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Rifaximin Improves Driving Simulator Performance in a Randomized Trial of Patients with Minimal Hepatic Encephalopathy

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Abstract

Background & Aims—Patients with cirrhosis and minimal hepatic encephalopathy (MHE) have driving difficulties but the effects of therapy on driving performance have not been assessed. We evaluated whether performance on a driving simulator improves in patients with MHE following treatment with rifaximin.

Methods—Patients with MHE who were current drivers were randomly assigned to placebo or rifaximin groups and followed for 8 weeks (n=42). Patients underwent driving simulation (driving and navigation tasks) at the start (baseline) and end of the study. We evaluated patients' cognitive abilities, quality-of-life (using the Sickness Impact Profile [SIP]), serum levels of ammonia, levels of inflammatory cytokines, and MELD scores. The primary outcome was percent who improved in driving performance, calculated by: total driving errors=speeding + illegal turns + collisions.

Results—Over the 8-week study period, patients given rifaximin made significantly greater improvements than those given placebo in avoiding total driving errors (76% vs. 31%, P=0.013), speeding (81% vs. 33%, P=0.005), and illegal turns (62% vs. 19%, P=0.01). Of patients given

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rifaximin, 91% improved their cognitive performance, compared with 61% of patients given placebo ($P=0.01$); they also made improvements in the psycho-social dimension of the SIP, compared with the placebo group ($P=0.04$). Adherence to the assigned drug averaged 92%. Neither group had changes in ammonia levels or MELD scores, but patients in the rifaximin group had increased levels of the anti-inflammatory cytokine interleukin-10.

Conclusions—Patients with MHE significantly improve driving simulator performance following treatment with rifaximin, compared with placebo.

Keywords

driving performance; cognitive function; cirrhosis; liver disease; IL-10

BACKGROUND

Patients with cirrhosis and cognitive dysfunction have deficits in attention, reaction time and working memory due to the domains affected by the spectrum of neuro-cognitive impairment in cirrhosis (SONIC)^{1, 2}. These deficits, also known as minimal hepatic encephalopathy (MHE) can predispose patients with cognitive dysfunction to impaired quality of life and difficulties in driving and navigation that require the use of the domains affected^{3–8}. To add to the challenge, MHE patients have an increased risk of driving offenses and have poor insight into their driving skills^{9–11}. The pathogenesis of cognitive dysfunction and hepatic encephalopathy in cirrhosis is related to gut-derived toxins and resultant neuro-glial injury in the setting of a systemic inflammatory milieu and therapy with gut-specific agents such as lactulose and rifaximin can improve cognition^{12–16}. However, it is unclear whether these therapeutic options can improve driving performance in this population. This is important because driving is a practical interpretation of the cognitive domains affected in MHE and there is a need to study therapy of these cognitive deficits in the setting of clinically relevant activities and outcomes^{1, 17}.

Therefore the current randomized, double-blind, placebo-controlled trial was undertaken with the aim to study the effect of rifaximin 550mg BID on driving performance using a driving simulator. Secondary outcomes studied were cognitive performance, quality of life and change in the systemic inflammatory milieu and neuro-glial function markers.

METHODS

The trial was conducted under an FDA investigational new drug number (77783) and was registered at www.clinicaltrials.gov number NCT00533910 before enrollment was initiated. Enrollment was performed in the Medical College of Wisconsin and the McGuire Veterans Affairs Medical Center.

Study patients

Patients with cirrhosis and cognitive dysfunction as defined by a Z score of less than -2 in at least 2 of the following tests, number connection tests A and B (NCT-A/B), digit symbol (DST) and block design test (BDT) as well as in the lures of the inhibitory control test (ICT) were included^{2, 18, 19}. All included patients had never had a prior episode of overt HE, were not on therapy for it, were not on any psycho-active medications apart from stable doses of selective serotonin re-uptake inhibitors and were current car drivers. We excluded patients with prior overt HE, who had abused alcohol or illicit drugs within 6 months, were not current drivers, whose mini-mental status examination score (MMSE) was <25, who were on other antibiotics and who were allergic to rifampin, rifaximin or rifamycin²⁰.

Study procedures

The protocol was approved by the institutional review boards at the Medical College of Wisconsin and the McGuire VA Medical Center. Initial informed consent for screening and cognitive testing was obtained as part of a separate ongoing protocol to study the natural history of MHE. For those meeting criteria for the current study, a second informed consent was obtained for participation in the randomized treatment trial the same day.

The trial included 3 visits; baseline, second visit at 4 weeks and last visit at 8 weeks.

Baseline visit—Patients were randomized equally into placebo and active drug based on blocks of 4 provided directly to the investigational pharmacy. The patients were therefore pre-randomized and were allocated in a blinded fashion. Un-blinding was permitted only in emergencies. During the first visit, the patients underwent evaluation by a hepatologist to exclude overt HE, MMSE, sickness impact profile (SIP) and the driving simulation. Patients also underwent evaluation for venous ammonia, ALT, AST, hemoglobin, platelet count and the model for end-stage-liver disease (MELD) score²¹. A portion of the serum was stored for analysis of inflammatory cytokines, endotoxin, endothelial-dysfunction markers and neuro-glial function markers. At the end of the visit, the patients were provided study drug for 4 weeks, a log to enter their adherence and to note down any symptoms that occurred between the visits and were asked to return the empty drug bottles at the second visit.

Second visit—Patients returned 4 weeks after their initial visit, during which time the adherence and tolerance to assigned medication was inquired about and the patients underwent blood draw for the above laboratory values. Patients underwent a physical exam by a hepatologist and MMSE to exclude overt HE. The patients were given the assigned drug for the next 4 weeks and were again given the log for adherence and symptoms for the last visit.

Last visit—Patients returned 4 weeks after their second visit for the final visit when they again underwent the procedures of the second visit as well as a repeat of the cognitive battery using different versions, SIP as well as the driving simulation. Final adherence was computed at this time on the basis of the return of study drug bottles.

Detailed testing procedures used

Driving simulator—The simulator used was the STISim Drive simulation software (Systems Technology Inc., Hawthorne, CA) was used in the simulator (Model BR1100, Los Gatos, CA www.beta-research.com), which had a computer screen, a steering wheel, a console consisting of a brake and accelerator, and automatic recordings of accidents and time taken for completion of tasks. This simulation software has been used in characterizing the effects of several disease processes such as HIV, aging, and sleep disorders on driving and in MHE^{3, 10, 21}. The overall simulation task consisted of 3 parts.

- a. *Training Simulation*: The first part was a 15-minute training run that was administered to all patients to familiarize them with the tasks and to ensure that they could comply with the directions that flashed across the computer screen. The training was done during both initial and last visits.
- b. *Drive Testing Task*: The second part was a 25-minute driving run and the two outcomes was the number of speeding tickets and collisions on the simulation. There were clear speed limits posted and all traffic rules and directions were provided through road signs. An audible siren indicated a speeding ticket. No minimum driving speed was required.

- c. **Navigation Task:** The navigation task, which consisted of driving through a virtual city that was modified version of the one used by Marcotte *et al.* which has been used in MHE patients before^{3, 22}. All patients were instructed to get from the beginning to the end of a path marked on a paper map. All turns were clearly marked with signs guiding patients to make legal turns and leading them to the marked destination. Turns that led patients off the marked path were considered illegal turns, and they were the primary outcome of this task. The task was set up to have 30 possible illegal turns, 3 of which had built-in accidents that clearly demonstrated to the patient that an illegal turn had been made. However, the remaining 27 possible illegal turns did not come with any clear indication that an illegal turn was being made. Only the first turn off of the marked path was counted as an illegal turn.

Cognitive battery—In NCT-A, a subject draws a line connecting consecutively numbered circles on a worksheet which measures psychomotor speed, and attention. In NCT-B the task alternates between connecting both numbers and letters²³. Therefore, NCT- B is often regarded as a test of executive function, specifically conceptual flexibility and working memory²⁴. The fundamental challenge of this paradigm reflects a subject's capacity to reliably bind items to order positions and to unbind and update those at each step in the sequence. The DST is a measure of complex visuo-motor tracking and learning which is relatively unaffected by intellectual ability, memory, or learning. This task emphasizes sustained attention, response speed and visuo-motor integration²⁵. The ICT requires an individual to pay attention to target stimuli and disregard lures. Poor performance on this measure suggests impairment in cortical association areas necessary for attention and analysis of critical visual features^{18, 26}. In the current study we focused exclusively on the number of lures responded to. The lure response requires a subject to evaluate each stimulus presented in a sequence, and to determine whether a particular stimulus matches another stimulus presented earlier in the sequence, within a specified time lag. The BDT is a very good measure of visual spatial ability in which subjects are instructed to complete designs with blocks in a timed manner. Measures of functional brain activation indicate correlation between BDT performance and increased glucose metabolism in the posterior parietal region, particularly in the right hemisphere²⁷. Similarly, poor BDT performance has been associated with lateralized lesions involving the right parietal area and does not involve the left lobe²⁸.

Quality of life with Sickness Impact Profile (SIP)—The SIP is a 136-part quality of life questionnaire that interrogates 12 different domains of daily functioning which are sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness, emotional behavior, and communication²⁹. Apart from a 12-dimension profile score and physical and psychosocial scores, a total score can be computed. Eating, recreation and pastimes, sleep and rest and work are coded separately. Patients mark only items that relate to their health within twenty-four hours and a high score indicates worse functioning²⁹. The SIP has been previously used in the characterization of patients with MHE^{8, 15}.

Serum markers of inflammation, endothelial function and neuro-glial function

—Serum was analyzed for inflammatory cytokines (TNF- α , IL-2, IL-6 and IL-10), endotoxin, endothelial dysfunction markers (asymmetric di-methyl arginine (ADMA), vascular cell adhesion molecule (VCAM) and soluble intercellular adhesion molecule (sICAM)) and neuro-glial injury markers (neuron-specific enolase (NSE) and s100B protein). These samples were analyzed using two replicates (the average was used for

analysis) using published methods by Assaygate Inc, Ijamsville, MD using bead-based suspension protein arrays^{30, 31}.

Adverse events

Those that were specifically inquired were nausea, vomiting, abdominal pain, flatulence, tenesmus and headache as well as the number of daily bowel movements. A relative change in these symptoms was studied between groups as well as other adverse events.

Outcomes and statistical analysis

The primary outcome was driving performance on the simulator, indicated by the proportion of patients who improved in the rifaximin group compared to the placebo group as measured by total errors. Total driving errors was defined as the sum of:

- a. Testing speeding tickets
- b. Testing collisions
- c. Navigation illegal turns

An intention-to-treat analysis was planned with the “last measurement carried forward” for all patients who did not come for their last visit. Statistical significance of differences in percent improved was assessed by the chi-square test.

Cognitive function: The change in mean Z score at baseline was compared between the 2 groups and the percentage that improved in the rifaximin and placebo group were compared. The change in individual test compared to baseline was also computed.

Quality of life: the change in total SIP, physical dimension, psycho-social dimension and the remaining independent predictors were performed between the 2 groups as well as compared to the baseline performance.

Blood markers: MELD score, venous ammonia, AST/ALT and specialized serum markers were compared between and within groups and also compared to the baseline concentrations. Correlation between driving performance, psychometric testing and SIP was computed using the Pearson correlation test.

Sample size

An open-label trial of probiotic yogurt in our center showed a 70% improvement in cognitive function over 8 weeks³². We assumed that improvement in driving performance would be highly correlated with cognitive function and assumed that 50% of patients in the rifaximin group would improve in their driving outcomes compared to 10% in the placebo group. With an alpha of 0.05 and a power of 80% we would require 20 patients in each group.

RESULTS

A total of 203 patients with cirrhosis were considered for this study. The majority, 97 patients were excluded due to use of psychoactive drugs (lactulose alone in 45, non-SSRI antidepressants in 21, rifaximin in 12, anti-seizure medications in 10 and benzodiazepines in 9), 38 were excluded because of normal performance on the cognitive battery and 26 were excluded because they were not current car drivers. Forty-two patients were ultimately included into the randomized placebo-controlled trial between October 2007 and February 2010 (twelve from the Wisconsin and 30 from Virginia).

Baseline characteristics

As shown in table 1, there were no significant differences in the demographic characteristics, details of cirrhosis and driving history between groups.

Flow of the study

42 patients were included in the trial; 1 placebo-assigned patient withdrew consent (the patient did not develop overt HE and was not hospitalized but decided not to come back due to logistical issues). None of the patients developed overt HE, developed infections, required antibiotics or were hospitalized throughout the trial. Apart from the one patient who did not return, the mean adherence was 92% (75% to 100%) with 2 patients taking <80% of study drug.

Driving performance

There was a significant improvement in mean number of speeding tickets and illegal turns compared to baseline only in the rifaximin group, while a non-significant trend was seen in collisions (Table 2). There was no significant change in any of the driving errors in the placebo group.

Total driving errors—A significantly higher proportion of patients in the rifaximin group experienced a reduction in total driving errors than in the placebo group (76% vs 33%, $p=0.013$, Table 3).

Speeding tickets—A significantly higher proportion of patients in the rifaximin group reduced their speeding tickets compared to the placebo group (81% vs 33%, $p=0.005$).

Illegal turns on navigation—A higher proportion in the rifaximin group reduced their illegal turns compared to the placebo group (62% vs 19%, $p=0.012$).

Collisions—A greater proportion of patients in the rifaximin group reduced their collisions than in the placebo group, but the difference was not statistically significant (43% vs 33%, $p=0.75$).

Driving outcomes (collisions, illegal turns and speeding tickets) at study initiation were correlated with individual cognitive test performances. There was a significant correlation between number of illegal turns and NCT-A ($r=0.54$, $p=0.0001$) and NCT-B ($r=0.30$, $p=0.05$). Collisions and speeding tickets were directly correlated with ICT lures ($r=0.35$, $p=0.02$ and $r=0.29$, $p=0.05$ respectively). There were no significant correlations between the rest of cognitive tests or driving outcomes.

Cognitive testing

Patients randomized to rifaximin had a significantly higher improvement in their mean Z-score of the total battery. The change in the total cognitive battery Z-score was significantly higher towards normal (1.13 ± 0.2) in the rifaximin group compared to the placebo group (0.42 ± 0.2 , $p=0.02$). There was a significant improvement in the NCT-B, DST, BDT and ICT in the rifaximin group compared to baseline while only the DST and BDT improved in the placebo group. NCT-A Z-scores did not change from baseline in either group (Table 4).

There was a significant correlation between improvement in mean cognitive Z-score and total errors ($r=-0.3$, $p=0.05$) as well as speeding tickets ($r=-0.4$, $p=0.01$). This implies that with increase in mean Z-score (i.e. improvement in cognitive performance) there was a decrease in total errors and speeding tickets.

Clinical status and severity of cirrhosis

There was no significant difference in the severity of cirrhosis and AST/ALT at baseline (Table 5). During the trial, none of the patients was hospitalized, developed overt HE or other complications of cirrhosis. MELD score (rifaximin end: 9.9 ± 3 vs placebo end 9.2 ± 3 , $p=0.43$), AST (rifaximin end: 73 ± 68 vs. placebo end: 82 ± 54 , $p=0.67$) and ALT (rifaximin end: 61 ± 66 vs. placebo end: 72 ± 59 , $p=0.57$) did not change significantly between groups. Venous ammonia levels also remained statistically similar (Rifaximin end: 50 ± 36 vs Placebo end: 46 ± 22 , $p=0.68$).

Quality of life

SIP scores were not different between rifaximin and placebo at baseline. There was a significant improvement in the psycho-social dimension but no change in the physical dimension or the independent domains was observed (Table 6).

Serum markers

There was a significant increase in the anti-inflammatory cytokine, IL-10 only in the rifaximin group. No other marker changed significantly within or between groups (Table 7).

At baseline, there was no correlation between the serum markers and either the cognitive battery or the driving performance. However, there was a significant positive correlation between NSE and working capacity ($r=0.4$, $p=0.038$), sleep and rest ($r=0.4$, $p=0.02$) and home management ($r=0.32$, $p=0.04$). There was also a trend towards a positive correlation between NSE and total SIP ($r=0.3$, $p=0.08$) and psychosocial aspects of SIP ($r=0.3$, $p=0.09$).

Safety

Six patients complained of nausea (3 rifaximin and 3 placebo), 2 of whom developed self-limited vomiting (1 rifaximin and 1 placebo). Five rifaximin and 5 placebo patients experienced abdominal pain while 9 placebo and 4 rifaximin patients complained of flatulence. Four patients assigned to rifaximin and 7 assigned to placebo recorded headache. One rifaximin patient developed limited flu-like symptoms while another developed constipation. Two patients (1 rifaximin and 1 placebo) developed self-limiting diarrhea of which one got tested and was negative for *Clostridium difficile* or fecal leucocytes and resolved within 3 days without antibiotics. One placebo patient had itching while another had anorexia and dry mouth. None of the adverse events required hospitalizations, emergency room visits, antibiotics or study drug discontinuation.

DISCUSSION

The randomized, placebo-controlled, double-blind trial demonstrates that patients randomized to rifaximin have a higher rate of improvement in total driving errors, specifically speeding tickets and navigation illegal turns on a driving simulator compared to those on placebo. This was accompanied by improved cognitive performance and psychosocial aspects of quality of life in the rifaximin group.

Driving requires balance and integration of different cognitive inputs, most of which are adversely affected in MHE¹¹. Motor vehicle driving depends on decisions made on a tactical, strategic and operational level³³. Strategic and operational decisions depend on adequate reaction time, sustained attention, visuo-motor coordination and the ability to inhibit responses within a specified period of time. Navigation skills also involve the overlay of working memory and visual perceptual skills. MHE patients have difficulties in all the above domains resulting in poor outcomes on a driving simulator, on structured driving tests and a higher rate of traffic offenses¹¹.

The current study confirms earlier studies of impaired driving and navigation skills on driving simulation in MHE patients which were correlated with cognitive performance. In the current study NCT performance (both A and B) was associated with navigational illegal turns in the entire group at baseline. Better NCT-A performance reflects strengths in visual scanning, and psychomotor speed while NCT-B places additional demands on cognitive flexibility and working memory. In a recent study of spatial navigation, Jacobs *et al* noted lateralized nondominant hemisphere specialization with the right temporal/occipital regions for spatial navigation³⁴. Whereas, both NCT-A and B have been shown sensitive to the information processing speed slowing associated with periventricular and deep white matter intensities³⁵, functional brain imaging studies indicate that NCT-B performance is also associated with frontal and medial temporal lobe atrophy³⁶. Our data provide additional support for the importance of the temporal lobe in navigational ability.

For all study subjects ICT lures were directly correlated with both speeding tickets, and collisions. ICT performance conforms to the “N-back task” paradigm³⁷. The defining characteristic of the N-back task is that it requires the continuous process of building, maintaining, updating, and releasing arbitrary bindings between items in temporal order positions³⁸. The ability to inhibit behavioral response is considered an important developmental milestone, reflective of frontal lobe maturation and a top-down control of posterior parietal cortex via dorsal lateral prefrontal cortex modulation. This neural network has been proposed for optimal working memory performance associated with inhibitory control³⁹. In a study of brain mapping using event-related functional MRI, Garavan *et al* provide additional support for the notion that response inhibition, as assessed by the ICT, reflects a cortical network involving feedback between frontal, insular, and the parietal regions (particularly in the right hemisphere)²⁶. The association between ICT lures and collision rate, likely reflects a breakdown in attending to visual stimuli and immediate inhibition/behavioral adjustment since this behavioral accommodation determines success or failure in avoiding collision. In contrast with collisions, a speed violation may reflect the inability to keep in working memory information regarding a previously presented speed limit sign. Given that performance on the DST, a measure of sustained attention and psychomotor speed was not associated with speeding violations, the relationship between speed violations and ICT performance likely reflects a breakdown in working memory, and defects in response inhibition.

In the trial, patients randomized to the treatment group had a significant reduction in the number of speeding tickets and illegal turns compared to the placebo group while collisions were not affected. Speeding tickets are indicative of difficulties in sustained attention and working memory which occur despite the presence of several speed limit signs, a controlled environment, a clearly visible speedometer in the display, a 15-minute training run as well as a clearly audible siren on speeding. Therefore a speeding ticket may reflect the inability to keep in the working memory information regarding a previously presented speed limit sign as well as a disregard or lack of memory for an audible siren indicating prior speeding. Navigation skills were impaired in the same map-based driving simulation study previously published by our group³. Illegal turns in this case represent a failure to take into account several cues on the map as well as on the driving simulator screen such as one-way signs and traffic signs signaling the legality of turns. Therefore even a single illegal turn reflects a breakdown in interpretation, working memory and spatial orientation³. Compared to their baseline performance, at the two month follow-up, 81% of rifaximin patients reduced their number of speeding violations. Similarly, 62% of these subjects reduced their number of illegal turns. The fact that only 2 of 5 cognitive test scores, NCT-B and ICT lures, was uniquely associated with rifaximin use provides insight into the cognitive abilities associated with driving performance change in these patients. The improvement in BDT and DST in

both groups indicates a learning effect (even after a gap of 2 months). Therefore interpretation of open-label MHE trials should be performed in that light.

Rifaximin was chosen over lactulose for this study because this therapy can be blinded and has been shown to improve cognition in MHE and overt HE in prior randomized controlled trials^{40, 41}. This trial confirms and extends cognitive improvement into the realm of driving simulation, specifically reduction of speeding tickets and illegal turns. Interestingly there was no difference in the collisions, although there was a slight trend towards improvement in rifaximin and worsening in placebo. Unlike speeding tickets and illegal turns, which are subtle, a collision is a dramatic and indelible outcome in the simulator, which may then increase the patient's insight into their driving and improve their focus. This could explain the lack of change in collisions while both speeding tickets and illegal turns improved in the rifaximin group. It is also possible that rifaximin could improve collisions in a larger cohort since there was a non-significant trend towards improvement. Therefore, the driving performance change seen in these patients likely reflects improved working memory, response inhibition, and cognitive flexibility. Based on these data we speculate that therapy may reflect change in the cortical network feedback between frontal, insular, and the parietal regions (particularly in the right hemisphere). Since the simulation can be viewed as a series of cognitive tests, these results are a reasonable extension of those prior studies demonstrating improved cognition with MHE therapy.

The study did not reveal any significant change in venous ammonia, development of overt HE or changes in the overall synthetic function. This may reflect the highly compensated nature of the included subjects. There has been recent interest in the role of inflammation and endothelial dysfunction in cirrhosis and specially HE^{13, 42, 43}. There was no change in endothelial function markers as well as inflammatory cytokines apart from IL-10, an anti-inflammatory cytokine, which was significantly elevated in the rifaximin group compared to placebo⁴⁴. It is involved in suppression of Th1 cytokines, MHC class II antigens, and co-stimulatory molecules on macrophages as well as negatively affecting NF- κ B. Interestingly IL-10 is intricately associated with the regulation of intestinal inflammation, raising the possibility, that rifaximin could also act by regulating local intestinal immunity and inflammation⁴⁵.

There was a significant improvement in the psycho-social aspect of the SIP in the rifaximin group but no other changes were observed. This partly replicates other therapeutic MHE trials but it is likely that the requirement that patients in this trial needed to be self-sufficient and independent car drivers would make any further improvement difficult¹⁵. It may also be due to the relatively shorter follow-up in our study compared to that in Prasad et al¹⁵. Importantly a correlation between NSE with SIP was observed. NSE is a neuronal cytoplasmic glycolytic enzyme which rises after traumatic brain injury as well as in stroke. Interestingly in traumatic brain injury NSE levels have been shown to predict recovery after the event and ultimate disability⁴⁶. The current study is the first to correlate its levels with the quality of life. Further studies are needed to study this relationship and to analyze whether NSE can be a good biomarker for MHE.

Driving capability in MHE and other medical disorders is a difficult issue that crosses medical, psychological and medico-legal boundaries^{33, 47}. At this time physicians are not trained to assess "fitness to drive" and cognitive tests alone are not able to distinguish good and bad drivers⁴⁸. Simulation results in MHE patients demonstrate difficulties in driving and navigation which extend to the road and in poor traffic outcomes^{9, 11}. The current study shows that patients with MHE have difficulties on a driving simulator and the rifaximin can improve navigation and speeding tickets. Driving simulation does not have the vestibular or the "in-the-scene" feel of actual driving but is still able to replicate driving under controlled

and stable conditions. The simulation is also an optimum method to study navigation skills, since it ensures similar conditions throughout the examination. Performing this study in an uncontrolled environment such as road-testing as well as gauging the effect of therapy on on-road driving outcomes would have diminished its objectivity. Also due to the fortunately rare occurrence of on-road driving outcomes, it would have exposed a significantly higher number of patients to the drug with poorly interpretable results. This study gives us a proof-of-concept that MHE therapy can improve driving performance in a controlled setting. The current study was with rifaximin, however, it is possible that other therapies for HE could also have a similar effect on driving performance. Also, since this was a short-term study, it is possible that resistance to rifaximin could develop with long-term use which may reduce its efficacy.

We conclude that there is improvement in total driving errors, specifically speeding and navigation on a driving simulator with rifaximin therapy. Treatment also improves cognitive testing as well as psycho-social aspects of quality of life in this population. This trial provides a proof-of-concept that improvement in clinically relevant outcomes such as driving performance can be observed with therapy for MHE using rifaximin. Further large-scale trials are needed to confirm these findings.

CONSORT FLOW: Rifaximin and driving simulation in MHE

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Sponsor involvement: Since this was an investigator-initiated project, Salix provided funding but was not involved in protocol design and implementation, data collection, analysis or interpretation of the study results.

Abbreviations

SONIC	spectrum of neuro-cognitive impairment in cirrhosis
MHE	minimal hepatic encephalopathy
ICT	inhibitory control test
NCT-A/B	number connection test A/B

DST	digit symbol test
BDT	block design test
MMSE	mini-mental status examination
SIP	sickness impact profile

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Figure 1.

There was a significant reduction in the percentage of patients who improved their total driving errors (16 of 21, 76%) in the rifaximin group (Figure 1A) compared to the placebo group (Figure 1B) (7 of 21, 33%, $p=0.013$).

Table 1

Baseline characteristics of the two groups

	Rifaximin (n=21)	Placebo (n=21)	P value
Age	55 ± 5	57 ± 5	0.14
Education	14 ± 2	14 ± 2	0.81
Alcoholic cirrhosis	5 (21%)	3 (14%)	0.69
MELD score (median)	9	9	0.79
Child score (A/B/C)	19/2/0	17/4/0	0.66
Venous ammonia	49 ± 28	43 ± 20	0.38
AST	67 ± 54	74 ± 48	0.69
ALT	60 ± 60	71 ± 57	0.56
Duration of driving (years)	34 ± 10	35 ± 12	0.62

There were no significant differences between the groups at baseline

Table 2

Detailed simulator outcomes compared to baseline

	Rifaximin baseline	Rifaximin end	P value rifaximin group	Placebo baseline	Placebo end	P value placebo group
Total errors	10.3 ± 6.2	5.5 ± 3.8	0.0001	7.2 ± 4.8	7.6 ± 3.9	0.77
Speeding tickets	4.4 ± 4.1	2.0 ± 2.0	0.006	2.6 ± 2.8	2.9 ± 3.1	0.70
Illegal turns	2.6 ± 3.4	0.9 ± 1.2	0.03	1.9 ± 2.7	1.5 ± 1.3	0.50
Collisions	3.2 ± 2.2	2.6 ± 1.9	0.27	2.7 ± 1.3	3.0 ± 1.9	0.50

All outcomes are expressed in mean ± SD. There was a significant improvement in all outcomes apart from collisions in the rifaximin group compared to their baseline using paired t-test. No significant improvement was seen in the placebo group compared to their baseline performance.

Table 3

Change in simulator outcomes by group

	Rifaximin group (n=21)	Placebo Group (n=21)	P value
Reduced total driving errors	16 (76%)	7 (33%)	0.013
Reduced speeding tickets	17 (81%)	7 (33%)	0.005
Reduced illegal turns	13 (62%)	4 (19%)	0.012
Reduced collisions	9 (43%)	7 (33%)	0.751

Results are presented as numbers with percentage in parentheses. All driving outcomes improved significantly in the rifaximin group compared to placebo apart from collisions.

Table 4

Change in cognitive tests during the trial.

	Rifaximin baseline Z score	Rifaximin end Z score	Placebo baseline Z score	Placebo end Z score	% improved rifaximin	% improved placebo
Mean total cognitive battery	-3.29±0.35	1.19±0.24 [#]	-2.65±0.36	0.46±0.17	91% [*]	61%
NCT-A	-3.22±0.74	-2.4±0.51	-1.91±0.34	-1.42±0.46	57%	57%
NCT-B	-3.80±0.89	-1.24±0.57 [#]	-2.34±0.79	-1.75±0.55	81% [*]	33%
DST	-3.11±0.30	-2.78±0.29 [#]	-3.12±0.22	-2.78±0.22 [#]	67%	62%
BDT	-2.92±0.28	-2.02±0.22 [#]	-2.59±0.39	-1.95±0.36 [#]	81%	67%
ICT lures	-3.38±0.73	-2.07±0.80 [#]	-3.31±0.94	-3.07±0.88	76% [*]	43%

[#] significant improvement within groups;

^{*} significant improvement in the rifaximin group compared to placebo. **The delta Z score was significantly higher towards normal (1.13±0.2) in the rifaximin group compared to the placebo group (0.42±0.2, p=0.02).** There was a significant improvement in 4 of the 5 cognitive tests in the rifaximin group compared to baseline while only 2 of the 5 tests in the placebo group improved compared to their baseline.

Table 5

Change in quality of life scores using Sickness Impact Profile from baseline.

	Rifaximin baseline	Rifaximin end	P value rifaximin group	Placebo baseline	Placebo end	P value placebo group
Total score	11±2	10±2	0.36	14±3	12±3	0.21
Psychosocial dimension	13±3	8±2	0.04	13±4	11±3	0.45
Physical dimension	7±2	7±2	0.62	7±2	6±2	0.51
Work	29±7	33±7	0.46	25±6	23±7	0.43
Sleep and rest	27±6	23±6	0.34	22±7	21±6	0.77
Eating	3±1	3±1	0.81	5±2	4±1	0.32
Home management	12±3	11±3	0.54	14±4	10±3	0.06
Recreation and pastimes	20±5	13±4	0.08	16±5	14±4	0.45

A higher score in the Sickness Impact Profile (SIP) indicates a worse quality of life. There was no significant change in quality of life measures compared to baseline using SIP apart from an improvement in the psycho-social dimension using the paired t-test. Neither the physical dimension nor the independent domains (work, sleep and rest, eating, home management and recreation and pastimes) changed significantly from baseline.

Table 6

Inflammatory cytokines, endotoxin, neuroglial markers and endothelial dysfunction markers in the trial

	Rifaximin baseline	Rifaximin end	P value rifaximin group	Placebo baseline	Placebo end	P value placebo group
Endotoxin(EU)	0.3 ± 0.3	0.3±0.3	0.61	0.2±0.3	0.2±0.2	0.83
Inflammatory cytokines						
IL-18	112±75	110±67	0.74	118±55	114±12	0.56
IL-6	38±114	51±168	0.33	18±31	16±24	0.28
IFN- γ	5±11	8±16	0.26	2±4	3±6	0.19
IL-2	10±25	11±33	0.33	5±12	6±19	0.59
IL-10	11±28	14±30	0.01	5±10	6±12	0.21
TNF- α	5±5	6±5	0.15	5±2	5±2	0.97
IL-1b	3.5±9	4±9	0.06	3±7	4±11	0.25
Endothelial dysfunction markers						
ADMA (μ mol/l)	0.51±0.10	0.53±0.13	0.27	0.52±	0.55±0.17	0.17
VCAM	1650793±555918	1679655±625175	0.47	1715009±1690953	1690953±505443	0.79
sICAM	634785±333960	642930±349249	0.78	637159±416049	675305±428942	0.08
Neuro-glial markers						
S100B (ng/ml)	45±147	51±163	0.10	31±64	15±8	0.31
NSE (ng/ml)	11390±14724	9892±9359	0.30	14084±18511	9922±7480	0.23

All measurements are in picograms/ml unless specified otherwise. There was no significant difference between the two groups at baseline with respect of any of the serum markers. Apart from a significant increase in the IL-10, there was no significant change in any inflammatory cytokines, endothelial dysfunction markers or neuro-glial injury markers during the trial using the paired t-test. The lower detection limit for IL-10 was 0.5 pg/ml (intra and inter-assay variability was 3% and 5% respectively). ADMA: asymmetric dimethylarginine, sICAM: soluble intracellular adhesion molecule, VCAM: vascular intracellular adhesion molecule, NSE: neuron specific enolase.