Drug Treatment of Toxemia of Pregnancy
—Indications and Limitations—

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Abstract: The cause of toxemia of pregnancy is still unclear, and therefore this condition is only treated symptomatically. Edema, hypertension, and proteinuria are the three key elements of this condition, but drug treatment generally targets only hypertension. Although hydralazine hydrochloride and methyldopa have long been used as antihypertensive therapies, newer drugs such as calcium antagonists have also become used frequently in recent years. The clinical use of these drugs, however, raises major issues, since some of them are contraindicated for pregnant women because of excessive fear of adverse drug reactions in the fetus. Conventional diuretics may cause excessive hemoconcentration during pregnancy, and therefore, it has become common practice to use them only in the puerperium. Since toxemia of pregnancy is viewed, in a sense, as chronic disseminated intravascular coagulation (DIC), anticoagulant therapy with aspirin is a treatment option. This paper describes practical drug treatment of toxemia of pregnancy and the issues involved in light of the aforementioned considerations.

Key words: Toxemia of pregnancy; Treatment; Antihypertensive drugs

Introduction

The etiology and pathology of toxemia of pregnancy still remain to be clarified, and toxemia of pregnancy even now is jokingly called a disease in theory only. Treatment of this condition is, therefore, no more than symptomatic treatment.

The present paper outlines the use of drugs in the treatment of toxemia of pregnancy, focusing on antihypertensive drugs with some discussion of sedatives and anticonvulsants.

Considerations in Drug Treatment of Toxemia of Pregnancy

1. Concept of toxemia of pregnancy and pathologic states subject to drug treatment

The cause of toxemia of pregnancy is still unclear, and therefore its treatment is restricted to symptomatic treatment. The triad of this condition comprises hypertension, proteinuria, and
edema. Edema localized in lower limbs is not considered to adversely affect the pregnancy, and hence is not the target of treatment. However, edema associated with hypoproteinemia, which is often accompanied by pleural effusion or ascites, should not be left untreated. If maintenance of pregnancy is required for a prolonged period, additional protein supplements are necessary. However, since no radical treatment is available for the cause of hypoproteinemia, i.e., leakage of protein into the urine, except for termination of pregnancy, the pregnancy should be terminated as needed after judging whether the fetus is viable outside the uterus.

Hypertension can be treated with various antihypertensive drugs. Thus, hypertension in toxemia of pregnancy is the best target of drug therapy in this condition. However, in such cases, placental function is often decreased, and fetal development delayed. These cases may often require termination of pregnancy as fetal distress becomes apparent along with the progression of pregnancy.

2. Considerations in drug treatment in pregnancy and puerperium

Drug treatment of this condition does have effects on the fetus during pregnancy and the neonate via milk, which should be considered. Drug treatment in pregnancy is also greatly restricted at present due to the increased risk of malpractice suits and enforcement of the Product Liability Law in Japan. As an extreme example, some drugs whose administration in pregnant women is permitted in western countries are contraindicated for pregnant women in Japan. The end result in some cases may be that the only way obstetricians can protect themselves from legal liability is to tell the patient that the condition is untreatable and advise termination of the pregnancy in light of the poor prognosis for the fetus. A further issue that must be addressed is that clinical trials in pregnant women are difficult to perform, and even if a pharmaceutical company overcomes technical difficulties, the reality is that they will not make a profit.

Japan Society for the Study of Toxemia of Pregnancy has discussed this matter at great length to establish guidelines for the use of these drugs to provide appropriate medical care. However, at present, when we consider the prognosis of a markedly immature fetus, obstetricians have no way to maintain a pregnancy other than using drugs for which pregnancy is specified as a contraindication or to be handled similarly to a specific contraindication, as long as the safety of the drug has been widely accepted (Table 1).1)

In general, when medication for toxemia of pregnancy is necessary after delivery, it is also often the case that breastfeeding is not permitted to allow the mother to rest. Many drugs are, unfortunately, secreted into breast milk and adversely affect the infant thus requiring the prohibition of breastfeeding. However, lactation should not immediately be allowed to stop, because if the period of medication is to be short, breastfeeding can be commenced after the end of medication.

### Use of Antihypertensive Drugs and Considerations

1. Goal of pressure lowering and precautions

It is necessary to maintain sufficient placental

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Efficacy rate (%)</th>
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<tbody>
<tr>
<td>No. of patients on medication</td>
<td>140</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>70</td>
</tr>
<tr>
<td>β- or α/β-blockers</td>
<td>29</td>
</tr>
<tr>
<td>Hydralazine hydrochloride</td>
<td>78</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>17</td>
</tr>
<tr>
<td>Furosemide</td>
<td>12</td>
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<tr>
<td>ACE inhibitors</td>
<td>3</td>
</tr>
</tbody>
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(Including overlapping medication) (Adapted from reference1)
blood flow during pregnancy. In cases of toxemia of pregnancy, increased blood pressure actually contributes to maintenance of placental circulation. In particular, placental function is often markedly lowered in patients with this condition, accompanied by delayed fetal development in the uterus. In such cases, caution should be taken to avoid an excessive drop in pressure because a drop in maternal blood pressure may lead to fetal distress. The target blood pressure reading is 140/90 mmHg, taking into consideration the minimum blood pressure necessary for maintaining placental blood flow, and blood pressure should not be allowed to fall below this level. In addition, candidates for antihypertensive therapy should be restricted to those patients with severe toxemia of pregnancy and a blood pressure of over 160/100 mmHg to 180/110 mmHg, and the therapy should be given only while the patient is hospitalized.

It should also be kept in mind that the objective of antihypertensive therapy for toxemia of pregnancy during pregnancy is to avoid eclampsia and hypertensive encephalopathy while maintaining fetal well-being.

2. Antihypertensive drugs used to treat toxemia of pregnancy

(1) Drugs commonly used to treat toxemia of pregnancy

Antihypertensive drugs commonly used to treat toxemia of pregnancy include hydralazine hydrochloride (Apresoline®) and methyldopa (Aldomet®).

Hydralazine hydrochloride is reported to be associated with teratogenicity in mice, and it has been suggested that there is a risk of thrombocytopenia in human fetuses. This drug should be used during pregnancy only when the benefit would surpass the risk. Oral formulations of this drug are easy to use, with toxemia of pregnancy specified as an indication in the package insert. Injectable formulations of the drug are indicated for hypertensive emergencies including eclampsia. In general, pressure control during pregnancy should be attempted with oral medication if possible, and injections should be used only during labor or when pressure must be rapidly reduced. Oral therapy should begin with an initial dose of 30–40 mg/day, and should not exceed 200 mg/day. Although the package insert specifies intramuscular or gradual intravenous injection of 1 A (20 mg) when the injection formulation is used, an intravenous drip infusion is recommended for patients in the obstetric field, particularly during pregnancy. Although this drug is reportedly unstable in glucose solution, usually 1 or 2 A dissolved in 500 ml of 5% glucose solution are used for patients with toxemia of pregnancy, in order to avoid an overdose of sodium. The infusion rate should be controlled while monitoring blood pressure. This drug is difficult to use after delivery because of its transfer into milk.

The safety of methyldopa during pregnancy and breastfeeding has not yet been established. However, its use is indicated when the benefit surpasses the risk, and is useful in lowering blood pressure in the puerperium. However, only oral formulations are available for this drug, and therefore difficult to use when pressure must be rapidly lowered or during labor. Therapy should begin with an initial daily dose of 1–3 tablets (250–750 mg), which should be increased by 250 mg at intervals of several days. The maintenance dose is 250–2,000 mg/day, taken as divided doses. Quick increases in the dose are necessary in toxemia of pregnancy since it takes a considerable time to achieve a sufficient drop in blood pressure. However, it is difficult to control pressure during pregnancy employing this therapy.

(2) Antihypertensive therapy with other drugs to treat toxemia of pregnancy

a. Calcium antagonists

Calcium antagonists not only have a depressor effect through inhibition of smooth muscle contraction, but also seem to improve uterine and placental blood flow through inhibition of uterine muscle contraction. Therefore, these drugs can be used to treat patients with toxemia of pregnancy before delivery. However,
these agents have been found to be teratogenic in animal experiments. Deformities generally occur in the early stage of pregnancy, but it is reasonable to think that these agents may be administered in the second or third trimester of pregnancy. However, the instructions for use of nifedipine (Adalat®) list pregnant women in the contraindications. In addition, the package insert for nicardipine (Perdipine®) states that the drug should not be used in pregnant women, although it is not listed as a contraindication.

In light of these problems, we do not necessarily recommend calcium antagonist therapy. However, they have potent depressor and uterine contraction-inhibiting effects, and sublingual administration of nifedipine 5–10mg is extremely effective in immediately lowering blood pressure. A survey of the Japan Society for the Study of Toxemia of Pregnancy (Table 1) revealed that calcium antagonists are frequently used for treatment of severe cases of toxemia of pregnancy, ranking next to hydralazine hydrochloride.

b. β-Blockers and α/β-blockers

These classes of drugs have the advantage in that they do not cause reflex tachycardia. β₁ blockades can be anticipated, but drugs having α-blocking actions as well are also used for preventing peripheral circulatory failure. The β-blockers include atenolol (Tenormin®), and the α/β-blockers include labetalol (Trandate®). The possibility of causing delayed fetal development in the uterus has been raised for atenolol, but since it is easy to use, it is indicated when the benefit surpasses the risk. On the other hand, as noted in the package insert, labetalol is not to be used in pregnant women, with this population included in the list of contraindications because its safety in pregnant women has not been confirmed yet. It may be safer to use drugs with high β₁ selectivity because β₂-stimulants are generally used to inhibit uterine contractions.

c. Diuretics

Furosemide (Lasix®) was once used regularly to reduce edema in toxemia of pregnancy, but no depressor effect can be expected from this drug. In addition, recent investigations have indicated that increased vascular permeability and hemoconcentration are among the pathological features of toxemia of pregnancy. The view that use of this drug during pregnancy worsens placental circulation by promoting hemoconcentration is becoming widely accepted. However, potent diuresis is necessary for water retention such as puerperal pulmonary edema, and therefore active use of this drug is recommended, in addition to d-mannitol and supplementation therapy for postpartum hypoalbuminemia.

Since the safety of Lasix® has not been established, the use of this drug in the early stage of pregnancy is limited to cases where the benefit surpasses the risk. In addition, the risk of hemoconcentration is specified for trichlormethiazide (Flutran®), but it may be used during pregnancy when the benefit surpasses the risk.

d. Angiotensin converting enzyme (ACE) inhibitors

ACE inhibitors are used frequently in the field of internal medicine. However, the renin-angiotensin system is enhanced during pregnancy and since one of the pathological features of toxemia of pregnancy is that the degree of such enhancement is lower than in normal pregnancy, medication with this series of drugs may be problematic. Furthermore, influences on the fetal kidney and severe oligohydramnios due to decreased fetal urine volume have been reported. Thus, ACE inhibitors are considered to be unsuitable as drugs to be used during pregnancy as an antihypertensive agent. The Captopril® package insert states that the drug should not be used in pregnant women. However, it also states that if it is used due to the lack of an alternative, administration should be minimal, and the condition of the fetus and the volume of amniotic fluid should be monitored.

Use of Sedatives and Anticonvulsants

Sedatives are used for the purpose of lowering blood pressure by rest or to prevent the
onset of eclampsia. Phenobarbital (Phenobal®) and chlorpromazine (Contomin®) are commonly used sedatives. Since the fetus is also affected, caution is necessary for the diagnosis of fetal distress on the fetal cardiotocogram.

If eclampsia is imminent or has developed, intravenous administration of diazepam (Cercine®) is effective. Combined use of an intravenous drip infusion of magnesium sulfate (Magnesol®) is also recommended.

Other Drugs

1. Anticoagulant therapy

Since toxemia of pregnancy is, in a sense, chronic disseminated intravascular coagulation (DIC), anticoagulant therapy is a treatment option for toxemia of pregnancy. Decreased antithrombin III (ATIII) and increased fibrin degradation products (FDP) are common findings, and ATIII supplementation is often required. Gabexate mesilate (FOY®) is used when DIC has developed. Attempts to use ATIII and heparin as therapies for toxemia of pregnancy have been reported in recent years.

These therapies are used to inhibit the formation of microthrombi. Aspirin, which has a platelet aggregation-inhibition action, is used to prevent the occurrence of this condition. Usually, Bufferin® for children, at a dose of 1 tablet/1 to 2 days, is given. Although the usefulness of this prophylactic method is documented in the high-risk group, the efficacy is not clear in the low-risk group for prevention of toxemia of pregnancy.

2. Other drugs used for toxemia of pregnancy

Dipyridamole (Persantin®) may be used for the treatment of proteinuria as another drug therapy for toxemia of pregnancy. Chinese herbal medicines such as Sairei-to have also been prescribed, but they have not been found to be effective in the treatment of severe toxemia of pregnancy for which drug treatment is generally indicated.

There are a number of reports on the use of Chinese herbal medicines in patients with toxemia of pregnancy, such as those documenting that the prophylactic use of Sairei-to in patients with a history of severe toxemia of pregnancy was equivalent to aspirin in preventing the onset of another episode of toxemia of pregnancy. However, these are not standard clinical studies using a sufficiently large number of patients or a strict method of double blinding.

Limitations of Drug Treatment

It is true that drug treatment of toxemia of pregnancy during pregnancy has its limitations, particularly in light of the effect on the fetus. In general, this condition often improves after pregnancy has ended. Therefore, artificial termination of pregnancy may be chosen if the fetus can live outside the uterus, but no absolute guidelines have been set down to help make this choice. The maternal indications for pregnancy termination proposed by Miyake et al. are shown in Table 2 as a reference.

Conclusion

Drug treatment of toxemia of pregnancy is still restricted to symptomatic therapies. Although it is true that there are many limitations due to considerations of the effect on the fetus and other factors, a favorable prognosis for the mother and the fetus even in severe cases is now becoming achievable with the careful use of drugs.

Better treatment targeted at the cause of tox-
emia of pregnancy including anticoagulant therapy, hopefully will be developed in the future.

REFERENCES