

Utilization of Baclofen in Maintenance of Alcohol Abstinence in Patients with Alcohol Dependence and Alcoholic Hepatitis with or without Cirrhosis

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Abstract — **Aim:** To report the efficacy and safety of baclofen in improving clinical state in patients with alcoholic hepatitis. **Method:** Single center, open, retrospective study analyzing the effects of baclofen utilized over 12 months in patients with alcoholic hepatitis with or without cirrhosis and alcohol dependence on these liver parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (Tbili), prothrombin time (PT), international normalized ratio (INR), albumin and Model for End-Stage Liver Disease (MELD) score. **Results:** Out of 40 patients, 35 were treated with baclofen. On average, baclofen was used for 5.8 months. A significant decrease in the mean AST, ALT, Tbili, INR, PT and MELD score was seen when comparing pre-baclofen use compared with post-baclofen use. Of the 35 patients who were started on baclofen, 34 (97%) remained abstinent. There were no serious adverse events. **Conclusions:** Baclofen's safety and efficacy in improving the clinical condition patients with alcoholic liver disease has been supported. Randomized prospective studies with longer duration of baclofen in this population may further optimize its use and corroborate efficacy.

INTRODUCTION

Continued alcohol consumption in the setting of alcoholic cirrhosis dramatically increases mortality despite medical and surgical interventions, increasing the hepatic venous pressure gradient in patients with alcohol-induced cirrhosis and increasing the risk of variceal bleeding (Luca *et al.*, 1997). Spontaneous regression of esophageal varices in those with cirrhosis can occur after strict abstinence from alcohol (Müting, 1990). Abstinence from alcohol is key as it aids in reversing liver fibrosis, thus avoiding or reversing liver failure. Complete abstinence from alcohol is the most effective and key component of treatment of patients with alcoholic liver disease.

There are few drugs approved that are aimed at reducing alcohol cravings and relapse in alcoholics. However, studies exploring their efficacies in patients with cirrhosis, given that some medications can be toxic to the liver, are lacking. Baclofen is predominantly excreted by the kidneys and its low liver metabolism (15%) makes it a safer drug to use in liver disease (Davidoff, 1985). Baclofen, a gamma-aminobutyric acid (GABA)-B receptor agonist, has been shown to enhance abstinence, reduce drinking quantity and reduce craving in alcoholic liver disease (Addolorato *et al.*, 2002).

Preclinical studies reveal baclofen's efficacy in reducing the levels of alcohol consumption in rats made physically dependent on alcohol via a vapor chamber (Walker and Koob, 2007) as well as in rats trained to prefer alcohol (Daoust *et al.*, 1987). Colombo *et al.* (2002) showed baclofen's utility in suppressing alcohol withdrawal signs in rats made dependent on alcohol. Baclofen reduces alcohol-seeking behavior in alcohol-preferring rats at acquisition, maintenance, and after a period of abstinence (Maccioni and Colombo, 2009). The first human open-label pilot study demonstrated how baclofen at 10 mg three times a day over 4 weeks was effective in reducing alcohol intake and cravings in 10 alcohol-dependent individuals (Addolorato *et al.*, 2000) and a double-blinded, randomized control trial supported this (Addolorato *et al.*, 2002).

Subsequent 12-week studies further demonstrated baclofen's role in promoting alcohol abstinence and decreasing alcohol craving and intake (Leggio *et al.*, 2008a,b). In a non-

placebo controlled trial of 30 mg/day of baclofen over 12 weeks conducted by Flannery *et al.* (2004), baclofen was shown to be reasonably tolerated and possibly helpful in reducing drinking, craving and anxiety in alcohol-dependent individuals. The above findings were further validated in a larger randomized, double-blind controlled study whereby baclofen at 30 mg/day was significantly better than placebo in increasing total abstinence (71 vs. 29% respectively), reducing alcohol cravings, intake, and lengthening the time to relapse with no significant adverse effects in alcohol-dependent patients with cirrhosis over a 12-week period (Addolorato *et al.*, 2007). This study only included patients with alcoholic liver disease.

Heydtmann *et al.* (2012) gave patients with alcoholic liver disease baclofen for a mean of 5 months and reported an average of 58.7% reduction in alcohol consumption and self-reported significant decrease in alcohol cravings. Moreover, a reduction in hospitalization was reported and was related to duration of treatment with tailored dose baclofen (mean dose 95 mg/day). Leggio *et al.* (2012) showed improvements in some liver tests (albumin, INR) in alcohol-dependent HCV-infected cirrhotic patients, and consistent with Addolorato *et al.* (2007), revealed the safety of baclofen in such patients, including a lack of renal or hepatic side effects. In contrast, Garbutt *et al.* (2010) in a 12-week trial revealed no such effect of baclofen (10 mg three times a day) in reducing heavy alcohol craving and drinking, nor in increasing the percentage of abstinence, but did report a positive effect on anxiety. No differences were seen in the percentage of days abstinent, time to first drink, or time to relapse between the baclofen and placebo group. The study did however suggest that the 30 mg/day dosing may not be adequate for some patients and doses may be adjusted and titrated.

Previously, published randomized controlled trials have tested baclofen at a dose of 30 mg/day (Addolorato *et al.*, 2002, 2007; Garbutt *et al.*, 2010) with no significant adverse effects reported. The tolerability and safety of baclofen then led investigators to use baclofen at higher doses. Two case reports revealed a significant reduction of alcohol consumption utilizing baclofen doses of up to 140 mg/day (Bucknam, 2007) and 270 mg/day (Ameisen 2005). Rigal *et al.* (2012)

used a mean baclofen dose at 1 year of 129 ± 71 mg/day, achieving an 80% abstinence rate at 1 year. A dose-dependent effect of baclofen on alcohol intake was demonstrated by Addolorato *et al.* (2011), whereby patients who received baclofen 20 mg three times a day (TID) had a 68% reduction in the number of drinks per day compared with placebo; baclofen 10 mg TID had a 53% reduction in the number of drinks per day compared with placebo; liver disease was absent in these patients. It is possible that higher doses can be used in the absence of liver disease.

Baclofen also appears helpful in patients with psychiatric co-morbidity (Dore *et al.*, 2011).

The current study was to assess the efficacy of baclofen over a relatively long interval in patients with alcoholic hepatitis with or without cirrhosis and alcohol dependence in real-life clinical settings. We predicted that liver tests will improve with the use of baclofen. Our study can be used as preliminary data in assessing the best duration of treatment and development of tolerance.

METHOD

Following ethics approval, a retrospective chart review was conducted on patients who received treatment for alcoholic hepatitis from 1 December 2008 to 31 December 2011 at Loma Linda University Medical Center (LLUMC). The inclusion criteria were: diagnosis of alcohol dependence or abuse according to DSM IV; evidence of alcoholic hepatitis (acute onset of symptomatic hepatitis, elevated liver tests, history of daily alcohol use) with or without cirrhosis on physical exam, laboratory values, or imaging, with or without concurrent hepatitis B or C; follow-up of up to at least 1 year with laboratory values; and the desire to abstain from alcohol. Exclusion criteria were: abnormal renal function or hepatorenal syndrome at initiation of baclofen, malignant disease, psychiatric illness treated with anti-psychotics, seizure disorders, active recreational drug use, and severe cardiac or pulmonary disease.

Demographic information, medical history and social history were retrieved from the electronic medical recording system. The following were collected from history, physical documents and follow-up notes: drink-drive conviction, tobacco and illicit drug use, highest education level, job, history of jaundice, prior GI bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepatocellular carcinoma, Hepatitis B, Hepatitis C, drinking history, and date of last alcohol drink. Laboratory variables collected included aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), Total Bilirubin (Tbili), international normalized ratio (INR), prothrombin time (PT), albumin, white blood cells (WBC), hemoglobin (Hgb), platelets (PLT), total protein, blood urea nitrogen (BUN), creatinine (Cr) and Model for End-Stage Liver Disease (MELD) scores. Values were obtained prior to and immediately after initiation of baclofen. Laboratory values were then reviewed at 3, 6 and 12 months after baclofen administration. Follow-up clinic notes were evaluated to assess for medication compliance and abstinence from alcohol. Compliance and abstinence were self-reported by patients and documented in the medication reconciliation and clinic note. Adverse events evaluated in follow-up visits included seizures, dizziness, drowsiness, confusion, headache and insomnia.

Baclofen treatment

When clinically somewhat improved—without hepatic encephalopathy and when decreasing serum bilirubin approached 10 mg/dl—baclofen was initiated prior to discharge at 5 mg thrice daily for 3 days. After 3 days, the dose was increased to 10 mg thrice daily indefinitely. Laboratory values were obtained prior to and immediately after baclofen initiation, and reviewed at 3, 6 and 12 months. Follow-up notes were reviewed for adverse effects and information regarding baclofen use and abstinence from alcohol (defined as avoidance of all alcohol consumption, and based on a questionnaire provided at follow-up visits inquiring on self-reported craving and alcohol consumption; if results of the questionnaire were unavailable, results were deduced from the clinic notes).

Analysis

Variables were summarized by calculating means for each patient at different time intervals of baclofen treatment. Paired two-sample *t* tests were utilized to assess group differences before and after treatment.

RESULTS

Our study criteria allowed inclusion of 40 patients. Two were excluded as they reported noncompliance at the initial follow-up visit, two because repeat laboratory tests were not available and one patient died. The characteristics of the remaining 35 are summarized in Table 1.

Duration of baclofen use ranged from 1 to 12 months (mean 5.8 median 5); 62.8% of the patients took baclofen for >12 weeks. A significant decrease in mean liver test scores and MELD scores were seen when comparing baseline and 12 month values—see Table 2.

An average 67.30% reduction in Total bilirubin, 42.10% in MELD score, 17.96% INR, 12.14% PT, 75.05% AST and 47.02% in ALT were reported at 12 months (Table 3).

An increase in albumin was noted, with a value of 3.11 g/dl at Month 0 and 3.45 g/dl at Month 12 ($P = 0.01$).

Of the 35 patients who were given baclofen, 1 (aged 85 years) experienced temporary drowsiness and confusion. One patient continued to consume alcohol while taking baclofen,

Table 1. Patient characteristics ($n = 35$)

Age (range 27–85 years old) (mean)	50.5
Gender	
Male	20 (57%)
Female	15 (43%)
BMI (mean)	29.66
Drinks per day (mean) ^a	12.5
Race	
Caucasian	26 (74%)
Hispanic	6 (17%)
African American	1 (3%)
Asian	1 (3%)
Native American	1 (3%)
History of jaundice	22 (63%)
History of gastrointestinal bleed	15 (43%)
History of ascites	19 (54%)
History of spontaneous bacterial peritonitis	3 (9%)
History of driving under the influence	9 (26%)

^a1 drink = 12 oz beer = 1.5 oz spirits = 5 oz wine.

Table 2. Liver parameters at baseline and 12 months

	Baseline (n = 35)	Month 12 (n = 35)	P
Total bilirubin (mg/dl)	14.01	4.58	0.00003
Model for End-Stage Liver Disease	19.07	10.68	0.00008
International normalized ratio	1.67	1.37	0.001
Prothrombin time (s)	16.14	14.18	0.04
Aspartate aminotransferase (μ/l)	247.17	61.66	0.03
Alanine aminotransferase (μ/l)	60.40	32.01	0.01
Albumin (g/dl)	3.11	3.45	0.01

Table 3. Percent reduction of liver parameters over time

Month	Tbili (n = 35)	MELD (n = 35)	INR (n = 35)	PT (n = 35)	AST (n = 35)	ALT (n = 35)
3	63.40%	36.84%	15.57%	10.53%	70.14%	45.18%
6	67.02%	42.10%	17.96%	12.33%	73.84%	46.36%
12	67.30%	42.10%	17.96%	12.14%	75.05%	47.02%

with no apparent ill effect. The remaining 34 patients (97%) were abstinent from alcohol while on baclofen therapy. No other adverse effects of baclofen were recorded. One patient died due to blunt trauma to the head unrelated to the medication.

DISCUSSION

Initiation of baclofen can be considered in the final days of hospitalization after a bout of alcoholic hepatitis when the total bilirubin level approaches 10 mg/dl (Choi and Runyon, 2012). GABA-B receptor agonists such as baclofen can aggravate hepatic encephalopathy and therefore should not be started until clinical evidence of hepatic encephalopathy has resolved. Given the ill effects alcohol abuse renders on society in terms of loss of life and loss of productivity equating to billions of dollars, baclofen's relatively low cost at \$10.83 per 100 days or less than \$40 per year (\$39.53 per 365 days at Costco (<http://www2.costco.com>)) suggests a cost-effective therapy.

Of the 35 patients treated, 34 abstained from alcohol and showed improvement in liver tests. Prior studies utilized baclofen over a period of 12 weeks and showed reduced alcohol cravings and more abstinence (Leggio *et al.*, 2008a,b). We have extended the period of baclofen use beyond 90 days (average use of baclofen 5.8 months) and found it safe and associated with abstinence. Compliance with baclofen was reasonable, given this sometimes recalcitrant population.

It has been suggested that patients with advanced liver cirrhosis require lower doses than patients with normal liver synthetic function (Ameisen, 2005; Bucknam, 2007). This study utilized a fixed dose of 10 mg thrice daily. Higher daily doses up to 95 mg/day (Heydtmann *et al.*, 2012) have been used, tailored to reduce craving and drinking. We also suggest that baclofen can be dose adjusted to each individual patient's needs, and can be used safely for an extended period in order to achieve its desired effect.

With regards to tolerability and safety, baclofen—at a relatively low dose of up to 30 mg/day—was well tolerated in our study, consistent with previous observations validating the

safety of baclofen in patients with higher severity of alcohol dependence (Leggio *et al.*, 2010), alcoholic liver disease (Addolorato *et al.*, 2011; Heydtmann *et al.*, 2012), as well as use in the laboratory setting with alcohol consumption (Evans and Bisaga, 2009; Leggio *et al.*, 2013).

As well as aiding the advantages of abstinence mentioned in Introduction, for patients awaiting liver transplant, baclofen might help maintain abstinence and prevent further alcohol-related complications.

Our observational study has limitations, being retrospective study using reviews by multiple physicians and no control group. No objective measures such as blood breath or urine measures of ethanol were used. Medication compliance and duration of adherence to baclofen were based on the patients' word.

In summary, the current study supports the use of baclofen—starting at a dose of 5 mg three times a day and titrating up to 10 mg three times a day—in the maintenance of alcohol abstinence and the improvement of liver markers in patients with alcoholic cirrhosis and alcohol dependence in real-life clinical settings. We propose that longer duration randomized controlled prospective trials of baclofen are needed to further evaluate its utility.

Conflict of interest statement. None declared.

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