Tailored dose baclofen in patients with alcoholic liver disease: A case series with 2-year follow-up of hospitalisation

Mathis Heydtmann¹, Benn Macdonald², James Lewsey², Neil Masson³, Leona Cunningham⁴, Aleksandra Imazarow⁴, Amanda Nardone⁴, Jan Cosgrave⁴, and Jonathan Chick⁵

¹Department of Gastroenterology, RAH Paisley, Paisley, UK, ²Institute of Health and Wellbeing, University of Glasgow, Lilybank Gardens, Glasgow, UK, ³Department of Psychiatry, Stobhill Hospital, Glasgow, UK, ⁴School of Psychology, University of Glasgow, Glasgow, UK, and ⁵School of Health Sciences, Queen Margaret University, Queen Margaret Dr, Musselburgh, UK

Abstract

Introduction: Alcohol addiction is a major health burden with its consequences including liver disease and frequent hospitalisations. We used tailored-dose baclofen in patients with alcoholic liver disease and investigated hospital re-admissions before and after baclofen dose was initiated as well as tolerability and patient-reported alcohol consumption.

Methods: Fifty-three hospitalised patients with alcoholic liver disease started tailored dose baclofen (median: 5.05 months, median highest dose before tapering down: 60 mg). Patients were followed-up for hospitalisation data from the health board database (mean hospitalisation follow up: 31 months) and patients were sent standardized questionnaires.

Results: Baclofen was generally well tolerated with dose reductions in four patients. In the 2 years after initiation of the treatment, patients spent on an average of 19.1 d in the hospital per year compared to 25.48 d before the treatment initiation ($p = 0.59$). Respondents (19 patients) reported a reduction in alcohol consumption by an average of 58.7% (240.1 g to 144.09 g).

Conclusions: After initiation of the baclofen treatment, there was a trend towards decrease in hospitalisations and in patients who answered the questionnaire, alcohol consumption decreased.

Keywords

Alcohol consumption, alcoholic liver disease, baclofen, consequences of drinking, craving, hospitalisation

History

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Introduction

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter of the nervous system interacting with glutamnergic and dopaminergic pathways (Olsen, 2002). These pathways are involved in a number of neurological and psychiatric conditions including alcohol dependence (Levy & Degnan, 2013). Baclofen is an agonist of the GABAβ receptor which was first synthesized in 1962 (Froestl, 2011). It has been used orally and by intrathecal infusion for decades, mainly to treat spasticity, its current licensed indication. There is evidence that baclofen improves addictive behaviour including alcohol withdrawal, cravings and alcohol consumption, in particular, in patients with liver disease (Addolorato et al., 2002, 2007; Agabio, Preti, & Gessa, 2013; Kumar, Sharma, Kumar, & Deshmukh, 2013; Morley et al., 2014). Two randomized placebo controlled trials (RCT) using fixed-dose baclofen for up to 12 weeks studying patients referred to an Italian medical unit, the second one including patients with advanced liver disease found significant improvements in alcohol intake, cravings and abstinence over a treatment period of 4 to 12 weeks (Addolorato et al., 2002, 2007). A RCT from a psychiatric US centre found in community recruited patients a significant improvement in state anxiety but no significant effect on alcohol craving or consumption (Garbutt, Kampov-Polevoy, Gallop, Kalka-Juhl, & Flannery, 2010) and an Australian trial suggests a benefit on alcohol consumption in patients with comorbid anxiety disorder (Morley et al., 2014). Clinical experiences of off-licence baclofen reported in single case reports and case series suggest a variable effective dose which is often significantly higher (up to 400 mg baclofen per day) than the ones used in the RCTs (Ameisen, 2005; Beaurepaire, 2014; Bucknam, 2007; Dore, Lo, Juckes, Bezyan, & Latt, 2011; Pastor, Jones, & Currie, 2012; Rigal, Alexandre-Dubroeucq, de Beaurepaire, Le Jeanne, & Jaury, 2012). We developed a treatment strategy tailoring dose and administration frequency to the response of individual patients including prn in addition to regular dosing (Heydtmann, 2011).

The aim of this study was to assess tolerability and acceptability of a treatment strategy using tailored dose baclofen in the patients with alcoholic liver disease and describe the clinical course in this cohort of patients.
Patients and methods

Clinical setting and follow-up

Over a one-year period (May 2008 to April 2009) tailored dose baclofen was initiated in a total of 53 patients out of UK license. Treatment with baclofen was approved by the clinical director and the study approved by the health board R&D department and the local ethics committee (WoSRES 10/S/1001/6). All the patients had alcoholic liver disease on clinical grounds as evidenced by abnormal liver biochemistry with exclusion of other aetiologies for chronic liver disease and a history of alcohol excess. They fulfilled ICD-10 diagnostic criteria for alcohol dependence syndrome (F10.2, WHO, 2007), had at least one medical hospital admission with alcoholic liver disease prior to baclofen initiation and reported motivation to become completely abstinent. The dosing regime evolved through recursively reviewing patient data which was prospectively collected for audit purposes. In all the patients traditional medication for treatment of their excess alcohol had been exhausted (acamprosate) or was contraindicated (disulfiram, in most cases due to chronic liver disease). Patients received verbal and written information on the treatment and consented to treatment including follow-up and data collection for audit of treatment outcome. Patients were typically started on 5 times daily dosing (in contrast to three times daily dosing in spasticity) of baclofen 5 to 10 mg and doses were increased gradually and decreased depending on response and side effects encountered. The treatment was open label, open ended aiming for complete abstinence and patients were allowed to take additional baclofen medication (half a regular dose) if the urge to consume alcohol became unbearable (“pill in the pocket” dosing). Maximum baclofen doses were similar or lower than described by groups using “high-dose baclofen” for this indication (Pastor et al., 2012 [4 cases, range: 75 mg to 125 mg baclofen/d]; Dore et al., 2011 [13 patients, range: 30 to 275 mg baclofen/d] and Beaurepaire, 2014 [17 patients, range: 310 to 630 mg baclofen/d]). Otherwise treatment for their alcohol problems was standard of care community-based treatment. The side effects led to treatment cessation, dose reduction or dose maintenance and regular monitoring depending on severity. In patients who were abstinent of alcohol and did not report any cravings the baclofen dose was slowly tapered down. Maximum daily doses (often only taken for a few days), dosing regimes, adverse and other clinical events were recorded at each consultation with the treating physician (MH) up to July 2009 and treatment duration was open ended aiming at the sustained abstinence with the lowest possible dose. In August 2009 the patient’s treatment was handed over to the treating general practitioner (end of clinical follow-up). Therefore, the period of baclofen treatment supervised by the investigator (clinical follow-up) was between 3 and 14 months for each patient included in the study. After clinical handover to their primary care physician, clinical information is limited but where information is available, most patients continued with baclofen treatment for some time.

Survival and hospitalisation data

Patient survival and hospitalisation data for emergency hospital admissions as well as accident and emergency attendances were available through the health board clinical information system of hospitalisation data collected for the Information Services Division (ISD) of Scotland. Data for hospitalisations between 2001 and 2012 inclusive were available allowing significantly longer follow-up of these hard endpoints than the clinical follow-up. In this cohort of patients treated with open label baclofen, hospitalisations and days spent in hospital were analysed before treatment initiation compared with the follow-up period after our intervention to investigate non-captured adverse effects and to study feasibility of including hospitalisations in a controlled prospective trial. The Wilcoxon-matched pairs sign test was used to assess for significant changes between “before” and “after” our intervention. Standard multiple regression analyses were conducted on all the patients who had baclofen treatment initiated. For each patient the same number of days prior to the start of the treatment as was available for follow-up were included in analysis 1 (A1). A second analysis included only patients who survived for at least 2 years (A2, n = 44; to exclude patients with end-stage liver disease). For both the analyses admission numbers and days in hospital were calculated per 365 days (pre-baclofen and post-baclofen start) and change in hospitalisations was analysed using linear regression. All the data were analyzed using the statistical package R (R Development Core Team, 2011).

Questionnaire survey

In May 2010 (after the end of clinical follow-up) all the patients alive were sent a set of standardized questionnaires as well as a generic questionnaire on alcohol consumption (current and 6 months before the start of the treatment), perceived side effects and effective doses. The standardized questionnaires included Treatment Satisfaction Questionnaire for Medication – TSQM (Atkinson et al., 2004) as well as current and pre-baclofen treatment measures on the following: alcohol craving (Alcohol Urge Questionnaire – AUQ (Bohn, Krahn, & Staehler, 1995)), harmful consequences of drinking (Drinker Inventory of Consequences Short Inventory of Problems – DrInC-SIP2R (Miller, 1995)), depression and anxiety (Hospital Anxiety and Depression Scale – HADS (Zigmond & Snaith, 1983)) and quality of life (ALQoL9 (Malet, Llorca, Beringuier, Lehert, & Falissard, 2006)). These validated questionnaires were also adapted for reporting retrospectively on the time 6 months prior to the individual’s treatment initiation.

Results

Demographics and clinical follow-up

Tailored dose baclofen was initiated in 53 patients (Figure 1). At the treatment initiation, 29 (55%) had non-cirrhotic liver disease, 11 (21%) Child A, 7 (13%) Child B and 6 (11%) Child C with cirrhosis. The median highest baclofen dose taken by a patient in a day was 60 mg (mean: 98.0 mg; range: 5–400 mg; Figure 2). Median duration of baclofen treatment was 3 months (mean: 5.05 months; range: 0.05–18 months; Figure 3). The average daily alcohol consumption of patients ranged from 9 g/d to 615 g/d (median: 240 g/d; mean: 240 g/d.
Figure 4). No correlation between the treatment dose and treatment duration was found \( (r = 0.24) \), nor between the treatment dose and daily alcohol consumption before the start of the treatment \( (r = 0.27, \text{Pearson’s}) \). Also, the baclofen doses used in the patients who were still drinking at time of the survey \( (5–400 \text{mg, median: 80 mg}) \) was comparable to the group of the patients who reported abstinence \( (30–400 \text{mg, median: 60 mg}) \), \( p \) for difference: n.s.

The relation between severity of liver disease (non cirrhotic/Child score for cirrhotic patients) and maximum dose of baclofen used is shown in Figure 2 \( (p = 0.16, \text{Kruksal–Wallis}) \). There were 37 patients who discontinued treatment with baclofen for the following reasons: patients not engaging with services, patients changed their mind after treatment begin and patients who were not willing to stop drinking any more \( (5 \text{ patients, 14%}) \), loss to follow-up without further information \( (17 \text{ patients, 32%}) \). Therefore, in total 22 patients, i.e. 42% dropped out from clinical follow-up from the treatment \( (\text{median highest baclofen dose: 60 mg/d, range: 30–400 mg}) \).

A number of patients reported sustained abstinence and absence of cravings \( (10 \text{ patients = 19%}) \), deterioration of liver disease \( (2 \text{ patients, 4%}) \), GP discontinued baclofen prescription \( (2 \text{ patients, 4%, treatment duration: 1 week and 2 weeks respectively}) \), side effects \( (1 \text{ patient, 2%: allergic skin reaction, maximum daily baclofen dose: 20 mg}) \). At follow-up visits blood was checked regularly with no unexpected changes in renal, liver biochemistry or synthetic liver function. Deaths 2 years after baclofen start were more common in patients who changed their mind and did not aim for abstinence any more \( (4 \text{ of 5 patients}) \) compared to the other patients who continued with the treatment and follow-up \( (5 \text{ of 48 patients}) \), \( p = 0.002, \text{Fisher’s exact test}) \.

### Follow-up of hospitalisation and survival data

The average duration of follow-up of case notes, survival and hospitalisation after starting baclofen treatment was 31 months (Figure 1). Causes of death in the 16 patients who died during the hospital data follow-up were: directly alcoholic liver disease-related deaths: 7 patients (44%), other alcohol related deaths: 4 patients (25%) and deaths not directly related to alcohol: 5 patients (31%). These 5 deaths were: Infection \( (3 \text{ patients, TB in one}) \), arteriosclerotic disease \( (1 \text{ patient}) \) and COPD \( (1 \text{ patient}) \).

In this cohort with alcoholic liver disease the survival rate was 91% and 83% for 1 and 2 year survival respectively (Figure 1). In the whole cohort of patients as well as those who survived at least 2 years there were rather fewer hospitalisations and fewer days spent in hospital in the follow-up period after our intervention compared to the same
time before treatment initiation in both analyses (Table 1). No correlation between highest baclofen dose and hospitalisations was found.

**Baclofen dose and self-reported alcohol consumption, safety and tolerability (Retrospective Questionnaire Survey)**

Of the 53 patients treated, 46 patients were alive at time of the questionnaire survey (Figure 1) and 21 patients (45.7%) completed the questionnaire (some with missing data). For baseline characteristics of the whole patient group, those who died and those who did/did not reply to the survey see Table 2.

Of the 21 patients who replied to the questionnaire, 9 patients (43%) had observed or reported transient side effects, mainly sleepiness (8 patients). Other side effects while on baclofen were: ‘wooziness’ (4 patients), urinary/faecal incontinence (3 patients), unsteadiness (3 patients), dizziness (3 patients), tingling (3 patients), gastro-oesophageal reflux (1 patient), and decreased libido (1 patient). Side effects were typically experienced during dose increase and at the higher end of the patients’ maximum dose (or on drinking alcohol while taking baclofen). Median highest baclofen dose in patients who reported side effects was 160 mg/d (range: 30–300 mg/d). Dose reduction was necessary in four patients: these were due to drowsiness (1), irritability, and urinary and faecal incontinence (1), dizziness, unsteadiness and gastro-oesophageal reflux (1) and decreased libido (1). Side effects ceased after dose reduction in all the patients. Patients who sent back the questionnaire reported a good level of satisfaction.
with baclofen (median global TSQM score: 65.2, reply from 18 patients).

The 19 patients who answered the questionnaire on alcohol consumption (missing data in 3 patients) reported an average reduction of consumption from a median of 205 g (mean of 240.1 g) alcohol per day 6 months prior to baclofen start to a median of 29.29 g (mean of 144.09 g) at time of survey (Figure 5), \( p = 0.009 \); best estimate of median reduction: 133.54 g alcohol/d; 95% CI: 34.56–275.87 g/d (paired Wilcoxon). The comparison of pre-baclofen (retrospectively reported) and post-baclofen self-reported psychometric measures in the patients showed an improvement in some outcome measures (Supplementary information online).

**Discussion**

There is an increasing interest in alcohol substitution, anti-craving and relapse prevention therapy for harm reduction in the treatment of patients with harmful alcohol consumption. A number of studies and case reports have shown a varying success of the GABA\(_B\) receptor agonist baclofen in alcohol excess and further trials are being conducted (Enserink, 2011). Although there is experience on its use in acute withdrawal (Lyon, Khan, Gessert, Larson, & Renier, 2011), most studies have concentrated on baclofen in reduction of alcohol consumption and (short-term) maintenance of abstinence (Addolorato et al., 2007; Leggio, Garbutt, & Addolorato, 2010; Leggio et al., 2012; Yamini, Lee, Avanesyan, Walter, & Runyon, 2014). This is the first study of tailored-dose baclofen in the patients with alcoholic liver disease looking at longer term outcome and reporting on patient’s...

**Table 2. Baseline characteristics of patients treated with tailored baclofen in alcoholic liver disease.**

| Description                                      | Patients who replied to the survey | Patients who did not reply to the survey | Patients who died before the survey | \( p \) For difference | All patients who received baclofen |
|--------------------------------------------------|-----------------------------------|------------------------------------------|------------------------------------|-------------------------|----------------------------------|
| Number of patients                               | 21                                | 25                                       | 7                                 | –                       | 53                               |
| % Male                                           | 61.90                             | 52.00                                    | 71.43                              | 0.601\(^a\)              | 58.49                            |
| Median age (years)                               | 52.71                             | 46.81                                    | 50.04                              | 0.571\(^b\)              | 50.12                            |
| Median baclofen treatment duration (months)      | 6                                 | 3                                        | 0.2                                | 0.00031\(^b\)            | 3                                |
| Cirrhosis stage                                  |                                    |                                          |                                    | 0.1068\(^c\)             |                                  |
| Pre-cirrhotic                                    | 13                                | 13                                       | 3                                 | 29 (55 %)                |                                  |
| Child A                                         | 2                                 | 8                                        | 1                                 | 11 (21 %)                |                                  |
| Child B                                         | 4                                 | 3                                        | 0                                 | 7 (13 %)                 |                                  |
| Child C                                         | 2                                 | 1                                        | 3                                 | 6 (11 %)                 |                                  |
| Median highest daily baclofen dose in mg/d (1st; 3rd quartile) | 80 (45; 180) | 60 (30; 90) | 30 (22.5; 60) | 0.165\(^b\) | 60 |
hospitalisation. Patients with complex medical and psychiatric profiles and cirrhosis were not excluded and in our experience from the same city survival is rather better than in a cohort of similar patients (91% 1 year and 83% 2-year survival in this cohort compared to 78% 1 year survival in the historical comparison) (Heydtmann & McDonald, 2013).

The strength of this real life experience with baclofen treatment in patients with alcoholic liver disease is offset by significant limitations. These are due to potential selection bias of the patients and the possibility of other interventions not controlled for in this study without the control group. There may have been a significant positive placebo effect given the attention “high-dose” baclofen has received in the lay press and on the internet (Rolland, Bordet, & Cottencin, 2012). Also, the low patient numbers, retrospective reporting of alcohol consumption and psychometric measurements in only 18 to 21 of 46 patients alive at the time of the survey limits the validity of the data from the questionnaire survey. However, this describes a real life experience and we tried to address some of these limitations by surveying patients some time after the attention these patients received throughout their baclofen treatment. There was a ‘washout period’ of over 1 year during which the patients were largely under the care of their GP (standard of care). We also assessed several outcome measures including the hard endpoint of the patients’ hospital admissions from the hospital database. This was important because of the relatively high rate of loss to clinical follow-up which is typical in this population (follow-up longer than 1 year is often not reported in studies of the patients with alcohol addiction) and because of the possible recall bias in the patients who replied to the questionnaire survey. The structured questionnaires suggested a possible benefit of baclofen treatment with regards to alcohol consumption with an acceptable side-effect profile (Supplementary data).

The strength of the study is the inclusion of real-life patients with significant co-morbidities and frequent (medical) hospitalisations which is typical for this patient group. Also, the treatment intervention was outside of a psychiatric department which may offer an easier access to specific treatment for some patients. Rigorous intention to treat analysis was performed including 14 patients who received baclofen treatment for 1 month or less. Some patients who received the treatment only for a very short period, and over 1 year prior to receiving the questionnaire, replied that they did not feel able to answer the questions which explains in part the relatively low response rate. The short treatment in some patients will have also influenced the power of the study. It is notable that a relatively short intervention could lead to seemingly positive effects although they have to be interpreted with caution given the limitations of the case series. In the questionnaire survey there was no improvement in quality of life (Supplementary data) with the reported decrease in alcohol consumption but it is possible that some of the patients already had too advanced alcohol-related disease limiting their quality of life.

The findings of this study confirm and expand observations in small randomized controlled trials with fixed (lower) dose baclofen in patients with liver disease (Addolorato et al., 2007, 2011; Leggio et al., 2010, 2012) and in case reports (Ameisen, 2005; Bucknam, 2007) or case series (Beaurepaire, 2014; Dore et al., 2011; Pastor et al., 2012; Rigal et al., 2012) of patients treated with higher doses (largely psychiatric outpatients). A dose-response effect of baclofen on alcohol consumption as well as on side effects have been reported but treatment is generally well tolerated if the dose is adjusted gradually (Dore et al., 2011; Muzyk, Rivelli, & Gagliardi, 2012; Rigal et al., 2012; Rolland et al., 2014). Although patients in our study took a relatively high maximum dose of baclofen (median: 60 mg, range: 5–400 mg) this dose was often reduced by the patients within a few days and the maximum dose was lower in our tailored-dosing compared to some studies of “high-dose baclofen” where the median was 145 mg (range: 30–400 mg) in one study (Rigal et al., 2012) or the inclusion criteria was a dose of over 300 mg in another study (Beaurepaire, 2014). The difference in baclofen dosing in the studies might have been due to differences in population groups studied as postulated previously (Heydtmann, 2011). In initial treatment some alcoholic patients reported a good effect after taking a dose of baclofen which weaned off after a few hours. This is compatible with the very short half life reported for baclofen which might even be shorter in alcoholics (although this has not been studied yet). We therefore developed the regime of 5 times a day dosing and the “pill in the pocket” treatment in these patients.

In our study, reduced alcohol consumption and craving was described by at least some patients long after discontinuation of medication and regular clinical review by the team. Our study also adds a health economics finding, i.e. in this population, our experience of the natural history in patients with alcoholic liver disease is an increase in hospitalisations over time which was not seen in the follow-up of some of the baclofen-treated patients. Even a slowing of progression in their medical conditions would be of value in patients with alcoholic liver disease. In this case series, after treatment initiation with tailored-dose baclofen reduced hospital admissions was found below levels prior to treatment start and this might be due to a positive effect on disease progression through our intervention. In our case series, the effect on readmission to hospital seemed to be in particular in older patients (data not shown) which may be a statistical effect or due to different sensitivity or metabolism or the drug. This study suggests that the benefit of anti-craving drugs on hospitalisations may be large enough in patients with alcoholic liver disease to be included as hard endpoint in future randomized controlled trials.

It has been postulated by Garbutt et al. (2010) that rather than having a direct effect on alcohol craving, baclofen’s anxiolytic effect may lead to the secondary effect of lower alcohol consumption which is compatible with a recent study with low patient numbers showing a significant effect on alcohol consumption in patients with comorbid anxiety (Morley et al., 2014). In contrast to this, we have not found a significant effect of baclofen on anxiety nor depression (HADS scores) in our study but patients more consistently reported a positive effect on cravings (Supplementary information). There are significant differences between the populations studied by the different reported trials (Agabio et al., 2013; Heydtmann, 2011; Muzyk et al., 2012). Most of the data in our uncontrolled patient group show a trend...
towards improvement in the parameters investigated with some changes being statistically significant. However, our patient numbers are low and there may be a differential benefit of baclofen in different populations. Given the variation in dose required by our patients for subjective suppression of craving we had previously postulated that patients with more advanced liver disease might require lower doses of baclofen to suppress cravings (Heydtmann, 2011).

Our patient group was not only selected by liver disease but also negatively selected by treatment failure with other medication. The patients treated with baclofen also tended to have a long history of excessive alcohol consumption, many reported cravings, thoughts or dreams of alcohol, anxiety or depression, consumption of alcohol to improve otherwise poor sleep and/or a family history of alcohol excess. It is possible that this sample contains an increased frequency of genetic variants within the GABA pathway potentially increasing response to baclofen compared to other studies (Leggio et al., 2013).

Conclusion

In summary, in our hands baclofen using doses tailored to patients with alcoholic liver disease is safe and accepted by patients who report a positive effect on alcohol craving, alcohol consumption and an acceptable side effect profile and we found a decreased rate of hospital admissions in our cohort on follow-up. The results of this study suggest that future randomised controlled trials could include survival rates and hospitalisation as outcome measures to investigate if baclofen can indeed help reduce hospitalisations in patients with alcoholic liver disease. Given the relatively low cost of baclofen, savings in health care costs may be found.

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Declaration of interest

None of the authors have any conflict of interest with regards to the study medication.

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