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TOLERABILITY AND SAFETY OF TELMISARTAN AS MONOTHERAPY OR COMBINED WITH HYDROCHLOROTHIAZIDE COMPARED WITH PLACEBO
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Data on safety and tolerability of telmisartan (T) and T + hydrochlorothiazide (HCTZ) in comparison with placebo (P) was consolidated from clinical trials.

Safety data were collected from 34 randomized multicenter trials. Patients had a minimum of mild-to-moderate hypertension (supine DBP 90-114 mmHg). Treatment (P: T 10-160 mg or T 10-160 mg + HCTZ 6.25-25 mg) was given for 7 days to more than 2 years. Uptitration was performed in some studies, with an increase of the T dose or the addition of HCTZ. The incidence and causality of adverse events and laboratory abnormalities were recorded.

819 patients received P, 6575 T and 2180 T+HCTZ. 23.5% were 65 years of age or older and 4.5% were 75 years or older. Patient-years of treatment were P 106, T 4018 and T+HCTZ 1568. Incidences of all-causality adverse events were P 38.2%, T 52.0% and T+HCTZ 59.5%. Incidences of treatment-related adverse events were P 10.5%, T 12.0% and T+HCTZ 12.8%, amounting to P 1.02, T 0.20 and T+HCTZ 0.18 such events per patient per treatment year. The most frequent treatment-related adverse events were dizziness and headache; incidences were similar in P, T and T+HCTZ treatment groups. Incidences were also similar in younger patients (less than 65 years) and the elderly (65 years or older). Events were mainly mild or moderate in intensity. Incidences of serious adverse events were P 1.1%, T 4.3% and T+HCTZ 5.6%, which amounts to 0.08 such events per patient per treatment year for P, 0.07 for T and 0.08 for T+HCTZ. The overall incidence of drug-related laboratory abnormalities was low in all treatment groups. Hyperuricemia and hypokalemia considered related to treatment occurred in 5 and 6 patients, respectively, treated with T+HCTZ. Incidences of discontinuation due to an adverse event were P 4.6%, T 4.5% and T+HCTZ 4.7%.

In conclusion, T and T+HCTZ are both well tolerated in patients of all ages and have placebo-like tolerabilities.

Key Words: Telmisartan, Telmisartan/Hydrochlorothiazide, Tolerability

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DIHYDROPYRIDINE CALCIUM CHANNEL BLOCKERS AND DEPENDENT EDEMA: A COMPARISON BETWEEN AMLODIPINE AND LERCANIDIPINE IN ESSENTIAL HYPERTENSIVE PATIENTS
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Background: Dependent leg edema complicates treatment with amlo- dipine (AMLO) and other dihydropyridine (DHP) calcium channel blockers (CCB’s) and frequently obliges to interrupt an otherwise highly effective therapeutic regimen. Among other possible explanations, DHP CCBs may alter the balance between pre- and post-capillary pressures by dilating preferentially precapillary arterioles of the cutaneous microcircu- lation, thus increasing capillary pressure and promoting fluid extrava- sation. In contrast, DHP CCBs such as lercanidipine (LERCA), which may relax both pre- and post-capillary vessels in in-vitro studies, may induce a lesser degree of dependent edema. However, this hypothesis has never been tested in man.

Methods: We compared the leg edema-forming potential of AMLO and LERCA according to a cross-over, sequence-randomized experimen- tal design carried out in 22 never treated mild-moderate uncomplicated essential hypertensive (EH) males (age: 48±5 yrs). Drugs were adminis- tered at doses (AMLO: 10 vs LERCA: 20 mg o.d.) equipotent on the basis of published titration studies. Active treatment was given for 2 weeks preceded and followed by 2 week wash-outs to allow the recovery of study variables to baseline. Leg weight (LW) was used as a surrogate measure of dependent edema; the parameter was measured by water plethysmography (accuracy within 5 grams; variation coefficient: 0.8%) at both legs and the data were averaged. Systolic and diastolic blood pressure (BP), the mean of at least 10 determinations) was recorded by an automated oscillographic device.

Results: (means±SD): AMLO (from 147±8/94±12 to 137±14/ 83±9 mmHg, p<.002) and LERCA (from 145±18/92±12 to 137±9/ 83±8 mmHg, p<.01) decreased BP to a similar extent. Both drugs increased LW: AMLO: from 3244±306 to 3324±293 grams, p<.001; LERCA: from 3256±279 to 3293±258 grams, p<.04), but the increase was greater during AMLO (80±91 vs 37±74 grams, p<.03).

Conclusions: These data, consistent with pharmacological differences previously reported at the in-vitro microvascular level, show for the first time in man that, for a similar drop in BP, the edema-forming potential of AMLO and LERCA, two CCBs belonging to the same DHP class, is not equivalent.

Key Words: Calcium Channel Blocker, Dependent Edema, Side Effects of Antihypertensive Treatment

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MODELING CLINICAL AND ECONOMIC OUTCOMES OF ANTIHYPERTENSIVE TREATMENT ALTERNATIVES
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The purpose of the study was to compare the costs and outcomes of antihypertensive therapeutic treatments (amlodipine besylate 10mg, feno- dipine 10mg, nifedipine 60mg, amloidipine/benazepril 2.5mg/10mg) for managed care patients with moderate to severe hypertension who had previously failed initial drug therapy (beta blockers or diuretics per nINC-VI).

A decision analysis model was developed to simulate hypertension management for a hypothetical cohort of patients with moderate to severe hypertension in a Managed Care Organization (n=200,000). Patients were distributed evenly between the four therapies (n=50,000). The model follows patients over the course of one year during which time patients may experience adverse drug reactions and success or failure of blood pressure control. Efficacy and tolerability estimates were obtained from a published meta-analysis and literature. Medical management was based on results from a physician survey. Costs included in the model were drug acquisition, routine follow-up, management of blood pressure control failure and adverse events. Model parameters were varied to test the stability of the conclusions (e.g., efficacy and tolerability were varied above and below the baseline).

Approximately 93% of patients responded to second-line therapy with amloidipine/benazepril at the end of one year, compared with 92% in the felodipine arm, 91% in the amloidipine besylate arm and 88% in the nifedipine arm. The percentage of patients who remained on initial therapy and did not require treatment modification (e.g., increase in dose, addition of a concomitant medication or a medication switch) due to drug intolerance or lack of blood pressure control was higher in the amloidipine/benazepril arm. The cost of amloidipine/benazepril was lower than the total cost of care of the other treatments: $51,700,000 for amloidipine/ benazepril versus $60,900,000, $58,100,000 and $60,950,000 for nifed- ipine, felodipine and amloidipine besylate, respectively. Increasing effi- cacy by one standard deviation resulted in a greater percentage of patients achieving BP control at a lower cost of treatment for all regimens. Amlodipine/benazepril remained the most effective at a lower cost because patients required fewer treatment modifications. Decreasing the efficacy estimate resulted in a slightly greater percentage of amloidipine