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CONFERENCE REPORT

Ghent Symposium on Alternative Sampling Strategies in Toxicology and Therapeutic Drug Monitoring

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Satellite Symposium on Alternative Sampling Strategies in Toxicology and Therapeutic Drug Monitoring under auspices of the International Association on Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT), 18-19 September 2014 in Ghent, Belgium.

Keywords: alternative sampling strategies, biological fluids, toxicology, therapeutic drug monitoring.

The IATDMCT Satellite Symposium on Alternative Sampling Strategies in Toxicology and Therapeutic Drug Monitoring was held in September 2014 at "Het Pand" in Ghent, Belgium. The theme of the 2-days meeting under auspices of IATDMCT was a mixed serving of alternative sampling strategies & alternative samples including micro samples (e.g. dried blood spots), hair, nails, oral fluid,and meconium. The agenda comprised advanced and relevant research topics in the key areas of alternative microsampling of biological fluids and tissue for bioanalysis and drug analysis. The congress provided a perfect platform for networking and the development of professional linking to participants and vendors offering instrumentation in this field of science. The meeting was an initiative from Prof. dr. Christophe Stove, Laboratory of Toxicology, Faculty of Pharmaceutical Sciences from Ghent University, Belgium under auspices of the IATDMCT. The event was structured as 2 days of oral presentations and poster sessions. The meeting received 180 delegates representing about twenty different countries. The meeting was held in the Culture and Convention Center of Ghent University called "Het Pand". This Culture and Convention Center is a former Dominican Monastery, located in the center of Ghent near the medieval port at the banks of the river Leie. The oldest parts of this impressive medieval building date from around the 13th century. The purpose of this article is an attempt to summarize the key highlights of this symposium and the key topics/discussions. The symposium program consisted of in total 36 oral lectures and 18 poster presentations. The scientific program of this symposium was divided into two separate parts, each part being the main scientific subjects presented on one of the two days.

The scientific subjects covered during the oral lectures presented on Day 1, Thursday September 18th were:
- *Micro sampling: automation and applications*
- *Keratinized matrices: nails and hair*
- *Micro sampling: new developments*
- *Micro sampling: EBF perspective and applications*

On the second Day, September 19th, the scientific focuses of the oral lectures were:
- *Oral fluid*
- *Breath, meconium and interstitial fluid*
- *Micro sampling: clinical applications of dried blood spots.*

■ Day 1 (18 September, 2014)

The first day started with the official welcome of the attendees and opening of the symposium by Prof. dr. Christophe Stove (Ghent University, Belgium). He explained the audience about the idea behind the symposium. He told that in the last years he had visited

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many specialized congresses but could not attend a congress that joined so many fields applying alternative sampling techniques as this symposium did. Bringing scientists from fields like toxicology, pharmaceutical analysis, clinical chemistry and others from academia, the industry and governmental institutions was the key idea to organize this multidisciplinary symposium. Attendees represented countries like Iceland, Brazil, Colombia, Australia, USA, UK, France, Spain, Portugal, Uzbekistan, Italy, Sweden, Norway, New Zealand and Greece.

The early morning session of talks focused on microsampling, automation and applications. The first plenary session was opened by **Jack Henion** from Quintiles (Bioanalytical and ADME Labs, USA). Jack Henion gave an overview of automated dried blood spots (DBS) elution robotic systems which are commercially available at the moment. Furthermore, he demonstrated a commercial filtration membrane device for rapid and accurately preparation of plasma from whole blood (Shimadzu, Novilytic). Furthermore, other techniques for a rapid analysis of organic compounds and purification were demonstrated. These included the application of TLC-MS for the measurement of the purity of commercial cannabis and the use and analytical power of atmospheric surface analysis to determine for example pesticides on fruit which could be done in seconds.

After the keynote lecture, several presentations on the use of DBS for different applications were presented by different speakers. **Stefan Mauch** (Hamilton Bonaduz AG, Switzerland) demonstrated that typical commercially available DBS cards are difficult to use in automated DBS-systems due to the quality of the DBS cards and the sampling of these cards by taking an aliquot from the dried spot. He introduced the audience to a new DBS card punching system and showed its robustness by presenting data obtained using this system for the validation of a DBS-based method for the drug Simvastin.

The third talk prior to the coffee break was by **Roland J.W. Meesters** (Universidad de los Andes, Colombia) who demonstrated the feasibility of the combination of high resolution mass spectrometry in combination with micro sampling techniques of blood and plasma in a pharmacokinetic study using acetaminophen as model drug. The presented data showed that the use of liquid plasma, dried blood spots and dried matrix on paper disks gave PK parameters that all were not significantly different for each micro sampling technique and the future power of micro sampling techniques in PK studies [1-3].

The second morning session contained different presentations on keratinized matrices, such as nails and hair.

The first speaker after the coffee break was **Markus Baumgartner** (Zürich Institute of Forensic Medicine, Switzerland) who gave a short overview of alternative sampling matrices and their limitation in bioassays. He demonstrated the use of nail sampling and backgrounds. A case study report was shown where a person died from an acute toxic dose of cocaine and where it was impossible to collect hair samples for drug testing since this person had bleached her hair. Collection of nail samples and analysis using different collection techniques (clipping, scraping and removal of complete nail) were compared and positive identification of the drug was confirmed in all three collection techniques.

The next talk was by **Bjorn Moosmann** (Institute of Forensic Medicine Freiburg, Germany) about finding cannabinoids in children's hair and the meaning of the positive identifications. He demonstrated data from 41 hair samples from children and 35 samples of drug consuming parents that were analyzed for cannabinoids and some of their metabolites. In all samples except one the THC-acid concentrations were higher than the THC concentrations and in 14 cases no THC could be identified despite the presence of THC-acid. From the findings he concluded that the major part of the positive cannabinoid identifications in children's hair had to come from a passive transfer of contaminated fingers or surfaces and not from inhalation or disposition from side stream smoking.

Eva Cuypers (Katholic University Leuven, Belgium) presented the application of Imaging Mass Spectroscopy for spatial distribution of drugs in hair samples. Using this technique it will become easier to obtain information about drugs inside the hair and also on external contamination and drug users. Furthermore it was demonstrated that using this technique it was possible to see the influence of decontamination solvents used for hair samples on the spatial distribution of the drug in the hair.

Pieter de Kesel (Ghent University, Belgium) talked about the correlation of paraxanthine/caffeine concentration ratios and their correlation in hair and plasma samples for *in-vivo* CYP1A2 phenotyping. A study in humans revealed that there was an overall significant correlation between paraxanthine/caffeine concentration ratios in hair and plasma. However, larger deviations between hair and plasma ratios in individual cases impede interpretation at the level of the individual.

The following two talks were about the measurement of ethylglucuronide in hair samples as indicator of chronic alcohol abuse. **Daniela Sorio** (University of Verona, Italy) introduced a sample and quick hair treatment protocol for the analysis of ethylglucuronide that worked quite well and presented the same sensitivity

using GC-NCI-MS as reported LC-MS/MS methods. The protocol was successfully applied for hair analysis of alcohol abstinent patients waiting for liver transplantations and undergoing alcohol withdrawal therapy [4].

The second talk on this subject was by **Jennifer Pascali** (dtoLABS, Italy) and she showed the use of GC-EI-MS/MS after extraction and derivatization of the ethylglucuronide by MSTFA. The method developed was completely validated and applied on hair samples collected from human subjects with knowing drinking habits and CDT values. In few samples ethylglucuronide could be quantified, concentrations ranged from <LLOQ to 39 pg/mg [5-7].

The third session on this day focused on new developments in micro sampling. After the lunch break and poster presentations **Neil Spooner** (GSK, United Kingdom) gave a keynote lecture on micro sampling for quantitative drug analysis and its latest developments. Neil Spooner presented a wide variety of micro sampling techniques used nowadays for quantitative bioanalysis. He demonstrated techniques that are applied for the micro collection of liquid blood and plasma as well dried blood and plasma samples. He gave a quite impressive overview about the process simplicity of the micro sample collection as well as the potential pitfalls scientists encounter during sampling, processing of the samples and analysis of the collected samples. Not only mainly manual based micro sampling techniques were covered during this talk, also automated as well as new developments and recent newly introduced instrumentation and techniques were presented. The keynote lecture was closed with potential future solutions in this rapidly evolving area of sample collection in life sciences.

The second lecture was presented by **Sara Capiau** (Ghent University, Belgium) who showed that the application of a potassium-based algorithm allows to correct dried blood spot samples for their difference in hematocrit value. Caffeine and paraxanthine were used as model compounds. Before correction of hematocrit differences between dried blood spots and whole blood concentrations ranged between approx. -30% to +20% with a mean difference of +6.6 % and after correction for hematocrit applying the potassium based algorithm the differences between the concentrations of caffeine and paraxanthine between dried blood spot and whole blood were reduced to approx. -20 and +19% with a mean difference of -3% [8].

Jeroen den Burger (VU Medisch Centrum, the Netherlands) presented another application of a potassium-based correction of analyte concentrations in dried blood spots. He demonstrated that potassium-based correction of the observed creatinine concentration in dried blood spots improved the agreement between creatinine concentrations measured in dried blood spots and in venous blood samples. He demonstrated preliminary data on the method validations and concluded that potassium as well as creatinine concentrations using this approach were within accepted accuracy and precision guidelines[8].

A major drawback in micro sampling techniques is the correct sampling of small volumes. **Gabriel Lenk** (KTH Royal Institute of Technology, Sweden) presented a newly developed chip which could produce defined dried blood spot samples directly form a finger prick. He did a study with 16 of these chips and demonstrated that the relative standard deviation of the chips when collecting blood was below 10% (8.8%). The chips were tested by applying blood spiked with amphetamine and he found that there was now an expected correlation between the initially applied volume of applied blood and the metered blood volume. He concluded that the application of this type of chip could solve some of the important problems connected to dried blood spot sampling such as unknown volume and the hematocrit effect [9].

The next speaker **James Rudge** (Phenomenex, United Kingdom) introduced the audience to a new micro sampling device as a potential alternative to DBS and pre-cutted DBS sampling. This device can be used for volumetrically precise blood sample collection. The novel device contains a porous hydrophilic "tip" with a controlled porous volume of 10 µL. When the tip is touched to any aqueous fluid the tip rapidly absorbs the fluid into its internal volume through capillary action. He demonstrated validation data and presented the applicability of this novel device using drug-spiked whole blood. The drugs were quantitated by LC-MS/MS analysis. This novel device demonstrated a bias due to the hematocrit effect of less than 15% and the stability of selected drugs over 14 days storage were <20% assay bias.

The last speaker of this midday session was **Bert Ooms** (Spark Holland, the Netherlands). He presented recent results from an assay which was developed for the quantitative analysis of immune suppressant drugs (Tacrolimus, Sirolimus, Everolimus and Cyclosporine A), using a full-DBS spot assay. The instrumentation applied in this assay was developed by the company and uses flow-through desorption with the possibility of increasing desorption of drugs from the blood matrix by heating. It was demonstrated that a significant improvement of drug recoveries could be obtained by application of heated flow-through desorption. Elevated recovery rates were observed even when a hematocrit range between 0.25 and 0.65 L/L were used [10, 11].

The last session of the first symposium day focused on micro sampling, the EBF perspective on it and ap-

plications. After the coffee break, **Philip Timmermans** (Janssen R&D, Belgium) presented on behalf of the European Bioanalysis Forum (EBF) an update on the present view and activities of the EBF on DBS applications in drug development. The EBF supports since 2008 the implementation of DBS in drug development and has carried out many studies to evaluate the potential of DBS as alternative or complementary blood sampling technique in drug development studies. These studies led in 2012 to a recommendation of the EBF on DBS. Philip presented an overview of the obtained results and recommendations given, based on the results of the studies that had been performed. In the second part of the talk he informed the audience that the EBF turned its activities away from DBS, recently. The EBF moved its focus from DBS to liquid micro sampling (LMS). Nevertheless, a better insight in the challenges of sampling and the analysis of very small samples is still needed at the moment. He presented the (future) experimental activities of the EBF on LMS and moreover how EBF intends to engage the bioanalytical community for input on liquid micro sampling as well to share obtained results, which could be part of a next recommendation of the EBF on LMS. This recommendation could be expected in 2015 [11-16].

The next lecture was given by **Wolfgang Weinmann** (Institute of Forensic Medicine, Switzerland) who talked about the potential of analysis of Phosphatidylethanol (Peth) in blood and DBS samples for alcohol abstinence testing. He presented a novel analysis method based on LC-MS/MS analysis using a D5-deuterated analogue of Peth. Results from a comparison study of data obtained from whole blood and DBS using volunteers were represented. Comparable concentrations were observed. The presenter stressed that the collection of capillary blood had the advantage that is was less invasive than venous blood and that it could be used for stabilizing Peth after sample collection. Micro sampling thus could avoid the pre-analytical generation of Peth due to the presence of alcohol in the blood samples.

Another approach for the follow-up of alcohol abuse was presented by **Franco Tagliaro** (University of Verona, Italy). He presented the application of a combined DBS and capillary electrophoresis analysis of carbohydrate deficient transferrin, a group of minor glycoforms of the protein transferrin. A reduced glycosylation degree and increased concentration is observed in serum from patients after chronic and sustained alcohol intake for several days. Blood samples were collected by fingerpick and venous blood collection in a group of 70 subjects. Sera and DBS samples were treated and extracts were analyzed by CE and HPLC. Significant correlation between results from DBS and sera and CE and HPLC analysis were shown [17-19].

The session of presentations on this first day was closed by a presentation of **Nele Sadones** (Ghent University, Belgium). She demonstrated a new, simple and rapid PCR method, directly starting from 0.5 mm DBS punches, allowing haptoglobin genotyping in a high throughput way. This new method avoided the time-consuming and expensive DNA extraction from samples and, in contrast to conventional methods, only requires a small amount of biological sample, reducing the contamination risk. Furthermore, due to use of DBS the patient could self-sample his blood [20-22]. The first symposium day was closed by a networking reception and poster presentation and dinner. After the dinner a sightseeing trip of the beautiful city of Ghent by boat was done by many of the symposium attendees.

■ Day 2 (19 September, 2014)

The morning session of day 2 had a focus on application of oral fluids in bioanalytical assays. The second day of the symposium was opened by **Marilyn Huestis** (National Institute on Drug Abuse, USA). She gave an impressive keynote lecture on the use of oral fluid in drugs of abuse testing. She demonstrated the potential and advantages of oral fluid testing in the forensic drug testing environment. Data showed that oral fluid offered a shorter drug detection window, with concentrations that were closer to blood than in urine. Furthermore, oral fluid offered a non-invasive and directly observable sample collection possibility. This resulted in a lower adulteration potential and eliminated the need for gender-appropriate sample collectors and phlebotomists. It was clearly shown that oral fluid has found its niche in drug testing.

The second talk of the morning session was given by **Sarah Wille** (NICC, Belgium). She presented a second talk on oral fluid and its applications in the oral fluid session. She informed the audience about the use of oral fluid by the Belgium national institute of criminalistics and criminology. She explained that the use of oral fluid as confirmation was less accepted and also has its limitations, however in specific settings oral fluid use could be of advantage compared to conventional biological matrices. Caution has to be taken since oral fluid concentrations of drugs depend on the collection device used and on the variability between and within collection devices. Furthermore, results of the Belgian DUID legislation were presented, demonstrating the usefulness of oral fluid as a valuable tool for reducing car accident risks.

The third presentation on oral fluid testing was given by **Stefan Steinmeyer** (Dräger Safety AG und Co.

KGaA, Germany). He demonstrated that one should be cautious when artificial oral fluid is used to asses analytical performance of oral fluid based drug screening devices. He concluded that even when physico-chemical factors such as viscosity, pH value etc. of artificial oral fluid were aligned, drug testing instrumentation performed different than with natural oral fluid. Therefore, proper validations could only be done with natural oral fluid to obtain a realistic validation of the drug testing instrumentation. Obviously, he explained that there is a need to develop a standardized performance protocol using real oral fluid specimens for evaluation screening of devices.

The variation of drug concentrations in oral fluid collected by different collection devices was also confirmed by the presentation of **Line Coucke** (Ghent University, Belgium). She showed data about a study with 12 subjects having an oral intake of codeine phosphate. Post-dose blood samples and oral fluid were taken by using two different oral fluid collection devices. Data showed that oral fluid data correlated better with plasma data using a certain type of oral fluid collection device than with the second device.

Micheal Böttcher (MVZ Labor Dessay, Germany) presented the screening of 6-acetylmorphine in oral fluid samples using LC-MS/MS in comparison to analysis with a new immunoassay. The study was done in more than 4000 subjects addicted to opiates and they showed that in 12 % of the samples at least one opiate could be detected, of which 6-AM was detected in 80 % of the samples. When the positive samples were analyzed by a 6-AM immunoassay 76% of the samples were positive. It was shown that cross- reactivity of morphine in the immunoassay was responsible for 0.1%, which could be of importance in case of morphine oral contamination. The use of oral fluid had advantages over conventional urine testing for recent heroin use and the good agreement between both methods allowed the use of an immunoassay for screening.

The last presentation of the specialized morning session on oral fluid sampling and applications was closed by **Shanlin Fu** (University of Technology Sydney, Australia). Shanlin demonstrated the impact of collection devices on concentrations of THC. He demonstrated that THC tends to bind to surfaces of plastic collection devices, leading to poor recoveries. He showed that the use of a detergent Triton X-100 could improve recovery rates significantly (>97%). Furthermore, he demonstrated that autoxidation rather than microbiological degradation also played a role in the loss of THC in oral fluid specimens, besides adsorption effects.

The second session of this symposium day had a focus on the alternative matrices breath, meconium and interstitial fluid. After the coffee break **Olof Beck** (Karolinska Institute, Sweden) opened the session with a keynote lecture on the potential use of exhaled breath for toxicological investigations. He demonstrated that common drugs can be detected in exhaled breath following intake. The drugs are transported through the respiratory system and end up in aerosol micro-particles which are normally created during breathing. Olof gave a review of the field of drug testing in exhaled breath but also showed a present study aimed to further explore, develop and validate exhaled breath as safe and effective non-invasive method for drug testing in a clinical setting. He closed the keynote lecture with the conclusion that testing of illicit drugs with exhaled breath testing technique is a promising, non-invasive alternative and complementary method to plasma and urine testing.

The second talk of this session was given by **Elena Lendoiro** (University of Santiago de Compostela, Spain). She showed data on a developed LC-MS/MS method which was successfully validated for the analysis of THC and its metabolites in meconium samples. The analysis of meconium was used to identify the in utero exposure to cannabis and assess the effects over the pregnancy and the neonate. It was shown that from 55 collected samples 3 samples were positively identified for cannabinoids, showing the potential applicability of this sample matrix for drug testing purposes.

Another application of meconium was presented by **Birgit Koch** (ErasmusMC, the Netherlands). She showed how meconium in a hospital setting could be used for studies determining the relationship between developing fetal alcohol syndrome or disorder and prenatal alcohol exposure. The alcohol exposure was determined by the analysis of fatty acid ethyl esters in the meconium samples and data showed that fatty acid ethyl esters above 4 nmol/mg were considered positive and could be linked to FASD prevalence. This approach was implemented in standard care in the local children's hospital and the screening is currently expanded to amphetamines and cocaine.

The last talk of this session was given by **Felix Comeau** (Alcohol Countermeasure Systems Corp., Canada). He presented an instrumentation for non-invasive alcohol detection using wavelength-modulated differential photo thermal radiometry. The results presented showed that the instrumentation could be optimized for measuring minute absorption of low concentrations of alcohol in strongly absorbing fluid like water and blood with the combination of sensitivity tuning parameters. He showed that the developed instrumentation demonstrated a potential to be used as a portable alcohol interlock sensor that could be fitted as a universal accessory in vehicles

[23].

The last session of the second and last day of this symposium focused on application of micro sampling of DBS in clinical applications. After the lunch break and the poster session **Jan-Willem Alffenaar** (University Medical Center Groningen, the Netherlands) opened the last presentation session of this symposium with a keynote lecture on personalized medicine. His keynote lecture showed the promises and challenges of DBS analysis in daily routine in a clinical setting. During clinical validations DBS results are compared with results from conventional venous blood collection. Important factors that have to be taken into account were hematocrit, spot size, paper type and partial or whole spot analysis. Furthermore education and guidance of both clinicians and patients are necessary during and after implementation of DBS for clinical purposes.

The next presentation was given by **Rafael Linden** (Universidade Feevale, Brazil). He showed preliminary data on the development and validation of a new bioanalytical assay. The aim of the assay was to determine tamoxifen and its metabolites in DBS using LC-MS/MS. A complementary validation of hematocrit effect, and long term stability and the correlation of DBS concentrations with plasma was still ongoing at the moment of his presentation.

The next speaker, **Lisbeth Patteet** (University of Antwerp, Belgium) introduced the audience to a multi-drug assay applying DBS samples and analysis by UP-LC-MS/MS. Lisbeth showed data on the validation of an assay that could analyze 15 antipsychotic drugs and 7 metabolites. DBS samples were prepared by 25 μL of blood and the method showed to be a reliable alternative for quantification of all antipsychotic drugs, except for olanzapine and its metabolite N-desmethylolanzapine.

The next presentation was given by **Valérie Thibert** (Thermo Scientific, France). Valérie showed data of an LC-MS/MS method for the analysis of 14 antidepressant drugs from DBS samples. The developed method performed well and the use of an on-line sample clean-up of the matrix resulting from DBS collection reduced the complexity of the LC-MS/MS workflow.

The last presentation of this symposium on applications of DBS in a clinical setting was given by **Camilla Linder** (Karolinska Institute, Sweden). She showed data obtained from a comparison study on antiepileptic drugs between DBS and plasma samples collected from children treated with these drugs. The results suggested that with proper conversion factors it could be possible in the near future to measure concentrations of these drugs in blood collected on filter paper, using the traditional plasma sampling therapeutic intervals.

After this last presentation the symposium was closed by **Prof. dr. Christophe Stove** by the announcement of best oral presentations and poster presentations. The price for best oral presentation during this symposium was presented to Eva Cuypers, while the best oral presentation for PhD students was awarded to Lisbeth Patteet. The best poster presentation was awarded to Roland JW Meesters, for his poster "Metabolomic Studies Applying Micro-sampling of Biological Fluids and Analysis by Gas Chromatography-Mass Spectrometry", while the best poster presentation for PhD students was given to Elizabeth Berm, for her poster "Critical time to dry a blood spot before analyzing a dried blood spot with LC-MS/MS".

Summary

The first symposium on alternative sampling strategies in toxicology and therapeutic drug monitoring under auspices of the IATDMCT demonstrated the interest and potential of alternative sampling strategies in toxicology and TDM. The theme, agenda and key note lectures attracted 180 attendees from different disciplines from academia and industry. Growing interest in alternative sampling strategies was evident, and attendees benefitted from the varied topics presented during these two days. This two-day symposium provided a vital opportunity for participants to learn, exchange, discuss views and experiences, as well as to network with the local and global scientists. The symposium is considered as a premier symposium on the field of alternative sampling strategies and will hopefully be followed by a second symposium on alternative sampling strategies in toxicology and therapeutic drug monitoring.

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