$GABA_B$ receptor function in healthy volunteers a pharmacokinetic and pharmacodynamic study of two doses of baclofen compared to placebo.

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Introduction

- Recent evidence suggests baclofen, a γ-aminobutyric acid type B (GABA-B) receptor agonist, reduces alcohol consumption and craving and promotes abstinence in alcoholics.
- However, characterisation of the GABA-B receptor system in clinical addiction is limited, and it is unclear why some patients require, or tolerate, higher doses to treat alcoholism. (de Beaurepaire 2014, Pastor *et al.* 2012)
- The current pharmacokinetic and pharmacodynamic study was designed to assess the effects of the GABA-B agonist, baclofen, on brain function in healthy volunteers.

Methods

- Eight healthy male volunteers completed a double blind randomised 3-way cross over study, receiving oral doses of placebo (vitamin C 100mg), 10mg and 60mg baclofen with an interval of at least 1 week between each study day.
- Subjective and objective measurements were taken at baseline (before medication) and at +30mins, 1, 2, 3, 4 and 6 hours after dosing.
- Objective measures included blood samples for analysis of plasma baclofen levels, heart rate and blood pressure, and a drawing task assessing motor coordination (zig-zag task, Tiplady *et al* 2003).
- Subjective measures included the Subjective High Assessment Questionnaire (SHAS) (Schuckit *et al* 1980), and visual analogue scales for sleepy, relaxed, tense and alert.

Pharmacokinetics: plasma baclofen concentration

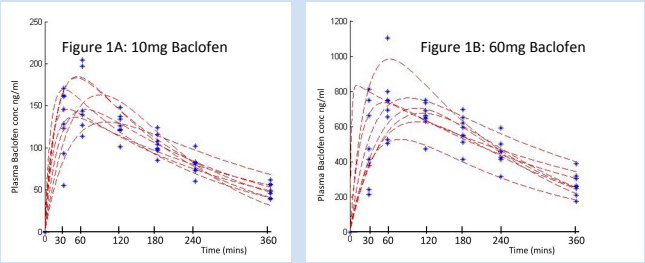

Figure 1; Plasma baclofen levels measured using liquid chromatograph mass-spectrometry (LC-MS) Free plasma concentrations (CP) of baclofen at time t were fitted using a non-linear least squares algorithm with a standard elimination (ke) - absorption (ka) model:

CP (t) = ((F·D·ka) / (Vd·(ka- ke)) (e^(-ket) - e^(-kat))

where F is the bioavailability of the drug, D is dose and Vd is volume of distribution.

Figure 1A: 10mg baclofen, average Tmax; 58.97 (±24.18) min, average Cmax 157.35 ng/ml (±20.75).
Figure 1B: 60mg baclofen, average Tmax; 78.95 (±34.63) min, average Cmax 731.12ng/ml (±137.32).
All samples after placebo show zero concentration of baclofen (data not shown).

Results: Blood Pressure

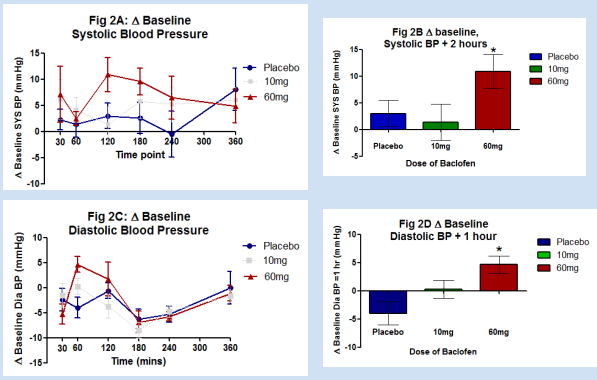

Figure 2: Change in systolic (Fig 2A) and diastolic (Fig 2C) blood pressure (BP) compared with baseline after 10mg or 60mg baclofen or placebo. Significant changes with 60mg baclofen vs placebo were seen in systolic BP at 120mins (Fig 2B), ($p<0.05$ Wilcoxon signed rank test) and in diastolic BP at 60min ($p<0.05$ Wilcoxon signed rank test)

Subjective results: Subjective High Assessment Scale

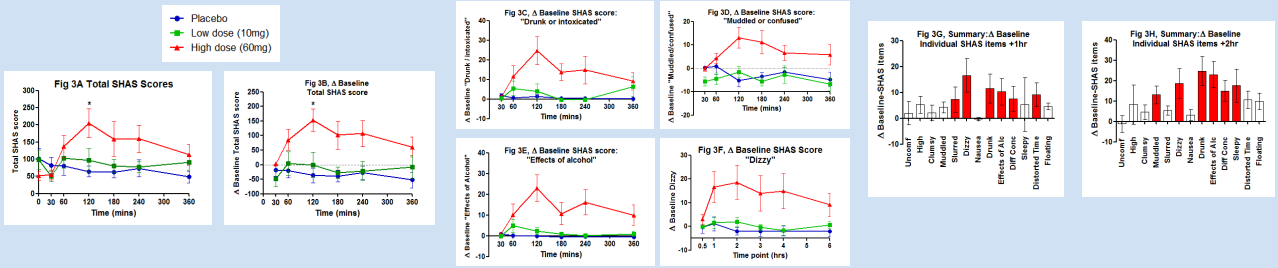

Figure 3A: Changes in total score on the subjective high assessment scale (SHAS) (Fig 3A) and compared with baseline (Fig 3B). SHAS uses a visual analogue scale asking participants to rate how "*" participants feel at that moment on a scale of 0-100. Figures 3C-F: Examples of individual item scores. Fig 3G/H: Individual SHAS items at the 1 and 2 hour time point after 60mg baclofen (change compared with baseline) indicating greater increase in items similar to those experienced after alcohol.

Results: Zig-Zag tracking task

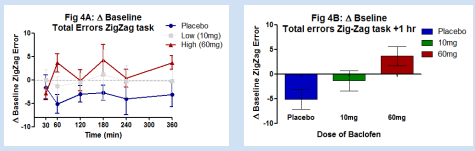

Figure 4A: Increase in total number of errors (accuracy) after 60mg baclofen compared with placebo. Data represent change from baseline. Fig 4B Significant increase in errors at 60mins with 60mg compared with placebo ($p<0.05$) Wilcoxon signed rank test).
No change in speed (time taken to complete task) data not shown.

Discussion

- There were changes in subjective measures peaking at 2 hours post dosing with baclofen 60mg compared with placebo, with a significant increase ($p<0.05$) in total SHAS scores with individual items, including feeling 'drunk or intoxicated', effects of alcohol and 'muddled or confused' particularly affected. Systolic blood pressure was significantly increased ($p<0.05$) at 2 hours post 60mg dose.
- Preliminary pharmacokinetic analysis of plasma baclofen suggests it may take slightly longer for the high dose (60mg) to reach maximum concentration compared with the lower dose (10mg).
- The impaired accuracy on the psychomotor task that we observed is similar to that in studies with ethanol

Conclusion

- This is the first detailed study looking at both pharmacokinetic and pharmacodynamic measures of baclofen in healthy volunteers. The objective and subjective measures used in this study are able to differentiate between placebo and 60mg baclofen. These findings will inform further research investigating the sensitivity of GABA-B receptors in alcohol addiction.

References:

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Acknowledgments

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