COMMITTEE REPORT

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Basic Research

Screening of an Angiotensin II Receptor Blocker with Low Adverse Fetal Effect using Adverse Event Reporting System and Mechanism of the Low Placental Transfer

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Objective: Administration of angiotensin II receptor blocker (ARB) to pregnant women is contraindicated due to the risk of inducing oligohydramnios. However, it is unclear if the ARBs on the market uniformly induce oligohydramnios. The aim of this study was to find an ARB that is less likely to develop oligohydramnios based on the frequency of side effects registered in the US Food and Drug Administration Adverse Event Reporting System (FAERS) and to show the mechanism of the lower risk of developing oligohydramnios in non-clinical studies.

Methods: We searched for cases registered in FAERS from 2004 to 2017, investigated the frequency of adverse event records of patients taking ARB showing oligohydramnios, and compared them among ARB drugs. We compared the antihypertensive effect of the selected ARBs and their fetal transfer in the model rats of hypertensive disorder of pregnancy with administration of L-NAME, a nonselective nitric oxide synthase inhibitor. The transport activity of organic anion transporting polypeptide (OATP) 2B1 was evaluated by using HEK293 cells transiently transfected with cDNA of human OATP2B1. The drug concentrations were measured by liquid chromatography with tandem mass spectrometry.

Results: Of the 6 ARBs investigated, olmesartan had the highest frequency of oligohydramnios, and irbesartan had the lowest frequency, with a 25-fold difference in reporting frequency. In pregnant hypertensive rats, both olmesartan and irbesartan showed remarkable antihypertensive effect, while only irbesartan showed the effect of improving fetal growth failure. Ratio of the plasma concentration in the fetus to that in the dam (F/M ratio) was measured. The F/M ratios of olmesartan and irbesartan were about 1.6 and 0.28, respectively, indicating that fetal transfer of irbesartan is relatively limited due to the flux in the placenta. OATP2B1 is one of drug transporters which is known to be expressed in the fetal-facing membrane in syncytiotrophoblasts. When the transport activity of both drugs by OATP2B1 was examined, it was shown that only irbesartan was transported.

Conclusion: The records in the database implied that irbesartan has a low risk of increasing amniotic fluid volume among the ARB drugs. Irbesartan showed lower fetal transfer at least in rats than olmesartan and irbesartan is a substrate of OATP2B1, indicating that irbesartan may be excreted by placental OATP2B1 from fetal plasma to maternal plasma.