Section II: Reviews

Antihypertensive Drugs In Aircrew

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Chronic diseases are relatively rare in the military aviator population, but essential hypertension is a distinct exception. Estimates of prevalence vary considerably, in part due to the typical lability of early hypertension in the young to middle-aged, predominantly Caucasian population characteristic of NATO air forces. Suffice it to say that, for most services, antihypertensive drugs represent some of the most common, if not the commonest, waivers for chronic medication use in aviation personnel.

OVERVIEW

After a century of research into the mechanisms of essential hypertension, understanding the pathogenesis of this disorder seems as elusive as ever. Undoubtedly, much of the reason for this is that even primary hypertension is a warning manifestation of one of a number of underlying disorders, none of which is well understood.[1] While there is no doubt that treatment of hypertension is associated with improved morbidity and mortality, we are nonetheless treating a complication of another disorder. Furthermore, the heterogeneity of the underlying disorders probably explains much of the variability in response to drug therapy.

With the caution that our understanding of the pathogenetic mechanisms of hypertension is rudimentary at best, two major "types" of essential hypertension are generally recognized. One is characterized by suppressed renin activity and a sensitivity to dietary sodium, the other by high renin activity and a lack of response to sodium intake. Generally, most hypertensives of African descent, and the majority of elderly hypertensives, appear to fit into the "salt-sensitive" category, whereas young to middle-aged Caucasian hypertensives are more often "salt-resistant," with high circulating renin levels. In salt-sensitive hypertension, the defect appears to be an inability to excrete the daily intake of sodium, until mean arterial pressure rises to a level that forces a pressure natriuresis.[2] The relative deficiency in natriuresis may be due to a renal defect in handling sodium, as data from transplant studies would suggest; [3,4] alternatively, it may be due to subtle abnormalities in the sympathetic nervous system or renin-angiotensin system. Salt-resistant hypertension has been postulated to be neurogenic in origin. Evidence in animals for sympathetic activation eventually inducing chronic blood pressure elevation is fairly clear; evidence is less conclusive in humans, but direct recording of sympathetic nerve traffic in the peroneal and brachial nerves has documented increased activity in borderline hypertensive subjects, and even greater activity in moderate and severe hypertensives.[5] While it must be stressed that such a classification is almost certainly simplistic, it does serve to provide some theoretical basis for observed differences in response to drug therapy.

It is beyond the scope of this discussion to delve into secondary hypertension. Even when workups for underlying renal or endocrine diseases are limited to those hypertensives who present with severe blood pressure elevations of recent onset, the yield of such workups is low. However, one diagnosis that should be considered is obstructive sleep apnea,[6] because it is significantly more common than other causes of secondary hypertension, and because sleep apnea is associated with its own aeromedical risks. Fortunately, this disorder can usually be ruled out rather easily, by questioning the bed partner about snoring and observed apneic episodes.

The major goal of antihypertensive therapy is to lessen the increased morbidity and mortality associated with hypertension, while avoiding

deleterious side effects. Such side effects are usually annoying, and occasionally morbid, in the civilian population, but could lead directly to early mortality in the aviation environment. It is important to note that any drug which reduces blood pressure is usually presumed to reduce the morbidity and mortality of hypertension, but for most classes of drugs this has yet to be shown.[7] Of the two cardiovascular events most likely to result from uncontrolled hypertension, a meta-analysis of primary prevention trials has shown that the increased risk of stroke could be negated by control of the blood pressure, while the increased risk of myocardial infarction was reduced by approximately half.[8]

The initial period of treatment with antihypertensive medication is marked by compensatory physiologic changes, such as resetting of baroreceptor reflexes and cerebral autoregulation. The clinical corollary, common to all antihypertensive drugs, is the fatigue that is often seen after the patient begins treatment. Because of these physiologic alterations, it is particularly important that the aviator starting an antihypertensive drug undergo an adequate ground trial before resuming aviation duties.

ANTIHYPERTENSIVE MEDICATIONS

Agents useful in the chronic treatment of hypertension may be classified into one of nine categories.[9] They are in no particular order: 1) diuretics, 2) beta-blockers, 3) angiotensin-converting enzyme inhibitors, 4) angiotensin receptor antagonists, 5) calcium channel blockers, 6) alpha-adrenergic blockers, 7) central alpha-adrenergic agonists, 8) direct vasodilators, and 9) peripheral adrenergic neuron antagonists.

Diuretics

Although over 40 years have elapsed since the synthesis of chlorothiazide, diuretics continue to be one of the more useful drugs for hypertension and, with the exception of beta-blockers, are the only class of drugs that have been proven to reduce hypertensive mortality. There have been scattered data suggesting a vasodilatory effect of thiazide diuretics, perhaps mediated through increased nitric oxide production or decreased sympathetic outflow.[10] However, such evidence is weak, and most research suggests that the hypertensive effect of diuretics is due, directly or indirectly, to natriuresis.[11] The initial response to thiazide diuretics is a 10-15% reduction in plasma volume, accompanied by a fall in cardiac output and a rise in peripheral vascular resistance. With chronic administration, however, blood volume and cardiac output return nearly to pretreatment levels, while total peripheral resistance declines.[12] This correlates well with the purported mechanism of salt-sensitive hypertension; when the relative defect in sodium clearance has been overcome by a drug-induced natriuresis, pressure natriuresis is no longer required, and cardiovascular homeostasis reverts to a more normal milieu.

Such a mechanism of action is obviously attractive in an aviation environment, since cardiac function and vascular reflexes are preserved, and indeed diuretics are an excellent therapeutic choice in the aviator – when they work. Although diuretic efficacy is not entirely limited to the low-renin hypertensive, these drugs tend to be most efficacious as monotherapy in those of African descent, and in the elderly. Since the typical military aviator in NATO is likely to be a Caucasian in the third to fifth decade of life, diuretics alone frequently prove to be insufficient to reduce blood pressure. On the other hand, they are highly effective drugs for combination therapy, particularly in conjunction with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and beta-blockers.

Adverse effects of diuretics include impotence, with an incidence perhaps as high as 31%.[13] Data on psychomotor performance is limited, but on the whole there appears to be no performance decrement.[14] The adverse effects from diuretics that have received the most attention have been metabolic derangements. Thiazides commonly cause potassium loss, usually reducing total body potassium by 5%.[15] They also induce a mild resistance to insulin, which in one study resulted in glucose intolerance in 3% of subjects.[16] Much recent attention has been given to the lipid effects of diuretics, as a possible explanation for the less-than-expected reduction in coronary events seen in primary hypertension trials. LDL levels typically increase by 5-15% in the first 12 weeks of diuretic therapy, with a return to baseline by one year. However, in the corresponding placebo groups, LDL fell by one year, with values 2-3% lower than the treatment group, and in the active treatment group cessation of diuretic therapy resulted in a further fall in lipid levels.[17] While this effect on lipids may contribute to the relative

lack of efficacy in preventing coronary events, it is unlikely to be a sufficient explanation. Since atherogenesis is a multifactorial disease, and hypertension is inextricably linked with other conditions, such as hyperlipidemia and diabetes, which also predispose to atherogenesis, it is probably naive to expect blood pressure reduction alone to abolish the associated risk of coronary disease. The metabolic effects of diuretics, with the possible exception of lipid derangements, are dose-related[17,18]; on the other hand, antihypertensive efficacy appears to be equivalent between higher and lower doses of diuretics. Three of four recent trials using low dose diuretics (e.g., 12.5-25 mg/day of hydrochlorothiazide), along with potassium sparing agents, showed much more significant reduction in deaths in the treatment group when compared with earlier high-dose trials.[19,20,21,22] Since these trials involved elderly patients, there was more opportunity to reduce mortality, and furthermore a given dose of drug was likely to be equivalent to a somewhat higher dose in young patients, given the slower drug clearance typical of the elderly. Nonetheless, it appears that optimal therapy of hypertension with diuretics consists of lower doses than have been used in the past. If the aviator fails to respond to 25 mg, or at most 50 mg, of hydrochlorothiazide, or an equivalent dosage of other diuretics, there is little point in using a higher dose.

Beta-blockers

This is a complex class of drugs, differing in selectivity, partial agonism, and the presence or absence of associated alpha-adrenergic blockade. Propranolol, timolol, and nadolol are nonselective beta-blockers, while metoprolol, atenolol, betaxolol, and bisoprolol are more selective for cardiac ($beta_1$) adrenergic receptors, at least in low doses. Pindolol, penbutolol, carteolol, and acebutolol have partial agonist activity, also known as intrinsic sympathomimetic activity (ISA); the first three are nonselective for beta receptors, while acebutolol displays $beta_1$ selectivity at low doses. Labetalol is a nonselective beta-blocker with ISA, but also blocks alpha-adrenergic receptors. Carvedilol is a nonselective beta-blocker which also blocks alpha receptors, although it displays no ISA; it has been promoted more for treatment of congestive heart failure than for hypertension. These drugs also differ in relative solubility, with propranolol, metoprolol, and timolol being more lipophilic, and atenolol, nadolol, and bisoprolol more hydrophilic.

The mechanism of blood pressure lowering from beta-blockade is not well understood, but has been attributed to negative inotropic and chronotropic effects resulting in a decreased cardiac output, as well as to inhibition of renin release. These agents work relatively well in hypertensives with high renin levels, particularly young, non-obese Caucasians. Beta-blockers are the only class of drugs besides diuretics demonstrated to decrease the morbidity of hypertension, on a level probably comparable with diuretics.[7]

Adverse effects due to beta-blockers are highly significant, and while some, such as precipitation or worsening of diabetes, heart failure, and claudication, are unlikely in the aviator population, other side effects are common in this age group. Much of the rationale for developing $beta_1$-selective agents, and beta-blockers with ISA, had been to avoid some of the distressing side effects associated with this class of drugs, but results have been mixed. $Beta_1$-selective blockers do improve the side effect profile, but precipitation of bronchospasm is a persistent concern even with low doses of these agents. Fatigue and diminished exercise tolerance are common complaints, which do not appear to be improved by agents displaying partial agonism.[23] Indeed, with the exception of metabolic profile, beta-blockers with ISA have yet to show any convincing advantage.[24] Central nervous system effects from beta-blockers are common, and include sleep disturbance and diminished concentration. Hydrophilic beta-blockers such as atenolol appear to have a lower risk of CNS effects, but results of objective testing have been contradictory.[14] Curiously, in primary and secondary prevention trials, lipophilic beta-blockers (propranolol, metoprolol, and timolol) have resulted in reduced complications, while hydrophilic beta-blockers (atenolol, sotalol) have not.[25] However, it seems premature to make any generalization at this point. Metabolic effects of most beta-blockers include lipid disturbance, with an increase in triglycerides and a decrease in HDL, although agents with significant ISA are lipid-neutral.[18] All beta-blockers, except the newer vasodilating agents such as carvedilol, worsen insulin resistance.[26] Impotence is a common complaint with this class of drugs.

Beta-blockers work well in combination with diuretics and with calcium channel blockers, although negative inotropy may be additive with the latter class of drugs. The combination of beta-blockers with ACE inhibitors or with angiotensin receptor antagonists has not proven to be particularly effective.[27]

Angiotensin-Converting Enzyme Inhibitors

The renin-angiotensin system is tightly linked to blood pressure control and volume status. Reduced sodium delivery or decreased perfusion to the kidney, as well as sympathetic activation, all stimulate renin secretion from the juxtaglomerular apparatus. Renin cleaves the inactive decapeptide angiotensin I from angiotensinogen. Angiotensin-converting enzyme (ACE) then cleaves the C-terminal dipeptide from angiotensin I, to form the vasoactive angiotensin II. ACE serves another role as the enzyme responsible for degrading bradykinin, hence its alternative name of kininase II. Angiotensin II, in addition to being a potent direct vasoconstrictor, also promotes aldosterone secretion and thus sodium retention, stimulates the sympathetic nervous system, and promotes cellular migration, proliferation, and hypertrophy, an effect documented in both vascular smooth muscle and in myocardium.[28]

Angiotensin II levels are nearly always within a range that exerts a direct effect on arterial pressure, both in normotensives and hypertensives, such that infusion of an ACE inhibitor causes an immediate reduction in blood pressure proportional to the prior level of angiotensin II.[29] However, with chronic administration of the drug a further fall in blood pressure often occurs, and peak hypotensive effects don't correspond well to peak serum concentration or to peak ACE inhibition.[30] Also, patients with normal or even low renin levels may respond to ACE inhibitors. As a rule, however, younger Caucasians usually respond well to ACE inhibitors, while black or elderly patients respond less well, at least to monotherapy. On the other hand, converting a low-renin to a high-renin hypertensive by diuresis or salt restriction often renders ACE inhibitors very effective in treating otherwise resistant individuals.

ACE inhibitors are divided into three groups based on the ligand interacting with the enzyme, either a sulfhydryl moiety in the case of captopril, a phosphinyl moiety in the case of fosinopril, or a carboxyl moiety in most of the remaining agents. Of the commonly available drugs, captopril and lisinopril are active drugs, while the remainder are administered as esterified prodrugs to enhance gastrointestinal absorption. With the exception of the sulfhydryl moiety, which may be responsible for the neutropenia and certain other side effects seen with high doses of captopril, the ACE inhibitors are more similar than different.

With the exception of cough, adverse effects are uncommon, explaining why ACE inhibitor therapy typically scores well on quality of life studies. Cough is the most common adverse effect, occurring in up to 20% overall; the risk is higher in women than in men, and in nonsmokers than in smokers. Probably because of its unusual nature as a drug side effect, cough was not even described in initial clinical trials. Presumed to be due to elevated levels of bradykinin, cough is most often seen within the first month, and is usually cross-reactive with other drugs in the class.[31] Angioedema, a potentially life-threatening effect, occurs in 0.1-0.2% of cases overall, with a higher risk in those of African descent. Although it usually appears within the first week of therapy, in some cases it has occurred after several years.[32] While originally assumed to also be due to bradykinin elevation, no conclusive evidence for this has been found, and at least two cases have occurred with angiotensin receptor antagonists, agents which do not cause elevated bradykinin levels. Neutropenia, an uncommon manifestation, was largely confined to early trials using high doses of captopril. Fetal toxicity is well described both in animals and humans. It is distinctive in that the period of known risk is the second and third trimesters; ACE inhibitors do not appear to be teratogenic in the first trimester.[33] Nonetheless, the female aviator desiring to become pregnant should, if at all possible, change to another antihypertensive drug prior to conception. Metabolically, ACE inhibitors are lipid-neutral, and may even improve insulin sensitivity.[18]

In normal volunteers, ACE inhibitors have either shown no change or an improvement in psychomotor testing. In hypertensive subjects, results of cognitive testing are limited. Captopril appeared to result in better cognitive scores than did methyldopa or propranolol, but in another study cilazapril, atenolol, and nifedipine appeared to be equivalent.[14] The acceleration effects of captopril have been measured in normal volunteers, with a

decrease in G-tolerance of 0.35 +Gz during gradual onset run.[34] However, G-tolerance was measured after only four days of captopril treatment in normotensive patients, so the significance of this observation is uncertain.

Angiotensin Receptor Antagonists

In addition to angiotensin converting enzyme inhibition, the renin-angiotensin axis may also be pharmacologically altered by blocking the angiotensin II receptor. Angiotensin receptor antagonists show efficacy which is comparable to ACE inhibitors, but avoid some of the side effects such as cough.[35] Except for uricosuria with losartan, they appear to have neutral metabolic effects as well.[36] These may well prove to be excellent antihypertensive agents for aviation purposes, but the available information is incomplete at this time.

Calcium Channel Blockers

Also known as calcium antagonists, this is a diverse group of drugs, originally represented by verapamil, a phenylalkylamine, diltiazem, a benzothiazepine, and nifedipine, a dihydropyridine. Nearly all the agents developed since then, such as nicardipine, nimodipine, nitrendipine, nisoldipine, amlodipine, felodipine, and isradipine, are dihydropyridine derivatives. A fourth class, benzimidazolyl tetralines, was introduced in the form of mibefradil, but this drug was recently withdrawn in all countries because significant inhibition of the cytochrome P-450 system resulted in rhabdomyolysis and *torsades de pointes* when mibefradil was taken in conjunction with a number of other drugs.[37]

Given the lack of structural homology between different classes of calcium channel blockers, the similarities between the classes are perhaps more surprising than the differences. All these agents act through inhibiting the movement of calcium into cells, by blocking voltage-dependent channels. All but mibefradil, a transient (T) channel blocker, inhibit the long-lasting (L) channels. Calcium is normally maintained in the extracellular space, with an extra- to intracellular gradient of over 10,000:1. Many cellular functions, notably smooth muscle contraction and hormone secretion, are regulated by small releases of calcium into the cytosol. Calcium channel blockers both reduce basal vascular tone, and blunt the usual response to pressor agonists like angiotensin II and vasopressin.[38]

As one might expect from a mode of action that involves a "final common pathway," calcium antagonists effectively reduce blood pressure in nearly all hypertensives regardless of race or age; they also reduce blood pressure in normotensives, albeit to a lesser extent. They are quite effective in combination with ACE inhibitors, but the combination of calcium channel blockers and diuretics seems relatively ineffective, perhaps due to the type of natriuresis induced by calcium antagonists.[38]

Although their effects on the peripheral vasculature are similar, the different classes of calcium channel blockers affect the heart differently, at least in vivo. Verapamil and diltiazem, as well as mibefradil, all decrease heart rate under rest and exercise conditions. They slow both the sinoatrial and atrioventricular nodes, an effect which is additive to that of beta-blockers. The dihydropyridines have no clinically evident effect on the cardiac conduction system, at least directly. However, the vasodilation induced by short-acting dihydropyridines results in sympathetic activation and tachycardia. This effect has been shown to be dependent on the rate of increase in plasma concentration of the drug.[39] All classes of calcium channel blockers vasodilate the coronary arteries, and all have negative inotropic effects, with verapamil reducing systolic function the most, and dihydropyridines the least.

The introduction of calcium channel blockers was greeted with considerable enthusiasm, since the combined effects of reduced myocardial oxygen demand and coronary vasodilation were considered to be ideal for reducing coronary mortality. However, with the exception of a single trial using verapamil, the results of approximately two dozen trials have been uniformly disappointing.[40] Whether the same will be true of hypertensive morbidity and mortality is unknown. The Shanghai Trial of Nifedipine in the Elderly showed a significant reduction in endpoints with the use of slow release nifedipine compared with a placebo, but it was neither blinded nor randomized.[41]

Adverse effects of calcium antagonists are limited, and rarely cause discontinuation. Ankle edema, a fairly common finding, is due to a direct effect on the microcirculation rather than fluid retention.[42] Data regarding cognitive effects has been limited to nifedipine. In a study of that drug in relatively young normotensive volunteers, no

effect was seen using a range of tests.[43] Two studies using nifedipine in elderly hypertensives have shown disparate results. In the first, memory recall and digit symbol substitution deteriorated when nifedipine was instituted, while atenolol showed no significant change.[44] In the second study, improvements were seen on several portions of a psychomotor test battery when either nifedipine or captopril was used.[45]

The purported adverse effect of greatest concern is the potential for increased coronary mortality with the use of calcium antagonists, a subject of hot debate in recent years. Beginning in 1995, three studies, two retrospective and one prospective, suggested an increased mortality associated with the use of short-acting calcium channel blockers.[46,47,48] Subsequent studies of patients receiving longer-acting calcium antagonists have not shown a similar increase in risk, although one of these studies did demonstrate an increased risk in those using short-acting calcium antagonists, when those were compared with beta-blockers.[49] As noted earlier, there is a physiologic rationale for these observations, since rapidly rising levels of nifedipine cause marked sympathetic activation, an effect not seen when levels are raised slowly. While this controversy has yet to be fully resolved, most authorities recommend that short-acting calcium antagonists be avoided for the treatment of hypertension, a recommendation that also makes sense with respect to patient compliance.

Given the direct relaxation of vascular tone induced by this class of drugs, there is certainly theoretic concern about the effect in G tolerance, but at the present time no data exist.

Alpha-adrenergic Blockers

This class of drugs, represented initially by prazosin, and more recently by doxazosin and terazosin, blocks alpha-$_1$ receptors in both arterioles and veins, reducing blood pressure acutely by about 15%.[50] They are additive to beta blockers, diuretics, and ACE inhibitors, but are not useful in combination with central alpha-adrenergic agonists. They display little reflex stimulation of cardiac output, probably because presynaptic alpha$_2$ receptors continue to inhibit norepinephrine release. Uniquely, they improve lipid levels, with a 10% decrease in the cholesterol/HDL ratio, and improve insulin sensitivity.[51] The tachyphylaxis seen with prazosin treatment of chronic heart failure does not appear to occur when the same drug is used to treat hypertension.

Unfortunately, the advantages of these drugs are largely outweighed by adverse effects. Because of the venodilatory action, these agents induce a greater reduction in standing than in supine blood pressure.[52] The postural syncope that proved to be such a problem with prazosin is less common with the newer agents, but it still occurs in nearly 2% of patients treated with doxazosin or terazosin. Approximately 20% of patients complain of orthostatic dizziness. Sedation has been reported in a variable but significant percentage of patients on prazosin. Such a profile of adverse effects makes these agents poor choices to treat the hypertensive aviator.

Central Alpha-adrenergic Agonists

Also known as alpha$_2$-adrenoceptor agonists, this is a fairly diverse class of drugs, represented by methyldopa, clonidine, guanabenz acetate, and guanfacine. The primary mode of action seems to be alpha$_2$ receptor stimulation in the brain stem, which leads to decreased sympathetic outflow. As drug dosage is raised, the antihypertensive effect is often reversed, perhaps due to peripheral alpha$_2$ stimulation.[53]

These agents show consistent efficacy regardless of race or age, and may be combined effectively with diuretics, and probably with ACE inhibitors and calcium channel blockers. They cause little or no change in cardiac output and, with the exception of methyldopa, they are neutral with respect to lipids and glucose. Unfortunately, disadvantages are highly significant, and include sedation, drowsiness, depression, and a readily measurable degradation of psychomotor performance.[14] Dry mouth is a common complaint. Withdrawal of the drug, especially in the case of clonidine, risks a rebound phenomenon characterized by elevated blood pressure, anxiety, and tachycardia. This syndrome is more severe with concomitant beta-blocker usage.[53] Like alpha blockers, these drugs appear to be poor choices to treat the hypertensive flyer.

Direct Vasodilators

Although in theory vasodilators should correct the underlying abnormality common to hypertension, they cause reflex activation of the sympathetic nervous system and the renin-angiotensin axis, rendering them nearly useless as monotherapy. Concomitant treatment with diuretics and even

beta-blockers is typically required. These agents act by entering the smooth muscle cell and causing direct vasodilation, and see their greatest utility in treating hypertensive emergencies. Only hydralazine and minoxidil are suitable for outpatient use. In addition to tachycardia and volume retention, hydralazine causes a lupus-like syndrome, the frequency of occurrence depending on dose and duration.[54] Minoxidil causes severe volume retention and hypertrichosis, and is generally reserved for severe refractory hypertension. These agents are not suitable for military aviation, and hypertension severe enough to require these drugs is probably incompatible with military aviation.

Peripheral Adrenergic Neuron Antagonists

Reserpine, guanethidine, and guanadrel are older drugs which are rarely used now in clinical practice. Reserpine causes significant sedation, while depression is common with higher doses. Guanethidine and guanadrel cause orthostatic and exertional hypotension, which is aggravated in a hot environment.[9] None of these drugs is compatible with the military aviation environment.

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