Discussion: Recent Data on the Safety and Efficacy of Newer Therapies in the Management of Hypertension

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Dr. Neutel: I think we’ve reached a crossroads in the therapeutics of hypertension and it may be time to make a decision as to whether we’re treating hypertension correctly.

To set the stage for our discussion, I’ll summarize some of what we’ve heard and pose some questions. We’ve been advised in the past by the Joint National Committee and we learn at medical school that the way to treat hypertension is with monotherapy—you choose one drug at a low dose and increase that dose until you get blood pressure control or reach the maximum dosage. If you don’t achieve goal blood pressure, you add a second drug. There are, however, problems with monotherapy.

The rationale behind this kind of approach is that if you use one drug, it’s more convenient for patients, there will be fewer side effects and, if there are adverse reactions, you will know which drug is causing them. Response rates with any single class of antihypertensive drug, however, are only about 45% to 55%; about half of the hypertensive population are going to need a second drug anyway.

Fairly high doses of one agent are usually necessary to achieve blood pressure control. We have heard that side effects are frequently dose-dependent. There are also increased dose-dependent metabolic side effects with some drugs and oftentimes increased cost.

The speakers in this symposium have presented data on the advantages of lower-dose combination therapy with two different classes of drugs. The response rate is increased to about 75% to 80% and side effects are lower than with moderate to large doses of single agents. Blood pressure control is achieved in a shorter period of time, patients require fewer clinic visits to achieve blood pressure control, and the cost may be less with some of the lower dose combinations than with some of the most commonly used monotherapies.

It would appear from some of the data presented by Dr. Frishman that we can achieve many of the objectives of ideal therapy with a new β-blocker/diuretic combination. We are at a crossroads and should ask ourselves: Is it always correct to use monotherapy as initial treatment or should we initiate therapy in many cases with low-dose combinations?

QUESTIONS AND ANSWERS

Perhaps I could start off by asking Dr. Abernethy a question. Do you decrease the duration of efficacy when you reduce the doses of the components of combinations?

Dr. Abernethy: Duration of action appears to be class-specific. There is a dissociation. For example, there is not a good relationship between drug concentration and antihypertensive effect with thiazide diuretics. If one assumed that one needed a long half-life thiazide-type diuretic for optimal antihypertensive effect, we’d always use chlorthalidone, but hydrochlorothiazide, which has a much shorter half-life, appears to have an equally effective antihypertensive effect. The same could be said of β-blockers. With the calcium antagonists, the antihypertensive effect is lost if doses are reduced or the type of drug used has a short duration of action. The same is generally true...
for the angiotensin converting enzyme (ACE) inhibitors and the α-blockers.

Dr. Moser: May I add something? In the case of ACE inhibitors, many of them are only effective for 8 to 12 h; when you add a small dose of a diuretic, duration of action is increased to 18 to 24 h.

Dr. Neutel: That’s true.

A question for Dr. Gifford: Would you treat a patient with heart failure with a blood pressure of 90/60 mm Hg with an ACE inhibitor?

Dr. Gifford: Very cautiously. I still think that it’s worthwhile trying to give a small dose of an ACE inhibitor, but you have to be careful. A further decrease in blood pressure may adversely affect renal function.

Dr. Moser: It’s of interest, Ray, that in the heart failure trials you reviewed most of the patients were already on a diuretic and digoxin before the ACE was added. There must not have been too many people who had a severe drop in their blood pressure.

Dr. Gifford: In fact, relative hypotension is not a contraindication to ACE inhibitor use.

Dr. Abernethy: Yes. I’d like to stress the importance of starting with a very small dose of an ACE inhibitor (6.5 mg of captopril, for example).

Dr. Neutel: Dr. Gifford, what should we use for patients with azotemia in place of ACE inhibitors?

Dr. Gifford: I would be very cautious about using an ACE inhibitor for a patient in heart failure or diabetic nephropathy with a creatinine level > 3.0 mg/dL. Other antihypertensive drugs—loop diuretics or an α-β-blocker—are probably better choices.

Dr. Neutel: Dr. Moser, can we use losartan as a substitute for ACE inhibitors in patients with congestive heart failure who have developed a cough?

Dr. Moser: We have some data on that. In short-term studies (up to about 3 months duration), it appears that losartan produces beneficial effects on both the hemodynamic and neurohormonal factors in congestive heart failure. Losartan does not cause a cough. However, it may not be as potent an antihypertensive drug as the ACE inhibitors, probably because its action does not result in an increase in bradykinin. My guess is that it can be used as a substitute in congestive heart failure.

Dr. Neutel: Studies are being done now with some of the newer angiotensin II antagonists in patients with heart failure. That data will probably be available within a reasonably short time.

What about the use of ACE inhibitors in patients with type I and type II diabetes mellitus with nephropathy?

Dr. Gifford: There is little doubt that their use is beneficial in type I diabetes mellitus with nephropathy. We do not have similar studies for type II diabetes mellitus. There are some data on prevention of nephropathy with an ACE inhibitor, but these are studies in normotensives and have not been published.

Dr. Moser: Although the ACE inhibitors have a special effect in nephropathy, it is important to reemphasize that in the studies that established this, more than three-quarters of the hypertensive patients required diuretics and β-blockers to lower the blood pressure to goal levels. In other words, several medications are necessary in the majority of hypertensive diabetics to reduce blood pressure to normal levels.

Dr. Gifford: Yes, that’s true. And we just don’t have the answer in type II diabetics yet. However, I do use ACE inhibitors in these patients if they have proteinuria and slight creatinine elevations.

Dr. Neutel: Yes, our data on side effects included sexual dysfunctions—i.e., libido and potency in men—and there were no significant changes in the patients treated with the low-dose combination compared to placebo. There have been some recent data regarding the effect on libido of women treated with higher doses of antihypertensive drugs. We tend to forget about this. This should be tracked carefully and may not be seen with lower doses.

Dr. Gifford: There were actually no sexual dysfunction complaints in the clinical trials with the low-dose β-blocker/diuretic combination.

Dr. Neutel: Yes, our data on side effects included sexual dysfunctions—i.e., libido and potency in men—and there were no significant changes in the patients treated with the low-dose combination compared to placebo.

At a recent symposium a neurologist noted that we should not pay any attention to diastolic blood pressure; most of the problems relate to systolic blood pressure. Dr. Moser, what are your comments about that?
**Dr. Moser:** It is quite clear from epidemiologic studies that an elevated systolic pressure is a more accurate predictor of risk for cardiovascular events than diastolic pressures. I would not, however, ignore elevated diastolic blood pressures.

**Dr. Neutel:** Is that what we’re going to see in JNC VI?

**Dr. Moser:** Well, you saw it in JNC V. There was an emphasis, really for the first time, on defining hypertension not by diastolic pressures alone but also by levels of systolic pressures. The FDA (US Food and Drug Administration), traditionally, has used a reduction in diastolic blood pressure compared to placebo as the criterion for drug efficacy, but my guess is that in the next several years the FDA will redefine efficacy to include a reduction in systolic blood pressure.

**Dr. Neutel:** This is an interesting question. In the data that Dr. Frishman showed comparing the ACE inhibitor enalapril with the long-acting calcium channel blocker amlodipine and the low-dose bisoprolol/HCTZ combination, it suggested a decreased quality of life with enalapril. The question is, don’t we normally see an improvement in quality of life with ACE inhibitors and how can you explain this?

**Dr. Frishman:** That’s what was seen in the study. The point to be made is that quality of life wasn’t adversely affected by the low-dose diuretic/β-blocker combination. In some of the early quality-of-life studies a high-dose β-blocker was used and in this comparison the ACE inhibitor came out quite well.

**Dr. Moser:** Can we add the fact that there are other large-scale, double-blind, placebo-controlled studies—for example, the Treatment of Mild Hypertension Study (TOHMS) and the V.A. study—that also showed no difference in quality of life improvement among different drugs. In the TOMHS study, the two drugs that improved quality of life more than the others were diuretics and β-blockers. This finding may come as a surprise to many people.

**Dr. Neutel:** Ray, is JNC VI prepared to say that low-dose combinations should be used as first-line treatment?

**Dr. Gifford:** I have no idea. I kind of think that they may suggest this approach as a reasonable alternative, but I don’t know.

**Dr. Neutel:** I personally think that we have to move in that direction. Dr. Abernethy, are you aware of any calcium channel blockers or ACE inhibitors that are being developed in low-dose combination with a diuretic?

**Dr. Abernethy:** I think that would depend on what you define as “low dose.” I don’t think there are any being developed in the 6.25 mg range (the dosage in the bisoprolol/HCTZ combination).

**Dr. Frishman:** One of the issues with a low dose of an ACE inhibitor is that cough is not a dose-dependent side effect. It can occur at doses of 1 mg of these agents. Side effects of many of the other drugs are dose-dependent, so that small doses of a diuretic produce very few symptomatic or metabolic side effects.

**Dr. Neutel:** One last question—Dr. Moser, should we limit the use of calcium channel blockers in our patients?

**Dr. Moser:** The answer is yes for the short-acting dihydropyridines; possibly yes for short-acting diltiazem and verapamil. We don’t know about the long-term effects of the longer-acting agents. Initial reports of excessive bleeding or an increase in malignancies with some of the calcium channel blockers are disturbing. We obviously need more data. We know that the calcium channel blockers are effective and well-tolerated by most people, but the data on cardioprotection or vascular protection have been disappointing to date.

**Dr. Gifford:** I agree. I think that we should not be using short-acting calcium antagonists, especially nifedipine. I don’t like using short-acting drugs of any type because you have to give them multiple times a day. I think if we’re going to use calcium antagonists, we should use the long-acting ones, whether they be the dihydropyridines or the long-acting forms of verapamil and diltiazem.

**Dr. Neutel:** Final comments?

**Dr. Abernethy:** I’d simply say that I think JNC V offers excellent instruction as to the approach to treatment, even though those guidelines were formulated well before the onset of the calcium blocker controversy. It was almost as if the committee were looking at a crystal ball when they made their recommendations about β-blockers and diuretics being used as preferred initial therapy.

**Dr. Frishman:** I agree.