SPECIAL ARTICLE

Report of the Panels* on Cardiovascular Drugs from the Drug Efficacy Study

DIVISION OF MEDICAL SCIENCES, NATIONAL RESEARCH COUNCIL

APPENDIX B. 4
PANELS ON CARDIOVASCULAR DRUGS

Statement on Criteria for Evaluation of Long-Acting Coronary Vasodilators in Treatment of Angina Pectoris

THE EVALUATION of an agent claimed to be effective in the management of angina pectoris in other than an acute attack should be based on convincing evidence that long-term administration of the agent does prevent or decrease the incidence and/or the severity of anginal pain. Unfortunately, meaningful objective evidence is difficult to obtain as has been pointed out by a number of authors.[3, 11, 14, 16, 20, 21]

The problems inherent in designing a meaningful study are numerous. Not the least is the variability of anginal pain. Some of the difficulties in developing convincing evidence are:

(1) In most patients there is a spontaneous fluctuation in the frequency and severity of angina pectoris. Symptoms may be constant for weeks or months, then change without apparent cause and without the patient's being aware of either remissions or exacerbations.[17]

(2) Angina pectoris may be aggravated by exposure to cold or by inhalation of cold air.[9] Therefore, seasonal factors should be considered in planning a drug evaluation.

(3) The patient with angina pectoris is responsive to reassurance. Therefore, in the initial stages of any therapy (even with placebo), the lessening of angina may be pronounced and be extended over several months.[5] The placebo effect may be such that 50% or more of the patients will claim to have been benefited.[15]

(4) Some patients respond well to nitroglycerin, others moderately, and still others not at all.[17] This must be borne in mind when the number of tablets of nitroglycerin that are taken daily by a patient is used as a measure

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of angina. Furthermore, the patient must be alerted to distinguish between the tablets taken to alleviate angina and those he may have taken to relieve pain from other conditions such as biliary colic, esophageal spasm, etc. Because the physician must depend on the word of the patient in characterizing the severity or duration of anginal pain, his estimate of patient reliability (a variable difficult to control) is important.

(5) The electrocardiographic exercise test has been proposed as an objective measure of patient response to anti-anginal drugs. Although the exercise test may provide objective data, results are not conclusive. If a drug is given prior to exercise, and it prevents or diminishes the ST-T changes during exercise, there is no assurance that it will be effective in the prevention of angina. If the drug does not prevent or diminish the ST-T changes with exercise, it probably will not be effective. In other words, the relation between clinical efficacy of long-acting coronary vasodilators and the results of the exercise electrocardiogram after single-test-dose administration has not been definitely established. Thus, this test can indicate only the anticipated, but not the actual, benefit of the test drug. Moreover, it is possible that nitrate tolerance may develop with the long-acting nitrates causing them to be less effective over the long-term, even though initially they may have prevented ST-T changes with exercise after single-test-dose administration. The development of nitrate tolerance also would invalidate the measurement of blood nitrate concentration as an indication of effectiveness.

(6) Finally, it must be borne in mind that the mechanism of action of nitrates or other types of coronary vasodilators in the relief of angina is not fully established. Although vasodilatation of the coronary arteries has been demonstrated with nitroglycerin, an increase in coronary blood flow may not occur in patients with coronary artery disease. It is not by any means certain that the mechanism of action is dependent on an increased coronary flow.[1, 2, 4, 6, 7, 8, 10, 12, 13, 18, 19, 21, 22] Therefore the package inserts should reflect that the mechanism of action of these drugs still remains speculative.

In view of these considerations, and despite the difficulties of clinical evaluation, a clinical approach must be used. After an extensive review of the literature, it is evident that no study has been reported that has taken into consideration all of the variables inherent in observing anginal pain. The one study that most closely fulfills the criteria outlined above led to the conclusion that the long-acting nitrates tested were without benefit.[5] The study suffered, however, from the small number of patients tested.

The situation would seem to call for a multihospital, cooperative, double-blind approach involving a large number of patients. Before beginning the study, patients should be carefully characterized with respect to severity of angina, response to nitroglycerin, and response to the exercise tolerance test. Because the beneficial effects of these agents may be observed only during certain intervals of the day, it would be desirable to record the number of nitroglycerin tablets needed to relieve angina in the morning, afternoon, and evening. The data collected should be analyzed with respect to these factors. Also, continuous daily monitoring with a portable electrocardiograph coupled with computer analyses may prove to be helpful in obtaining objective correlations to clinical observations while patients are on long-term therapy.

In summary, the Panel concludes that the efficacy of long-acting coronary vasodilators has not yet been adequately established. Also, the Panel has attempted to outline the criteria for the proper evaluation of long-acting anti-anginal drugs before valid conclusions with respect to clinical efficacy can be drawn.

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Statement on Use of Corticosteroids In Rheumatic Fever and Shock

A. Acute Rheumatic Fever

The criteria for the use of steroids in acute rheumatic fever are presently predicated on the manifestations of the disease in specific patients. There is as yet no agreement regarding the criteria for use of the steroids in the general medical community, but those most widely accepted are as follows:

(1) Acute Rheumatic Fever with Severe Carditis and Cardiac Failures

Steroid therapy is instituted in these patients by most physicians. Although no controlled prospective studies have been performed, a fairly extensive clinical experience suggests that steroids are very effective in shortening the duration and minimizing the symptoms and signs of acute myocarditis and failure.[6, 7, 13] The incidence of severe myocardial involvement in rheumatic fever has dropped significantly, and it is most unlikely that a prospective controlled study will be forthcoming. Thus, the widespread impression of the value of steroids in this type of patient should probably be accepted as evidence to justify their use. Most studies suggest that the prognosis for residual valvar damage has not been influenced by the use of steroid.[4, 5, 9–11] In one study, however, there was a suggestion that long-continued treatment may be effective in decreasing the late incidence of rheumatic valvar damage.[7] The present trend is not to use steroids chronically; because a long course is advised, and the complications possibly outweigh the advantages.

(2) Acute Rheumatic Fever with Mild or Minimal Carditis (No Significant Cardiomegaly, but Grade I-II Apical Systolic Murmur)

The value of steroid therapy in this situation has not been resolved. There is general acceptance of the fact that the symptoms (arthralgia, fever, malaise) are readily relieved by steroids, but the main question still to be answered is whether steroids influence the development of subsequent valvar disease.

(3) Acute Rheumatic Fever with No Obvious Heart Disease

One of the main difficulties in determining the indications for steroids is the problem of definitive diagnosis of rheumatic fever in the absence of carditis. It is presently generally accepted that steroids should not be administered to this group of patients in view of the complications of these drugs. Also, there is a suggestion that, if heart disease is not present in the attack, it is not likely to develop later if subsequent attacks of rheumatic fever are prevented.[8]

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B. Use of Corticosteroids in Shock

(1) Nonsurgical shock

The term "nonsurgical shock" needs clarification. Such terminology could include septic, anaphylactic, neurogenic, and cardiogenic shock.

Available evidence on the use of corticosteroids in the treatment of shock associated with gram-negative infections remains controversial. The pathogenesis of shock initiated by gram-negative bacteremia has not been well defined. Although the use of antibiotics and fluid volume replacement is well established, controversy exists on the use of sympathomimetic agents (alpha- and beta-adrenergic stimulants) and sympatholytic agents (alpha-adrenergic blockers). By using high doses of corticosteroids, Sambhi and associates believed they reversed the effects of endotoxin by decreasing peripheral resistance and increasing cardiac output; however, their data are not conclusive.[16] Other retrospective studies have demonstrated a decrease in mortal-

ity when high doses of corticosteroids were used in combination with sympathomimetic amines and antibiotics.[19, 20] When lower dosage (1 g/day hydrocortisone) has been used, improvement in mortality has not been noted.[6, 13]

There is evidence from experimental work that high doses of corticosteroids protect animals against endotoxic shock, whether administered before or after the injection of endotoxin.[10–12, 14, 22, 25, 27] These agents appear to protect tissues from the deleterious effects of endotoxin.[14, 23, 28] Although the results of these studies have been encouraging, further studies are needed to clarify the protective role of these agents in endotoxic shock, and prospective clinical studies are needed before efficacy can be definitively established.[24]

The role of corticosteroids in the treatment of anaphylactic shock has not been well defined, although several reports in the literature suggest a beneficial effect.[3, 5, 15, 26] Most agree that the primary therapy for anaphylaxis with shock includes the administration of epinephrine and plasma volume replacement.[26] Based on theoretical grounds and clinical impressions, the Panel's recommendations support the use of corticosteroids in anaphylaxis to suppress ongoing immunologic injury; however, adequate evidence has never been presented to substantiate such a use.

The use of corticosteroids in neurogenic shock has not been well documented. In one study on shock associated with cranial trauma, there was a prompt restoration of blood pressure following the administration of corticosteroids; however it is not clear what role the concomitant fluid replacement had. The authors suggested a direct action on the CNS with a reduction in swelling and pressure and, consequently, a secondary cardiovascular improvement and reversal of shock.[18]

The value of corticosteroids in myocardial infarction with shock is in question.[21] It has not been documented that adrenal insufficiency occurs in shock associated with myocardial infarction.[8] Experimental evidence of the reduction in size of infarctions produced in the laboratory has not been confirmed.[7, 8] Clinically, there is contradictory evidence regarding the effects of corticosteroids on the survival rates of patients with myocardial infarction.[1, 2, 4, 17] In one controlled study, the mortality of the patients with shock was not improved with the administration of 0.5 g/day of hydrocortisone.[17] In a case reported recently, massive doses of corticosteroids (150 mg/kg hydrocortisone or its equivalent) did acutely improve circulatory status, but the patient died.[2] Such large doses may produce sufficient salt and water retention to compromise the circulation further.

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(2) Surgical Shock

The term surgical shock needs clarification. Relative or absolute adrenal insufficiency may be exposed by the stress of surgery and cause the patient to go into shock. Weil states that corticosteroid hormones can reverse shock from adrenal insufficiency, and he lists adequate clinical and experimental evidence to document this fact.[11] Objective evidence has failed to show, however, that adrenal insufficiency is a major factor in the progression of shock.[6] Furthermore, similar documentation is not available for other types of shock (e.g., endotoxic, anaphylactic, cardiogenic, neurogenic) that may be encountered during surgical procedures.

It is well established that the primary treatment of hemorrhagic shock is correction of hypovolemia. The use of corticosteroids in this type of shock has been suggested.[9]

The literature on experimental hemorrhagic shock suggests beneficial responses to large doses (10-50 mg/kg) of hydrocortisone or its equivalent[1-3, 5, 7, 12]; however, favorable results have not been uniform.[4]

The clinical efficacy of corticosteroids in hemorrhagic shock remains unproved, and prospective controlled clinical studies will be necessary to establish effectiveness.[10]

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(3) Shock Unresponsive to Conventional Therapy

In the treatment of shock unresponsive to conventional therapy (blood and fluid replacement, antibiotics, etc.), the question of relative or absolute adrenal insufficiency may arise. Although the available evidence fails to show that adrenal insufficiency is a major factor in the progression of shock,[1, 3, 4] the stress of shock may expose a previously unrecognized Addisonian or patients who respond like Addisonians to stress (e.g., in myxedema, thyrotoxicosis, chronic alcoholism, or patients on prolonged corticosteroid therapy).[2] In these critically ill patients, the administration of corticosteroids may be useful in reversing shock[4] if adequate conventional treatment is also provided. Efficacy of corticosteroids in the treatment of shock without adrenal insufficiency, whether hypovolemic, anaphylactic, septic, or cardiogenic, has not been completely established, although these agents are frequently used.

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C. General Comments

The role that corticosteroids may have in a therapeutic regimen for shock has not been defined. The effects of corticosteroids have been studied on cardiovascular hemodynamics of animals subjected to hemorrhagic and septic or "endotoxin" shock. In some studies, very large doses of corticosteroids have been used. Although hemodynamic improvement has been noted, especially in "endotoxin" shock, the relationship of this observation to clinical shock in man remains conjectural.

It has not been possible to perform in man studies sufficiently well controlled to establish whether corticosteroids produce benefit in shock of various etiologies.

Clinical studies done on critically ill patients have been difficult to interpret, because other modes of therapy might have altered the result. The Panel believes that there is suggestive evidence that the adrenocortical steroids may be of value in shock associated with gram-negative infections but that prospective controlled studies will be necessary to elucidate the role of corticosteroids in this and other types of clinical shock.

Recommended Package Insert For the Digitalis Preparations

The following may be useful as a recommended package insert for the digitalis preparations:

A. Name of drug . . . .

B. Description . . . .

C. Actions (Pharmacology)

The principal action of digitalis is to increase the force of contraction of the heart. In a patient with congestive heart failure, this drug action may be evident as less dyspnea or orthopnea, as a decrease in heart rate, as a fall in venous pressure, or as a diuresis with accompanying weight loss. The direct, as well as the vagal, effect of digitalis prolongs the atrioventricular conduction. In the presence of atrial fibrillation, this will result in a lowering of ventricular rate. The increase in myocardial automaticity induced by toxic doses of digitalis may be evident in the ventricle (ventricular extrasystole, tachycardia, or fibrillation), in the atrium (paroxysmal atrial tachycardia with block, nodal tachycardia, or, rarely, atrial fibrillation or flutter). An additional toxic effect is that of abnormal prolongation of atrioventricular conduction (in the form of first-, second-, or third-degree heart block).

D. Indications

The indications of use of (drug name) depend on the major actions of digitalis and are as follows:

(1) For its inotropic effect, increase in contractility, (drug name) is indicated for the treatment of congestive heart failure, whatever the etiology (rheumatic, hypertensive, coronary arterial, etc.). Generally, it is less effective in disorders not primarily of cardiac origin such as severe anemia, fluid overload associated with nephritis, pericardial tamponade, or constriction, severe pulmonary disease, and such metabolic disorders as beri-beri and thyrotoxicosis. Nevertheless, it may be an adjunct in the treatment of myocardial inadequacy of any cause.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digitalis intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

(2) For its effect in prolonging atrioventricular conduction directly or by reestablishing normal vagal tone when congestive heart failure is treated successfully, (drug name) is indicated for the treatment of arrhythmias such as atrial fibrillation or atrial flutter, (drug name) may be expected to block some impulses from the atrium and thereby decrease the ventricular rate.

(3) By mechanisms not clearly defined, (drug name) is indicated for the treatment of paroxysmal atrial or nodal tachycardia. Probably by its vagal action, (drug name) frequently results in abrupt cessation of these arrhythmias or prevention of their recurrence.

CAUTION: Many of the arrhythmias for which digitalis is advised are identical with those reflecting digitalis intoxication. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if the clinical situation permits.

E. Contraindications

The suspected presence of digitalis intoxication, as evidenced by nausea, vomiting, or various arrhythmias (see effects of overdosage) in a patient receiving digitalis, is a contraindication to its further use.

F. Precautions

The therapeutic toxic ratio appears to be diminished in patients with severe heart disease. In such patients, the signs of digitalis toxicity may become present at doses only slightly larger than that needed for the

therapeutic effect. Rarely, signs of digitalis intoxication even precede any overt therapeutic benefit.

Particular caution in dose administration must be exercised in:

(1) ventricular irritability manifested by extrasystoles.
(2) moderate to severe impairment of renal function.
(3) severe pulmonary decompensation.
(4) patients depleted of potassium (e.g., by diuretics, chronic diarrhea, prolonged vomiting, corticosteroid therapy, dialysis, and infusion of intravenous fluids without potassium replacement).
(5) premature infants and aged patients.
(6) presence of an acute myocardial infarction.
(7) second-degree or complete heart block. (It may be advisable to insert a temporary or permanent pacemaker before using digitalis in patients with advanced heart block.)
(8) electrical conversion.

G. Adverse Experiences (Side Effects)

(List local reactions to intramuscular preparations and local irritative effects on the gastrointestinal system if large doses are given at one time.)

H. Effects of Overdosage

Among the common manifestations of toxicity are anorexia, nausea, vomiting and various cardiac arrhythmias, including:

ventricular premature beats
ventricular tachycardia
ventricular fibrillation
A-V dissociation
nodal tachycardia
sinus tachycardia
paroxysmal atrial tachycardia with A-V block
first-degree heart block
second-degree heart block
complete heart block

Atrial fibrillation or flutter is an uncommon manifestation of toxicity.

In patients with severe myocardial impairment or with potassium depletion, these arrhythmias may occur simultaneously with, or may precede, the gastrointestinal symptoms. Mental confusion, particularly in elderly patients, is not infrequent. Other, less common, side effects include diarrhea, delirium, visual abnormalities, and gynecomastia in the male. With (drug name) the duration of toxicity is not likely to be more than (half-life of drug) unless there is impairment of renal function.

I. Treatment of Toxicity

If toxic manifestations have appeared after the time for peak effect and are not serious, the only treatment that may be required is to withhold (drug name) for several days.

For more serious intoxication with abnormal cardiac rhythms, treatment may be initiated with potassium salts, procaine amide, lidocaine, quinidine, or diphenylhydantoin. Potassium chloride may be given orally in divided doses totaling 4-6 g per day (adults) or 1-2 g per day (children) provided renal failure is not present. Potassium chloride also may be administered as an intravenous infusion containing 40 mEq in 500 cc of 5% dextrose in water over the course of 2-3 hr and repeated, if required, until a total of 80 mEq have been given (1 mEq of KCl = 74.5 mg). Further potassium therapy may be indicated if coexistent potassium depletion is present. Before this course of treatment is followed, it should be established that urine output is adequate and, if possible, that the serum potassium concentration and BUN or creatinine are within normal limits. *Potassium should not be given in the presence of advanced degrees of heart block.* The patient should be monitored electrocardiographically and the infusion halted immediately upon the appearance of elevation or peaking of the T waves.

For children, the intravenous dose of potassium chloride should be 5-10 mEq.

J. Dose and Administration

There is great biologic variation in the amount of (drug name) needed to achieve and maintain therapeutic action. The suggested doses are, therefore, to be used *only* as a guide. Less (drug name) should be given

initially and as a maintenance regimen if excretion may be impaired as in moderate to severe renal disease. The recommended doses may produce evidence of toxicity in patients with acute myocardial infarction, severe pulmonary disease, or far-advanced heart failure, in the premature infant, and in the elderly patient. Potassium loss sensitizes the heart to digitalis intoxication even at recommended doses. The use of diuretic agents and other electrolyte manipulations are major causes of potassium depletion in cardiac patients. Under these conditions, the usual doses of (drug name) should be reduced until the potassium deficiency is corrected.

Initial digitalizing or "loading doses" are advised when the effect is needed promptly; otherwise, the administration of repetitive daily maintenance doses will cause a gradual cumulation.

It is seldom, if ever, warranted to give the entire digitalizing dose at once. Generally, one fourth to one half of the estimated total digitalizing dose is given initially. The remainder is given in divided doses, at intervals great enough for each dose to reach peak action, until the desired effect is obtained. By mouth, (drug name) attains peak action in (minutes or hours). Parenterally, peak effect is to be expected in (minutes or hours).

A section should be included, as appropriate, citing the specific recommended doses for:

(1) adults and children over age 10
(2) infants and children up to age 10
(3) premature infants.

K. How Available (Packaging Information) ....

L. References ....

Recommended Package Insert For Reserpine Preparations Used in the Treatment Of Hypertension

The following may be useful as a recommended package insert for reserpine preparations used in treatment of hypertension:

A. Actions

Reserpine is the principal active alkaloid obtained from the root of *Rauwolfia serpentina*. One of its principal actions is to release and deplete catecholamine stores in the sympathetic nerve endings. The degree of depletion varies both with the dose of reserpine and with the duration of administration. With a parenteral dose of 4 to 5 mg, release and significant depletion of catecholamines occur within several hours. The effect of repeated oral doses of 0.5 to 1 mg daily is cumulative over a period of several weeks, producing a gradual decrease of tissue catecholamine stores.

Following oral doses of reserpine of about 0.5 mg per day, catecholamine depletion is incomplete, and reflex sympathetic vasoconstrictor responses are only incompletely inhibited, so that orthostatic hypotension rarely occurs following recommended oral doses. Although the pressor effect of tyramine and similar catecholamine-releasing sympathomimetics may be blocked, the response to direct sympathetic nerve stimulation is only partially inhibited. The depression of sympathetic nerve function is reflected in decreases in heart rate and blood pressure. The latter is associated with a fall in total peripheral resistance without significant change in cardiac output or renal blood flow.

In addition to its effect on catecholamines, reserpine also releases serotonin from its body stores. There is some evidence to suggest that the central sedative effects of reserpine are associated with depletion of these amines in the brain.

B. Indications

Oral reserpine has an antihypertensive effect when used in the recommended doses. Individual responsiveness varies greatly from no response to excellent control of blood pressure. The higher range of the therapeutic dose scale (1 mg or more per day) produces a more consistent antihypertensive effect, but it probably increases the rate of side reactions, particularly psychic depression. Because of these limitations, reserpine alone often does not provide adequate blood pressure control and is, therefore, commonly used as an adjunct with other antihypertensive agents, such as the "thiazides," hydralazine, or guanethidine. Although reserpine causes a mild

reduction in sinus rate, it is not recommended for the treatment of tachycardias.

The effects of parenteral reserpine usually become manifest 1 to 3 hours after the injection of an effective dose. The parenteral route is indicated in the treatment of hypertensive emergencies, such as acute hypertensive encephalopathy, in which it is desirable to reduce the blood pressure promptly. Parenteral reserpine has been used in the treatment of pre-eclamptic and eclamptic toxemia of pregnancy, but its use has been considered undesirable by some because it passes the placental barrier, producing sedation, coryza, and possibly respiratory embarrassment in the newborn infant, an obligatory nose-breather. If nasal congestion is present at birth, the nursery personnel should be alerted to assure proper positioning of the infant on its side or in a prone position and to apply nasal topical vasoconstrictors to facilitate an adequate airway.

C. Contraindications

Reserpine should not be given to patients who have a history of mental depression. It is also contraindicated in patients receiving electroconvulsive therapy.

D. Side Effects

The most important adverse reaction is mental depression. The incidence has been variously estimated between 2 and 20% and appears to be related to dosage and to the emotional stability of the patient. The depression induced by reserpine may persist for several months after the drug is withdrawn and may be severe enough to result in suicide. Recognition of depression may be difficult, because the reaction is often disguised by somatic complaints. The more important diagnostic features are despondency, early-morning insomnia, loss of appetite, impotence, and self-deprecation. Because prompt withdrawal of the drug at the first appearance of such symptoms may abort the development of a full-blown depression, the patient or a member of the family should be warned of this possibility.

It was formerly thought that reserpine precipitated hypotensive reactions or bradycardia during anesthesia and surgery. However, recent evidence indicates that the incidence of such reactions is no higher in reserpine-treated patients than in hypertensive patients of similar age who have not received reserpine. Hypertensive patients have a higher risk of intraoperative hypotension and other complications than do normotensive patients. There is no evidence that discontinuing reserpine therapy in such patients 1 to 2 weeks preoperatively diminished the likelihood of hypotensive or other complications during anesthesia. If hypotension does occur during surgery in reserpinized patients, it responds to appropriate therapy. Should a pressor be required, one with a "direct" action (norepinephrine, metaraminol, phenylephrine, methoxamine) is preferable.

The most frequent side effect of reserpine is nasal stuffiness. Topically applied nasal decongestants can be used if necessary, particularly at night, or the dose of the drug can be reduced. Other common side effects are lassitude, which should not be confused with true depression; nightmares, which require reduction in dosage or discontinuation of the drug; increased appetite; and mild diarrhea.

Single parenteral or large oral doses of reserpine markedly increase gastric acidity, but a similar effect of continuous oral doses within the usual therapeutic range has not been demonstrated. The drug should be administered cautiously in patients with a history of peptic ulcer. If symptoms suggesting peptic ulcer recurrence develop during administration, the drug should be discontinued. A history of peptic ulcer disease may be considered a relative but not an absolute contraindication to the use of reserpine in the treatment of hypertension.

Although evidence that reserpine exacerbates ulcerative colitis is lacking, it is probably unwise to administer reserpine in patients with a history of ulcerative colitis because of its tendency to increase bowel motility.

Like several other antihypertensive drugs, reserpine may produce sodium retention and increased plasma volume. It also partially

depletes the myocardial stores of catecholamines. However, the drug may be given safely to hypertensive patients with congestive heart failure, although it is generally advisable to use a thiazide in addition.

E. Dosage and Administration

Treatment of hypertension is usually initiated with a thiazide. When reserpine is used, the recommended oral dose for adults is 0.5 to 1 mg daily for 1 week, followed by a maintenance dose of 0.25 to 0.5 mg daily. Higher doses should be used cautiously, because the risks of serious mental depression and other side effects will be considerably increased at such dosages.

Reserpine should be administered parenterally in the short-term treatment of hypertensive crises. Because of varying responsiveness, a titration procedure should be used. An initial dose of 0.5 to 1 mg given intramuscularly or intravenously is followed at intervals of 3 hours, if necessary, by doses of 2 and 4 mg until the blood pressure falls to the desired level. If the 4-mg dose is ineffective, other antihypertensive agents should be used. Initial doses larger than 0.5 mg may induce severe hypotension, particularly in patients with cerebral hemorrhage.

F. Packaging Information

(1) Reserpine tablets. Describe.
(2) Reserpine parenteral. Describe.

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Statement on Use of Sympathomimetic Amines in Treatment of Hypotension and Shock

Although all the "vasopressors" under appropriate conditions are effective in raising the blood pressure in hypotensive patients, the efficacy of these drugs in the treatment of "shock" remains controversial. Any appraisal of efficacy must be qualified because of the paucity of controlled clinical data. These drugs may be effective in some patients in shock in whom it is necessary to increase blood pressure to provide adequate perfusion of the heart and brain. However, the injudicious use of these drugs could reduce perfusion to the splanchnic organs and to the kidney because of vasoconstriction of the arterial beds. In addition, if these potent vasoconstrictor agents are used for a long period, the resulting vasoconstriction could prevent adequate expansion of circulating volume and may cause perpetuation of the "shock state." Recent evidence has suggested that plasma volume may be reduced in all types of shock and that the measurement of central venous pressure is the most useful means of assessing the adequacy of the circulating blood volume. Therefore, these drugs could be harmful if they were used for long periods instead of blood or plasma volume expanders when the principal reason for hypotension is decreased circulating volume.[1-5]

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Statement on Use of the Thiazide Diuretics

Most of the evidence now available on the efficacy of thiazide diuretic compounds has been obtained through studies on chlorothiazide and hydrochlorothiazide. Information of similar depth and quality is not available for the congeners and analogues of these compounds. Therefore, there must be reservations about the relative antihypertensive effectiveness and the incidence of toxicity during long-term treatment with these drugs.

The thiazide diuretic compounds make two recognized and significant therapeutic contributions to cardiovascular disease. First, the relief of cardiac failure, which can be explained by the saluretic and diuretic properties, producing a reduction in plasma volume

and improving cardiac efficiency. Second, the antihypertensive effects, which may be explained in part by the diuretic properties. This mechanism seems to operate during the early phases of treatment, when negative salt-and-water balances have been produced. However, another mechanism must also operate, inasmuch as over several months of treatment these balances become positive without loss of the hypertensive effect. A third, but surprisingly not well-documented, beneficial effect is the improvement noted in patients with angina pectoris. This is usually attributed to the relief of cardiac failure or hypertension; however, there is a suggestion that the angina alone might be improved. Further studies to investigate this suggestion should be encouraged.

When used in combination with other antihypertensive drugs, thiazides may either add to or potentiate the depressor effects of such other drugs. Available evidence indicates that potentiation occurs when these diuretics are used with ganglionic or peripheral adrenergic blocking drugs. Information on their combined use with other antihypertensive drugs is not sufficient to distinguish additive from potentiating effects.

Thiazide diuretics diminish, but do not abolish, responsiveness to norepinephrine; however, the diminution is not sufficient to preclude effectiveness of this pressor for therapeutic use.

Statement on Use of Xanthines in Congestive Heart Failure and Angina Pectoris

Theophyllines (ethylenediamine, 480-720 mg; isopropanolamine, 500 mg; acetate, 500 mg), administered intravenously to normal persons and to patients with congestive heart failure, will increase cardiac output and decrease right atrial pressure. The latter has been attributed to increased cardiac contractility and venodilation.[1, 2, 4, 5] Available evidence indicates that this intravenous dose range produces an initial peak blood level of greater than 20 μg/ml and that levels of at least 10 μg/ml persist for at least 1 hr.[9] Therefore, levels of 10-20 μg/ml have been associated with the desired hemodynamic effects. More data on the cardiovascular effects of lower blood levels resulting from smaller intravenous dosage or intramuscular administration (500 mg) would be of benefit in establishing efficacy of these preparations at the recommended doses.

Although blood levels have been established for oral and rectal administration of theophyllines, similar hemodynamic studies would be helpful to confirm the usefulness of such preparations. When such theophylline derivatives as theophylline sodium glycinate,[9, 10] and aminophylline[8, 10] are administered orally, there appears to be considerable variation in absorption, regardless of whether plain or enteric-coated tablets are used. Aminophylline (500-600 mg) and theophylline sodium glycinate (640-950 mg) administered orally are most commonly associated with 1-hr blood levels below 10 μg/ml, although some patients eventually achieve levels of 10-15 μg/ml.[8–10] Although similar absorption data exist for the rectal administration of aminophylline,[3] lower,[9, 11, 12] blood levels by this route of administration have also been reported. It should be emphasized that hemodynamic effects are unknown at these lower blood levels. Chronic oral administration in high dosage (500-1000 mg) is usually associated with gastrointestinal irritation. Chronic rectal administration may be associated with serious local side effects (e.g., rectal irritation and strictures).

Few studies show convincing data on the benefit of xanthines in coronary artery disease. Experiments performed in normal animals have shown increases in coronary blood flow; however, these observations are of questionable value in evaluating the efficacy of these drugs. The increments in coronary blood flow were minimal, and the measurements were taken by coronary A-V O_2 difference, rather than by a direct technique. There is some question as to whether this increase in coronary flow meets the enhanced oxygen utilization by the increased cardiac output. This could account for the observed coronary vasodilation. There are no similar data avail-

able for animals with experimental coronary arterial stenosis.[6]

Russek reported that elixir of theophylline administered orally under double-blind conditions produced subjective improvement in patients with angina pectoris that correlated with improvement in exercise ECG pattern.[7] The dosage used would be expected to yield blood levels of about 11 μg/ml.[8, 12]

Because of the difficulties in maintaining adequate and sustained blood levels with these preparations, plus the problems of tolerance, further studies are needed to confirm the efficacy of xanthines in coronary artery disease.

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