PMDA Alert for Proper Use of Drugs

Pharmaceuticals and Medical Devices Agency

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# Adverse Events in Pregnant Women and Foetuses Associated with Use of Angiotensin II Receptor Blockers and Angiotensin Converting Enzyme Inhibitors

ARBs or ACE inhibitors are drugs that should not be administered to pregnant women because adverse foetal events have been reported. In Japan, several cases have been intermittently reported in patients who were continuously treated with ARBs or ACE inhibitors even after pregnancy was diagnosed. Adverse events possibly associated with maternal ARB or ACE inhibitor use have also been reported intermittently in foetuses.

Healthcare professionals are encouraged to review the following precautions. Please pay careful attention when administering ARBs or ACE inhibitors.

- **ARBs and ACE inhibitors should not be administered to pregnant women or to women who may be pregnant.**
- **If pregnancy is confirmed during administration, this drug should be discontinued immediately.**
- **When women with child-bearing potential need to be treated with ARBs or ACE inhibitors, they should be informed that ARBs or ACE inhibitors can affect a foetus and advised repeatedly that they should consult with their physician immediately if pregnancy is confirmed.**

## ■ Please note the precautions in the package inserts.

Sample information on the Precautions in the package inserts of ARBs or ACE inhibitors is as follows:

**Contraindications (This drug should not be administered to the following patients:)**

Pregnant women or women who may be pregnant (See Use in Pregnant, Parturient and Nursing Women section)

**Use in Pregnant, Parturient and Nursing Women**

This drug should not be administrated to pregnant women or to women who may be pregnant. If pregnancy is diagnosed during administration, this drug should be discontinued immediately.
(Foetal or neonatal death, oligohydramnios, foetal or neonatal hypotension, renal failure, hyperkalaemia, skull hypoplasia, and extremity contracture/malformation of brain, skull, or face/pulmonary dysplasia possibly caused by oligohydramnios, etc. have been reported in pregnant patients in their second or third trimester treated with ARBs including this drug or ACE inhibitors. An overseas retrospective epidemiological study suggested that the relative risk of foetal malformation during the first trimester was higher in the group of ACE inhibitor users than the group of antihypertensive drug nonusers.)

See the package inserts for other precautions on ARBs and ACE inhibitors. Package inserts can be searched for and viewed on the PMDA website（http://www.pmda.go.jp）(only available in Japanese language).

## Typical case reports

Case 1: Suspected drug-valsartan/amlodipine besilate

<table>
<tr><td rowspan="2">Sex/<br>Age</td><td rowspan="2">Reason for use<br>(complications)</td><td rowspan="2">Daily dose/<br>Treatment<br>duration</td><td colspan="2">Adverse reactions</td></tr>
<tr><td colspan="2">Clinical course and therapeutic measures</td></tr>
<tr><td rowspan="5">Mother<br>in her<br>30s<br><br>Male<br>offspring</td><td rowspan="5">Hypertension<br>(obesity)</td><td rowspan="5">valsartan<br>80 mg /<br>amlodipine<br>5 mg<br>(unknown)</td><td colspan="2">Mother; oligohydramnios, preterm premature rupture of membranes, and premature labour<br>Offspring; premature baby, hypocalvaria, renal tubular disorder, and low birth weight baby</td></tr>
<tr><td>Day 1 of administration (unknown gestation)</td><td>The mother started to take valsartan/amlodipine besilate.<br>(gravida 1, para 1, smoker, no alcohol consumption, unknown if contraceptive was used)</td></tr>
<tr><td>Day of discontinuation (estimated 24-week gestation)</td><td>The mother visited her previous doctor because a pregnancy test was positive. The foetus appeared at 24 weeks gestation. The mother had anhydramnios. Administration of valsartan/amlodipine was discontinued.</td></tr>
<tr><td>1 day after discontinuation</td><td>The mother was referred to this hospital.</td></tr>
</table>

| Sex/ Age | Reason for use (complications) | Daily dose/ Treatment duration | Adverse reactions | |
|---|---|---|---|---|
| | | | Clinical course and therapeutic measures | |
| | | | 8 days after discontinuation (estimated 25 weeks gestation) | The foetal bladder was identified. But there was no amniotic fluid. |
| | | | 29 days after discontinuation (estimated 28 weeks gestation) | Amniotic fluid volume increased to a normal level. |
| | | | 52 days after discontinuation (31 weeks gestation) | Membrane rupture and labour pain occurred. Emergency caesarean section was performed because the mother had given birth through caesarean section in the previous delivery.<br><br>Findings of offspring:<br>Sex, male<br>Body height, 40.5 cm<br>Body weight, 1700 g<br>1-minute Apgar score, 6; 5-minute Apgar score, 9<br>Congenital anomaly,<br>skull hypoplasia and renal tubular disorder<br>Abnormality other than congenital anomaly, jaundice<br>No pulmonary displasia |
| | | | 108 days after discontinuation (56 days old) | Neonatal outcome was alive. |
| Concomitant medications: none | | | | |

Case 2: Suspected drug-telmisartan/hydrochlorothiazide

| Sex/ Age | Reason for use (complications) | Daily dose/ Treatment duration | Adverse reactions | |
|---|---|---|---|---|
| | | | Clinical course and therapeutic measures | |
| Mother in her 40s<br><br>Male offspring | Hypertension | telmisartan 40 mg / hydrochlorothiazide 12.5 mg (34 days) | Mother; premature labour, oligohydramnios, and foetal growth restriction<br>Offspring; hypotension, oliguria, renal impairment, low birth weight baby, and renal tubular acidosis | |
| | | | Approximately 4 years before administration | Hypertension was diagnosed but left untreated. |
| | | | Approximately 8 months before administration | Urine protein was positive but left untreated. |
| | | | | The mother did not recognize her pregnancy until the day of delivery. |
| | | | Day 1 of administration (estimated 25 weeks gestation) | Telmisartan/hydrochlorothiazide was prescribed to treat hypertension. The mother started to take telmisartan/hydrochlorothiazide without recognizing her pregnancy. |
| | | | Date unknown | Foetal growth became poor. |

| Sex/ Age | Reason for use (complications) | Daily dose/ Treatment duration | Adverse reactions | |
|---|---|---|---|---|
| | | | Clinical course and therapeutic measures | |
| | | | Day of discontinuation (34 days after administration) (estimated 30 weeks gestation) | The mother visited hospital A for a detailed examination of renal disorder. Her pregnancy was confirmed at this visit, and she was transferred to hospital B on the same day. The day of last menstruation was unknown; however, it was estimated to be 7 months ago, and the gestational age appeared to be approximately 34 weeks. Because the estimated body weight of the foetus was 1500 g, the foetal growth was considered equivalent to 30 weeks gestation. Oligohydramnios was found. Systolic blood pressure was 190 to 200 mmHg. The amniotic cavity was very small, and severe variable deceleration was frequently found on a foetal monitor. Emergency caesarean section was therefore performed. Delivery time was 17:48 (premature labour).<br><br>Findings of offspring:<br>Sex, male<br>Body height, 39.9 cm<br>Body weight, 1400 g (very low birth weight baby)<br>Congenital anomaly and other abnormalities were found:<br>hypotension (average blood pressure was at the 40 mmHg), anuria, and renal failure were prolonged. |
| | | | 1 day after discontinuation (1 day old) | Administration of dopamine hydrochloride to the offspring was started at 2:35. After administration, the offspring remained unresponsive to catecholamine, and oliguria was found. |
| | | | 2 days after discontinuation (2 days old) | Furosemide 1.5 mg was administered intravenously for the treatment of oliguria at 15:00, but the offspring did not recover. The blood pressure was controlled by adjusting the dose of dopamine hydrochloride according to the offspring's condition. |
| | | | 5 days after discontinuation (5 days old) | Urine output gradually increased and the dose of dopamine hydrochloride was reduced. |
| | | | 6 days after discontinuation (6 days old) | Oliguria was remitted. |
| | | | 9 days after discontinuation (9 days old) | Dopamine hydrochloride 3 γ was administered to the offspring. Although urine output increased, severe renal failure remained with 7.01 mg/dL of serum creatinine and 12.5 mg/dL of uric acid. |
| | | | 11 days after discontinuation (11 day old) | Hypotension was remitted in the offspring. |
| | | | Date unknown | Renal tubular acidosis occurred in the offspring. |
| | | | 40 days after discontinuation (40 days old) | Although serum creatinine tended to decrease in the offspring, metabolic acidosis remained. Administration of sodium bicarbonate was started in the offspring. |
| | | | 62 days after discontinuation (62 days old) | The offspring was discharged from hospital. The offspring was followed up for mild renal failure and renal tubular acidosis as an outpatient. |
| Concomitant medicines: amlodipine besilate, carbocisteine, and bakumondoto | | | | |

Case 3: Suspected drug-candesartan cilexetil

<table>
<tr><td>Sex/<br>Age</td><td>Reason for use<br>(complications)</td><td>Daily dose/<br>Treatment<br>duration</td><td colspan="2">Adverse reactions<br>Clinical course and therapeutic measures</td></tr>
<tr><td rowspan="6">Mother<br>in her<br>30s<br><br>Female<br>offspring</td><td rowspan="6">Essential<br>hypertension</td><td rowspan="6">12 mg<br>(unknown)</td><td colspan="2">Mother; oligohydramnios<br>Offspring; foetal renal failure and transient limb extension disorder</td></tr>
<tr><td>Day of<br>administration<br>(3 years ago)</td><td>The mother started to take candesartan cilexetil for the treatment of essential hypertension. The mother had been followed up for her pregnancy since the first trimester in a local obstetric clinic. Her pregnancy was diagnosed to be complicated with chronic hypertension and the mother continued to take candesartan cilexetil. Blood pressure remained under 140/90 mmHg.</td></tr>
<tr><td>Day of<br>discontinuation<br>(30 weeks and 2<br>days gestation)</td><td>The mother was transferred to a facility with a perinatal medical center because oligohydramnios was found at regular check up for pregnancy. Before transferring, amniotic fluid volume was not measured. Blood pressure was 145/88 mmHg and protein urine was negative at the arrival of the facility. Rupture of membranes was considered to be ruled out based on findings from the examination. Amniotic Fluid Index (AFI) was 0 cm. Estimated body weight of the foetus was 1363 g and considered normal for gestational age. No morphological abnormalities was found in bilateral kidneys; however, no urine accumulation was identified in the bladder even from several examinations. Although her thorax was not bell-shaped, thoracic circumference/abdominal circumference was 0.74, indicating mild pulmonary hypoplasia. No abnormal morphology was found in other organs.<br>Her physician considered that oligohydramnios was caused by foetal renal failure, and replaced candesartan cilexetil with methyldopa.</td></tr>
<tr><td>5 days after<br>discontinuation<br>(31 weeks<br>gestation)</td><td>Urine accumulation was found in the bladder 5 days after discontinuation of candesartan cilexetil.</td></tr>
<tr><td>9 days after<br>discontinuation<br>(31 weeks and 4<br>days gestation)</td><td>The amniotic fluid volume increased 9 days after discontinuation of candesartan cilexetil. AFI was 2.3 cm. After that, the amniotic fluid volume did not decrease and AFI was 3 to 6 cm.<br>The baseline foetal heart rate (FHR) had an upper limit of normal (160 bpm), baseline variability was low, and no temporary tachycardia was found at all.<br>A week after discontinuation, the baseline FHR decreased to 140 bmp, and temporary tachycardia was frequently found.<br>The blood pressure was not increased in the mother after the treatment was replaced with methyldopa.</td></tr>
<tr><td>42 days after<br>discontinuation<br>(36 weeks and 2<br>days gestation)</td><td>Labour was induced with oxytocin because of premature rupture of membranes. The mother delivered vaginally.<br><br>Findings of offspring:<br>Sex, female<br>Body height, 40.5 cm<br>Body weight, 2416 g<br>1-minute Apgar score, 8; 5-minute Apgar score, 8<br>Umbilical cord arterial blood pH, 7.305<br>Congenital anomaly and other abnormalities were found:<br><br>The offspring cried in a small sterilized area for delivery. No obvious respiratory disorder was found. The chest X-ray test did not show thoracic hypoplasia. No skull hypoplasia was found. Mild transient limb extension disorder was found.<br>Urinary output was found after 6 hours after birth. Serum creatinine was within the normal range. Urine beta 2 microglobulin slightly increased.<br>The ultrasound test showed no abnormal morphology but increased brightness in the kidneys.</td></tr>
<tr><td colspan="5">Concomitant medicines; unknown</td></tr>
</table>

- Fifty-eight adverse events in 25 pregnant women and foetuses that are possibly associated with the use of ARBs or ARB combination products in pregnant women (reported between fiscal year 2011 and 2013)

Pregnant women

| Type of ADRs | Term of adverse reaction | Number of ADR cases |
|---|---|---|
| Pregnancy, puerperium and perinatal conditions | Oligohydramnios | 9 |
| | Premature labour | 2 |
| | Foetal growth restriction | 2 |
| | Preterm premature rupture of membranes | 1 |
| | Threatened labour | 1 |
| | Pre-eclampsia | 1 |
| | Polyhydramnios | 1 |
| Surgical intervention | Uterine dilation and evacuation | 1 |

Foetuses/ neonates

| Type of ADRs | Term of adverse reaction | Number of ADR cases |
|---|---|---|
| Congenital, familial and genetic disorders | Premature baby | 4 |
| | Foetal death | 2 |
| | Osteogenesis imperfecta | 2 |
| | Pulmonary hypoplasia | 2 |
| | Rib hypoplasia | 2 |
| | Potter's syndrome | 2 |
| | Low birth weight baby | 2 |
| | Congenital absence of cranial vault | 1 |
| | Hypocalvaria | 1 |
| | Cleft lip and palate | 1 |
| | Phalangeal hypoplasia | 1 |
| | Patent ductus arteriosus | 1 |
| | Foetal malformation | 1 |
| | Congenital cystic kidney disease | 1 |
| | Congenital anomaly | 1 |
| Renal and urinary disorders | Renal failure neonatal | 4 |
| | Renal impairment | 2 |
| | Renal failure | 1 |
| | Renal tubular disorder | 1 |
| | Renal tubular acidosis | 1 |
| | Oliguria | 1 |
| Respiratory disorders | Neonatal asphyxia | 1 |
| | Respiratory failure | 1 |
| Musculoskeletal disorders | Joint contracture | 1 |
| Cardiovascular disorders | Hypotension | 1 |
| Nervous system disorders | Epilepsy | 1 |
| Hearing disorders | Hearing impaired | 1 |

- Five adverse events in 3 pregnant women and foetuses that are possibly associated with the use of ACE inhibitors in pregnant women (reported between fiscal year 2011 and 2013)

Pregnant women

| Type of ADRs | Term of adverse reaction | Number of ADR cases |
|---|---|---|
| Pregnancy, puerperium and perinatal conditions | Oligohydramnios | 1 |

Foetuses/ Neonates

| Type of ADRs | Term of adverse reaction | Number of ADR cases |
|---|---|---|
| Congenital, familial and genetic disorders | Renal aplasia | 1 |
| | Congenital cystic kidney disease | 1 |
| Renal and urinary disorders | Renal failure | 1 |
| | Kidney enlargement | 1 |

# ARBs and ACE inhibitors approved in Japan

| | Nonproprietary Name | Brand Name |
|---|---|---|
| ARBs | azilsartan | Azilva |
| | irbesartan | Avapro, Irbetan |
| | olmesartan medoxomil | Olmetec |
| | candesartan cilexetil | Blopress and the others |
| | telmisartan | Micardis |
| | valsartan | Diovan and the others |
| | losartan potassium | Nu-lotan and the others |
| ARB combination products | azilsartan /amlodipine besilate | Zacras |
| | irbesartan/amlodipine besilate | Aimix |
| | irbesartan/trichlormethiazide | Irtra |
| | olmesartan medoxomil/azelnidipine | Rezaltas |
| | candesartan cilexetil/amlodipine besilate | Unisia |
| | candesartan cilexetil/hydrochlorothiazide | Ecard |
| | telmisartan/amlodipine besilate | Micamlo |
| | telmisartan/hydrochlorothiazide | Micombi |
| | valsartan/amlodipine besilate | Exforge |
| | valsartan/cilnidipine | Atedio |
| | valsartan/hydrochlorothiazide | Co-dio |
| | losartan potassium/hydrochlorothiazide | Preminent and the others |

| | Nonproprietary Name | Brand Name |
|---|---|---|
| ACE inhibitors | alacepril | Cetapril and the others |
| | imidapril hydrochloride | Tanatril and the others |
| | enalapril maleate | Renivace and the others |
| | captopril | Captoril and the others |
| | quinapril hydrochloride | Conan |
| | cilazapril hydrate | Inhibace and the others |
| | temocapril hydrochloride | Acecol and the others |
| | delapril hydrochloride | Adecut |
| | trandolapril | Preran, Odric, and the others |
| | benazepril hydrochloride | Cibacen and the others |
| | perindopril erbumine | Coversyl and the others |
| | lisinopril hydrate | Zestril, Longes, and the others |

**The Japan Drug Information Institute in Pregnancy (JDIIP) 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.**

**Please find further information on the JDIIP in the National Center for Child Health and Development at the following website:**
http://www.ncchd.go.jp/kusuri/index.html
**(Japanese language only)**

**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 Pharmaceutical Affairs Law.
* 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 responsibilities on them, but is provided to promote the proper use of drugs.

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