SYNERGISTIC ROLES OF HEPATIC ENCEPHALOPATHY AND OBSTRUCTIVE SLEEP APNEA IN DISTURBANCE OF SLEEP ARCHITECTURE IN PATIENTS WITH CIRRHOSIS

Poster Presentation
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M. Kappus, L. Moses, D.M. Heuman, J.S. Bajaj. I 46th Annual Meeting of the European Association for the Study of the Liver

Background

Sleep disturbances in cirrhosis are often attributed to hepatic encephalopathy (HE). With the increasing prevalence of NASH, it is common to encounter obese cirrhotics with obstructive sleep apnea (OSA). Few previous studies have attempted to distinguish between effects of OSA and HE onsleep architecture. Normal sleep has early (N1/N2), deep (N3/N4) and REM phases. N3/N4 stages determine the restfulness and have physically and mentally restorative functions.

Aim

To evaluate the interaction between OSA and HE on sleep architecture in cirrhosis.

Methods

- Records of cirrhotics who underwent polysomnography between 2007 and 2010 were reviewed for MELD score, HE (defined by record review/medications), OSA, symptoms necessitating the sleep study, %time spent in early stage (N1/N2), deep (N3/N4) and REM sleep and periodic limb movements (PLM) were recorded.
- HE patients were compared to non-HE patients.

Results

- 46 cirrhotics (58 yrs, 93% men, BMI 34±4, MELD 8, 50% HCV, 19% alcohol, Diabetes 43%,HTN 93%) were included.
- All underwent the study due to subjective problems (41% snored, 32% daytime sleepiness).
- 89% had OSA and 21% had controlled HE (all HE pts also had OSA).
Sleep results:Median sleep efficiency was 77% with 29 hypopneas, 5 apneas, 67 arousals and 23 PLMs.
- The mean sleep latency was 23 min; the mean % of sleep consisted of N1(11%), N2 (57%), N3 (3%), N4(0.4%) and REM (11%); indicating a severe disruption. N3/N4 were absent in 67% of pts.
- HE, MELD score and sleep architecture: There was a significant correlation between MELD score and PLM ($r=0.45, p=0.04$) and with % in N1 sleep ($r=0.33$, $p=0.037$) but not other phases.
- Since the majority had OSA, there was no significant difference in sleep efficiency ($p=0.5$), hypopneas($p=0.9$), apneas ($p=0.5$) or arousal($p=0.7$) in cirrhotics with or without HE.
- Compared to patients with OSA alone, patients with HE+OSA spent a significantly higher % time in early (N1+N2) sleep (77% vs. 65%, $p=0.007$) but not in REM.
- 100% of pts with HE+OSA had no demonstrable N3/N4 sleep compared to only 29% of non-HE cirrhotics($p=0.021$).

Conclusion

- In cirrhotics with OSA, the added presence of HE significantly shifts the sleep architecture towards early, non-restorative sleep and impairs deep sleep.

SEVERITY OF CHRONIC COGNITIVE IMPAIRMENT IN CIRRHOSIS INCREASES WITH NUMBER OF EPISODES OF OVERT HEPATIC ENCEPHALOPATHY

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Bajaj J, Schubert C, Sanyal AJ, Bell D, Pisney L, and Heuman DM I J Hepatol 2010; 52(Suppl 1):S66

Objective

To determine if recurrent acute episodes of hepatic encephalopathy (HE) may lead to progressive chronic cognitive impairment

Methods

- Patients with cirrhosis and ≥1 prior HE episodes, in clinical remission on lactulose/rifaximin, and with mini-mental status exam >25 were enrolled
- All patients underwent test battery [number connection A/B (NCT A/B), digit symbol (DST) and block design (BDT)] and the inhibitory control tests (ICT, lures and targets are outcomes)
- Number of HE episodes and hospitalizations and duration between the 1st hospitalization and current testing were correlated with individual psychometric tests

Results

- 50 patients (mean MMSE 27, 40 on lactulose, 5 on rifaximin, 5 on both)
- Mean follow-up was 13 ± 12 months with a median of 2 HE episodes (range 1-13) and 1 HE hospitalization (range 1-7)

Results (cont.)

- Precipitating factors for first hospitalization:
  - Infections: 18
  - TIPS: 10
  - Medications: 7
  - Spontaneous: 15
- 33 patients had > 1 HE hospitalization
- Mean test scores were highly abnormal
  - NCT-A: 48±22 seconds
  - NCT-B: 149±87 seconds
  - DST: 41±13
  - BDT: 26±15
  - ICT lures: 15±9
  - ICT targets (% correct): 89±12%
- Scores that were highly correlated with number of HE episodes:
  - ICT lures: r=-0.50, p=0.002
  - ICT targets: r=-0.46, p=0.009
  - NCT-B: r=0.35, p=0.047
  - DST: r=-0.46, p=0.009
- Psychometric performance and number of hospitalizations were also correlated:
  - ICT lures: r=-0.59, p=0.0001
  - ICT targets: r=-0.44, p=0.015
  - NCT-B: r=0.35, p=0.05
  - DST: r=-0.46, p=0.009
- Scores that were significantly correlated with time from first HE episode to testing:
  - ICT lures: r=-0.48, p=0.007
  - DST: r=-0.36, p=0.04

Conclusion

- In cirrhosis, deficits in working memory, psychomotor speed, attention, and response inhibition increase with the number and severity of episodes of overt HE
- The metabolic derangements that produce overt HE may cause chronic neurological injury that is not readily reversible

DRIVING SIMULATION AND COGNITIVE TESTING CAN IMPROVE INSIGHT INTO IMPAIRED DRIVING SKILLS IN CIRRHOTIC PATIENTS WITH MHE

Poster Presentation
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Background

Cirrhotic patients with MHE have difficulty driving, but often lack insight into their impaired driving skills. Improved personal insight may reinforce physician recommendations against driving and reduce risk of harm from motor vehicle accidents.

Aim

To define the impact of cognitive testing, including driving simulation, on personal insight into driving skills.

Methods

- Cirrhotic patients who were current drivers, without overt HE were asked to rate their driving skills on a Likert scale from 0-10 (self-assessment of driving skill [SADS]).
- Driving history was obtained, and they then underwent cognitive testing and driving simulation, after which SADS was re-obtained.
- Cognitive testing included digit symbol, line tracing (errors/time), serial dotting, number connection A/B, block design, and inhibitory control test (ICT: lures and targets are outcomes).
- Driving simulation consisted of 3 parts: training, testing (outcomes=crashes, speeding); and navigation (outcomes=illegal turns, crashes).

Results

- 65 cirrhotic patients were included (55% male, 60% HCV; mean age=55, education=12 yrs, MELD=9, years of driving experience=37).
- 31% reported an actual accident/moving violation in the last yr; however the pre-test SADS for pts with/without these offenses was statistically similar, indicating poor insight (8 vs 8, p=0.79). 51% met had MHE using ICT and 45% using other tests.
- Simulator crashes were only significantly correlated with ICT performance (lures, r=0.3, p=0.03 and targets r=-0.3,p=0.008).
- Prior to testing and simulation, median SADS was 7; this decreased to 5 after these procedures. SADS decreased after testing in 16 (25%; SADS-D) with % decrease averaging 18% (range 0-90%); SADS did not change in 49 (75%; SADS-N).
- Decrease in SADS after testing was found in 40% of patients whose ICT performance was abnormal, but only 15% of patients with normal ICT performance (p=0.045).
- There was a significantly higher rate of illegal turns in SADS-D compared to SADS-N (median 1 vs. 0,p=0.04).
- The percent reduction in SADS score correlated significantly with the number of illegal turns (r=0.4; p=0.01) and navigation crashes (r=0.38; p=0.03).
- %SADS reduction also significantly correlated with digit symbol (r=0.38) and line tracing errors (r=0.36).

Conclusion

- Cirrhotic patients gain insight into impairment of driving skills after experiencing navigation errors during driving simulation or performing poorly on cognitive tests.

RIFAXIMIN IMPROVES COGNITIVE FUNCTIONS AND HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH MINIMAL HEPATIC ENCEPHALOPATHY: A PROSPECTIVE RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED TRIAL (THE RIME TRIAL)

Poster Presentation
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Sidhu S, Goyal O, Mishra BP, Sood A, Chhina RS, and Soni RK | Gastroenterology 2010;139:e18-e19

Objective

To assess the efficacy of rifaximin in improving neuropsychometric (NP) test performance and health related quality of life (HRQOL) in patients with minimal hepatic encephalopathy (MHE)

Methods

- Patients with cirrhosis without prior history of encephalopathy were screened for presence of MHE by 5 NP tests (number and figure connection tests, picture completion, digit symbol and block design tests)
  - MHE was diagnosed if any 2 NP tests were deranged beyond 2 SD of normal
  - NP test results were expressed as Z scores, indicating the differences (in SD) between observed and expected scores
- HRQOL was assessed by Sickness Profile questionnaire psychometric tests

Results

- Of 284 eligible patients, 115 (40.9%) were diagnosed to have MHE
- 21 patients refused consent; 94 patients were randomized to receive placebo (n=45) or rifaximin 1200 mg/day (n=49) for 8 weeks
  - 14% of patients were lost to follow-up

Results (cont.)

	Rifaximin (n=49)		Placebo (n=45)	
Improvement				
-at 2 weeks	28/49 (57.1%)*		8/45 (17.8%)	
-at 8 weeks	37/49 (75.5%)*		9/45 (20%)	
Mean number of abnormal NP tests				
-baseline	2.35 (2.17-2.53)		2.31 (2.03-2.59)	
-at 2 weeks	1.29 (1.02-1.56)	p=0.002	2.03 (1.74-2.31)	
-at 8 weeks	0.81 (0.61-1.02)	p=0.000	1.97 (1.69-2.25)	p>0.05
Mean Z score				
-baseline	-2.54 (-2.81- -2.27)		-2.61 (-2.89 - -2.33)	
-at 8 weeks	-1.44 (-1.84 - -1.03)	p=0.000	-2.26 (-2.55 - -1.98)	p>0.05
Mean Total Sickness Impact Profile Score				
-baseline	11.67 (10.31-13.03)		9.86 (8.66-11.06)	
-at 8 weeks	6.45 (5.59-7.30)	p=0.000	8.51 (7.35-9.67)	p=0.82

*p<0.001, rifaximin compared to placebo

- Improvement in HRQOL correlated with improvement in NP tests (r=0.376, p=0.002)
- Two patients in rifaximin group had minor GI symptoms

Conclusion

- Rifaximin at a dose of 1200 mg/day significantly improves both cognitive functions and HRQOL in patients with MHE
- Rifaximin is safe and well tolerated

FUNCTIONAL CORE MODULATION FOLLOWING TREATMENT OF MINIMAL HEPATIC ENCEPHALOPATHY WITH L-ORNITHINE L-ASPARTATE: A POTENTIAL NOVEL MECHANISM OF ACTION

Poster Presentation
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46th Annual Meeting of the European Association for the Study of the Liver

Introduction

Minimal hepatic encephalopathy (MHE) is common in patients with cirrhosis and heralds progression to overt hepatic encephalopathy (OHE). Treatments are based on those used for OHE but astrocyte swelling may not be the primary mechanism of pathology or therapeutic target in MHE. Functional magnetic resonance imaging (fMRI) has not been applied in assessing efficacy of L-ornithine Laspartate (LOLA).

Methods

- 21 patients with well compensated biopsy-proven mixed aetiology cirrhosis and previous PHES defined MHE were treated with LOLA for 4 weeks.
- Baseline and 4-week clinical review, blood chemistry, and psychometric evaluation (Psychometric Hepatic Encephalopathy Score (PHES) and Cognitive Drug Research Score (CDRS, United BioSource)) were performed.
- Images were acquired using a 3-Tesla MR scanner (Achieva, Philips Medical Systems, Best, Netherlands) using a 3D T1-weighted sequence with a GE 8-channel head coil.
- 150 slices were obtained with a slice thickness of 1.2mm, TR of 9.64ms, TE of 4.60ms and flip angle of 8°. Volumetric MRI of the brain was paired with fMRI using a highly simplistic visuo-motor task.
- Regional brain volume (BV) and neural activation change (Blood Oxygenation Level Dependent (BOLD)) was assessed within the MRI software library (FSL, Oxford UK) using regional Structural Image Evaluation, using Normalisation, of Atrophy (SIENAr) and fMRI expert analysis tool (FEAT).

Results

- No change in clinical or biochemical state was noted.
- Significant improvements in CDR score and PHES score were observed (PHES Mean difference (MD) +1.2, p=0.008, CDRS MD +1.2, p =0.003, Speed of Memory z-score (SoM) MD +0.6, p=0.005, Quality of Executive Memory z-score (QoEM) MD+0.4, p=0.002, paired t-testing).
- Regional assessment of BV did not detect statistically significant modification of local grey matter volume following permutation testing.
- Significant BOLD signal change was detected in the posterior cingulate and ventral-medial pre-frontal cortex. This correlated robustly with SoM and QoEM.
- There was evidence of increased visual cortex activation accompanying improved psychometric performance.

Conclusion

- Core metabolic and structural regions of the brain showed altered function following treatment with LOLA. This was associated with improved psychometric performance, but not loco-regional change in BV suggesting LOLA may improve performance via mechanisms unrelated to low grade cerebral oedema.

LONG-TERM ADMINISTRATION OF RIFAXIMIN IMPROVES THE PROGNOSIS OF PATIENTS WITH ALCOHOL-RELATED DECOMPENSATED CIRRHOSIS: A CASE-CONTROL STUDY

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Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis-Zouboulis I, Karamanolis DG, and Ladas SD I AASLD Abstract 19, Oral Presentation 10/31/10

Objective

To evaluate the effect of intestinal decontamination with rifaximin on the long-term prognosis of patients with alcohol-related cirrhosis (Child-Pugh >7) and ascites

Methods

- Study included patients who had participated in a previous 4-week rifaximin study
- Patients whose liver hemodynamics improved continued to receive rifaximin 1200 mg daily
- Each patient matched by age and sex to 2 controls with decompensated alcohol-related cirrhosis
- All patients abstinent from alcohol for at least the preceding 6 months
- Patients were followed for up to 5 years, death, or liver transplantation

Results

	Rifaximin (n=23)	Controls (n=46)	*P* value
Variceal bleeding (%)	35.0%	59.5%	*P*=0.011
Hepatic encephalopathy (%)	31.5%	47.0%	*P*=0.034
Spontaneous bacterial peritonitis (%)	5.5%	46.0%	*P*=0.027
Hepatorenal syndrome	4.5%	51.0%	*P*=0.037
Death after 5 years follow-up	7 / 23 (30.4%)	24 / 46 (52.2%)	--
5-year cumulative probability of survival (%)	61%	13.5%	*P*=0.012

Conclusion

- Long-term administration of rifaximin is associated with reduced risk of developing complications of portal hypertension and with improved survival in patients with alcohol-related decompensated cirrhosis

RIFAXIMIN IMPROVES DRIVING SIMULATOR PERFORMANCE IN MINIMAL HEPATIC ENCEPHALOPATHY: A DOUBLE-BLIND, PLACEBO-CONTROLLED, PROSPECTIVE RANDOMIZED TRIAL

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Bajaj JS, Heuman DM, Saeian K, Hafeezullah M, Bell DE, Sterling RK, Stravitz R, Wegelin JA, White M, and Sanyal AJ
46th Annual Meeting of the European Association for the Study of the Liver

Objective

To evaluate the effect of rifaximin on driving simulator performance in patients with minimal hepatic encephalopathy in a randomized, double-blind, placebo-controlled trial

Methods

- Minimal hepatic encephalopathy (MHE) patients were diagnosed using a cognitive battery of 5 tests
  - All who were current car drivers without overt HE were included in an 8-week trial
- Trial involved at baseline
  - Driving and navigation simulation
  - Quality of life and Sickness Impact Profile
  - Ammonia
  - Meld score
- Patients were randomized into rifaximin 550 mg or placebo BID
- All tests repeated on the 8 week visit

Results

	Rifaximin (n=21)	Placebo (n=21)
Reduction in speeding tickets	-2.46*	0.46
% who reduced speeding tickets	81%*	19%
Reduction in illegal turns on navigation	-1.67*	-0.43
% who reduced illegal turns	61%*	21%
Improvement in mean cognitive Z score	1.13*	0.3
% who improved cognitive tests	91%*	61%

*Significantly better compared to placebo.

- There was no change in either group in
  - Total / physical Sickness Impact Profile
  - Ammonia
  - MELD score
- The Sickness Impact Profile psycho-social score improved from 12 to 8 (p=0.05) in the Rifaximin group compared to a change from 13 to 11 (p=0.5) in the placebo group

Conclusion

- Rifaximin significantly improved driving violations and navigation skills on a driving simulator and enhanced cognitive performance in cirrhotics with MHE

BURDEN OF CIRRHOSIS AND HEPATIC ENCEPHALOPATHY ON PATIENTS AND CAREGIVERS

Poster Presentation
March 31, 2011
Berlin, Germany

Bajaj JS, Heuman DM, Bell DE, White M, Gilles H, Luketic VA, Sterling RK, Stravitz R, Wade J, Gibson DP, Sanyal AJ
AASLD Abstract 174, Oral Presentation 11/01/10

Objective

To define the burden of cirrhosis on patients and caregivers from a financial and caregiver stress perspective

Methods

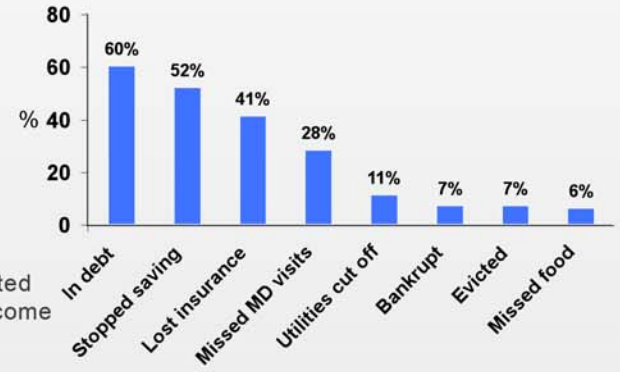
- Demographics, cirrhosis/HE severity and other complications, employment income, and socio-economic change after cirrhosis diagnosis were analyzed
- Caregiver was given the 'Perceived Caregiver Burden' (PCB) questionnaire consisting of 5 parts (financial, abandonment, schedule impact, personal health, and entrapment) and the 'Interpersonal Support Evaluation List' (ISEL) social support questionnaire
- Socio-economic and financial parameters were compared between patients with and without HE and patients with and without other complications

Results

- Patient profiles
  - 62 patients (58 years, 49 men, MELD 13, 80% HCV, 54% veterans)
  - 45% had HE (22% severe HE), 17% variceal bleed, and 10% prior spontaneous bacterial peritonitis
- Caregiver profiles
  - 62 caregivers (54 years, 23 men, 35 years of relationship, 79% shared housing)

Results (cont.)

- Family finances and cirrhosis
  - Median family income: $30K
    - Significantly lower in HE patient families compared to others ($20K vs. $37.5K, p=0.02)
  - 59% had >$10K out-of-pocket expenses for cirrhosis treatment
  - Median emergency finances were $20K - $50K, but were <$5K when debt was accounted for
    - If income stopped, median family savings would last 3 - 6 months
  - 43% of patients became unemployed after cirrhosis diagnosis
  - 81% of HE patients were less employable compared to 34% with other complications
- Caregiver burden
  - Mean PCB score was 65 (test scores can range from 27 to 135, 135 being worst)
    - Significantly higher for those caring for HE patients (76 vs. 62, p=0.02) and severe HE (77 vs. 63, p=0.01), but not for other complications
    - Higher scores were due to impact on schedule (p=0.0005), personal health (p=0.017), and entrapment (p=0.05)
    - On multivariate analysis, PCB score was affected by MELD, severe HE, ISEL score, and family income



Conclusion

- Cirrhosis and its complications, especially HE, place a significant financial burden on the family and are associated with caregiver stress

LONG TERM EFFICACY AND SURVIVAL IN PATIENTS TREATED WITH THE GUT-SELECTIVE ANTIBIOTIC RIFAXIMIN (550 MG BID) FOR THE MAINTENANCE OF REMISSION FROM OVERT HEPATIC ENCEPHALOPATHY

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K.D. Mullen, F. Poordad, L. Rossaro, M. Jamal, J. Talwalkar, S. Huang, K. Merchant, E. Bortey, W.P. Forbes
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Background

Rifaximin 550 mg BID reduced the risk of breakthrough hepatic encephalopathy (HE) by 58% over 6 months ($p< 0.0001$) in cirrhotic patients in a randomized, double-blind, placebo-controlled trial (RCT), and was further evaluated in an open label maintenance trial (OLM) in 128 new and 152 rollover RCT patients.

Methods

- Cirrhotic patients (n = 299) with a history of ≥ 2 overt HE episodes and a Conn score (CS) ≥2 within 12 months were enrolled into the RCT.
- Upon completion/withdrawal from the RCT, rifaximin or placebo patients with a CS ≤2 could begin open-label rifaximin in the OLM.
- Breakthrough HE was defined as an increase to CS ≥2 or CS and asterixis grade increase of 1 each if baseline CS=0.

Results

- Sixty of 70 rifaximin-treated patients in the RCT who enrolled into the OLM had remained in remission at completion/withdrawal and were followed for up to 1008 days.
- Forty-three (72%) of these patients did not experience breakthrough overt HE (average exposure = 630 days), and the time to first breakthrough overt HE episode was lower than that noted for placebo in the RCT (hazard ratio [HR] =0.11 [95% CI: 0.07-0.19, $p< 0.0001$]) with lower corresponding rates of occurrence (0.2 vs. 1.6 events/ PEY [person years of exposure], respectively [$p < 0.0001$]).
- Furthermore, for the 82 placebo patients in the RCT who crossed over into OLM and began open-label rifaximin, a 79% reduction in the risk of experiencing breakthrough overt HE was observed compared to their prior 6-month placebo treatment (rifaximin vs. placebo HR=0.21 [95% CI: 0.10 - 0.44, $p < 0.0001$]).
- Breakthrough overt HE for these 82 patients occurred at an event rate of 0.4/ PEY in OLM (rifaximin) which was significantly lower than the 1.5/PEY noted during the RCT ($p< 0.001$).
- Regardless of treatment, mean MELD score change rates were minimal in both the RCT and OLM.
- Event rates for death were similar (0.2 placebo vs. 0.1 rifaximin HR=0.58 [95% CI: 0.30 - 1.13]), and safety was not adversely impacted with increased rifaximin exposure.

Conclusion

- Rifaximin afforded continued protection from breakthrough HE and did not adversely affect expected mortality.