ANTIHYPERTENSIVE DRUG INTERACTIONS

Medical Grand Rounds

William A. Pettinger, M. D.

Tom and Lula Gooch Auditorium

University of Texas Health Science Center at Dallas

February 5, 1976

ANTIHYPERTENSIVE DRUG INTERACTIONS

SUMMARY

Complications of hypertension are by far the greatest *preventable* public health problem in the United States today. Pharmacologic interventions which primarily involve drug interactions are the generally available and effective means of preventing or delaying these hypertensive complications.

Mechanisms of beneficial antihypertensive drug interactions involve simultaneous reduction or control of blood volume (diuretic agents) and decrease of peripheral resistance. Reduction of peripheral resistance without producing intolerable side effects has recently been achieved by a complex drug interaction. This interaction involves simultaneous vasodilation and inhibition by beta adrenergic blocking agents of reflex activation of the renin-angiotensin axis. Clonidine, by effects similar to propranolol, can substitute for propranolol, or add to, the beneficial effects of this important drug interaction.

Adverse interactions of antihypertensive drugs most frequently involve the diuretic agents in combination with digitalis glycosides, and/or hypoglycemic drugs.

Our primary interest in the clinical component of our investigative program in recent years is the beneficial interaction between vasodilating and beta-adrenergic receptor blocking drugs. I would like to first review with you some of the evidence for a mechanism involving altered renin release in this drug interaction and how this relates to your clinical use of the drugs involved. We will then review some of our new information on a potential role for clonidine (Catapres) in this interaction and then proceed to the adverse drug interactions.

Vasodilating antihypertensive drugs such as hydralazine are very potent and have been around for a long time. Their site and mechanism of action is ideal in that they reverse the hemodynamic abnormality of hypertension, which is increased peripheral resistance at the afferent arteriolar level. Yet, hydralazine has been relatively ineffective over the years until it was combined with the beta-adrenergic receptor blocking drug, propranolol. Propranolol was first combined with the vasodilating drugs, hydralazine or minoxidil with the intention of controlling the cardiac stimulation resulting from the carotid sinus baroreceptor reflex mechanism (1-3).

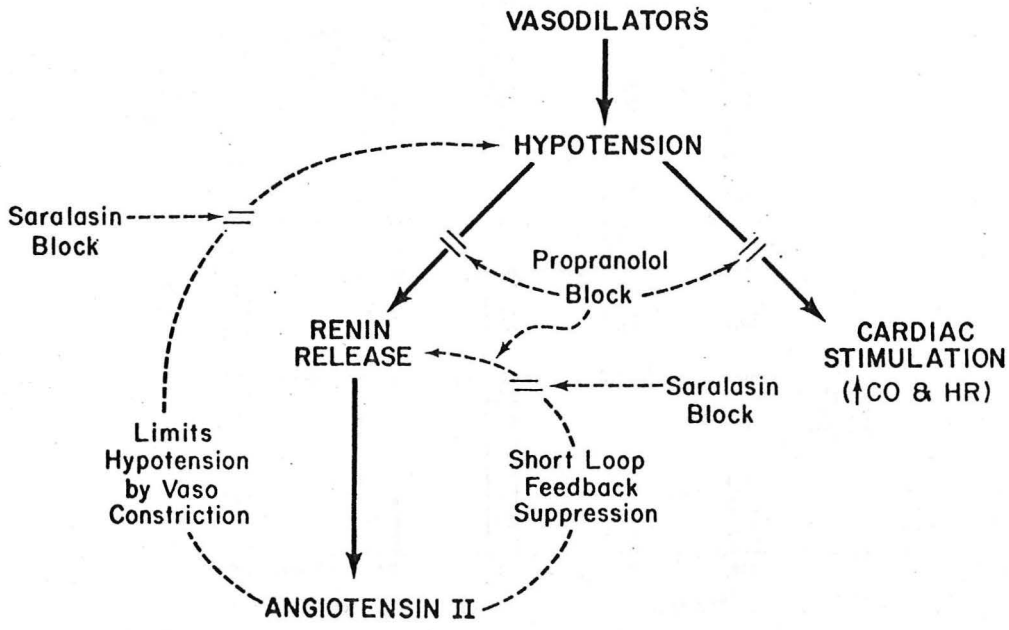

Figure 1. Diagram of the vasodilatory-beta-blocker drug interaction (4). Propranolol can block at two different sites in this interaction which contribute to asymptomatic control of high blood pressure. Saralasin is a selective angiotensin antagonist (5,6) used to quantify the pharmacologic activity of angiotensin in vivo.

The cardiac stimulation was effectively controlled but in addition, propranolol either potentiated the hypotensive action of these two vasodilating drugs or in some way produced an additive antihypertensive action. We have investigated the mechanism of this potentiation and have summarized our interpretation in Figure 1.

Vasodilating antihypertensive drugs induce renin release in normotensive (7) and in spontaneously hypertensive rats (8) which can be impaired by prior administration of propranolol (7, 8). This impairment of vasodilatory drug induced renin release is believed to be the mechanism of propranolol potentiation of vasodilatory drug hypotensive action in animals (8) and in hypertensive man (4). When propranolol administration is discontinued in vasodilatory drug (minoxidil) treated subjects, increased renin release occurs (Figure 2). The resulting increment in circulating angiotensin can then assume a dominant role in maintenance of blood pressure as shown in Figure 3.

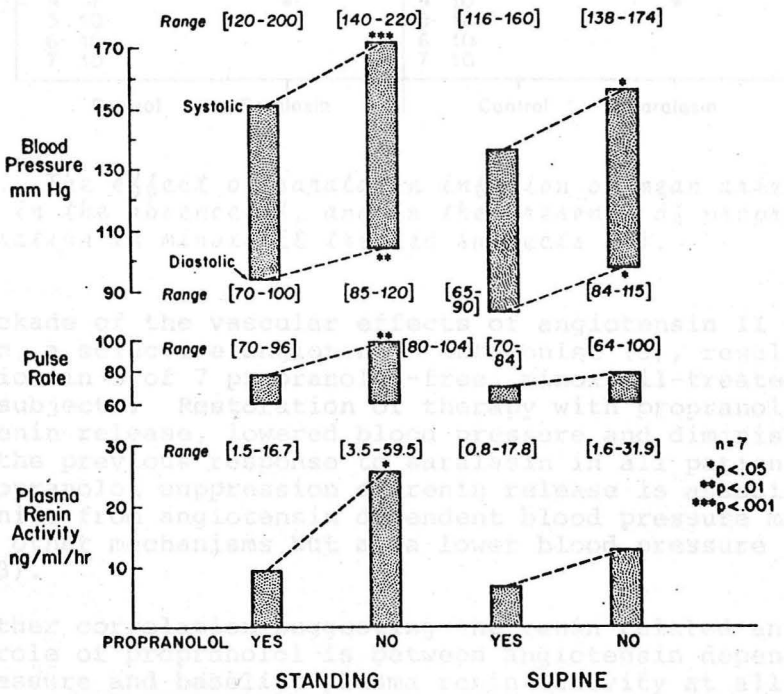

Figure 2. Effect of discontinuing propranolol administration for at least two days in minoxidil treated subjects (4). Numbers in parentheses are the range of values. Students paired-t test was used to calculate probability values.

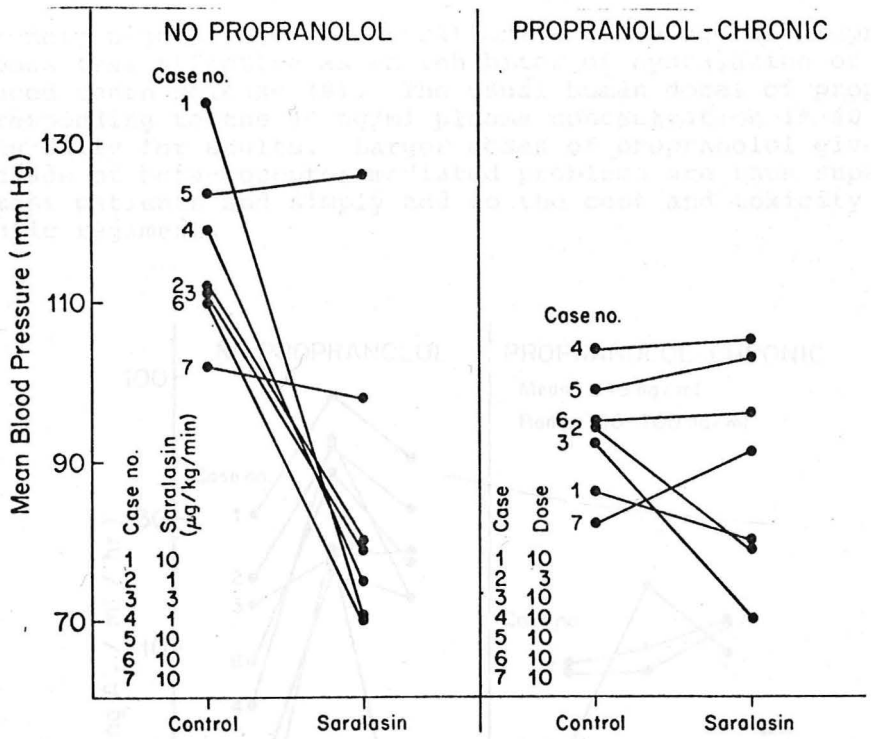

Figure 3. The effect of saralasin infusion on mean arterial pressure in the absence of, and in the presence of propranolol administration in minoxidil treated subjects (4).

Blockade of the vascular effects of angiotensin II using saralasin, a selective angiotensin antagonist (5), resulted in hypotension in 5 of 7 propranolol-free, minoxidil-treated hypertensive subjects. Restoration of therapy with propranolol impaired renin release, lowered blood pressure and diminished or ablated the previous response to saralasin in all patients. Thus, propranolol suppression of renin release is associated with a shift from angiotensin dependent blood pressure maintenance to other mechanisms but at a lower blood pressure level (Figure 3).

Another correlation suggesting the renin related antihypertensive role of propranolol is between angiotensin dependence of blood pressure and baseline plasma renin activity at all renin levels in minoxidil treated subjects (Figure 4). The precision of this correlation ($p < .001$) indicates that the degree to which propranolol suppresses plasma renin activity is directly related to reduction of angiotensin vasoconstriction or antagonism of vasodilatory drug induced blood pressure lowering. Thus, the peripheral resistance is reduced by the vasodilatory antihypertensive drug and the body's compensatory mechanism, release of renin-angiotensin, is blocked by propranolol.

Page Missing in Original Volume

extremely high plasma concentrations (>1,000 ng/ml) propranolol becomes less effective as an inhibitor of hydralazine or minoxidil induced renin release (8). The usual human doses of propranolol corresponding to the 40 ng/ml plasma concentration is 40 mg, four times daily for adults. Larger doses of propranolol given for blockade of beta-receptor mediated problems are thus superfluous in most patients and simply add to the cost and toxicity of therapeutic regimens.

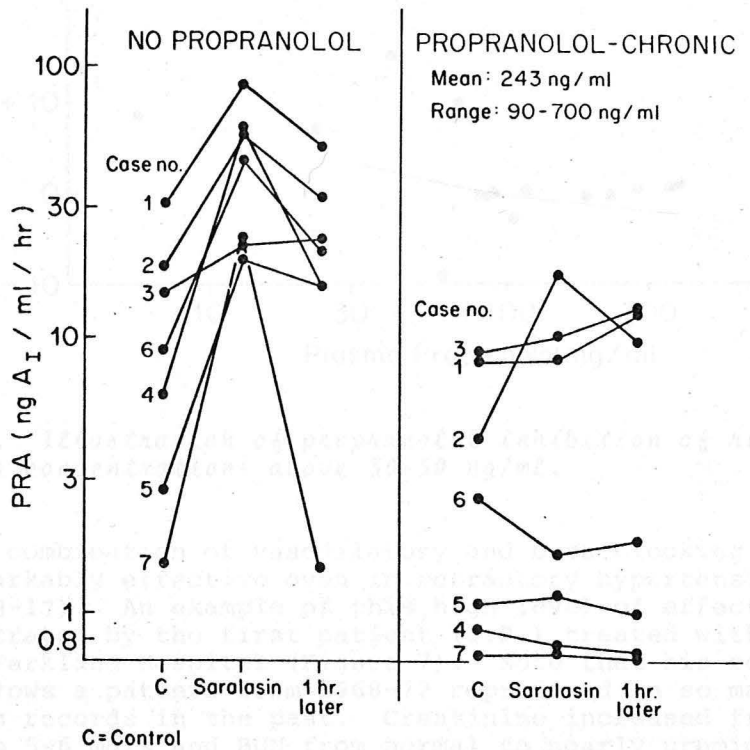

Figure 5. The effect of saralasin infusion on plasma renin activity in seven minoxidil treated subjects in the absence (on the left) and in the presence of propranolol (on the right). In addition to the blockade of saralasin induced renin release by propranolol, note the unexplained but remarkable persistence of elevated PRA one hour after saralasin infusion. The hemodynamic effect of saralasin dissipates within 10 minutes after discontinuing the infusion. Case #2 had the highest plasma propranolol level of 700 ug/ml at the time of the study (see text).

The small additional increment in blood pressure lowering resulting from much higher doses of propranolol (12) appears to be mediated through mechanisms other than known beta-adrenergic receptors.

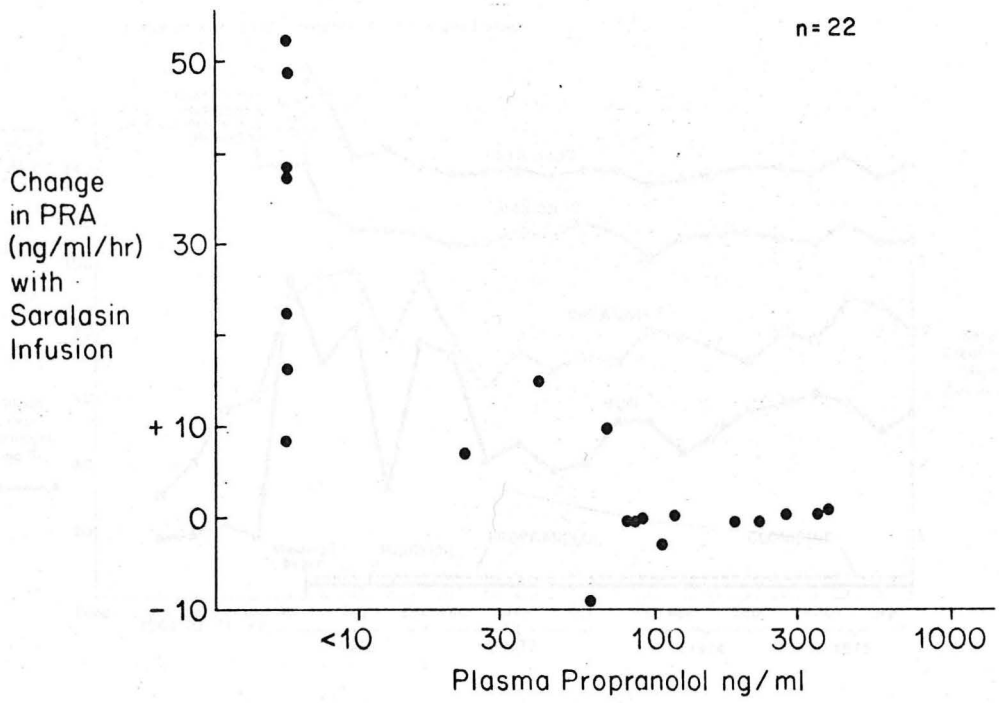

Figure 6. Illustration of propranolol inhibition of renin release in plasma concentrations above 30-50 ng/ml.

The combination of vasodilatory and beta-blocking drugs has been remarkably effective even in refractory hypertensive subjects (13-17). An example of this high level of effectiveness is illustrated by the first patient (J.P.) treated with minoxidil here at Parkland Hospital (Figure 7). Note that his renal function follows a pattern from 1968-72 reproduced in so many of the patient's records in the past. Creatinine increased from normal levels to 5-6 mg/% and BUN from normal to nearly uremic levels during the same interval. Conventional antihypertensive drugs were prescribed in nearly optimal doses but high blood pressure remained uncontrolled. On 4/21/72, he was admitted to Parkland Hospital for evaluation as a candidate for nephrectomy. On the second day of hospitalization, he suffered a stroke resulting in coma and was considered to no longer be a candidate for nephrectomy. We started R$_x$ with minoxidil and propranolol which induced reasonably good blood pressure control for two-three months and very good thereafter. Initially, renal function appeared to decrease with reduction of the high blood pressure, but then improved. A source of concern to us at this time after recently adding on data for the last year is whether we are seeing a very slow trend toward deteriorating renal function. Recurrent mild urinary tract infection may be contributing to part of this apparent, but slow deterioration of renal function. Nevertheless, the positive slope of the curve over the past four years is less then the four years prior to initiation of therapy with minoxidil.

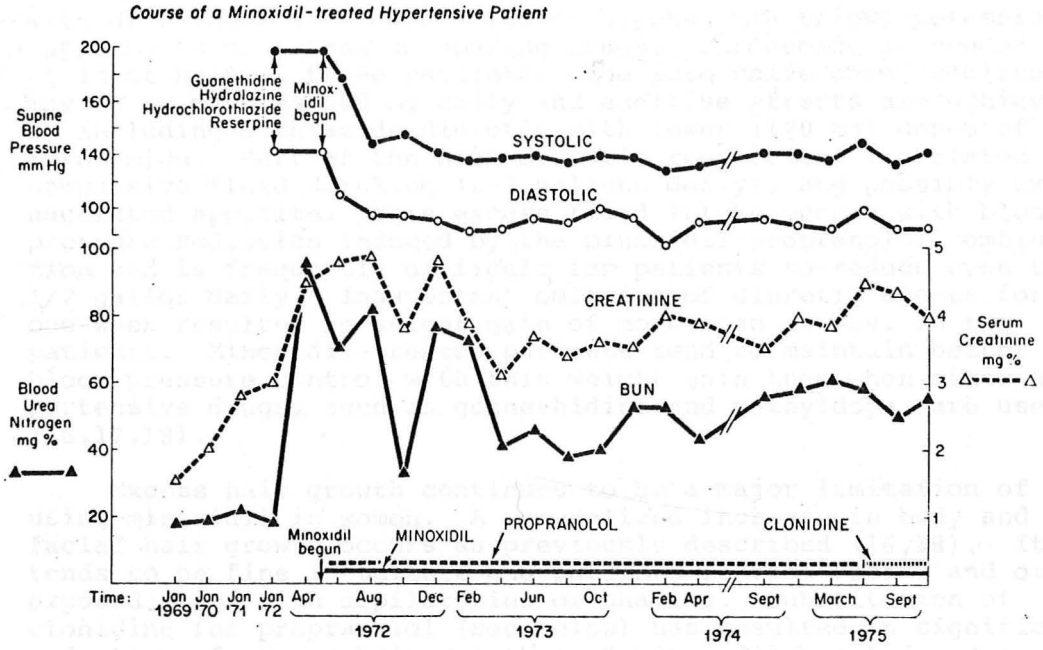

Figure 7. Long term response of the first patient treated at Parkland with the minoxidil-propranolol-diuretic combination.

Thus far, we have treated 32 of these remarkably severe hypertensive patients using the minoxidil-propranolol combination for more than six months. Blood pressure can usually be controlled at or near normal levels in most of the patients with relatively few of the disabling symptoms common to other potent drugs, such as reserpine, guanethidine, or ganglionic blocking agents. Nevertheless, there are still problems. They are: reflex cardiac stimulation, fluid retention, excess hair growth, incomplete response, and the still lingering possible toxicities of a right atrial lesion first noted in canine studies and pulmonary hypertension in man.

Minoxidil is not yet available for your use by prescription, but approval may occur within a year. Also there are close similarities between minoxidil and other vasodilators such as hydralazine in their interactions with propranolol and/or clonidine as discussed below.

The problem of reflex cardiac stimulation is well controlled in most patients but may occasionally and temporarily require quinidine-type drugs to control ventricular extrasystoles (18). Fluid retention can be controlled by titration of diuretic agents against the weight gain. Thiazide-type drugs are used initially

with or without (see discussion of hypokalemia below) potassium supplements or potassium sparing drugs. Furosemide is needed in at least half of these patients. The furosemide dose required may be as much as 600 mg daily and additive effects are achieved by including a thiazide diuretic with lower (120 mg) doses of furosemide. Part of the high diuretic requirement is related to compulsive fluid drinking (2-3 gallons daily), and possibly exaggerated appetite. This excess fluid intake occurs with blood pressure reduction induced by the minoxidil-propranolol combination and is frequently difficult for patients to reduce even to 1/2 gallon daily. Inadvertant omission of diuretic agents for one week resulted in weight gain of more than 30 lbs. in two patients. Minoxidil-treated patients tend to maintain better blood pressure control with this weight gain than when other hypertensive drugs, such as guanethidine and methyldopa, are used (16,17,18).

Excess hair growth continues to be a major limitation of using minoxidil in women. A generalized increase in body and facial hair growth occurs as previously described (16,18). It tends to be fine in texture and patients control facial and other exposed areas with depilatories or shaving. Substitution of clonidine for propranolol (see below) has resulted in significant reduction of excess hair growth in 3 minoxidil-treated women.

Pathologic changes were noted in the right atrium of normal dogs given high doses of minoxidil chronically (19). These lesions did not alter hemodynamic nor electrophysiologic properties of the right atrium and could not be demonstrated in rats or monkeys. The issue concerning its occurrence in man is unclear at this time. We have had two cases with right atrial lesions here of patients dying from other causes. There is some differences of interpretation in species comparison of the histologic changes but we are sufficiently suspicious at this time to restrict use of minoxidil to refractory hypertensive subjects.

Pulmonary hypertension has been reported in minoxidil-treated subjects from several centers (20,21). As a result, we have done right heart catheterization in 14 consecutive patients treated with minoxidil for at least six months. One of the 14 patients had increased pulmonary vascular resistance and thus pulmonary hypertension, per se. Several other patients had elevated pulmonary wedge pressures from increased cardiac output or elevated left atrial pressures from their longstanding hypertensive heart disease. Dr. Jim Atkins is comparing these results with data from other treated and untreated hypertensive subjects of similar age undergoing cardiac catheterization at Parkland Hospital. In essence, the cardiac and pulmonary lesions are unresolved issues at this time which currently restrict the use of this potent antihypertensive to those patients having a definitive indication for its use; that is, inadequate response to other available agents.

The vasodilatory beta blocker drug interaction can be conceptualized in a slightly different manner as schematically diagrammed in Figure 8.

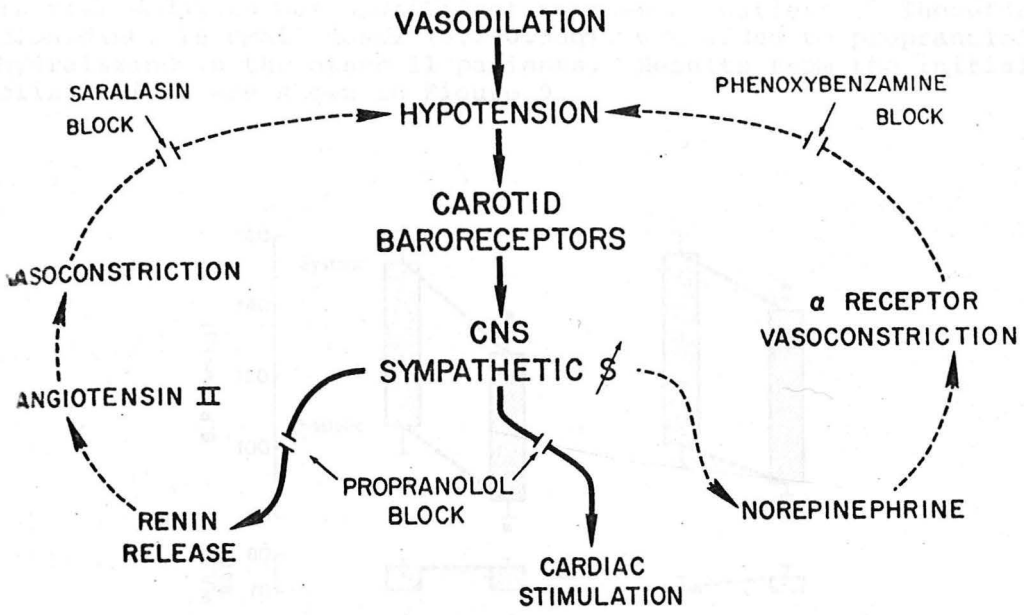

Figure 8. Extension of the vasodilator-beta-blocker antihypertensive drug interaction to include the alpha-adrenergic vasoconstrictor effect. Propranolol does not alter this receptor mechanism and, in fact, may augment its effect by leaving the vasoconstrictor action unopposed by blocking the beta-mediated vasodilation.

While propranolol is effective in blocking the beta-receptor-mediated increment in renin release and cardiac function, the alpha-adrenergic vasoconstrictor receptor goes unopposed. In the majority of patients using a vasodilatory-beta-blocking combination, the vasodilating effects of hydralazine or minoxidil are sufficient to counteract the alpha-adrenergic vasoconstriction. However, in 5 of our 29 minoxidil-treated patients six months ago, this was not the case. Their diastolic blood pressure remained above 100 mm Hg and in two patients it was much higher. There are two pharmacologic approaches to this problem. One is the use of alpha adrenergic blocking drugs such as phentolamine (Regitine) and phenoxybenzamine (Dibenzyline) or to depress cardiovascular-renal sympathetic neuronal activity using clonidine, a drug acting at the central nervous system level, to do this (22). Recent discovery of a receptor mechanism whereby clonidine inhibits renin release was an additional incentive to try clonidine as a substitute for propranolol in the vasodilatory beta-blocker drug interaction (23).

We have systematically substituted clonidine for propranolol in 14 minoxidil treated subjects. In the first 3 patients, clonidine

in 0.4-0.6 mg daily doses was directly substituted for propranolol. Initial sedation was significant in these 3 patients. Therefore, clonidine, in small doses (0.2-0.3ug), was added to propranolol-hydralazine in the other 11 patients. Results from the initial clinic visit are shown in Figure 9.

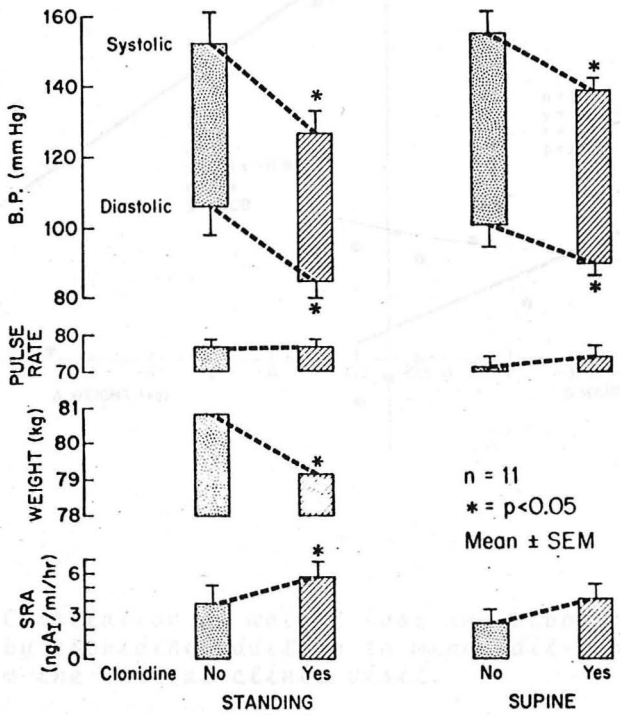

Figure 9. The effect of adding clonidine 0.2-0.4 mg daily to the minoxidil-propranolol-diuretic combination in eleven patients.

On the first clinic visit after addition of 0.2-0.4 mg daily of clonidine in 11 patients, blood pressure lowering occurred ($p < .05$) in both the supine and standing positions. Heart rate was not changed. The weight decreased by an average of two kilograms by mechanisms unknown at this time. This weight loss correlated closely with the fall in blood pressure (Figure 9) and was inversely related to serum renin activity. The well known negative sodium and water balance stimulus to renin release apparently dominated any inhibitory effect of this low dose of clonidine. Additional studies are underway to clarify these interesting endocrine-fluid-electrolyte alterations.

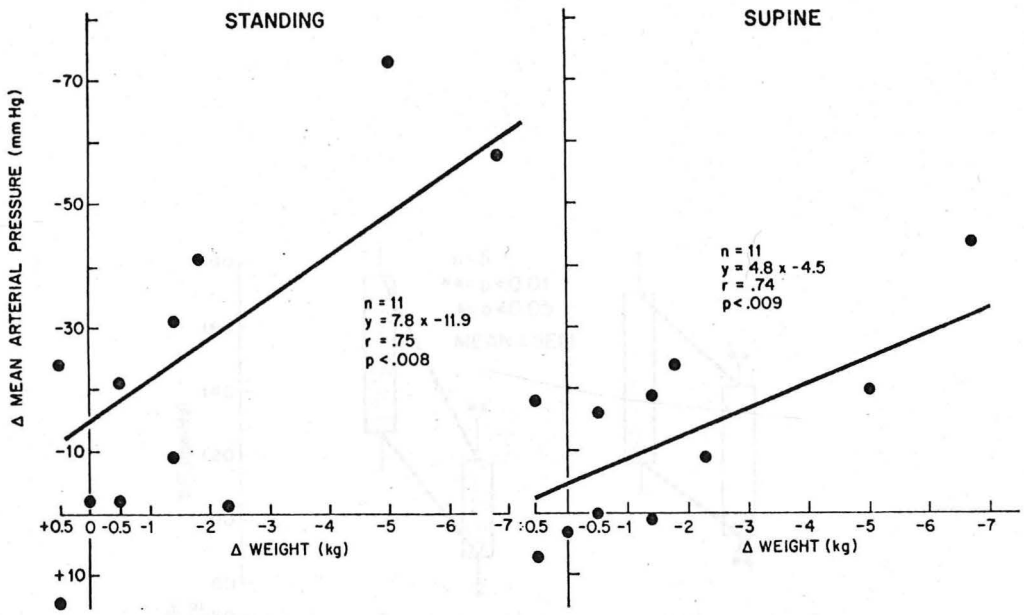

Figure 10. Correlation of weight loss and blood pressure lowering induced by clonidine addition to minoxidil-propranolol. These are data from the initial clinic visit.

A more remarkable effect of clonidine is noted when the 5 minoxidil-propranolol treated subjects who sustained diastolic blood pressure > 100 mm Hg are considered separately (Figure 11).

Unfortunately, side effects of clonidine (sedation and nausea and vomiting) precluded continued use in 2 of these patients. In the other 3, withdrawal of propranolol resulted in loss of blood pressure control. However, the use of clonidine and propranolol simultaneously resulted in marked improvement in the quality of blood pressure control in the 3 patients.

Clonidine adequately substituted for propranolol during chronic therapy in 8 of the 15 patients (Figure 12). Differences between propranolol and clonidine occurred in standing blood pressure (lower on clonidine - $p < .05$) higher ($p < .05$) standing pulse rate, higher serum renin activity in both supine ($p < .05$) and standing ($p < .01$) positions with a tendency to weight loss. This weight loss from clonidine contributed in a major way to management of edema in 3 of the patients.

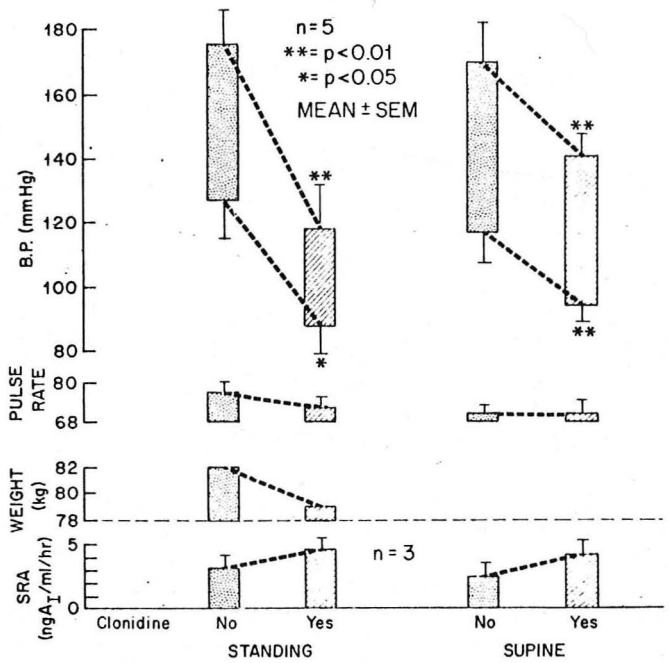

Figure 11. The effect of clonidine addition to minoxidil-propranolol in the 5 uncontrolled hypertensive patients. Data are from the initial clinic visit after starting clonidine.

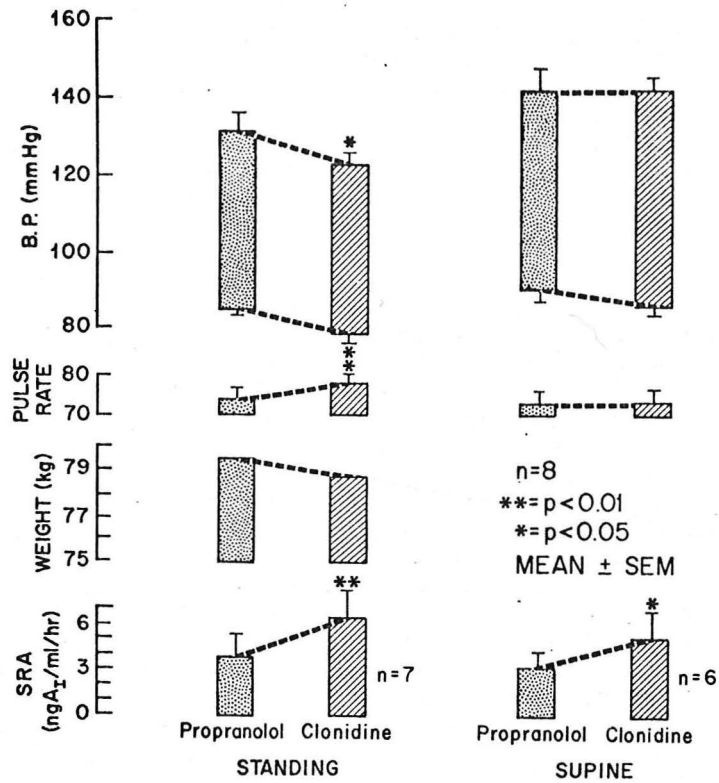

Figure 12. Comparison of clonidine versus propranolol in minoxidil treated subjects. "Propranolol" hemodynamic values are the mean of four consecutive visits prior to clonidine and the "clonidine" values are the first four consecutive visits on this drug at a constant dosage. One value for exercise serum renin activity was obtained prior to clonidine and the on clonidine value was obtained on the last day of the four consecutive clinic visits.

Substitution of clonidine resulted in significant reduction in the minoxidil induced hair growth in 3 women. This problem is not prevented by clonidine but the frequency of using depilatories or shaving was reduced to one-third of that required during use of propranolol.

Propranolol was generally better accepted than clonidine because of the tendency for clonidine to induce sedation and a dry sensation of the oral mucosa. By administering at least half of the clonidine dose at bedtime, the daytime sedation was considerably reduced. However, propranolol may be contraindicated in some patients because of allergy, bronchial asthma, symptomatic bradycardia and a few hypertensives because of worsening of heart failure by this drug. Clonidine should be a suitable substitute in these patients. It also produces effects additive to propranolol in small doses (0.2-0.4 mg) which produce few or no side effects. The reader is referred elsewhere for additional details concerning use of clonidine (24).

There is an additional site of beneficial drug interaction depicted in Figure 8. Peripherally acting alpha adrenergic blocking agents can prevent the unopposed vasoconstriction occurring in these vasodilatory beta-blocker drug treated patients. Phenoxybenzamine has been tried in 3 of the minoxidil-propranolol treated subjects, 2 men and 1 woman, who sustained diastolic pressure above 100 mm Hg. It was effective in all 3 but was discontinued in favor of clonidine because it interfered with sexual function in the male, as does guanethidine.

Interactions involving the guanadinium (guanethidine) antihypertensive drugs and tricyclic antidepressant agents were recently reviewed along with monoamine oxidase (MAO) inhibitors (18). Use of the guanidinium drugs is declining because of the effects of peripheral sympathetic neuron blockade and MAO inhibitors are rarely used because of interactions with vasoactive amines (18).

Interactions involving the diuretic agents are of the first order of importance. Non-diuretic agents are dependent on an interaction with diuretics for their efficacy. Blood pressure lowering by all interventions triggers activation of compensatory mechanisms. These are activation of the sympathetic nervous system with norepinephrine release, renin release → angiotensin → aldosterone → sodium water retention and possibly even antidiuretic hormone release. We find the latter mechanism (hypothesis) attractive in our very severely hypertensives because of the compulsive water drinking behavior and tendency to massive fluid retention in these patients when blood pressure is reduced using minoxodil-propranolol. An argument against ADH as the dominant mediator of this compulsive drinking behavior and fluid retention is the maintenance of serum sodium near normal levels.

Whatever the mechanism for fluid retention, diuretic agents are the mainstay of controlling this effect. In general, the diuretic dosage needed is directly related to the potency of antihypertensive agents used for reduction of the blood pressure. Inadequate diuresis with expansion of extracellular and possibly intracellular volumes severely limits antihypertensive action of guanethidine, methyldopa, reserpine, clonidine, and propranolol and, to a lesser extent, minoxidil.

One of the most frequent and potentially fatal diuretic drug interactions are mediated through hypokalemia. These interactions involve digitalis-type drugs and hypoglycemic agents. They can be best explained by the unique properties of cardiac pacemaker cells, particularly the property of spontaneous diastolic depolarization (Figure 13). The heart rate is controlled and altered by a host of factors which can change the slope of phase 4 in Figure 13, the polarity of the cell and the threshold potential for onset of the rapid phase of depolarization. Under normal conditions, the rate of diastolic depolarization of pacemaker cells in the sinus node occurs more rapidly than in other conductive (pacemaker) cells throughout the heart. However, under pathologic conditions such as hypoxia either general or localized, tissue injury, excess

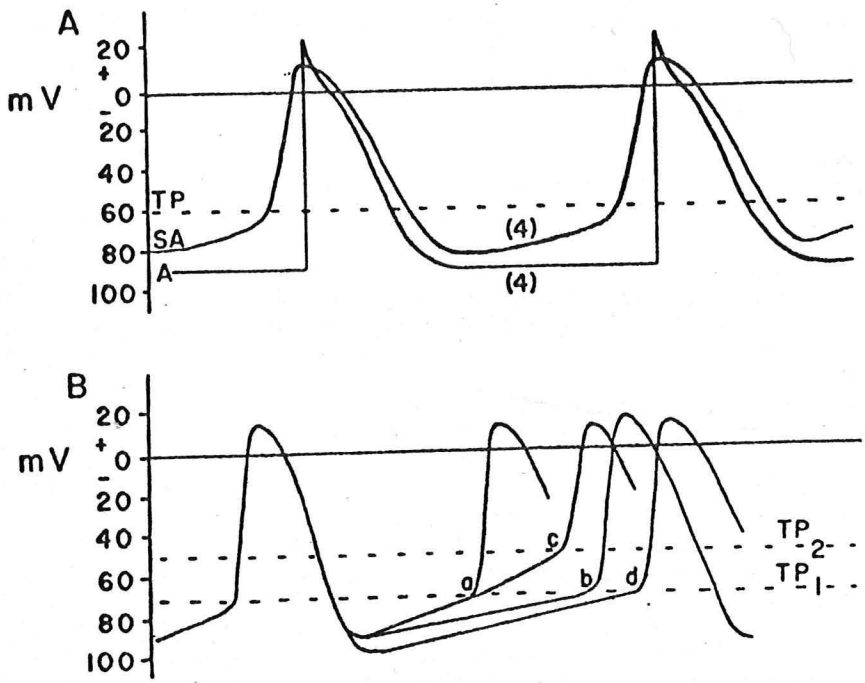

Figure 13. Schematic differences between pacemaker and non-pacemaker cells in the heart (above) and electrical mechanisms of altering rate of pacemaker firing (below).

catecholamine levels, etc. diastolic depolarization can occur more rapidly leading to atrial or ventricular extrasystoles, tachycardias, or fibrillation. Digitalis in <u>low</u> doses tends to decrease the rate of spontaneous diastolic depolarization and can reverse arrhythmias of heart failure. In higher doses, digitalis can increase diastolic depolarization, an effect which is augmented by hypokalemia. This augmentation occurs even with modest reductions of serum potassium (i.e. to 3.0 meq/L). Catecholamines also increase the slope of diastolic depolarization in pacemaker cells and many events increase circulating local catecholamines. Particularly potent events include hypoxia, hypoglycemia, hypotension, myocardial injury or infarction and stroke. Insulin-(or other hypoglycemic agents) induced hypoglycemia in the digitalis treated hypokalemic patients combines many of the potent factors predisposing to fatal ventricular fibrillation through altered diastolic depolarization. Additionally, the setting of the diabetic hypertensive with heart disease occurs relatively frequently. The tendency to development of hypokalemia is directly related to: 1) dose of diuretic (thiazide or furosemide; 2) sodium intake which

influences the quantity of sodium presented to the distal tubular mechanism exchanging sodium for potassium; 3) dietary potassium (inversely related). Excretion of potassium can be impaired pharmacologically by simultaneous use of aldosterone antagonists (spironolactone) or by triampterine. Administration of potassium chloride as an elixir or as slow release tablets can also be used to counter the potassium losing state.

For the additional reason that diuretic agents tend to intensify the glucose intolerance of diabetic agents, the lowest effective dose of thiazide (50 mg of HCT or its equivalent) or furosemide (40 mg) is used in moderate and intermediate hypertensive patients. Greater emphasis is placed on dietary salt restriction (i.e. 30-65 meq daily) and on the non-diuretic component of the regimen in proportion to the factors predisposing to cardiac complications.

If hypoglycemic agents are given, methyldopa and/or clonidine is/are preferred over vasodilator-beta blocking drugs for the additional reason that propranolol can potentiate the action of hypoglycemic agents and hide the symptoms of impending hypoglycemic coma. Congestive heart failure can be effectively treated in part of the severely hypertensive patients by normalizing blood pressure, thus eliminating the need for digitalis. If digitalis is needed, either spironolactone or triampterine should be included as necessary to control serum potassium in the 3.5-4.8 meq/L range. Some potassium supplementation (20-40 meq/D) may be required along with restriction of dietary sodium (no salt added and exclude heavily salted foods).

In conclusion, skillful use of beneficial interactions of antihypertensive drugs is the determinant of success in achieving our goal of asymptomatic normalization of high blood pressure. The more severe the hypertension, the greater the skill required. The need for hypoglycemic agents and/or digitalis glycosides complicates to a considerable degree the potentially hazardous drug interactions of cardiac arrhythmias and/or hypoglycemic coma. Because of the potential for benefit to your individual patient and to society at large ($$), a level of excellence should be expected in the management of hypertensive patients(to prevent renal failure or heart attacks)commensurate with that expected in dialysis and coronary care centers.

REFERENCES

1. Gilmore, E., Weil, J., and Chidsey, C.A.: Treatment of essential hypertension with a new vasodilator in combination with beta-adrenergic blockade. N. Engl. J. Med. 282:521-527, 1970.

2. Zacest, R., Gilmore, E., and Koch-Weser, J.: Treatment of essential hypertension with combined vasodilation and beta-adrenergic blockade. N. Engl. J. Med. 286:617-622, 1972.

3. Gottlieb, T.B., Katz, F.H., and Chidsey, C.A.: Combined therapy with vasodilator drugs and beta-adrenergic blockade in hypertension: A comparative study of minoxidil and hydralazine. Circulation 45:571-582, 1972.

4. Pettinger, W.A., and Mitchell, H.C.: Renin release, saralasin and the vasodilator-beta-blocker drug interaction in man. N. Engl. J. Med. 292:1214-1217, 1975.

5. Pals, D.T., Masucci, F.D., Dennins, G.S., Sipos, F., and Fessler, D.C.: Role of the pressor action of angiotensin II in experimental hypertension. Circ. Res. 29:673-681, 1971.

6. Pals, D.T., and Masucci, F.D.: Plasma renin and the antihypertensive effect of 1-Sar-8-Ala-Angiotensin II. Eur. J. Pharmacol. 23:115-119, 1973.

7. Pettinger, W.A., Campbell, W. B., and Keeton, K.: Adrenergic component of renin release induced by vasodilating antihypertensive drugs in the rat. Circ. Res. 33:82-86, 1973.

8. Pettinger, W.A., and Keeton, K.: Altered renin release and propranolol potentiation of vasodilatory drug hypotension. J. Clin. Invest. 55:236-243, 1975.

9. Vander, A.J., and Geelhoed, G.W.: Inhibition of renin secretion by angiotensin II. Proc. Soc. Exp. Biol. Med. 120:399-403, 1965.

10. Blair-West, J.R., Coghlan, J.P., Denton, D.A., Funder, J.W., Scoggins, B.A., and Wright, R.D.: Inhibition of renin secretion by systemic and intrarenal angiotensin infusion. Am. J. Physiol. 220:309-315, 1971.

11. Keeton, T.K., Pettinger, W.A., and Campbell, W.B.: The effects of altered sodium balance and adrenergic blockade on renin release induced by angiotensin antagonism. In press, Circ. Res., 1976.

12. Hollifield, J., Sherman, K., and Shand, D.: Propranolol proposed dual antihypertensive activity. Circulation 52 (suppl. II):98, 1975.

13. Limas, C.J., and Freis, E.D.: Minoxidil in severe hypertension with renal failure: Effect of its addition to conventional antihypertensive drugs. Am. J. Cardiol. 31: 355-361, 1973.

14. Pettinger, W.A., and Mitchell, H.C.: Minoxidil - An alternative to nephrectomy for refractory hypertension. N. Engl. J. Med. 289:167-171, 1973.

15. Mehta, P.K., Mamdani, B., Shansky, R.M., Mahurkar, S.N., and Danea, G.: Severe hypertension: Treatment with minoxidil. J. Am. Med. Assoc. 233:249-252, 1975.

16. Wilburn, R.L., Blaufuss, A., and Bennett, C.M.: Long-term treatment of severe hypertension with minoxidil, propranolol, and furosemide. Circulation 52:706-713, 1975.

17. Hull, A.R., Long, D.L., Prati, R.C., Pettinger, W.A., and Parker, T.F.: The control of hypertension in patients undergoing regular maintenance hemodialysis. Kidney Int. 7: (suppl. II):S184-S187, 1975.

18. Pettinger, W.: Treatment of hypertension in the patient with renal disease. In Press, The Kidney (Brenner, B.M., and Rector, R.C., eds.), W.B. Saunders Co., Philadelphia, Pennsylvania, 1976.

19. DuCharme, D.W., Freyburger, W.A., Graham, B.E., and Carlson, R.G.: Pharmacologic properties of minoxidil: A new hypotensive agent. J. Pharmacol. Exp. Ther. 184:662, 1972.

20. Wilburn, R.L., Blaufuss, A., and Bennett, C.M.: Long-term treatment of severe hypertension with minoxidil, propranolol and furosemide. Circulation 52:706-713, 1975.

21. Tarazi, R.C., Magrini, F., Dustan, H.P., Bravo, E.L., and Garvey, J.: Pulmonary hypertension with diazoxide and minoxidil. Am. J. Cardiol. 35:172, 1975.

22. Van Zwieten, P.A.: The central action of antihypertensive drugs, mediated via central α-receptors. J. Pharm. Pharmacol. 25:89-95, 1973.

23. Pettinger, W.A., Campbell, W.B., Keeton, T.K., and Harper, D.C.: Evidence for a renal alpha adrenergic receptor inhibiting renin release. In Press, Circ. Res., 1976.

24. Pettinger, W.A.: Drug Therapy: Clonidine, a new antihypertensive drug. N. Engl. J. Med. 293:1179-1180, 1975.