

DIABINESE®

(chlorpropamide) 100-mg and 250-mg Tablets

BRIEF SUMMARY

DIABINESE® (chlorpropamide) Tablets

Contraindications: Diabinese is not indicated in patients having juvenile or growth-onset diabetes mellitus, severe or unstable "brittle" diabetes, and diabetes complicated by ketosis and acidosis, diabetic coma, major surgery, severe infection, or severe trauma.

Diabinese is contraindicated during pregnancy. Serious consideration should be given to the potential hazard of its use in women of childbearing age who may become pregnant.

Diabinese is contraindicated in patients with serious impairment of hepatic, renal, or thyroid function.

Precautions: Use chlorpropamide with caution with barbiturates, in patients with Addison's disease or in those ingesting alcohol, antibacterial sulfonamides, phenylbutazone, salicylates, probenecid, dicoumarol or MAO inhibitors.

Warnings: DIABINESE (CHLORPROPAMIDE) SHOULD NOT BE USED IN JUVENILE DIABETES OR IN DIABETES COMPLICATED BY ACIDOSIS, COMA, SEVERE INFECTION, MAJOR SURGICAL PROCEDURES, SEVERE TRAUMA, SEVERE DIARRHEA, NAUSEA AND VOMITING, ETC. HYPOGLYCEMIA, IF IT OCCURS, MAY BE PROLONGED.

Adverse Reactions: Usually dose-related and generally respond to reduction or withdrawal of therapy. Generally transient and not of a serious nature and include anorexia, nausea, vomiting and gastrointestinal intolerance, weakness and paresthesias. Certain untoward reactions associated with idiosyncrasy or hypersensitivity have occasionally occurred, including jaundice (rarely associated with severe diarrhea and bleeding), skin eruptions rarely progressing to erythema multiforme and exfoliative dermatitis, and probably depression of formed elements of the blood. With a few exceptions, these manifestations have been mild and readily reversible on the withdrawal of the drug.

Diabinese should be discontinued promptly when the development of sensitivity is suspected.

Jaundice has been reported, and is usually promptly reversible on discontinuance of therapy. THE OCCURRENCE OF PROGRESSIVE ALKALINE PHOSPHATASE ELEVATION SHOULD SUGGEST THE POSSIBILITY OF INCIPENT JAUNDICE AND CONSTITUTES AN INDICATION FOR WITHDRAWAL OF THE DRUG.

Leukopenia, thrombocytopenia and mild anemia, which occur occasionally, are generally benign and revert to normal, following cessation of the drug.

Cases of aplastic anemia and agranulocytosis, generally similar to blood dyscrasias associated with other sulfonylureas, have been reported.

BECAUSE OF THE PROLONGED HYPOGLYCEMIC ACTION OF DIABINESE, PATIENTS WHO BECOME HYPOGLYCEMIC DURING THERAPY WITH THIS DRUG REQUIRE CLOSE SUPERVISION FOR A MINIMUM PERIOD OF 3 TO 5 DAYS, during which time frequent feedings or glucose administration are essential. The anorectic patient or the profoundly hypoglycemic patient should be hospitalized.

Rare cases of phototoxic reactions have been reported. Edema associated with hyponatremia has been infrequently reported. It is usually readily reversible when medication is discontinued.

Dosage: The mild to moderately severe, middle-aged, stable diabetic should be started on 250 mg daily. Because the geriatric diabetic patient appears to be more sensitive to the hypoglycemic effect of sulfonylurea drugs, older patients should be started on smaller amounts of Diabinese, in the range of 100 to 125 mg daily. After five to seven days following initiation of therapy, dosage may be adjusted upward or downward in increments of 50 to 125 mg at intervals of three to five days. Patients who do not respond completely to 500 mg daily will usually not respond to higher doses. Maintenance doses above 750 mg daily should be avoided.

Supply: 100 mg and 250 mg, blue, D-shaped, scored tablets.

More detailed professional information available on request.

References: 1. Bunn HF. Glycosylated hemoglobins and diabetes mellitus. *Resident and Staff Physician*. 24:53-57, December 1978. 2. Koening RJ, Peterson CM, Kilo C, et al. Hemoglobin A_{1c} as an indicator of the degree of glucose intolerance in diabetes. *Diabetes*. 25:230-232, March 1976. 3. Koening RJ, Cerami A. Synthesis of hemoglobin A_{1c} in normal and diabetic mice. Potential model of basement membrane thickening. *Proc Natl Acad Sci USA* 72:3687-3691, September 1975. 4. Koening RJ, Peterson CM, Jones RL, et al. Correlation of glucose regulation and hemoglobin A_{1c} in diabetes mellitus. *N Engl J Med* 295:417-420, August 19, 1976. 5. Peterson CM, Jones RL. The utility of hemoglobin A_{1c} in diabetes mellitus and preliminary studies with chlorpropamide. *Diabetes in Theory and in Practice*. New York, Biomedical Information Corporation, 1978, pp 28-33.

LETTERS TO THE EDITOR

APARTHEID AND MEDICAL EDUCATION

To the Editor:

I have read the article in the Journal by Phillip Tobias, "Apartheid and Medical Education: The Training of Black Doctors in South Africa" (*J Natl Med Assoc* 72 (4):395-410, 1979). I must congratulate you on being able to secure his consent to undertake this paper. It was indeed very courageous of him to write in such a forthright manner. It is an article that is worth preserving.

Dr. James Obi
University of Benin
Benin City, Nigeria

LEUCOPENIA AND THROMBOCYTOPENIA WITH CIMETIDINE

To the Editor:

Leucopenia and thrombocytopenia, rare hematologic side effects of cimetidine therapy, are reversible.¹⁻⁵ The myelotoxicity may manifest within days or months and the bone marrow study may reveal an active² or hypocellular marrow.⁵

Case Report

A 64-year-old woman was admitted to Downstate Medical Center for bilateral uretero-transverse colostomy with a single midline stoma. Thirteen years prior to this admis-

sion she underwent a Wertheim radical hysterectomy and radiation therapy for uterine cervical cancer, followed by cutaneous ureterostomy for contracted bladder and bilateral ureteric stricture. She underwent ureterocolostomy three days after admission. Postoperatively the patient became febrile and received gentamicin and clindamycin. She developed upper gastrointestinal bleeding on the third postoperative day and was placed on intravenous cimetidine 300 mg every six hours. On the fifth day of cimetidine therapy, leucopenia and thrombocytopenia were noted. Three days after the discontinuation of cimetidine the leucocyte and platelet count returned to normal (Table 1).

Discussion

Myelotoxicity of cimetidine is a rare phenomenon that is reversible. Leucopenia and thrombocytopenia may manifest within days² or months,¹ and bone marrow studies may show normal² or hypocellular⁵ marrow. Byron⁶ suggests that the hematologic side effects are due to H₂ receptor antagonism of pleuripotent stem cells. However, this view is not universally accepted⁷ and needs further clarification.⁸ The underlying disease state and concomitant use of other drugs may also play a role in causing the leucopenia and thrombocytopenia.⁸

Although it cannot be proven

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Long-acting Zaroxolyn[®]

(metolazone) Pennwalt

Before prescribing, see complete prescribing information in the package insert, or in PDR, or available from your Pennwalt representative. The following is a brief summary. **Indications:** Zaroxolyn (metolazone) is an antihypertensive diuretic indicated for the management of mild to moderate essential hypertension as sole therapeutic agent and in the more severe forms of hypertension in conjunction with other antihypertensive agents. Also, edema associated with heart failure and renal disease. Routine use in pregnancy is inappropriate. **Contraindications:** Anuria, hepatic coma or precoma, allergy or hypersensitivity to Zaroxolyn. **Warnings:** In theory cross-allergy may occur in patients allergic to sulfonamide-derived drugs, thiazides or quinethazone. Hypokalemia may occur, and is a particular hazard in digitalized patients; dangerous or fatal arrhythmias may occur. Azotemia and hyperuricemia may be noted or precipitated. Considerable potentiation may occur when given concurrently with furosemide. When used concurrently with other antihypertensives, the dosage of the other agents should be reduced. Use with potassium-sparing diuretics may cause potassium retention and hyperkalemia. Administration to women of child-bearing age requires that potential benefits be weighed against possible hazards to the fetus. Zaroxolyn appears in the breast milk. Not for pediatric use. **Precautions:** Perform periodic examination of serum electrolytes, BUN, uric acid, and glucose. Observe patients for signs of fluid or electrolyte imbalance, namely hyponatremia, hypochloremic alkalosis and hypokalemia. These determinations are particularly important when there is excessive vomiting or diarrhea, or when parenteral fluids are administered. Patients treated with diuretics or corticosteroids are susceptible to potassium depletion. Caution should be observed when administering to patients with gout or hyperuricemia or those with severely impaired renal function. Insulin requirements may be affected in diabetics. Hyperglycemia and glycosuria may occur in latent diabetes. Chloride deficit and hypochloremic alkalosis may occur. Orthostatic hypotension may occur. Dilutional hyponatremia may occur. Zaroxolyn 10 mg tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin sensitivity. **Adverse Reactions:** Constipation, nausea, vomiting, anorexia, diarrhea, bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis, syncope, dizziness, drowsiness, vertigo, headache, orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain, leukopenia, urticaria, other skin rashes, dryness of mouth, hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, raised BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, and acute gouty attacks. **Usual Initial Once-Daily Dosages:** mild to moderate essential hypertension—2½ to 5 mg; edema of cardiac failure—5 to 10 mg; edema of renal disease—5 to 20 mg. Dosage adjustment is usually necessary during the course of therapy. **How Supplied:** Tablets, 2½, 5 and 10 mg.

References: 1. Data on file, Medical Department, Pennwalt Pharmaceutical Division. 2. Van Hoose MC, Cutler RE: Antihypertensive efficacy of metolazone (Zaroxolyn[®]) alone and combined with reserpine in treatment of essential hypertension. *Curr Ther Res* 20:266-276, 1976. 3. Cangiano JL, Campos JA, Trevino A IV, et al: The effects of metolazone in the long-term treatment of essential hypertension. *Curr Ther Res* 16:778-785, 1974. 4. Cangiano JL: Effects of prolonged administration of metolazone in the treatment of essential hypertension. *Curr Ther Res* 20:745-750, 1976. 5. Dornfeld L, Kane RE: Metolazone in essential hypertension: The long-term clinical efficacy of a new diuretic. *Curr Ther Res* 18:527-533, 1975. 6. Materson BJ, Oster JR, Perez-Stable EC: Antihypertensive effects of metolazone (Zaroxolyn). *Curr Ther Res* 16:890-896, 1974.



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TABLE 1. SERIAL HEMOGLOBIN, WHITE CELL, AND PLATELET COUNTS

Day	Hemoglobin gm/100 ml	White cells cu mm	Platelets cu mm
-7	10.1	7,500	—
-2*	11.7	16,400	220,000
1	9.8	9,200	—
2	9.4	6,000	—
4	11.4	4,300	95,000
5	10.5	3,000	—
7	11.9	4,900	—
8	11.4	5,200	245,000

*Postoperatively patient was febrile

that cimetidine caused the leucopenia and thrombocytopenia in our patient, no other etiological agents could be noted, as all other medications were continued through this period. Unfortunately a bone marrow study was not obtained in our patient.

Summary and Conclusions

A 64-year-old woman who received cimetidine for upper gastrointestinal bleeding developed reversible leucopenia and thrombocytopenia. We recommend close monitoring of leucocytes and platelets in all patients receiving cimetidine and prompt withdrawal of the drug when myelotoxicity develops. A bone marrow study during the acute and recovery phase is helpful in understanding the pathology involved.

Dr. Kota L. Chandrasekhara
Fellow in Gastroenterology
Dr. Swaminath K. Iyer
Director, Division of Medicine
Assistant Professor of Medicine

Dr. Richard J. Macchia
Associate Professor of Urology
Department of Urology
State University of New York,
Downstate Medical Center,
Brooklyn, New York

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