Introduction

Both pregabalin (PGB, Lyrica®) and carbamazepine (CBZ, Tegretol®) are anticonvulsant drugs that have been approved for the treatment of conditions related to neuropathic pain (Shiner and McAuley, 2005; Dworkin et al., 2009). Pregabalin is specifically approved for the treatment of diabetic peripheral neuropathy and postherpetic neuralgia, while carbamazepine is approved for trigeminal neuralgia.

The purpose of the present studies was to expand on the preclinical profile of PGB and CBZ, focusing on the rat spared nerve injury (SNI) model of neuropathic pain. Specifically 5 studies were conducted.

1. Investigate multiple doses of PGB (3-30 mg/kg IP and oral) and carbamazepine (10-60 mg/kg IP) against heightened sensory reactivity (tactile and cold allodynia) characteristic of the SNI model.

2. Compare with potency in the MES test and effect on paw withdrawal latency.

3. Following SNI surgery the majority of animals adopt a characteristic gait and paw position which might reflect guarding behaviour. We therefore assessed doses of PGB effective in (1) against various gait parameters affected by SNI surgery.

4. Investigate the effect of chronic (2x daily) IP PGB treatment to see if efficacy against an evoked tactile and thermal (cold) stimulus was enhanced by repeated treatment (Dworkin et al., 2009).

5. The pharmacokinetics of PGB were studied to establish plasma concentrations necessary for preclinical efficacy for comparison to therapeutic levels in humans (Whiteide et al., 2008).

Given the extensive clinical experience with both pregabalin (Lyrica®) and carbamazepine (Tegretol®) in neuropathic pain therapy, this provides opportunity to translate clinical experience back to the preclinical setting.

Methods

Animals

Adult, male, Sprague-Dawley (SD) rats were used throughout.

SNI Surgery

Rats were anaesthetised prior to acupuncture dorsum and the sciatic nerve was exposed between the malleoli. The sural nerve was then cut, leaving the sciatic nerve intact. In sham operated animals the sciatic nerve was only exposed. Following surgery, the overlying muscle and skin was then sutured. With the rats in this study the right hind paw was used for all measurements.

Evoked Sensory Measures

Evoked tactile and thermal (cold) stimulus was enhanced by repeated treatment (see Bauer et al., 2009).

Measurement of Burrowing

A group of 20 SD rats were first trained to cross a walkway as previously described. Next, n=10 received SNI surgeries, and n=10 received sham control surgery. One week following surgery, rats were randomly divided into two groups based on equivalent overall burrowing scores, based on a cut-off of 4260 ± 246 4h for SNI operated rats. Static paw measures of toe spread (TS), limb rotation (LR), stride length (SL) and print length (PL) were taken for each animal using footprint paper. A cross-over design was adopted in experiment 3a, following familiarization to the burrowing procedure, rats were randomly divided into two groups based on equivalent overall burrowing scores, based on a cut-off of 4260 ± 246 4h for SNI operated rat are shown.

Measurement of Gait

PGB concentration (all Bioanalytical measures conducted by NoAb BioDiscoveries).

Measurement of Evoked Responses:

Latency of tactile (Von Frey) and cold (acetone drop) stimulus followed by a burrowing test. A cross-over design was adopted in experiment 3a, following familiarization to the burrowing procedure, rats were randomly divided into two groups based on equivalent overall burrowing scores, based on a cut-off of 4260 ± 246 4h for SNI operated rat are shown.

Results

A. Effect of PGB and CBZ on responses to evoked sensory stimuli in SNI prepared rats.

B. Characterisation of SNI surgery on gait – effect of pregabalin on gait changes

C. Characterisation of SNI surgery on burrowing – effect of pregabalin and carbamazepine.

D. Characterisation of chronic pregabalin treatment on evoked responses in SNI rats

E. Characterisation of the pharmacokinetic property of pregabalin

Summary and conclusions

1. Consistent with an anticonvulsant profile, both PGB and CBZ prevented MES-induced seizures, CBZ being the more potent. Testing both drugs in the SNI model under an equivalent dosing regimen identified PGB to be the more effective, based on efficacy (tactile and cold allodynia) and tolerability.

2. SNI surgery produced enduring changes to pain gain and gait. PGB failed to affect any of these changes which may suggest they are unrelated to pain per se.

3. SNI surgery produced a deficit in burrowing behaviour. Consistent with effect against evoked measures, PGB but not CBZ reversed the burrowing deficit.

4. Chronic PGB treatment did not result in greater efficacy against the evoked hypersensitivity responses. No tolerance developed to PGB.

5. PK studies revealed PGB (10 mg/kg IP) to be effective at plasma levels corresponding to therapeutically relevant concentrations (4-8 μg/ml).

6. Overall these data support improved pharmacokinetic tolerability for PGB compared to CBZ in the SNI model, which is consistent with findings for both drugs reported in other nerve injury models and also clinical experience (Dworkin et al., 2009). There is also good correspondence between plasma [PGB] across species.

References


E. Characterisation of the pharmacokinetic property of pregabalin

D. Characterisation of chronic pregabalin treatment on evoked responses in SNI rats

C. Characterisation of SNI surgery on burrowing – effect of pregabalin and carbamazepine.

B. Characterisation of SNI surgery on gait – effect of pregabalin on gait changes

A. Effect of PGB and CBZ on responses to evoked sensory stimuli in SNI prepared rats.