The objectives of this study were to compare the effects on 24-hour ambulatory blood pressure (BP) as well as on the magnitude of leg edema of treatments using LER, amlopidine (AML), or hydrochlorothiazide (HCT) in patients with confirmed ambulatory hypertension (daytime systolic BP >135 mmHg). A total of 121 eligible patients (66M/55F, mean age of 62.7 ± 7.1 yrs) were randomized to either LER 10 mg (n=39), AML 5 mg (n=39) or HCT 12.5 mg (n=43) for 4 weeks. They were then force-titrated to LER 20 mg, AML 10 mg and HCT 25 mg for 4 weeks of treatment. Ambulatory BP monitoring was performed at baseline and after each of the 4-week treatment period (week 4 and 8). The magnitude of leg edema was evaluated using the leg volume measured by water displacement volumetry at the same timepoints both in the morning at trough and in the afternoon.

Daytime ambulatory systolic/diastolic BP were comparable for the LER (150.0/88.6 mmHg), AML (153.2/88.7 mmHg) and HCT (151.8/86.5 mmHg) treatment groups at baseline. Mean daytime systolic/diastolic BP (mm Hg) were reduced by treatments with LER (-3.4/-0.9 and -5.6/-2.1), AML (-10.2/-4.7 and -17.4/-9.2) and HCT (-3.9/-1.3 and -6.8/-3.5) at week 4 and week 8, respectively. However, LER induced BP decrements significantly (p<0.001) less pronounced than those obtained after AML treatment but comparable to HCT treatment. Changes in leg volume were significantly (p<0.05) more important with AML in the morning as compared with LER at week 4 (+27.6/-39.2 ml) and at week 8 (+128.0 vs -19.0 ml). Similarly, leg volumes with AML as compared with LER were significantly different at week 4 (+21.6 vs -2.6 ml) and week 8 (+138.0 vs +36.3 ml), as measured in the afternoon. HCT decreased leg volume in the morning and in the afternoon at week 4 (-22.6 and -0.8 ml) and at week 8 (-47.6 and -11.1 ml), respectively.

The results of the present study demonstrate that the dihydropyridine calcium antagonist LER induced significantly less leg edema than AML but similarly to HCT as measured by leg volume. However, this beneficial effect of LER was associated with significantly less antihypertensive efficacy on ambulatory BP as compared with AML.

Key Words: Ambulatory Blood Pressure Monitoring, Calcium Antagonists, Leg Edema

P-166
HEPATOCELLULAR NECROSIS ASSOCIATED WITH LABETALOL
Robert C Long, Deborah S King, Marion R Wofford, Kimberly G Harkins, Jimmy L Stewart. Medicine, University of Mississippi Medical Center, Jackson, MS.

Hepatocellular injury secondary to antihypertensive therapy is a rare complication. It has been described with calcium channel blockers, angiotensin converting enzyme inhibitors, thiazide diuretics, hydralazine and beta blockers but is best characterized in association with methyldopa. There have been case reports of labetalol-induced hepatitis and the manufacturer’s package insert was revised after a series of 11 cases published in 1991. This side effect of labetalol is not commonly listed in tables of drug-induced hepatotoxicity and can be overlooked because of its rarity.

A 51-year-old female with severe uncontrolled hypertension, BP of 200/100, was referred to a tertiary care hypertension clinic and started on labetalol. She denied history of ethanol abuse or intravenous drug use. Past medical history was significant for methyldopa-induced hepatitis 17 years prior and a blood transfusion 22 years prior, secondary to blood loss from a gynecology procedure. All laboratory assessments were normal. Approximately 3 months after starting labetalol she presented with a 1-2 week history of nausea, abdominal pain, fatigue and dark urine. She was admitted to the hospital, her home antihypertensive medications were held and nicardipine was used for blood pressure control.

On physical exam she was jaundiced with icteric sclera and a slightly tender liver that was palpable 2 cm below the costal margin. Labs revealed total bilirubin of 24, alanine transaminase 3813, aspartate transaminase 5228, prothrombin time 22.3 (INR 2.0). Extensive testing for autoimmune and infectious causes of hepatitis were negative. A liver biopsy showed acute hepatitis with bridging necrosis. During her hospitalization she developed fulminant hepatic failure, hepatic encephalopathy and hepatorenal syndrome. She required liver transplant and is now stable.

This case emphasizes the importance of appreciating the potential of labetalol to cause hepatocellular necrosis severe enough to require a liver transplant. It is important to keep all medications in mind when a patient presents with elevated liver enzymes. We found no known reports of labetalol and methyldopa hepatotoxicity occurring in the same patient. It may be prudent to follow patients with a history of idiosyncratic hepatitis secondary to drug therapy more closely when initiating medications that have been associated with liver toxicity.

Key Words: Adverse Effects, Antihypertensive Medications

P-167 MP-12
EVALUATION OF ANTIHYPERTENSIVE MEDICATION ADHERENCE IN A VETERAN POPULATION

This study evaluates antihypertensive medication adherence using Department of Veterans Affairs pharmacy databases. Automated data extraction routines capture pharmacy, ICD-9, laboratory, and patient demographic data on a monthly basis. We included patients with a diagnosis of hypertension (ICD-9 codes 401.1 to 401.9) who had a history of medication use during July 2002 through December 2003. Medications in the following drug classes were studied: thiazides (TZ), beta blockers (BB), ACE inhibitors (ACE), angiotensin receptor blockers (ARB), calcium channel antagonists (CA) and alpha blockers (AB). We excluded patients with serum creatinine of ≥2.5 and those receiving K sparing diuretics alone. The first date of prescription filling for each patient within the date range is the index date from which fill and refill dates are collected for one year to calculate possession ratio (MTOT) and days out of medication ratio (MOUT).

Data elements for analysis are medication class as listed above, patient’s age, gender, ethnicity, VA facility, and co-diagnosis with diabetes, schizophrenia/psychosis, and dementia. The potential effect of these variables on adherence were examined using logistic regression analysis with patients categorized as adherent if MTOT is 80% or greater. In the six VA classes there were 79,055 patients with average age per group ranging from 67.4-72.9 years. 97% were male and when ethnicity was recorded 74.5% were Caucasian, 14% African-American and 5% each Hispanic and Asian. The largest number of patients (22,233) took an ACE whereas a small number used ARB (3,729). Unadjusted adherence rates based on MTOT ranged from 77.9% for TZ to 83.3% for ARB (p<0.01). Similar findings were noted using the MOUT parameter. 8% of patients using an ACE had at least two ICD9 codes for diabetes as compared to 4.6% getting TZ. A dementia and a schizophrenia/psychosis diagnosis occurred in each drug class in up to 3.3% and 3.4% of patients, respectively. Drug class and age were independent predictors of adherence with odds ratios of 1.019 and 1.014, respectively. We conclude that adherence rates with antihypertensive medications are remarkably high. Although there are statistical differences by drug class, these differences are small.

Key Words: Medication Adherence, Pharmacoepidemiology