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Safety of antihypertensive therapies:
A series of interactive panels (Part II) – Controversies in hypertension

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During the annual meeting of the American Society of Hypertension, a panel of experts was convened to assess and present the most up to date information regarding controversial aspects of the management of hypertension. A previous issue of *Scientific Update* dealt with the first part of the symposium in which new data on the safety of calcium channel blockers was discussed. Two subsequent panels addressed issues that, although less controversial, continue to be areas in which there is no universal consensus: the role of combination therapy and salt restriction in the management of the hypertensive patient.

1) Rationale for and safety of combination antihypertensive therapy:

a) Lessons from combination therapy in VA studies (Barry Materson, MD, MBA; Professor of Medicine, University of Miami School of Medicine): The VA Cooperative Study on Monotherapy of Hypertension included a substudy of patients who had not achieved target BP with two different single drugs and in whom the two drugs that had failed were combined.[1,2] The mean diastolic BP was 96 mmHg and the majority had what now would be considered Stage I or II hypertension. The patients were randomized to one of 6 drugs or placebo and the responders were defined as those achieving a diastolic BP <90 mmHg.

A total of 1292 patients were randomized and 745 achieved BP control with their first drug and were studied on it for 2 years while 547 did not respond and were advanced to the second phase of the study. Of them, 410 patients completed the washout period, their BP returned to the baseline, and they were randomized to a second drug (but not to placebo). The responders completed the study whereas the non-responders (179) underwent a second washout period and 102 patients went on to phase III in which the two drugs were combined. Interesting lessons can be derived from this analysis. When hydrochlorothiazide was one of the two drugs combined there was a 77% response rate in systolic BP compared to 46% when it was not included in the combination ($p=0.002$), for diastolic BP, the response was 69% versus 51% respectively ($p=0.067$). Although the latter did not achieve statistical significance, these results do suggest that a combination including hydrochlorothiazide is more likely to succeed.[1]

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Further analysis of the data allowed assessment of response to the first drug, as well as the additional response rate to the second drug and to the combination. Some of the most interesting results were found with calcium antagonists.[3] For instance when diltiazem was used as a first drug it achieved a 75% response rate, prazosin as a second drug produced an additional response rate of 6% and the total combination response rate was 86%. In contrast, if treatment was initiated with prazosin the initial response rate was only 56%, diltiazem added a substantial 22%, and with the combination, the response rate was 84% which was identical to that seen with the opposite order of drug administration. A different effect was observed with other combinations also involving calcium antagonists. For instance, when diltiazem was given first, the response rate was 75% as discussed above, captopril produced an additional 17% response and the combination had an excellent rate of 97% response. However, when therapy was initiated with captopril the initial response rate was only 54%, diltiazem added 17%, and the combination had a response rate of 88%. This difference with the opposite order of drug administration did not reach statistical significance but it suggested that the order of the drugs may have an impact on the outcome. As well, this *post-hoc* analysis demonstrated that diltiazem was highly effective when used as the initial therapy in this hypertensive population and that combination therapy can achieve high rates of control even when the individual components have failed. These results provide support for the concept of sequential therapy in which the first drug would be the one considered best according to the individual patient profile. Inadequate response would lead to monotherapy with the second best drug. The combination of the two would be considered if the second drug also failed.

b) Rationale and safety of ACE-Inhibitor combination with calcium channel blockers (William B. Applegate, MD; Professor and Chairman of Preventive Medicine, Department of Preventive Medicine, University of Tennessee): Given that a significant proportion of hypertensive patients are not controlled with the first drug, a fixed combination of antihypertensive agents may be considered in certain patients. A combination can often have potential additive or synergistic effects and it is possible that one drug may offset the side effects of the other (eg. edema, with some calcium antagonists is offset by the addition of an ACE-inhibitor or diuretic). Another argument is that maintaining the first drug at a lower level while going to a low dose of a second drug may result in equal or better BP control and less side effects than increasing the initial drug. For instance, HCTZ dose-response flattens somewhat between 25 and 50 mg but the side effects increase markedly. Results of two hypertension studies utilizing calcium antagonists and ACE-Inhibitors[4] were presented. The first was a multicenter, randomized, double-blind, parallel dose-response trial with enalapril alone or in various dose combinations with long-acting diltiazem (diltiazem ER). The population consisted of 336 patients (217 men, 119 women, mean age = 54.7 years) and both short term (12 weeks) and long term (1 year) follow up periods were included. In the short term results, no difference was observed between enalapril 5 mg and the combination of enalapril 5 mg/diltiazem 60 mg. A small additional effect was seen on diastolic BP control with enalapril 5 mg/diltiazem 120 mg. In contrast, with the combinations enalapril 5 mg/diltiazem 180 mg or enalapril 5 mg/diltiazem 240 mg a 20-24% additional improvement was achieved in BP control rate with the addition of the second drug. The responders were followed for a year and good overall maintenance of control was observed. Approximately 25% of the cohort, however, needed to be titrated up from their therapy at 12 weeks. In terms of side effects the results were quite favorable as a 14% rate of side effects was seen with enalapril alone compared with a range of 9-19% with the combinations and 8.6% with placebo. For instance, the combination of enalapril 5 mg/diltiazem 180 mg had a rate of side effects of 15% which is not different from enalapril alone. This suggests that if the doses of the combination are kept reasonably low, a marked improvement in BP control can be achieved with additive incidence of adverse effects which is similar to that of the individual drugs.

The second study utilized monotherapy with amlodipine, benazepril or their combination. Ambulatory 24

hour BP recordings were used to assess response to treatment. Greater monotherapy efficacy was observed with the amlodipine than with the benazepril but the combination was more efficacious than either drug alone. A dose-response relationship in BP-lowering was observed with each of the combination doses. The incidence of side effects for the combination was similar to that of benazepril alone but the combination, while producing better BP control, offset the tendency for peripheral edema in amlodipine patients. In conclusion, these two studies demonstrated that the calcium antagonist/ACE-Inhibitor combinations are effective and well tolerated; their use could be associated with potential physiologic and hemodynamic benefits which need to be further explored in future studies.

2) Can dietary salt restriction make antihypertensive therapy more effective and safer:

a) Effect of dietary salt on BP and renal hemodynamics (Matthew R. Weir, MD; Professor and Head, Division of Nephrology and Clinical Research Unit, University of Maryland): Although salt has been part of the human diet for thousands of years and is known to be a critical factor in BP regulation, the threshold and precise relationship between dietary salt and BP is not fully understood. There is significant variability between individuals in BP response to changes in dietary salt. This variation is highly reproducible in individual subjects, approximates a gaussian distribution, and is persistent over time. Consequently, the role of dietary salt restriction in the management of hypertension has been the subject of some controversy. In his presentation, Dr. Weir argued that there is important recent clinical evidence demonstrating that BP, salt sensitivity and insulin resistance frequently coexist. As well, neurohormonal systems, in particular the sympathetic nervous system and the renin angiotensin system, could play a critical role underlying the association of salt sensitivity, insulin resistance and an impaired pressure-natriuresis response. Thus, dietary salt sensitivity may be a phenotype for those patients with associated hypertension, insulin resistance and cardiovascular risk clustering. Even if their coexistence as a phenotype is accepted, it is not known whether there is a cause-effect relationship or they are merely epiphenomena. However, it does seem to be clear that responses of BP to dietary salt create two kinds of phenotypes: a salt-sensitive and a salt-insensitive one. The salt-insensitive individual would exhibit no BP response, an increase in renal blood flow and no increase in glomerular filtration rate in response to dietary salt. Clinically, these individuals would not present with a clustering of cardiovascular risks. Of interest are the observations that correlate aging with the radioisotopically measured decline in renal blood flow in normotensive, borderline and definite hypertensive individuals. The decline in renal perfusion leads to activation of local intrarenal neurohormonal systems that facilitate salt and water retention resulting in an impaired pressure-natriuresis response and clinical evidence of dietary salt sensitivity. In turn, this would lead to higher BP and further vascular damage and decreased renal perfusion.

A clinical study examining dietary salt and proteinuria as a surrogate marker for renal damage was performed on an outpatient basis and included 22 patients, mean age 60 and mean BP of 153/96.[5] The patients were randomized to a low or a high salt diet for two weeks. Those patients exhibiting at least a 3 mm Hg change in BP with dietary salt were classified as salt-sensitive. Renal hemodynamics consistently showed an increase in glomerular filtration rate only in the salt-sensitive patients which correlated with an increase in protein excretion in the urine not observed in the salt resistant population (a change of 55 mg protein/24 hours, $p=0.003$). A second study was designed to investigate the correlation between insulin resistance and salt sensitivity.[6] It included 10 otherwise healthy obese hypertensives with a mean age of 60 years. The patients had normal renal function and exhibited glucose intolerance but none had diabetes; the mean BP was 158/95. All subjects were studied on both high and low salt diets. A total of 50% of the patients exhibited salt-sensitivity and evidence of an increased glomerular filtration fraction which was associated with increased insulin resistance. These findings must be interpreted as suggesting an association, not a cause-effect relationship, between salt-sensitivity and insulin resistance.

Therefore, obesity with its associated glucose intolerance and hyperinsulinemia could also be abnormally related to salt and water handling disturbances. These associated phenotypic manifestations would occur characteristically in patients that clinically present with a clustering of cardiovascular risk factors. Although these preliminary results are indeed quite interesting there is a clear need for further studies to test this hypothesis.

b) Effects of dietary salt on blood pressure control and antihypertensive properties of drugs (George L. Bakris, MD, FACP; Associate Professor of Preventive and Internal Medicine. Director, Chicago Westside Hypertension Research Consortium. Rush-Presbyterian-St. Luke's Medical Center, Chicago): High salt intake increases glomerular filtration rate in subjects that are either salt-sensitive or diabetic. The reduction in sodium intake to ≤ 100 mEq/day attenuates the increase in glomerular filtration rate observed in animal models of diabetes, an effect that is related to both altered intrarenal hemodynamics and subsequent changes in glomerular membrane permeability. A soon to be published meta-analysis by a Canadian group looked at all salt restriction trials in hypertension and asked two fundamental questions: 1) does a low salt diet lower BP and 2) does a low salt diet prevent the development of hypertension in normotensive individuals. The conclusions of the meta-analysis were that dietary salt restriction does lower BP in patients with pre-existent hypertension but it does not necessarily prevent the development of hypertension.[7]

Dr. Bakris presented the results of his recent study designed to examine the relationship between salt intake and the antiproteinuric effects of nifedipine XL or long-acting diltiazem.[8] A total of 20 diabetic hypertensive patients were studied. The patients were taken off their antihypertensive medication, started on a low salt diet (150 mEq/day) and placed on clonidine for a washout period of two weeks after which nifedipine XL was substituted for the clonidine. After one month the diet was changed to high sodium (250 mEq/day) and the patients were followed for another month with the necessary titration of nifedipine XL to maintain BP control (all patients also required diuretics to maintain BP<140/90). A second washout period was then instituted with clonidine treatment followed by therapy with diltiazem CD using the same protocols previously described for low and high dietary salt intake. The most profound reduction in proteinuria was observed in the patients on the low salt diet treated with diltiazem CD. The high salt diet partly blunted the antiproteinuric effects although diltiazem CD still had a superior antiproteinuric effect over the nifedipine XL. These results confirmed previous studies with calcium antagonists and ACE-Inhibitors demonstrating a dependency of the antiproteinuric effects on dietary salt intake. In conclusion, if BP and proteinuria reduction are accepted as important surrogate end-points then the management of hypertension should include dietary salt restriction and, in selected patients, therapy with drugs that reduce proteinuria.

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