Wilms' tumor complicating pregnancy: Report of a case

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Genitourinary symptomatology is commonly associated with pregnancy. Hematuria, either microscopic or macroscopic, usually is associated with hemorrhagic cystitis or urinary calculi. The following case represents an unusual disease process manifesting during pregnancy and presenting with gross hematuria. A renal carcinoma, more specifically Wilms' tumor, complicated the pregnancy.

Renal carcinoma complicating pregnancy is a rare phenomenon, with less than 50 cases having been reported in the literature. The majority of kidney tumors diagnosed in conjunction with pregnancy have been renal cell carcinomas.[1] Wilms' tumor (nephroblastoma) complicating pregnancy is extremely rare; in fact, this combination has been reported only 4 times.[2-5]

Definitive therapy in the puerperium is relatively straightforward. However, antepartal diagnosis and treatment of renal tumor is complicated by the presence and status of the developing fetus. This paper presents a case report and discussion of antepartal management of renal tumor—in this instance, Wilms' tumor—complicating pregnancy.

Report of case

A 19-year-old white woman (gravida 1, para O) presented at 32 weeks' gestation with a chief complaint of painless gross hematuria. The patient had received ultrasonographic verification of pregnancy at 7 weeks' gestation, and she had been followed since approximately 8-9 weeks' gestation. The prenatal course was complicated by transient first trimester nausea, muscle tension cephalalgia, and suspected cystitis. Routine laboratory studies revealed an A-positive blood type, negative rapid plasma reagin test, and immunity to rubella.

Symptoms that suggested lower urinary tract infection led to urinalysis at 23 weeks' gestation; this revealed 10-12 red blood cells per high power field and 5-7 white blood cells per high power field, with white blood cell clumping and a small amount of bacteria. The urine culture and sensitivity studies demonstrated mixed culture, which indicated probable contamination. A 7-day course of oral amoxicillin (500 mg. 3 times daily) was prescribed. Repeat urinalysis was performed at 26 weeks' gestation because of persistent symptoms, and it revealed 7-9 red blood cells per high power field, 10-12 white blood cells per high power field, and a moderate amount of bacteria. Urine culture again demonstrated a mixed culture and probable contamination. A complete blood count obtained at the same time revealed a leukocyte count of 16,800/cu. mm., with a differential distribution of 4 percent band forms, 72 percent segmented neutrophils, and 11 percent lymphocytes. These findings were thought to be secondary to progressive urinary tract infection. Hemoglobin concentration and hematocrit reading were 11.2 gm./dl. and 32.1 percent, respectively, with normal indices.

At this time, the patient admitted to poor compliance with the previous antibiotic therapy, and she was placed on a regimen of oral cephalexin (500 mg. 4 times a day) for 7 days. One week following initiation of this therapy, she reported a regression of symptoms, and repeat urinalysis also indicated improvement.

At 32 weeks' gestation, the patient complained of gross hematuria and the passage of clots. She denied pain but reported occasional contractions. The patient was afebrile. Physical examination re-

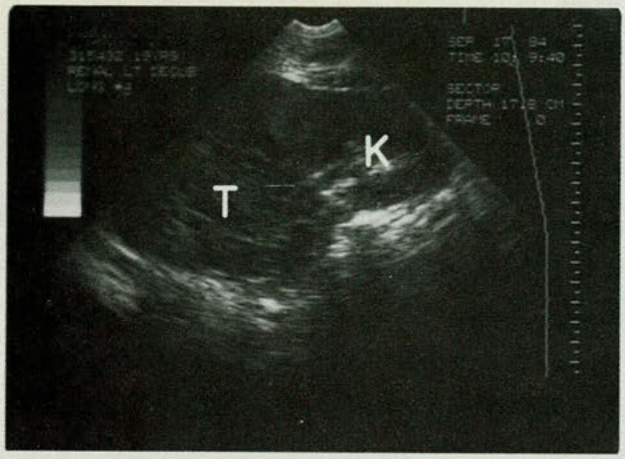

Fig. 1. *Sonogram of left kidney revealing a 12.5 × 10.5 cm. mass involving the superior pole.*

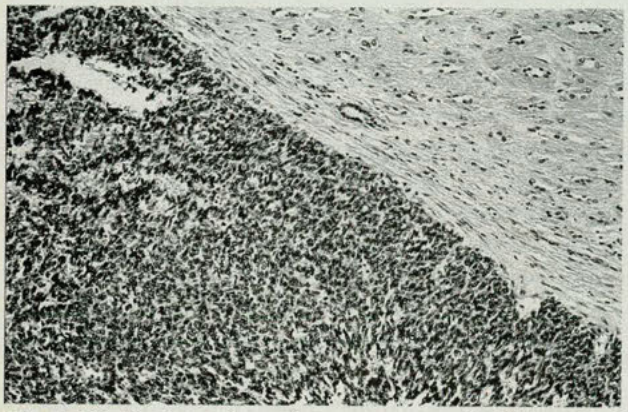

Fig. 2. *Histologic specimen demonstrates poorly differentiated Wilms' tumor (nephroblastoma).*

vealed mild suprapubic tenderness and minimal left flank tenderness on percussion. The cervix was closed, without evidence of bleeding or discharge. Urine obtained by catherization had a cloudy, red appearance, and urinalysis revealed 4+ occult blood and 3+ protein. Microscopically, the red blood cells per high power field were too numerous to count; further evaluation was not possible because of interfering red blood cells.

Hospital course

On admission, complete genitourinary ultrasonography was performed and urologic consultation was obtained. Differential diagnoses at admission were nephrolithiasis/ureterolithiasis, focal glomerulitis, glomerulonephritis, renal carcinoma, and hemorrhagic cystitis.

The ultrasonic evaluation of the genitourinary system revealed a large (12.5 × 10.5 cm.) complex mass involving the superior pole of the left kidney (Fig. 1). Limited intravenous pyelography was performed, with nonvisualization of the upper collecting system of the left kidney and nondelineation of the cortical margin. Lucency within the upper left ureter consistent with a blood clot also was noted. A 12.5 × 10.5 cm. tumor involving the upper left kidney was the final radiographic interpretation.

Because of the uncertain nature of the renal mass, intraoperative retrograde ureteral washings were obtained utilizing intravenous sedation and local anesthesia (1 percent lidocaine). The washings revealed atypia, but no definite malignant cytology could be identified.

Following general surgical and oncologic consultation, exploratory and definitive surgery (most likely total nephrectomy) was recommended to the patient. The patient consented and underwent left nephrectomy, partial left ureterectomy, and partial adrenalectomy under balanced general anesthesia. She was maintained in the right oblique position to avoid excessive vena caval compression, and continuous fetal monitoring was performed throughout the entire operation. The patient and infant tolerated the surgery, and the postoperative course was essentially normal. Pathologic evaluation of the renal mass was consistent with poorly differentiated Wilms' tumor of the left kidney (Fig. 2); this diagnosis was supported by pathologic consultation with two university centers.

Because the need for additional treatment in the form of irradiation and chemotherapy was indicated for this aggressive tumor, delivery of the infant upon verification of maturity was the next goal, as advocated by Ney and associates[1] and Anderson and Atkinson.[6] Amniocentesis was performed 6 days following nephrectomy, and the lecithin-sphingomyelin ratio was 2.1:1, and phosphatidylglycerol was present. A low transverse cervical cesarean section was performed at 33-34 weeks' gestation, with abdominal delivery of a viable male infant weighing 4 lb., 7 ½ oz. Apgar scores were 9 and 9 at both 1 and 5 minutes. Postoperatively the patient responded well, and she was discharged on the fourth postoperative day. Follow-up oncologic evaluation and discussion of further therapy was scheduled for the 2-week postoperative visit.

The patient arrived for this visit without complaint. However, she stated that after consultation with her minister, she had decided against further definitive therapy and that she wished to rely on continued prayer and faith healing. Despite continued efforts by her family and physicians, she refused to undergo appropriate chemotherapy and radiation and was lost to follow up.

Course of disease

Eleven months later, the patient was seen again at a nearby hospital emergency room, where she complained of chest pain. A chest x-ray revealed a 1.4-cm. lesion of the left lung, which was thought to be consistent with pulmonary metastasis. She finally agreed to hospitalization and further evaluation approximately 1 month later, and, on admission, the physical examination revealed a mass effect of the upper left abdomen and also in the left flank area. Subsequent computerized axial tomographic and NMR evaluation of the abdomen revealed a 25-cm. mass extending from the left hemidiaphragm into the pelvic area. The mass also extended into the left lobe of the liver and the retroperitoneum.

After being told of these findings, the patient consented to chemotherapy. Actinomycin D and vincristine were initiated. After 4 months of chemotherapy, physical examination returned to normal, and repeat computed tomographic scanning of the abdomen revealed reduction of the tumor to 10 cm., and repeat chest roentgenography revealed complete resolution of the left lung lesion.

Because of the known aggressiveness of this type of tumor, the patient's initial refusal of chemotherapy following surgical excision meant an extremely poor prognosis. However, her dramatic response to chemotherapy 15 months after surgery was encouraging. More recent follow-up has demonstrated a renewed metastatic process.

Discussion

Wilms' tumor (nephroblastoma) is the most common renal tumor diagnosed in children, with more than 75 percent of cases occurring before the fifth year of life.[7] This tumor in adulthood is reported only infrequently in the literature. Nephroblastoma is an aggressive, mixed tumor containing epithelial, muscular, and connective tissue elements. Grossly, the tumor usually is encapsulated and is located at one pole of the kidney beneath the renal capsule, as was true in the present case (Fig. 3). The tumor metastasizes early either by direct extension or via the blood and/or lymphatic system. Direct invasion of the liver, spleen, intestines, and lungs has been reported, as has brain and bone metastasis. Approximately 20 percent of cases are metastatic at the time of diagnosis.[7]

The most common presenting symptom is a mass, with less than 50 percent of patients experiencing hematuria; approximately one-third of patients present with pain, and 10 percent have fever. Nephrectomy is the mainstay of therapy. Currently, postoperative radiation and combination chemotherapy are the accepted mode of treatment in most medical centers, with actinomycin D and vincristine being the most common chemotherapeutic agents utilized. Prognosis is directly related to histologic grade, as determined by the Second National Wilms' Tumor Study classification system (Table 1).[8] Patients with unfavorable histologic characteristics (cellular anaplasia and sarcomatous features) have a relapse rate approaching 50 percent despite the present therapeutic modalities.[7]

In the present case, gross hematuria was the presenting complaint. The patient experienced no significant pain and was afebrile. No mass was palpable on examination; however, the patient was obese. Intraoperative evaluation of the tumor revealed an intact renal capsule without extrarenal extension, categorized as Group I carcinoma.

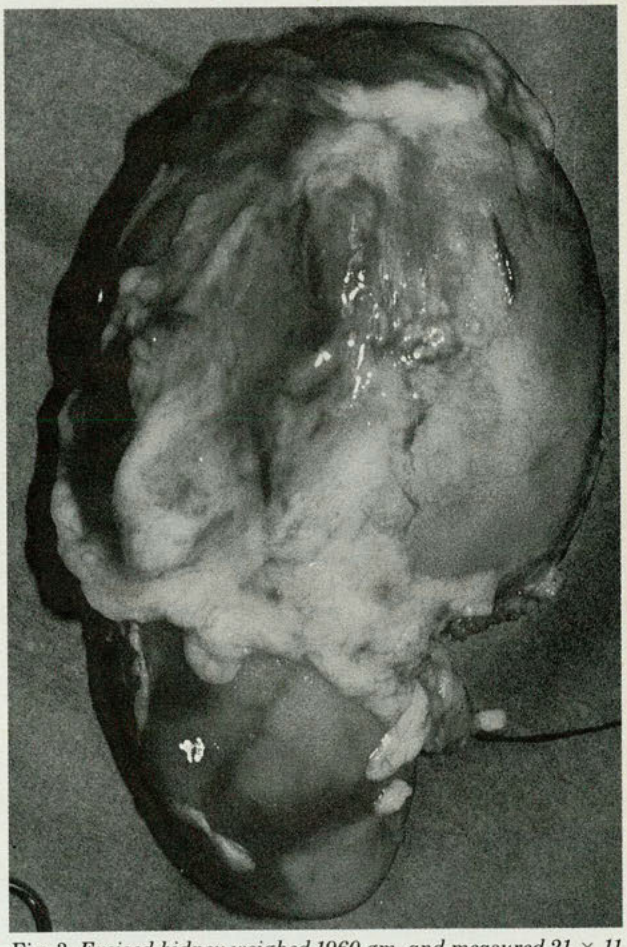

Fig. 3. *Excised kidney weighed 1960 gm. and measured 21 × 11 × 8 cm. A 12 × 10 × 8 cm. Wilms' tumor is seen to involve the superior pole.*

TABLE 1. NATIONAL WILMS' TUMOR STUDY[8] CLASSIFICATION SYSTEM.*

Group	Criteria	Comment
I	Tumor is limited to kidney and is completely excised.	The surface of the renal capsule is intact. The tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of excision.
II	Tumor extends beyond the kidney but is completely excised.	There is local extension of the tumor, that is, penetration beyond the pseudocapsule into the perirenal soft tissues or periaortic lymph node involvement. The renal vessels outside the kidney substance are infiltrated or contain tumor thrombus. There is no residual tumor apparent beyond the margins of excision.
III	Residual nonhematogenous tumor is confined to abdomen.	Any one or more of the following occur: (1) the tumor has undergone biopsy or rupture before or during surgery; (2) there are implants on peritoneal surfaces; (3) there are involved lymph nodes beyond the abdominal periaortic chains; and/or (4) the tumor is not completely removable because of local infiltration into vital structures.
IV	There is hematogenous metastases.	Deposits beyond Group III (for example, to lung, liver, bone, and brain).
V	Bilateral renal involvement occurs either initially or subsequently.	

*The patient's group is decided by the surgeon in the operating room and confirmed by the pathologists. If the histologic diagnosis and grouping will take longer than 48 hours, the surgical grouping stands, the patient is registered, and treatment is begun.

Summary

An unusual cause of hematuria arising during pregnancy, renal carcinoma, is presented. Wilms' tumor in a 19-year-old person is an uncommon occurrence. The fact that this case presented during pregnancy is even more unusual; it is only the fifth reported case in the literature.

The prognosis for this patient was initially promising due to the early stage of the tumor at the time of surgery. Adjuvant chemotherapy and radiotherapy would have provided a complete treatment regimen. The patient's refusal of both treatments has lead to diffuse metastasis and a very poor long-term prognosis.

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CONTRAINDICATION: Hydrochlorothiazide—Hydrochlorothiazide is contraindicated in patients with anuria and those who have previously demonstrated hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs.

WARNINGS: Captopril—Neutropenia/Agranulocytosis—Neutropenia (<1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine <1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present. Neutropenia has appeared within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evaluation of the hypertensive or heart failure patient should always include assessment of renal function. If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria—Total urinary proteins >1 g/day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (>150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy, patients with prior renal disease or those receiving captopril at doses >150 mg/day should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

Hydrochlorothiazide—Use with caution in severe renal disease. May precipitate azotemia in patients with renal disease. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS: General: Captopril—*Impaired Renal Function*—Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible (see DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]). *Surgery/Anesthesia*—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Hydrochlorothiazide—Observe all patients for signs of fluid or electrolyte imbalance, particularly when the patient is vomiting excessively or receiving parenteral fluids. Warning signs include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and nausea and vomiting. Hypokalemia may develop when severe cirrhosis is present or without adequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of the heart to the toxic effects of digitalis. Because captopril reduces the production of aldosterone, concomitant therapy with captopril reduces the diuretic-induced hypokalemia. Fewer patients may require potassium supplements and/or foods with a high potassium content (see Drug Interactions, Agents Increasing Serum Potassium).

Any chloride deficit is generally mild and may not require specific treatment, exceptions include liver disease or renal disease. Dilutional hyponatremia may occur in edematous patients in hot weather; use water restriction, rather than salt administration except when the hyponatremia is life-threatening. In actual salt depletion, replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients. Latent diabetes mellitus may become manifest. Antihypertensive effects may be enhanced in the postsympathectomy patient. Progressive renal impairment, indicated by rising nonprotein nitrogen or blood urea nitrogen, requires a careful reappraisal of the necessity of therapy. Serum PBI levels may decrease. Calcium excretion is decreased. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed during prolonged therapy.

Laboratory Tests—Serum and urine electrolyte levels should be regularly monitored (see WARNINGS, [Captopril and Hydrochlorothiazide], also PRECAUTIONS [General, Hydrochlorothiazide]).

Drug Interactions—Captopril—*Hypotension—Patients on Diuretic Therapy:* Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose. *Agents Having Vasodilator Activity:* In heart failure patients, vasodilators should be administered with caution. *Agents Causing Renin Release:* Captopril's effect will be augmented by antihypertensive agents that cause renin release. *Agents Affecting Sympathetic Activity:* The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution. *Agents Increasing Serum Potassium:* Give potassium sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution. *Inhibitors Of Endogenous Prostaglandin Synthesis:* Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Hydrochlorothiazide—When administered concurrently the following drugs may interact with thiazide diuretics: *Alcohol, barbiturates, or narcotics*—potentiation of orthostatic hypotension may occur. *Antidiabetic drugs (oral agents and insulin)*—Hyperglycemia induced by thiazides may require dosage adjustment of the antidiabetic drug. *Other antihypertensive drugs*—additive effect or potentiation. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. *Corticosteroids, ACTH*—intensified electrolyte depletion, particularly hypokalemia. *Preanesthetic and anesthetic agents*—effects of preanesthetic and anesthetic agents may be potentiated; adjust dosage of these agents accordingly. *Pressor amines (e.g., norepinephrine)*—possible decreased response to pressor amines but not sufficient to preclude their use. *Skeletal muscle relaxants, nondepolarizing (e.g., tubocurarine)*—possible increased responsiveness to the muscle relaxant. *Lithium*—should not generally be given with diuretics; diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with CAPOZIDE.

Drug/Laboratory Test Interactions—Captopril—may cause a false-positive urine test for acetone.

Hydrochlorothiazide—Discontinue thiazides before carrying out tests for parathyroid function (see PRECAUTIONS [General, Hydrochlorothiazide]).

Carcinogenesis, Mutagenesis and Impairment of Fertility—Captopril—Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Hydrochlorothiazide—Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether this drug affects fertility in males or females.

Pregnancy: Category C—Captopril—There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Hydrochlorothiazide—Studies in pregnant rats using captopril and hydrochlorothiazide individually and in combination, each agent in doses up to 1350 mg/kg, failed to show evidence of embryotoxicity, fetotoxicity, or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CAPOZIDE should be used during pregnancy, or in patients likely to become pregnant, only if the potential benefit justifies the potential risk to the fetus.

Pregnancy—Nonteratogenic Effects—Hydrochlorothiazide—Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the benefit be weighed against possible hazards to the fetus. Hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other reported reactions.

Nursing Mothers: Both captopril and hydrochlorothiazide are excreted in human milk. A potential exists for serious adverse reactions in nursing infants from both drugs, therefore, decision whether to discontinue nursing or to discontinue therapy should take into account the importance of CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) to the mother.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOZIDE should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Captopril—Reported incidences are based on clinical trials involving approximately 7000 patients. *Renal*—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients. *Hematologic*—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported. *Dermatologic*—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients. *Cardiovascular*—Hypotension may occur, see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients. *Dysgeusia*—About 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Hydrochlorothiazide—*Gastrointestinal System*—anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, and sialadenitis. *Central Nervous System*—dizziness, vertigo, paresthesias, headache, and xanthopsia. *Hematologic*—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia. *Cardiovascular*—orthostatic hypotension. *Hypersensitivity*—purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis; cutaneous vasculitis), fever, respiratory distress including pneumonitis, and anaphylactic reactions. *Other*—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, and transient blurred vision. Whenever adverse reactions are moderate or severe, reduce or withdraw therapy.

Altered Laboratory Findings: Elevations of liver enzymes have been noted in a few patients but no causal relationship to captopril use has been established. Rare cases of cholestatic jaundice and of hepatocellular injury with or without secondary cholestasis have been reported in association with captopril administration. A transient elevation of BUN and serum creatinine may occur, especially in patients who are volume-depleted or who have renovascular hypertension. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in the serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Captopril—Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

Hydrochlorothiazide—In addition to diuresis, overdosage of thiazides may produce varying degrees of lethargy which may progress to coma within a few hours, with minimal respiratory and cardiovascular depression and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function. In addition to gastric lavage and supportive therapy for stupor or coma, symptomatic treatment of gastrointestinal effects may be needed. Degree of removal by hemodialysis has not been clearly established. Measures to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function should be instituted.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED (SEE INDICATIONS AND USAGE). CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) should be taken one hour before meals. CAPOZIDE may be dosed bid or tid. Because captopril and hydrochlorothiazide are excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOZIDE (Captopril-Hydrochlorothiazide Tablets). Available in tablets of 25 mg captopril combined with 15 mg hydrochlorothiazide, 25 mg captopril combined with 25 mg hydrochlorothiazide, 50 mg captopril combined with 15 mg hydrochlorothiazide, and 50 mg captopril combined with 25 mg hydrochlorothiazide in bottles of 100.

(J4-005C)

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