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Toxicology - Therapeutic Drug Monitoring

Cod: W298

VALIDATION OF A NEW AND FAST METHOD FOR THE MAIN MOLECULAR SPECIE OF THE PHOSPHATIDYL ETHANOL (PETH 16:0-18:1) MEASUREMENT IN BLOOD BY LIQUID CHROMATOGRAPHY–TANDEM MASS SPECTROMETRY

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Background
Phosphatidyl Ethanol (Peth) is a "pathological" phospholipid, formed via the action of phospholipase D only in the presence of ethanol. The blood PEth concentration has been demonstrated to correlate with the amount of alcohol consumed, even though the relationship varies considerably between individuals. Main molecular specie is PEth 16:0-18:1. At the moment it is the most promising marker of alcohol abuse .
Aim of the paper is the valuation of a fast method for the PEth 16:0-18:1 measurement in whole blood by HPLC-MS/MS. A comparison with the routine method proposed by Helander will be done.
Methods
The pre-analytical phase consists in a precipitation of the proteins in a single step starting from 100 L of whole blood, deuterated internal standard d5-Peth 16:0-18:1 included. Calibration is possible by a certificated standard produced by Red- Hot Diagnostics(Sweden). The analytical phase is performed on HPLC/MS-MS (Nexera Shimatzu and 4000QTRAP ABSciex) with ESI source in negative ionization. Chromatographic separation is obtained by a C18 column with a binary gradient. Run time is 5 minutes.
Results
Imprecision: two samples of whole blood at 0.3 to 0.6 M (concentrations which correspond to the cut-off and double the cut-off) were analyzed in 5 replicates in 3 different analytical series (intra assays imprecision) with CV% respectively 4.2% and 2.9% and in 5 different analytical series (inter assays imprecision) with CV% 6% and 4.3 respectively
Linearity calculated by dilution scale of the calibrator: between 0.078 and 5,0 M.
LOQ: determined as signal/ noise ratio greater than 10. In matrix it is 0.1 M.
Recovery: two samples in water and two samples in whole blood at the same concentration of 1 M were prepared. When we use the following formula (100 x Area ratio average blood samples / area ratio average water samples), recovery percentage was 99.6%.
Comparison with the Helander routine method : Y =1.02 X + 0.04 ; R2= 0.9899
Conclusion
This fast method has all the requirements to be useful in a routine laboratory with an elevated number of PEth tests.

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Toxicology - Therapeutic Drug Monitoring

Cod: W299

ETHANOLEMIA IS A NEGLECTED CAUSE OF UNDERESTIMATED NATREMIA AS MEASURED BY INDIRECT POTENTIOMETRY.

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Background:
Acute alcoholism is a cause of hospitalization in emergency units. Most often, natremia is determined by indirect potentiometry assay. However, if ethanolemia is high, the osmolality of plasma is greater than normal and therefore may lead to a possible cause of incorrect results of natremia. Here, we present the comparison of natremia measured either by indirect potentiometry (IP), or by direct potentiometry (DP) when ethanolemia is higher than 80 mg/dL.
Methods:
The study was conducted in 51 patients admitted in the emergency department of the Centre Hospitalier Universitaire of Nantes during July and August 2016. For each patient, a blood sample was collected using heparinized tube and the following parameters were measured in the plasma: ethanolemia (enzymatic-UV), glucose (Hexokinase), urea/bun (urease) and natremia (indirect potentiometry) with Cobas Roche 8000/6000 analyzer; and natremia (direct potentiometry, Radiometer ABL 835 blood gaz analyzer), and osmolality (freezing point depression /cryoscopy, Advanced Instruments).
Results:
Ethanolemia measured in the patients' blood ranged from 80 to 600 mg/dL (mean: 273 ± 101), glucose from 3.4 to 7.8 mmol/L (mean: 5.17 ± 1.04), urea from 1.3 to 7.3 mmol/L (mean: 3.27 ± 1.32) and osmolality from 318 to 461 mosm/kg (mean: 362 ± 27.7). None of the 51 patients had an increase plasma proteins or plasma lipids. Natremia measured by indirect potentiometry ranged from 130 to 149 mmol/L (mean: 141 ± 4.07) and by direct potentiometry from 133 to 152 mmol/L (mean: 145 ± 3.85). The differences between the two methods for natremia ranged from -1.0 to 9.0 mmol/L (mean: 3.67 ± 1.97). Excepted in one case, natremia was higher when measured by direct potentiometry. We observed a strong correlation between osmolality and ethanolemia: $y = 0.259x + 291.71$, $r=0.943$. Statistical analysis shows a significant difference between IP and DP (paired t-test, IC = 3.113 to 4.22, $r = 0.88$, $p < 0.0001$). In this cohort, 21/51 (41.2%) patients were falsely diagnosed in normonatremia by IP, whereas they presented in fact hypernatremia and 2/51 (3.9%) patients were falsely diagnosed as presenting hyponatremia by IP whereas they presented normonatremia .
Conclusion:
For patients presenting a positive ethanolemia, we recommend to systematically measure natremia by direct potentiometry, and most particularly when the ethanolemia is higher than 200 mg/dL so as to avoid an invalid diagnosis.

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Toxicology - Therapeutic Drug Monitoring

Cod: W300

EVALUATION OF IMMUNOASSAY IMPLEMENTATION FOR THE DETERMINATION OF IMMUNOSUPPRESSIVE DRUGS ON THE BECKMAN COULTER AU680 ANALYZER IN A CLINICAL SETTING.

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BACKGROUND AND AIM: Immunosuppressive drugs (ISD) are used for the control of tissue rejection following transplantation. Because of the narrow therapeutic index, it is important to monitor blood ISD levels in transplant recipients. Although liquid chromatography coupled to mass spectrometry (LC-MS) represents the gold standard for ISD quantification, immunoassays might prove faster, easier and prone to automation for clinical ISD monitoring. The study evaluates, in a clinical setting, the suitability of Thermo Scientific immunoassays for the determination of cyclosporine both in Low and High range (LR and HR CsA), tacrolimus (TAC), mycophenolic acid (MPA) and everolimus (EVER) on the AU680 clinical chemistry analyzer (Beckman Coulter).
METHODS: Blood samples from patients receiving CsA (n=233), MPA (n=134), TAC (n=191) or EVER (n=128) were collected and tested by both UPLC-MS/MS (Chromsystems reagents) and immunoassays. CsA/MPA assays used a Cloned Enzyme Donor Immunoassay (CEDIA) while TAC/EVER assays used a Quantitative Microsphere System (QMS). All reagents, calibrators, controls were supplied by Thermo Fisher Scientific. Precision, sensitivity, linearity and accuracy were evaluated according to the CLSI guidelines. Method comparison was carried out by Spearman's correlation, Passing-Bablok regression and Bland-Altman analysis.
RESULTS: Concerning precision studies, the coefficient of variation for all the immunoassays was lower than 6% (within day) and 9% (between days). Both immunoassay linearity and sensitivity data were consistent with manufacturer's specifications. Correlation analysis revealed a good agreement between the immunometric and UPLC-MS/MS results for all the ISD patient samples ($r > 0.87$, $p<0.0001$ for TAC; $r>0.91$, $p<0.001$ for CsA/MPA/EVER). Nevertheless, immunoassay data showed a positive average bias respect to UPLC-MS/MS measures for all the ISDs: 24.4 ng/mL for LR CsA, 117.2 ng/mL for HR CsA, 1.1 µg/mL for MPA, 4.9 ng/mL for TAC and 0.5 ng/mL for EVER.
CONCLUSIONS: Data demonstrated acceptable performance of AU680 analyzer in terms of precision and sensitivity. The bias between UPLC-MS/MS and immunoassay results is consistent with previous data and suggests appropriate therapeutic reference ranges based on the detection method used.

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Toxicology - Therapeutic Drug Monitoring

Cod: W301

THE EFFECT OF LEAD LEVELS ON NEUTROPHIL-LYMPHOCYTE RATIO, PLATELET-LYMPHOCYTE RATIO AND MEAN PLATELET VOLUME

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Objective: Lead is one of the most toxic elements which may cause acute, subacute or chronic poisoning through environmental and occupational exposure. Lead exposure is known to increase inflammatory response by causing oxidative stress through the production of reactive oxygen species (ROS). Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and mean platelet volume (MPV) have become increasingly useful as predictive and prognostic tools in patients with various inflammatory and ischemic conditions. The aim of this study was to determine the prognostic effect of the NLR , PLR and MPV on workers with lead exposure.

Methods: Nine hundred twenthy eight samples were collected from the patient database at the Istanbul Occupational Diseases of Hospital (Istanbul, Turkey). The hospital-based data were obtained by the date interval of January and June 2015. Blood lead levels were measured on atomic absorption spectrophotometer (AS 7000, Japan) and NLR, PLR, MPV parameters were calculated from the complete blood counts (HMX, Beckman Coulter, USA). The participants were divided into five groups according to the blood lead levels as 0-10 μg/dL (Group 1), 11- 20μg/dL (Group 2), 21-29 μg/dL (Group 3), 30- 39μg/dL (Group 4) and > 39 μg/dL (Group 5). The normal distribution of data was determined by using a Kolmogorov-Smirnov test. Mann-Whitney U test was applied for non-normal distribution parameters . The mean and median values were calculated by using this subset of analyte values. The relation between NLR, PLR, MPV and lead was evaluated by inter-group and correlation analysis.

Results: Mean and median NLR values of Group 1, Group 2, Group 3 ,Group 4 and Group 5 were 1.6 (1.5), 1.70 (1.5), 1.8 (1.7), 1.90 (1.7),and 2.11(1.96), respectively. Mean and median PLR values of Group 1, Group 2, Group 3, Group 4 and Group 5 were 92 (86), 88 (83), 97 (94), 101 (92), and 103(94), respectively. The mean PRL and NLR values increased progressively inaccordance with the lead concentration among groups ($p<0.001$). NRL and PRL values demonstrated positive correlation with lead levels, respectively ($r=0.17$, $r=0.10$; $p<0.001$). There were no significant differences between MPV and lead levels. The results of current study demonstrated that NLR and PRL values were related with lead levels.

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Toxicology - Therapeutic Drug Monitoring

Cod: W302

PERFORMANCE EVALUATION OF DIMENSION TAC ASSAY AND COMPARISON WITH OTHER COMMERCIAL TACROLIMUS ASSAY

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BACKGROUND: Therapeutic monitoring of tacrolimus (TAC) is essential for reducing the organ rejection and adverse effects. The measurements of TAC in whole blood is performed by immunoassays or liquid chromatography-tandem mass spectrometry (LC-MS/MS) and many automated platforms have been developed. The aim of the present study was to evaluate the analytical performance of Dimension TAC assay (Siemens Healthineers, USA) which was upgraded reagent from the previous Dimension TACR assay.

METHODS: The evaluation was performed based on the Clinical and Laboratory Standards Institute (CLSI) guidelines. The evaluation consisted of determination of the precision, linearity, limit of blank (LoB), limit of detection (LoD), limit of quantitation (LoQ), and reagent lot-to-lot using three lot number. A correlation study was conducted using Dimension TACR assay, Architect Immunoassay (Abbott Diagnostics), Elecsys (Roche Diagnostics), MassTrak LC-MS/MS (Waters Corporation). We collected each sample more than 40 from kidney, liver and heart transplant recipients.

RESULTS: The total CV for the low, middle and high level quality control materials were 7.3%, 5.1% and 5.7%, respectively. The linear range where the coefficient of determination was >0.99 of the Dimension TAC assay was 1.61–31.72 ng/mL. The LoB, LoD, and LoQ was 0.29 ng/mL, 0.47 ng/mL, and 1.02 ng/mL, respectively. Correlation analysis indicated that results of the Dimension TAC assay was comparable to Dimension TACR assay, Architect Immunoassay and Elecsys in liver and heart transplants [correlation coefficients (r)=0.856~0.982]. In kidney transplants, Dimension TAC assay showed the less correlation with Architect Immunoassay and Elecsys [r= 0.558 and 0.775]. The results of these assay were slightly higher than those of MassTrak (mean bias 1.563-2.619 ng/mL) in all transplant groups. And we found few lot-to-lot reagent variation in the reagents which were evaluated [r >0.993].

CONCLUSIONS: The overall analytical performance of Dimension TAC assay is acceptable for therapeutic monitoring in clinical practice. This assay showed the higher concentrations than mass spectrometry which was consistent with results in previous study.

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Toxicology - Therapeutic Drug Monitoring

Cod: W303

HYPERAMMONEMIA ASSOCIATED WITH VALPROIC ACID IN CHILDREN WITH EPILEPSY

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Background: Valproic acid (VPA), is widely used in pediatrics as an effective anticonvulsant. A documented side effect of VPA therapy has been the elevation of the serum ammonia level. In some cases, hyperammonemia may be clinically significant, resulting in hyperammonemic encephalopathy, even with normal liver function and despite normal doses and serum levels of VPA. Aim: To record and evaluate the risk frequency of hyperammonemia and hyperammonemic encephalopathy in children with idiopathic epilepsy in VPA monotherapy.
Materials and Methods: This is a retrospective study of 316 paediatric patients (168 boys/148 girls) aged 0–17 years from November 2010 to October 2016, on VPA monotherapy. Serum VPA concentration was measured (therapeutic range 50-100 mg/L, toxic level >150 mg/L). Serum ammonia level and liver function tests were performed to the patients presented with recurrent seizures, confusion, personality change, irritability, ataxia, visual disturbance, lethargy, and somnolence. Patients with serious hepatic dysfunction, metabolic disorders, or severe infections were excluded. Hyperammonemia was defined as a plasma ammonia level >93 N-μg/dl and severe hyperammonemia >150 N-μg/dl (normal range 29-70 N-μg/dl). Serum ammonia level, serum valproic acid level and liver function tests were performed by DxC600/BECKMAN-COULTER automated analyzer.
Results: Among the 316 patients treated with VPA, 8 (3 boys/5 girls) (2.54%) had ammonia levels >93 N-μg/dl (mean: 121.25+-26.10) and 3 (1 boy/2 girls) of these 8 (37.5%) aged 2, 7 and 17 months, developed hyperammonemic encephalopathy. Hepatic function tests were normal and there was a positive correlation between the plasma ammonia level and the serum concentration of VPA (82-116 mg/L). Withdrawal of VPA and L-carnitine supplementation resulted in normalization of ammonia levels within 18-36h and encephalopathy resolution.
Conclusions: Our study demonstrated that pediatric patients with epilepsy treated with VPA, aged 3 years or younger and of female gender, had an increased risk of hyperammonemia and valproic acid-induced hyperammonaemic encephalopathy. Physicians should be aware of this potential complication and check ammonia levels in patients taking VPA who present with alterations in mental status. Treatment with L-carnitine may be beneficial in reducing ammonia levels.

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Toxicology - Therapeutic Drug Monitoring

Cod: W304

HEPATOPROTECTIVE EFFECT OF AGMATINE IN ACUTE CHLORPROMAZINE INDUCED LIVER INJURY

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Background:
Chlorpromazine (CPZ) is an important member of the phenothiazines, a widely used class of antipsychotic agents. Chronic treatment with neuroleptics increases free radical production. Present study focused on potentially beneficial effects of agmatine (AGM) on oxidative stress development in liver during CPZ treatment in rats. We wanted to examine efficiency of antioxidant protection of AGM through the determination of malondylaldehyde (MDA) in rat liver homogenate, as well as plasma concentrations of MDA after the treatment.
Methods:
CPZ was applied intraperitoneally at a single dose of 38.7 mg/kg (CPZ group). The second group was treated with both CPZ and AGM at single doses of 38.7 mg/kg and 75 mg/kg, respectively (CPZ+AGM group). AGM was applied immediately after the CPZ. The third group of animals was treated i.p. with normal saline followed by a single daily dose (75 mg/kg) of AGM i.p (AGM group). The control group was treated with 0.9% saline solution. Rats were sacrificed by decapitation 24 h after treatment. Lipid peroxidation analysis in the liver homogenates and in the plasma were measured as MDA production, assayed in the thiobarbituric acid reaction as described by Girotti et al. The results are expressed as nmol/mg proteins in liver homogenates or μmol/l in plasma.
Results:
Significant rise in liver MDA concentration was found 24 h after administration of CPZ ($P<0.05$). Similar to this, plasma MDA concentration was significantly higher in CPZ-treated group in comparison with the control group at the same time interval. There is a significant negative correlation between MDA concentration in the liver and plasma of CPZ-treated animals ($r = -0.89$, $P<0.0001$). The results of our investigation have shown the important role of oxidative stress in acute CPZ-induced liver injury. Our results pointed at hepatoprotective effects of AGM, which can reduce the concentration of MDA in the liver and plasma. This study has shown that liver and plasma MDA concentrations were significantly increased in the CPZ treated group in comparison with the control group.
Conclusion: Analysis of data showed that treatment with AGM significantly attenuated oxidative stress indicators as evidenced by lowering MDA concentrations in the liver and in plasma of rats.

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Toxicology - Therapeutic Drug Monitoring

Cod: W305

INFLUENCE OF RENAL INSUFFICIENCY ON PHARMACOKINETICS OF METHOTREXATE

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Background: Methotrexate (MTX), in low dose is one of the most frequently used antirheumatic drugs in patients with rheumatoid arthritis (RA), because of its benefit and risk profile. Glomerular filtration is the dominant pathway of MTX elimination. Our study wants to determine the effects of impaired renal function on the pharmacokinetics of MTX in RA patients and possible hepatotoxicity.

Methods: 38 RA patients were included in this study. MTX was administered intramuscularly (7.5-15mg). Subjects were divided into three groups, according to their creatinine clearance (CLCR); group 1: CLCR lower than 45 ml/min; group 2: CLCR between 45 and 80 ml/min and group 3: CLCR higher than 80 ml/min. Blood samples were collected from each subject, 2, 12 and 24 hours after drug administration. We determined concentrations of MTX and transaminase liver enzymes.

Results: MTX concentrations were 1.2 to 1.5-times higher in group 1 than in groups 2 and 3. Total MTX t1/2 eliminations were 23h in group 1, 12.8 hours in group 2 and 10.5 hours in group 3. Linear regression revealed good correlations between clearance values of MTX and creatinine clearance. Elevated ALT/AST levels occurred in 30% patients, 12 hours after MTX therapy in group 1, 10% and 7% of patients in group 2 and 3.
Highest level of ALT is 96 IU/L, AST 62 IU/L.

Conclusions: Eliminations half life was significantly increased and total clearance was significantly reduced with the degree of renal impairment. Longer elimination half life induced increased chance of liver dysfunction.

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Toxicology - Therapeutic Drug Monitoring

Cod: W306

BIOCHEMICAL EVALUATION OF THE TOXIC EFFECT OF ELECTRONIC WASTE LEACHATE ON LIVER OF WISTAR ALBINO RAT

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Background
Electronic Waste Leachate (EWL) has become an emerging global environmental and human health issue. Exposure to these substances has been proposed to induce hepatotoxicity, nephrotoxicity and neurotoxicity in humans. Information on the potential of EWL to induce cytotoxicity is scarce in Nigeria. This study was carried out to determine the toxic effect of EWL on liver of albino rat (Rattus norvegicus).

Method
EWL was obtained from Oke-padre Ibadan Nigeria dump site and simulated using the American society for testing and materials (ASTM) method. Forty (40) male strain albino rats were randomly assigned into 8 groups of 5 rats each to determine acute toxicity. Rats were fed on pellets and water ad-libitum. Group 1 - Control Group (CG) were given deionized water; while the Experimental Groups (EG) 2 to 6 were treated with (20%, 40%, 60%, 80% and 100%) of the EWL respectively; and groups 7 and 8 were given 20mg/kg of PbCl2 and 40mg/kg of CuCl2 per body weight respectively, orally for 14 days.24 hours after last administration, the rats were sacrificed;Blood biochemical analysis of Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT) and Alkaline phosphatase (ALP) using International Federation for Clinical Chemistry Method. Total protein (TP) and Albumin (ALB) were analysed using biuret and bromocresol green methods respectively.The results were analysed using ANOVA at p=0.05 and Post Hoc.

Results
Mean concentration of AST (158.4±24.1iu/l) and ALT (62.6±9.7iu/l) were significantly higher in EG2 compared to AST (99.0±41.6iu/l) and ALT (46.2±12.7iu/l) in CG. While a significant decrease was observed for ALP in EG3 (234.20±120.4iu/l) and EG4 (138±40.7iu/l) compared to CG (422.00±111.7iu/l).There was a significant increase in the TP (8.32±0.4g/dl) and ALB (4.60±0.2g/dl) in EG4 compared to CG (7.18±0.4g/dl and 3.86±0.4g/dl) respectively.

Conclusion
Leachate from the electronic waste dumpsite from Oke Padre Ibadan induced liver dysfunction in rats. Proper treatment of electronic waste is imperative to prevent possible health risks to humans.

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Toxicology - Therapeutic Drug Monitoring

Cod: W307

COMPARISON OF CYCLOSPORINE MEASUREMENT USING TWO IMMUNOASSAYS ON AUTOMATIC IMMUNOLOGICAL ANALYZERS.

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Background: Therapeutic Drug Monitoring and immunosuppressants dosage adjustment is part of the transplant patients' therapy protocol, because it improves the clinical outcome.
Methods: After a manual pre-treatment procedure to precipitate proteins and extract the drug, the cyclosporine (CsA) concentrations of 140 whole blood samples from transplant recipients, were measured on automatic immunological analyzers. We used Fluorescence Polarized ImmunoAssay (FPIA) on AxSYM and Chemiluminescent Microparticle ImmunoAssay (CMIA) on Architect i2000SR. For the statistical analysis, all the results were compared in accordance with the Evaluation Protocol Assessment Protocol EP9 - A2 of CLSI Passing-Bablok linear regression analysis and differences diagram by Bland - Altman.
Results: In FPIA the concentration range was 43.1-1082.90, the arithmetic mean was 361.68 and the median was 332.95. In CMIA the concentration range was 28.90-1083.00, the arithmetic mean was 307.32 and the median was 272.70. According to the Cusum test of linearity (p = 0.40), there is no significant deviation from linearity. The Passing-Bablok linear regression equation is of the form y = -8.118750 + 0.875000 x. The estimated bias between the two methods (CMIA – FPIA), from differences diagram by Bland-Altman, is -54. The Pearson correlation coefficient (r=0.9190) indicates good linear correlation between the two methods. The Spearman correlation coefficient (rho=0.9378) indicates strong monotonic correlation between the two methods.
Conclusion: In general, CsA assay on Architect i2000SR (CMIA method) gives lower levels compared to those on AxSYM (FPIA method), as shown by the method comparison and evaluation analysis. This may be attributed to the fact, that the ARCHITECT CsA assay has significantly reduced CsA metabolite interference.

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Toxicology - Therapeutic Drug Monitoring

Cod: W308

CAPILLARY VERSUS VENOUS THERAPEUTIC DRUG MONITORING OF TACROLIMUS AND CYCLOSPORINE A: ACCURACY AND PATIENT SATISFACTION

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Background: Following transplants, patients are placed on Tacrolimus (Tac) or Cyclosporine A (CsA) to lower the risk of organ rejection. These medications have a narrow therapeutic window so lifelong therapeutic drug monitoring (TDM) is performed. However, TDM has many challenges including frequent blood draws that are often analyzed at different labs since patients reside far away from the original transplant center. Unfortunately, these assays are not harmonized, so results for Tac and/or CsA may be vastly different even if the two labs use the same methodology making it difficult to serially monitor patients. Therefore, this study examined the use of the Mitra microsampling collection device and compared the results to a venous (VEN) blood draw. The study also examined the stability of the dried blood samples and overall patient satisfaction with the capillary (CAP) collection process.
Methods: After Mayo Clinic IRB approval was obtained, 50 patients prescribed Tac and 15 prescribed CsA were enrolled and consented into the study. After instruction, two 20 µL devices were collected immediately before the VEN blood draw. All samples were then sent to the lab and analyzed using a validated high-performance liquid chromatography tandem mass spectrometry assay. A satisfaction survey was then completed by the patients. Additional devices were also spotted using three pools of de-identified residual blood across the analytical measuring range. The devices were then stored at 25C and tested in duplicate on day 0, 1, 3, 7, 14, and 28 and compared to the original value.
Results: CsA dried blood spots were stable up to 7 days with an average difference of <10% (actual -8.2%), but subsequent testing showed >20% difference on days 14 and 28. Tac dried blood spots showed more variability, but were stable up to 3 days. CAP results showed a slight negative bias for both CsA (slope = 0.940 R^2=0.917) and Tac (slope = 0.840 R^2=0.824) which likely was caused by milking during the collection process. Finally, the patient survey's showed 78% of the patients preferred the CAP collection option, while 12% had no preference and 10% preferred to have a VEN collection.
Conclusion: In the end, this project showed good correlation, but a larger study would need to be performed to verify the results and the ability to collect samples at home and mail them back to the lab. If successful, this new protocol would allow: less blood to be collected (20 µL vs 4 mL), lower shipping costs and improved patient satisfaction.

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Toxicology - Therapeutic Drug Monitoring

Cod: W309

HIGH LEVELS OF METHOTREXATE IN A PATIENT WITH LYMPHOMA. A CASE REPORT

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Background
Methotrexate (MTX) (4-amino-N10-metilpteroil glutamic acid) is an analog of aminopterin, folic acid antagonist, it has an intracellular metabolism to poliglutamil-methotrexate, can be converted back to MTX by cellular hydrolases. The most important mechanism of action is inhibition of thymidylate synthetase, resulting in an inhibition of DNA synthesis-
65-80% of MTX is excreted renally unmetabolized in the first 12 hours after administration, 20-35% is secreted biliary and metabolized or transferred to other compartments. Biliary secretion becomes important in patients with renal failure in which drug clearance is lower and the risk of toxicity increase. Part of MTX is metabolized by intestinal flora and removed as inactive metabolite.
The half-life of MTX in serum is about 7-10 hours, although in some patients can reach 26 hours, being undetectable at 52 hours.

Method and results
45 year old male diagnosed with non-Hodgkin lymphoma, he was treat with high MTX doses iv 18600 mg. Biochemical parameters before starting treatment with MTX were normal. Serum levels of MTX at 24 hours were 27 mmol/L, creatinine 2.28 mg/dL (0.70 -1.20 mg/dL), urea 55.5 mg/dL (10-50 mg/dL) BUN. Folinic acid rescue and other corrective measures such as hydration and urine alkalinization, analytical controls at 30 and 36 hours showed similar levels of MTX with a small increase in creatinine (2.42 mg/dL). Analytical control at 42 hours MTX levels began to declin slowly (20, 17, 16, 9.5, 4 mmol/L at 42, 48, 56, 66 and 72 hours). At days 8 MTX levels was 0.54 mmol/L with a creatinine of 2.03 mg/dL, urea 93.6 mg / dl and BUN 43.71 mg/dL.

Discussion
Kidney failure by tubular damage is one of the adverse effects of treatment with MTX and determines a decreased excretion of the drug with an increased risk of toxicity it is even fatal. Capacity of hepatic metabolism of MTX has a large interindividual variability. This may be another cause of high drug levels in this patient. Serial monitoring of MTX levels is important to monitor patients treated with this drug and therapeutic decision making aimed at avoiding drug toxicity.

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Toxicology - Therapeutic Drug Monitoring

Cod: W310

SIMULTANEOUS SCREENING OF 20 DRUGS OF ABUSE IN ORAL FLUID IN UNDER 20 MINUTES WITH THE USE OF THE NEW BIOCHIP ANALYSER EVIDENCE MULTISTAT

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Background. Oral fluid represents an excellent alternative matrix for monitoring drug intake in treatment, workplace and driving under the influence of drugs. The collection of oral fluid is quick, simple and non-invasive and can be easily observed. Rapid drug screening can play a vital role in drug testing particularly where safety is critical. Biochip array technology enables the simultaneous screening of multiple drugs from a single sample and when applied to the Evidence MultiSTAT, the time to result is reduced as shown in this study for the detection of 20 drugs of abuse from a single oral fluid sample.
Methods. Simultaneous competitive chemiluminescent immunoassays on a biochip surface and applied to the Evidence MultiSTAT analyser were employed. This fully automated system processes a self-contained cartridge containing all the components required for the assays and has the capacity to assess two biochips in under 20 minutes. Sampling oral fluid against a cut-off sample, the results obtained are qualitative.
Results. Drug classes detected with the associated cut-off values: 1ng/mL (fentanyl, LSD, buprenorphine), 50ng/mL (ketamine, amphetamine, methamphetamine, barbiturates), 2ng/mL (THC, 6-MAM, alpha PVP), 10ng/mL (benzodiazepines, UR144, opiates), 4ng/mL (methadone, tramadol), 5ng/mL (PCP, JWH018), 20ng/mL (benzoylecgonine), 8ng/mL (oxycodone). Precision evaluation (+50% and -50% cut-off samples analyzed across 2 analyzers): percentage agreement values were 97.5% (PCP, alpha PVP and buprenorphine) and 100% for all the other assays. Accuracy evaluation (assessment of 100 samples prepared in Intercept I2 buffer): percentage agreement values were in the range of 94%-100%. The percentage agreement values with LC/MS for authentic oral fluid samples (n=90) were: 100% (methamphetamine), 97.8% (methadone), 94.4% (benzodiazepine and amphetamine), 91.1% (opiate) and 90% (6-MAM).
Conclusion. Data indicate that with the automated Evidence MultiSTAT system, twenty drug classes can be screened in less than 20 minutes with reproducible and accurate qualitative results. The cut-offs achieved are extremely sensitive and applicable for an oral fluid matrix. This reported new application, is an effective, quick and user friendly solution for oral fluid screening.

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Toxicology - Therapeutic Drug Monitoring

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EFFECT OF TIME AND STORAGE TEMPERATURE ON ACETYLCHOLINESTERASE ACTIVITY IN BLOOD FROM ORGANOPHOSPHATE INSECTICIDE-EXPOSED WORKERS

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Measuring the acetylcholinesterase activity in blood is useful in evaluating long-term exposure to organophosphate insecticides. Considering that delays between the time of sampling and time of testing are common, our challenge was to establish time and storage temperature during which the activity of acetylcholinesterase in blood does not significantly change.

The blood was collected in EDTA tubes from 10 randomly chosen organophosphate insecticide-exposed workers and stored at 4 ºC before testing. Having in mind that there is no certified control material that has been available for use, we prepared pooled sample from lab staff, whose reference value has been determined. After blood centrifugation and separation plasma from erythrocytes, the erythrocytes were then diluted 600-fold in water. The enzyme activity in diluted samples and pool was measured with Ellman colorimetric method at 412 nm, using phosphate buffer pH 7.4 as an assay buffer, 5,5'-dithio-bis(2-nitrobenzoic acid) as an indicator and acetylthiocholine as a substrate. The remaining erythrocytes from each sample and pool were divided into 2 groups and stored at -20 ºC and at -80 ºC for 30 days. After that period of time and thawing process, the samples and pool were prepared and activity of enzyme was measured in the same way as 30 days before. The activity of acetylcholinesterase is expressed in IU/L of blood.

Comparing the values of acetylcholinesterase activity in samples measured before freezing (original values) with those measured after, we established that the activity in both groups has changed (decreased or increased) up to 10 % . Statistically significant difference ($p<0.05$) in activity has been noticed in group of sample stored at -20 ºC. Also, it has been observed that the activity of enzyme did not significantly decrease or increase ($p>0.05$) in group of sample stored at - 80º C.

Based on results obtained in this study we can conclude that separated erythrocytes from EDTA whole blood can be stored for at least 30 days at -80º C without significant changes in acetylcholinesterase activity.

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Toxicology - Therapeutic Drug Monitoring

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PERFORMANCE EVALUATION OF THE EMIT II PLUS BUPRENORPHINE ASSAY

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Background: Buprenorphine, a semisynthetic opioid, is used as a substitution drug for treatment of opioid addiction, but has a high potential for abuse and addiction. A new assay for measurement of buprenorphine has been developed by Siemens Healthineers on the Viva-E® Drug Testing System, with protocols on the V-Twin® Drug Testing System and Viva-ProE™ System. The Emit® II Plus Buprenorphine assay has a cutoff of 5 ng/mL.
Methods: Precision was evaluated at the cutoff and multiple levels according to CLSI EP5-A2. Recovery was studied by spiking buprenorphine into human urine at levels that span the assay range (0–25 ng/mL). On-instrument stability was assessed by testing the assay controls over a 35-day period. Specimens (127) were analyzed and the results compared to those of LC MS/MS. Cross-reactivity with structurally related drugs was assessed at a concentration of 100,000 ng/mL. The effect of common interferences was assessed by spiking the interferents into human urine in the presence of buprenorphine at the control levels of 3 and 7 ng/mL.
Results: Qualitative repeatability CVs (rate) for all levels ranged from 0.48 to 0.85%, and within-lab CVs ranged from 0.78 to 1.17%. Semiquantitative repeatability CVs (ng/mL) ranged from 1.81 to 3.99%, and within-lab CVs ranged from 2.31 to 7.91%. The assay's limit of detection was found to be 0.7 ng/mL on all systems. The assay quantified buprenorphine-spiked samples between 2 and 25 ng/mL within ±10% of nominal values. At the 5 ng/mL cutoff, the percent agreement of specimens between the Viva-E analyzer and LC-MS/MS was 94%. Discordant samples were within ±25% of the cutoff by both methods. The percent agreement of specimens between the Viva-E and Viva-ProE systems was 98%. The assay reagents demonstrated similar detection of buprenorphine and norbuprenorphine in urine with minimal cross-reactivity (<0.01%) to the structurally related opioids. Potentially interfering substances gave acceptable results relative to the 5 ng/mL cutoff. The reagents were stable onboard the Viva-E system for a minimum of 4 weeks.
Conclusion: The Emit II Plus Buprenorphine assay on the Viva-E and V-Twin Systems and Viva-ProE System is a suitable screening method for urine specimens at the cutoff level of 5 ng/mL for both qualitative and semiquantitative analysis of buprenorphine.

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Toxicology - Therapeutic Drug Monitoring

Cod: W314

"CHINESE PATENT MEDICINE AS A POTENTIAL SOURCE OF MERCURY POISONING" 25 YEARS LATER

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BACKGROUND: A clinical report published in the summer of 1992 presents a research as an awareness effort concerning the potential hazards of the Chinese patent medicines that contain mercury(II) sulfide (HgS) or mercury(I) chloride (Hg2Cl2). That research discusses certain specific reported cases of mercury poisoning caused by such medicines and the toxicity of the two mercurials, which are commonly used in Chinese patent medicines. The 1992 report also includes a table that lists 18 mercurial-containing Chinese patent medicines. The report acknowledges that Chinese patent medicines are not regulated by the U.S. Food & Drug Administration (FDA). Still, it says that they "are readily available over-the-counter in Asian communities" in the United States. The purpose of this investigation is to observe the availability of the Chinese patent medicines that contain HgS in the fall of 2016, almost 25 years later.
METHODS: In the fall of 2016, an undergraduate Chinese student made inquiry about the availability of the Chinese patent medicines that contained HgS on the 18-membered list that had been published in 1992. The student visited several (6) Asian stores in New England and listed several available Chinese patent medicines that contained Zu-Sha (cinnabar, which is ≥96% HgS).
RESULTS: The list of the Chinese patent medicines that contained Zu-Sha at some or all of the 6 visited Asian stores included the following 9 mercurial-containing medicines listed on the 18-membered list: (1) Xi Gua Shuang, (2) An Gong Niu Huang Wan, (3) An Shen Bu Nao Wan, (4) Bai Zi Yang Xin Wan, (5) Zhu Sha An Shen Wan, (6) Qi Li San, (7) Zi Jin Ding, (8) Bao Ying Dan, (9) Hu Po Bao Long Wan.
CONCLUSIONS: We found 9 of the 18 (50% of the) listed Chinese patent medicines containing mercurials still available in the United States market. Considering the fact that the 6 visited Asian stores were all in only a certain part of New England, we expect mercury-containing Chinese patent medicines to be widespread in the United States. This is a human health concern that needs to be addressed by regulatory agencies in the United States more seriously.

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Toxicology - Therapeutic Drug Monitoring

Cod: W315

CHRONIC EXPOSURE TO KALACH 360 SL INDUCED ENDOCRINE DISRUPTION AND OVARY DAMAGE IN FEMALE RATS.

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Kalach 360 SL (KL) is a glyphosate (G) surfactant-based herbicides applied in agriculture in Tunisia and throughout the world, which has been demonstrated to represent a risk to non-target organisms. The aim of this study was to investigate the morphological and biochemical aspects of ovary injury after rats exposure to Kl. Female wistar rats were randomly divided into three groups: group 1 was used as a control; group 2 orally received 0.07 ml of KL, (corresponding to 126 mg of G/ Kg) and group 3 orally received 0.175 ml of KL (corresponding to 315 mg of G /Kg) for 60 days. KL chronic exposure in rats impaired folliculogenesis, ovary development and decreased estrogen secretion. Moreover, KL exposure promoted oxidative stress: malondialdehyde and advanced oxidation in protein product levels were increased whereas glutathione peroxidase, superoxide dismutase and catalase activities were decreased. We conclude that KL induces endocrine disruption and ovary damage in female rats.

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INTERFERENCE OF HYDROXOCOBALAMIN ON BEKMANN COULTER USUAL CLINICAL CHEMISTRY TESTS AND ON BLOOD GAS ANALYZER RAPIDLAB 1265 (SIEMENS).

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Introduction: Intoxication with cyanide occurs after confined-space smoke inhalation during fires due to the production of carbon monoxide and hydrogen cyanide or in suicides and criminal cases.
Various symptoms are observed, from the breakdown of many organs to coma and sometimes death. Cyanokit® = hydroxocobalamin binds cyanide to give cyanocobalamin, a non-toxic complex excreted in urines. The red crystals of hydroxocobalamin color biological fluids, and this can interfere in the results of biochemical analyzes which are useful to observe the state of health of the patient.
The objective of this study is to identify the data affected by this coloration during the analyses carried out by Beckman Coulter‘s AU5400 and RapidLab 1265.

Materials and methods: Hydroxocobalamin (Merck) is dissolved in distilled water and add to a poolof human plasma or total blood at 7 concentrations. These concentrations are chosen to be as close as possible from concentrations in blood in therapeutic uses. The percentage of interference is determined for emergency biochemical parameters by comparing with blood free from hydroxocobalamin.

Results: We sort the results in 5 different categories: positive bias over and under 10% and negative bias over and under 10%. The last category contains the analytes that are not affected by the presence of hydroxocobalamin. There is an increase or decrease of up to 40% for the parameters required for monitoring of intoxicated patients. This is particularly true for the determination of carboxyhemoglobin and liver function tests.

Conclusion: We showed that hydroxocobalamin causes interference problems on some biochemical parameters measured on AU5400 Rapidlab and 1265. These data are important for the care of cyanide poisoned patients, as knowledge of the analytical limits of our analysers in this situation allows us to give more reliable results to physicians.

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Toxicology - Therapeutic Drug Monitoring

Cod: W317

PERFORMANCE EVALUATION OF THE ATELLICA CH CARBAMAZEPINE, THEOPHYLLINE, AND VANCOMYCIN ASSAYS*

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Background: The purpose of the investigation was to evaluate the analytical performance of the Atellica™ CH Carbamazepine (Carb), Theophylline (Theo), and Vancomycin (Vanc) Assays on the Atellica™ CH Analyzer**. The assays are based on a homogeneous particle-enhanced turbidimetric inhibition immunoassay (PETINIA) technique that uses a synthetic particle conjugate and analyte-specific antibody. Analyte present in the sample competes with analyte on the particles for available antibody, thereby decreasing the rate of aggregation. The rate of aggregation is measured using bichromatic turbidimetric readings at 545 nm and 694 nm.
Methods: Performance testing included precision and method comparison. Assay precision was evaluated using Clinical and Laboratory Standards Institute (CLSI) guideline EP05-A3. Each sample was assayed in duplicate twice a day for 20 days. Method comparison studies were conducted according to CLSI EP09-A3, with Deming regression of patient sample results compared with results from the Dimension® RxL Integrated Chemistry System.
Results: For Carb, within-lab precision ranged from 1.2 to 2.4% CV. For Theo, within-lab precision ranged from 2.0 to 2.2% CV. For Vanc, within-lab precision ranged from 1.8 to 2.7% CV.
The Carb method comparison study yielded a regression equation of y = 0.98x – 0.06 μg/mL, with r of 0.998, versus the CRBM assay on the Dimension RxL system. The Theo method comparison study yielded a regression equation of y = 0.97x + 0.1 μg/mL, with r of 0.993, versus the THEO assay on the Dimension RxL system. The Vanc method comparison study yielded a regression equation of y = 1.04x – 1.04 μg/mL, with r of 0.997, versus the VANC assay on the Dimension RxL system.
Conclusions: The Atellica CH Carbamazepine, Theophylline, and Vancomycin Assays tested on the Atellica CH Analyzer demonstrated acceptable precision. Method comparison results showed acceptable agreement with an on-market comparative analyzer.
*Under development. Not available for sale.
**The products/features (here mentioned) are not CE marked and are not commercially available. Due to regulatory reasons their future availability cannot be guaranteed. Please contact your local Siemens organization for further details.

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Toxicology - Therapeutic Drug Monitoring

Cod: W318

ANTI-VIRAL AND ANTIRETROVIRAL DRUGS ASSAYS: RESULTS OF A FIVE YEARS EXTERNAL QUALITY ASSESSMENT SCHEMES (EQAS)

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BACKGROUND
The development of HIV treatment combining various drugs has emphasised the necessity for serum drug determination in therapeutic drug monitoring (TDM) of anti-viral and antiretroviral drugs. The need for inter-laboratory external quality assessment survey has been first raised by the members of the pharmacology group of the French Research Agency against AIDS (ANRS) to meet ISO 15189 requirements. ASQUALAB, as an organiser of EQAS surveys in the field of TDM, has been in charge of the development, design and organisation of this survey.
The aim of this survey is to evaluate the reliability of the results provided by the laboratories and the performance of the method used as well. This exercise is intended to lead to the improvement of the analytical methods used and to facilitate the development of standard methods.
METHODS
Human serum pool was spiked with the 17 antiretroviral drugs actually used: abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, etravirine, lamivudine, lopinavir, maraviroc, nevirapine, raltegravir, rilpivirine, ritonavir, tenofovir and 6 antiviral drugs: acyclovir, daclatasvir, ganciclovir, ledipasvir, ribavirin, sofosbuvir, then lyophilised. Eight samples were shipped to 34 laboratories for the 4 surveys of the year; each of them included 2 different samples.
RESULTS
- The number of participants was depending on the molecule under investigation from 6 to 26 laboratories.
- Most of the participants (90%) used liquid chromatography tandem mass spectrometry methods.
- The inter-laboratory mean observed calculated according to ISO 13528 is quite similar to the value corresponding to the weighted molecule.
- Inter-laboratory variations expressed as coefficients of variation, for molecules with at least 20 participants, range from 8 to 19%, and are less than 13% for 80% of the molecules.
- More than 80% of the results provided by the participants are lying within the acceptable limits defined as biases of the mean value (+/-20% for the lowest level and +/-15% for the highest level), depending on the molecule.
CONCLUSION
The spiked concentrations were chosen to include both the therapeutic range of the anti-HIV and antiviral drugs and the lowest concentrations found in pharmacokinetics studies. This is a useful tool for increasing inter-laboratory consistency of the results and consequently to improve TDM efficacy in this field.