Umbilical cord blood concentrations of labetalol hydrochloride administered to patients with pregnancy induced hypertension, and subsequent neonatal findings

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Aim: We measured umbilical cord blood and maternal plasma concentrations of labetalol hydrochloride (labetalol) at delivery in women with pregnancy induced hypertension (PIH) who received labetalol treatment, and also investigated the influence of labetalol on neonatal findings.

Methods: We surveyed background, neonatal findings, and health checkups after birth among PIH patients who received labetalol. Umbilical cord blood was collected within 15 min after delivery and venous blood within 2 h. Umbilical cord blood and maternal plasma concentrations of labetalol were measured using liquid chromatography-tandem mass spectrometry.

Results: PIH was evaluated as severe hypertension in 20 patients and mild hypertension in 9 according to the Guidelines for the Management of PIH. Umbilical cord blood concentrations of labetalol were 17.2 ± 11.4 ng /ml in the 150 mg /day group (n = 22) and 32.8 ± 11.6 ng /ml in the 300 mg /day group (n = 7). Mean maternal plasma concentrations of labetalol in the 150 mg /day and 300 mg /day groups were 29.2 ± 21.0 ng /ml and 49.3 ± 12.6 ng /ml, respectively. The 300 mg /day group also included 2 low-birthweight neonates, whose Apgar scores were 5 after 1 min but returned to normal values after 5 min. There were no abnormalities in Apgar score or umbilical cord blood pH in any other neonates and no abnormal findings at neonatal checkups. Patients who continued drug therapy after delivery even performed breast feeding.

Conclusions: There was some correlation between labetalol concentrations in umbilical cord blood and in maternal plasma (r = 0.688), with the former corresponding to 60% to 70% of the latter.

Introduction

Hypertensive pregnancy disorders affect about 10% of all pregnant women around the world. Because excessive increases may result in cerebral disorders, antihypertensive treatment should be given to women with severe hypertension during pregnancy. Patients with hypertension (140/90 mmHg or greater) from 20 weeks of gestational age until 12 weeks after delivery or those with hypertension and proteinuria unrelated to incidental pregnancy-associated complications are regarded as having pregnancy induced hypertension (PIH). For national standardization of drug therapy for PIH, the Japan Society for the Study of Hypertension in Pregnancy prepared “Guideline 2009 for care and treatment of hypertension in pregnancy (PIH)”. Methyldopa, hydralazine, and labetalol are recommended as antihypertensive treatments for pregnant women. The guidelines also state that calcium antagonists should only be used after obtaining informed consent. These drugs are also recommended in international guidelines. In Japan, the package inserts state that labetalol is...
contraindicated for pregnant women but were revised in June 2011 to include the following: “Labetalol should be administered to pregnant women or those who may be pregnant only when its therapeutic advantages may exceed its disadvantages. For administration, the maternal and fetal states must be carefully observed to avoid an excessive decrease in blood pressure. When there are abnormalities such as blood-pressure fall and bradycardia in fetuses/neonates, appropriate treatment should be performed”.

In this study, we measured umbilical cord blood and maternal plasma concentrations of labetalol at delivery in pregnant women who were treated with labetalol after a diagnosis of PIH. We also investigated neonatal data and findings at health checkups to examine the influence of labetalol on neonates.

Materials and methods

Subjects
Study subjects were pregnant women who consulted the Department of Obstetrics and Gynecology at the Japanese Red Cross Medical Center between April 2010 and August 2011, were taking labetalol tablets due to a diagnosis of PIH, and provided written informed consent after 20 weeks of gestational age. The labetalol could have been combined with a continuous nifedipine preparation or nicardipine/magnesium sulfate injection on delivery or in the case of emergency. Patients treated with other hypotensive drugs were excluded, as were those with multiple pregnancy, stillbirth, or origin other than East Asian descent.

Prior to this study, the protocol was approved by the Ethics Review Boards of the Japanese Red Cross Medical Center and Keio University Faculty of Pharmacy.

Survey items
We investigated the dose of labetalol and administration period, patient age, gestational age, previous delivery, form of delivery, type of PIH, combined drugs, neonatal body weight, Apgar score, umbilical cord blood pH, and health checkup findings in the subjects.

The type of PIH was classified as gestational hypertension, preeclampsia, superimposed preeclampsia, or eclampsia. Symptoms were subclassified as mild PIH or severe PIH, as follows.

Mild PIH: Blood pressure is $\geq 140/90$ mmHg but $<160/110$ mmHg after 20 weeks of gestation, and proteinuria is $\geq 300$ mg/24 h without exceeding 2.0 g/24 h or 3 + dipstick.

Severe PIH: Blood pressure is $\geq 160/110$ mmHg, and proteinuria exceeds 2.0 g/24 h or 3 + dipstick.

Onset was subclassified into early onset (EO) or late onset (LO), as follows.

EO: PIH emerges earlier than 32 weeks of gestation.
LO: PIH emerges after 32 weeks of gestation.

Blood samples
Umbilical cord blood was collected within 15 min after delivery, and maternal venous blood within 2 h (the interval when oral administration of labetalol was investigated). Blood samples were placed in heparin-containing containers, immediately centrifuged at 3,000 rpm for 6 min, and frozen/stored at -80°C until measurement.

Measurement of labetalol concentration
Umbilical cord blood or maternal plasma samples at 0.2 ml were mixed with internal standard solution (propranolol), pretreated by deproteinization with acetonitrile, and analyzed using liquid chromatography-tandem mass spectrometry (LC/MS/MS system; Agilent 1200 Series, API4000 [AB Sciex Pte. Ltd.]). A CAPCELL PAK MGIII column (Shiseido Co., Ltd., Tokyo, Japan) was used for gradient analysis (2.0 mm I.D. × 50 mm L., 5 μm) of the mobile phase (10 mM ammonium acetate solution and acetonitrile) at 0.5 ml/min. Using positive ion mode electrospray ionization, the monitored ions for labetalol and the internal standard substance were established at m/z ratios of 329 to 162 and 260 to 116, respectively.

Results

Subjects
The number of deliveries (single pregnancy) between April 2010 and August 2011 (survey period, 17 months) was 3,895. Of those, 193 women had PIH, and of those, 29 were enrolled in this survey.

Labetalol doses were 150 mg/day (50 mg × 3 times a day) in 22 patients, with an administration period of 10.91 ± 8.93 days, and 300 mg/day (100 mg × 3 times a day) in 7 patients with an administration period of 8.14 ± 6.36 days. The 150 mg/day and 300 mg/day labetalol doses were combined with a continuous nifedipine preparation in 2 and 3 patients, respectively. Antihypertensive treatment was used at delivery in 15 patients: nicardipine injection in 9, magnesium sulfate in 4, and a combination of the two agents in 2.

Mean patient age was 37.9 ± 3.9 years (mean ± SD) (150 mg/day group, 38.4 ± 3.9 years; 300 mg/day group, 36.4 ± 3.7 years) and mean gestational age was 36.3 ± 3.5 weeks (150 mg/day group, 37.1 ± 2.9 weeks; 300 mg/day group, 33.7 ± 4.2 weeks). Regarding previous delivery, there were 22 primiparae (150 mg/day group, 18; 300 mg/day group, 4). With respect to form of delivery, 21 patients underwent cesarean section (150 mg/day group, 15; 300 mg/day group, 6).

PIH subtype was evaluated as severe in 20 patients and
Umbilical cord blood concentrations of labetalol

mild in 9. All patients who received labetalol combined
with continuous nifedipine preparation had severe PIH.
Types of PIH and doses of labetalol are shown in Table 1.

Umbilical cord blood and maternal plasma
congentrations of labetalol
Mean umbilical cord blood concentrations of labetalol
in the 150 and 300 mg/day groups were 17.3 ± 11.4
(interval from labetalol administration until blood
collection, 6.1 ± 3.5 h) and 32.8 ± 11.6 ng/ml (5.2 ± 3.3
h), respectively. Umbilical cord blood concentrations
of labetalol and interval from labetalol administration
until blood collection are presented in Figure 1. Mean
maternal plasma concentrations of labetalol in the 150
and 300 mg/day groups were 29.2 ± 21.0 (6.9 ± 3.7 h)
and 49.3 ± 12.6 ng/ml (5.5 ± 3.6 h), respectively. The
maternal plasma concentration of labetalol and interval
from labetalol administration until blood collection are
presented in Figure 2. There was a correlation between
umbilical cord blood and maternal plasma concentrations
of labetalol ($r = 0.688$, Figure 3).

Neonatal findings
Birthweights in the mild and severe hypertension groups
were 2,611.2 ± 598.3 and 2,104.0 ± 712.3 g, respectively.
There were 18 low-birthweight neonates (less than 2,500

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Timing of onset</th>
<th>Urinary protein</th>
<th>Dose of labetalol (number of patients)</th>
<th>Subtotal</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P</td>
<td>150 mg/day</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>H</td>
<td>EO</td>
<td>p</td>
<td>150 mg/day</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absent</td>
<td>150 mg/day</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p</td>
<td>300 mg/day</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>H</td>
<td>LO</td>
<td>p</td>
<td>300 mg/day</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Absent</td>
<td>300 mg/day</td>
<td>0</td>
<td>2</td>
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<tr>
<td>h</td>
<td>EO</td>
<td>p</td>
<td>150 mg/day</td>
<td>0</td>
<td>2</td>
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<td></td>
<td></td>
<td>Absent</td>
<td>150 mg/day</td>
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<td>2</td>
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<tr>
<td></td>
<td></td>
<td>p</td>
<td>300 mg/day</td>
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<tr>
<td>h</td>
<td>LO</td>
<td>p</td>
<td>300 mg/day</td>
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<tr>
<td></td>
<td></td>
<td>Absent</td>
<td>300 mg/day</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

H, severe hypertension; h, mild hypertension; P, severe proteinuria; p, mild proteinuria; EO, early onset; LO, late onset.

Table 1. Sub-Type of PIH and dose of labetalol

Figure 1. Umbilical cord blood concentration of labetalol hydrochloride administered to patients with PIH.
Umbilical cord blood concentrations of labetalol with
respect to the interval after oral administration are shown.
○, Patients treated at 300 mg/day (100 mg × 3 times a
day); ●, Patients treated at 150 mg/day (50 mg × 3 times a
day).

Figure 2. Maternal plasma concentration of labetalol hydrochloride administered to patients with PIH.
Maternal plasma concentrations of labetalol with respect
to the interval after oral administration are shown. ○, Patients treated at 300 mg/day (100 mg × 3 times a day);
●, Patients treated at 150 mg/day (50 mg × 3 times a day).
Of these, birthweights ranged from 1,500 g to 2,499 g in 12 cases and < 1,500 g in 6. Apgar scores after 1 min and 5 min and umbilical cord blood pH with respect to birthweight are shown in Table 2. Of the neonates weighing < 1,500 g at birth, 2 showed an Apgar score of 5 after 1 min that rose to 9 after 5 min. The 18 low-birthweight neonates were admitted for weight control. There were no abnormal findings.

Neonatal findings at health checkups
After delivery, antihypertensive treatment was completed for 3 patients in the 150 mg/day group. The other 26 patients continued to receive the following treatments: labetalol alone, 12 patients; continuous nifedipine preparation alone, 12; and combination therapy, 2. There were no abnormalities regarding findings such as weight gain at health checkups (mean interval after birth, 34.9 ± 20.8 days; range, 12 to 90 days) for any of the neonates. Furthermore, all subjects performed breast-feeding (complete breast-feeding, 20; mixed feeding, 9).

Discussion
Labetalol is an $\alpha\beta$-blocker that exhibits antihypertensive actions through $\beta$-receptor and selective $\alpha_1$-receptor blockage. It does not influence cardiac output but does slowly decrease blood pressure by reducing peripheral vascular resistance.3,4) Because labetalol also decreases cerebral perfusion pressure without influencing the cerebral flow index,5) it may help prevent severe preeclampsia.1) At international society meetings, labetalol injection has been presented as a first-choice drug6–10) and, with the recent revision of the package inserts, may be increasingly administered to PIH patients in Japan.

Administration of labetalol in Japan is described as follows: “Administration should be started at 150 mg/day. When there is no response, the dose may be gradually increased to 450 mg/day, which should be divided into 3 doses per day”. In our study, the 150 mg/day group consisted of 22 patients, and the 300 mg/day group consisted of 7. In the latter group, the type of PIH was evaluated as HP-EO in 3 patients, H-EO in 1, HP-LO in 1, and H-LO in 2. All 7 patients in the group had severe PIH (Table 1).

With respect to the pharmacokinetics of labetalol administered to healthy adults as a single dose, the Tmax, Cmax, and T1/2 after a 50 mg dose were reportedly 0.97 h, 21.77 ng/ml, and 17.22 h, respectively. Pharmacokinetics after a 100 mg dose were 1.22 h, 59.73 ng/ml, and 17.65 h, respectively.11) In our study, we measured the maternal plasma concentration of labetalol in 29 patients with PIH. Some showed high values: 92.9 ng/ml (1 h after oral administration at 50 mg), 74.4 ng/ml (5 h after oral administration at 50 mg), and 69.0 ng/ml (1 h after oral administration at 100 mg) (Figure 2).

Michel et al. reported that umbilical cord blood and maternal plasma concentrations of labetalol hydrochloride administered to patients with PIH. There was a correlation between umbilical cord blood and maternal plasma concentrations of labetalol ($r = 0.688$). Regression line, $y = 0.43x + 6.40$.

![Figure 3. Correlation between umbilical cord blood and maternal plasma concentrations of labetalol hydrochloride administered to patients with PIH. There was a correlation between umbilical cord blood and maternal plasma concentrations of labetalol ($r = 0.688$).](image)

**Table 2. Sub-type of PIH and neonatal findings**

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Cesarean section (persons)</th>
<th>Mean birth weight (g)</th>
<th>Birth weight (persons)</th>
<th>Apgar score after 1 minute</th>
<th>Apgar score after 5 minutes</th>
<th>Umbilical cord blood pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (n = 20)</td>
<td>15</td>
<td>2,104.0 ± 712.3</td>
<td>&lt;1,500 g (6)</td>
<td>7.2 ± 1.7</td>
<td>9.2 ± 0.4</td>
<td>7.306 ± 0.052</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,500 to 2,499 g (8)</td>
<td>8.5 ± 0.5</td>
<td>9.4 ± 0.5</td>
<td>7.316 ± 0.033</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥2,500 g or more (6)</td>
<td>8.8 ± 0.4</td>
<td>9.5 ± 0.5</td>
<td>7.314 ± 0.036</td>
</tr>
<tr>
<td>h (n = 9)</td>
<td>6</td>
<td>2,611.2 ± 598.3</td>
<td>&lt;1,500 g (0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,500 to 2,499 g (4)</td>
<td>8.5 ± 0.6</td>
<td>9.5 ± 0.6</td>
<td>7.305 ± 0.037</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥2,500 g or more (5)</td>
<td>8.2 ± 0.4</td>
<td>9.4 ± 0.5</td>
<td>7.327 ± 0.041</td>
</tr>
</tbody>
</table>

H, severe hypertension; h, mild hypertension.
administration to pregnant women (n = 4) at 330 mg/day were 42 ng/ml and 64 ng/ml, respectively. In the present study, the umbilical cord blood/maternal plasma concentration ratio was 0.66. Our subjects with PIH displayed mean umbilical cord blood and maternal plasma concentrations of labetalol in the 150-mg/day group (n = 22) that were 17.3 ng/ml and 29.2 ng/ml, respectively (6.1 h and 6.9 h [mean] after oral administration at 50 mg, respectively). The umbilical cord blood/maternal plasma concentration ratio was 0.59. In the 300-mg/day group (n = 7), mean umbilical cord blood and maternal plasma concentrations were 32.8 ng/ml and 49.3 ng/ml, respectively (5.2 h and 5.5 h [mean] after oral administration at 50 mg, respectively). The concentration ratio was 0.67. There was also a correlation between umbilical cord blood and maternal plasma concentrations of labetalol (r = 0.688), suggesting that the umbilical cord blood concentration of labetalol corresponds to approximately 59 to 67% of its maternal plasma concentration in both European/American and Japanese patients.

One study indicated that administration of labetalol to pregnant women caused neonatal bradycardia and fetal growth restriction. Furthermore, Eguchi et al. reported that the incidence of intrauterine growth retardation and proportion of premature birth-related low-birthweight neonates were high in PIH patients. In our study, 14 of the 20 severe PIH patients delivered low-birthweight neonates. In 6 of those cases, neonatal birthweights were <1,500 g. On the other hand, 4 of the 9 mild PIH patients delivered low-birthweight neonates, although they weighed >1,500 g. This finding confirmed that severe PIH patients may deliver low-birthweight neonates.

In 2 neonates weighing <1,500 g, Apgar scores were 5 after 1 min but returned to normal after 5 min. Although we could not specify whether this was related to labetalol administration, umbilical cord factors, immaturity, or other factors, there may be no influence from labetalol. In other neonates, there were no abnormalities in Apgar score or umbilical cord blood pH.

After delivery, antihypertensive treatment could be discontinued for 3 patients in the 150 mg/day group. However, for the other 26 patients, treatment was continued. All subjects performed breast feeding. At the health checkup 1 month after birth, there were no problems regarding findings such as weight gain.

The umbilical cord blood transfer of labetalol is approximately 60 to 70% of its maternal plasma concentration.

**Acknowledgments**

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**Conflict of interest**

None.

**References**