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Hypotension and ischaemic stroke associated with aliskiren in the ALTITUDE trial: Sensitisation of the Bezold–Jarisch reflex?

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Abstract

Hypotension and syncopal attacks have been reported in association with drugs which block the renin–angiotensin–aldosterone system (RAAS). It has been proposed that the underlying mechanism is due to sensitisation of the Bezold–Jarisch reflex leading to withdrawal of sympathetic tone, profound and prolonged bradycardia, and hypotension. Sensitisation of this reflex occurs in the presence of blockade of the RAAS. In the ALTITUDE trial the use of the direct renin inhibitor, aliskiren, was associated with hypotensive episodes and an excess of ischaemic stroke. It is hypothesised that this is best explained by activation of the Bezold–Jarisch reflex, which may be particularly important in circumstances where there is dual blockade of the RAAS.

Keywords

Hypotension, syncopy, ischaemic stroke, ALTITUDE, aliskiren

De Boer and colleagues recently reported in this journal[1] an explanation for the excess of reports of hypotension associated with aliskiren in aliskiren trial in type 2 diabetes using cardio-renal disease endpoints (ALTITUDE) trial. They pointed out that baseline blood pressures were very well controlled and that patients could become hypotensive when aliskiren was added to a treatment regimen which also included another blocker of the renin–angiotensin–aldosterone system. I would like to suggest an additional mechanism.

We have previously reported the occurrence of syncopal attacks in patients who received angiotensin receptor blockers (ARBs) for the treatment of hypertension[2] and we have provided an explanation for the reports of similar syncopal attacks and dizziness that occurred in association with valsartan in the valsartan antihypertensive long-term use evaluation (VALUE) trial.[3] We now suggest that a similar mechanism may be responsible for the reports of hypotension and possibly the excess of ischaemic stroke associated with the direct renin inhibitor, aliskiren, in the ALTITUDE trial,[4] particularly when the drug is added to a treatment regimen that includes another blocker of the renin–angiotensin–aldosterone system.

The underlying mechanism is most likely explained by sensitisation of the Bezold–Jarisch reflex[5] conditioned by the withdrawal of the effect of angiotensin II. Angiotensin II exerts its effect by a central mechanism which serves to ameliorate the vagally-induced bradycardia, and withdrawal of sympathetic tone, consequent upon activation of the afferent pathways of this reflex.[6] The Bezold–Jarisch reflex is initiated by stimulation of chemosensitive and mechanosensitive receptors in the wall of the left ventricle. Afferent pathways are carried by the vagus nerve to cardiovascular regulatory nuclei in the brain stem. Efferent pathways involve vagally induced bradycardia and withdrawal of sympathetic tone. Activation of the pathway causes vaso-vagal syncope, which could account for the exertional syncope of aortic stenosis, the haemodynamic response to inferoposterior myocardial infarction, hypovalaemic shock and the syncope associated with passive tilting.

The Bezold–Jarisch reflex, originally described by Von Bezold and Hirt and later by Jarisch,[5] might be triggered, or ameliorated, by various drugs or hormones. Angiotensin II could attenuate the hypotensive and vagal components of this reflex.[5] In contrast, severe hypotension and long-term bradycardia has been reported when

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the renin–angiotensin–aldosterone system is blocked by infusions of renin inhibitors, and is attributed to an exaggeration of the Bezold–Jarisch reflex.[7] Such a mechanism might also contribute to the hypotensive response to the first dose of an ACE inhibitor when used in the treatment of heart failure. Hypotension may also be a problem during anaesthesia in patients who receive angiotensin converting enzyme (ACE) inhibitors.

The report of hypotension and ischaemic stroke in association with the use of aliskiren in the ALTITUDE trial supports the hypothesis that renin inhibition may remove the modulating effects of angiotensin II on the Bezold–Jarisch reflex and, perhaps in circumstances when a vaso-vagal reaction is likely to arise, there is sensitization of the pathway and exaggeration of the withdrawal of sympathetic tone, vasodilatation and profound bradycardia. This risk may be increased in the context of dual blockade of the renin–angiotensin–aldosterone system, as was the case in ALTITUDE.

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