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Evaluation of pharmacotherapy for pregnancy-induced hypertension

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Purpose：The purpose of this study was to survey the use of hypotensive agents, for the treatment of pregnancy-induced hypertension (PIH), and to examine the neonatal and neonatal patient characteristics and prognoses.

Methods：A retrospective investigation was conducted by the use of medical records for all deliveries between 2006 and 2010 at the Japanese Red Cross Medical Center .

Results：The maternal age, Cesarean section rate, and proportion of underweight neonates were greater in women with PIH than that in the overall study population. Labetalol hydrochloride and a nifedipine sustained-release preparation were administered as the hypotensive agents of choice before and after delivery. The overall incidence of PIH during the study period was approximately 4%, and this did not change markedly from year-to-year. However, there were increases in the maternal age and proportion of patients receiving hypotensive agents. The birth weight of the infants also increased slightly, and there was a decrease in the neonatal admission rate during the study period.

Conclusions： Administration of hypotensive agents such as labetalol hydrochloride and a nifedipine sustained-release preparation for PIH during pregnancies may improve neonatal prognoses.

Key Words: Perinatal statistics, Pregnancy-induced hypertension, Hypotensive agents, Labetalol hydrochloride, Nifedipine

Introduction

In August 2000, the Japanese Red Cross Medical Center was authorized as a “Baby Friendly Hospital (BFH),” by the United Nations Children Fund (UNICEF) and the World Health Organization (WHO). In November 2001, the hospital was also authorized as a perinatal medical center by the Tokyo Metropolitan Government; the same agency subsequently designated the hospital as a perinatal medical center for maternal critical care (a super-perinatal center) in March 2009. Since then, pregnant women requiring critical care have also been admitted for care under the direction of critical care staff.

Statistical reports published by the Japanese Ministry of Health, Labour and Welfare[1] have indicated that the birth and perinatal mortality rates are decreasing every year in Japan. At the same time decreases in the numbers of obstetricians and obstetric clinics/hospitals, coupled with older

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mothers giving birth, have markedly increased the number of high-risk patients. As a result, the number of pregnant women requiring drug therapy has increased in the major hospitals. In response to this trend, "Guidelines for the Management of Pregnancy-Induced Hypertension (PIH)"[2] were established by the Japan Society for the Study of Hypertension in Pregnancy in 2009.

In this study, we aimed to survey the use of hypotensive agents, for the treatment of PIH, and to examine the neonatal and neonatal patient characteristics and prognoses.

Methods

Maternal characteristics (age, primipara/multipara, and delivery type (normal or Cesarean section) and birth weights of the babies were extracted from the hospital records of women who delivered a baby in the hospital between 2006 and 2010. In addition, for mothers diagnosed with PIH and their neonates, the study examined the use of hypotensive agents administered to mothers (before, during, and after delivery) and the subsequent neonatal observations (Apgar score, umbilical cord venous blood pH, and additional hospital care), based on medical records. Furthermore, the mothers were also classified with respect to the underlying disease resulting in the hypertension, the severity of their hypotension, and the timing of onset, according to the Guidelines for the Management of Pregnancy-Induced Hypertension. Pregnant women with Down's Syndrome and those delivering multiple children were excluded from the study.

Results

1. Total delivery count and PIH patients

There were a total of 12,140 deliveries between 2006 and 2010. The number of deliveries increased every year, as did the number of patients with PIH. However, the overall incidence of PIH was approximately 4% in each year. Advanced age (defined as women ≧ 35 years old) was more common in PIH patients (50%–60%) than in the total population of women delivering children within the study period. The primiparity rate was similar between women experiencing PIH and those who did not. However, the numbers of Cesarean sections and underweight neonates were higher in PIH patients (Table 1, 2).

Table 1. Total deliveries and pregnancy-induced hypertension statistics (PIH)*

	2006	2007	2008	2009	2010
Total number of deliveries	2129	2331	2478	2477	2725
Proportion of advanced-age mothers (%)[1]	35.2	37.4	35.3	36.5	40.2
Proportion of primiparas (%)	63.4	62.5	59.5	60.5	63.3
Cesarean section rate (%)	19.2	19.9	20.6	18	19.1
Proportion of low-birth-weight neonates (%)[2]	13.6	13.9	13	12.1	12.7
Number of patients with PIH	78	82	94	106	105
Incidence of PIH (%)	3.7	3.5	3.8	4.3	3.9
Proportion of advanced-age mothers (%)[1]	60.3	48.8	53.2	56.6	62.9
Proportion of primiparas (%)	62.8	63.4	64.9	63.2	71.4
Cesarean section rate (%)	38.5	51.2	48.9	34.9	54.3
Proportion of low-birth-weight neonates (%)[2]	42.3	42.7	38.3	26.4	35.2

* These statistics exclude women who delivered multiple children

1) Advanced age defined as those mothers ≥35 years old

2) Low-birth-weight neonate defined as a birth-weight < 2,500 g

Table 2. Comparison of women diagnosed with and without pregnancy-induced hypertension (PIH)

	Number of patients		*P* value
	PIH	non-PIH	
Advanced-age at time of delivery	263	4493	<0.05
Proportion of primiparas	303	7501	NS
Cesarean sections	212	2346	<0.05
Proportion of low-birth-weight neonates	169	1580	<0.05

χ^2-test

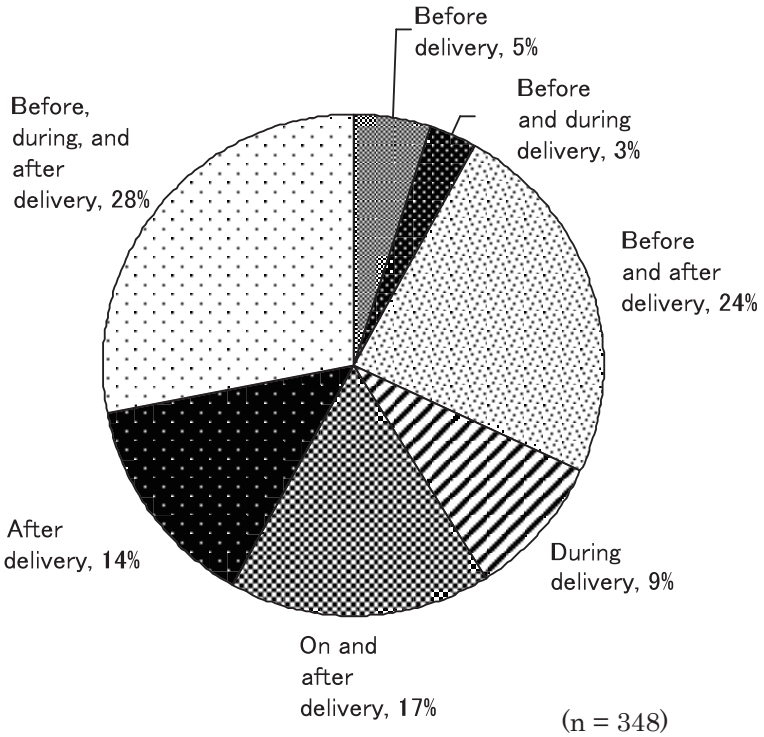
2. Use of hypotensive agents in PIH patients

Of the 465 patients diagnosed with PIH, hypotensive agents were administered to 348 (74.8%), with the annual percentage rate increasing over the 5-year study period (Table 3). In patients treated with hypotensive agents, the timing of therapeutic drug administration was also examined. The proportion of patients who received these agents before, during, and after delivery was the highest (28%), followed by patients who received them only before and after delivery (24%) (Figure 1).

Table 3. Use of hypotensive agents in patients with pregnancy-induced hypertension (PIH)

Year	2006	2007	2008	2009	2010	Total
PIH patients (n)	78	82	94	106	195	465
Treatment with hypotensive agents (n)	50	63	66	82	87	348
Proportion of patients receiving hypotensive agents (%)	64.1	76.8	70.2	80.2	82.9	74.8

Figure 1. Timing of treatment with hypotensive agents (2006–2010)



3. Type of hypotensive agents and maternal side effects

Combination therapy with labetalol hydrochloride and a nifedipine sustained-release preparation (Adalat® L) was the most commonly administered therapy. However, the number of labetalol hydrochloride (Trandate®) doses administered before delivery increased each year. During delivery, nicardipine hydrochloride injection (Perdipine®) was the most commonly administered therapeutic, followed by magnesium sulfate injection (Magnesol®, Magsent®), which was employed to prevent eclampsia. In a few patients, a combination therapy was administered. After delivery, the number of administered doses was similar between labetalol hydrochloride and the nifedipine sustained-release preparation (Table 4).

There were no serious maternal side effects associated with the use of the hypotensive agents described in the patient records. However, the most commonly observed mild side effects consisted of labetalol hydrochloride-related dizziness (3 episodes), increase in the hepatic enzyme level (1 episodes), malaise (1 episodes), nifedipine sustained-release preparation-related headaches (16 episodes), dull headaches (4 episodes), dizziness (4 episodes), facial discomfort (1 episodes), flare of the face (1 episodes), hot flushes/sweating (1 episodes), palpitation increase in the hepatic enzyme level (1 episodes).

4. Disease type and severity

Of the 465 patients diagnosed with PIH, the hypertension severity was recorded as severe in 206 individuals. Marked proteinuria was noted in 50 of these individuals, and protein was absent from the urine of 115 patients. The severity of hypertension was evaluated as mild in 247 patients. In these patients, marked proteinuria was noted in only 6 individuals, and protein was absent from the urine of 186 individuals. PIH occurred during the early phase of pregnancy in most patients with severe preeclampsia. However, in the other patients, it occurred most often during late phase . There was no specific annual tendency (Table 5).

5. Patients with eclampsia

Eclampsia was observed in only 4 individuals with PIH, whereas pregnancy-related eclampsia was not observed in any patient. Eclampsia during labor was noted in 3 patients, and puerperal eclampsia in 1; all 4 patients were having their first pregnancy (Table 6). Two of the 3 patients experiencing eclampsia during labor did not receive a hypotensivie agent. These 2 patients experienced a rise in blood pressure during Phase I of delivery, leading to a convulsive attack, and resulting in emergency Cesarean sections being performed. The third patient received a hypotensive agent before and during delivery. In spite of this treatment, a convulsive attack occurred during Phase II of delivery, and vacuum extraction delivery was conducted. In the patient with puerperal eclampsia, an emergency Cesarean section for placental abruption was performed at Week 27 of pregnancy and a convulsive attack occurred 8 hours after surgery. In all patients with eclampsia, the maternal and neonatal prognoses were favorable.

Table 4. Type of hypotensive agent, timing, and number of doses administered to patients with pregnancy-induced hypertension

Timing		Hypotensive agent	Year					Total
			2006	2007	2008	2009	2010	
Before delivery	Monotherapy	Labetalol hydrochloride	15	22	24	35	35	131
		Nifedipine sustained-release preparation	4	0	3	0	2	9
		α-Methyldopa	1	1	1	0	1	4
		Hydralazine	0	0	1	0	1	2
	Combination therapy	Labetalol hydrochloride + nifedipine sustained-release preparation	9	8	8	10	22	57
		Others	0	1	1	1	0	3
During delivery	Monotherapy	Nicardipine injection	18	19	6	16	16	75
		Magnesium sulfate injection	6	13	10	15	10	54
	Combination therapy	Magnesium sulfate injection + nicardipine injection	2	4	6	8	4	24
After delivery	Monotherapy	Labetalol hydrochloride	18	27	31	19	15	110
		Nifedipine sustained-release preparation	10	9	14	32	46	111
		Nifedipine once-a-day sustained-release preparation	0	1	0	2	6	9
	Combination therapy	Labetalol hydrochloride + nifedipine sustained-release preparation ,	5	15	10	9	7	46
		Others	2	4	0	1	1	8

Table 5. Disease type, severity, and timing of onset in patients with pregnancy-induced hypertension

Disease type	Severity		Number of episodes	Timing of onset	2006	2007	2008	2009	2010	Total
	Blood pressure	Proteinuria								
Preeclampsia	Severe	Severe	50	Early	6	6	3	1	11	27
				Late	2	5	10	2	4	23
	Severe	Mild	41	Early	3	1	0	5	0	9
				Late	5	4	4	5	14	32
	Mild	Severe	6	Early	0	1	0	0	0	1
				Late	1	1	2	1	0	5
	Mild	Mild	55	Early	3	3	1	0	1	8
				Late	7	10	15	5	10	47
Hypertension in pregnancy	Severe	Absent	115	Early	3	4	8	7	2	24
				Late	16	13	14	34	14	91
	Mild	Absent	186	Early	2	4	1	4	3	14
				Late	29	27	34	40	42	172
Superimposed preeclampsia[1)]			8		1	2	2	1	2	8
Eclampsia (Refer to Table 6.)			4		0	1	0	1	2	4

[1)] Patients with superimposed preeclampsia: 1 patient with IgA nephropathy, 1 with nephrotic syndrome, 1 with glomerular nephritis, and 5 with essential hypertension

Table 6. Patients with eclampsia (2006–2010)

	Gestational age on delivery	Primipara/multipara	Diagnosis	Admission management	Drug therapy		
					Before delivery	During delivery	After delivery
1	39 w 0 d	Primipara	Eclampsia during delivery	0day (Transport)	None	Magnesium sulfate injection	Labetalol tablets Nifedipine sustained-release tablets
2	40 w 6 d	Primipara	Eclampsia during delivery	10 days	Labetalol hydrochloride tablets	Nicardipine injection	Nifedipine sustained-release tablets
3	27 w 6 d	Primipara	Puerperal eclampsia (after 8 hours of delivery)	0day (Transport as an emergency)	Labetalol hydrochloride tablets	Magnesium sulfate injection	Nifedipine sustained-release tablets
4	41 w 4 d	Primipara	Eclampsia during delivery	4 days	None	Emergency Cesarean section for eclampsia attacks Diltiazem Propofol Fentanyl Midazolam	At the onset of eclampsia attacks: Magnesium sulfate injection Nifedipine sustained-release tablets (systolic blood pressure: 120 mmHg or more)

w = weeks; d = days

6. Neonatal findings in PIH patients

Annual changes were not observed in the average neonatal Apgar scores or in the umbilical cord venous blood pH levels. However, the maternal age and neonatal birth weights increased slightly. The post-delivery admission rate of the neonates decreased over the time period of the study (Table 7). When comparing the neonatal observations in 2006 with those in 2010, there were no significant differences in any of the parameters. However, despite a 1-year rise in the average maternal age, the average pregnancy period increased by 0.5 weeks, and the birth weight increased by 100 g or more (Table 8).

7. Type/severity of PIH and neonatal findings

The maternal and neonatal characteristics are shown in conjunction with the use of hypotensive agents in each patient group (Table 9). There were no marked differences in maternal age; however, the gestational age on delivery was less in preeclampsia patients with severe hypertension. The Cesarean section rate was also the highest in preeclampsia patients with severe hypertension and marked proteinuria. The neonates also did not demonstrate any marked differences in the umbilical cord venous blood pH. However, the Apgar score was lower in infants delivered to mothers who experienced preeclampsia with severe hypertension and marked proteinuria. Additionally, the neonatal birth weight in this group was less than 2,000 g, and these neonates had the highest hospital admission rate. The proportion of patients receiving hypotensive agents before, during, and after delivery was higher in the mothers with severe hypertension. However, in mothers experiencing mild hypertension, approximately 30% of the patients also received hypotensive agents before delivery, and 40%–60% after delivery. In spite of the perinatal administration of hypotensive agents to their mothers, none of neonates demonstrated a related adverse event. (Table 9 and 10).

Table 7. Neonatal characteristics (single pregnancy) in patients with pregnancy-induced hypertension

Year	Number of patients	Maternal age (years)	Gestational age (weeks)	Birth weight (g)	AP1[1)]	AP5[2)]	Umbilical cord venous blood pH	Neonatal admission rate (%)
2006	77	34.4 ± 3.6	36.8 ± 3.2	2426.7 ± 715.0	8.2 ± 1.2	8.4 ± 1.8	7.30 ± 0.06	34.6
2007	82	34.4 ± 4.1	36.8 ± 2.9	2499.2 ± 720.3	8.4 ± 1.0	8.7 ± 1.2	7.28 ± 0.05	34.1
2008	94	35.1 ± 3.4	37.3 ± 2.5	2530.0 ± 583.4	8.4 ± 0.9	9.2 ± 0.8	7.31 ± 0.04	23.4
2009	104	34.8 ± 3.8	37.6 ± 2.3	2673.0 ± 572.9	8.3 ± 1.0	9.0 ± 1.1	7.31 ± 0.05	22.6
2010	104	35.4 ± 3.8	37.3 ± 2.8	2562.6 ± 615.4	8.1 ± 1.0	9.1 ± 0.9	7.30 ± 0.05	21.9

Mean ± S.D.

[1)] AP1: Apgar score at 1 minute

[2)] AP5: Apgar score at 5 minutes

Table 8. Comparison of neonatal characteristics in 2006 with those in 2010

	2006 (n=77)	2010 (n=104)	*P* value
Maternal age (years)	34.4 ± 3.6	35.4 ± 3.8	0.15
Gestational age (weeks)	36.8 ± 3.2	37.3 ± 2.8	0.41
Birth weight (g)	2426.7 ± 715.0	2562.6 ± 615.4	0.27
AP1[1)]	8.2 ± 1.2	8.1 ± 1.0	0.92
AP5[2)]	8.4 ± 1.8	9.1 ± 0.9	0.04*
Umbilical cord venous blood pH	7.30 ± 0.06	7.30 ± 0.05	0.82

Mean ± S.D. Student's t-test $p<0.05$

[1)] AP1: Apgar score at 1 minute

[2)] AP5: Apgar score at 5 minutes

Discussion

This study served as survey of PIH, as a pregnancy-related disorder, between 2006 and 2010 at a major Japanese hospital. The PIH management guidelines indicate that "the continuation of pregnancy with drug administration prolongs the pregnancy period, and promotes fetal growth compared to positive delivery induction"[2]. The incidence of PIH in the total number of pregnancies during the 5-year study period was approximately 4%, and did not show any marked changes over time. However, the proportion of patients receiving hypotensive agents increased. This may reflect an increase in the number of severe PIH patients, as drug therapy is primarily selected for these patients. Despite an increase in the average maternal age over the study period, a prolongation of the pregnancy period, an increase in the birth weight, and a decrease in the neonatal admission rates were noted, suggesting that PIH control, including drug therapy, improved neonatal outcomes.

The results showed that labetalol hydrochloride and sustained-release nifedipine were the most commonly selected hypotensive agents. This is in spite of α-methyldopa and hydralazine being the recommended first-choice agents in the 2009 PIH management guidelines, which were based on the results of a large-scale study[3] and meta-analysis[4]. The dose of labetalol hydrochloride was 150–300 mg/day, and that of the nifedipine preparation was 20–40 mg/day. Before delivery, monotherapy with labetalol hydrochloride was administered in the highest proportion of patients, followed by combination therapy with labetalol hydrochloride and a nifedipine sustained-release preparation. After delivery, the number of patients receiving monotherapy with sustained-release nifedipine was larger. In patients requiring long-term control, a once daily nifedipine sustained-release preparation (Adalat® CR) was selected for an increasing number of patients. In addition, a long-lasting calcium antagonist, amlodipine besilate, and the angiotensin II receptor blockers (ARBs), candesartan and valsartan, were also employed. The increasing use of once daily calcium antagonists may have been the result of the publication of

Table 9. Severity of pregnancy-induced hypertension and neonatal characteristics (2006–2010)

Disease type	Severity		Number of episodes	Maternal age (years)	Gestational age (weeks)	Cesarean section rate (%)	Proportion of patients receiving hypotensive agents (%)			Birth weight (g)	AP1[1]	AP5[2]	Umbilical cord venous blood pH	Neonatal admission rate (%)
	Blood pressure	Urinary protein					Before delivery	During delivery	After delivery					
Preeclampsia	Severe	Severe	50	34.3 ± 5.3	33.6 ± 4.3	80.0	74.0	52.0	88.0	1765.2 ± 828.1	7.6 ± 1.7	9.0 ± 0.6	7.30 ± 0.06	64.0
	Severe	Mild	41	34.9 ± 4.2	35.6 ± 4.2	46.3	48.8	58.5	78.0	2232.3 ± 875.4	8.1 ± 1.8	9.4 ± 0.9	7.29 ± 0.07	31.7
	Mild	Severe	6	32.8 ± 2.9	37.7 ± 1.4	50.0	33.3	16.7	66.7	2662.5 ± 579.0	8.8 ± 0.4	9.3 ± 0.5	7.34 ± 0.06	16.7
	Mild	Mild	55	34.6± 4.6	37.1 ± 3.7	45.5	27.3	23.6	45.5	2481.9 ± 864.1	8.5 ± 1.2	8.8± 2.6	7.29 ± 0.05	30.9
Hypertension in pregnancy	Severe	Absent	115	35.7 ± 4.4	37.6 ± 3.0	45.2	49.6	53.9	75.7	2626.2 ± 691.8	8.4 ± 1.3	9.4 ± 0.7	7.30 ± 0.08	25.2
	Mild	Absent	186	34.6 ± 5.1	38.5 ± 2.5	30.1	36.6	21.0	43.5	2849.1± 605.6	8.6 ± 1.2	9.4 ± 1.3	7.30 ± 0.08	14.5

Mean ± S.D.

[1] AP1: Apgar score at 1 minute

[2] AP5: Apgar score at 5 minutes

Table 10. Comparison of neonatal characteristics from the severe blood pressure patients in 2006 with those in 2010

	2006 (n=36)	2010 (n=49)	*P* value
Maternal age (years)	34.4 ± 5.1	36.0 ± 4.3	0.16
Gestational age (weeks)	35.3 ± 4.5	35.9 ± 4.2	0.56
Birth weight (g)	2126.8 ± 878.2	2250.7 ± 859.8	0.51
AP1[1]	7.8 ± 2.2	8.2 ± 1.2	0.41
AP5[2]	7.7 ± 3.6	9.3 ± 0.9	0.03*
Umbilical cord venous blood pH	7.271 ± 0.125	7.308 ± 0.050	0.16

Mean ± S.D.　　Student's t-test　*p<0.05

[1] AP1: Apgar score at 1 minute

[2] AP5: Apgar score at 5 minutes

Guidelines for Hypertension Treatment[5]. The relatively low-level use of ARBs may be the result of their being contraindicated due to fetal toxicity caused by a decrease in the amniotic fluid volume in the second to third pregnancy trimesters.

The hypotensive agents used in this study did not have any serious side effects in the mothers, and no side effects were reported in the neonates. However, the primary maternal side effects included labetalol hydrochloride-related dizziness and nifedipine-related headaches and dizziness; the headaches were difficult to distinguish from those related to blood-pressure increases.

This survey revealed that, over the 5-year period, the gestational period in mothers with preeclampsia was less in those with severe hypertension in pregnancy, and the rate of Cesarean sections was also higher than that in the overall study population. The birth weight of neonates delivered to mothers with preeclampsia was also lower. These results were similar to those of a previous study[6] that found that the prognoses for women and neonates were less favorable when the mother exhibited hypertension with proteinuria than when hypertension, alone, was observed. Similarly, the current study demonstrated that the neonatal admission rate was the highest in preeclampsia patients with severe hypertension. The major reasons for neonatal admission included low birth weight (most neonates), meconium aspiration syndrome, apparent neonatal death, and heart disease. The proportions of patients receiving hypotensive agents before, during, and after delivery were also higher in the severe hypertension group. However, in the mild hypertension group, a substantial proportion of patients also received hypotensive agents. It was shown that, even when hypertension was mild, hypotensive agents were administered to prevent blood pressure changes and eclampsia during pregnancy, during delivery, and after delivery.

During the survey period, there were 4 episodes of eclampsia. In addition to blood pressure rises during pregnancy, an increase in the cerebral pressure, related to birth pains during delivery, and changes in circulatory kinetics after Cesarean section may induce eclampsia attacks. To prevent eclampsia attacks, blood pressure control is important. However, the importance of restricting straining during transvaginal delivery and control of circulatory kinetics after Cesarean section should also be emphasized.

In some patients with PIH, kidney hypofunction has been observed[7]; caution is needed when administering agents where the primary route of clearance is through the kidney. When urinary protein is present, the blood albumin level decreases slightly. Therefore, the plasma level of an agent that is highly protein bound may increase, resulting in an increased level of the compound being bio-available. The protein binding rate of labetalol hydrochloride is 50%, and this agent is excreted in the kidney; therefore, monitoring kidney function is important. Furthermore, the protein binding rate of nifedipine ranges from 92%–98%, also suggesting that caution is needed when there is a decrease in the blood albumin level. Nifedipine, however, is almost completely metabolized in the liver; only a trace of the original compound is excreted in the kidney. Both agents may deteriorate kidney function via a decrease in the renal reflux pressure related to a fall in blood pressure. Liver dysfunction must be considered[8) 9)].

During the survey period, the package inserts of both labetalol hydrochloride and the nifedipine preparations indicated that these agents were contraindicated for use in pregnant women. However, this contraindication was removed in June 2011, after the conclusion of this study. As a result, the 2 agents will likely be administered to an increasing number of patients. As the 2 agents were previously contraindicated for pregnant women, information on their use in pregnant and lactating women has been minimal. Therefore, to ensure the safety of these drugs during pregnancy and lactation, additional data should be collected. The current 5-year survey involved only a single hospital. However, the results suggest that the control of PIH, including its management using drug therapy, is useful.

Disclosure

This study was an unsponsored epidemiological investigation.

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