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OCENA TRANSPORTU PRZEZŁOŻYSKOWEGO ERYTROMYCYNY STOSOWANEJ W TERAPII OKOŁOPORODOWEJ GBS

Rozprawa na stopień doktora nauk farmaceutycznych

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STRESZCZENIE W JĘZYKU ANGIELSKIM

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THE EVALUATION OF TRANSPLACENTAL TRANSFER OF ERYTHROMYCIN USED IN PERINATAL GBS THERAPY

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Abstract

Erythromycin is widely used in antibacterial therapy. It belongs to a group of macrolide antibiotics. Due to the low toxicity and broad spectrum of activity it can be used in obstetrics. It can be administered orally and parenterally. After oral administration the highest serum concentration occurs after 2-3 hours, when given intravenously it is approximately 1 hour. The half-time of erythromycin in human serum varies from 1 to 2 hours and the therapeutic concentration is maintained for 6 hours. It is characterized by good penetration to many tissues and organs, however the tranplacental transfer is reported to be low (about 3%). It is excreted primarily in bile (20-30%) and only small amount is excreted in the urine, depending on the route of administration: 2-5% when given orally and 12-15% when given intravenously.

During pregnancy erythromycin can be administered orally or intravenously, depending on medical indications. The oral form is mainly used in respiratory tract infections, the intravenous application is used in patient health care. Among the most common indications it should be mentioned about the prophylaxis in cases of premature rupture of membranes and amniotic fluid leaking, as well as genital tract infections. One of the indication for using erythromycin in pregnant women is perinatal prevention of fetal GBS infections. So far, the question, whether intravenous erythromycin therapy allows to achieve drug's therapeutic level in fetus serum, remains to be open.

The aim of this study was to determine the concentration of erythromycin in maternal blood serum and cord blood serum - umbilical vein and umbilical artery serum. The results of this work allowed to evaluate the penetration of erythromycin through the placenta and find the correlation between the concentration of erythromycin in maternal serum and cord blood serum, as well as to check the influence of some factors on the level of concentration of erythromycin in cord blood serum. Erythromycin was given to pregnant women with GBS infection or

pregnant women who were qualified for the perinatal GBS antibiotic prophylaxis – in accordance with the PTG recommendations.

The study covered 77 patients of the Department of Perinatology and Gynecology, Polish Mother's Memorial Hospital Research Institute in Lodz. The inclusion criteria were the following: identified GBS infection or the occurrence of indications - in accordance with the PTG guidelines - to implement the prevention of perinatal GBS infections. The women were given erythromycin lactobionate intravenously. The first group (62 patients) received 600 mg of erythromycin, the second group (15 patients) 900 mg of erythromycin. In all cases it was a single infusion. Erythromycin was given about 4 hours before delivery. After about 1.5 hours after termination of infusion maternal and cord blood samples were taken, all samples were obtained in parallel. Blood samples were centrifuged, serum was separated, samples were frozen and sent to the Department of Biopharmacy. Serum erythromycin concentration were estimated using ELISA method.

For each patients personal data and medical records were collected, it was: maternal age, maternal body weight, gestational age at delivery, a multitude of pregnancy, mode of delivery, maternal parity: number of pregnancies and number of live births, date of birth, time of drug administration and time of sample collection, other features or diseases associated with the pregnancy. Neonatal data were also collected, it was: neonatal sex, neonatal birth weight and Apgar score.

The results have been statistically analyzed and presented in the form of tables and graphs.

The average maternal drug concentration in the sample was: for the first study group 2144,66 ng/ml and for the second 3000,16 ng/ml. The mean fetal serum concentration of erythromycin for the first group was: 51,19 ng/ml and 50,69 ng/ml - respectively for umbilical vein and umbilical artery; and for the second group it was: 54,09 ng/ml and 53,10 ng/ml - respectively for umbilical vein and umbilical artery. Transplacental transfer of erythromycin was approximately 3% for the first group and 2% for the second group.

The results of umbilical vein and umbilical artery serum erythromycin concentration – for each group – were lower than MIC_{50} and MIC_{90} value for the sensitive strains of *S.agalactiae*. MIC_{50} and MIC_{90} value was achieved only in maternal serum, in all analyzed cases, both for the first and second group.

Among the factors that presumably could have an impact on the low value of erythromycin concentration in cord blood serum the following should be mentioned: placental barrier and the parameters related with the drug molecule. Erythromycin as a drug of high molecular weight, hydrophilic character and high propensity to bind to plasma proteins, demonstrate difficulty in crossing the placental barrier.

This study found that despite increasing the dose of erythromycin there was no significant increase of erythromycin concentration in cord blood serum and hence in the neonate serum at the time of delivery. In addition, limited transplacental passage of erythromycin suggests dubious efficacy in the treatment of intrauterine infections.

The correlations between cord blood serum erythromycin concentration and certain variables characterizing mothers (maternal age, maternal body weight, gestational age at delivery, results of peripheral blood counts) and neonates (sex and birth weight) were calculated. In both group there was no statistically significant correlation between umbilical vein and umbilical artery serum erythromycin level and maternal age, maternal body weight, gestational age of delivery and neonate sex. However, in the second group there was statistically significant correlation between cord blood serum erythromycin level and neonate birth weight. With the growth of neonate birth weight the lower level of erythromycin was observed.

In summary, this analysis show that using the standard protocol of erythromycin regimen the therapeutic levels at fetal blood serum can not be achieved, drug concentration is to low to inhibit the growth of *Streptococcus agalactiae*. Nevertheless, in the maternal blood serum therapeutic erythromycin levels was achieved. Therefore, although efficacy of erythromycin in the treatment of fetal intrauterine infections appears to be limited, it is possible to treat maternal infections without undue fetal exposure. The results of this study confirm that erythromycin is one of the safer antibacterial drugs that is not questionable during pregnancy. It is an excellent alternative for patients who are allergic to penicillin, erythromycin does not have teratogenic effects and has a long history - from the 1950s - of safe use in pregnant patients.