

Diabetic Nephropathy Requires a Delicate Balance

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CHICAGO — Tight blood pressure control is crucial in caring for pregnant women with diabetic nephropathy, but medication management must factor in potential fetal risks, Dr. Phyllis August said at a meeting on clinical nephrology sponsored by the National Kidney Foundation.

In reviewing the management strategies for pregnant women with pre-existing diabetic nephropathy and lupus nephropathy, she noted that the most effective management begins even before conception. Yet even though preconception counseling can improve outcomes, physicians typically care for gravid women who already have significant disease.

“Overall, the outcome in pregnancy is related to the baseline blood pressure and level of renal function at the beginning of

pregnancy,” said Dr. August, professor of medicine at the Weil Medical College of Cornell University, New York.

ACE inhibitors and angiotensin-receptor blockers (ARBs) are vital in the treatment of diabetic nephropathy in women who are trying to conceive, but these agents are potentially quite harmful to the developing fetus, she noted.

To derive the maximal benefit from these medications, Dr. August suggested switching to a safer agent (such as methyl-

dopa or labetalol) as soon as a patient misses her menstrual period. “The overwhelming evidence for the adverse effects of ACE inhibitors and ARBs relates to second and third trimester exposure,” she said.

Dr. August also recommended performing a cardiac evaluation before conception in women with long-standing type 1 diabetes.

“Significant renal disease is associated with preeclampsia and renal complications,” she noted. Chronic kidney disease also increases the risk of intrauterine growth retardation and pre-term birth.

In the past, women with diabetic nephropathy tended to have a high rate of maternal complications, including

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over nephropathy, hypertension, and death due to unrecognized coronary artery disease.

However, the outcomes for pregnant women with diabetic nephropathy have improved. A recent study detected no difference in the

rate of decline in renal function between a group of women with diabetic nephropathy who became pregnant and another group that did not.

Lupus nephropathy can be quite challenging for both patients and physicians, Dr. August noted. “There is a poor outcome when the disease is active at conception,” she said. A high percentage of patients—as many as 50%-80%—will experience a disease flare during pregnancy if they have active disease at conception. On the other hand, only 10%-40% of women who are in remission at conception will have a flare.

Physicians may safely use azathioprine to treat pregnant women with lupus nephritis. Dr. August also advocated delivery during the third trimester in gravid women whose lupus nephritis is deteriorating quickly. The mother’s condition often improves quickly after delivery.

Women with lupus and antiphospholipid antibody syndrome are also at higher risk of fetal loss, arterial and venous thrombosis, renal vasculitis, and preeclampsia. Women with this syndrome may benefit from taking low-molecular-weight heparin, with or without aspirin.

Although the outlook has improved for women with certain types of chronic kidney disease who wish to bear children, the chance of a good pregnancy outcome in women with end-stage renal disease on dialysis remains poor.

Women on dialysis who do get pregnant have a high incidence of adverse outcomes such as second trimester pregnancy loss, prematurity, and congenital abnormalities. For these women, attempting pregnancy “should never be encouraged,” Dr. August said. ■

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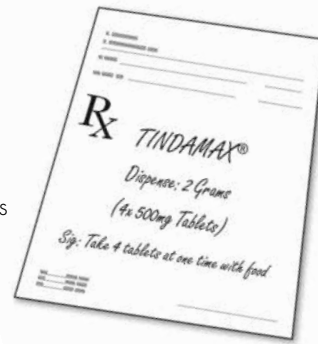
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Carcinogenicity was seen in mice and rats treated chronically with another agent in the nitroimidazole class (metronidazole). (See PRECAUTIONS). Although such data have not been reported for tinidazole, unnecessary use of tinidazole should be avoided. Its use should be reserved for conditions shown in INDICATIONS AND USAGE.

INDICATIONS AND USAGE:

Trichomoniasis: Caused by *T. vaginalis* in both sexes. **Giardiasis:** Caused by *G. duodenalis* (*G. lamblia*) in adults and patients older than 3 years of age. **Amebiasis:** Intestinal amebiasis and amebic liver abscess caused by *E. histolytica* in adults and patients older than 3 years of age.

CONTRAINDICATIONS:

Contraindicated in patients with hypersensitivity to tinidazole, any component of the tablet, or other nitroimidazole derivatives and during first trimester of pregnancy.

WARNINGS:

Convulsive seizures and peripheral neuropathy, characterized mainly by numbness or paresthesia of an extremity, were reported in patients treated with nitroimidazole drugs including tinidazole. Appearance of abnormal neurologic signs demands prompt discontinuation of therapy. Use with caution in patients with CNS diseases.

PRECAUTIONS: General: Tinidazole should be used with caution in patients with evidence of or history of blood dyscrasia. Patients with severe hepatic disease metabolize nitroimidazoles slowly, resulting in accumulation of parent drug in plasma. Accordingly, usual recommended doses should be used cautiously in these patients. Known or previously unrecognized candidiasis may present more prominent symptoms during therapy and requires treatment with an antifungal agent.

Information for patients: Take with food. Avoid alcoholic beverages while taking Tindamax and for 3 days afterward.

Laboratory tests: Tinidazole may produce transient leukopenia and neutropenia; however, no persistent hematological abnormalities attributable to tinidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended if retreatment is necessary.

Drug interactions: Potential effect of tinidazole on other drugs: Warfarin and other oral coumarin anticoagulants. Tinidazole may enhance the effect of warfarin and other coumarin anticoagulants, resulting in prolongation of prothrombin time. Dosage of oral anticoagulants may need to be adjusted during tinidazole co-administration and up to 8 days after discontinuation. **Alcohols, Disulfiram.** Preparations containing ethanol or propylene glycol should be avoided during tinidazole use and for 3 days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur. Psychotic reactions were reported in alcoholic patients using metronidazole and disulfiram concurrently. Tinidazole should not be given to patients who have taken disulfiram within the last 2 weeks. **Lithium.** Metronidazole was reported to elevate serum lithium levels. Consideration should be given to measuring serum lithium and creatinine levels after several days of simultaneous lithium and tinidazole treatment to detect potential lithium intoxication. **Phenytoin, Fosphenytoin (a pro-drug).** Concomitant administration of oral metronidazole and IV phenytoin was reported to result in prolongation of the half-life and reduction in clearance of phenytoin. **Cyclosporine, Tacrolimus.** Several case reports suggest that metronidazole can potentially increase levels of cyclosporine and tacrolimus. During tinidazole co-administration with either of these drugs, the patient should be monitored for signs of calcineurin-inhibitor associated toxicities. **Fluorouracil.** Metronidazole was shown to decrease clearance of fluorouracil, resulting in increase in side-effects without increase in therapeutic benefits. If concomitant use of tinidazole and fluorouracil cannot be avoided, the patient should be monitored for fluorouracil-associated toxicities. **Potential effect of other drugs on tinidazole:** Simultaneous administration of tinidazole with drugs that induce liver microsomal enzymes (cytochrome P-450) such as phenobarbital, rifampin, phenytoin, and fosphenytoin may accelerate elimination and decrease plasma level of tinidazole. Simultaneous administration of drugs that inhibit activity of liver microsomal enzymes, such as cimetidine and ketoconazole, may prolong half-life and decrease plasma clearance of tinidazole, increasing plasma level of tinidazole. **Cholestyramine.** Cholestyramine was shown to decrease oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate dosing of cholestyramine and tinidazole to minimize any potential effect on bioavailability of tinidazole. **Oxytetracycline.** Oxytetracycline was reported to antagonize the therapeutic effect of metronidazole. **Drug/Laboratory test interactions:** Tinidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and hexokinase glucose. Values of zero may be observed.

Carcinogenesis, Mutagenesis, Impairment of fertility: Metronidazole was reported to be carcinogenic in mice and rats. In several studies metronidazole showed evidence of pulmonary, hepatic, and lymphatic tumorigenesis in mice and mammary and hepatic tumors in female rats. Tinidazole carcinogenicity studies in rats, mice or hamsters have not been reported. Tinidazole was mutagenic in the TA 100, *S. typhimurium* tester strain both with and without the metabolic activation system. Mutagenicity results were mixed (positive and negative) in TA 1535, 1537, and 1538 strains. Tinidazole was also mutagenic in a tester strain of *Klebsiella pneumoniae*. Tinidazole was positive for *in vivo* genotoxicity in the mouse micronucleus assay. In a 60-day fertility study, tinidazole reduced fertility and produced testicular histopathology in male rats at

600 mg/kg/day (approx 3-fold the highest human therapeutic dose based upon body surface area conversions). Spermatogenic effects resulted from 300 and 600 mg/kg/day dose levels. The no observed adverse effect level for testicular and spermatogenic effects was 100 mg/kg/day (approx 0.5-fold the highest human therapeutic dose based upon body surface area conversions).

Pregnancy: Teratogenic effects: Pregnancy Category C: Use of tinidazole in pregnant patients has not been studied. Since tinidazole crosses the placental barrier and enters fetal circulation it should not be used in pregnant patients in the first trimester. Embryo-fetal developmental toxicity studies in pregnant mice indicated no embryo-fetal toxicity or malformations at the highest dose level of 2,500 mg/kg. In a study with pregnant rats a slightly higher incidence of fetal mortality was observed at a maternal dose of 500 mg/kg. Because animal reproduction studies are not always predictive of human response and because there is some evidence of mutagenic potential, use of tinidazole during pregnancy requires that potential benefits of the drug be weighed against possible risks to both mother and fetus. (See Contraindications). **Nursing mothers:** Tinidazole is excreted in breast milk in concentrations similar to those seen in serum, and can be detected in breast milk for up to 72 hours following administration. Interruption of breast-feeding is recommended during tinidazole therapy and for 3 days following the last dose. **Pediatric use:** Other than in treatment of giardiasis and amebiasis in pediatric patients older than 3 years of age, safety and effectiveness of tinidazole in pediatric patients have not been established. **Geriatric use:** Dose selection for an elderly patient should be cautious, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS:

Among 3,669 patients treated with a single 2 g dose of tinidazole, in both controlled and uncontrolled trichomoniasis and giardiasis clinical studies, adverse effects were reported by 11.0% of patients. For multi-day dosing in controlled and uncontrolled amebiasis studies, adverse effects were reported by 13.8% of 1,765 patients. Reported adverse effects from clinical trials were generally mild and self-limiting. Common ($\geq 1\%$ incidence) adverse effects reported by body system follow.

		2 g	Multi-day dose
GI	Metallic/bitter taste	3.7%	6.3%
	Nausea	3.2%	4.5%
	Anorexia	1.5%	2.5%
	Dyspepsia/cramps/epigastric discomfort	1.8%	1.4%
	Vomiting	1.5%	0.9%
	Constipation	0.4%	1.4%
CNS	Weakness/fatigue/malaise	2.1%	1.1%
	Dizziness	1.1%	0.5%
Other	Headache	1.3%	0.7%

Other adverse effects reported with tinidazole include: CNS: 2 serious adverse reactions include convulsions and transient peripheral neuropathy including numbness and paresthesia. Other CNS reports include vertigo, ataxia, giddiness, insomnia, drowsiness; GI: tongue discoloration, stomatitis, diarrhea; Hypersensitivity: urticaria, pruritis, rash, flushing, sweating, dryness of mouth, fever, burning sensation, thirst, salivation, angioedema; Renal: darkened urine; Cardiovascular: palpitations; Hematopoietic: transient neutropenia, transient leukopenia; Other: candida overgrowth, increased vaginal discharge, oral candidiasis, hepatic abnormalities including raised transaminase level, arthralgias, myalgias, arthritis. Rare reported adverse effects include bronchospasm, dyspnea, coma, confusion, depression, furry tongue, pharyngitis and reversible thrombocytopenia. Adverse events reported in pediatric patients were similar in nature and frequency to adult findings including nausea, vomiting, diarrhea, taste change, anorexia, and abdominal pain.

DOSAGE AND ADMINISTRATION:

It is advisable to take tinidazole with food to minimize incidence of epigastric discomfort and other GI side-effects. **Trichomoniasis:** In both sexes, a single 2 g oral dose. **Giardiasis:** In adults, a single 2 g dose. In pediatric patients older than 3 years of age, a single dose of 50 mg/kg (up to 2 g). **Amebiasis: Intestinal:** In adults, a 2 g dose per day for 3 days. In pediatric patients older than 3 years of age, 50 mg/kg/day (up to 2 g per day) for 3 days. **Amebic liver abscess:** In adults, a 2 g dose per day for 3-5 days. In pediatric patients older than 3 years of age, 50 mg/kg/day (up to 2 g per day) for 3-5 days.

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