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EDITORIAL

The X-cellent Study

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In their report, London et al[1] compared, in elderly subjects with hypertension, the long-acting diuretic compound indapamide 1.5 mg sustained-release (SR) with placebo, as well as with the AT_1receptor blocker candesartan and with the calcium entry blocker amlodipine. Most of the results were focused on subjects with isolated systolic hypertension in whom the three active treatments produced the same brachial systolic blood pressure (SBP) reduction by comparison with placebo but that differed markedly in their effectiveness in regard to diastolic blood pressure (DBP). Whereas candesartan and amlodipine reduced DBP, this reduction was not observed with indapamide SR, resulting, exclusively in this latter group, in a selective reduction of brachial pulse pressure (PP). The finding was observed regardless of whether conventional or ambulatory blood pressure (BP) measurements were performed. The investigators presented their results in terms of improvement of cardiovascular risk but poorly mentioned the possible pathophysiologic mechanisms linked to their findings, as well as the corresponding findings in cardiovascular pharmacology.

Along the study, only brachial BP, and not aortic or carotid BP, was measured. The point is important to consider. It is well established that as a consequence of propagation of pressure wave and resulting wave reflections, SBP and PP are significantly higher in peripheral than in central arteries, whereas DBP and mean arterial pressure are nearly the same along the arterial tree.[2,3] The difference approximates 11 to 14 mm Hg. Thus, in the study of London et al,[1] as in other published data in the literature,[3–5] aortic or carotid SBP and PP might have been modified differently by comparison with brachial SBP or PP, and this difference might be largely influenced by the mechanism of action each of the three drugs studied. For instance, as a possible consequence of hypovolemia and reduced stroke volume, the diuretic indapamide might have preferentially decreased central SBP and PP, and even to a larger extent than brachial SBP and PP. In a recent double-blind cross-over study, Morgan et al[5] showed that a selective reduction of central SBP and PP, by comparison with reduction of brachial SBP and PP, was observed preferentially with use of angiotensin converting enzyme inhibitors, and mainly when these agents were compared to β-blocking drugs (which were not evaluated in the London et al study).[4,5] In fact, the diuretic compound indapamide SR produced only a reduction of brachial SBP but no change of DBP, thus causing a selective reduction of PP by comparison with the other antihypertensive agents. This hemodynamic profile is particularly observed with drugs affecting mainly arterial stiffness or wave reflections or a combination of both factors. In any case this effect can be caused by a reduction of stroke volume as a consequence of salt and water depletion, which, by definition, will cause a decrease of both brachial SBP and DBP. Clearly with the angiotensin enzyme inhibitor and the calcium blocker used in the study of London et al,[1] this property was attenuated or even had disappeared by comparison with indapamide SR. Finally, in this trial a clear confirmation of the differential effects of the studied antihypertensive agents is needed. The study should have included measurements of aortic stiffness and carotid wave reflections.

Although poorly studied in the literature in terms of cardiovascular pharmacology, the diuretic compounds are currently the principal agents susceptible to reduce selectively SBP and PP in elderly individuals with long-term treatment for hypertension.[6] The mechanism of action of these agents, which is classically described as limited to sodium and water balance and arteriolar reactivity, has never been the object of clear-cut investigations focused on human large arteries. However numerous animal studies have shown the effects of sodium intake and diuretic compounds on the structure and function of hypertensive small and large arteries. Increased sodium intake in rats attenuates the mechanisms of myogenic tone and endothelium-dependent flow dilatation at the site of small mesenteric arteries.[7] Diuretics, in turn, might have opposite effects.[7] On the other hand proteoglycans located within the arterial wall has, as a major property, the ability to bind sodium ions. In the presence of high sodium intake this finding may be associated with increased arterial stiffness, which may be reversed by indapamide.[8] Sodium excess in hypertensive animals is usually associated with a changed phenotype of smooth-muscle cells, mainly caused by an increase in their secretory properties with resulting collagen accumulation.[9] On the contrary indapamide is able to

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reduce the amount of collagen of large vessels.[8] Finally, in many animal models of hypertension the indapamide compound has been shown to reduce arterial stiffness independently of MBP.[9] At the exception of aldosterone antagonists, indapamide is the diuretic compound with which the structural changes of the vessel wall have been mostly investigated, either alone or in association with angiotensin-converting enzyme inhibition.[9]

In conclusion, studies involving cardiovascular epidemiology have recently emphasized the interest of diuretics in the long-term treatment of hypertension, as wall as the major interest of their use with low doses.[4,6,10] The modern aspects of their arterial properties remain to be established with more details in long-term follow-up, mainly in elderly patients.

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