The Renin Inhibitor Aliskiren Is a Potent and Long-Acting Antihypertensive in Double Transgenic Rats Expressing Human Renin and Angiotensinogen Genes

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Background: Angiotensin II (AII) is a potent vasoconstrictor and may contribute to the development of hypertension. The purpose of this study was to compare the antihypertensive responses of i.v. and p.o. aliskiren to those of enalapril and valsartan in two double transgenic rats (dTGR) expressing human renin and angiotensinogen genes.

Methods: Studies were conducted on 5.5- to 10.7-week-old male dTGR (Jr/REN, mLQ J x Jr/AOGEN/L1623) instrumented with chronically indwelling femoral arterial and venous catheters (exteriorized through a tether system). Aliskiren (hemifumarate salt) was administered i.v. (0.003-3 mgEq/kg) or p.o. (0.3-30 mgEq/kg) as single or escalating cumulative doses on a given day followed by at least 3 days of recovery before the next treatment. Enalapril (0.003-1 mgEq/kg i.v.; 0.1-1 mgEq/kg p.o.) and valsartan (0.001-1 mgEq/kg i.v.; 0.001-10 mgEq/kg p.o.) were given in a like manner. Mean arterial pressure (MAP) was monitored before (“baseline”) and for up to 72 hours after dosing. In separate experiments, arterial blood samples were collected for pharmacokinetic analyses of aliskiren.

Results: Each agent dose-dependently (i.v. and p.o.) lowered MAP (baselines ~203 mmHg), and were at least 30% effective at CV events. This analysis evaluates BP control, angina frequency and episodes and CV events in CAD patients with HTN and ischemia (classic angiographic lesions, age >/= 70 years, and diabetes). The primary outcome (PO) was defined as a composite of MI, stroke, and death. Treatment strategy and followed 3.2 years (mean). Trandolapril and HCTZ were available in both strategies to achieve JNC VI BP goals (</=140/90 or </=130/85 in diabetes or renal dysfunction). The PO was time to first occurrence of death (all-cause), nonfatal MI or nonfatal stroke. This analysis indicates that the time administration of low-dose ASA with respect to the rest-activity cycle of each patient could provide a valuable approach not just for the secondary prevention of cardiovascular disease, but also in the added BP control of patients with mild hypertension and poor compliance with HDR.

Conclusions: Extended therapy with E improved coronary hemodynamics and reduced myocardial collagen suggesting that aldosterone may be involved in mediating age- and hypertension-related cardiac fibrosis.

The Effects of Aspirin on Blood Pressure in Untreated Hypertensive Patients Are Dependent on the Time of Drug Administration

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Background: An administration time-dependent effect of low-dose aspirin (ASA) on blood pressure (BP) has been previously documented in normotensive volunteers, patients with mild hypertension, and pregnant women at high risk for preeclampsia [Herrmida et al. Hypertension. 2003;41:651-656 and 2003;41:1259-1267]. We have extended these results by investigating the influence of ASA on BP in previously untreated hypertensive patients who received ASA at different times of the day according to their rest-activity cycle.

Methods: We studied 264 untreated patients with mild hypertension (101 men, 163 women), age 43.6±12.6 (mean±SD) years of age, randomly divided in 3 groups: non-pharmacological hypertensive diet-recommendations (HDR); the same HDR and ASA (100 mg/day) before bedtime. BP was measured every 20 min from 07:00 to 23:00 hours and every 30 min at night for 48 consecutive hours before and after 3 months of intervention. The circadian pattern of BP in each group was established by population multiple-component analysis.

Results: After 3 months of non-pharmacological intervention, there was a small and non-significant reduction of BP (0.4 and 0.5 mm Hg for systolic and diastolic BP; P>0.584). BP was slightly elevated after ASA on awakening, mainly during nocturnal resting hours (increase of 2.7 and 1.5 mm Hg in the 24-hour mean of systolic and diastolic BP; P<0.020). A highly significant BP reduction was observed by the patients who received ASA before bedtime (decrease of 7.1 and 4.6 mm Hg in systolic and diastolic BP; respectively; P<0.001).

Conclusion: This trial corroborates the highly significant administration-time dependent effect of low-dose ASA on BP in untreated patients with mild hypertension. Results indicate that the timed administration of low-dose ASA with respect to the rest-activity cycle of each patient could provide a valuable approach not just for the secondary prevention of cardiovascular disease, but also in the added BP control of patients with mild essential hypertension and poor compliance with HDR.

Blood Pressure Control, Angina Episodes, and Cardiovascular Outcomes in Patients With Ischemia: The International Verapamil/Trandolapril Study

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INTRODUCTION: More than 60% of patients with ischemia also have hypertension (HTN) and are at high risk for CV events. This analysis evaluates BP control, angina frequency and episodes and CV events in CAD patients with HTN and ischemia (classic angiographic lesions, age >/= 70 years, and diabetes). The primary outcome (PO) was defined as a composite of MI, stroke, and death. Treatment strategy and followed 3.2 years (mean). Trandolapril and HCTZ were available in both strategies to achieve JNC VI BP goals (</=140/90 or </=130/85 in diabetes or renal dysfunction). The PO was time to first occurrence of death (all-cause), nonfatal MI or nonfatal stroke. This analysis indicates that the timed administration of low-dose ASA with respect to the rest-activity cycle of each patient could provide a valuable approach not just for the secondary prevention of cardiovascular disease, but also in the added BP control of patients with mild hypertension and poor compliance with HDR.

Conclusions: Despite decreased indices of cardiac oxygen demand in the At strat-egy, patients in the Ve strategy had a greater reduction of anginal episodes, suggesting an alternate mechanism of action for reduced anginal symptoms from verapamil-SR.