557 **OVERWEIGHT RISK FACTOR OF ALCOHOLIC STEATOSIS.**
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We have shown previously that overweight is a risk factor for alcoholic cirrhosis. In order to better understand this association, the aim of this study was to know if overweight was also a risk factor for the alcoholic liver disease at an early stage ie steatosis and acute alcoholic hepatitis. Patients and Methods : 1666 alcoholic patients (1230 men, 436 women, mean age 50±12 years) (mean±SD) were studied. According to liver biopsies 216 patients had normal livers, 477 steatosis without fibrosis, 315 fibrosis with or without steatosis, 140 acute alcoholic hepatitis (AAH) without cirrhosis, 287 cirrhosis without AAH and 231 cirrhosis with AAH. Eight variables were studied as risk factors : age, sex, daily consumption of alcohol during the previous 5 years, the total duration of alcohol abuse, daily consumption of wine, beer and aperitifs which are expressed as a percentage of the total daily alcohol intake and overweight (body mass index (BMI) $\geq$ 25 in women and $\geq$ 27 in men). BMI was calculated according to the minimum weight in the last ten years. In a first analysis, patients with steatosis without fibrosis were compared to patients with a normal liver. In a second analysis patients with AAH with or without cirrhosis were compared to patients without AAH. A stepwise logistic regression was used to consider confounding variables and intercorrelations among the variables adjusted for all others variables. Results : In the first analysis, when all the 8 variables were taken into consideration, overweight for at least ten years is the only variable which represents an independent risk factor of steatosis ($p<0.001$) (odds ratio 2.5 - 95% confidence interval 1-6.6). In the second analysis female sex and overweight are shown to be independent risk factors of AAH. After adjustment for cirrhosis overweight is no longer an independent risk factor of AAH. Conclusion : These results suggest that the possible potentiation of metabolic effects of ethanol ingestion and overweight exists already at the stage of steatosis without fibrosis and might lead to cirrhosis even in the absence of AAH.

558 **AMLODIPINE THERAPY IN ACUTE ALCOHOLIC HEPATITIS: A RANDOMISED CONTROLLED TRIAL.**
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Acute alcoholic hepatitis (AAH) has a one year mortality of 30-70%, but the only accepted specific therapy - corticosteroids - is limited to severely ill patients (Discriminant Function >32). In view of recent evidence suggesting a hepatoprotective effect of dihydropyridine calcium channel blockers in animal models of liver injury, we carried out a double blind, prospective randomised controlled study of amlodipine in AAH to evaluate if 1 year survival was improved.

62 patients admitted to hospital with AAH were randomised to receive 5mg amlodipine daily (10mg if prothrombin time < 3s prolonged) or placebo for one year. There were no significant differences in demographic, clinical or laboratory characteristics in treated and placebo groups (DF: amlodipine patients 31.2 ± 5.5, placebo 31.7 ± 5.2).

Of 32 patients receiving amlodipine, there were 11 deaths (34%), 6 in the first 4 weeks, whereas 14 (47%) of the placebo patients died (7 within 4 weeks). Causes of death were similar in the amlodipine and placebo groups with liver failure predominant (14 deaths). Analysis by the Cox proportional hazards model after adjustment for other prognostic factors showed survival was not influenced by active treatment (P=0.07).

One patient in each group was withdrawn because of the development of hypotension but this did not recur on reintroduction of the tablets. There were no other treatment/placebo related adverse events. Amlodipine is well tolerated in alcoholic hepatitis but has no hepatoprotective role and does not improve survival.

559 DECREASED CONSTITUTIVE MURINE CYTOCHROMES P450 BY STAPHLOCCOCAL ENTEROTOXIN B (SEB). SI Shedlofsky, R Tosheva, J Scheurer, and *JE Snawder. Dept. Veterans Affairs Medical Center/University of Kentucky, Lexington, KY and *National Institute Occupational Safety Health, Cincinnati, OH

Inflammation caused by gram-negative endotoxin (LPS) is associated with impaired hepatic P450-mediated drug metabolizing activity. However, gram-positive bacteria also commonly cause the sepsis syndrome. To evaluate effects of the gram-positive inflammatory stimulant SEB, C3H/HeN mice (male, 25g) were injected ip with either saline, LPS (0.5mg/kg), or SEB (3mg/kg), and hepatic microsomes prepared and serum harvested 24h later. Serum amyloid A (SAA) measured the intensity of the hepatic acute phase response. Total spectral P450, ethoxyresorufin-O-deethylase (EROD, -CYP1A1/2), paranitrophenol-OHase (PNP -CYP2E1), and benzyloxy-O-deethylase (BROD -CYP3A) were assayed and immunoblots for each P450 isoform prepared using commercial antibodies. Data are mean ±SD for 4-7 mice in each group.

	Saline	LPS	SEB
SAA (relative units)	450 ±36	681 ±61	661 ±118
Total P450 (nmol/mg)	0.95 ±0.09	0.62 ±0.09	0.66 ±0.06
EROD (pmol/mg/min)	82 ±16	59 ±18	54 ± 6
CYP1A2 (rel. units)	1.43 ±0.32	1.04 ±0.34	0.92 ±0.09
PNP (nmol/mg/min)	1.08 ±0.26	0.74 ±0.42	0.48 ±0.05
CYP2E1 (rel. units)	0.36 ±0.05	0.16 ±0.05	0.14 ±0.03
BROD (pmol/mg/min)	6.42 ±0.63	6.29 ±1.1	5.01 ±0.51
CYP3A (rel. units)	0.72 ±0.11	0.55 ±0.10	0.49 ±0.05

SEB increased SAA and decreased total P450 to the same extent as LPS and also depressed activities of each specific P450 isoform and amount of specific protein > or = to LPS. 3mg/kg was as effective as 6mg/kg and a time course showed maximal depression at 24h.

Conclusion: The gram-positive inflammatory stimulant SEB depresses hepatic P450s as well as LPS. This suggests that patients with gram-positive sepsis are likely to have impaired hepatic drug metabolism.

560 **MONOETHYLGLYCINEXYLIDIDE (MEGX) AND LIDOCAINE (LIDO) DETERMINATION AFTER ORAL LIDO ADMINISTRATION TO ACUTE HEPATITIS AND CIRRHOTIC PATIENTS.** A. Muñoz, M. Bartellini, C. Miguez, M. Rubio, A. Podestá, D. Levi, R. Terg. Liver Unit. Hospital de Gastroenterología B.Udaondo; ININFA-CONICET. Buenos Aires, Argentina.

The production of MEGX after i.v. infusion of LIDO has been proposed as a quantitative test of liver function. **Aim:** to analyze the utility of plasmatic determinations of LIDO and MEGX in pts. with acute hepatitis and chronic liver disease. **Material and methods:** twenty one cirrhotic pts. (Child-Pugh A 10, B 7, C 4), 9 pts. with acute hepatitis and 9 healthy control subjects received 5 mg/kg LIDO in gelatin capsules (Astra) after an overnight fast. Serum concentrations of LIDO and MEGX were measured by TDx-Abbott at 30, 60, 120, 180 and 240 minutes after LIDO. LIDO and MEGX pharmacokinetics were correlated with 15 clinical and biochemical variables. **Results:**

Plasma concentration of LIDO (μg/ml)

	30 min	60min	120 min	180 min	240 min
Control	0.57±0.41	0.86±0.48	0.69±0.34	0.51±0.25	0.37±0.16
Hepatitis	0.29±0.21	0.73±0.41	1.05±0.37*	0.90±0.34*	0.76±0.31*
Cirrhosis	0.84±0.61#	1.41±0.59*#	1.85±0.34*#	1.62±0.30*#	1.35±0.38*#

Plasma concentration of MEGX (ng/ml)

Control	151±90	401±115	484±153	488±132	363±83
Hepatitis	122±119	327±207	612±170	647±91*	600±86*
Cirrhosis	60±82*	156±116*#	299±161*#	354±163*#	325±121#

$p < 0.05$ compared with control * and hepatitis # groups.

There was a negative correlation in cirrhotics between ASAT and MEGX 60 min, and a positive correlation between previous ascites and LIDO 30-180 min ($p < 0.05$). The ratio LIDO/MEGX, Tmax of MEGX, T½, AUC and Cmax of LIDO in cirrhotic pts. were increased with respect to control and hepatitis groups ($p < 0.05$). AUC and Cmax of MEGX in cirrhotics were lower than control and hepatitis groups ($p < 0.05$). T½ of MEGX in hepatitis group was greater in relation to controls ($p < 0.05$). **CONCLUSIONS:** our results suggest that 1) MEGX test after oral LIDO administration could be utilized to evaluate liver function.2) This test may be useful in diagnosing compensated cirrhotic pts.