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IS LACK OF MORNING SICKNESS TERATOGENIC? A PROSPECTIVE CONTROLLED STUDY. R. R. Boskovic, MD, The Hospital for Sick Children, Toronto, Canada.

Introduction: Case control studies have suggested that nausea and vomiting of pregnancy (NVP) has a protective effect against specific malformations. These suggestions have been interpreted as if lack of NVP may put mothers at an increased teratogenic risk.

Objective: To evaluate whether lack of NVP increases the overall rates for major malformations.

Method: A prospective, cohort controlled study comparing pregnancy outcome in women not experiencing NVP with those experiencing NVP at two levels of severity. Women who called the Motherisk program about first trimester exposure to drugs but without NVP were included. The NVP Healthline enrolled two groups of women with NVP exposed to doxylamine-pyridoxine (DiclectinÒ) for morning sickness. These women were exposed during first trimester of gestation to either higher than standard dose (5-12tbl/day) or a standard dose (1-4 tbl/day) of Diclectin. The women were followed up 4-6 months after of the expected date of birth to ascertain pregnancy outcome.

Results: There were no major malformations among offspring of 130 women not experiencing NVP. There were two major malformations among 246 women experiencing NVP. The two groups were of similar distribution of gestational ages, birth rates, as well as rates of miscarriages and stillbirths.

Conclusions: Lack of NVP does not effect the overall rates of major malformations. The results of retrospective, case control studies should not be used to alarm women about such risk.

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CAN SALIVA BE USED FOR THERAPEUTIC DRUG MONITORING OF PROTEASE INHIBITORS IN HIV-INFECTED CHILDREN? N. Y. Rakhmanina, MD, J. N. van den Anker, MD, PhD, J. Sever, MD, H. Spiegel, MD, PhD, S. L. Soldin, PhD, Children's National Medical Center, The George Washington University, Washington, DC.

Purpose: HIV-infected children may become a target category for therapeutic drug monitoring (TDM) of antiretroviral therapy (ART) due to the unpredictability of plasma concentrations. Studies suggest that saliva could be used instead of blood for TDM. This has distinct advantages in pediatrics as saliva sampling is painless and prevents blood loss. The purpose of this study was to determine the total concentrations of lopinavir and ritonavir in plasma of children with HIV infection and compare them with the total saliva concentration.

Methods: 15 pediatric patients (median age 8.9 years) receiving combination ART were enrolled. Unbound lopinavir and ritonavir were separated by ultrafiltration. The drug serum and saliva concentrations were determined by a tandem-mass spectrometric method using Sciex APT-2000. Routine statistical methods were used to examine the relation between total drug plasma and saliva concentrations.

Results: The relation between total saliva and serum concentrations of lopinavir and ritonavir were highly significant with r values of 0.991 for ritonavir ($Rit_{totalSal} = 0.043 \times Rit_{totalPl} + 108.7$, $p < 0.001$) and 0.993 for lopinavir ($Lop_{totalSal} = 0.019 \times Lop_{totalPl} - 59.26$, $p < 0.0001$).

Conclusion: This pilot study demonstrated a significant linear correlation between total saliva and serum concentrations of lopinavir and ritonavir. The measurement of concentrations of these drugs in saliva may be useful for application of TDM of PIs in pediatric patients.

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PHARMACOKINETICS OF ROFECOXIB IN CHILDREN. D. J. Edwards, PharmD, R. P. Prescilla, MD, D. A. Fratarelli, MD, D. Haritos, MD, J. V. Aranda, MD, PhD, Wayne State University, Children's Hospital of Michigan, NICHD Pediatric Pharmacology Research Unit Network, Detroit, MI.

Rofecoxib is a selective COX-2 inhibitor approved for pain control and the treatment of arthritis in adults. There are no published pharmacokinetic data in children. We investigated the disposition of rofecoxib in children with sickle cell hemoglobinopathy admitted for pain episodes. Subjects (5 males, 3 females) aged 3 to 14 years (mean 8.9 years) with normal liver and kidney function received a single oral dose of rofecoxib (1 mg/kg, maximum 50 mg) as a suspension. The mean dose was 35.6 mg (range 15-50 mg). Blood samples were collected for up to 72 hours following drug administration and plasma assayed for rofecoxib using HPLC. Peak concentrations of rofecoxib averaged 582 ± 129 ng/mL with a median t_{max} of 4.0 hours. Two subjects were discharged at 12 hours and subsequent blood samples were not obtained preventing characterization of elimination. In the remaining 6 subjects, oral clearance (Cl/F) averaged 1.32 ± 0.35 mL/min/kg with an elimination half-life of 14.8 ± 4.5 hours. The results are consistent with studies in adults reporting clearance to be ~120 mL/min with a half-life of 17 hours and suggest that rofecoxib disposition is similar in children and adults.

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IMMUNOHISTOCHEMICAL LOCALISATION AND MRNA QUANTIFICATION OF P-GP IN HUMAN TERM PLACENTAS - NO IMPACT OF CORTICOSTEROID ADMINISTRATION FOR PRETERM LABOR. R. Serreau, M. Fakhoury, G. Bonihay, Y. Medard, M. Peuchmaur, A. Mokhdad, J. Oury, E. Jacqz-Aigrain, Robert Debre Hospital, Jean Rostand Hospital, Paris, France.

P-glycoprotein (P-gp) is an energy-dependent efflux pump expressed in the syncythiotrophoblast of human placenta throughout pregnancy, suggesting a potential functional importance of Pgp during pregnancy. Human data are limited and the effects of maternal treatment with corticosteroids in case of preterm labor have not known.

After maternal consent, placenta from term pregnancies ($n = 20$) or term pregnancies treated with betamethasone for preterm labor ($n = 43$) were studied. Betamethasone (12 mg twice at 24 hour interval) was administered between 22 and 34 week's gestation, interval between end of treatment and birth was 35 ± 26 days. Immunohistochemical localisation by a sandwich staining method with Dako 3522 and F4 Kamiya monoclonal antibodies in paraffin embedded human placenta showned that P-gp is located in the endothelial cells without evidence for expression in the syncythiotrophoblast. P-gp mRNA and the constititively expressed mRNA 18S) were measured by RT-PCR and results expressed as the ratio of Pgp over 18S mRNA. PgP was highly expressed in the placenta but Pgp/18S mRNA ratio was not different at term between normal pregnancies and pregnancies treated with betamethasone. A acute effect of betamethasone on P-gp expression cannot be rulled out, as the free interval between betamethasone and birth was more than three weeks and will be investigated by additional studies.