Acetylcholinesterase inhibition in the treatment of hypotension

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Pyridostigmine reduces tilt induced hypotension

Assuming an upright posture causes translocation of approximately 800 ml of blood from the intrathoracic venous compartment to veins of the buttocks, pelvis, and legs. The bulk of venous pooling occurs within the first 10 seconds and the total pooling is complete within three to five minutes.[1] The normal compensatory cardiovascular response to this orthostatic stress is a neurogenically mediated increase in heart rate and systemic vascular resistance. Patients with autonomic failure do not increase systemic vascular resistance, and the decrease in cardiac output during standing is also significant.[1] The resulting cerebral hypoperfusion causes postural lightheadedness, visual blurring, syncope, focal cerebral ischaemia, and even unexplained falls. In these patients orthostatic hypotension may be significantly exacerbated by prolonged recumbency, food or alcohol ingestion, physical exertion, and vasoactive drugs. Patient education directed at avoidance of these stressors, volume expansion with increased sodium and water intake,[2] and physical countermanoeuvres to activate the skeletal muscle pump to prevent venous pooling constitute the mainstay of treatment of orthostatic hypotension.[1] This conservative strategy offsets many of the dynamic and rapid changes in blood pressure that occur during normal activities of daily living. Improved cerebral autoregulation in some patients with autonomic failure may also reduce symptoms of orthostatic hypotension.

Drugs that expand the plasma volume (fludrocortisone) or that supplement peripheral α adrenergic activity (midodrine) are the main pharmacological modes of treatment of these patients. However, the efficacy of these drugs is often unpredictable, depending on the interaction between residual autonomic activity, neurohumoral counter-regulatory mechanisms, and the pharmacological agent. For example, administration of aldosterone analogues such as fludrocortisone to normal subjects on an adequate salt intake initially causes sodium and water retention leading to weight gain and a rise in blood pressure. However, within a few days, spontaneous diuresis ensues and plasma volume returns to near normal values—a phenomenon known as the aldosterone escape. Some of the counter-regulatory mechanisms implicated in the aldosterone escape include reductions in the secretion of renin-angiotensin, increased secretion of atrial natriuretic factor, and pressure natriuresis. Baseline sympathetic activity is also significantly diminished by fludrocortisone, even when no increase in plasma volume is observed. Acute administration of the α adrenergic agonist midodrine increases blood pressure, total peripheral resistance, and venomotor activity but decreases heart rate, plasma volume, and muscle sympathetic nerve activity. The diminished heart rate and sympathetic activity are likely to reflect acute activation of baroreceptors, whereas the hypovolaemia is probably related to α adrenergic mediation of vascular smooth muscle contraction.

Given this level of unpredictability it is interesting that we know very little about the long term value of these commonly used treatments. The longest placebo controlled study of the efficacy of midodrine was only six weeks,[3] and there is no placebo controlled trial showing long term efficacy of fludrocortisone in autonomic failure. Both of these drugs have potentially deleterious side effects, the most feared being supine hypertension to a level sufficient to cause target organ damage.[4]

From the above discussion it is evident that a drug that would amplify dynamic residual autonomic function without the escape phenomena described above and without promoting supine hypertension would be very desirable. In this edition of the journal, Singer *et al* describe the efficacy a potentially *ideal* therapeutic agent, pyridostigmine, in reducing tilt induced hypotension.[5] These investigators suggest that the mechanism of action is the potentiation of sympathetic cholinergic ganglionic transmission. Thus sympathetic activity would be amplified during orthostatic stress and would be minimised while supine. One would imagine, therefore, that those patients with preserved ganglionic transmission would be preferentially improved by pyridostigmine. There was, however, no difference in the response of patients with peripheral and central autonomic failure, nor was the response related to the severity of autonomic failure. Whether pyridostigmine would serve to reduce supine hypertension is also unknown as many patients with peripheral autonomic failure have supine hypertension even after complete ganglionic blockade.[4] Despite these limitations, given the paucity of effective agents for the treatment of orthostatic hypotension, a properly designed multicentre placebo controlled trial of the efficacy of pyridostigmine in the treatment of autonomic failure would be welcomed by those who treat patients with this condition.

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