The Effect of a Thromboxane Synthetase Inhibitor, Sodium Ozagrel, on Pregnancy-induced Hypertension

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Abstract: *Synthetic selective thromboxane synthetase inhibitor, sodium ozagrel was administered intravenously to 5 pre-eclamptic pregant women at 29 - 35 weeks gestation. Dose of ozagrel was 80 - 160 mg/day and was infused continuously for 8 - 22 days.*

Systolic and diastolic blood pressure decreased gradually and became stable in all patients after administration of ozagrel. Clinical signs improved and proteinuria decreased. In one patient, blood pressure became stable at first but then became uncontrollable. Caesarean section was performed in 2 patients because of fetal distress and severe hypertension. All neonates were well-developed without any complications.

Thromboxane B_2 to 6-keto-$PGF_{1\alpha}$ ratio and 2,3-dinor-thromboxane B_2 values decreased after administration of sodium ozagrel.

Sodium ozagrel seems likely to be useful and effective for stabilization of blood pressure and prevention of exacerbation. The results of this initial clinical study are very encouraging with respect to the treatment and prevention of pregnancy-induced hypertension. (Thai J obstet Gynaecol 1991; 3:39-44.)

Key words: pregnancy-induced hypertension, thromboxane, prostacyclin, thromboxane synthetase, sodium ozagrel

Pregnancy-induced hypertension (PIH) has been suggested to be caused by an impaired production of prostacyclin (PGI_2) and increased generation of thromboxane A_2 (TXA_2)[1,2]. PGI_2 is a potent vasodilator and an inhibitor of platelet aggregation and of uterine contractility. On the other hand, TXA_2 increases vasoconstriction, stimulates platelet aggregation, increases uterine contractility and decreases uterine blood flow. It is widely accepted that PGI_2 and TXA_2 involved in the control mechanisms of microcirculation and blood pressure. Therefore, the higher level of PGI_2 in peripheral blood rather than TXA_2 is required to prevent or treat PIH.

Sodium ozagrel (Sodium (E)-3-[p-(1H-immidazole-1-yl methyl) phenyl]-2-propenoate, Ono Pharmaceutical Co., Ltd., Osaka, Kissei Pharmaceutical Co., Ltd., Matsumoto), one of the stable imidazole derivatives, was synthesized as a potent selective inhibitor of thromboxane synthetase in Japan in 1978. In Japan, sodium ozagrel has been used clinically for the treatment of vasospasm of cerebral vascular diseases and coronary diseases since it inhibits vasospasms and platelet aggregations. The reason for the study was to investigate whether sodium ozagrel can be used as an alternative for the treatment of PIH.

Materials and Methods

After informed consent was obtained, sodium ozagrel (80- 160 mg/day) was administered intravenously to five pre-eclamptic pregnant women at 29- 35 weeks gestation for 8-22 days. Three cases had a family history of hypertension and one case had a past history of PIH. In four cases, combined therapy of other antihypertensive drugs was needed. Clinical signs, fetal growth, fetal heart rate, placental function tests, and renal function test were monitored during the treatment.

Thromboxane B_2 (TXB_2), 6-keto-$PGF_{1\alpha}$ in blood and 2,3-dinor-TXB_2 in urine were measured by RIA techniques[3,4].

Results

The clinical characteristics of the patients with PIH are shown in Table 1.

Ozagrel decreased and stabilized systolic and diastolic blood pressure gradually in all patients and hypertension recurred by cessation of ozagrel (Figs.1-3). Clinical signs improved in all cases and protein in urine decreased in four out of five patients. In one patient, blood pressure became stable at first but then became uncontrollable. In this case, caesarean section was performed because of uncontrollable maternal hypertension. In the other case, caesarean section was performed because of fetal distress without maternal hypertension. There were three vaginal deliveries. All neonates were well-developed without any complications (Table 2).

Table 1 Clinical characteristics of 5 patients with PIH and treatment

Case	Age G-P	Obstetrical history Family history	Gastational weeks at onset of PIH Complications	Gastational weeks at onset of the treatment Dose of Sodium Ozagrel (mg/day)×duration	Other drugs	Side effects
1	38 5-2	Abortion 3× 1978. NVD(40W) PIH, IUGR 1988. IUFD(36W) PIH, IUGR	31W(HPE) liver dysfunction (33W)	31W 80mg×22days	labetalol 300mg ⇒ 400mg nifedipine 10mg ⇒ 20mg	elevated liver enzyme
2	43 4-4	NVD 4× Hypertension (mother, father)	31W(HPE)	34W 80mg×18days	labetalol 300mg nifedipine 20mg ⇒ 30mg	(−)
3	26 1-0	Abortion 1× Hypertension (father)	25W(HPE) premature labor oligohydramnios	29W 160mg×8days	labetalol 300mg ⇒ 450mg	(−)
4	35 0-0	Hypertension (mother)	34W(HPe) GDM premature labor	35W 160mg×9days	direvalol 200mg	(−)
5	29 2-0	Abortion 2×	20W(HPE) renal dysfunction (35W) premature labor oligohydramnios	35W 160mg×8days	albumin 5 g furosemide 40mg	(−)

N-acetyl-β-D-glucosaminidase (NAG) values in urine, which represent the function of the renal tubules, also decreased in three out of four measured cases after administration of sodium ozagrel, coincident with the

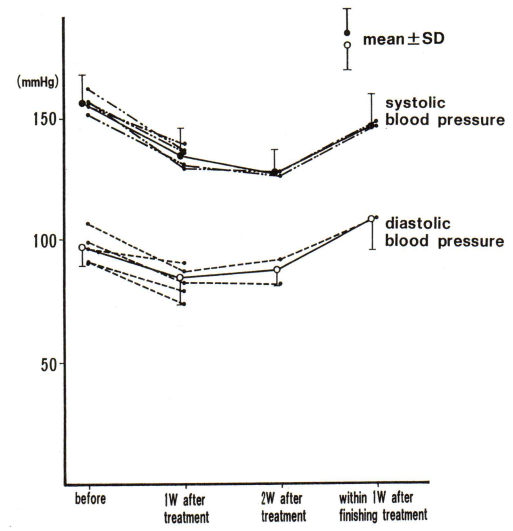


Fig. 1 Changes of blood pressure with ozagrel therapy.

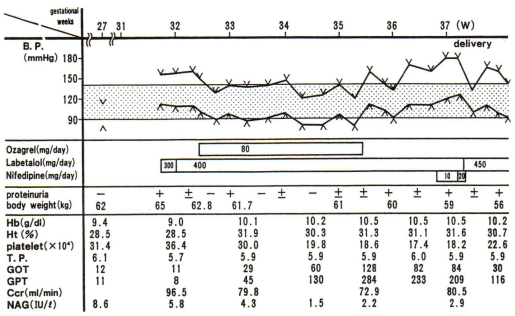


Fig. 2 Course of clinical measurements, laboratory test values and treatment in case No.1.

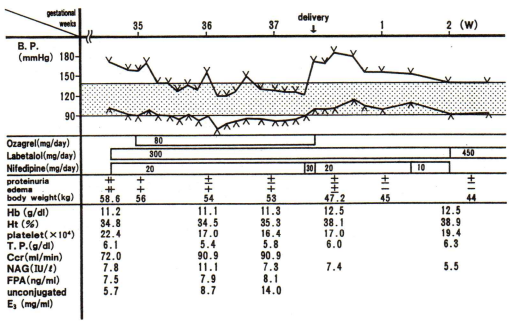


Fig. 3 Course of clinical measurements, laboratory test values and treatment in case No.2.

Table 2 Clinical outcome and neonatal course

Case	Gestational weeks at delivery	Mode of delivery	Blood loss	Weight and pathology of the placenta	Neonatal body weight and findings	Neonatal course
1	37W 1D	V	118 ml	450g small infarcts	1,988g, ♂ (LFD) Apgar 9	Hyper-bilirubinemia. good
2	37W 4D	V	204 ml	360g small infarcts	2,536g, ♀ (AFD) Apgar 8	good
3	30W 3D	C/S (fetal distress, preeclampsia)	230 ml	240g premature placenta with scattered small infarcts	1,112g, ♂ (LFD) Apgar 5	Hyper-bilirubinemia. PDA good
4	36W 3D	Forceps (fetal distress)	1095 ml	750g no infarct	3,412g, ♀ (HFD) Apgar 9	good
5	36W 3D	C/S (fetal distress)	680 ml	310g multifocal infarcts	1,694g, ♂ (LFD) Apgar 8	good

disappearance of proteinuria, but creatinine clearance values did not change (Fig. 4). Human placental lactogen and unconjugated estriol values in plasma in case 1 and 2 increased within normal range during treatment but after cessation of treatment those values, especially unconjugated estriol value, decreased (Figs. 3,5).

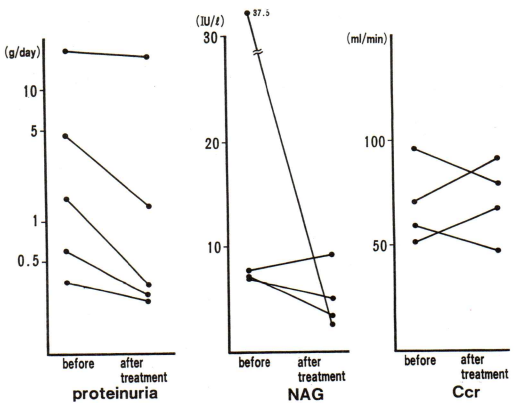


Fig. 4 Changes of the renal function test values after administration of sodium ozagrel.

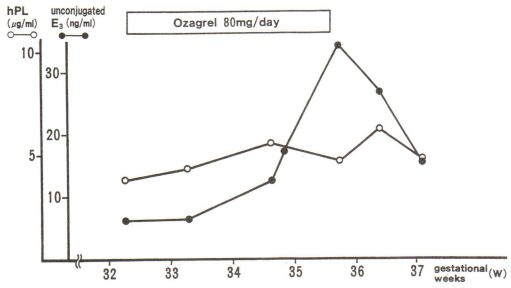


Fig. 5 Changes of hPL and unconjugated estriol values in case No.1 by administration of sodium ozagrel.

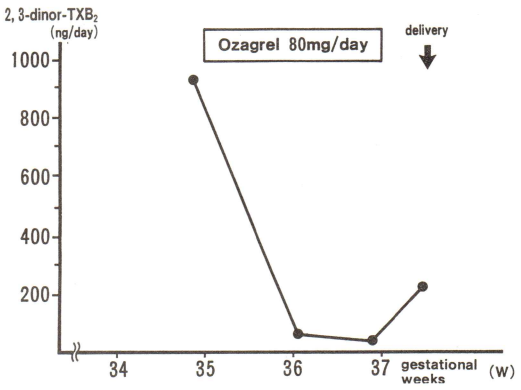


Fig. 7 Changes of urinary 2, 3-dinor-TXB_2 values in case No.2 by administration of sodium ozagrel, 80 mg/day.

TXB_2 concentrations in plasma and TXB_2/6-keto-$PGF_{1\alpha}$ ratio decreased after treatment, but changes of 6-keto-$PGF_{1\alpha}$ concentrations were not noted (Fig. 6). Urinary 2,3-dinor-TXB_2 concentrations, that is a metabolite of thromboxane, decreased after treatment (Fig. 7).

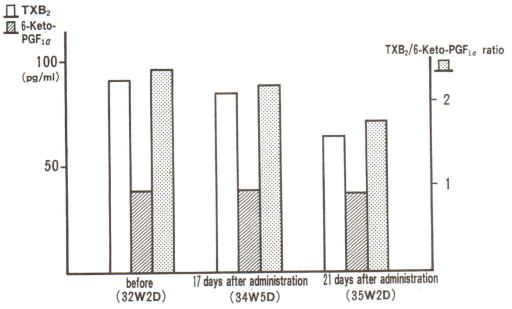


Fig. 6 Plasma concentrations TXB_2 and 6-keto-$PGF_{1\alpha}$ in case No.1 before and after administration of sodium ozagrel.

Discussion

In 1977, Moncada[5] reported that imidazole derivatives had an inhibiting effect on thromboxane synthetase. Needleman[6] reported that imidazole promoted prostacyclin production in the arterial wall. Sodium ozagrel, one of the imidazole derivatives, was synthesized in 1978 and then manufactured in Japan. Its molecular weight is 250 and its half life is very short, 40 minutes, in blood. So, continuous intravenous infusion is necessary because of its short half life and its rapid secretion into the urine. The pharmacological action of sodium ozagrel is its selective and strong inhibition of thromboxane synthetase[7], and it does not work on cyclooxygenase, prostacyclin synthetase and lipoxygenase[8]. Its physiological action is the inhibition of vasospasms and platelet aggregations. Increasing production of PGI_2 is explained by the increased PGH_2, a precursor of PGI_2, by inhibition of TX synthetase (Fig.8).

In patients with cerebral vascular diseases and coronary diseases, plasma TXB_2 and 6-keto-$PGF_{1\alpha}$ concentrations during treatment of sodium ozagrel have been reported[9]. TXB_2 levels decreased and 6-keto-$PGF_{1\alpha}$ lev-

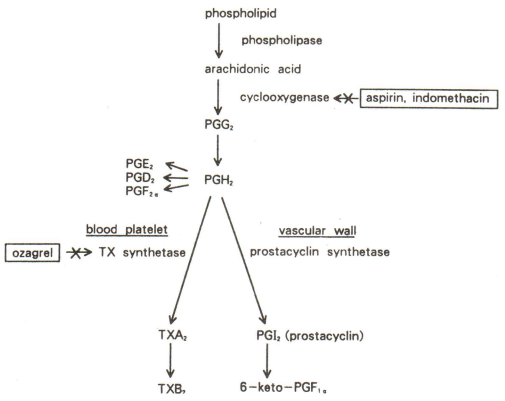


Fig. 8 A metabolic pathway of arachidonic acid and inhibitors of the enzyme.

els were increased significantly after administration of ozagrel[8,9]. In cases of pre-eclampsia, plasma TXB_2 and urinary TXB_2 metabolite concentrations markedly decreased but 6-keto-$PGF_{1\alpha}$ levels did not change. It was reported that in pre-eclampsia, activity of prostacyclin synthetase were lowered, compared with thromboxane synthetase activity, because the endothelial cells on the vascular wall had been damaged[10]. It seems likely that prostacyclin production in the vascular wall is restricted in pre-eclampsia, and clinical application of sodium ozagrel for severe PIH seems to be ineffective, since blood pressure was uncontrollable in one case in spite of administration of ozagrel. However, the study showed that sodium ozagrel has an inhibiting effect of thromboxane synthetase *in vivo* as well as *in vitro*.

Sodium ozagrel was also effective not only for improvement of hypertension but also for improvement and prevention of exacerbation of proteinuria, function of the renal tubules and placental function. It seems probable that ozagrel affects the renal tubules rather than the glomerulus. A mechanism of ozagrel action is still uncertain *in vivo*, but it might improve the renal and placental microcirculations by prevention of vasospasm and platelet aggregation.

Sodium ozagrel in maternal circulation is easily transferred into the fetus because of its small molecules. But there are no adverse effects in neonates because of its rapid metabolic clearance. In some animal experiments, fetal anomaly and death were not reported.

Sodium ozagrel seems likely to be useful and effective for stabilization of blood pressure and improvement of microcirculation and prevention of exacerbation. Results of this initial clinical study are encouraging enough to introduce the new treatment and prevention of PIH.

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