The renin-angiotensin system (RAS) plays a central role in the control of blood pressure, and in particular is felt to play a crucial role in neurogenic hypertension. The RAS appears to act through two mechanisms, affecting the acute control of blood pressure through the pressor action of angiotensin II, and the long-term regulation of cardiovascular remodeling through the growth factor properties of angiotensin II.

While all known actions of the RAS are mediated through angiotensin II alone, it is important to review the metabolic process leading to its production, since it is possible to intervene at several points along the pathway. Renin is released by the kidney in response to a number of stimuli, including decreased renal perfusion, circulating blood volume and/or sodium load to the kidney, and increased sympathetic nervous system activity. Renin cleaves four amino acids from angiotensinogen, a fourteen amino acid glycoprotein derived predominantly from the liver. The resulting decapeptide angiotensin I is converted to the octapeptide angiotensin II primarily by the action of angiotensin-converting enzyme (ACE), which circulates in the plasma. This is not a particularly specific system; angiotensin I can also be converted by other enzymes, such as cardiac chymase and tonin, while ACE itself plays another role as kininase, inactivating circulating bradykinin. Although the RAS has previously been viewed as a circulating neuroendocrine system, recent studies have shown evidence of angiotensin producing systems within tissues. Tissue renin-angiotensin systems appear to be responsible for angiotensin II-induced hypertrophy in myocardium and vascular smooth muscle. Furthermore, since angiotensin II, as an octapeptide, is unable to penetrate most of the blood-brain barrier, the majority of the angiotensin receptors in the central nervous system probably respond to locally generated angiotensin.

There are several points along the renin-angiotensin cascade which are susceptible to intervention. Renin release can be inhibited by the use of beta blockers. Inhibition of the second step, the cleavage of angiotensinogen by renin, would appear to be particularly attractive since it is rate-limiting, but compounds currently known to inhibit that reaction have low bioavailability and a short duration of action. The most widely used approach has been the inhibition of ACE. ACE inhibitors have been very successful antihypertensives because of efficacy at lowering blood pressure and favorable side effect profiles. While studies evaluating their efficacy in actually reducing hypertensive morbidity and mortality are only now being completed, they have clearly been effective in reducing morbidity and mortality in heart failure and diabetic nephropathy. Besides blocking the conversion of angiotensin I, ACE inhibitors also prevent the degradation of bradykinin and prostacyclin. It is not clear whether the latter effect is beneficial or not, since the resulting elevated levels of these vasodilators may be at least partially responsible for some of the clinical effects of ACE inhibitors. However, it is likely that elevated bradykinin levels are to blame for the dry cough that occurs in 5-10% of patients taking ACE inhibitors.

The fourth method of inhibiting the renin-angiotensin system consists of blockade of the angiotensin II receptor. In addition to avoiding interference with kinin metabolism, antagonizing the angiotensin II receptor is theoretically more effective than ACE inhibition, since other enzymes are capable of generating angiotensin II. The concept is not new; saralasin, an octapeptide analogue of angiotensin II, was first studied nearly three decades ago. However, saralasin proved useful only in research applications, since it could only be given by constant intravenous infusion, and showed partial agonist activity. It was the development of losartan potassium, an imidazole with good
enteral availability, a long duration of action, and no agonist activity, that allowed the first clinical application of angiotensin receptor antagonism.

**ANGIOTENSIN II RECEPTORS**

Two principal angiotensin receptors have been identified on the basis of binding studies, and have been labeled AT1 and AT2. All known cardiovascular effects of angiotensin II, including vasoconstriction, beta-adrenergic stimulation, and aldosterone release, appear to be mediated by the AT1 receptor, of which losartan is a specific inhibitor. While the function of the AT2 receptor is uncertain, it appears to inhibit angiogenesis, and is postulated to play a significant role in fetal development. In the adult, AT2 receptors are most widespread in the central nervous system. In addition, AT3 and AT4 receptors have been recently described, but have yet to be characterized. Losartan therapy results in a rise in renin and angiotensin II; although the effect of increased stimulation of AT2 receptors by elevated angiotensin II levels has been an area of concern, to date no deleterious effects have been identified.

**PHARMACOKINETICS OF LOSARTAN**

Losartan is readily absorbed, and undergoes rapid hepatic metabolism to an active metabolite, EXP-3174, via the cytochrome P-450 system. Absorption is not affected by food. Times to peak concentration are 1 hour for losartan, and 3.5 hours for the active metabolite. The peak effect on blood pressure occurs 6 hours after the dose. Mean elimination half-lives average 2.1 hours for losartan, and 6.3 hours for EXP-3174; at 24 hours after acute or chronic dosing, only the metabolite is still detectable in plasma. EXP-3174 is a non-competitive antagonist of the AT1 receptor, with a potency 10-40 times that of the parent compound. It is probably for this reason that 63-74% of the peak antihypertensive effect is maintained at the 24 hour trough. Blood pressure effects have been found to more closely parallel levels of the metabolite rather than of losartan. Fewer than 1% of subjects fail to metabolize losartan to EXP-3174; in those individuals, the AT1 receptor is blocked by losartan alone, and even though the half-life of the parent compound is prolonged in that situation, the drug appears to be less efficacious.

The pharmacokinetics of both losartan and its active metabolite are linear, and not affected by repetitive dosing. Although clearance is both by hepatic and renal mechanisms, only hepatic impairment appears to affect plasma half-life. In rats, losartan crossed the blood-brain barrier after a single intravenous dose of 3 mg/kg, but not after a single oral dose of 10 mg/kg or 3 consecutive daily doses of 3 mg/kg. However, chronically administered losartan does appear to cross into the CNS, since administering losartan in the drinking water modifies the dipsogenesis induced by angiotensin II.

**DRUG EFFECTS**

Experimentally and clinically, AT1 receptor blockers, in the presence of an activated renin-angiotensin system, decrease systemic vascular resistance without significantly affecting cardiac output or heart rate. The lack of reflex tachycardia may reflect the blockade of AT1 receptors on postganglionic sympathetic neurons, which decreases norepinephrine (noradrenaline) secretion. Wood et al. found that in normotensive, salt-replete animals, intravenous losartan had no effect, although the pressor response to angiotensin II was blocked, whereas in animals pretreated with furosemide, blood pressure was reduced. Results in normotensive humans have been similar. While up to 120 mg of losartan has little measurable effect in salt-replete individuals, the systemic pressor response to angiotensin II is blocked, from a threshold effect at 10-20 mg to a maximal effect at 80-120 mg. In normals who were salt-depleted by a low sodium diet plus furosemide, losartan induced a dose-related fall in systolic and diastolic blood pressure.

The response of the renin-angiotensin system to losartan in normals is mirrored by its effectiveness in hypertensive individuals. One randomized, double-blind, multicenter study evaluated 491 patients with mild to moderate essential hypertension on varying doses of losartan (10-150 mg) compared with placebo, extending over 8 weeks. Losartan 50 mg resulted in significant reductions of systolic and diastolic blood pressure at 24 hours after dosing. Maximal reduction occurred between 4 and 6 weeks, and was maintained throughout the study; approximately 70% of the maximal reduction had occurred by one week of therapy. Several studies have examined increasing the dose of losartan from 50 mg to 100 mg daily; there appears to be a small additional benefit. As one would suspect from studies in normals, and from similar studies with ACE inhibitors, the addition of hydrochlorothiazide enhances the antihypertensive efficacy of losartan.
Whether losartan will have a beneficial effect on left ventricular hypertrophy (LVH) similar to that seen with ACE inhibitors is still to be determined. In rats, losartan does reduce LVH, even at doses too low to control blood pressure. Losartan is natriuretic in the volume-depleted state, without altering glomerular filtration rate in normals or hypertensives. It is also uricosuric, and causes a modest decrease in serum uric acid concentrations. Interestingly, this effect does not appear to be mediated by the AT$_2$ receptor, since neither EXP-3174 nor other AT$_2$ antagonists such as irbesartan have exhibited this effect.

Plasma renin and angiotensin II levels rise with losartan therapy. In healthy subjects, losartan doses of 100 mg daily or higher result in increases of renin and angiotensin II up to ten times baseline. The rise in renin is exaggerated in the volume-depleted state. Although there has been concern that rebound hypertension would occur upon withdrawal from the drug, this has not been observed, perhaps because of the gradual decline of plasma levels of EXP-3174. It may also be due to the fact that, compared with normotensives, hypertensives have a diminished rise in renin activity when placed on losartan, due to less feedback inhibition in the untreated state. The presumed lack of effect of losartan on bradykinin metabolism is supported by physiologic data. In a study of human forearm blood flow, both 20 and 100 mg doses of losartan blocked reductions in blood flow associated with arterial infusions of angiotensin I and angiotensin II, while not affecting bradykinin–induced vasodilation. By comparison, enalapril in the same study inhibited the response to angiotensin I, did not affect the response to angiotensin II, and enhanced vasodilation from bradykinin.

SAFETY

General
In Phase II and Phase III trials, approximately 2900 subjects received losartan, about 2000 of those as a single drug, the rest in combination with a diuretic. Sixteen trials were double-blind, while four were open, with a duration of 8-12 weeks. Clinically, dizziness was the only side effect noted significantly more often with losartan that with placebo, occurring in 4.1% versus 2.4% respectively. Cough occurred in 3.1% of losartan-treated patients, compared with 2.6% of placebo-treated subjects. Laboratory adverse events occurred with equal frequency between the two groups. In long-term use, losartan has tended to cause a rise in serum potassium levels, although no patient needed to discontinue the drug due to hyperkalemia.

The lack of effect of losartan on cough frequency has been confirmed by two studies which evaluated patients who had previously experienced cough on ACE inhibitors. Both studies found that losartan was not associated with cough any more frequently than was hydrochlorothiazide, while both were associated with cough much less frequently than was lisinopril.

Post-marketing surveillance has uncovered a small number of serious complications. Those that have been confirmed by rechallenge include migraine, Henoch-Schönlein purpura, hepatitis, pancreatitis, and psychosis. Although bradykinin has been presumed to cause the angioedema that is occasionally seen with ACE inhibitors, cases of angioedema have already been associated with losartan. In the case reported by Sharma and Yium, the patient had had an earlier episode of angioedema shortly after receiving intravenous enalapril.

The fetotoxicity seen with ACE inhibitors appears to be shared by losartan. In animal studies, losartan appeared to have no effect on fetal development in the first half of gestation. However, when given in the last half of pregnancy, it was associated with serious fetal toxicity.

Specific Organ Systems
The central nervous system is of particular interest in angiotensin research. Angiotensin II is known to centrally stimulate drinking and salt appetite, and to modulate release of pituitary hormones. The CNS is heavily populated with angiotensin II receptors in the hypothalamus, circumventricular organs, and autonomic control centers of the medulla. In the mammalian brain, there is a strong association between angiotensin II immunoreactivity and catecholamine cell bodies and terminals. Angiotensin II appears to stimulate release of both norepinephrine and dopamine. Available studies of cognitive effects of losartan are sketchy. Losartan has been shown to reduce the performance impairment due to alcohol, while losartan alone appeared to be no different from control. In a preliminary report, Braszko noted that, in the rat, angiotensin II increased passive behavior recall seven-fold, and doubled the amount of time spent exploring new objects, effects that were abolished by losartan, and to a lesser extent by an AT$_2$ blocker. On the other hand, Shepherd et al,
studying rodents in two models of anxiety and two models of working memory, found no effect of losartan or an AT$_2$ blocker.\textsuperscript{30} There is essentially no data on other organ systems of interest to aviation. The significant increase in dizziness seen in Phase II and III trials likely represents the usual adjustment in cerebral perfusion that occurs when any hypertensive therapy is initiated; nonetheless, it should be noted that no information on vestibular testing is available. No data is available concerning ocular effects, or effects of losartan on the QT$_c$ interval. Although cardiovascular effects of losartan through the RAS have been widely explored, no data exists concerning acceleration.

CONCLUSION

Losartan potassium, 50-100 mg/day, seems to be a reasonable medication to consider for the control of hypertension in aviators. Although it may affect release of catecholamines, it seems to leave autonomic responses intact. The side effect profile appears to be favorable, and generally equal to placebo, and for the 5-10% of patients who experience cough on ACE inhibitors it could be a particularly useful drug. Further testing is certainly indicated before the drug is employed in aircrew; for most organ systems of interest to aviation medicine there is no data, while in the central nervous system there exists some evidence of potential interaction.

REFERENCES


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