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慢性肾衰高磷血症诱导的血管钙化与心血管疾病的相关性及防治进展

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摘要：血管钙化(VC)已经成为慢性肾病(CKD)患者心血管疾病(CVD)死亡率逐年升高的关键因素，而其决定性因素归因于高磷血症。在高磷酸盐条件下，血管平滑肌细胞(VSMC)能够将其表型转变为成骨细胞/软骨细胞样群，在VC的发生和发展中起着重要作用。这些转分化的VSMC通过产生局部促钙化环境、钙和磷酸盐沉淀和磷酸钙晶体生长的病灶位点，积极地促进VC。升高的细胞外磷酸盐水平通过复杂的细胞内信号转导途径诱导VSMC的骨-/软骨转分化，但其机制仍不完全清楚。本文综述了CKD高磷血症诱导的VC与CVD的联系及其治疗进展，这对于CKD患者VC的有效治疗具有重要意义。
关键词：慢性肾衰；高磷血症；血管钙化；心血管疾病；血管平滑肌细胞；信号通路
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T3 药物代谢

基因编辑技术创新构建大鼠药物代谢模型及其应用

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摘要：药物代谢酶和转运体不仅在药物代谢与药代动力学以及毒理学研究中占有重要地位，而且参与多种疾病的调控，在维持人体健康方面起着重要作用。尽管药物代谢酶和转运体非常重要，但目前可用于研究药物代谢的动物模型仍然很少。尤其构建新颖的基因敲除大鼠模型更是有利于开展药物代谢、药理以及毒理相关的研究。CRISPR核酸酶作为一种新的靶向基因编辑工具，在动物模型构建方面取得了令人欣喜的效果。我们已创新利用CRISPR技术成功构建特定Cyp系列基因敲除大鼠模型，转运体*P-gp*和*Oatp1b2*基因敲除大鼠模型，并对其基因型和代谢功能进行系统验证和评价。上述大鼠药物代谢新模型可广泛应用于药物代谢、化学物毒性和致癌性相关的研究，促进了DMPK相关机制的研究，加强了药物代谢与药理学/毒理学的关系。
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Systematic external evaluation of published population pharmacokinetic models of tacrolimus in adult liver transplant recipients

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Abstract: OBJECITVE Diverse tacrolimus population pharmacokinetic (popPK) models in adult liver transplant recipients have been established to describe its PK characteristics in the last two decades. However, their extrapolated predictive performance remains unclear. Therefore, in this study, we aimed to evaluate their external predictability and identify their potential influencing factors. **METHODS** The external predictability of each selected popPK model was evaluated using an independent dataset of 59 patients with 404 trough concentrations prospectively collected from Huashan Hospital. Prediction- and simulation-based diagnostics and Bayesian forecasting were conducted to evaluate the model predictability. Furthermore, the influence of the model structures on predictive performance was investigated. **RESULTS** Sixteen published popPK models were assessed. In prediction-based diagnostics, the prediction error within ±30% was below 50% in all the published models. The simulation-based normalised prediction distribution error test and prediction- and variability-corrected visual predictive check indicated large discrepancies between the observations and simulations in most of the models. Bayesian forecasting demonstrated improvement in model predictability with 2−3 prior observations. Additionally, the predictive performance of the nonlinear Michaelis-Menten model was superior to that of linear one- and two-compartment models with first-order elimination, indicating the underlying nonlinear kinetics of tacrolimus in liver transplant recipients, which was consistent with the findings in adult kidney transplant recipients. **CONCLUSION** The published models performed inade-

quately in prediction- and simulation- based diagnostics. Bayesian forecasting could improve predictive performance of the models. Furthermore, incorporating non-linear kinetics in tacrolimus popPK modelling should be considered to improve model predictability.

Key words: tacrolimus; adult liver transplant recipients; population pharmacokinetics; external evaluation; non-linear kinetics

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Metabolomics study of Shenfu Injection on mid-stage cardiogenic shock rats by UPLC-Q-TOF/MS

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Abstract: OBJECTIVE To study the effects of Shenfu Injection (SFI) on the potential endogenous markers of experimental mid-stage cardiogenic shock rats by UPLC-Q-TOF/MS and look out the different biomarker groups and the molecular mechanism. **METHODS** Male SD rats were randomly divided into five groups, which were the normal control group, model group, and 15 mL·kg^{-1} SFI group. Except for the normal control group, others were ligated the root of left anterior descending coronary arteries to establish the mid-stage model of cardiogenic shock rats. One hour after administration of SFI or saline by femoral venous catheter, the blood samples were collected from abdominal aorta, and the plasma were pretreated via protein precipitation and analyzed by UPLC-Q-TOF/MS. Data were processed by PCA and PLS-DA. **RESULTS** All groups could be distinguished by metabolomics successfully. Compared with the model group, 14 pathological biomarkers have changed significantly (P<0.05). And SFI can significantly increase 2 ingredients, i.e. cysteineglutathione disulfide, oxidized glutathione. It can also significantly decrease 11 ingredients, such as dimethylbenzimidazole, imidazolelactic acid, isovalerylglutamic acid, l-gamma-glutamyl-l-isoleucine, n-acetylglucosamine 6-sulfate, adenosine 3′, 5′-diphosphate, agmatine, diadenosine hexaphosphate, cysteineglutathione disulfide, oxidized glutathione, hexadecanedioic acid, glutamylphenylalanine (P<0.05). According to the metabolic pathways of relevant endogenous markers, it is suggested that SFI may affect the model rats through arginne and proline metabolism, sulfur metabolism, glutathione metabolism and purine metabolism, among them adenosine 3′,5′-diphosphate, agmatine and oxidized glutathione were recognized as the key potential biomarkers of the related metabolic pathway. **CONCLUSION** This study primarily clarified the therapeutic effect of SFI on mid-stage cardiogenic shock rats, which may be related to improving the levels of endogenous metabolites in serum and then restoring the metabolism to be normal *in vivo*.

Key words: Shenfu Injection; mid-stage; cardiogenic shock; metabolomics; UPLC-Q-TOF/MS

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Evaluation of assays for aminoglycosides in serum: a comparison of accuracy and precision based on external quality assessment

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Abstract: OBJECTIVE To compare the accuracy and precision of commercial assay techniques in the measurement of gentamicin, tobramycin, and amikacin in serum. **METHODS** Human plasma samples were spiked with known concentrations of amikacin, gentamicin, and tobramycin and provided to worldwide laboratories. The methods participating in the study include Enzyme multiplied immunoassay technique (EMIT), fluorescence polarization immunoassay (FPIA), Kinetic interaction of microparticle in solution (KIMS), particle enhanced turbidimetric

inhibition immunoassay (PETINIA), Cloned Enzyme Donor Immunoassay (CEDIA), Quantitative Microsphere System (QMS), Chemiluminescence, Vitros and so on. The accuracy and precision were compared between assays and between drugs. **RESULTS** 273 results of amikacin, 534 results of gentamycin and 207 results of tobramycin measurements were analyzed. Satisfactory rate was 83.88%, 86.27%, 93.72% for amikacin, gentamycin, and tobramycin. Significant differences in both accuracy and precision between techniques were present for all drugs. Coefficients of variation ranged from 1.06% to 15.61%, from 2.88% to 25.16% and from 1.84% to 26.97% , for amikacin, gentamycin, and tobramycin, respectively. The percentage difference ranged from −7.46% to 6.57%, from −20.78% to 18.68% and from −33.22% to 41.52%, for amikacin, gentamycin, and tobramycin, respectively. Detection limits were from 0 to 2.76 and 0.12 to 1.04 for amikacin and gentamicin. **CONCLUSION** All assays performed to a satisfactory standard for measurement, but significant differences in both accuracy and precision between techniques were present for all drugs. All assays need more accuracy and precision of therapeutic drug measurements.

Key words: aminoglycosides; immunoassays; TDM; amikacin; gentamicin; tobramycin

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Involving nonlinear kinetics to improve predictive performance of population pharmacokinetic models for cyclosporine in adult renal transplant recipients: a comparison of modelling strategies

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Abstract: OBJECTIVE Cyclosporine (CsA) follows nonlinear PKs in renal transplant recipients who received Neoral-based triple immunosuppressive therapy. Some of these nonlinear properties have been considered in physiologically-based pharmacokinetic (PBPK) modeling, but are rarely incorporated into CsA population pharmacokinetic (popPK) modeling processes. Therefore, the aim of this study was to determine the potential influence of nonlinearity and the functional forms of covariates on popPK model predictability. **METHODS** A total of 2969 CsA whole-blood measurements, including 1328 predose and 1641 2-h postdose concentrations, were collected from 173 patients who underwent their first renal transplantation. PopPK analysis was performed using the NONMEM® software package. Four popPK models based on different modeling strategies were developed to investigate the discrepancy between empirical and theory-based, linear and nonlinear, compartmental kinetic model and empirical formula on model predictability. Potential covariates were screened using a stepwise approach. Bootstrap, prediction-based and simulation-based diagnostics (prediction-corrected visual predictive checks) were performed to determine the stability and predictive performance of these four models. **RESULTS** The predictability of popPK model improved when nonlinearity was considered. Theory-based nonlinear model which incorporate nonlinear property based on known theoretical relationships performed better than the other two compartmental models. The nonlinear Michaelis-Menten model showed a remarkable improvement of predictive performance over that of the other three compartmental models. The saturated binding of CsA to erythrocytes, tapering prednisolone dose in early postoperative days and the influence of CsA daily dose on metabolismmay contributed to the nonlinearity. **CONCLUSION** Incorporating nonlinear properties is likely to be a promising approach for improving CsA model predictability. However, the resources of CsA nonlinear kinetics need further investigation. Until then, the nonlinear MM empirical model can be used for CsA dose adjustments.

Key words: cyclosporine; population pharmacokinetics; nonlinear kinetics; modelling strategies

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No effect of acylpeptide hydrolase polymorphisms on pharmacokinetics of sodium valproate in healthy Chinese male volunteers

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Abstract: OBJECTIVE Sodium valproate (VPA) is one of the most common prescribed antiepileptic drugs (AEDs). Genetic variation in genes encoding drug-metabolizing enzymes may contribute the inter-individual variability in VPA pharmacokinetics. Our previous study showed that acylpeptide hydrolase (APEH) polymorphisms might affect the VPA plasma concentration in Chinese epilepsy patients by increasing the urinary excretion of valproate-glucuronide (VPA-G), the major metabolite of VPA. This study aimed to investigate the effects of APEH rs3816877 on the pharmacokinetics of VPA in healthy Chinese male volunteers. **METHODS** Thirteen subjects enrolled in this clinical trial were genotyped for APEH rs3816877 by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). All volunteers received an oral dose of 1000 mg of VPA sustain tablets (Depakine, Sanofi). The peripheral venous blood and urine were sampled for up to 72 h and 24 h post dose, respectively. The concentration of VPA and VPA-G in plasma and urine were determined by the high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) system. The pharmacokinetic parameters were calculated using standard non-compartmental model. **RESULTS** No significantly different C_{max}, T_{max}, $t_{1/2}$, *CL*, *V*d, $AUC_{0-72\ h}$, and $AUC_{0-\infty}$ were observed between APEH rs3816877 C/C group and C/T group. However, the subjects carrying rs3816877 C/C genotype were characteristics with significantly higher urinary excretion of VPA-G than those with C/T genotype. **CONCLUSION** Our study suggested that APEH rs3816877 may have no effect on the pharmacokinetics of VPA in healthy Chinese male volunteers.

Key words: sodium valproate; acylpeptide hydrolases; pharmacokintics; pharmacogenetics.

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Population pharmacokinetic modeling for mycophenolic acid and its main glucuronide metabolite in Chinese kidney transplant recipients

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Abstract: OBJECTIVE To develop an integrated model of MPA and MPAG in kidney recipients, and to evaluate the effect of clinical covariates and genotypes on mycophenolic acid (MPA) and 7-O-mycophenolic acid glucuronide (MPAG) disposition. **METHODS** Data were collected from 191 adult Chinese mycophenolic acid, including 24 patients with full concentration-time profiles and 167 with trough concentrations. They contained 962 MPA measurements and 746 MPAG measurements. Population pharmacokinetic analysis was performed using NONMEM®. **RESULTS** The PK of MPA and MPAG were best described by a three-chain compartment model. Significant correlations were found between the clearance of MPA (CLMPA) and albumin levels (ALB), and between the clearance of MPAG (CLMPAG) and the creatinine clearance (CCR) .CLMPA was 13.7 $L \cdot h^{-1}$ and the CLMPAG was 1.3 $L \cdot h^{-1}$ for the Chinese kidney transplant recipients with ALB 42 $g \cdot L^{-1}$ and CCR 72 $mL \cdot min^{-1}$. **CONCLUSION** The MPA data was described adequately by a 2-compartment model with linear elimination, while MPAG was described using a 1-compartment model. ALB, CCR affected CLMPA and CLMPAG respectively. The impact of gene polymorphisms of enzymes and transporters did not affect pharmacokinetic of MMF in kidney transplant recipients in our study, including UGT1A9, UGT1A8, UGT2B7, OATP1B3, MRP2.

Key words: mycophenolate mofetil; mycophenolic acid; kidney transplant recipients

Metabolomics combined with serum pharmacochemistry discovering effective compounds of Fangji Huangqi Tang against nephrotic syndrome

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Abstract: OBJECTIVE An integrative strategy was established to discover the effective compounds and their therapeutic targets using Fangji Huangqi Tang (FHT) aiming at inhibiting nephrotic syndrome (NS) as a case study. **METHODS** The adriamycin-induced nephropathy

rat model was evaluated by histopathology analysis and urine protein. The serum biomarkers (pathological marker) related to NS model were characterized by metabolomics, and the metabolites which could be regulated to normal levels after administration with FHT were defined as FHT-regulated biomarkers (effective marker). Moreover, the potential effective compounds were identified by comparison of drug serum between control and model rats. Furthermore, they were further screened based on the correlation analysis between effective marker with the potential effective compounds. At the same time, the potential target of effective ingredients was found by network pharmacology technology. **RESULTS** The results of serum metabonomics showed that 15 metabolites, including 3-Hydroxybutyric acid, L-phenylalanine and linolenic acid, were associated with renal damage. Among them, 6 effective markers were uric acid, 2-methylbutyrylcarnitine and 10- HDA. Metabolic pathway analysis showed that, phenylalanine, tyrosine and tryptophan biosynthesis, linoleic acid metabolism, phenylalanine metabolism, sphingolipid metabolism were the key pathway associated with NS. The correlation analysis showed that nine constituents such as fanGhinoline, atractylenolide Ⅲ, cycloastragenol, glycyrrhetinic acid were recognized as effective compounds, whose potential protein targets participated in MAPK signaling pathway, GnRH signaling pathway and aldoaterone-regulated sodium reabsorption. **CONCLUSION** This study provides a methodological reference for the study of the efficacy material base of other traditional Chinese medicineand also provides an important basis for the target of FHT against NS.

Key words: Fangji Huangqi Tang; metabolomics; serum pharmacochemistry; effective components; nephrotic syndrome

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A CYP716A enzyme function of oleanane oxidase in biosynthesis of triterpenoid in *Polygala tenuifolia* willd

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Abstract: OBJECTIVE To study the CYP716A enzyme function of oleanane oxidase in the biosynthesis of triterpenoid in *Polygala tenuifolia* Willd. **METHODS** Our research use phylogenetic analysis of different cytochrome P450 monooxygenases (P450s) related to the biosynthesis of polygala saponin aglycone, we found that CYP716A249 (GenBank: KY385302.1) is possibly to play the role of oleanane oxidase, and catalyze the β-amyrin to formed oleanolic acid, which is the skeleton of polygala saponin aglycone. Therefore, the expression plasmid pRS425-TYS1p-GgbAS-TYS1t was constructed for introducing the bAS into *Saccharomyces cerevisiae* W303a to obtain strain Sb1. Then, the plasmid pRS304-ADH1p- PtOAS- ADHIt- ALAIp- CPR- ALA1t was transferred into Sb1 to construct strain Sb1Pt_O, in order to confirm the function of CYP716A249. Finally, the function of CYP716A249 enzyme was identified in *S. cerevisiae* through metabolite detection by ultra performance liquid chromatography- mass spectrometry (UPLC- MS), gas chromatography-mass spectrometry (GC-MS) and nuclear magnetic resonance (NMR). **CONCLUSION** We found that CYP716A249 is likely to play the role of β-amyrin synthase by phylogenetic analysis, catalyzed the β-amyrin to form oleanolic acid through phylogenetic analysis.

Key words: *Polygala tenuifolia*; CYP716A249; gene expression; oleanolic acid; biocatalysis

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Effect of Chinese herb Danzhi Xiaoyao pills on pharmacokinetics of venlafaxine in beagles

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Abstract: OBJECTIVE To investigate the effects of Chinese herb Danzhi Xiaoyao pills on the pharmacokinetics of venlafaxine and its metabolites *O*-desmethylvenlafaxine (ODV) and *N*-desmethylvenlafaxine (NDV) in beagles by using ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). **METHODS** Six beagles (half male, half female) were chosen to test, being fasted before the experiment but having free access to drinking water one day before fed drugs. After oral administration of venlafaxine hydrochloride tablets (10.28 mg·kg^{-1}), the blood samples were collected in succession at different points in time. After one-week washout period, Danzhi Xiaoyao pills (0.6 g·kg^{-1}) were given through oral administration to the six beagles every morning until the seventh day, venlafaxine hydrochloride tablets (10.28 mg·kg^{-1}) were given after feeding Danzhi Xiaoyao pills (0.6 g·kg^{-1}) half an hour and blood samples were collected continuously at different points. All samples were analyzed by UPLC-MS/MS, and the main pharmacokinetic parameters of venlafaxine, ODV and NDV were computed by DAS 2.0. **RESULTS** The C_{max} of the venlafaxine group (control group) and the combination group (experimental group) were (2267.26±252.89) μg·L^{-1} and (1542.64±190.73) μg·L^{-1}, respectively. The $AUC_{(0-\infty)}$ of the two groups were (13934.79±3609.23) μg·h·L^{-1} and (8001.91±2167.58) μg·h·L^{-1}, respectively. The ODV C_{max} of the two groups were (2253.80±215.81) μg·L^{-1} and (2721.37±118.20) μg·L^{-1}, and $AUC_{(0-\infty)}$ were (13974.99±2784.04) μg·h·L^{-1} and (17539.44±1894.29) μg·h·L^{-1}, respectively. The NDV C_{max} of the two groups were (50.98±5.76) μg·L^{-1} and (58.74±12.33) μg·L^{-1}, and $AUC_{(0-\infty)}$ were (179.26±34.94) μg·h^{-1}·L^{-1} and (220.68±51.41) μg·h^{-1}·L^{-1}, respectively. After administration of Danzhi Xiaoyao pills, the C_{max} and $AUC_{(0-\infty)}$ of venlafaxine decreased significantly, indicating that the plasma exposure of venlafaxine decreased. The increase of C_{max} and $AUC_{(0-\infty)}$ of ODV and NDV indicated a rise in plasma exposure. **CONCLUSION** Danzhi Xiaoyao pill can accelerate the metabolism of venlafaxine in beagles. In clinical, when venlafaxine was co-administrated with Danzhi Xiaoyao pills, dose adjustment of venlafaxine should be taken into account.

Key words: beagle; UPLC-MS/MS; Danzhi Xiaoyao Pills; venlafaxine; ODV; NDV; drug-drug interaction

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lncRNA HNF4α-AS1参与调控转录因子和细胞色素CYP450表达

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摘要：目的 细胞色素P450酶系（CYP450s）是体内主要的氧化代谢酶系。临床上70%以上的处方药物经由CYP450s催化代谢。研究表明，转录因子参与CYP450s的表达调控，其中转录因子HNF4α在CYP450s的转录调控中发挥重要的作用。近期发现转录因子附近的一些非编码RNA（lncRNA）参与其邻近基因的调节。lnc-HNF4α（HNF4α-AS1）与HNF4α相邻，是HNF4α基因的互补反义RNA。本文目的是探讨在肝癌细胞Huh7中lncRNAHNF4α-AS1对转录因子与CYP450s表达的调控作用。**方法** 在肝癌细胞huh7上进行功能缺失实验敲除HNF4α以及功能缺失实验敲除HNF4α-AS1与功能获得实验过表达HNF4α-AS1，q-PCR法检测lncRNA和代谢酶以及转录因子mRNA的表达。**结果** 在肝癌细胞Huh7中，siRNA有效干扰HNF4α后，HNF4α-AS1表达降低，*CYP*（*1A2*，*2E1*，*2B6*，*2C8*，*2C9*，*2C19*，*3A4*）的mRNA的表达以及转录因子（*PXR*，*CAR*，*AhR*）mRNA表达降低。在Huh7细胞中，siRNA有效干扰HNF4α-AS1后，CYP（*1A2*，*2C8*，*2C9*，*2C19*，*3A4*）的表达以及核受体*PXR*的mRNA表达升高，有效过表达HNF4α-AS1后，*CYP450s*以及核受体*PXR*的mRNA表达下降。**结论** lncRNAHNF4α-AS1参与调控转录因子与细胞色素CYP450s的表达。

关键词： CYP450s；HNF4α-AS1；HNF4α；转录因子；

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甘草酸二铵调节CYP450酶和血浆蛋白结合率对奥美拉唑药代动力学的影响

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摘要：目的 临床上，为了提高疗效或减少副作用，通常采用联合药物治疗。奥美拉唑是一种质子泵抑制剂，用于消化不良，消化性溃疡，胃食管反流的治疗。甘草酸二铵与奥美拉唑联合用药可用于病毒性肝炎和肝硬化并伴有消化性溃疡的患者。然而，甘草酸二铵与奥美拉唑之间的药物相互作用尚不清楚。**方法和结果** 在课题的研究中，发现奥美拉唑与甘草酸二铵联合使用能明显增加奥美拉唑的AUC、

AUMC、C_{max}。因此，继续使用LC-MS/MS来检测大鼠体内奥美拉唑的血浆蛋白(BRPP)的结合率，发现甘草酸二铵可以降低大鼠的BRPP。此外，还发现甘草酸二铵可以特异性抑制CYP2C19和CYP3A4的酶活性，这两种酶参与了奥美拉唑的代谢。这些结果表明甘草酸二铵可抑制奥美拉唑的代谢，增加奥美拉唑的血浆浓度。**结论** 甘草酸二铵通过抑制CYP2C19和CYP3A4的活性，降低奥美拉唑的BRPP，从而影响奥美拉唑的药代动力学。

关键词： 甘草酸二铵；奥美拉唑；LC-MS/MS；细胞色素P450酶；药物相互作用

UHPLC-MS/MS法测定大鼠血浆中黄芪建中汤13种成分浓度

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摘要：目的 采用超高效液相色谱串联质谱(UPLC-MS/MS)建立测定黄芪建中汤在大鼠血浆中芒柄花苷、芒柄花素、毛蕊异黄酮、毛蕊异黄酮苷、紫檀烷、紫檀烷苷、异黄烷、异甘草苷、甘草素、甘草苷、甘草次酸、肉桂酸和环黄芪醇13种入血成分浓度的方法，为黄芪建中汤的药代动力学研究提供基础。**方法** 大鼠血浆经过乙腈提取后上清吹干，甲醇复溶，进行液相色谱-质谱分析。色谱柱：ACQUITY-UPLCHSST3(100 mm×2.1 mm，1.8 μm)，流动相：0.1%甲酸水溶液-乙腈，流速：0.25 mL·min^{-1}，柱温：40℃。用电喷雾离子源进行正离子多反应监测扫描(MRM)分析。考察该方法的专属性、标准曲线与定量下限、准确度与回收率、基质效应、残留效应和稳定性。同时，探讨上述13种成分在大鼠体内的药代动力学特征。**结果** 大鼠血浆中这13种成分呈良好的线性关系(r>0.990)。在目标化合物出峰时间处，未观察到基质的内源性成分干扰。日内、日间相对标准差(RSD)均小于15%；回收率为78.3%~108.8%，基质效应为91.2%~109.3%。**结论** UHPLC-MS/MS法快速、灵敏、准确、选择性强、重复性好，能够有效地解决复方中的干扰问题，适用于大鼠血浆中13种成分的浓度测定。

关键词： 超高效液相色谱串联质谱；黄芪建中汤；血药浓度

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HPLC-DAD/MS法测定辛伐他汀滴丸储存中有关物质含量变化

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摘要：目的 采用HPLC-DAD/MS法检测辛伐他汀滴丸在储存过程中有关物质含量和数量的变化，并对比已知杂质A，B，C，D，E，F和G，对本品中的有关物质进行归属分析。**方法** 采用Eclipse Plus C18色谱柱(2.1 mm×100 mm，3.5 μm)，以100%乙腈为流动相A，0.5%甲酸水溶液为流动相B，梯度洗脱，流速为0.3 mL·min^{-1}；检测波长238 nm、265 nm。**结果** 辛伐他汀与各杂质能完全分离，辛伐他汀加样回收率、精密度、重复性均符合要求，溶剂、空白辅料无干扰。实验分析了8批不同生产日期的辛伐他汀滴丸，我们在265 nm处检测出辛伐他汀及13种有关物质，其中m/z分别为436.9(A)、439.1(G)、855.5(D)、423.3的4种杂质在储存过程中含量会有所增加，但并未产生新的杂质，而主成分辛伐他汀含量则相对减少。**结论** 建立了辛伐他汀滴丸中辛伐他汀及杂质HPLC-DAD/MS检测方法，检测出辛伐他汀滴丸在储存过程中某些杂质含量会增加。

关键词： 辛伐他汀；滴丸；有关物质；含量变化；液质联用

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基于LC-MS代谢组学的注射用黄芪多糖活性成分对巨噬细胞吞噬活性的影响

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摘要：目的 采用LC-MS代谢组学方法，研究注射用黄芪多糖活性部位对小鼠单核巨噬细胞白血病细胞Raw 264.7吞噬活性的影响。**方法** 采用中性红法检测注射用黄芪多糖的不同分子量部分对Raw 264.7吞噬活性的影响，筛选出活性成分，并对细胞培养液和细胞裂解液进行LC-MS分析，结合多元统计分析和代谢通路分析，探索其作用机制。**结果** 注射用黄芪多糖的小分子量部位在浓度为30 mg·L^{-1}时能显著增强Raw 264.7的吞噬活性。与对照组相比，注射用黄芪多糖活性部位作用于Raw 264.7后，细胞内外共发现41种差异代谢物，主要调控氨基酸代谢、能量代谢及抗氧化作用。

关键词： 注射用黄芪多糖；吞噬；代谢组学；氨基酸代谢；能量代谢；抗氧化

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蓓萨罗丁固体分散体制备及药物代谢动力学检测

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摘要:目的 研究蓓萨罗丁制备成固体分散体的可能及药物代谢动力学特征。**方法** 本研究利用粉末X射线衍射表征了蓓萨罗丁与Pvp-30形成的一种固体分散体。通过建立灵敏度高,特异性强的LC-MS方法检测蓓萨罗丁和固体分散体在SD大鼠体内药物代谢动力学及组织分布特征。本研究设置蓓萨罗丁尾静脉注射组、蓓萨罗丁固体灌胃组、分散体固体灌胃组共3组,用LC-MS检测单剂量给药后不同时间血浆及组织中的药物含量。**结果** 3组血浆的C_{max}分别为 5140.85 ± 787.643、631.008 ± 299.112 和 (3011.877 ± 2239.637)μg·L^{-1},药时曲线下面积(AUC_{0-t})分别为5142.2±962.98,7333.92±2279.11 和(10174.03±5583.43) μg·h·L^{-1}。固体分散体给药组的绝对生物利用度比原药组提高了43.48%,同时体内各组织中药物含量明显提高。**结论** 蓓萨罗丁与Pvp-30制备成固体分散体提高了生物利用度及组织含量,这为蓓萨罗丁晶型药物临床前及临床研究提供了数据支持, 也为蓓萨罗丁在人体内的测定提供了参考。

关键词: LC-MS; 蓓萨罗丁; 固体分散体; 生物利用度; 组织分布
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伊立替康不良反应与UGT1A1基因多态性和血药浓度关系的研究

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摘要:目的 研究伊立替康不良反应的发生率及严重程度与UGT1A1基因多态性和SN-38血药浓度的关系。**方法** 筛选晚期结直肠癌65例,抽取患者外周血进行UGT1A1*28基因多态性测定,并采用FOLFIRY化疗方案,测定患者伊立替康活性代谢物SN-38血药浓度及化疗过程中出现的不良反应情况,分析不良反应及疗效与UGT1A1基因多态性及SN-38血药浓度的关系。**结果** 65例UGT1A1*28患者中野生型患者50例,杂合突变患者15例,未发现纯合突变患者。UGT1A1*28突变患者3-4级迟发性腹泻的发生率显著高于野生型患者(P<0.01),但3-4级中性粒细胞减少无显著相关性。50例UGT1A1*28野生型患者中,CSN-38 1.5 h≥42.83 μg·L^{-1}与CSN-38 49 h≥14.27 μg·L^{-1}的患者3-4级迟发性腹泻,中性粒细胞减少的发生率同CSN-38 1.5 h < 42.83 μg·L^{-1}与CSN-38 49 h<14.27 μg·L^{-1}的患者相比无显著性差异,但CSN-38 1.5 h≥42.83 μg·L^{-1}与CSN-38 49 h≥14.27 μg·L^{-1}的患者疗总缓解率及疾病控制率显著高于CSN-38 1.5 h<42.83 μg·L^{-1}与CSN-38 49 h<14.27 μg·L^{-1}的患者(P<0.05);15例突变型患者中,CSN-38 1.5 h≥48.63 μg·L^{-1}与CSN-38 49 h≥16.27 μg·L^{-1}的患者3-4级迟发性腹泻,中性粒细胞减少的发生率显著高于CSN-38 1.5 h < 48.63 ng·mL^{-1}与CSN-38 49 h < 16.27 ng·mL^{-1}的患者(P<0.05),但缓解率及疾病控制率无显著性差异。**结论** 对UGT1A1*28野生型且CSN-38 1.5 h<42.83 μg·L^{-1},CSN-38 49 h<14.27 μg·L^{-1}患者,可适量增加CPT-11化疗剂量来提高近期疗效。对于UGT1A1*28突变型且CSN-38 1.5 h≥48.63 μg·L^{-1}或者CSN-38 49 h≥16.27 μg·L^{-1}患者来说可降低化疗剂量,减少3-4级不良反应的发生;更好的实现临床个体化用药。

关键词: 伊立替康; SN-38; 不良反应; UGT1A1; 血药浓度; 基因多态性
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DNA甲基化参与PXR介导的CYP3A4的表达

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摘要:目的 DNA甲基化作为表观遗传学的关键组成部分,在基因的表达调控中发挥重要作用。本实验旨在研究DNA甲基化对PXR(孕烷X受体)介导的*CYP3A4*基因表达的影响。**方法** 以HepG2细胞为研究对象,① 用甲基转移酶抑制剂5-Aza-2-dC处理细胞,并过表达PXR质粒,检测处理前后*CYP3A4*和*PXR* mRNA的表达;② 构建pCpGL-CYP3A4-启动子(P)和pCpGL-CYP3A4-启动子&增强子(EP)质粒,进行体外甲基化,通过双荧光素酶报告基因系统检测荧光素酶活性;③ EP甲基化和未甲基化质粒转染细胞,用ChIP-qPCR技术检测CYP3A4启动子区PXR的富集;④ EP甲基化和未甲基化质粒转染细胞,24 h后加入10 μmol·L^{-1}利福平诱导,48 h检测*CYP3A4* mRNA的表达。**结果** ① 5-Aza-2-dC能够显著促进*CYP3A4*和*PXR* mRNA的表达(P<0.05),呈浓度和时间依赖性;过表达PXR质粒同时暴露5-Aza-2-dC,*CYP3A4* mRNA表达水平分别是过表达PXR质粒组和5-Aza-2-dC组的1.77倍和1.85倍(P<0.05);② EP未甲基化质粒+PSG5-PXR表达质粒组荧光素酶活性是对照组的1.88倍,而EP甲基化质粒+PSG5-

PXR表达质粒组是对照组的1.05倍，两者有显著性差异（P<0.05）；③ EP未甲基化组PXR在CYP3A4启动子远端、中间和近端的富集分别为甲基化组的5.8，5.5和8.9倍；④ 利福平诱导后，EP未甲基化组*CYP3A4* mRNA的表达量是对照组的2.4倍（P<0.05），而EP甲基化组CYP3A4 mRNA表达量无显著变化。**结论** CYP3A4增强子区甲基化能够抑制PXR介导的CYP3A4的表达，且不受利福平诱导。

关键词： DNA甲基化；PXR；CYP3A4；基因表达
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平衡透析法结合LC-MS/MS研究奥克梯隆型皂苷元的大鼠血浆蛋白结合率

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摘要：目的 研究奥克梯隆型皂苷元奥克梯隆（ocotillol）的大鼠血浆蛋白结合率。**方法** 采用甲醇沉淀蛋白法对大鼠血浆和磷酸盐缓冲液中的待测物ocotillol和内标人参三醇（PT）进行提取，色谱分离采用Gemini C18柱（50 mm×4.6 mm，3 μm），以0.1%甲酸水溶液和0.1%甲酸乙腈溶液为流动相进行梯度洗脱；质谱检测采用电喷雾（ESI）离子源，正离子多反应监测模式（MRM）。并根据FDA指导原则从专属性、线性、定量下限（LLOQ）、准确度、精密度、提取回收率、基质效应以及稳定性等方面进行系统的方法学验证。以平衡透析法为基础，通过建立的液相色谱串联质谱（LC-MS/MS）法测定平衡后透析袋内血浆和透析袋外缓冲液中的ocotillol浓度，计算血浆蛋白结合率。**结果** LC-MS/MS法测定ocotillol的线性关系良好（r≥0.995），质控样品的日内、日间精密度（RSD）均<11.68%、提取回收率较高且可重现，无明显的基质效应，样品在室温放置12 h、反复冻融三次、−80℃放置20 d以及处理后自动进样器放置24 h等条件下均能保持稳定。Ocotillol在低、中、高3个浓度下与大鼠的平均血浆蛋白结合率为（84.55±1.69）%，且3个浓度间的血浆蛋白结合率数据无显著性差异。**结论** Ocotillol与大鼠血浆蛋白有较强的结合作用。

关键词： 奥克梯隆型皂苷元；血浆蛋白结合率；液相色谱串联质谱法；平衡透析法
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茵陈术附汤挥发性成分在大鼠体内药代动力学研究

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摘要：目的 茵陈术附汤出自清代《医学心悟》，由茵陈、白术、附子、干姜、肉桂、炙甘草组成，是治疗阴黄证肝脏疾病的经典方剂。本研究旨在阐明茵陈术附汤多种挥发性成分的药动学规律。**方法** 采用顶空固相动态微萃取结合气质联用（HS-SPDE-GC-MS）方法，聚二甲基硅氧烷的毛细管色谱柱进行顶空固相动态微萃取，建立大鼠血浆茵陈术附汤挥发性成分（α-蒎烯、莰烯、β-水芹烯、桉树脑、龙脑、可巴烯、石竹烯、α-姜烯、姜黄烯、反式肉桂醛、苍术酮）分析方法，并进行方法学考察。SD大鼠灌胃茵陈术附汤挥发油26 μL·kg^{-1}，血浆经HS-SPDE-GC-MS分析，计算药代动力学参数。结果方法学考察内源性成分不干扰11个成分，各成分线性关系、日内及日间准确度、精密度和回收率符合要求；各贮存条件下稳定。大鼠给药后血浆测定了上述11种成分。苍术酮、桉树脑、α-姜烯、β-水芹烯、可巴烯AUC_{0-t}为1510，254，171，69和64 μg·h·L^{-1}，莰烯和姜黄烯AUC_{0-t}<50 μg·h·L^{-1}；桉树脑、β-水芹烯和莰烯T_{max}<30 min；α-姜烯、姜黄烯、苍术酮、可巴烯T_{max}为1.0-2.0 h。桉树脑、α-姜烯、莰烯、可巴烯、姜黄烯、苍术酮和β-水芹烯$t_{1/2}$分别为1.8，1.9，2.1，2.3，2.3，2.7和3.5 h。**结论** 建立和验证了11个挥发性成分HS-SPDE-GC-MS的大鼠血浆浓度测定方法，阐释了茵陈术附汤挥发性成分在体内的药动学规律。

关键词： 茵陈术附汤；挥发性成分；顶空固相动态微萃取结合气质联用；药动学；大鼠
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UPLC-MS-MS测定来自中药九里香中九里香酮的血药浓度

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摘要：目的 建立测定来自传统中药九里香中的九里香酮的UPLC-MS-MS的方法，并用于测定其在SD大鼠中的血药浓度。**方法** SD大鼠分成4组，每组6只，雌雄各半，分别灌胃给药九里香酮（20，50和125 mg·kg^{-1}）和尾静脉注射给药（20 mg·kg^{-1}），于不同时间点取血进行血药浓度测定。九里香酮在35℃下用C18柱进行分离，流动相为水和乙腈梯度洗脱，流速为0.3 mL·min^{-1}。质谱在电喷雾正离子模式下，采用三重四级杆质量分析器进行多重反应监测（MRM）：九里香酮为m/z 259.10→131.00，内标（香豆素）为m/z 146.93→90.94。**结果** 九里香酮在4.0~1600 ng·mL^{-1}范围内线性良好（r^2>0.998），提取回收率大于90%，日内精密度小于9.8%，日间精密度小于12.3%，室温放置4 h稳定性相对偏差（RE%）为7%，−20℃环境冻融稳定性RE%为14.8%。经过非房式模型估算药代动力参数，九里香酮的末端消除半衰期（$t_{1/2}$）分别为（2.69±1.28）h，（2.18±0.80）h，（2.51±0.70）h和（2.80±1.96）h；峰浓度（C_{max}）分别为（0.32±0.10）mg·L^{-1}，（0.51±0.14）mg·L^{-1}，（0.98±0.17）

mg·L^{-1}和(0.95±0.19) mg·L^{-1};$AUC_{(0-\infty)}$分别为(1.46±0.49) h·mg·L^{-1},(2.23±0.47) h·mg·L^{-1},(5.93±1.41) h·mg·L^{-1}和(3.76±0.70) h·mg·L^{-1}。**结论** 成功建立了测定九里香酮浓度的UPLC-MS-MS的方法,并成功用于测定SD大鼠中的九里香酮的血药浓度。

关键词: 九里香酮; 九里香; 药代动力学; UPLC-MS-MS
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多种DL1801共晶化合物的大鼠体内药代动力学研究

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摘要:目的 通过制备DL1801 - MA和DL1801 - FA 2种共晶化合物来改善DL1801的代谢特征,并对其进行了大鼠体内药代动力学特征评价。**方法** 将SD大鼠随机分组,按20 mg·kg^{-1}的剂量通过灌胃方式给药。于给药后15,30,45 min,1,1.5,2,3,4,6,8,12和24 h取血。通过LC-MS对样品中的药物浓度进行测定,绘制血药浓度-时间曲线。**结果** DL1801晶A型,DL1801 - MA和DL1801 - FA共晶化合物的最大血药浓度(C_{max})分别为40.177±14.659,79.404±15.557和(38.933±25.172) μg·L^{-1}。达峰时间(T_{max})分别为0.583±0.382,0.25±0.00和(3.000±2.646) h 。药时曲线下面积(AUC_{0-t})分别为73.67±30.505,143.109±15.709和(178.02±190.745) μg·L^{-1}·h。与DL1801晶A型相比,DL1801 - MA共晶化合物的峰浓度提高了78%,AUC_{0-t}增加了94.3%,可以达到较高的血药浓度和生物利用度;而DL1801 - FA共晶化合物,达峰时间明显后移,AUC_{0-t}增加了141.6%,可以实现长效作用和较高的生物利用度。**结论** DL1801的共晶化合物与DL1801晶A型相比,在大鼠体内药代动力学过程中显示出一定差异,对于改善和稳定药物的代谢特征具有重要意义。

关键词: DL1801; 共晶化合物; 药代动力学
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T4 教学与科普

来华留学临床医学教育面临的问题及对策

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摘要: 随着我国综合国力和国际地位的不断提升,越来越多的国际学生选择来华学习医学,来华医学留学生教育发展迅速。截止2018年底,来华留学生达49万多人,学历留学生25.8万多,其中,医学来华留学生6.8万多,医学本科留学生4.69万人,临床医学留学生近4万人。由于我们成建制的举办来华留学生临床医学专业教育(英语授课)即MBBS的时间较短,各高校在办学条件、办学资质、入学标准及师资力量等方面存在较大差异,致使来华医学留学生的培养质量参差不齐,在一定程度上影响了中国高等医学教育的声誉。教育部高度重视来华医学留学生教育质量,提出了一系列"提质增效、质量优先"的措施。一是贯彻实施教育部、外交部、公安部《学校招收和培养国际学生管理办法(42号令)》和教育部《来华留学生高等教育质量规范(试行)》,强调质量,促进来华留学的内涵发展;二是制定《来华留学生临床医学专业本科教育(英语授课)质量控制规定》,严格规范来华留学生临床医学专业本科教育的全过程,包括入学标准、培养过程及毕业要求等,使各高校有章可循;三是根据《42号令》《来华留学生高等教育质量规范(试行)》《质量控制规定》的相关规定,制定来华留学生临床医学专业招生及录取标准,对基本条件、语言要求、学业要求等提出具体标准,提高留学生的生源质量;四是建立MBBS入学考试题库,实施来华医学留学生教育入学考试制度,多次召开MBBS入学考试题库建设专家研讨会,研讨MBBS入学考试题库的建设,组织命题专家队伍,着手题库建设;筹备MBBS入学后的水平测试工作,考试对象为各高校一年级新生,考试科目包括数学、物理、化学、生物学等;五是建立来华留学临床医学专业教育评估审核、质量认证和专项调研等措施的质量监控机制,对培养单位和招生计划实施动态管理。目前已经制定了《来华留学生临床医学专业本科教育(英文授课)认证指标体系(草案)》,今后将依据指标体系对招收来华留学生临床医学专业学校的办学定位、办学理念、办学条件、教学能力、管理水平及教育质量等进行综合评估,了解和掌握学校的整体办学能力和教育水平,认证结果将作为审定招生单位和计划等决策与管理的依据,认证周期根据认证结论可设定2-8年不等;六是建立专业化的评估认证专家队伍,发挥行业协会的引领和监管作用,加大对高校的监管力度,定期组织专家对各培养学校进行调研、督导和评估,对各高校的教学过程及培养质量进行监管。帮助各高校提高培养质量,及时发现问题,对问题较多的院校提出整改意见。

来华留学经历了十几年的快速增长后,已经进入以"提质增效"为核心的战略转型期,能否实现从量变到质变,开启以质量为核心的发展模式,既关系到实现2020年来华留学50万目标的含金量,也关系到我国从"留学大国"成为"留学强国"关键。应当质量优先,规范管理,实现来华留学内涵式发展,打造来华留学临床医学教育国际品牌;学校应高度重视,从全局出发,解放思想,提高认识,加强内涵建设,提质增效,抓好质量工程,统筹兼顾,开启以质量为核心的发展模式,将来华留学教育纳入学校的整体发展规划,加快推进趋同化培养,整体协调,健康推进。坚持扩大开放,做强中国教育,推进人文交流,不断提升我国教育质量、国家软实力和国际影响