# Nicotine Metabolite Ratio in Smokers: A Real World Experience

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mofetil (Cellcept ®) 500 mg b.i.d. Blood levels of tacrolimus were 7.5 and 7.2 ng/mL on January 5th and 10th 2017, respectively. Mycophenolate blood levels fluctuated between 0.2 to 4.5 mg/L during January - February 2017.

Because of diarrhea caused by *Camphylobacter jejuni,* clarithromycin (Klacid®) was given in doses 500 mg b.i.d since January 12th 2017. To prevent elevation of tacrolimus level due to expected drug interaction, the dosage of tacrolimus was lowered to 1 mg b.i.d. Despite of this, the level of tacrolimus reached to 43.0 ng/mL on January 16th. Although the evening dose was excluded, the level remained 31.0 and 46.8 ng/mL, respectively before and after the morning dose on January 17th. The treatment with claritromycin was discontinued (on day 5th) and tacrolimus was temporally excluded. Tacrolimus levels in following days were: 23.4 (Jan 18th), 13.3 (Jan 19th) and 5.8 ng/mL (Jan 20th), respectively. Tacrolimus was added to therapy using following doses: 0.5 mg on Jan 20th and 1 mg b.i.d on Jan 21st and 22nd. On Jan 23rd the pre-dose tacrolimus level dropped to 3.8 ng/mL. As inhibitive effect of claritromycin disappeared, tacrolimus 1.5 mg b.i.d was given. Tacrolimus level of 5.1 ng/mL was found during routine control on Feb 9th.

Decline of tacrolimus level was simulated with the aid of MW-Pharm 3.30 software. As no population data were available in this version, the nitrazepam model was used successfully.

Tacrolimus model in the latest version of MW-Pharm 4.0 (1.3.5.558 version) was tested a posteriori but the model was not able to consider fluctuation of metabolism of tacrolimus due to drug interaction after the clarithromycin withdrawal.

## NICOTINE METABOLITE RATIO IN SMOKERS: A REAL WORLD EXPERIENCE

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**Background:** The ratio of two metabolites derived from nicotine smoking, 3'-hydroxycotinine (3HC) and cotinine (COT) (nicotine metabolite ratio, NMR), reflects the activity of the liver enzyme CYP2A6 and it has been shown to predict response to smoking cessation drugs in clinical trials. The aim of the present study is to facilitate translation of study findings in the real life clinical practice.

**Methods:** We carried out a clinical validation of a mass spectrometer-based method for measuring the NMR in both plasma and saliva samples obtained from 71 smokers attending the Smoking Cessation Centre of the University Hospital of Pisa. We also performed a real-time PCR analysis for fast genotyping of CYP2A6.

**Results:** The mean COT and 3HC concentrations in plasma were 260.3 and 80.2 ng/ml, respectively, whereas those in saliva were 298.3 and 137.3 ng/ml, respectively. Linear regression analyses showed a significant ($p<0.001$) relationship among metabolites levels measured in plasma and saliva with correlation coefficients ($r$) of 0.951 for COT, 0.841 for 3HC, and 0.694 for NMR. While the mean NMR values for slow metabolizers (NMR<0.31) were superimposable in plasma and saliva samples (i.e., 0.21±0.01), they differed in those smokers having a normal/fast metabolizer phenotype (0.39±0.01 and 0.48±0.02, respectively). The percentages of slow metabolizers were 42.8% in plasma and 22.4% in saliva samples. The specific CYP2A6*9 variant allele (c.-48T>G) in the CYP2A6 locus associated with decreased nicotine metabolism was identified in 36% of smokers, including heterozygous (30%) and homozygous (6%) genotypes.

**Conclusions:** These findings provide evidence that salivary NMR measures were comparable to plasma levels in a real-life setting. Nonetheless, the reliability of a saliva test for measuring the phenotype for nicotine metabolic status in individual smokers needs further investigation.

## PHARMACOKINETICS OF VALPROATE AND LAMOTRIGINE COMBINED THERAPY IN PREGNANCY AND ITS EFFECT ON THE NEWBORN – A CASE REPORT

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**Background:** In a previous paper we found that birth length and weight were inversely related to maternal and umbilical cord levels of valproate (VPA), but not to dose. In a case report we tried to determine, whether it is possible to use this data for prediction of fetal plasma concentrations during pregnancy.

**Methods:** A 30-year-old woman (59 kg prior to pregnancy) was treated by a combined therapy of VPA (Orfiril long®, 800 mg/day) and lamotrigine (Lamictal®, 200mg/day) for pseudoabsences. Plasma levels of both drugs were measured at steady-state before, during and after pregnancy and also during the delivery. Levels of VPA were measured by gas chromatography and levels of lamotrigine (LTG) by high performance liquid chromatography. Apparent oral clearance (Cl) was calculated for both drugs: daily dose (mg/kg)/serum concentration (mg/L).

**Results:** Drug levels before the pregnancy were 67.9 mg/L for VPA and 15.2 mg/L for LTG. By the time of delivery both levels have decreased to 32.2 mg/L for VPA and 6 mg/L for LTG in maternal serum. Values measured in umbilical cord were 41.6 mg/L (129% of maternal value) for VPA and 5.9 mg/L for LTG (100% of maternal value). Apparent oral clearance of VPA was increased by 171% (from 0.2 L/24 h to 0.54 L/24 h) and of LTG by 143% (from 0.22 L/24 h to 0.54 L/24 h) at the end of 3rd trimester. The birth length was 43 cm and weight 2.15 kg.

**Conclusions:** The low total values of LTG clearance can be attributed to interaction with VPA. The difference between maternal levels and the levels in umbilical cord can be used for prediction of VPA fetal levels during the 1st trimester = 81 mg/L, which is possibly teratogenic and could explain the low birth length.

## PHARMACOKINETICS OF SSRI AFTER ROUX-EN-Y-GASTRIC-BYPASS—REVIEW OF THE LITERATURE AND CASE STUDY

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**Background:** The prevalence of obesity is growing; WHO reports that in 2014 13% of adults aged 18 years and over were obese. A growing number of patients are treated with surgery, laparoscopic Roux-en-Y Gastric Bypass (RYGB) being considered the gold standard. Because of changes in intestinal anatomy, changes in pharmacokinetics are to expect.

The point prevalence of depression in Sweden is 5.2%; 20-50% of patients undergoing bariatric surgery in the US have a medical history of mood disorder.

However, documentation for changes in pharmacokinetics of antidepressive agents of type selective serotonin reuptake inhibitors (SSRI) is sparse.

**Methods:** Literature was reviewed using PubMed with search terms as follows:

Biliopancreatic Diversion with Duodenal Switch, BPD/DS, gastric band, gastric sleeve, gastric bypass, roux-en-Y, bariatric surgery, SSRI, psychopharmacology, selective serotonin reuptake inhibitor[s] and the names of the individual agents. From the reference lists additional references were identified. Only English-language articles were included.

Three patients, treated with sertraline, were included; serum concentrations were taken eight weeks before, three month after and twelve month after surgery.