The Use of Chlorothiazide or Hydrochlorothiazide with Reserpine in the Office Treatment of Hypertension

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Introduction

Essential hypertension is an important problem in the office practice of medicine. Twenty to 25 per cent of the adults in the United States are affected. This disease has serious implications in cardiac, cerebrovascular and renal degeneration. According to insurance statistics, the height of the blood pressure may be correlated with life expectancy. Yet, prior to the past decade, treatment of hypertension was almost primitive. Ten years ago mild to moderate cases were treated with dietary changes, weight loss, rest and mild sedatives. A few drugs were employed, such as theophylline, nitrates, thiocyanates and veratum preparations. These drugs were effective for only short periods or at doses which were toxic. The largest proportion of these cases was helped little and the disease would continue to progress. Severe cases were treated with extreme restriction in dietary salt and protein (rice diet) or sympathetic nervous system surgery.

Since 1950, a number of potent antitensive agents have been introduced including hydralazine, the ganglionic blocking agents, new veratum derivatives and the rauwolfia preparations. These, singly and in combination, have been employed successfully in many patients including severely affected ones. Their use, however, involves complicated regimens, frequent and careful observation, development of tolerance and many annoying or even dangerous side effects. Patients with mild or moderate hypertension usually have few or no symptoms and do not happily accept these agents. Yet treatment is necessary because of the prognosis of their disease. What is needed, therefore, is a regimen that is acceptable to the patient with simplicity and relative freedom from side reactions and which can be continued with good results for many years. The synthesis of chlorothiazide and hydrochlorothiazide and their employment in the management of hypertension promises to be a hallmark of achievement in medical therapeutics. Several workers have noted the synergistic effect of the rauwolfia derivatives and the benzo- thiazides in lowering elevated blood pressure and it is this combination of agents which we selected to use in our study.

Methods and Materials

For this study, 60 patients with fixed essential hypertension were chosen from our private practice of medicine. Records were available for these patients dating back in many instances 10 to 30 years. All but a few were known in the office for more than a year. This was a great advantage in controlling our study in that patients with intermittent, labile hypertension or patients with pressures elevated temporarily due to a current stressful situation could be eliminated. Also patients that were known to do well with mild sedation and reassurance were not in-
cluded. All patients were subjected to a complete physical examination prior to the study. Electrocardiograms, chest x-ray examinations and urinalyses were done routinely. Blood urea nitrogen determinations were secured in most cases, especially when indicated by suggestive urine findings. The majority of the patients including all of the younger patients and other patients with suggestive signs or symptoms were hospitalized at some time prior to the study to eliminate specific causes of hypertension such as renal disease, pheochromocytoma and coarctation of the aorta.

The study was started initially with chlorothiazide and reserpine in early 1958. When hydrochlorothiazide became available, it was substituted in most of the patients. Later, a tablet containing hydrochlorothiazide, reserpine and potassium was given to 30 of the patients. The patients presented have been followed from two to 30 months on the drugs. Many of the patients had been on reserpine prior to this study. They were continued on this and a thiazide derivative added to the regimen. The dosage of each of the two drugs was adjusted independently in each patient by giving extra reserpine in addition to that already in the combined tablets when necessary. In the majority of patients, the amount of reserpine in the combined tablets seemed sufficient. Some patients required extra reserpine initially, but after several weeks the dose could be reduced. The patients were seen three days after being started on the regimen; then at one-week intervals. When the pressures were stable and side effects, if any, controlled, the patients were checked every two weeks. The tablets were carefully counted at each visit to determine if the medication was being taken as directed. The medication was given the same degree of reassurance that all previous remedies (usually without success) had been prescribed. The patients rested in the office in a sitting position for at least one half hour prior to the recording of the sitting blood pressure by the office nurse. The pressures were checked 15 minutes later by the physician to determine any marked lability.

No system of placebos was instituted, but in a group of patients the thiazides were interrupted for one of the following reasons:

1. development of side effects
2. the patient did not return for a prolonged period of time for various reasons
3. by design on part of investigator to test the efficacy of the medication in some of the moderate, uncomplicated cases.

![FIGURE 1: Age distribution of patients.](data:image/png;base64,___)
In the latter two groups, the effect of reinstitution of the medication could also be demonstrated.

All of the patients were on a salt-poor (not "salt-free") regimen. They were instructed to take at least 8 ounces of citrus or tomato juice daily.

**Results**

The findings of this study are summarized in Figures 1, 2, 3, 4, and 5. The doses of medication used were those which seemed optimum to the investigators, i.e., those lowest doses that gave as near to maximal blood pressure reduction without side effects. In seven instances, the thiazides had to be discontinued. This was most frequent early in the study and often due to patient rejection. This will be discussed more fully in the section on side effects. Most of these patients who were previously on reserpine and one who had a sympathectomy ten years before showed good blood pressure reductions within a week of adding a thiazide to the regimen. Those who had not been on reserpine usually required two to five weeks for near maximal response. This probably represents the latent period in the action of reserpine and could be decreased by adding additional reserpine initially. Some patients responded in a few days who had not taken reserpine prior to the study.

The thiazide derivative proved quite successful as an adjunct with reserpine in the management of mild to moderately severe essential hypertension. There were only four cases (6.7 per cent) in whom the regimen failed to produce a significant blood pressure response. In another seven patients (11.6 per cent), the thiazides were withdrawn. With more experience in the administration of these agents and good patient cooperation, the figure could be reduced to a minimum. With most individuals who experienced side effects, they were mild, transient and simple to control. A glance at Figure 4 demonstrates the greater effectiveness of combined therapy over reserpine alone. This is not completely valid since milder cases, well controlled on reserpine, were not included in this study. There seemed to be little difference in the effectiveness of chlorothiazide and hydrochlorothiazide. However, 50 mg. of hydrochlorothiazide appeared more effective than 500 mg. of chlorothiazide and probably as effective as 750 mg. of chlorothiazide. There appeared to be no development of tolerance to the regimen though some patients were followed over two years. Interrupting the treatment allowed rapid rise...
in pressure and starting treatment again invariably produced the previous good results. The addition of KC1 to the regimen did not appear to effect the blood pressure. *It was our impression that the vast majority of the patients could be controlled with 25 mg. or 50 mg. of hydrochlorothiazide and 0.125 mg. of reserpine combined in one or two tablets daily without side effects.*

**Side Effects**

Twenty of the 60 patients experienced some side effects from the regimen. The most common complaint was that of weakness. This usually developed in three to 10 days. Five patients had actual syncope. One fell, fracturing several ribs, causing pneumothorax. This syncopal episode occurred after three days on 150 mg. of hydrochlorothiazide and 0.375 mg. reserpine. Later, with reduced dosage, the patient tolerated the drugs well and is now maintained normotensive without discomfort. For the majority, the dizziness or weakness was transient and easily controlled by reducing the dose and/or adding extra potassium to the diet. This extra potassium was given in the form of enteric-coated potassium chloride 1 to 4 gm. daily and by urging the patient to drink large amounts of citrus or tomato juice. Later, tablets incorporating 8 grains of KC1 with hydrochlorothiazide and reserpine were given. Even with these, it was necessary at times to give additional potassium. Often it was possible to discontinue the KC1 after a while without recurrence of weakness. One experienced anorexia. This diminished when the dose was decreased. The patient tolerated the mild anorexia because of the excellent result on his blood pressure. The medication was withdrawn in seven because of side effects. In four of these cases, the patient refused to accept even a reduced dose. Three more did not seem to tolerate any without weakness. Many workers*1,*2 have demonstrated that the thiazides can cause prolonged reduction in serum potassium levels. It has also been shown that potassium deficiency may cause renal tubular changes.* For this reason, we did frequent urinalyses and when suspicious, blood urea nitrogen determinations during this study. No patient exhibited change in urinary findings during this time. Four who had

![Graph](Image)

**FIGURE 4:** Pressure changes by using combined therapy as compared to reserpine alone.
been well maintained on digitalis showed signs of toxicity soon after starting the thiazides. One with auricular fibrillation developed bradycardia. The other three with normal sinus rhythm showed numerous extrasystoles. They were all controlled by reducing the digitalis and thiazide dose and by adding extra potassium to the diet. No idiosyncrasy such as skin eruption or blood dyscrasia was produced in our patients.

Discussion

Rauwolfia derivatives such as reserpine probably decrease blood pressure by increasing blood vessel caliber. This is thought to be accompanied by reduction of sympathetic activity by blocking of afferent impulses centrally.11 Thiazide derivatives are thought to effect a decrease in pressure by reducing blood volume by diuresis.12 A combination of these two agents with their different effects on hemodynamics has produced a regimen which appears to be quite successful in the office management of mild to moderately severe essential hypertension over prolonged periods of time. The drugs are effective together in relatively low doses and on a simple schedule (once stabilized) which is readily accepted and easily followed by the patient. This combined therapy is more effective than reserpine alone. Moreover many patients who previously were unable to tolerate antitensive doses of reserpine because of such side effect as depression, irritation of peptic ulcer, diarrhea, insomnia and nasal stuffiness were able to accept the smaller doses of reserpine in this regimen with good result and no recurrence of their previous toxic symptoms.

This regimen served a dual purpose in patients with hypertensive heart and edema. These patients required far fewer mercurial injections. They also experienced far fewer episodes of paroxysmal nocturnal dyspnea. This was welcomed both by patient and physician.

SUMMARY

1. Sixty patients with mild to moderate benign essential hypertension were selected from a private office practice of medicine and placed on a regimen of antitensive therapy including reserpine and a benzothiadiazine for two to 30 months.
2. This combined therapy produced significant blood pressure reduction in all but four (6.7 per cent) patients.
3. In seven more patients, the drug was withdrawn because of side effects. This figure could be greatly reduced with experience in use of the drug and patient cooperation.
4. A total of 20 experienced side effects. Most were mild and easily controlled. In none was there severe or permanent toxic effect.
5. It was concluded that this regimen was successful and practical for prolonged administration in mild to moderately severe benign essential hypertension.

ACKNOWLEDGMENT: The chlorothiazide and hydrochlorothiazide and reserpine used in this study were provided by the Merck, Sharp and Dohme Co. in combined tablets available as Diupres, Hydropres 25, Hydropres 50, and Hydropres with potassium.

RESUMEN

1. Se escogieron sesenta enfermos con hipertensión benigna moderada y esencial, de la práctica privada y se colocaron bajo un régimen de tratamiento antitensivo incluyendo la reserpina y una tiazida por dos a 30 meses.
2. Esta terapia combinada produjo considerable descenso de la presión en todos menos 4 (6.7 por ciento) de los enfermos.
3. En otros siete enfermos la droga hubo de retirarse por los efectos colaterales. Esta cifra podría ser grandemente reducida con la experiencia en el uso de la droga y con la cooperación del enfermo.
4. Se observó un total de 20 efectos colaterales. La mayoría son moderados y fáciles de dominar. En ninguno hubo efecto toxico grave o permanente.
5. Se concluye que este régimen es útil y practico para la administración prolongada en la hipertensión moderada benigna esencial.

RESUMÉ
1. Soixante malades atteints d'hypertension essentielle bénigne, dont le degré d'atteinte était de faible à modéré, furent choisis parmi la clientèle privée et soumis à un régime de traitement antitensionnel comprenant la résépine et le thiazide pendant une période allant de deux à trente mois.
2. Ce traitement associé produisit une réduction nette de la pression sanguine chez tous les malades sauf quatre (6.7%).
3. Chez sept autres malades, le produit fut cessé à cause des complications qu'il provoqua. Ce chiffre pourrait être grandement réduit avec l'expérience que l'auteur a maintenant du produit et grâce à la collaboration du malade.
4. Un total de 20 malades a subi des effets toxiques. La plupart furent faibles et aisément jugulés. Dans aucun cas il n'y eut d'effet toxique grave ou permanent.
5. L'auteur conclut que ce traitement fut satisfaisant et pratique pour une administration prolongée dans l'hypertension essentielle bénigne, avec atteinte faible ou modérément grave.

ZUSAMMENFASSUNG
1. 60 Kranke mit leichter bis mässig schwerer gutartiger essentieller Hypertonie wurden aus einer internistischen Privatpraxis ausgewählt und einer zwei bis 30 Monate lang dauernden antihypertensiven Therapie unterzogen einschließlich Reserpin und Thiazid.
2. Diese kombinierte Therapie bewirkte eine wesentliche Blutdrucksenkung bei allen -außer 4 Patienten (6.7%).
5. Es läßt sich der Schluß ziehen, dass dieses therapeutische Vorgehen erfolgreich war und für eine sich über lange Zeit erstreckende Anwendung bei leicht bis mittelschweren Fällen gutartiger essentieller Hypertonie geeignet ist.

REFERENCES