Ultrasonographic evaluation of neonatal intracranial hemorrhage

LESLIE HOOD, D.O.
Dublin, Ohio

Approximately half of all premature neonates who are younger than 34 weeks' gestation or who weigh less than 1,500 grams at birth develop intracranial hemorrhage (ICH). Numerous causative factors for ICH have been found, with most related to the neonates' immature, developing brains, the stresses associated with the birth process, and the life-sustaining treatment required thereafter. The most common site of hemorrhage is the subependymal germinal matrix; there is frequent extension of bleeding into the ventricular system and, occasionally, directly into the brain parenchyma itself. Real-time ultrasonography has proved to be very sensitive in diagnosing clinical significant pathology. The optimal times for performing ultrasonography appear to be 4 and 14 days, with repeat scanning recommended at 3 months if no abnormality is seen on the initial ultrasonograms. More frequent scanning is recommended when an abnormality is diagnosed early. Because the ICH is not clinically apparent in approximately 50 percent of all cases, a high degree of physician suspicion is necessary for all premature neonates.

Since the advent of modern neonatal intensive care units, there has been a marked increase in survival of premature infants. However, while the incidence of mortality in premature neonates from respiratory diseases has declined, there has been a corresponding increase in the incidence of intracranial hemorrhage (ICH). With the development of real-time mobile ultrasound units, radiologists are now able to easily diagnose neonatal intracranial abnormalities and follow their progression. Recent studies[1-3] have reported a 40 to 60 percent incidence of ICH in infants younger than 34 weeks' gestation or those with a birth weight less than 1,500 grams. At least half of these bleeds are intraventricular.

This paper discusses the neuropathology, possible causative factors, timing, diagnosis, and classification of neonatal ICH. In addition, a comparison of diagnostic yield from ultrasonography versus computed tomography (CT) is presented.

Neuropathology

Both periventricular ICH and intraventricular ICH usually originate from capillaries in the subependymal germinal matrix. This highly vascular structure is largest at 24-32 weeks' gestation; it involutes progressively and is absent in full-term infants. It lies above the caudate nucleus and just beneath the ependymal lining of the lateral ventricles. The matrix at the level of the head of the caudate nucleus and foramen of Monro is the primary site of hemorrhage in most infants. This area of rapidly developing neural tissue consists of sheets of primitive cells, connective tissue, and many thin-walled veins.

In many instances, the ICH may remain localized to the germinal matrix areas and will appear on the ultrasonographic scan as a subependymal hemorrhage. The bleeding, however, may rupture through the ependyma into the ventricular cavity and enter the lateral ventricles. If bleeding persists, the entire ventricular system may fill with blood, flowing through the foramen of Monro to the third ventricle and the aqueduct of Sylvius to the fourth ventricle. Hemorrhaging into the subarachnoid space may occur if the blood continues to flow through the foramina of Magendie and Luschka.

Infrequently, hemorrhage may arise in the choroid plexus.[4] Cerebral hemorrhage occasionally may occur from direct extension of a matrix bleed into the surrounding brain parenchyma. Hydrocephalus, which results from obstruction of cerebral spinal fluid pathways by clot, ependymitis, or basilar arachnoiditis, is a frequent finding.

Pathogenesis

Many causative factors have been attributed to ICH. Some of these are concerned with the distribution and regulation of cerebral blood flow, intravascular pressures, and vascular integrity. Prior to 32-34 weeks' gestation, there is a disproportionate abundance of total cerebral blood flow to the subependymal region. In addition, there is evidence that the autoregulatory blood pressure mechanism in these neonates is not fully developed.[2] Therefore, stress factors that elevate or fluctuate arterial pressure, combined with the failure of autoregulatory mechanisms and the preferential flow to the germinal matrix, may explain the high incidence of subependymal hemorrhage.

Neonatal ICH has been associated with pneumothorax, hypoxia, acidosis, mechanical ventilation, and patent ductus arteriosus.[3] Additional theories of pathogenesis involve infarction secondary to thrombosis of the deep cerebral vessels, increased venous pressure, pulmonary diseases, administration of excessive sodium bicarbonate, and maternal aspirin ingestion.[5,6]

There appears to be a significant increase in the incidence of ICH in vaginally delivered infants and in those whose mothers had longer labors.[3] Correlations have been found between intrapartum hemorrhage, such as placenta previa or abruptio placentae, and subsequent ICH.[3] Significantly, more infants with intraventricular hemorrhage had Apgar scores <5 at 5 minutes.

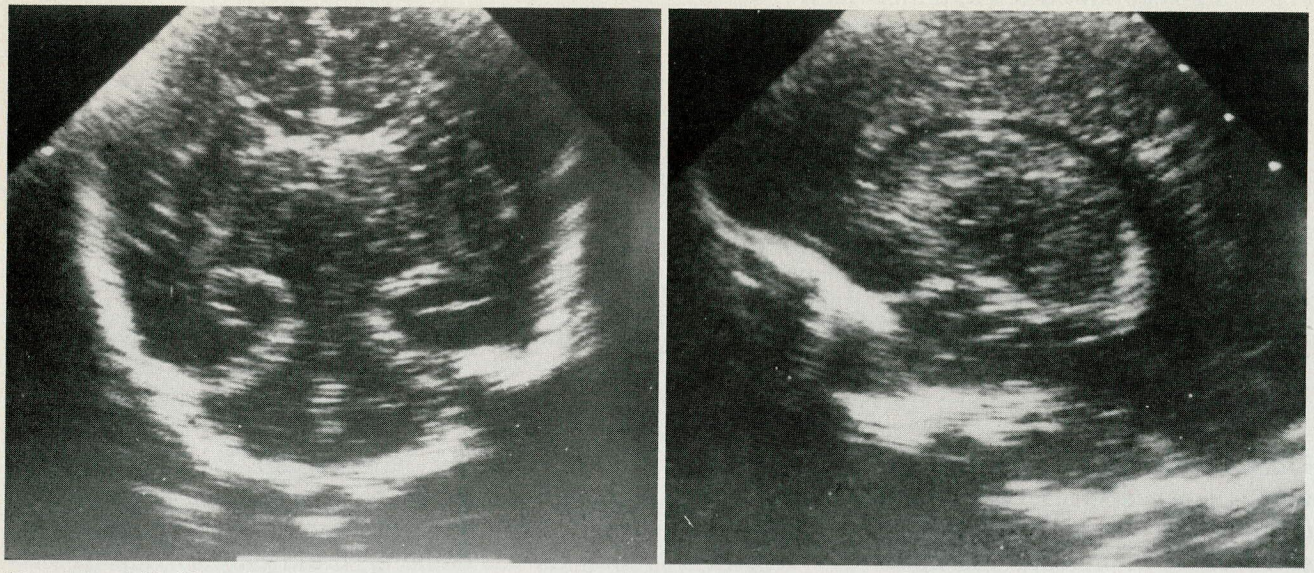
Very significant correlations between ICH and extreme blood pressure fluctuation or the administration of rapid colloid infusions to treat hypotension was found.[3] However, slow transfusion of packed red blood cells did not seem to increase the incidence of ICH.[3]

Diagnosis and evaluation

Cranial ultrasonography may be of benefit in evaluating increased head size, seizures, abnormal neurologic examination, apnea, birth trauma, meningitis, and congenital abnormalities. It is routinely used for screening premature infants who have a marked increased risk for ICH. It has been shown in prospective studies of premature infants that only about half of the examples of ICH were predicted on the basis of clinical criteria.[7] The most reliable sign has proved to be an unexplained fall in the hematocrit reading or a failure of the hematocrit value to rise after transfusion.[2]

Ultrasonographic technique

Utilizing the anterior fontanelle as a window, cranial ultrasonography can be performed routinely in the neonatal intensive care unit. Using either a 5-MHz or 7.5-MHz transducer, scanning is begun in a coronal plane anteriorly, with progressive angulation of the transducer posteriorly. Scanning then is performed in the sagittal plane, beginning in the midline and progressing to the right and left. Axial scans with the transducer placed at an angle of 15-20 degrees above the canthomeatal line can also be performed if needed.



Figs. 1A and 1B. *Normal (grade 0) intracranial ultrasonograms. In* Figure 1A, *a coronal scan angled posteriorly shows small, slit-like ventricles lying superiorly to the echogenic choroid plexus. In* Figure 1B, *the body of the lateral ventricle and the occipital horn can be seen on the sagittal views. The echogenic choroid plexus is again noted posteriorly, with the area of the thalamus lying anteriorly to the choroid plexus.*

ICH grading

The most common, currently used grading system for ICH was developed by Burstein and associates.[5] According to their criteria, a grade O is normal, with no evidence of ICH. Grade I is defined as hemorrhage that is confined to the subependymal germinal matrix, and a grade II hemorrhage is present when the subependymal bleed extends into the ventricle but does not cause ventricular dilatation. Subependymal hemorrhage (SEH) with ventricular extension and dilatation is classified as grade III ICH. A grade IV bleed is diagnosed when the original SEH site ruptures and causes intraventricular hemorrhage (IVH) as well as intraparenchymal hemorrhage (IPH). Adjustment to the classification for hemorrhages that originate at sites other than the germinal matrix and for IPH without IVH can be made.

Figures 1A and 1B are examples of normal (grade O) ultrasonograms. Figs. 2A-2G depict SEH with IVH and ventricular dilatation (grade III ICH), and Figs. 2H and 2I demonstrate typical grade IV ultrasonographic findings. Extensive choroid plexus ICH with primary IPH extension is portrayed in Figures 3A and 3B.

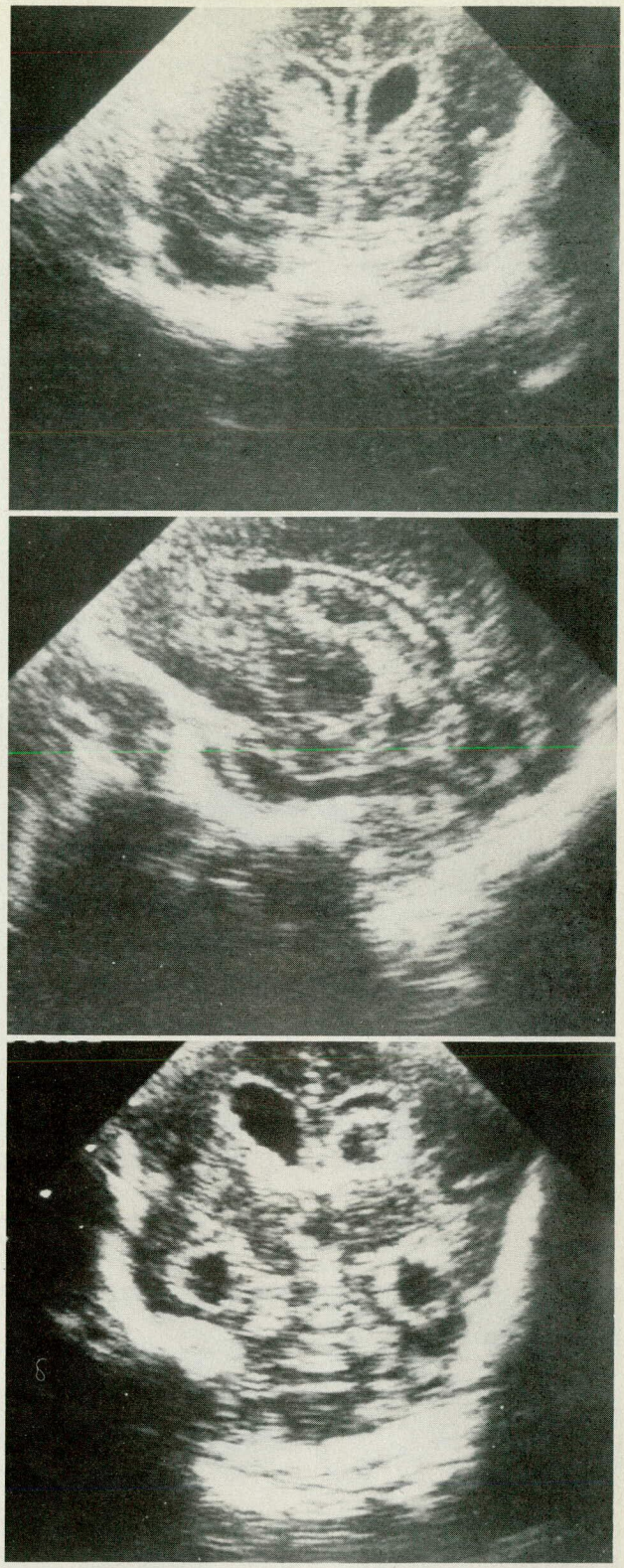
Optimal timing of ultrasonography

Inasmuch as ICH occurs twice as often as predicted by clinical examination, optimal timing of ultrasonography is needed to give the best diagnostic yield at the lowest cost. Although the majority of intracranial hemorrhages will occur within the first 2 days after birth, scanning performed at days 4-7 will give maximum diagnostic efficiency for early ICH.[1] Ventricular dilatation lags behind IVH, and, although it is frequently seen at day 4, the maximum efficiency for diagnosis and analysis of the extent of dilatation appears to be day 14. The extension of previously seen hemorrhage or documentation of new hemorrhage can also be made at this time. If both the 4- and 14-day scans are normal, repeat scanning at 3 months is recommended to document the absence of delayed ventricular dilatation.[1,3]

If an ultrasonographic abnormality is identified, more frequent examinations (at least weekly) are recommended to evaluate the extent of bleeding and ventricular enlargement. Assessment can also be made as to when intervention for hydrocephalus may be needed.

Ultrasonography versus computed tomography

Numerous studies[5,6,8-11] comparing the effectiveness of ultrasonography and CT in evaluation of the neonatal brain have been performed. Certain limitations and benefits are associated with both



Figs. 2A-2G. *Ultrasonograms depict progressive (Grade III) neonatal ventricular hemorrhage. In Figures 2A and 2B, coronal and sagittal views show prominent area of echogenicity reflecting subependymal hemorrhage in the base of the right lateral ventricle. There is associated mild ventricular dilatation. Two days later, repeat scanning shows progressive bilateral ventricular dilatation. The coronal view (Fig. 2C) shows additional area of hemorrhage in the left subependymal region with a central cystic sonolucency.*

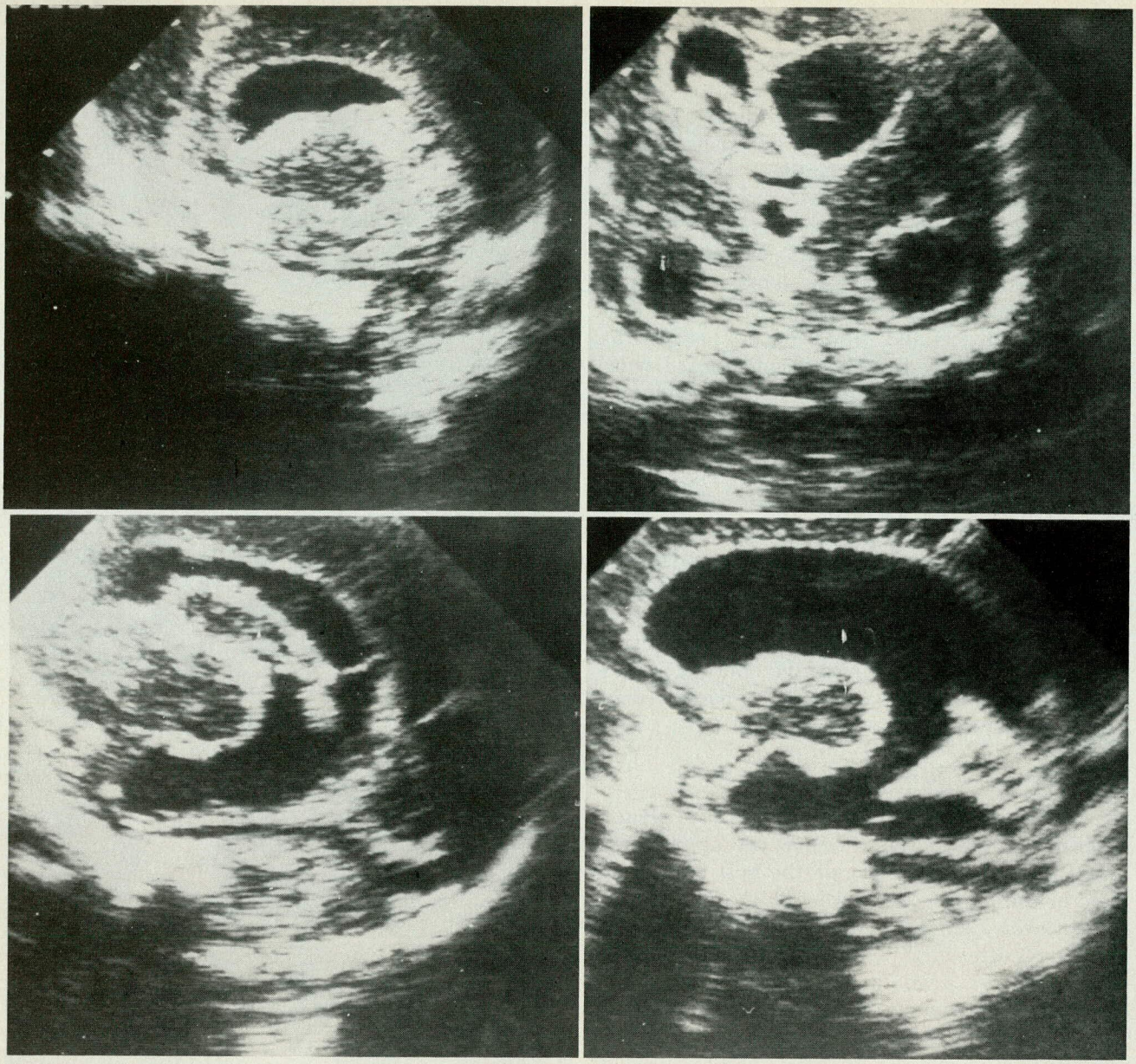
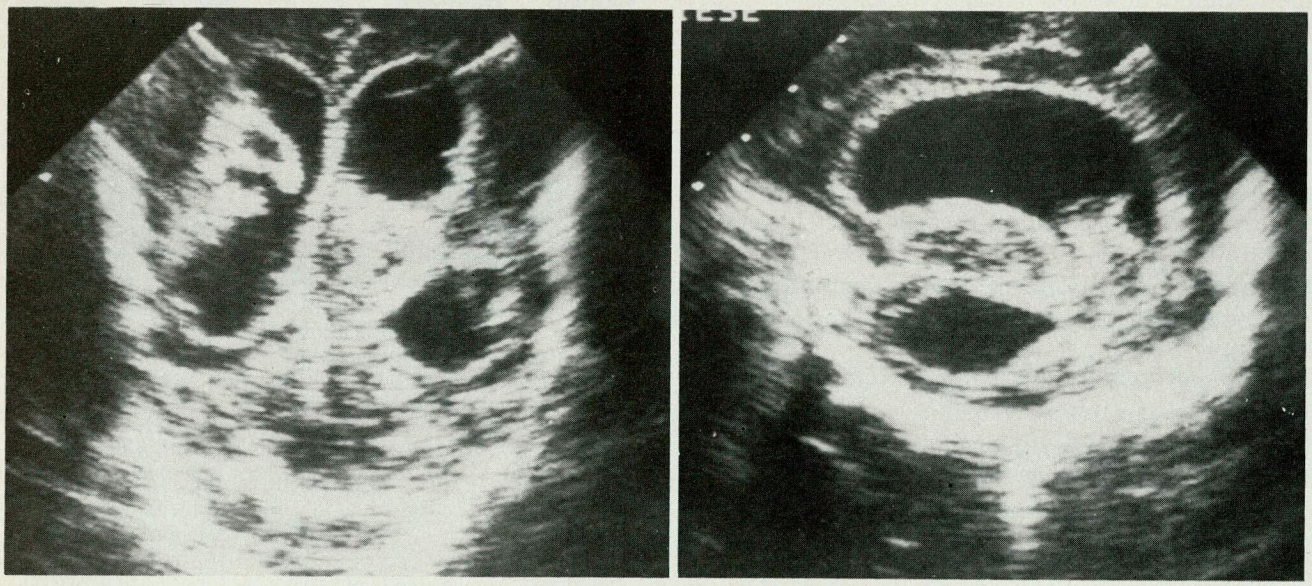
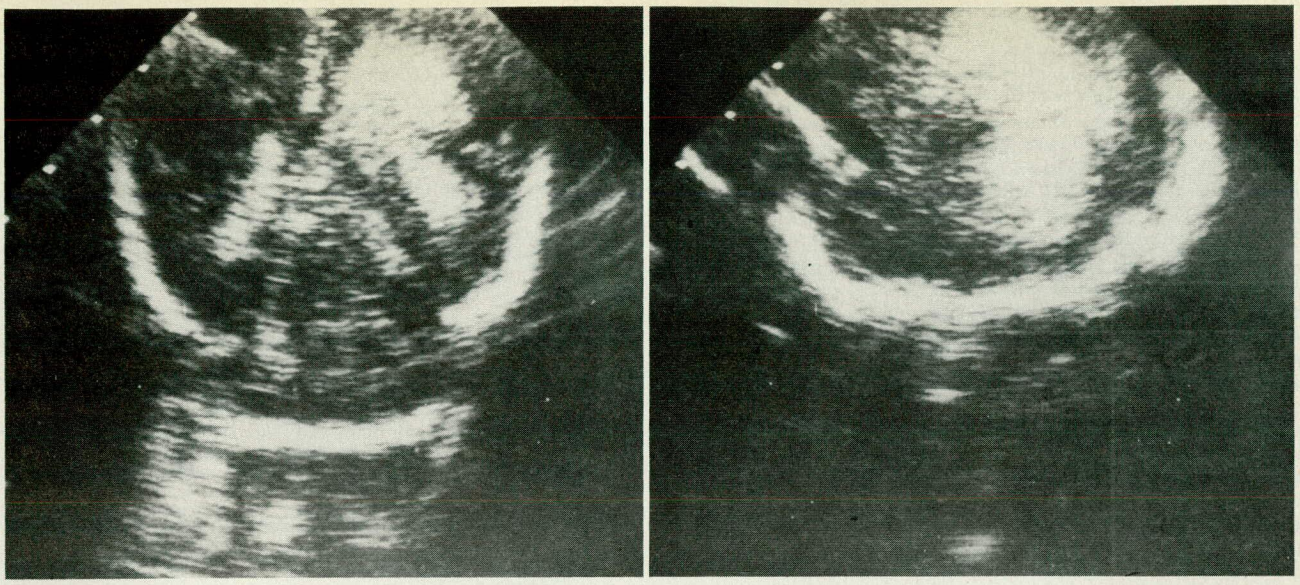


Fig. 2D. *Layering of clot in the dilated ventricle is seen in the sagittal view.* In Figures 2E-2G, *progressive hydrocephalus is demonstrated. Coronal view (Fig. 2E) shows a significant increase in ventricular dilatation. Clot or an area of repeat hemorrhage is seen at the base of the right lateral ventricle (Figs. 2E and 2F). Mass effect, with shifting of the midline to the right, is present. The left ventricle shows marked dilatation of lateral and temporal horns (Fig. 2G).*



Figs. 2H and 2I. *Grade IV ICH ultrasonograms from the same patient depicted in Figs. 2A-2G. Massive hydrocephalus is now present, and the area of increased echogenicity in the left thalamic region is consistent with intraparenchymal hemorrhage in this area.*



Figs. 3A and 3B. *Large echogenic area of hemorrhage, which originates from the region of the choroid plexus, is seen on the left. Primary intraparenchymal extension, which obliterates the lateral ventricle on the left, also is present.*

procedures.

Ultrasonography is limited in that it does not visualize the entire brain. It also has little benefit in the evaluation of bony abnormalities. Artifacts in the ultrasonographic image, especially directly below the transducer, causes peripheral lesions to be missed. Ultrasonography also frequently does not include the superficial subdural space or superior lateral edges of the brain. Real-time ultrasonography is beneficial in that it allows the examiner a continuous image in multiple planes for evaluating pathologic intracranial changes.

Ultrasound equipment is portable, which allows the examination to be performed in the safe environment of the neonatal intensive care unit. This alleviates the necessity of transporting the infant to the radiology department or the use of warming devices, which usually are necessary for CT because of the low temperature required for scanner operation. Sedation is not needed for ultrasonography. In addition, CT uses ionizing radiation, which has potential adverse long-term effects, especially if serial examinations are necessary. Ultrasonography is also comparably less expensive.

Diagnostically, CT and ultrasonography have been shown to be highly accurate and essentially equivalent in their capabilities to diagnose hydrocephalus and intracranial hemorrhage. CT is clearly superior in detecting subarachnoid hemorrhages, bony abnormalities, diffuse parenchymal abnormalities, very small intraventricular hemorrhages, and small subdural collections.[8,10,11] The clinician, however, must decide whether the added information computed tomography may offer is worth the difficulty in obtaining it. In most instances, the added information gained by computed tomography will not cause a change in the patient's management.

Inasmuch as ultrasonography and CT are both sensitive for clinically significant intracranial pathology, it is presently recommended that routine screening should be performed with ultrasonography. Computed tomography should be used when there is unexplained progressive neurologic deterioration or when a ventricular shunting procedure is contemplated and the site of obstruction (communicating versus noncommunicating hydrocephalus) cannot be determined.

Prognosis

In general, there appears to be direct correlation between extent and site of hemorrhage and subsequent morbidity and mortality.[12] Infants with subependymal hemorrhage or small intraventricular bleeds have good prognosis. Mild hydrocephalus usually requires no treatment, while marked ventricular enlargement has a much poorer prognosis and shunting procedures are often required. Most infants with intracerebral extension of the hemorrhage will die.

Summary

Cranial ultrasonography appears to be the diagnostic modality of choice in evaluation of neonatal intracranial hemorrhage. Excellent anatomic detail is obtained at the patient's bed side, allowing the infant to remain in the neonatal intensive care unit. Inasmuch as one half of ICH are not clinically diagnosed, ultrasonography should be routinely performed on all high-risk infants.

1. Partridge, J.C., et al.: Optimal timing for diagnostic cranial ultrasound in low-birth-weight infants. Detection of intracranial hemorrhage and ventricular dilatation. J Pediatr 102:281-7, Feb 83

2. Volpe, J.J.: Current concepts in neonatal medicine. Neonatal intraventricular hemorrhage. N Engl J Med 304:886-91, 9 Apr 81

3. McDonald, M.M., et al.: Timing and antecedents of intracranial hemorrhage in the newborn. Pediatrics 74:32-6, Jul 84

4. Reeder, J.D., Kaude, J.V., and Setzer, E.S.: Choroid plexus hemorrhage in premature neonates. AJNR 3:619-22, Nov-Dec 82

5. Rumack, C.M., and Johnson, M.L.: Perinatal and infant brain imaging. Year Book Medical Publishers, Chicago, 1984

6. Babcock, D.S., and Han, B.K.: Cranial ultrasonography of infants. Williams and Wilkins Co., Baltimore, 1981

7. Lazzara, A., et al.: Clinical predictability of intraventricular hemorrhage in preterm infants. Pediatrics 65:30-4, Jan 80

8. Siegel, M.J., et al.: Cranial computed tomography and real-time sonography in full term neonates and infants. Radiology 149:111-6, Oct 83

9. Grant, E.G., et al.: Real-time ultrasonography of neonatal intraventricular hemorrhage and comparison with computed tomography. Radiology 139:687-91, Jun 81

10. Rumack, C.M., and Johnson, M.L.: Neonatal brain scanning. Diagn Imaging pp. 28-33, Feb 83

11. Quisling, R.G., et al.: Temporal comparative analysis of computed tomography with ultrasound for intracranial hemorrhage in premature infants. Neuroradiology 24:205-11, 1983

12. Sauerbrei, E.E., et al.: Ultrasonic evaluation of neonatal intracranial hemorrhage and its complications. Radiology 139:677-85, Jun 81

Edwards, M.K., et al.: Cribside neurosonography. Real-time sonography for intracranial investigation of the neonate. AJR 136:271-5, Feb 81

Grant, E.G., et al.: Real-time sonography of the neonatal and infant head. AJR 136:265-70, Feb 81

Accepted for publication in February 1986. Updating, as necessary, has been done by the author.

Dr. Hood is chief resident in the Department of Radiology at Doctors Hospital, Columbus, Ohio, where George O. Faerber, D.O., FAOCR, is resident trainer.

Dr. Hood, Doctors Hospital, North, 1087 Dennison Avenue, Columbus, Ohio 43201.

When patients on K^+-sparing diuretics need more control...

KEEP SPARING POTASSIUM,

BUT LEAVE THE POTASSIUM-SPARING DIURETICS BEHIND

SQUIBB®

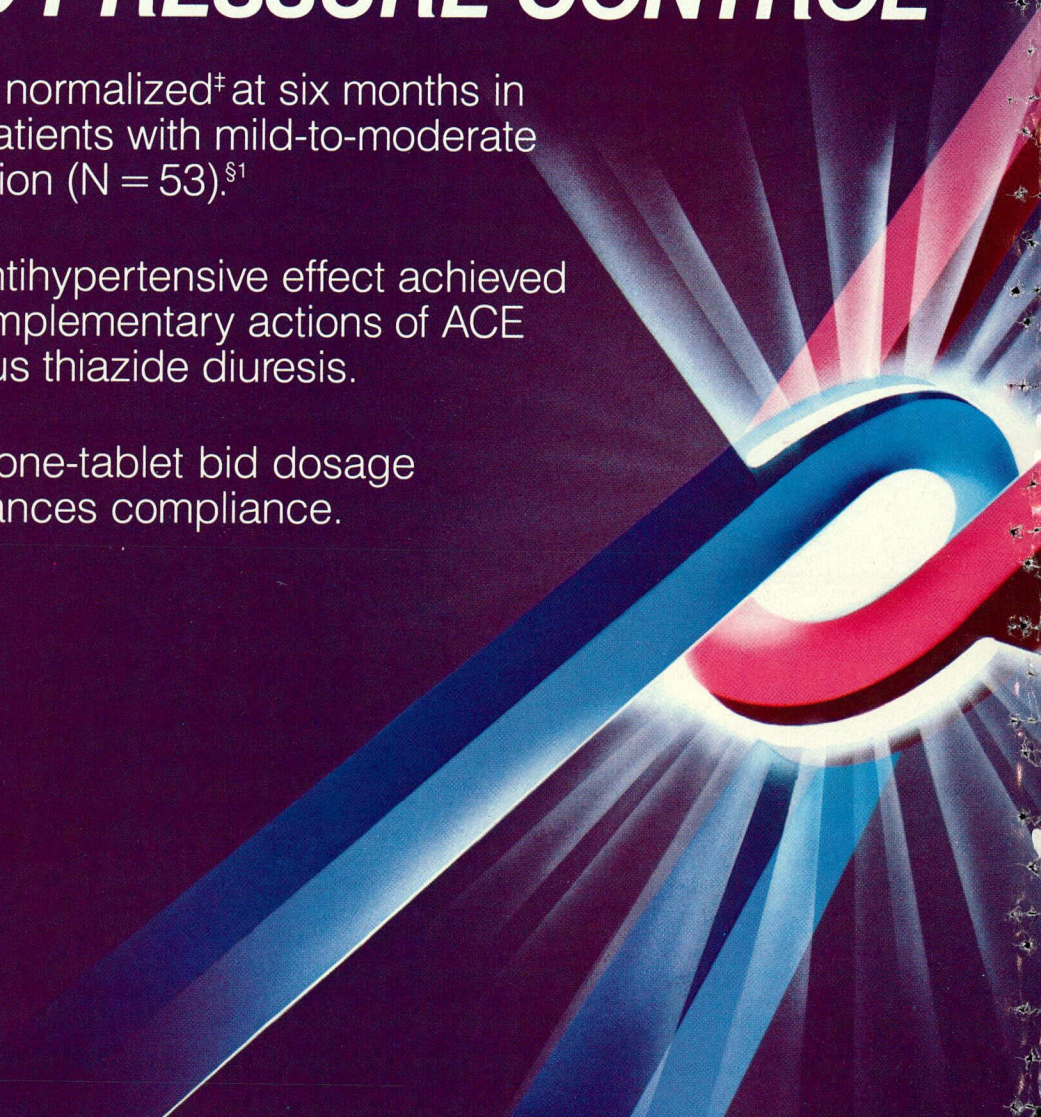
ACE* INHIBITOR

Capozide®

CAPTOPRIL–HYDROCHLOROTHIAZIDE TABLETS

OUTSTANDING SINGLE-TABLET BLOOD PRESSURE CONTROL†

- Pressure normalized‡ at six months in 86% of patients with mild-to-moderate hypertension (N = 53).§[1]
- Additive antihypertensive effect achieved through complementary actions of ACE inhibition plus thiazide diuresis.
- Convenient, one-tablet bid dosage regimen enhances compliance.



*Angiotensin Converting Enzyme

†**This fixed combination drug is not indicated for initial therapy of hypertension. It may be appropriate if the fixed combination represents the dosage as titrated to the individual patient's needs. In using CAPOZIDE, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. See INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS in the brief summary, which follows.**

‡Normalized = diastolic pressure < 91 mm Hg.

§Dosage was CAPOZIDE 25/25 (captopril 25 mg and hydrochlorothiazide 25 mg per tablet) bid.

WITH BUILT-IN POTASSIUM-SPARING ACTIVITY

- ACE inhibition conserves potassium by minimizing aldosterone secretion —can reduce thiazide-induced hypokalemia.

- In a multicenter clinical study, CAPOZIDE blunted the decrease in serum potassium that was seen with hydrochlorothiazide alone.[2]

ACE INHIBITOR*

capozide®

CAPTOPRIL–HYDROCHLOROTHIAZIDE TABLETS
25/15, 25/25, 50/15, 50/25

HELPS KEEP POTASSIUM UP, BLOOD PRESSURE DOWN

*Angiotensin Converting Enzyme

References:
1. Lederle RM: Captopril and hydrochlorothiazide in the fixed combination multicenter trial. J Cardiovasc Pharmacol 7:S63–S69, 1985.
2. Weinberger MH: Influence of an angiotensin converting-enzyme inhibitor on diuretic-induced metabolic effects in hypertension. Hypertension 5(Suppl III):132S–138S, 1983.

Please see brief summary of prescribing information on adjacent page.

CAPOZIDE®
Captopril-Hydrochlorothiazide Tablets

INDICATIONS AND USAGE:—CAPOZIDE (Captopril-Hydrochlorothiazide Tablets) is indicated for the treatment of hypertension. **This fixed combination drug is not indicated for initial therapy of hypertension. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.** In using CAPOZIDE, consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOZIDE may be used for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, CAPOZIDE should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to other drug combinations.

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)

SQUIBB®

INNOVATORS IN CARDIOVASCULAR MEDICINE

536-505 Issued: August 1986