

## POSTERS

27 JUNE, MONDAY

## RESPIRATORY DISEASES

## P1

## MULTIVARIATE PATIENT SIMULATION FOR CLINICAL TRIAL OPTIMIZATION IN COPD

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**Objectives:** Clinical Trial Simulation (CTS) can be a valuable tool to improve drug development [1]. However, in order to obtain realistic simulation scenarios, the patients included in the CTS process must be representative of the target population. This is particularly important when covariate effects exist that may affect the outcome of a trial. The objective of this exercise is to evaluate the performance of different methods to simulate demographic covariates of patients for a Chronic Obstructive Pulmonary Disease (COPD) trial.

**Methods:** Virtual patients with varying demographic characteristics were simulated by re-sampling with replacement, sampling from a univariate distribution and sampling from a multivariate distribution. Simulations of continuous and categorical covariates were performed in R according to the method described by Tannenbaum et al. [2]. A KPD model was used to generate FEV1 responses in the COPD trials and results compared with the data from a real patient population.

**Results:** Covariate simulation using a multivariate distribution allows covariate correlations to be characterised using an empirical distribution. Moreover using the multivariate distribution is also possible to simulate new populations stratifying for specific covariates of interest.

**Conclusions:** Multivariate distribution methods may be applied to continuous and categorical covariates. This procedure is valuable for the optimisation of the design of clinical studies in which covariate effects are known to influence treatment outcome (pharmacokinetics or pharmacodynamics).

**References:**

1. Girard P. (2005) Clinical Trial Simulation: A Tool for Understanding Study Failures and Preventing Them. *Basic & Clinical Pharmacology & Toxicology*. 96:228–234.

2. Tannenbaum et al. (2006) Simulation of Correlated Continuous and Categorical Variables using a Single Multivariate Distribution. *Journal of Pharmacokinetics and Pharmacodynamics*. 33 (6):773–794.

## P2

## THE COMBINED EFFECT OF DIAZEPAM AND VERAPAMIL ON TRACHEAL RESPONSE CAUSED BY ACETYLCHOLINE AND HISTAMINE IN GUINEA PIGS

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The goal of this *in vitro* study conducted upon experimental animals comprised assessment of the combined effect of diazepam and verapamil on the response of the smooth musculature of an isolated respiratory organ (trachea) of a guinea pig to histamine and acetylcholine. Thereby, local mechanisms of the smooth musculature were examined, and other neurohumoral influences were excluded. Guinea pigs of both genders, weighing between 500 and 700 g, were used in the experiment. The research involved a total of 10 guinea pigs that were euthanized, their tracheae being subsequently collected. The isolated organ samples were split into two groups (A and B). Acetylcholine, applied at concentrations between 1E-06 M and 1E-03 M, yielded a concentration-dependent smooth muscle contraction (slope:  $24.98 \pm 3.18$ ,  $r = 0.99$ ,  $P < 0.01$ ); pD2 = 4.73; EC50 =  $5.11 \pm 0.91$ . A 1-min incubation of the isolated organ by a combination of diazepam and verapamil (1E-05M) significantly decreased the acetylcholine-induced contraction (slope:  $22.1 \pm 8.3$ ;  $r = 0.99$ ,  $P < 0.01$ ); EC50 =  $3.660 \pm 0.19$ . Diazepam and verapamil brought about a substantial abatement of smooth muscle contraction in a concentration of 1E-04 M as well (slope:  $14.31 \pm 6.7$ ,  $r = 0.93$ ,  $P < 0.05$ ); EC50 =  $2.81 \pm 0.782$ . In concentrations between 1E-06 M and 1E-03 M, histamine evoked a concentration-dependent contraction of the guinea pigs' tracheal smooth muscle (slope:  $25.58 \pm 3.18$ ,  $r = 0.96$ ,  $P < 0.05$ ) pD2 = 4.5, which was blocked by a concentration of 1E-05 M of the diazepam-verapamil combination.

### P53 DOES PREGNANCY AFFECTS INTRAVENOUS PARACETAMOL DISPOSITION? A PAIRED ANALYSIS

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**Introduction:** As a part of the pharmacokinetic (PK) study on 2 g intravenous (iv) loading dose paracetamol in pregnant women, intra-subject (pregnant vs non-pregnant state) PK differences were investigated.

**Patients and Methods:** Following informed consent, a subgroup of six pregnant women who underwent a cesarean section and received a 2 g loading dose of iv paracetamol were admitted again for the same loading dose administration scheduled for at least 10 weeks after the pregnancy. At both visits, blood samples were collected at the same predetermined time points (1, 2, 4 and 6 h after drug administration). A one-compartmental linear PK model in a naïve pooled approach was used. Paired data were compared using nonparametric Wilcoxon signed-rank test. Clinical data were reported as median (range).

**Results:** Forty-eight plasma concentration-time points were collected in six women. Median (range) age was 32 (27–37), gestational age 38 (33–39) weeks, postpartum week 11.2 (10.7–15). When observations in pregnancy were compared to non-pregnant state, median (range) C<sub>max</sub> [23.06 (13.88–32.32) vs 64.5 (38.49–75.75) mg/l] were significantly lower during pregnancy ( $P = 0.0312$ ) while no difference was observed in C<sub>trough</sub> [4.08 (2.88–8.17) vs 5.73 (2.66–11.88) mg/l,  $P = 0.0625$ ]. Naïve pooled paracetamol half-lives were 1.99 vs. 2.13 h, clearances 28.73 vs. 21.20 l/h and distribution volumes 82.34 vs 65.26 l in pregnant vs non-pregnant state respectively.

**Conclusion:** Following an iv paracetamol loading dose, pharmacokinetic intra-individual differences between pregnant and non-pregnant state were in line with differences observed between pregnant women and healthy volunteers. These pharmacokinetic estimates might be of pharmacodynamic relevance.

### P54 MEDICATIONS WITH ANTICHOLINERGIC EFFECTS AND THEIR USE IN ELDERLY PATIENTS

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**Introduction:** Medications with anticholinergic effects may commonly cause unrecognised adverse drug reactions. Changes in pharmacokinetics of drugs and age-related decline in cholinergic neurotransmission, contribute to the increased sensitivity of older patients to anticholinergic effects. Therefore the aim of the present study was to evaluate the use of anticholinergic medications in elderly patients and to identify risk factors which increase the probability of prescription of such drugs.

**Methods:** The study was carried out on a sample of 1636 patients aged  $\geq 65$  years hospitalised in three municipal hospitals. The most important risk factors influencing the use of anticholinergic medications were identified using the binary logistic regression model.

**Results:** Hospitalisation led to a significant increase in the use of anticholinergic medications. Their occurrence at the time of hospital admission and discharge was 10.5% and 14.2%, respectively ( $P < 0.001$ ). A higher total number of prescribed drugs was found in the group of users compared to non-users, at both hospital admission ( $7.2 \pm 3.5$  vs.

$5.7 \pm 3.1$ ;  $P < 0.001$ ) and discharge ( $8.7 \pm 3.1$  vs.  $7.5 \pm 2.9$ ;  $P < 0.001$ ). Constipation, urinary incontinence and retention, immobilisation, gastroduodenal ulcer disease, depression, Parkinson's disease and epilepsy were found to be the most important risk factors for prescription of anticholinergic medications.

**Conclusion:** In patients with the presence of risk factors mentioned above, the active search for drugs with anticholinergic properties is necessary in order to reduce the patients' anticholinergic burden.

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### P55 PHARMACOKINETICS OF ZONIZAMIDE IN NEONATAL PERIOD AND DURING LACTATION

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**Introduction:** To investigate neonates capacity to eliminate zonisamide and the excretion to breast milk in women treated with zonisamide during pregnancy.

**Methods:** Zonisamide concentrations were measured by high-performance liquid chromatography (HPLC) in plasma and in breast milk in two women with epilepsy treated with zonisamide during pregnancy and in their offspring. Blood samples were obtained at delivery from the mother, the umbilical cord, and from the newborns on three occasions during 5 days after delivery and at breastfeeding. One of the patients was investigated both at delivery and during lactation, and one patient was studied at delivery only.

**Results:** The umbilical cord plasma/maternal plasma ratios of zonisamide were close to one. Plasma levels in the newborns declined rather slowly and at 72 h postpartum zonisamide plasma levels in the infants were approximately 65% of the cord plasma. The elimination half-life in the neonates was estimated to approximately 100 h. At sampling 9 days after delivery the milk/plasma concentration ratio was 0.8. The zonisamide plasma concentration in the infant was 10.1  $\mu\text{mol/l}$  (approximately 17% of the mother's plasma levels).

**Conclusions:** Our limited observations suggest free transfer of zonisamide over placenta and indicate a rather low capacity in the newborn to eliminate zonisamide. Transfer of zonisamide to breast milk is extensive. No adverse effects were observed in the infant.

### P56 A CASE REPORT OF RADIOIODINE TREATMENT OF HYPERTHYROIDISM IN EARLY PREGNANCY

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In March 2010, a pregnant woman visited our outpatient clinic, seeking advice about effect of radioiodine treatment on fetal development. At the time of visit, gynecologist estimated she was in 9th gestational week. In January 2010, she received I 131 (1 mCi) for hyperthyroidism, not knowing she was pregnant.

According to FDA classification of drugs in pregnancy, I 131 has X in all trimesters, and is contraindicated in pregnancy. Iodine is concentrated in fetal thyroid with greater affinity compared to mothers thyroid, the ability of fetal thyroid to concentrate iodine develops from 10th week of pregnancy and its administration during pregnancy may cause severe and potentially irreversible hypothyroidism in neonates. Pregnancy should be ruled out prior to its use, therefore pregnancy test before administration is advisable.

In this case, I 131 was administered in very early stage of pregnancy, but the question remains how long it could retain in the thyroid, the time of its elimination and the possibility of further exposition of embryo to radioactivity. The patient was warned of the potential hazard but encouraged to continue the pregnancy with additional consultation of nuclear medicine specialist for the further evaluation of the uptake of radioiodine

**P238**  
**DRUG INTERACTION BETWEEN LAMOTRIGINE AND VALPROIC ACID USED AT DELIVERY AND DURING LACTATION – A CASE REPORT**

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**Introduction:** Lamotrigine and valproic acid have become two of the three major drugs using in the treatment of pregnant women with epilepsy. Concomitant administration of valproic acid significantly decreases lamotrigine clearance at delivery by about 65%. Regular therapeutic drug monitoring of antiepileptic drugs during pregnancy and postpartum is recommend. In our case report we show a woman treated by combination of lamotrigine and valproic acid at delivery and during first postnatal month. We analyzed maternal clearance, transport through the placenta and to maternal milk and exposure in breastfed infant of both antiepileptic drugs.

**Methods:** The patient was treated with combination of lamotrigine and valproic acid. Milk and blood samples from the mother and her breastfed infant were collected at delivery and during first postnatal month. Maternal serum levels were used for the estimation of apparent oral clearance. Paired milk and maternal, infant and maternal and infant and milk concentrations were used for estimation of the ratios. Valproic acid concentrations were measured by gas chromatography and lamotrigine concentrations by high-performance liquid chromatography.

**Results:** The infant lamotrigine concentration (13.6 mg/l) was found at delivery equal to the maternal (12.3 mg/l). The infant valproic acid concentration (43.4 mg/l) was measured at delivery by about approximately 40% higher than in the mother (31.7 mg/l). Four days after delivery was found the infant lamotrigine concentration (12.7 mg/l) similar to maternal (11.7 mg/l) and the infant valproic acid concentration (13.5 mg/l) as third compared to maternal (37.8 mg/l). After that were measured the infant lamotrigine concentrations (6.7–6.9 mg/l) approximately half of the maternal levels (14.0–15.2 mg/l), the infant valproic acid levels were under detectable limit. The milk/maternal serum concentration ratios ranged between 0.59–0.78 for lamotrigine, the milk valproic acid concentrations were under detectable limit for all the time. Maternal lamotrigine and valproic acid clearances were similar all the time.

**Conclusion:** In our case report we showed interaction between lamotrigine and valproic acid. Main reasons of relatively high breastfed infant lamotrigine concentrations are treatment by high maternal lamotrigine dose in connection with inhibition effect of valproic acid, transport to maternal milk and immature metabolizing pathway of breastfed infant. Therapeutic monitoring of infant lamotrigine concentrations appears to be the most relevant method for analysis of lamotrigine exposure in breastfed infants.

**P239**  
**SERUM LEVELS OF LAMOTRIGINE IN BREASTFEEDING MOTHERS, MATERNAL MILK AND NURSED INFANTS**

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**Introduction:** The clearance of lamotrigine quickly returns close to pre-pregnancy levels in the first 1–2 weeks after delivery leading to symptoms of toxicity in women whose dose has been increased during pregnancy. Therefore frequent lamotrigine level monitoring is necessary not only during pregnancy but also after delivery. Lamotrigine excretion into breast milk was reported, however the data on the lamotrigine transfer into breast milk and the risk of exposure to the breastfed infants remain sparse and only a limited number of studies have actually measured infant blood levels. In our study we followed up lamotrigine transport from breastfeeding mothers to the maternal milk and their breastfed infants and analyzed maternal lamotrigine clearance in monotherapy 6–10 days after delivery in comparison with the time of delivery.

**Methods:** Maternal, infant and milk concentrations were analyzed 6–10 days after delivery in a cohort of 21 women between the years 2001–2009. The request forms for routine therapeutic drug monitoring were used as the data source. Maternal concentrations were used for the estimation of apparent oral clearance. Paired milk and maternal and paired infant and maternal concentrations were used for the estimation of the milk/maternal serum and the infant/maternal serum concentration ratios. Paired values of maternal clearance were used for the estimation of changes in lamotrigine clearance between the time of delivery and approximately 1 week after delivery. Lamotrigine concentrations were measured by high-performance liquid chromatography. Statistical tests were performed using GraphPad Prism version 5.00 for Windows.

**Results:** The lamotrigine concentrations varied from 1.1 to 12.6 mg/l in the maternal serum, from 0.0 to 3.8 mg/l in the infant serum and between 0.4 and 4.5 mg/l in the milk. The milk/maternal serum concentration ratios ranged from 0.21 to 0.74 and the infant/maternal serum concentration ratios from 0.00 to 0.74. Highly significant correlations were found between the milk and the maternal serum levels, the infant and the maternal serum levels and the infant serum and the milk lamotrigine levels. Values of the infant/maternal serum concentration ratios were calculated significantly lower than values of the milk/maternal serum concentration ratios. Significant correlation was not found between the infant/maternal serum concentration ratios and the milk/maternal serum concentration ratios. Maternal lamotrigine clearance decreased by about 33% after delivery.

**Conclusions:** Our data showed the interindividual variability of the infant/maternal serum lamotrigine concentration ratios caused probably by the different activity of the infant metabolizing enzymes UGT1A4 and 2B7 in conjunction with the interindividual variability in the milk/maternal serum concentration ratios. The potential adverse effects of lamotrigine should be associated with the higher concentrations in breastfed infants.

**P240**  
**MONITORING OF VALPROIC ACID CONCENTRATIONS IN BREASTFEEDING MOTHERS, MATERNAL MILK AND NURSED INFANTS**

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**Introduction:** Only carbamazepine and lamotrigine are prescribed during pregnancy more often than valproic acid. Regular therapeutic monitoring of valproic acid during pregnancy and postpartum is recommended but the data on the valproic acid transfer to the milk and the risk of exposure to the breastfed infants remain sparse and only a limited number of studies have actually measured the infant blood levels. In our study we followed up valproic acid transport from the breastfeeding mothers to the maternal milk and their breastfed infants and analyzed the influence of co-medication with enzyme-inducing antiepileptic drugs.

**Methods:** Maternal, infant and milk concentrations were analyzed 6–10 days after delivery in a cohort of 27 women between the years 1991–2009. The request forms for routine therapeutic drug monitoring were used as the data source. Paired milk and maternal, paired infant and maternal and paired infant and milk concentrations were used for estimation of the milk/maternal serum, the infant/maternal serum and the infant serum/milk concentration ratios. Valproic acid concentrations were measured by gas chromatography. Statistical tests were performed using GraphPad Prism version 5.00 for Windows.

**Results:** The valproic acid concentrations varied from 17.0 to 69.0 mg/l in the maternal serum, from 0.0 to 17.5 mg/l in the infant serum and between 0.0 and 32.8 mg/l in the milk. The milk/maternal serum concentration ratios ranged from 0.00 to 0.96, the infant/maternal serum concentration ratios from 0.00 to 0.61 and the infant serum/milk concentration ratios between 0.00 and 8.75. Any significant correlations were not found between the milk and the maternal serum concentrations, between the infant and the maternal serum concentrations and between the infant serum and the milk valproic acid concentrations. No significant differences of both maternal, milk and infant concentrations and all ratios were

observed between valproic acid monotherapy + non-enzyme-inducing antiepileptic drugs and valproic acid + enzyme-inducing antiepileptic drugs subgroups. Seventeen percent of values of the milk/maternal serum concentration ratios were found higher than reported maximal value 0.10.

**Conclusions:** Our data showed the interindividual variability of the infant/maternal serum valproic acid concentration ratios caused probably by the different activity of the infant metabolizing enzymes CYP2C9, CYP2C19 and UGT2B7 in conjunction with the interindividual variability in the milk/maternal serum concentration ratios. The potential adverse effects of valproic acid could be associated with the higher concentrations in breastfed infants.

## P242

### COMPARATIVE ASSESSMENT OF THE GROWTH CURVES IN EU AND US

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**Introduction:** Allometric scaling may be applied along with other physiologically based adjustments to predict paediatric pharmacokinetics using demographic variables such as weight and BMI. Validated growth curves from several EU countries are available including Germany, Italy, Spain, and Sweden. For modeling purposes it may be advantageous to have a centralized database that is relevant across the EU continent. The objective of this analysis is to compare available growth curves across EU countries to those of the CDC and the WHO databases.

**Methods:** Published growth curves from EU countries, CDC and WHO were used to extract the age-matched body weight (WT) and Body Mass Index (BMI) in boys and girls between the ages of 0 and 18 years. The WT was back calculated using the height and BMI if unavailable. The median values were compared across the following age groups where available:

**Infants and Toddlers (28 day to 23 months)**

**Children (2–11 years)**

**Adolescent (12–18 years)**

**Results:** The aged-matched median body weights across EU countries, WHO, and CDC scales appear comparable, especially when considering the associated variability demonstrated by the 5th and 95th percentile curves. The median values were within  $\pm 12\%$  of the CDC database. A trend of higher WT was observed in German and Italian boys relative to CDC. The maximum difference of 12% occurred at age 9.5 in Italian boys.

**Conclusion:** The current analysis suggests that the CDC database can be adequately used for allometric scaling modeling in EU submissions.

## P243

### MONITORING OF VALPROIC ACID CONCENTRATIONS DURING DELIVERY IN MOTHERS AND THEIR INFANTS

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**Introduction:** Valproic acid has become one of the three major drugs in the treatment of pregnant women with epilepsy and its regular therapeutic monitoring during pregnancy is recommended. Literature data about intrauterine growth retardation associated with the maternal use of valproic acid are controversial and relationship between valproic acid concentrations and birth weight (and length) has not been analyzed. In our study we followed up valproic acid transport through the placenta and demonstrated maternal and umbilical cord serum levels, its ratio, maternal clearance and influence of co-medication with enzyme-inductive antiepileptic drugs. We analyzed the relationship between birth weight (and length) and daily dose, dose related to the body weight, and maternal and infant valproic acid concentrations.

**Methods:** Maternal and umbilical cord serum levels were analyzed during delivery in a cohort of 56 women between the years 1991–2009. The request forms for routine therapeutic drug monitoring were used as the data source. Maternal concentrations were used for the estimation of apparent oral clearance and paired infant and maternal concentrations for estimation of the infant (umbilical cord)/maternal serum concentration ratios. Valproic acid concentrations were measured by gas chromatography. Statistical tests were performed using GraphPad Prism version 5.00 for Windows.

**Results:** The valproic acid concentrations varied from 5.3 to 59.5 mg/l in the maternal serum and between 5.4 and 72.1 mg/l in the umbilical cords serum. The infant/maternal serum concentration ratios ranged from 0.64 to 2.49 (mean 1.47). Concomitant medication with enzyme-inducers increased significantly clearance of valproic acid by about 40%. Highly significant correlations were found between maternal and umbilical cord valproic acid serum levels, both in monotherapy (and/or combination with lamotrigine) and in combination with enzyme-inducers. The infant/maternal valproic acid concentration ratios correlated inversely with the maternal valproic acid levels. Significant inversely correlations were found between birth weight and maternal valproic acid concentrations, and birth length and maternal and infant valproic acid concentrations.

**Conclusions:** Our data from the large cohort showed the interindividual variability of umbilical cord/maternal serum concentration ratios of valproic acid caused probably by the different activity of the placental metabolizing enzyme UGT2B7 and active transport system associated with genetic polymorphism. The potential teratogenic effect of valproic acid seems to be associated with the higher concentrations in the fetus but not with the maternal dose.

## P244

### SERUM LEVELS OF LAMOTRIGINE IN BREASTFEEDING MOTHERS, MATERNAL MILK AND NURSED INFANTS

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**Introduction:** The clearance of lamotrigine quickly returns close to pre-pregnancy levels in the first 1–2 weeks after delivery leading to symptoms of toxicity in women whose dose has been increased during pregnancy. Therefore frequent lamotrigine level monitoring is necessary not only during pregnancy but also after delivery. Lamotrigine excretion into breast milk was reported, however the data on the lamotrigine transfer into breast milk and the risk of exposure to the breastfed infants remain sparse and only a limited number of studies have actually measured infant blood levels. In our study we followed up lamotrigine transport from breastfeeding mothers to the maternal milk and their breastfed infants and analyzed maternal lamotrigine clearance in monotherapy 6–10 days after delivery in comparison with the time of delivery.

**Methods:** Maternal, infant and milk concentrations were analyzed 6–10 days after delivery in a cohort of 21 women between the years 2001–2009. The request forms for routine therapeutic drug monitoring were used as the data source. Maternal concentrations were used for the estimation of apparent oral clearance. Paired milk and maternal and paired infant and maternal concentrations were used for the estimation of the milk/maternal serum and the infant/maternal serum concentration ratios. Paired values of maternal clearance were used for the estimation of changes in lamotrigine clearance between the time of delivery and approximately 1 week after delivery. Lamotrigine concentrations were measured by high-performance liquid chromatography. Statistical tests were performed using GraphPad Prism version 5.00 for Windows.

**Results:** The lamotrigine concentrations varied from 1.1 to 12.6 mg/l in the maternal serum, from 0.0 to 3.8 mg/l in the infant serum and between 0.4 and 4.5 mg/l in the milk. The milk/maternal serum concentration ratios ranged from 0.21 to 0.74 and the infant/maternal serum concentration ratios from 0.00 to 0.74. Highly significant correlations were found between the milk and the maternal serum levels, the infant and the mater-

nal serum levels and the infant serum and the milk lamotrigine levels. Values of the infant/maternal serum concentration ratios were calculated significantly lower than values of the milk/maternal serum concentration ratios. Significant correlation was not found between the infant/maternal serum concentration ratios and the milk/maternal serum concentration ratios. Maternal lamotrigine clearance decreased by about 33% after delivery.

**Conclusions:** Our data showed the interindividual variability of the infant/maternal serum lamotrigine concentration ratios caused probably by the different activity of the infant metabolizing enzymes UGT1A4 and 2B7 in conjunction with the interindividual variability in the milk/maternal serum concentration ratios. The potential adverse effects of lamotrigine should be associated with the higher concentrations in breast-fed infants.