PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

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Precautions for Use of the Drugs Inhibiting the Renin-Angiotensin System (ACE Inhibitors, ARB, Etc.) in Women of Child-bearing Potential

- The package inserts for drugs inhibiting the renin-angiotensin system (hereinafter referred to as “RAS inhibitors”) caution against administering them to pregnant women, and the precautions have been disseminated to healthcare professionals by “PMDA Alert for Proper Use of Drugs” No.10 issued in September 2014.
- This time, following the revision of package insert to add 2. below, “PMDA Alert for Proper Use of Drugs” No.10 was updated. The reasons for this revision are as follows: Cases have been reported in which these drugs were used continuously during pregnancy and foetal and neonatal adverse events were suspected; in some cases, these drugs were used in women without recognizing that they were pregnant.
- When administering an RAS inhibitor, the following points[*1] should be reviewed, and RAS inhibitors should not be administered to pregnant women.

1. RAS inhibitors should not be administered to pregnant women or women who may be pregnant.

2. The necessity of administering an RAS inhibitor to women of child-bearing potential should be carefully considered. Also, if administration is considered necessary, attention should be paid to the following points.

- The absence of pregnancy should be confirmed prior to and during administration.
- When pregnancy is detected, administration of this drug should be discontinued immediately.
- Patients should be informed that this drug can affect foetuses and neonates, and should be advised repeatedly that they should consult with their attending physician if pregnancy is detected or suspected[*2], or pregnancy is planned.

*1 Precautions common to RAS inhibitors are described in this document. For the details of precautions of each drug, package inserts for each drug can be searched for and viewed on the PMDA website (https://www.pmda.go.jp/) (only available in Japanese).

*2 Delayed menstruation or amenorrhoea, hyperemesis gravidarum (symptoms of morning sickness), continuation of the high-temperature phase in cases where basal body temperature is measured, etc.

●Reports of cases*

- Cases have been intermittently reported in which RAS inhibitors were used during pregnancy and adverse foetal and neonatal outcomes (renal failure, aplasia of skull, lung, and kidney, death, etc.) are suspected, even after 2014 when “PMDA Alert for Proper Use of Drugs” No.10 was issued.
- Among them, there have been cases in which RAS inhibitors had been used since before pregnancy and they were continuously used in women without recognizing that they were pregnant.

Fiscal Year	2014	2015	2016	2017	2018	2019	2020	2021	2022
Number of cases in which adverse foetal and neonatal outcomes were suspected to be due to exposure to RAS inhibitors during pregnancy	4	6	4	2	0	4	0	3	1
Among the above cases, the number of the cases for which it was stated in the column of clinical course, etc. of the case report form that pregnancies had not been recognized	2	2	2	2	0	0	0	3	0

*Tabulated using the case reports on adverse drug reactions in Japan reported to the PMDA between April 2014 and December 2022

Typical case reports

Case 1. Suspected drug: Candesartan cilexetil

Patient		Daily dose/ administration duration	Adverse reaction	
Sex/ Age	Reason for use (complication)		Clinical course and treatment	
Mother in her 30s Female offspring	Hypertension (diabetes mellitus)	Unknown (approximately 2 years)	Offspring: Cleft lip and palate, skull hypoplasia	
			Day 1 of administration	The mother was diagnosed with diabetes mellitus and hypertension and she was treated with oral administration of metformin and candesartan cilexetil at another hospital.
			Approximately 2 years after administration	The mother was primiparous. Pregnancy was spontaneously achieved. However, she did not recognize her pregnancy. She noticed bloating during the second trimester of pregnancy, and therefore visited the other hospital.
			Approximately 2 years after administration (Day of discontinuation)	Gestational age was estimated to be 33 weeks and 5 days based on the timing of the last menstruation and ultrasound findings. The mother was referred to this hospital for inpatient management. After admission to this hospital, treatment regimens for diabetes mellitus and hypertension were changed to insulin injection and oral administration of methyldopa. Foetal ultrasound during hospitalization showed no sign of oligohydramnios. No other foetal malformation was noted.
			24 days after discontinuation (0 days old)	Labour pain occurred spontaneously at 37 weeks and 1 day gestation. Since decreased foetal heart rate was confirmed before delivery, the mother had a cephalic vaginal delivery using vacuum extraction. The offspring was appropriate-for-dates female with a body weight of 2 436 g. 1-minute Apgar score, 8; 5-minute Apgar score, 9. Umbilical cord arterial blood gas pH, 7.212 Umbilical cord arterial blood gas BE, -7.6 mmoL/L. After birth, respiratory status was stabilized with oxygen administration. The offspring was hospitalized for having been born from the mother with diabetes mellitus. Physical findings at the time of hospitalization: Opening of anterior/posterior fontanel (8 cm × 8 cm) and dehiscence of sagittal suture were observed. While no peculiar face was noted, there were cleft lip and palate. Vitality of the offspring was good. Muscle tightness of the four limbs was well kept without contracture. No hypothyroidism was noted. X-ray images showed skull hypoplasia from the frontal bone to the occipital bone. Ultrasound revealed no apparent sign of malformation in the brain and heart, or intracranial haemorrhage.
			25 days after discontinuation (1 day old)	On head CT images of the offspring, ossified areas of the frontal bone/parietal bone/occipital bone/temporal bone were found to be small and separated.
			28 days after discontinuation (4 days old)	No hypothyroidism was observed in the offspring.
			36 days after discontinuation (12 days old)	Since systemic condition and weight gain of the offspring were good, the offspring was discharged from the hospital.
			3 months after discontinuation (3 months old)	Therapeutic response was good. A head CT showed that cranial ossification progressed compared with that immediately after birth, and cranial osteogenesis was appropriate for 3 months old.
Concomitant drugs: Metformin hydrochloride Note: Shinya Abe, et al. Perinatal Medicine. 2017; 47: 1353-1355.				

Case 2. Suspected drug: Olmesartan medoxomil

Patient		Daily dose/ administration duration	Adverse reaction	
Sex/ age	Reason for use (complication)		Clinical course and treatment	
Mother in her 30s First child: Female offspring Second child: Male offspring	Moyamoya disease (none)	20 mg (1 year)	Mother: Oligohydramnios Offspring (first child, second child): Pulmonary hypoplasia, foetal kidney enlargement, neonatal kidney enlargement, neonatal proximal renal tubular dysgenesis, neonatal respiratory failure	
			Day 1 of administration (1 year ago)	The mother had been orally taking olmesartan medoxomil 20 mg since 1 year before pregnancy as a treatment of moyamoya disease. Pregnancy was spontaneously achieved. She did not recognize her pregnancy until a family member pointed out that her abdomen became larger. Therefore, she made an initial visit to the obstetrics and gynecology department of hospital A. Gestational age was calculated to be 27 weeks and 2 days. Since the sexes of the foetuses were male and female, it was diagnosed as diamniotic dichorionic twin pregnancy.
			Day of discontinuation (28 weeks and 2 days gestation)	Since both foetuses had oligohydramnios, the mother was referred to a secondary maternity facility (hospital B) at 28 weeks and 2 days gestation. She was admitted to hospital B on the same day. Although oral administration of ARB was discontinued after admission to hospital B, the amniotic fluid volume did not increase. Accordingly, she was urgently transported to this hospital at 30 weeks and 2 days gestation.
			From day of discontinuation to 26 days after discontinuation (28 weeks and 2 days gestation to 32 weeks 0 days gestation)	Transabdominal ultrasound at the time of admission to this hospital showed that the maximum vertical pocket (MVP) for both foetuses was 0 cm. Both kidneys were presented with high echogenicity. TC/AC was measured for multiple times from 28 weeks and 2 days gestation to 32 weeks and 0 days gestation. Minimum TC/AC was 0.73 for the first child and 0.71 for the second child. Pulmonary hypoplasia was suspected in both foetuses. Both kidneys of the first child were enlarged. The right kidney of the first child had an anteroposterior width of 41 mm, transverse width of 21 mm and long diameter of 55 mm (normal anteroposterior width: 22.4±1.7 mm, normal long diameter: 40.6±2.8 mm), and the left kidney had an anteroposterior width of 36 mm, transverse width of 25 mm and long diameter of 53 mm. Both kidneys of the second child were also enlarged. The right kidney of the second child had an anteroposterior width of 36 mm, transverse width of 24 mm and long diameter of 53 mm, and the left kidney had an anteroposterior width of 32 mm, transverse width of 26 mm and long diameter of 53 mm. Bladder with a diameter of 10 mm was observed in both foetuses.
			26 days after discontinuation (32 weeks 0 days gestation)	Ultrasound at 31 weeks and 1 day gestation showed no amniotic cavity for both foetuses; however, an amniotic cavity with the MVP exceeding 1 cm was confirmed for the first time at 32 weeks and 0 days gestation (approximately 5 weeks after discontinuation of ARB).
			30 days after discontinuation (32 weeks and 4 days gestation)	Labour pain occurred. Since the first child was in breech presentation, an emergency caesarean section was performed. Neonatal findings (first child): Sex, female 1-minute Apgar score, 4; 5-minute Apgar score, 6 Umbilical cord arterial blood pH, 7.129 Neonatal findings (second child): Sex, male 1-minute Apgar score, 6; 5-minute Apgar score, 7 Umbilical cord arterial blood pH, 7.175 The offspring were intubated and placed on ventilator management after birth. However, respiratory failure was serious, and there was no urine output. Both offspring died 15 hours after birth. Autopsy (kidneys): The first child had the right kidney with a weight of 20.0 g and left kidney with a weight of 20.0 g. The second child had the right kidney with a weight of 22.5 g and left kidney with a weight of 27.0 g. Compared to a normal weight of 15.0±4.4 g, the kidneys of both offspring were remarkably enlarged. Histological investigation (kidneys): Poor differentiation and decreased number of proximal/distal renal tubules (especially proximal renal tubules) due to poor development of these renal tubules were noted. CD10 immunostaining of glomerular epithelial cells (glomerular foot process)/proximal renal tubules showed significant decrease in the number of proximal renal tubules. Autopsy (lungs): The first child had the right lung with a weight of 11.5 g and left lung with a weight of 12.5 g. The second child had the right lung with a weight of 12.0 g and left lung with a weight of 14.5 g. These weights were less than 50% of the normal weight of 31.2±9.0 g for neonates delivered after 32 weeks gestation. Histological investigation (lungs): As for maturity of the lungs, the lungs of both offspring had developed to terminal sac period (equivalent to that of a foetus at 26 weeks to 38 weeks gestation). However, radial alveolar count (2 for the first child and 1 for the second child) was significantly smaller than the normal range of 4 to 5 for a full-term neonate. Since there was no tumour in pleural cavity or diaphragmatic hernia, it was diagnosed as pulmonary hypoplasia due to oligohydramnios.
Suspected concomitant drugs: None Note: Daisuke Saito, et al. Kagoshima Journal of Obstetrics and Gynecology. 2021; 29: 49-54.				

Case 3. Suspected drug: Valsartan

Patient		Daily dose/ administration duration	Adverse reaction	
Sex/ age	Reason for use (complication)		Clinical course and treatment	
Mother in her 30s Female offspring (0 days old)	Mother; hypertension (Mother; asthma, gastrooesophageal reflux disease, upper abdominal pain) (Offspring; low birth weight baby, neonatal respiratory distress syndrome)	40 mg (391 days)	Offspring: Skull hypoplasia, neonatal renal impairment	
			Day of administration	Since home blood pressure was not controlled, administration of valsartan was initiated. Vonoprazan fumarate was also taken from Day 202 to Day 209 of administration. Rabeprazole sodium was switched to esomeprazole magnesium hydrate once. On Day 300 of administration, esomeprazole magnesium hydrate was switched back to rabeprazole sodium. The mother had received a prescription of theophylline for asthma, and loxoprofen sodium hydrate and teprenone for low back pain.
			Date unknown	The mother consulted with an internist after feeling foetal movement, but it was judged to be intestinal movement.
			Day 391 of administration (Day of discontinuation)	The mother took a self-pregnancy test. After confirming a positive result, she visited an obstetrician. Blood pressure was 184/123 mmHg. She was severely obese, weighing 117 kg, an increase of 27 kg since her last pregnancy. Since HbA1c was relatively high at 6.1%, glycosuria during pregnancy was suspected. Amniotic fluid volume was normal. Administration of valsartan and amlodipine besilate was discontinued, and was switched to nifedipine.
			3 days after discontinuation (0 days old)	The offspring was delivered by caesarean section due to hypertension and breech presentation. Gestational age was 36 weeks and 4 days, birthweight was 2 336 g, and Apgar score was 7/7. The offspring was hospitalized at the neonatal department for having respiratory disorder and having been born from a mother who was taking an angiotensin II receptor blocker. Renal disorder and skull hypoplasia were observed. The skull was thin, and the anterior fontanel (5 ×4.5 cm) and the posterior fontanel (3 × 3 cm) were widely open. Tongue-shaped bone defect at the distal end of the right long bone was noted. Furthermore, neonatal idiopathic respiratory distress syndrome was diagnosed. Endotracheal intubation was performed, and pulmonary surfactant preparation (120 mg/kg) was administered. Ventilator management was necessary. Midazolam was used (0.1 mg/kg/day) for sedation.
			4 days after discontinuation (1 day old)	Furosemide (1 mg/kg) and normal saline solution (5 mL/kg) were administered twice for oliguria. Due to a high phosphorus level and a low calcium level, administration of calcium gluconate hydrate was initiated (3 mL/kg/day).
			6 days after discontinuation (3 days old)	Uric acid and creatinine levels increased. Serum sodium level showed a decreasing tendency due to polyuria. Volume of infusion fluid was increased and 10% NaCl supplementation was initiated. Oral administration of furosemide (1 mg/kg/day) and spironolactone (1 mg/kg/day) was initiated. Blood pressure was stable at 70/40 mmHg.
			14 days after discontinuation (11 days old)	Administration of calcium gluconate hydrate was discontinued.
			15 days after discontinuation (12 days old)	Artificial ventilation was discontinued, and extubation was performed. Administration of midazolam was completed.
			16 days after discontinuation (13 days old)	Oxygen administration was discontinued, and positive pressure ventilation was initiated. Serum creatinine and uric acid levels were normalized. Fractional excretion of sodium (FENa) and renal failure index (RFI) were still high.
			17 days after discontinuation (14 days old)	Administration of furosemide and spironolactone was completed.
			19 days after discontinuation (16 days old)	Positive pressure ventilation was completed.
			27 days after discontinuation (24 days old)	Administration of 10% NaCl was completed.
			29 days after discontinuation (26 days old)	Urinary NAG level was still high at 24.1 IU/L. Serum osmolality and urine osmolarity were normal. PCO_2 was normalized. The offspring was fed concomitantly with injection of liquid nutrition. Since urine output volume was slightly high, the offspring was fed with a slightly high volume of milk. MRI: There was no apparent abnormality in the head. Lobes in both kidneys were relatively large. Kidney ultrasound: Glomerular structures were not clearly visible.
			43 days after discontinuation (40 days old)	FENa and RFI were normalized. Urinary NAG level was still high. Total amount of milk was orally fed, and urine output volume became stabilized. Weight gain was poor. Milk for treatment was used due to milk allergy. Subsequent weight gain was good.
			49 days after discontinuation (46 days old)	The offspring recovered from renal disorder, but did not recover from skull hypoplasia.

Laboratory test value

	0 days old	3 days old	5 days old	11 days old	26 days old	40 days old
Serum creatinine (mg/dL)	0.53	1.49	1.21	0.52	0.24	0.21

Concomitant drugs: Amlodipine besilate, nifedipine, vonoprazan fumarate, esomeprazole magnesium hydrate, rabeprazole sodium, theophylline, loxoprofen sodium hydrate, teprenone

Case 4. Suspected drug: Azilsartan

Patient		Daily dose/ administration duration	Adverse reaction	
Sex/ age	Reason for use (complication)		Clinical course and treatment	
Mother in her 30s Offspring (unknown)	Hypertension (diabetes mellitus, obesity)	20 mg (2 days) ↓ 40 mg (16 days)	Mother: None Mother's medical history, predisposition and others: Smoking Offspring: Neonatal renal failure, neonatal hypotension, acute kidney injury, hypotension, cerebral ischaemia, meconium aspiration syndrome, pulmonary oedema, respiratory failure, hypoxic-ischaemic encephalopathy	
			Before administration	Gravida 1, para 1, smoker, no alcohol consumption The mother did not recognize her pregnancy because her menstrual cycles had been irregular.
			Day 1 of administration	The mother experienced aggravation of difficulty breathing 1 month before delivery. Hypertension, cardiac failure and diabetes mellitus were diagnosed. Oral administration of azilsartan (20 mg/day), nifedipine, azosemide, spironolactone, and empagliflozin was initiated.
			Day 3 of administration	The dose of azilsartan was increased (40 mg/day).
			Day of discontinuation (Day 17 of administration)	Abdominal pain and genital haemorrhage were observed. As pregnancy was discovered, delivery was performed. Administration of azilsartan was discontinued (last administration on that date).
			(0 days old)	<Clinical course of the offspring> New Ballard score was 38 points, and maturity of the offspring was equivalent to that of 38 weeks gestation. Meconium stain and laboured respiration were observed, and meconium aspiration syndrome was suspected. However, laboured respiration gradually improved, and oxygenation was maintained. In a room air setting, ampicillin/aztreonam (ABPC/AZT) was administered. At the time of admission, blood pressure was 60/29 (40) mmHg (drug-induced hypotension in neonate). Blood Cys-C level was 7.07 mg/L, Cre level was 1.33 mg/dL, and BUN was 19 mg/dL. Abdominal ultrasound revealed increased echogenicity of the renal cortex and disruption of renal blood flow in the diastolic phase (acute renal failure in neonate). It was considered to be attributed to oral administration of azilsartan in the mother. However, no electrolyte abnormality or metabolic acidosis was observed. Maintenance infusion of 10% glucose fluid was performed, and the clinical course was followed up.
			-	Anuria was still persisting 24 hours after birth. Since hyperkalaemia occurred, administration of furosemide and glucose-insulin therapy was initiated. Pulmonary oedema developed 36 hours after birth. The offspring was placed on directional positive airway pressure (DPAP). Administration of dopamine hydrochloride (DOA) 4 gamma and antidiuretic hormone (ADH) 0.001 U/kg/min was initiated to increase blood pressure and improve renal blood flow.
			3 days after discontinuation	Diuresis was not achieved. Cre and BUN increased to 4.43 mg/dL and 28 mg/dL, respectively. Intubation was performed. Ventilator management and continuous haemodiafiltration (CHDF) were initiated.
			6 days after discontinuation	Spontaneous urination was gradually observed, thereafter. Therefore, CHDF was discontinued. Neonatal acute renal failure and neonatal drug-induced hypotension were recovering.
			10 days after discontinuation	After discontinuation of CHDF, spontaneous urination was maintained. Accordingly, DOA/ADH was completed.
			15 days after discontinuation	On head MRI images, laminar necrosis of the left cerebral hemisphere and hypointense areas in deep white matter around the anterior horns of both lateral ventricles (cerebral ischaemia in neonate) were observed. They were considered to be signs of hypoxic encephalopathy. The offspring did not recover from cerebral ischaemia in neonate.
			16 days after discontinuation	During the clinical course, the offspring sometimes presented with myoclonus-like limb tremor and pedaling-like motion. However, recorded brain waves showed no abnormal findings.
			18 days after discontinuation	Feeding and weight gain were good. No metabolic acidosis was noted. The offspring was discharged from the hospital with a body weight of 3 414 g.
			Date unknown	Clinical outcomes of meconium aspiration syndrome, pulmonary oedema, respiratory failure and hypoxic encephalopathy were unknown.

Laboratory test value

	Day of discontinuation (0 days old)	3 days after discontinuation	13 days after discontinuation	18 days after discontinuation
Blood pressure (mmHg)	60/29, 60/40	75/55	70/45	-
Cys-C (mg/L)	7.07	-	-	-
Blood creatinine (mg/dL)	1.33, 2.04	4.43	2.01	-
BUN (mg/dL)	15, 19	28	15	-
Body weight (kg)	2.6	2.6	2.6	3.414

Concomitant drugs: Nifedipine, azosemide, spironolactone, empagliflozin, lansoprazole

•RAS inhibitors approved in Japan

(As of April, 2023)

Angiotensin II receptor blockers (ARBs)

Non-proprietary name	Brand name
Azilsartan	Azilva and the others
Irbesartan	Avapro, Irbetan, and the others
Olmesartan medoxomil	Olmetec and the others
Candesartan cilexetil	Blopress and the others
Telmisartan	Micardis and the others
Valsartan	Diovan and the others
Losartan potassium	Nu-Lotan and the others
Azilsartan/ amlodipine besilate	Zacras, ZilMlo
Irbesartan/ amlodipine besilate	Aimix, Iluamix
Irbesartan/ trichlormethiazide	Irtra
Olmesartan medoxomil/ azelnidipine	Rezaltas
Candesartan cilexetil/ amlodipine besilate	Unisia, Camshia
Candesartan cilexetil/ hydrochlorothiazide	Ecard, Cadethia
Telmisartan/ amlodipine besilate	Micamlo, Teramuro
Telmisartan/ amlodipine besilate/ hydrochlorothiazide	Micatrio
Telmisartan/ hydrochlorothiazide	Micombi, Telthia
Valsartan/ amlodipine besilate	Exforge, Amvalo
Valsartan/cilnidipine	Atedio
Valsartan/ hydrochlorothiazide	Co-Dio, Valhydio
Losartan potassium/ hydrochlorothiazide	Preminent, Losarhyd

Angiotensin-converting enzyme inhibitors (ACE inhibitors)

Non-proprietary name	Brand name
Alacepril	Cetapril and the others
Imidapril hydrochloride	Tanatril and the others
Enalapril maleate	Renivace and the others
Captopril	Captoril and the others
Temocapril hydrochloride	Acecol and the others
Delapril hydrochloride	Adecut
Trandolapril	Odric and the others
Benazepril hydrochloride	Cibacen and the others
Perindopril erbumine	Coversyl and the others
Lisinopril hydrate	Zestril, Longes, and the others

Direct renin inhibitor

Non-proprietary name	Brand name
Aliskiren fumarate	Rasilez

Angiotensin receptor-neprilysin inhibitor

Non-proprietary name	Brand name
Sacubitril valsartan sodium hydrate	Entresto

The Japan Drug Information Institute in Pregnancy (JDIIP) in the National Center for Child Health and Development provides consultation services to women who are concerned about the influence of drugs on foetuses. Patients who need more detailed information can be referred to the JDIIP.

JDIIP:
http://www.ncchd.go.jp/kusuri/index.html
(only in Japanese)

About this information

- PMDA Alert for Proper Use of Drugs communicates to healthcare providers with clear information from the perspective of promoting the proper use of drugs. The information presented here includes such cases where the reporting frequencies of similar reports have not decreased despite relevant alerts provided in package inserts, among Adverse Drug Reaction/infection cases reported in accordance with the PMD Act.
- We have tried to ensure the accuracy of this information at the time of its compilation but do not guarantee its accuracy in the future
- This information is not intended to impose constraints on the discretion of healthcare professionals or to impose obligations and responsibility on them, but is provided to promote the proper use of the drugs.
- This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Access to the most up to date safety information is available via the PMDA medi-navi.

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