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Newer considerations in the choice of an initial antihypertensive agent *

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Most physicians have a «favorite» antihypertensive medication, used perhaps because of the confidence that comes with familiarity. Aside from familiarity, however, how should a physician choose the initial medication(s) for a given patient? One of the reasons why the choice of the initial antihypertensive agent is important is because it will often be taken for the longest time. The principal factors that we consider are listed in Table 1 and discussed below.

1. Antihypertensive Efficacy

Despite extravagant claims made by the proponents of varying classes of antihypertensive agents, it must be emphasized that, with few exceptions, most of the available medications, when used appropriately, are approximately similar in their antihypertensive efficacy.

2. Safety

In light of the approximately equivalent antihypertensive efficacy and the wide spectrum of adverse effects that attend the use of the several classes of antihypertensive drugs, the clinician must consider such potential adverse effects as a major factor when choosing an antihypertensive agent. In this regard, the unanswered question of the true nature of the putative cardiovascular risk of the longterm administration of diuretics is an important area for future investigation.

3. Patient Acceptance

Although certain side-effects of drugs may not necessarily be a threat to the well-being of a patient, they may be sufficiently disturbing to interfere with drug acceptance and hence diminish compliance. Examples include impotence with the use of guanethidine or somnolence and decreased mental activity noted commonly with administration of several of the sympatholytic agents.

4. Cost

All too frequently the physician prescribes a specific drug without bothering to determine if another agent within the same class and with similar properties may have a distinct cost advantage to the patient. A considerable cost differential may exist for medications that might be interchangeable for a given patient.

5. Number of doses per day

Although compliance is by no means assured by a medication that can be taken once daily, most patients prefer the simplest regimen, and this is an important factor in the choice of a drug. Fortunately, several antihypertensive medications can now be taken either once a day (e.g., the diuretic chlorthalidone, the betablocker atenolol, the converting enzyme inhibitor enalapril) or twice a day (numerous agents, including the sympatholytic drugs clonidine and guanabenz, several beta-blockers, and the vasodilator hydralazine).

6. Need for laboratory follow-up

A consideration that is often overlooked in choosing a medication is the requirement for laboratory follow-up. For instance, hypokalemia need not be sought when using inhibitors of the

Table I. Factors in the choice of an antihypertensive drug

1. Antihypertensive effects
2. Safety
3. Patient acceptance
4. Cost
5. Numbers of doses per day
6. Need for laboratory follow-up
7. Mechanism of action
8. Potential interaction with other drugs
9. Additional salutary effects

Table II. Use of antihypertensive drugs in patients with underlying problems

Symptom or conditions	Drugs tending to ameliorate the problem	Drugs tending to exacerbate (or confound) the problem
Anxiety	Propranolol Reserpine Clonidine Methyldopa Guanabenz	Pargyline
Insomnia	Reserpine Clonidine Methyldopa Guanabenz	Beta-blockers Pargyline
Headache	Propranolol Reserpine Clonidine Methyldopa	Hydralazine Minoxidil Prazosin
Palpitations	Beta-blockers Reserpine Clonidine Methyldopa Guanabenz Calcium-entry blockers	Pargyline
Functional diarrhea	Clonidine Guanabenz	Reserpine Guanethidine
Diabetes		Diuretics Beta-blockers
Gout		Diuretics
Hyperkalemia		Converting enzyme inhibitors Beta-blockers Potassium-sparing diuretics
Liver disease		Methyldopa
Edema	Calcium-entry blocker and ACE inhibitors	Hydralazine, Minoxidil

sympathetic nervous system. Similarly, the plasma lipid profile ned not be determined routinely when using prazosin. Patients receiving diuretics, therefore, usually require more frequent laboratory determinations, at least during the first year of therapy. Such a consideration may influence patient acceptance and compliance, since the cost of laboratory examinations may nullify, at least in part, the cost advantage of a certain class of drugs.

7. Mechanism of action

The availability of numerous antihypertensive agents means that the clinician has access to medications that act by differing mechanisms. The physician can take advantage of these differences by selecting antihypertensive agents to meet a specific treatment goal. As an example, in a young patient with systolic hypertension related to a hyperadrenergic state, one might select a beta-blocker whose primary mode of action is to lower the heart rate and thus cardiac output. Conversely, in an elderly patient with essential hypertension, one might wish to take advantage of the recently discovered efficacy of calcium channel blockers in such patients, or use a converting enzyme inhibitor in a patient with high renin hypertension.

8. Potential interaction with other drugs

Pharmacologic interactions are an important consideration in the selection of an antihypertensive agent, whether for the initiation of therapy or when adding an additional agent. As a example, if a patient requires a tricyclic antidepressant, one should avoid the use of guanethidine, methyldopa, or clonidine as the antihypertensive agent since blood pressure lowering efficacy of these agents may be blunted by the antidepressant.

9. Additional salutary effects

A final consideration in the selection of an antihypertensive drug is the additional salutary effects that may be afforded by such agents. For example, one may wish to select a beta-blocker as the initial antihypertensive drug in patients with myocardial infarction who may benefit from the cardioprotective effects of these agents. Another example is the disparate effects of beta-blockers on renal perfusion. Nadolol preserves RPF and GFR, whereas propranolol tends to decrease renal perfusion. Thus, in certain patients, the clinician might wish to favor those beta-blockers that maintain renal perfusion. Table 2 provides a compilation of antihypertensive agents that tend either to mitigate or exacerbate various underlying conditions.

THE CHOICE OF AN INITIAL ANTIHYPERTENSIVE DRUG

Using the above broad guidelines, one can rationally approach the initiation of pharmacological antihypertensive therapy. There is considerable controversy with regard to what the appropriate initial antihypertensive agent should be [1-11]. In spite of accruing data including those from the recently published British Medical Council Working Party report, there is certainly no consensus regarding this issue. Nevertheless, as an example, we would like to review those specific factors that should be considered by the clinician in deciding between the two groups of agents that are used most frequently in the United States, to initiate therapy, diuretics and beta-blockers [1].

1. With some exceptions related to age and race it is clear that both classes of drugs are efficacious in their antihypertensive effects in patients with essential hypertension. Initial suggestions for the superiority of beta-blockers over diuretics have not been substantiated [2].

2. Both beta-blockers and diuretics produce symptomatic and metabolic side-effects [5]. Although not inordinate with either class of agent, side-effects are probably more commonly noted with beta-blockers. Earlier claims that beta-blockers induce substantially fewer biochemical side effects have not been borne out [5, 6]. For example, although hypokalemia is not seen with beta-blockers, these agents tend to produce abnormalities of lipid an carbohydrate metabolism similar to those observed with diuretic administration [6, 7].

The recent attention focused on drug-induced adverse lipid effects warrants a detailed discussion of this topic. One of the new approaches to antihypertensive therapy is so-called comprehensive risk management. This term implies the attempt to reduce all of the coronary artery risk factors simultaneously (elevated blood pressure, smoking, obesity, sedentary life style, abnormal lipid profile, etc.). The advocates of this approach, who are becoming increasingly numerous and convincing, are very concerned that some classes of antihypertensive agents, particularly diuretics an beta-blockers, exert adverse effects on the lipid profile. This might explain, at least in part, why most studies have not shown a reduction in coronary artery disease events following antihypertensive therapy. Although as pointed out by Weinberger [7] it is not known whether the changes in lipids caused by some antihypertensive agents represent the same risk to patients as do spontaneous changes, it semms likely that they do.

3. Patient acceptance is good for both of these classes of agents. In the MRC study, the dropout of patients for suspected adverse reactions in men was very similar for diuretics versus beta-blockers. In women, the dropout for this reason was somewhat greater for beta-blockers [2].

4. Largely because of the need to check the serum potassium concentration periodically, particularly in patients at risk such as those with underlying organic heart disease, requirement for laboratory testing is greater with patients taking diuretics than for those taking beta-blockers. In light of the known propensity for diuretics to induce fluid and electrolyte abnormalities, serum electrolytes, uric acid, BUN, and creatinine should be determined periodically. In reality, a single automated determination is probably as cost effective as ordering fewer of these tests indiviually. Beta-blocker therapy mandates periodic tests as well. In this case, a chest x-ray to assess for increasing cardiomegaly and an ECG usually suffice. With both classes of agents, plasma lipid evaluations should be carried out both before and during therapy, since either type of medication may alter blood lipids in an unfavorable direction.

5. Certain diuretic agents and some beta-blockers can be prescribed once a day in order to reduce blood pressure. It should be emphasized that the available data indicate that most beta-blockers must

Table III. Factors influencing the choice of diuretics VS. Beta-blockers as step-1 agents

In favor of Diuretics	In favor of Beta-Blockers
Less expensive.	Particular efficacy in a young patient with systolic hypertension.
Fewer of certain side effects (e.g., little or no exercise intolerance no insomnia).	Another indication for beta blockers, such as recent myocardial infarction or migraine headaches.
Less immediately serious side-effects (e.g., congestive heart failure is not produced) *	Perhaps somewhat greater potency in certain patients.
Fewer absolute or relative contraindications (e.g., congestive heart failure heart block, marked peripheral vascular disease, and bronchospasm are not contraindications).	When diuretic-induced hypokalemia is a poblem.
Probably fewer drug interactions.	Somewhat lesser need for laboratory surveillance (e.g., hypokalemia is not produced).
Greather efficacy in an older patient (over 60 years)	
In general, a simpler regimen and titration procedure.	
Greater long-term experience, at least in the United States.	

* The question of the importance of chronic changes in blood lipids with either class of medication is unresolved.

be taken at least twice a day to obtain their cardioprotective effects.

6. Another consideration, which has received extensive publicity, is the cardioprotective effects of the beta-blocker agents. It is clear that beta-blockers reduce the risk of second myocardial infarction and sudden death in a patient with a recent myocardial infarction. There are no data available at present, however, demonstrating a primary protective effect (i.e. against an initial myocardial infarction).

7. Finally, a major consideration differentiating the two classes of agents is cost. Currently, in most Western countries today, beta-blockers are several times more expensive than the usual doses of most diuretics necessary to lower blood pressure to a similar degree.

Having weighed the factors that enter into a decision for prescribing an initial antihypertensive drug, it is apparent that one can prescribe either a diuretic or a beta-blocker in the majority of patients with essential hypertension. Diuretics should be used with greater caution in patients with overt diabetes or gout. On the other hand, beta-blockers should not be used in patients with atrial-ventricular conduction defects, obstructive lung disease, and overt congestive heart failure. After excluding the above contraindications, one is left with approximately 75 per cent of the essential hypertensive population who are amenable to either mode of therapy. Our own recommendation is to favor the use of beta-blockers in the young patient, especially if he or she has systolic hypertension and does not engage in vigorous physical exercise. We recommend diuretics as the drug in patients above the age of 55 and perhaps in black patients. Furthermore, one should lean toward the use of a beta-blocker in patients with a history of a recent myocardial infarction.

NONDIURETIC MONOTHERAPY FOR HYPERTENSION

Nondiuretic monotherapy (aside from that involving the use of beta-blockers) is a controversial topic in the field of antihypertensive management [12-19]. For the purpose of this discussion, we define monotherapy as the use of a single agent, other than a diuretic, for the therapy of hypertension. Of course, during premarketing trials, every antihypertensive agent must have been shown to lower the blood pressure to a greater degree than a placebo. This does not imply, however, that the medication is suitable for long-term monotherapy. For example, when hydralazine is employed by itself,

Table IV. Antihypertensive agents whose use for monotheraphy has been suggested

1. Beta-blockers.
2. Combined alpha-beta blockers (e.g., labetalol).
3. Nifedipine, diltiazem, verapamil.
4. Captopril and enalapril.
5. Prazosin.
6. Clonidine and guanabenz.
7. Methyldopa.

Table V. Purported desiderable features of monotherapy for hypertension

1. Simplicity.
2. Increased potency.
3. Fewer metabolic side effects.
4. Improved compliance.
5. Ease of adding additional agents if necessary, particularly a diuretic.
6. Additional therapeutic benefits, such as relief of angina by beta-blockers or calcium antagonists.

Table VI. Potential disadvantages of monotherapy for hypertension

1. Step-care (diuretic or in some cases beta-blocker first [1]) is still the «official line» (1).
2. Loss of additive effect of multiple agents.
3. Limited number of proven appropriate agents.
4. Insufficient potency for many patients, even those with mild hypertension.
5. Some agents are relatively expensive.
6. Some agents require multiple doses.
7. Loss of counterbalancing of certain side-effects.
8. Possibility of tolerance or pseudotolerance.
9. Greater incidence of postural or exercise-induced hypotension.
10. Need for higher dose of agents, which increases the time for titration, the chance of side effects, and the cost.
11. Withdrawal syndromes may be more problematic than with diuretics.
12. More of a problem if unexpected surgery is necessary.

the antihypertensive efficacy is short-lived because of the blood pressure-elevating influences of increases in cardiac output and fluid retention. Of interest, preliminary evidence suggests that sodium retention is not a concomitant of chronic monotherapy with clonidine (at least using relatively low dosages), or guanabenz, nor does it appear to occur with the converting enzyme inhibitors or calcium channel blockers.

A list of several of the medications that have been suggested for this approach is shown in Table 4. Because monotherapy has been already discussed with respect to beta-blockers (regarding the question of diuretics versus beta-blockers), we will not include that specific aspect herein.

One reason for the controversy attending the subject of nondiuretic monotherapy is the relative meagerness of specific data in the literature (except regarding beta-blockers). Our discussion, therefore, will be in general terms.

The potential advantages of monotherapy are shown in Table 5. They include simplicity, fewer metabolic side effects (in comparison to diuretics), provision of additional therpaeutic benefits (such as relief of angina), and perhaps, in some cases, greater potency. On the other hand, there are several potential disadvantages (Table 6), which include the above-mentioned possibility of tolerance or pseudotolerance, greater incidence of postural or exercise-induced hypotension, the more complicated titration process, and the risk of a withdrawal syndrome. In this regard, it appears that, in general, the use of low dosages of the converting enzyme inhibitors and certain of the calcium antagonists is associated with quite a low incidence of side-effects. The findings of recent studies also indicate that these two classes of a gents (as is the case with prazosin, labetalol, and probably pindolol) do not produce perturbations of lipids or glucoregulatory hormones. Finally, two important disadvantages of monotherapy are a greater cost to the patient and the fact that for complete blood pressure control relatively large doses will often be required, even in patients with mild hypertension. Unfortunately, this latter consideration augments not only the cost but the chance of undesirable, occasionally limiting side effects.

At this juncture, what should be the viewpoint of the clinician, who may be bombarded with promotional material regarding the value of monotherapy with this or that antihypertensive medication? We recommend an open-minde approach, because nondiuretic monotherapy will frequently constitute excellent therapy in many patients. As we have emphasized, this often appears to be the case with beta-blockers and may prove to be the case, at least in ceratin patients, with the converting enzyme inhibitors and calcium channel blockers. Furthermore, if a patient is begun on monotherapy with inadequate control of the blood pressure, a diuretic can certainly be added easily enough, with a final result not necessarily much different from that of starting with the diuretic first. In general, we believe that more information is needed (especially long-term efficacy studies), before nondiuretic monotherapy with all of the agents listed in Table 6 (other than with beta-blockers) can be recommended for routine application.

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