MEDICAL INTELLIGENCE

CURRENT CONCEPTS IN THERAPY

Antihypertensive Agents. II. Benzothiadiazine Compounds, Rauwolfia and Hydralazine*

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THE apparent great variety of antihypertensive agents represents for the most part minor variations on a few prototype compounds. The more effective antihypertensive drugs can be included under the following groupings: saluretic agents; rauwolfia preparations; hydralazine; ganglion-blocking drugs; and sympathetic-blocking agents.

Saluretic Agents

Chlorothiazide and the many varieties of related benzothiadiazine derivatives are used widely in the treatment of hypertension not only for their modest intrinsic antihypertensive effect but also for their ability to enhance the blood-pressure-reducing activity of other drugs. Benzothiadiazines act on the proximal and distal convoluted tubules to increase the excretion of sodium, chloride and potassium.

When chlorothiazide is administered in a dose of 500 mg. twice daily to nonedematous hypertensive patients a negative sodium balance lasting approximately forty-eight to seventy-two hours develops.[1] The excess of excreted salt is derived primarily from a loss of isotonic total extracellular fluid, with a resulting reduction in plasma volume.[2] After the initial diuresis unknown compensatory mechanisms prevent further depletion of body salt despite continued administration of the drug.

The moderate hypovolemia is associated with a decrease in cardiac output.[3,4] After long continued administration of chlorothiazide the plasma and total extracellular volumes and cardiac output, but not the blood pressure, are at least partially restored.[5-7] The mechanism of the maintained antihypertensive effect during this later period remains undetermined.[2,6,7]

The customary dose of chlorothiazide is 500 mg. twice daily. Some patients respond to a smaller dose, such as 250 mg. twice daily or 500 mg. once daily, which may be given before noon to cover the peak periods of dietary sodium ingestion. The larger dose is usually given initially, and after several weeks it can frequently be lowered without losing the antihypertensive effect. The other benzothiadiazine diuretics differ from chlorothiazide only in potency and duration of action. For example, hydrochlorothiazide has a similar duration of effect, but 50 mg. is as effective as 500 mg. of chlorothiazide. Chlorthalidone (Hygroton) has a longer duration of action so that 100 mg. given once daily is equivalent approximately to 500 mg. of chlorothiazide given twice daily. Aside from these differences in dosage the various drugs can be used interchangeably, and none seem to have significant advantages over the others in antihypertensive effectiveness or lesser toxicity.

The toxic effects include dermatitis, bone-marrow depression and thrombocytopenic purpura. Hyperuricemia is fairly common and can result in clinical gout.[8,9] Hyperglycemia may occur, usually without acidosis. The most common disturbance is hypokalemia, usually with serum potassium levels between 3.0 and 3.5 milliequiv. per liter.[10] When lower levels are observed additional factors producing potassium depletion such as heart failure, diarrhea and secondary aldosteronism like that seen in malignant hypertension should be suspected. On the other hand, hyponatremia or hypochloremia is relatively uncommon except when the benzothiadiazines are given to patients in whom such electrolyte disturbance may occur from the basic process.

Rauwolfia Serpentina

Although a number of alkaloids have been extracted from *Rauwolfia serpentina* the most effective derivative is reserpine. The search for other alkaloids that are antihypertensive without the side effects of reserpine has resulted in the production of compounds with considerably weakened antihypertensive effects.

In the laboratory animal reserpine reduces the catechol amine content of the tissues.[11,12] The drug also affects the metabolism of the brain, as evidenced by changes in its content of nor-epinephrine and serotonin.[11,12]

Reserpine by the parenteral route in doses of 2 to 4 mg. is used in the management of hypertensive emergencies,[13,14] such as acute hypertensive encephalopathy and eclamptic toxemia of pregnancy.[15] The sedative and antihypertensive effects develop gradually an hour or two after the drug has been administered. Repeated doses are given as often as is necessary to maintain a reduced level of blood pressure. Reserpine can be supplemented when necessary with chlorothiazide, hydralazine by the parenteral route, veratrum and, in extremely resistant cases, blocking agents administered cautiously by titration.

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The principal hazard in the treatment of hypertensive "crises" is the precipitation of hypotensive collapse in patients with renal damage. The drastic change in renal hemodynamics produces oliguria and resulting nitrogen retention. Hemiparesis or other signs of critically reduced cerebral blood flow may appear during severe hypotension. Fortunately, the latter usually recede with prompt treatment of the collapse. Reserpine and hydralazine are less apt than veratrum and particularly the blocking agents to produce sudden severe hypotension. The blocking agents are more potent, however, and are often resorted to when milder measures fail.

In chronic hypertension reserpine is given by mouth, usually in an initial dose of 0.5 mg. twice daily for two weeks, followed by a lower maintenance dose of 0.25 mg. once daily or less.[16] The antihypertensive effectiveness is quite variable from one patient to another, but on the average it is only moderate, producing a reduction of about 5 to 10 mm. of mercury in the basal diastolic blood pressure.[17] As a consequence rauwolfia or reserpine is frequently used as adjunctive therapy with other antihypertensive agents.

The most common side effect, nasal congestion, together with increased appetite and frequency of bowel movements may represent unopposed parasympathetic activity resulting from the depletion of catechol amines. Nightmares can be sufficiently disturbing to demand reduction in dosage or discontinuation of the drug. Obsessive, compulsive and aggressive traits often give way to a more philosophical attitude toward job demands, time schedules and the like (the so-called tranquilizing effect).[18] In some patients the emotional reaction is a distasteful lethargy necessitating further reduction in dosage. A more serious psychic reaction, distinctly different from the lethargic effect, is the appearance of a true depression at any time during the course of treatment.[19] This reaction is indistinguishable from the depressed phase of manic-depressive pyschosis or of involutional melancholia. The disorder may pass unrecognized since the patient often rationalizes his depressed feelings on the basis of innate deficiencies or environmental factors or may convert them into symptoms mimicking organic disease. The reaction is especially dangerous because it may lead to suicide before the depression is recognized. For this reason it seems mandatory to warn patients at the time that treatment is begun of the infrequent but definite depressive tendency of the drug, and to indicate the importance of discontinuing the medication if a severely depressive mood change develops.

Hydralazine

Hydralazine (Apresoline) exhibits the unique hemodynamic properties of increasing cardiac stroke volume and rate, decreasing total peripheral resistance and redistributing blood flow to favor the renal, splanchnic and coronary circulations.[20-22] As a result of the markedly decreased peripheral resistance and increased stroke volume the reduction in diastolic pressure is greater than that of the systolic.

Hydralazine has been used parenterally in doses of 10 to 15 mg. in an attempt to lower blood pressure in hypertensive emergencies. It is almost always given in addition to parenterally administered reserpine when the latter fails by itself to achieve an adequate control.

In chronic hypertension the drug is administered orally. The initial doses may precipitate acute side effects of headache, palpitation and dyspnea on exertion that tend to diminish as treatment progresses.[23] These side effects can often be circumvented if two precautions are observed: small, widely spaced beginning doses (25 mg. once daily or 10 mg. twice daily) with gradual elevation to the effective level (25 to 50 mg. two or three times daily) over a period of several weeks; and concomitant treatment with a saluretic agent or rauwolfia or both. Thus, hydralazine is best tolerated when used as an adjunct in rather small dosage. Doses are sometimes raised above 200 mg. per day for short periods to obtain an antihypertensive effect, after which the dose is reduced to below this level for maintenance. High doses should not be continued for more than several weeks.

The severe toxic reactions, which are more common with continued administration of the larger doses, resemble disseminated lupus erythematosus, with arthritis, dermatitis and lupus cells in the blood.[24,25] Occasionally, after the drug is withdrawn arthralgias and increased sedimentation rate in the blood may persist although the usual result is a complete reversal of the toxic process.

General Considerations

The three drugs discussed above can be considered antihypertensive agents of moderate effectiveness as compared to the more potent blocking agents to be discussed later. Their principal advantages are as follows: acute hypotensive reactions, particularly orthostatic hypotension, are not produced in the dosage customarily employed; and the effective dose levels are fairly standard from one patient to another so that less manipulation is required.

Because of individual variations in reactivity of different patients one may respond with a significant fall of blood pressure to a saluretic agent, and another to rauwolfia, whereas a third would require a combination of several agents. The majority of hypertensive patients fall into the last group. For these reasons each case should be considered an individual therapeutic experiment. A common routine is to begin with chlorothiazide alone, the other drugs being added one at a time as the occasion demands. This permits observation of the response to each agent for both

therapeutic effect and side reactions so that the most effective and best tolerated drug or combination for the particular patient will be made evident.

Controlled trials have demonstrated that the antihypertensive effects of these agents are essentially additive.[26] Despite great individual variation the *average* response of a *group* of patients to a combination of these agents approximates the sum of the average response to each drug individually. The advantage of greater antihypertensive effectiveness of such combinations, however, is offset by the increased exposure to toxic effects and, incidentally, the increased expense to the patient. Frequently, after months of intensive treatment the level of blood pressure becomes modified so that adequate control can be maintained on a reduced dose schedule.

References

1. Freis, E. D., Wanko, A., Wilson, I. M., and Parrish, A. E. Chlorothiazide in hypertensive and normotensive patients. *Ann. New York Acad. Sc.* **71**:450-455, 1958.
2. Freis, E. D. Mechanism of antihypertensive effects of diuretics: possible role of salt in hypertension. *Clin. Pharmacol. & Therap.* 1:337-344, 1960.
3. Dustan, H. P., Cumming, G. R., Corcoran, A. C., and Page, I. H. Mechanism of chlorothiazide-enhanced effectiveness of antihypertensive ganglioplegic drugs. *Circulation* **19**:360-365, 1959.
4. Frohlich, E. D., Schnaper, H. W., Wilson, I. M., and Freis, E. D. Hemodynamic alterations in hypertensive patients due to chlorothiazide. *New Eng. J. Med.* **262**:1261-1263, 1960.
5. Wilson, I. M., and Freis, E. D. Relationship between plasma and extracellular fluid volume depletion and antihypertensive effect of chlorothiazide. *Circulation* **20**:1028-1036, 1959.
6. Conway, J., and Lauwers, P. Hemodynamic and hypotensive effects of long-term therapy with chlorothiazide. *Circulation* **21**:21-27, 1960.
7. Winer, B. M. Antihypertensive actions of benzothiadiazines. *Circulation* **23**:211-218, 1961.
8. Oren, B. G., Rich, M., and Belle, M. S. Chlorothiazide (Diuril) as hyperuricacidemic agent. *J.A.M.A.* **168**:2128, 1958.
9. Dreifus, L. S., Onesti, G., Brest, A. N., and Moyer, J. H. Effect of diuretics on uric acid metabolism. In *Hypertension: Recent advances.* Edited by A. N. Brest and J. H. Moyer. 660 pp. Philadelphia: Lea, 1961. P. 262.
10. Freis, E. D. Treatment of hypertension with chlorothiazide. *J.A.M.A.* **169**:105-108, 1959.
11. Brodie, B. B., Pletscher, A., and Shore, P. A. Evidence that serotonin has role in brain function. *Science* **122**:968, 1955.
12. Maxwell, R. A., Ross, S. D., Plummer, A. J., and Sigg, E. B. Peripheral action of reserpine. *J. Pharmacol. & Exper. Therap.* **119**:69-77, 1957.
13. Freis, E. D. Hypertensive emergencies. *M. Clin. North America* (in press).
14. Finnerty, F. A., Jr. Therapy of hypertensive emergencies. In *Hypertension: Recent advances.* Edited by A. N. Brest and J. H. Moyer. 660 pp. Philadelphia: Lea, 1961. P. 528.
15. *Idem.*[14] P. 535.
16. Wilkins, R. W. Rauwolfia alkaloids and serotonin antagonists in hypertension. *M. Clin. North America* **45**:361-373, 1961.
17. Veterans Administration Cooperative Study on Antihypertensive Agents. II. *Arch. Int. Med.* (in press).
18. Wilkins, R. W. Clinical usage of Rauwolfia alkaloids, including reserpine (Serpasil). *New York Acad. Sc.* **59**:36-44, 1954.
19. Freis, E. D. Mental depression in hypertensive patients treated for long periods with large doses of reserpine. *New Eng. J. Med.* **251**:1006, 1954.
20. Reubi, F. Renal hyperemia induced in man by new phthalazine derivative. *Proc. Soc. Exper. Biol. & Med.* **73**:102, 1950.
21. Freis, E. D., et al. Hemodynamic effects of hypotensive drugs in man: l-hydrazinophthalazine. *Circulation* **8**:199-204, 1953.
22. Rowe, G. G., et al. Effects of l-hydrazinophthalazine upon coronary hemodynamics and myocardial oxygen metabolism in essential hypertension. *J. Clin. Investigation* **34**:696-699, 1955.
23. Freis, E. D. Hydralazine: pharmacology and clinical application. In *Hypertension: Recent advances.* Edited by A. N. Brest and J. H. Moyer. 660 pp. Philadelphia: Lea, 1961. P. 291.
24. Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H. Rheumatic and febrile syndrome during prolonged hydralazine treatment. *J.A.M.A.* **154**:23-29, 1954.
25. Fedor, I. A. Febrile syndrome during prolonged hydralazine treatment for hypertension. *New Eng. J. Med.* **251**:273, 1954.
26. Veterans Administration Cooperative Study on Antihypertension Agents. III. *Arch. Int. Med.* (in press).