coronary artery disease and clinical outcomes in dual antiplatelet-treated Han Chinese patients

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Aim: To evaluate the association of *PON1* genetic variants with the susceptibility to coronary artery disease (CAD) as well as clinical endpoints in aspirin and clopidogrel dual antiplatelet-treated Han Chinese patients with CAD after percutaneous coronary intervention (PCI). **Methods:** 538 Han Chinese patients undergoing PCI and received dual-antiplatelet therapy were sequentially recruited and followed up to 1 year. 539 healthy controls were enrolled during the same period. The effect of 5 genetic variants in *PON1* and *CYP2C19**2 on the disease risk and clinical outcome of major adverse cardiac events (MACE) in 1 year or bleeding in 6 months was assessed. **Results:** *CYP2C19**2 was associated with a higher risk of MACE (*P*=0.0098), but a lower risk of bleeding events (adjusted *P*=0.0016). *PON1* Q192R was significantly associated with a lower risk of bleeding events (OR: 0.61, 95% CI: 0.43–0.87, *P*=0.0066). Haplotype bearing *PON1*-126C allele was associated with a higher risk to CAD (OR: 1.48, 95% CI: 1.04–2.09, *P*=0.029) and a higher risk of bleeding events (OR: 1.68, 95% CI: 1.10–2.56, *P*=0.017), compared to the most frequent haplotype. The transcription activity of haplotype p-162A-126C-108C in *PON1* promoter was 2.6 fold higher than that of the most frequent haplotype (p-162G-126G-108T). **Conclusion:** Haplotype bearing *PON1* -126C allele contributes to the disease risk and the risk of bleeding events in dual antiplatelet-treated CAD patients after PCI.

Keywords: paraoxonase 1; genetic variant; dualantiplatelet; bleeding

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S3.4

Intensive monitoring of adverse drug reactions in cancer patients on chemotherapy

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Aim: In India, adverse drug reaction (ADR) rates and incidences in relation to number of drugs prescribed or patients exposed have been assessed only in few survey and projects. Hence, our aim was to monitor and analyze the pattern of ADRs in cancer patients receiving chemotherapy in a tertiary care hospital. **Methods:** An intensive monitoring program was carried out in Department of Radiotherapy and Oncology, Kasturba Hospital, Manipal, a tertiary care hospital in South India. Case records, drug charts, medical and nursing notes of patients receiving chemotherapy were reviewed for presence of any evidence of ADRs. **Results:** 154 patients were reported to have ADR/ADRs in a period of one year and were followed-up prospectively. Reactions observed were nausea, vomiting, alopecia, fever, neutropenia, thrombocytopenia, anemia, peripheral neuropathy, hand foot syndrome, constipation, oral ulcers, blackening of nails, skin rash, scaling of body, sensory neural hearing loss, ear pain, breathlessness and paralytic ileus. All reactions were of type A. Naranjo's algorithm showed that all ADRs were 'probable'. **Conclusion:** The present study showed that chemotherapy has a high potential to cause adverse effects. Thus, there is a need for vigilant ADR monitoring to prevent morbidity and mortality due to ADRs.

Keywords: adverse drug reaction; tertiary; chemotherapy; Naranjo's algorithm

S3.5

Analysis of 56 cases of suspected death caused by drugs

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Aim: The purpose of this paper is to analyze the main characteristics and general patterns of between patients, drugs, the way of treatment and death of adverse drug reaction (ADR), to provide references for clinical rational drug use. **Methods:** A total of 56 cases, collected from Jan 2011 to Dec 2012 in Yunnan Center for ADR monitoring, were analyzed retrospectively, especially focusing on the analysis and discussion of five typical cases. **Results:** Among the suspected drugs involving death cases, the proportion of antimicrobial agents is the highest (39.29%, 22 cases), followed by traditional Chinese medicine injection (17.86%, 10 cases). The common performances of ADR are anaphylactic shock and allergic reactions (44.64%, 25 cases), followed by respiratory damage and circulatory system damage. The major treatments are intravenously guttae (96.43%, 54 cases). There are 45 cases occurred in county-level hospitals, township central hospitals and private clinics, which amount to 80.36%. **Conclusion:** The widespread use of antimicrobial drugs and traditional Chinese medicine injections, intravenous drip, multiple drug combination could increase the risk of serious ADR and even deaths, at the same time, the level of medical institutions and medical service quality are the key factors that cannot be ignored.

Keywords: adverse drug reaction; death; analysis of reports; rational drug use

S3.6

Protective effect of atorvastatin on contrast-induced nephropathy in aged diabetics underwent coronary artery interventional therapy

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Aim: In this study, the protective effect of different doses of atorvastatin on contrarst-induced nephropathy (CIN) in aged diabetics underwent coronary artery interventional therapy were investigated. **Methods:** 100 aged diabetics who underwent coronary artery interventional therapy with 64-slice spiral computed tomography were randomized to receive high dose of atorvastatin (80 mg/d, *n*=40) or low dose of atorvastatin (20 mg/d, *n*=40) treatment for 2-3 d before coronary artery interventional therapy with 64-slice spiral computed tomography. 1, 3, and 5 d after the administration of a radiocontrast agent.Serum creatinine(Scr), creatinine clearance rate (CcR), blood urea nitrogen (BUN), urine-β2 microglobulin and microalbumin(mALB)were also assessed at the same time. **Results:** In low dose group, comparison with the value before coronary artery interventional therapy with 64-slice spiral computed tomography, Scr and urine -β2 microglobulin significantly increased (P<0.01), but Ccr significantly reduced at d 1 and d 3 after angiography (P<0.01). Scr, Ccr and urine-β2 microglobulin levels at d 7 after angiography had no significant change compared with baseline (P>0.05). In the high dose group, compared with the value before coronary artery interventional therapy with 64-slice spiral computed tomography, Scr and urine-β2 microglobulin significantly increased (P<0.05) and Ccr reduced at d 1 and d 3 after angiography (P<0.05). Scr, Ccr and urine-β2 microglobulin levels at d 5 after angiography had no significant change compared with baseline (P>0.05). Compared with the low group, the values of Scr and urine-β2 microglobulin significantly reduced (P<0.01), but Ccr significantly increased at d 1 and d 3 after angiography in atovastatin-treated group (P<0.01). Scr, Ccr and mALB levels at d 5 after angiography had no significant change compared with baseline(P>0.05). There was no significant change in BUN levels compared with baseline after angiography in two group (P>0.05). **Conclusion:** Taking high dose of atorvastatin before coronary artery interventional therapy in aged diabetics may prevent patients from the contrast-induced nephropathy.

Keywords: atorvastatin; aged diabetics; contrast-induced nephropathy; protective effect; coronary artery interventional therapy

S3.7

A cross-sectional survey on disease constitution of elderly inpatients in Xuanwu Hospital, Capital Medical University in 2011

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Aim: To learn about the local diseases constitution and provide baseline data for further study. **Methods:** Elderly (≥60 years old) inpatients records in the Xuanwu Hospital in 2011 were collected. All the discharge diagnosis were standardized according to the International Classification of Disease, 10th Edition. Data including general information of the inpatients and discharge diagnosis were analyzed by Microsoft Excel 2003. **Results:** There were 13807 elderly inpatients, accounting for 39.8% of all the inpatients, and males were more than females (1.3:1). Average kind of disease in each patient was 4.4, ranging from 1 to 11. For patients with only one disease, nervous system diseases (26.2%) ranked first. For patients with two diseases, circulatory system diseases ranked first both in the primary (21.5%) and secondary (45.6%) disease. All the diagnosis included 18 categories; circulatory system diseases (42.5%) ranked first. The primary diagnosis included 18 categories; circulatory system diseases (31.1%) ranked first. In the circulatory system diseases, cerebral infarction (17.9%) ranked first. There is significant difference in various age and gender subgroups of patients with cerebral infarction (P<0.05). **Conclusion:** Elderly disease constitution is complex. Primary diagnosis is mainly circulatory system diseases. In the following studies attention should be paid on drug utilization of circulatory system diseases to provide evidence for making the China specific elderly caring clinical pathway.

Keywords: disease constitution of elderly inpatients; cross-sectional survey

S3.8

High level of IL-12 and gene polymorphisms in *IL-12B* on -6415CTCTAA/GC and rs3212227 were associated with penicillin allergy

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Aim: IL-12, a strong candidate gene for allergic diseases, can induce inflammation factors produced by natural-killer and T lymphocytes. This study was to investigate the possible roles of *IL-12B*-6415 (CTCTAA/GC) site in the promoter region and *IL12B* 3′ untranslated region (UTR) (C/A), this SNP is now designated rs3212227 in penicillin allergy, and to explore the association between the polymorphisms of IL-12 gene and the levels of specific IgEs in penicillin allergy. **Methods:** IL-12 serum levels of 319 penicillin allergic patients were measured by enzyme-linked immunosorbent assay. Sites-6415 (CTCTAA/GC) and rs3212227 (C/A) were studied by polymerase chain reaction restriction fragment length polymorphism. Specific IgE were measured by radioallergosorbent test (RAST). **Results:** Penicillin-allergic patients had the higher level of IL-12 than control (15.8 pg/mL *vs* 13.5 pg/mL) (P<0.05). And in patients, IL-12 level was significantly correlated to four types of specific IgE (BPO: P<0.05, APO: P<0.05, BPA: P<0.01 and APA: P<0.01). 6415GC/10841C had higher frequency in patients (27.0%) compared with control subjects (19.4%)(P<0.01). **Conclusion:** The serum IL-12 level and gene polymorphisms of *IL-12B* on -6415CTCTAA/GC and rs3212227 were associated with penicillin allergy. It also suggests that -6415GC/-10841C type haploid may serve as a risk factor in Chinese patients allergic to penicillin.

Keywords: IL-12; polymorphisms; allergy; penicillin

S3.9

Emerging artemisinin resistance in Southeast Asia?

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Malaria remains one of the major global public health problems. The major problem which limits the control of this infection is resistance of *Plasmodium falciparum* to most of the available antimalarial drugs. Artemisinin-based combination therapies (ACTs) have become the counterpiece of global malaria control to halt the impending epidemics of drug resistant malaria. They are now the recommended first-line treatment for uncomplicated *P. falciparum* in all malaria endemic countries to improve efficacy and delay development and selection of drug-resistant parasites. Despite the precautionary measure however, artemisinin resistant *P. falciparum* malaria has recently been reported in western Cambodia and the bordering areas of Thailand, the well recognized hotspot of MDR *P. falciparum*. Until comprehensive coverage with effective malaria vaccine is available, and with only a handful of effective antimalarial drugs available, the development of artemisinin resistance by malarial parasites would be a challenge for the current global malaria control programs. The situation accentuates the importance of closer surveillance and containment in parallel with effective malaria control program to avoid the emergence of new foci of resistance and to limit the spread of the resistant parasites to other areas. Intense efforts are being pursued worldwide to confirm, characterize, and contain resistance to artemisinins. The urgency of these efforts is increased by the paucity of alternative antimalarials should artemisinins fail.

S3.10

Association study between aberrant DNA methylation in promoter of DDAH2 gene and dysfunction of EPCs in CAD patient

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Aim: it has been demonstrated that circulating EPCs may be a biomarker for vascular function and cardiovascular risk in patients with coronary artery disease patients (CAD). Recent studies suggest that dimethylarginine dimethylaminohydrolase2 (DDAH2) participate in the differentiation of EPCs and regulate the senescence and function of EPCs. Our previous studies have showed hypermythalytion of DDAH2 is involved in the apoptosis of endothelial cells induced by homocysteine. Therefore, we hypothesis that DNA methylation of DDAH2 promoter plays important roles in the regulation of EPCs function and is closely associated with the origin and development of AS. **Methods:** Peripheral blood mono-nuclear cells (PBMC) from 25 AS positive patients (coronary angiography to coronary artery branches in at least one vessel stenosis >50% defined as CAD) and 15 negative patients (angiographically normal) were collected by density gradient centrifugation and then were induced to differentiate into EPCs.

EPCs function was assayed by their adhesive capacities to hemaleucin and the expression of DDAH2 mRNA were analyzed by Real time-qPCR. Bisulfite genomic sequencing method was used for the detection of the DNA methylation level of DDAH2 promoter. **Results:** The adhesion function of EPCs from CAD patients was significantly decreased, accompanied by decreased expression of DDAH2 mRNA. The promoter of DDAH2 in EPCs from CAD patients is hypermethylated and is negatively related to EPCs adhesion function.

Conclusion: Aberrant methylation in promoter of DDAH2 gene is positively related to dysfunction of EPCs in CAD patients, suggesting a key role of epigenetic in development of AS.

Keywords: endothelial progenitor cells; atheroslcerosis; DNA methylation; dimethylarginine dimethylaminohydrolase; homocysteine

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S3.11

Drug-drug interactions between triazoles antifungal agents and calcineurin inhibitors in hepatic transplantation and bone marrow transplantation recipients

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Aim: To assess the frequency of potential drug-drug interactions (PDDIs) and consequences of interactions between triazoles antifungal agents and calcineurin inhibitors (CNIs) in hepatic transplantation (HT) unit and bone marrow transplantation (BMT) unit. **Methods:** We performed a retrospective observational study of 86 hospitalized adults receiving systemic triazoles antifungal agents and CNIs treatment simultaneously in HT and BMT units of the Third Affiliated Hospital of Sun Yat-sen University, China between 2008 and 2012. All treatment episodes with triazoles and CNIs co-administration were examined and all PDDIs-serious events occurring during treatment were adjudicated for clinical DDIs between triazoles antifungal agents and CNIs. **Results:** There were 120 treatment episodes with triazoles and CNIs co-administration, of which 98 episodes were in hepatic transplantation (HT) care and 22 episodes were in Bone Marrow Transplantation (BMT) care. 82 PDDIs from 120 episodes were identified related to the co-administration of voriconazole and ciclosporin (26.8%), voriconazole and tacrolimus (34.1%), fluconazole and ciclosporin (13.4%), fluconazole and tacrolimus (15.9%), itraconazole and tacrolimus (9.8%), respectively. The most frequent adverse drug reactions (ADRs) associated with PDDIs were moderate which presented headache (42.6%), elevated blood pressure (31.7%), renal function abnormal (12.1%) and so on. **Conclusion:** In HT and BMT patients, co-administration of triazoles and CNIs can lead to many PDDIs. It is clinical pharmacists' responsibility to manage drug-drug interactions. Clinicians should also be alert to the PDDIs between triazoles and CNIs as well as the ADRs caused by PDDIs.

Keywords: drug-drug interactions; triazoles antifungal agents; calcineurin inhibitors

S3.12

Clinical prediction and diagnosis of Alzheimer's disease based on microRNA panel

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Aim: Alzheimer's disease diagnosis is time-consuming and challenging, serum-based biomarkers are the least expensive and invasive modality for screening and routine monitoring. In this study, we investigated let-7g, miR-197, miR-126 and miR-29a expression levels in serum with the intention to identify a panel of miRNAs for diagnosis of MCI and AD. **Methods:** qRT-PCR assay was applied to evaluate the expression levels of let-7g, miR-197, miR-126 and miR-29a. Logistic regression model was constructed to diagnosis MCI and AD using a training cohort (n=150) based on miRNA panel, and the model was validated using an independent cohort (n=52). Additionally, biochemical information analysis and CoMI (Context-Specific miRNA Regulation Network) were used to predict the target gene of those differential expression miRNAs in the neuropathic pathway of Alzheimer's disease. **Results:** The expression levels of those four miRNAs were significantly lower in MCI and AD group than those in NDC group, Pearson correlation analysis showed that the expression levels of those four miRNAs had significant positive correlation to MMSE score. Additionally, we identified a miRNA panel that demonstrated diagnosing role for MCI and AD. When combine with mini mental state examination (MMSE) scores, the panel demonstrated a better diagnosing role for MCI and AD. Moreover, the pathways regulated by those four miRNAs changed at different stage of AD and some pathways were corrected with neurofibrillary tangles (NTF) scores. **Conclusion:** Four differential expressed miRNAs were potential circulating diagnostic bio-markers which may be helpful in diagnosis of MCI and AD.

Keywords: Alzheimer's disease; diagnosis; microRNA; biomarkers

S3.13

Determination of SHV-typed extended-spectrum β-lactamases in *E. coli*, *K. pneumonia* and *P. aeruginosa* of China and their susceptibilities to 10 β-lactam antibiotics

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Bacteria producing Extended-spectrum β-lactamases (ESBLs), have risen dramatically and been recognized a global healthy problem. In this research, we investigated the genotype distributed of extended-spectrum β-lactamases of Escherichia coli *(E. coli)*, Klebsiella pneumonia *(K. pneumonia)* and Pseudomonas aeruginosa *(P. aeruginosa)* clinical isolated in the Chengdu Second Hospital of China and the related drug resistance analysis. Clinical isolated ESBLs-producing strains were detected by double-disk method. Gene fragments of ESBLs were amplified by PCR. Pyrosequencing and Sanger sequencing were used to study SHV genotyping of clinical isolated, gene polymorphisms related with the ESBLs genotype were investigated. Meanwhile the antimicrobial susceptibility of cefepime, cefazolin, cefotaxime, cefuroxime, cefoperazone, ampicillin, piperacillin Imipenem, cefoxitin and cefotazidime was determinded by the agar dilution method in Mueller-Hinton agar. There were 90 produce ESBLs, producing the SHV gene fragment is 74 % (67/90). 90 strains producing ESBLs were completely sensitive to the Imipenem, and most of them were sensitive to the cefepime, cefoxitin and ceftazidime, MIC_{50} were from 4 to 32 μg/mL. Some strains were resistant to cefoperazone, cefotaxime, MIC_{50} was 32, 128 μg/mL respectively. They were resistant to ampicillin, piperacillin, cefuroxime and Cefazolin, MIC_{50}>256 μg/mL respectively. The Pyrosequencing results showed that the SHV is mainly SHV-1 (52%), SHV-11 (31%), and SHV-12 (16%) in this hospital. The proportion of resistant to cefepime, cefoxitin, cefotazidime was 17%, 26%, 34% for the SHV-1 strains, respectively; 48%, 62%, 71% the SHV-11 strains, respectively; and 36%, 82%, 73% for the SHV-12 strains, respectively. SHV was one kind of the prevalent genotypes of ESBLs in clinical isolates of *E. coli*, *K. pneumonia* and *P. aeruginosa* in this hospital.

Keywords: microbial sensitivity tests; molecular epidemiology; beta-lactamases; genetics

S3.14

An integrated approach for revaluating the rationality and safety of traditional Chinese medicine injections in clinical use

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Aim: Authoritative evaluation criteria for the rationality and safety of traditional Chinese medicine injections (TCMIs) in clinical use have still not been established. This approach attempts to improve the situation. **Methods:** A total of 240 medical cases from a certain hospital during 2011, were selected randomly, and different aspects were evaluated by several means, such as the consistency between clinical use and description of TCMIs, drug utilization research on TCMIs, logistic regression analysis on TCMIs adverse drug reaction/events, and so on. **Results:** There were poor consistency between clinical use and description of TCMIs. Drug utilization research revealed overdosage and super-concentration administration of TCMIs, which had the efficacy of modifying rheological properties of blood. Logistic regression analysis showed that, administration concentration as a protective factor was a valid indicator for evaluation and prediction of the adverse drug reactions/events of TCMIs. **Conclusion:** Revaluating the rationality and safety of TCMIs in clinical use should be evolved through different perspectives, such as the consistency between clinical use and description, drug utilization research and logistic regression analysis.

Keywords: traditional Chinese medicine injections; rationality; safety; drug utilization research; adverse drug reaction/event
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S3.15

UCP-1 and UCP-2 gene polymorphism on patients with shivering after cesarean section under spinal anesthesia

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Aim: To study UCP-1 and UCP-2 gene polymorphism of patients shivering after cesarean section under spinal anesthesia and to explore the factors for post cesarean section shivering. **Methods:** 200 cases of obstetric patients who had lumbar epidural anesthesia for cesarean section were observed. The following were recorded before anesthesia, the injected anesthetics, basic vital signs, and other factors of shivering. All patients with UCP-1 and UCP-2 were genotyped by polymerase chain reaction-Restriction fragment length polymorphism analysis. **Results:** Mean arterial pressure decreased 5 min and 10 min after anesthesia significantly (P<0.05). There was 70.5% incidence of cesarean section maternal perioperative hypotension and 29.5% non-hypotensives; cesarean section maternal perioperative shivering was 66.5%, ranging from grade 2-5, accounting for 11.2%, 7.5%, 30.8%, and 50.5%, respectively. Some patients Body mass index within the third trimester of pregnancy was greater than 25 and others less than 25 and shivering impact between the two was not statistically significant (P=0.383>0.05); shivering incidence in emergency cesarean was 84.6%, non-emergency cesarean shivering was 60%, between the two statistical difference (P=0.002<0.05); under ambient temperature of 23°C in operating room, shivering incidence was 83.6%, and above 23°C, shivering incidence was 61.4%, between the two was a statistically significant difference (P=0.009<0.05); UCP-1 promoter gene-3826AA type, -3826AG type, and -3826GG type in this group of patients accounted for 45.5%, 40% and 18.5%, perioperative incidence of shivering were 62.7%, 72.5% and 62.2%three statistical difference (P=0.361>0.05); UCP-2 gene promoter-866AA type,-866AG type and-866AG type accounted for 30.5%, 51.5% and 18%, shivering rates were 73.8%, 72.5% and 47.2%, respectively, three statistical difference (P=0.024<0.05). Anesthetic block plane, hypotension and surgery duration of shivering was not statistically significant. **Conclusion:** Ambient temperature is an important factor of the impact of cesarean section Perioperative shivering, there was a high shivering incidence in UCP-2 promoter gene-866AA type-and-866AG type patients and low in type UCP-2 promoter gene-866GG type patients, therefore genetic factor is a beneficial in cesarean section perioperative shivering.

Keywords: cesarean section; shivering; UCP-1; UCP-2

S3.16

Bioequivalence study of simvastatin in healthy volunteers

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Aim: To assess the bioequivalence of two simvastatin tablet formulations in 24 male healthy volunteers. **Methods:** The study was performed according to an open-label, randomized, single-dose, two-period crossover design with a one week washout interval. Plasma samples were obtained over a 24 h period. Plasma simvastatin concentrations were analyzed by combined liquid chromatography coupled to tandem mass spectrometry (LC-MS-MS) with positive ion electrospray ionization using multiple reaction monitoring (MRM). From the simvastatin plasma concentration *vs* time curves, the pharmacokinetic (PK) parameters AUC_{last}, AUC_{0-inf} and C_{max} were obtained by WinNonlin 6.3. **Results:** The limit of quantification was 0.1 ng/mL for plasma simvastatin analysis. The intra-subject variability of simvastatin was as high as 41%. And the geometric mean and the 90% confidence interval (CI) test/reference ratios of the PK parameters were in a large range. **Conclusion:** Since the intra-subject variability of simvastatin was higher than 30%, it was concluded that simvastatin was a highly variable drug, which means a larger sample size is needed to demonstrate bioeuqivalence of the two formulations.

Keywords: simvastatin; bioeuqivalence; liquid chromatography coupled to tandem mass spectrometry (LC-MS-MS); highly variable drugs

S3.17

One case report of intervention in immunosuppressive agents convertion from cyclosporine to tacrolimus in a renal transplant patient harboring CYP3A5*3/*3 genotype by clinical pharmacist

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Aim: To explore the work pattern of clinical pharmaceutical care associated with immunosuppressive agents convertion from cyclosporine to tacrolimus in renal transplant patients by the methods of therapeutic drug monitoring and genetic testing. **Methods:** We coducted the Medication Reconciliation (Med-Rec) of clinical data and drugs information for the renal transplant who had being suffered from seriously chronic constipation caused by cyclosporine after renal transplantation. According to the basic information and metabolic enzyme CYP3A5*3/*3 genotype of the patient, clinical pharmacist recommended that rhubarb sodium and bicarbonate tablets should not be used for treating constipation and the immunosuppressive agents should be switched from cyclosporine to tacrolimus (the initial daily dose of tacrolimus was 4 mg). **Results:** Fortunately, the clinician accepted the recommendation of clinical pharmacist enventually. After convertion from cyclosporine to tacrolimus, renal function of the patient has been stable and the phenomenon of constipation has not happened again. **Conclusion:** If the renal transplant patients have being suffered from seriously chronic constipation caused by cyclosporine after renal transplantation, clinical pharmacist should pay special attention to this seriously adverse reaction during the long-term pharmaceutical care. Immunosuppressive agents switching from cyclosporine to tacrolimus may be a good choice to prevent and treat the chronic constipation. In addtion, clinical pharmacists can help clinicians to develop and optimize the treatment plan by the means of TDM and gene detecting.

Keywords: clinical pharmacist; cyclosporine; tacrolimus; renal transplantation; CYP3A5*3/*3 genotype

S3.18

Analysis of genetic polymorphisms of CYP450 gene in healthy Chinese Han population

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Aim: To detect the genetic polymorphisms of major CYP450 gene in Chinese Han male and female population. **Methods:** The polymorphism alleles of CYP450 1A2, 2C9, 2C19, 2D6, 3A4 and 3A5 were determined in 238 healthy Chinese Han male and female healthy volunteers by PCR-RFLP and ASA-PCR, calculating the rate of mutations alleles and using SHEsis to analysis the linage disequilibrium of sites. **Results:** The distribution frequencies of CYP1A2*1C, CYP1A2*1D, CYP1A2*1F, CYP2C9*2, CYP2C9*3, CYP2C9*13, CYP2C19*2, CYP2C19*3, CYP2D6*10, CYP3A4*18B and CYP3A5*3 were 20.8%, 57.2%, 54.4%, 0.2%, 3.5%, 0.4%, 30.5%, 6.2%, 49.3%, 22.1% and 73.1%,respectively. Variants difference compared with Caucasian groups, similar with study in Chinese and other Asian groups previously. The median standards of linkage disequilibrium consist between the CYP3A4*18B and CYP3A5*3. **Conclusion:** The eleven CYPs SNPs mutation sites can be detected in Chinese Han male and female population, and the distribution frequency is variants differences compare with Caucasian groups.

Keywords: CYP450; Chinese; Han; healthy volunteers; genetic polymorphism

S3.19

Three protective CYP2E1-SNPs associated with CsA-induced liver injury in Chinese population

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Aim: The purpose of this study was to evaluate the association of CYP2E1 polymorphism with CsA-induced liver injury and to elucidate the possible molecular mechanism using gene function research. **Methods:** A total of 200 subjects, who were orally taking Cyclosporin A to prevent rejection reaction post

organ-transplanting or to cure the autoimmune disease, were recruited from Qilu Hospital of Shandong University (Ji-nan, China) between January 2011 and December 2012. All the subjects were divided into CsA-induced liver injury and control group by the results of liver function tests. The CsA-induced liver injury group included 46 patients, and control group 154 subjects. The CYP2E1 genotypes of rs3813865, rs3813866, rs8192766, rs3813867, rs2031920, rs2031921, rs3813870, rs2031922, rs2070672, rs2070673, rs2515641, rs2480257, and rs2480256 were identified in blood samples collected from all participants. The genotypes of SNPs were counted, and their distributions between the case and control groups were compared by the χ^2 test to test the hypothesis of association between CYP2E1 polymorphism and CsA-induced liver injury. The odds ratios (OR) with 95% confidence intervals (CI) were estimated using logistic regression models. And then the wild or targeted mutation type of CYP2E1 DNA was transfected into HepG2 cells with pGL3 as the vector. The promoter activities of both types of DNA were determined using Dual-Luciferase Reporter Assay System with blank pGL3 as control and Renilla luciferase as internal reference. The promoter activities of both types of DNA with CsA-treatment were also determined using the same method. **Results:** The CYP2E1 genotypes of rs3813865 (-1653G>C), rs3813870 (-929A>G) and rs2070672 (-352A>G), with odds ratios (OR) of 0.643 (95% CI: 0.303–1.368), 0.698 (95% CI: 0.336–1.450) and 0.498 (95% CI: 0.220–1.123), were significantly associated with decreased risks of CsA-induced liver injury, indicating as protective genotypes for CsA-induced liver injury. Further analysis revealed that the combined haplotype of the three protective genotypes decreased the activity of CYP2E1 promoter by 40% compared with that of wild genotype. CsA treatment increased both wild type and mutative haplotype of CYP2E1 promoter activities by 20% in $HepG_2$ cells. **Conclusion:** The study demonstrated that the CYP2E1 genotypes of rs3813865 (-1653G>C), rs3813870 (-929A>G) and rs2070672 (-352A>G) conferred lowered risk for developing CsA-induced liver injury, and it might be the molecular mechanism of the three protective genotypes to decrease the activity of CYP2E1 promoter, and inducing CYP2E1 promoter activity might be the possible cause of CsA-induced liver injury.

Keywords: CYP2E1; genetic polymorphism; cyclosporin A; drug-induced liver injury

S3.20

Altered expression of miR-21 is related to PTEN expression and clinicopathologic features of colorectal carcinoma

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Aim: To investigate the expressions of microRNA-21 (miR-21) and PTEN in colorectal carcinoma (CRC), and explore their correlation. **Methods:** Real-time PCR was used to detect the expression of miR-21 in 105 cases of colorectal carcinoma and tumor-adjacent normal tissue after operation. Moreover, 16 pairs of colorectal carcinoma and normal tissues were chosen to evaluate the PTEN protein levels by Western blot. Construct the recombinant eukaryotic expression and short hairpin (shRNA) expreesion vectors of microRNA-21 and PTEN, and transfect them into human colorectal cancer cells. Then, real-time PCR and Western blot were used to detect the expression of PTEN mRNA and protein, respectively. **Results:** The miR-21 expression in colorectal carcinoma was significantly higher than that in tumor-adjacent normal mucosa (P<0.01), with average up-regulated level of 3.45. The expression of miR-21 was associated with TNM stage (P<0.01)、histological differentiation (P<0.01), depths of invasion (P<0.01), lymphnode metastasis (P<0.01) and Carcinoembryonic Antigen CEA (P<0.01). Moreover, there was a negative correlation between the expression of miR-21 and PTEN protein (r=-0.694, P<0.01). After transfection with pre-miR-21 or anti-miR-21 plasmid, PTEN mRNA expression in human colorectal cancer cells was not changed, but the protein expression was down-regulated or up-regulated significantly. **Conclusion:** miR-21 may play an oncogen role in the development and progression of CRC involved in regulating tumor suppressor PTEN.

Keywords: colorectal carcinoma; microRNA-21 (miR-21); PTEN

S3.21

Identification of PEAR1 single-nucleotide polymorphisms and their influences on the variation in Prasugrel pharmacodynamics

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Aim: The platelet responses to antiplatelet drugs are highly variable. However, the associated mechanisms are poorly defined. The present study aimed to investigate PEAR1 genetic polymorphisms and pharmacogenetic variability in the pharmacodynamics of prasugrel, a new oral antiplatelet agent, in 36 healthy Han Chinese subjects. **Methods:** All subjects received prasugrel as loading dose (LD) on d 1 and maintenance dose (MD) from d 2 till d 11; and the randomized treatment groups (12 subjects in each) included the following: (a) 60 mg LD/10 mg MD, (b) 30 mg LD/7.5 mg MD, and (c) 30 mg LD/5 mg MD. The inhibition of adenosine diphosphate-induced platelet aggregation was measured pre- and post-prasugrel administration using the VerifyNow P2Y12 assay. The genetic sequence of PEAR1 exons and previously reported single nucleotide polymorphisms (SNPs) in PEAR1 gene were investigated. **Results:** A total of 28 SNPs were identified in the PEAR1 locus with three novel SNPs. The minor alleles of 6 SNPs (rs3737224, rs41273215, rs11264580, rs6671392, rs822441, and rs822442), which were within a 4-kb region and were in strong linkage disequilibrium, were found to be associated with reduced platelet responsiveness to prasugrel. In addition, the subjects carrying GG genotype of the rs12041331, having strong linkage with rs12566888, showed greater platelet aggregation than GA carriers at 24 h after 11 repeat doses in 30 mg LD/7.5 mg MD group. **Conclusion:** Further studies with larger sample size are recommended to explore the clinical importance of PEAR1 SNPs in prasugrel and other antiplatelet therapy.

Keywords: *PEAR1*; Han Chinese subjects; prasugrel; genetic polymorphism; pharmacodynamics

S3.22

A novel anti-rheumatic drug, iguratimod for RA – an initial clinical trial

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Aim: Rheumatoid arthritis (RA) is a chronic inflammatory disease. In order to evaluate the efficacy and safety of iguratimod in treatment for RA patients in China, an initial clinical trial was conducted. **Methods:** 1) Clinical pharmacokinetics of iguratimod was studied on healthy Chinese humans: 32 healthy volunteers were divided into four groups. The groups received three single oral doses (25, 50 or 75 mg) and one multiple oral dose (25 mg, Bid) of iguratimod, respectively. Plasma was collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, 48 h after administration. Plasma concentration of iguratimod was measured by HPLC. 2) Phase II clinical trial of iguratimod in treatment on RA patients: A total of 239 RA patients were enrolled in a double-blind, randomized manner and treated respectively with nimesulide or iguratimod (50 mg/d). The follow-up period was 60 d; ACR 20 score was the primary endpoint. 3) Phase III clinical trial of iguratimod in treatment on RA patients: A total of 591 RA patients were enrolled in a double-blind, randomized manner and treated respectively with placebo, nimesulide or iguratimod (50 mg/d). The follow-up period was 60 d; ACR 20 score was the primary endpoint. **Results:** The pharmacokinetic data were fit to a one-compartment model with first-order absorption after single doses (25, 50, and 75 mg) of iguratimod. At phase II clinical trial, response rates for the ACR 20 and ACR 50 of iguratimod were superior to nimesulide group at 4 week (P<0.05), and ACR 50 response rate of iguratimod was also superior to nimesulide group at 8 week (P<0.05). At phase III clinical trial, response rate for the ACR 20 of iguratimod were superior to nimesulide group at 4 week and 8 week (P<0.05). At effective dose, iguratimod was proven to be tolerable and safe for RA patients in phase II and III clinical trials. **Conclusion:** Iguratimod significantly improved the clinical symptoms of RA patients by selectively inhibiting COX-2 activity and showed the accompanying capability of immunoregulation by inhibiting some cytokines compared with nimesulide. (The trial registration number of Phase II clinical trial of Iguratimod in treatment of rheumatoid arthritis: www.chictr.org/cn, ChiCTR-TRC-10000849; Phase III clinical trial of Iguratimod in treatment of rheumatoid arthriti: www.chictr.org/cn,

ChiCTR-TRC-10000850.)

Keywords: iguratimod; rheumatoid arthritis; selective COX-2 inhibitors; clinical trial

S3.23

Effects of *CYP3A4*1G*, *CYP3AP1*3* and gender on pharmacokinetics of simvastatin and simvastatin acid in healthy Chinese volunteers

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Aim: To study effects of *CYP3A4*1G* (G>A), *CYP3AP1*3* (G>A) and gender on pharmacokinetics of simvastatin and simvastatin acid. **Methods:** The polymorphisms of *CYP3A4*1G* and *CYP3AP1*3* were determined by polymerase chain reaction-restriction fragment length polymorphism. Serial blood samples were obtained up to 24 h after a single dose of 40 mg simvastatin intake in healthy Chinese volunteers. Plasma concentrations of simvastatin and simvastatin acid were detected by HPLC/MS/MS. **Results:** weight-adjusted apparent volume of distribution (NV_d/F) of simvastin in *CYP3A4*1G* AA genotype was higher than GG genotype. However, dose-normalized by the body weight C_{max} (NC_{max}) in AA genotype was lower than in GG genotype. NV_d/F of *CYP3AP1*3* AA genotype was higher than GA genotype, while NC_{max} of AA genotype was lower than GA genotype. NC_{max} of simvastatin acid was higher in females than males. **Conclusion:** *CYP3A4*1G* or *CYP3AP1*3* has some effects on NV_d/F and NC_{max} of simvastatin, and the NC_{max} of simvastatin acid is higher in female than male.

Keywords: *CYP3A4*1G*; simvastatin; simvastatin acid; pharmacokinetics; *CYP3AP1*3*

S3.24

The association study in the diversity of two SNPs sites of β_2-AR and EH of Chinese Han population in Kunming

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Aim: To analyze the diversity of 46 and 79 , the two single nucleotide polymorphism (SNPs) sites of β_2-AR coding regions polymorphism, and the genotype distribution of Chinese Han population collected from Kunming in Yunnan Province, and to discuss β_2-AR SNPs distribution and the relationship between different people with essential hypertension (EH) in different area and different race. **Methods:** Genotype of the two SNPs were determined by PCR-RFLP method in unrelated population. **Results:** These two SNPs both have three genotypes. In EH group, there are significant differences (P<0.05) both in genotype distribution and allele distribution at position 46, only genotype distribution at position 79. **Conclusion:** The distribution of β_2-AR gene SNPs in Kunming Han population is different from which in other area and race people.

Keywords: single nucleotide polymorphism; Kunming Han population; β_2 adrenergic receptors; essential hypertension

S3.25

Pharmacokinetics of peramivir trihydrate and sodium chloride injection in Chinese healthy volunteers

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Aim: To study the pharmacokinetics of peramivir trihydrate and sodium chloride injection in Chinese healthy volunteers. **Methods:** 30 healthy volunteers were enrolled and administered with single or multiple doses of 150, 300, or 600 mg peramivir trihydrate and sodium chloride injection by intravenous drip infusion (n=10 for each dose level). The concentrations of peramivir in human plasma and urine were determined by HPLC-MS/MS. The main pharmacokinetic parameters were calculated with WinNonLin 5.0 software. **Results:** The main pharmacokinetic parameters of peramivir after single dose of 150, 300 and 600 mg peramivir trihydrate and sodium chloride injection were as follows: C_{max} were (10.95±1.98), (20.50±2.08), and (44.22±7.00) μg/mL; AUC_{0-t} were (20.28±3.72), (43.54±7.79), and (96.47±11.42) $\mu g \cdot mL^{-1} \cdot h$; V were (30.54±7.24), (36.36±5.4), and (36.45±14.29) L; CL were (7.58±1.30), (7.02±0.94), and (6.29±0.75) L/h; accumulative urine excretion rate of 24 h (Ae%) were (72.20±22.10)%, (82.25±11.61)%, and (82.00±8.46)%, respectively. The main pharmacokinetic parameters of peramivir after multiple dose of 150 and 300 mg peramivir trihydrate and sodium chloride injection were as follows: $C_{max, ss}$ were (10.48±1.28) and (20.19±2.73) μg/mL; AUC_{0-t} were (19.25±2.94) and (44.40±6.41) $ng \cdot mL^{-1} \cdot h$; CL_{ss} were (7.92±1.04) and (6.88±0.94) L/h; accumulation ratio were (1.03±0.03) and (1.03±0.02); Ae% were (70.98±15.91)% and (73.39±10.94)%, respectively. **Conclusion:** The process of peramivir in the dosage range of 150–600 mg did not show any significant departure from linear dynamic feature. There was no accumulation after multiple dosing. Peramivir was mainly eliminated from urine in parent drug.

Keywords: peramivir trihydrate; sodium chloride; pharmacokinetics; Chinese healthy volunteers

S3.26

Site-specific hypomethylation within promoter CpG island of PON1 was associated with bleeding events in dual antiplatelet-treated Han Chinese patients after PCI

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Aim: To evaluate the role of the DNA methylation of the CpG island within the *PON1* promoter on the clinical efficacy of the dual-antiplatelet therapy of aspirin and clopidogrel in patients with CAD after percutaneous coronary intervention (PCI). **Methods:** 538 patients undergoing PCI and received dual-antiplatelet therapy were sequentially recruited and followed up to 1 year. Bisulfite PCR-sequencing was used to screen specific sites with methylation difference among patients with major adverse cardiac events (MACE), bleeding, and neither of them. Then, the effect of site-specific methylation detected by pyrosequencing on MACE or bleeding was assessed. **Results:** Initial screening showed that methylation of the first 5 CpG sites among 19 sites was higher in patients with MACE, but lower in patients with bleeding. Quantitative analysis of site-specific methylation showed that there was no significant association of methylation status with time-to-MACE. However the methylation of *PON1*-160 site was significantly higher in patients without bleeding (51.0%) than that in patients with bleeding (40.0%) in 6-month following up after PCI. Logistic regression analysis showed that lower methylation of *PON1*-160 site was a risk factor for bleeding events (adjusted OR: 1.026, 95%CI: 1.005–1.047, P=0.017). **Conclusion:** In conclusion, site-specific hypomethylation within promoter CpG island of PON1 contributes to the risk of bleeding events in dual antiplatelet-treated CAD patients after PCI.

Keywords: CpG island; DNA methylation; dual-antiplatelet therapy; aspirin; clopidogrel; percutaneous coronary intervention (PCI)

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S3.27

Surveillance of bacterial resistance from hospitals in China

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Aim: To summarize the resistance of clinical isolates in several regions of China. **Methods:** Antimicobial susceptibility testing of the clinical isolates were carried out according to an agreed protocol using Kirby-bauer(KB). **Results:** Detection rates of MRSA were 50.6%. Compared with the previous data, detection rates of MRSA is being decreased year by year. No strains of resistant to vancomycin, teicoplanin and linezolid were found. Found that 54 of vacomycin-resistant *E. feacium*, including van A-type(54), van B- type(17), and van F-type(7). Enterobacteriaceae strains were still highly sensitive to carbapenems antibiotic. The resistance rates in *P. aeruginosa* are relatively stable in recent year, in addition to imipenem and meropenem resistant rates were about 30%. Most antimicrobial resistant rates in *Acinetobacter spp.* were increased significantly. Carbapenem resistant rate in *Acinetobacter spp.* had exceeded 60%. **Conclusion:** Antibiotic resistance is still rising in the clinical isolates in the some hospitals, which poses a serious threat to the clinical practice.

Keywords: bacterial durg resistance; antimicrobial agents; bacterial susceptibility testing; pan-resistant organisms