

Endothelin receptor antagonist has limited access to the fetal compartment during chronic maternal administration late in pregnancy

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Background: Endothelin receptor A (ET_A) antagonism improves placental perfusion and fetal growth in several rat models of fetal growth restriction. It has been reported that direct administration of ET_A antagonists to newborn rats has resulted in neonatal demise due to failure of the ductus arteriosus to close, raising concerns about the safety of their use late in pregnancy. Endothelin has a prominent role in the pathophysiology of fetal growth restriction. We have previously reported normal pregnancy outcome, and normal birth weight, growth and oxygenation of rat pups from ET_A antagonist-treated dams. The relative plasma levels of the antagonist in maternal and fetal circulation have not been determined.

Objective: To determine the levels of an ET_A antagonist in maternal and fetal plasma following chronic maternal administration of the antagonist.

Methods: Timed pregnant Sprague-Dawley rats (225-250 grams) were treated with ABT-546 (ET_A antagonist, 10 mg/kg/day, Abbott Laboratories) or vehicle, by subcutaneous osmotic pump (implanted under combined ketamine/xylazine/acepromazine anesthesia, 40, 8, and 1.3 mg/kg, respectively), from gestation day 14 through 21 (term=22 days). Six pregnant rats were euthanized on day 21 and maternal plasma was collected from blood drawn from the vena cava. Fetal plasma was obtained from blood collected by incision across the neck at the jugular vein and was pooled for each litter. Plasma was assayed by HPLC for ABT-546 concentration. Results are presented as mean ± SE. Statistical analysis was by paired samples *t* test.

Results: Fetal plasma levels of the ET_A antagonist were 46-fold lower than maternal levels (0.016 ± 0.002 and 0.736 ± 0.123 µg/ml, respectively, *p*=0.002).

Conclusions: Maternally administered ET_A antagonist has limited access across the placenta into the fetal compartment. These results corroborate our previous results showing normal neonatal rat survival and oxygenation following chronic maternal treatment with an ET_A antagonist. ET_A antagonism, delivered maternally, produces sufficiently low fetal plasma levels of antagonist so as not to present a survival threat to the neonatal pups. The beneficial effects of ET_A antagonism that lead to normal fetal growth in growth-restriction models occur in the maternal, not the fetal, compartment.