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ID 28. Increased neonatal morbidity after intrauterine exposure to antipsychotics

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Background: Use of antipsychotic drugs during pregnancy has more than doubled in Sweden in the last decade. Antipsychotic drug exposure during pregnancy is associated with increased neonatal morbidity, with especially CNS-symptoms being warned of by both the American Food and Drug Administration and the European Medicines Agency. However, the severity of the symptoms and to what extent they are caused by the medication or the underlying disease is hard to approach with studies and still somewhat unclear and debated.

Methods: The study was a register-based study on prospectively collected data, combining data from the Swedish Medical Birth Register (MBR), the Prescribed Drug Register (PDR), the Swedish Neonatal Quality Register (SNQ), and the Perinatal Revision South Register (PRS). The study population consisted of all singleton births in Sweden, a total of 1,307,487 infants, registered in the MBR between July 1, 2006, and December 31, 2017. Exposure of an antipsychotic drug (ATC-code N05A except for lithium and the antipsychotics used as antiemetics) was defined as a prescription registered in the PDR during or 1 month before pregnancy and/or self-reported use registered in the MBR. Late pregnancy exposure was defined as a prescription filed in the last 3 months of pregnancy. Risk ratios (RR) were calculated for admission to neonatal care, the main outcome, and for the separate neonatal morbidities.

Results: Crude RR for admission to neonatal care after intrauterine exposure to antipsychotics was 2.17 (95% CI 1.94–2.43) and for exposure during late pregnancy 2.73 (95% CI 2.45–3.04) when compared with the general population. The risk increase was lower but stayed significant after adjustment for parity, maternal age, BMI, smoking and concomitant medication and when compared with children to women treated with antipsychotics before or after but not during pregnancy. The incidence of several neonatal morbidities such as respiratory disorders, jitteriness and hypoglycemia was significantly increased amongst children exposed to antipsychotics (Table 1).

Conclusion: Our results support a strong correlation between intrauterine exposure to antipsychotics and the need of specialized neonatal care. The risk is largest after use of antipsychotics in late pregnancy.

Neonatal outcomes	Exposed during pregnancy n=2677 %	Antipsychotics before/ after but not during pregnancy n=34492 %	Not exposed n=1 262 047 %	Exposed vs not exposed p	Exposed vs antipsychotics before/after pregnancy p
Admission to neonatal intensive care	19.3	11.6	7.8	<0,0001	<0,0001
Respiratory symptoms					
Transient tachypnea of the newborn	6.9	4.1	2.7	<0,0001	<0,0001
Persistent pulmonary hypertension (PPHN)	1	0.6	0.4	<0,0001	0.02
Respiratory distress syndrome (RDS)	0.8	0.9	0.5	0.15	0.77
Respiratory treatment	6.3				
CPAP		3.7	2.4	<0,0001	<0,0001
Ventilator treatment	0.8	0.9	0.5	0.11	0.89
Hyperbilirubinemia	6.3	5.3	4.3	<0,0001	0.02
Hypoglycemia	5	3.2	2.2	<0,0001	<0,0001
Feeding difficulties	2.8	1.6	1.1	<0,0001	<0,0001
CNS-related disorders	1.8	0.5	0.3	<0,0001	<0,0001
Withdrawal symptoms from therapeutic drugs	1.3	0.2	0	<0,0001	<0,0001

Gree = reference incidence in general population. Yellow = Incidence x1-2 compared to the normal population.
Re = Incidence more than double than in the normal population.

(ID 28) - Table 1. Neonatal morbidity amongst infants exposed to antipsychotics, infants to mothers using antipsychotics before or after but not during pregnancy and non-exposed infants.

None declared.

ID 407. Determination of endocrine disruptors levels in human milk and risk assessment of neonatal exposure

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Background: The benefits of breastfeeding for the immune system, growth and health status later in life, are widely known. However, maternal exposure to pollutants, such as pesticides, parabens and bisphenol A can result in breast milk contamination and infant exposure. Exposure to endocrine disruptors during development, beginning from the fetal period until puberty, may cause harmful health effects for human. The aim of this study was to estimate the burden of human milk from Cretan women with methyl, ethyl, propyl, butyl and benzyl parabens, bisphenol A, bisphenol analogues F and S, triclosan and triclocarbam and the risk assessment of neonatal exposure.

Methods: Fifty-three milk samples (5 ml) were treated with phosphoric acid and hydrolyzed with b-glycuronidase/b-glycuronidase sulfate (50 °C, 4 h) and extracted with acetonitrile (7.5 ml) with salts addition (MgSO4, sodium citrate tribase/dibase, NaCl). Clean up of the supernatant was performed with PSA and $MgSO_4$. Organic phase was dried, reconstituted to acetonitrile and injected in LC-MS with an APCI ionization source.

Results: The method was linear ($R^2 > 0.992$), accurate (range: 86.4–109.2%) and precise (%RSD range: 4.3–22.6) and provided low detection limits (from 0.01 to 0.04 ng/ml). The mean concentrations for parabens ranged from 0.47±0.60 (butyl) to 3.53 ± 9.60 ng/ml (ethyl), for bisphenol S and A were 0.42 ± 0.43 and 0.37 ± 0.83 ng/ml, respectively, and 3.05 ± 7.23 ng/ml for triclosan. Methyl paraben was the most frequently detected compound (95.7%) among parabens, followed by propyl (74.5%), ethyl (40.4%), benzyl (31.9%) and butyl (21.3%). Triclosan, bisphenols A and S were detected in 93.6, 63.8 and 10.6% of the samples, respectively. The hazard index (HI) was calculated for risk assessment based on the detected levels of each analyte, the daily milk consumption per infant weight and reference limits for safe exposure. The mean calculated HI values were lower than 0.1 for all analytes.

Conclusion: The findings indicate that the compounds are detectable in human milk at low levels. The risk assessment approach showed that exposure is safe for newborns (HI<1). Despite the presence of these contaminants in human milk, the benefits of the breastfeeding are still impressive.

None declared.

ID 468. Population pharmacokinetics of fentanyl in very preterm infants

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Background: Fentanyl is a synthetic opioid widely used in neonatal intensive care unit, however its optimal dose has not been determined in preterm infants. The aim of this work was to develop a population pharmacokinetic model for a new formulation of fentanyl 5 µg/mL in preterm infants and test the influence of genetic variants (SNPs) on the PK.

Methods: This PK/PG study is part of a PK/PD/PG study designed to optimize fentanyl dosage for procedural pain in newborn preterm infants. 25 infants received 0.5 µg/kg before skin-breaking procedures or 2 µg/kg before tracheal intubation. The median gestational age and weight were 27 weeks and 0.85 kg, respectively. Population pharmacokinetic modelling was undertaken with NONMEM 7.4. Body weight and postmenstrual age (PMA) were included in the model using an allometric weight scaling and a sigmoidal maturation function, respectively. To test the influence of 153 SNPs on the clearance (CL), a screening process was first done using

multiple linear regression with Plink 1.9. The SNPs selected were then tested as categorical covariates in the PK model using NONMEM 7.4.

Results: A two compartment model provided the best fit. The estimates of the PK parameters (standardized to 70 kg) were: CL = 69.9 7 L/h (CV 8%), central volume of distribution = 174 L (CV 12%), peripheral volume of distribution = 15.6 L/h (CV 23%), and inter-compartmental clearance = 5.6 L/h (CV 34%). The allometric weight exponent was fixed to 0.75 for CL and 1 for volumes. The parameters of the maturation function were fixed to values previously published. The model showed that three SNPs induced a significant increase of the CL: rs111517339 T/TA coding for the receptor ATP Binding Cassette Subfamily C Member 1 (ABCC1) and rs11079921 T/C as well as rs8077268 C/T coding for ABCC3.

Conclusion: A population PK/PG model was successfully developed to describe the fentanyl concentration in preterm infants. The CL in this population was affected by PMA and weight. The study shows that SNPs coding for ABCC1 and ABCC3 receptors explain a part of the variability of the fentanyl elimination.

None declared.