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Preclinical Safety Margins of the Potent and $Na_V1.6$ Selective Inhibitor, XEN901, in Relation to Non-Selective Sodium Channel Blockers

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INTRODUCTION

- Sodium channel inhibitors are widely used as anti-epileptic drugs (AEDs) but seizure control is often inadequate at maximally tolerated doses.
- The currently used sodium channel inhibitors are non-selective: they are nearly equipotent on isoforms widely expressed in the CNS ($Na_V1.1$, $Na_V1.2$, $Na_V1.6$).
- XEN901, currently in clinical development (phase 1), is highly selective for inhibition of $Na_V1.6$.
- We compared the safety margin of XEN901 to the safety margins of non-selective sodium channel inhibitors.

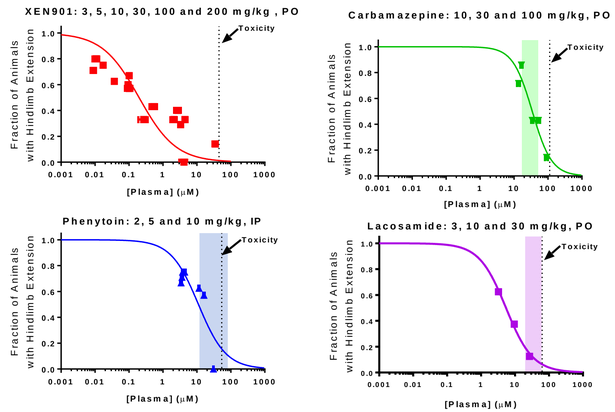
Maximal Electroshock Seizure (MES) Mouse Model

- MES produces generalized tonic-clonic seizures (GTC) with extension of the hindlimbs in mouse.
- Stimulation parameters: 60 Hz, 50 mA, pulse width and duration of 0.5 msec and 0.2 sec respectively, applied by corneal electrodes.
- Binary seizure readout – animals were monitored for presence/absence of the hindlimb tonic extensor component of the seizure.
- Young adult (5-8 weeks) male CF-1 mice were used.
- This assay is highly predictive of clinical efficacy of Na_V antagonists against human partial seizures.

Model of Behavioral Toxicity: Rotarod in Mouse

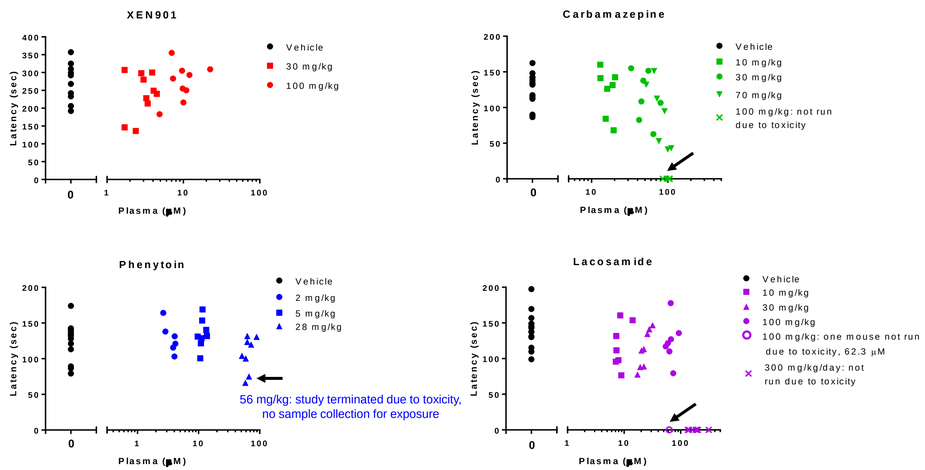
- Rotarod assesses a compound's effect on motor coordination and balance: impairment, often termed neurotoxicity, is measured.
- The time (latency) it takes for the mouse to fall off the rod rotating under continuous acceleration (from 5 to 30 RPM, over 240 sec) is used as an indication of such impairment.
- Animals were trained for 3 days before testing: 3 sessions a day.
- Phenytoin, Carbamazepine and Lacosamide were tested in house while XEN901 experiment was performed at a CRO using a different protocol: continuous acceleration from 0 to 40 RPM over 360 sec. Training consisted of 4 sessions (5 RPM, 60 sec) the day before testing.

Efficacy of Selective & Non-Selective Sodium Channel Inhibitors in Mouse MES Assay



Efficacy in the mouse MES Assay is plotted vs measured plasma concentrations for XEN901, Carbamazepine, Phenytoin, and Lacosamide. The vertical dotted line in all the plots corresponds to the plasma concentration at which behavioral toxicity (hypoactivity, ataxia, tremors, loss of balance) was observed. The shaded areas on the graphs for Carbamazepine, Phenytoin, and Lacosamide correspond to reported effective plasma concentrations for human patients. PO: oral; IP: intraperitoneal.

Effects of Selective & Non-Selective Sodium Channel Inhibitors on the Motor Performance in Rotarod



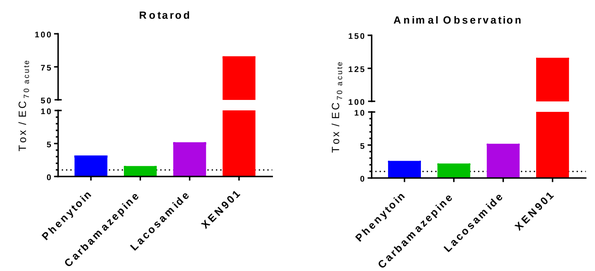
Latency (sec) to fall off the rotarod is plotted vs measured plasma concentrations for XEN901, Carbamazepine, Phenytoin, and Lacosamide. Arrow indicates minimal plasma level at which adverse behavioral events were observed in an animal. Latency was analyzed using one-way ANOVA with post hoc test (Dunnett's multiple comparisons). Carbamazepine at 70 mg/kg: p=0.015.

XEN901: Improved Safety Margin over other Na_V Inhibitors

Compound	MES EC_{70} Plasma (μM)	Rotarod Toxic Plasma Levels (μM)	Animal observation Toxic Plasma Levels (μM)
XEN901	0.264	>22	>35
Phenytoin	20	63	>52
Carbamazepine	60	95	131
Lacosamide	12	62	62

EC_{70} = plasma concentration where 70% of mice were protected from the hindlimb tonic extensor in MES assay.

Toxic = minimum plasma concentration at which adverse behavioral events were observed.



CONCLUSIONS

- Clinical efficacy of sodium channel inhibitors is achieved at 1-6 times the EC_{70} in the mouse MES assay.
- Rotarod and animal observation data indicate that the potent, selective $Na_V1.6$ inhibitor, XEN901, may offer an improved safety margin compared with traditional, non-selective sodium channel AEDs.
- The relatively large safety margin observed for XEN901 in the mouse MES assay suggests that therapeutically effective plasma concentrations may be attained in clinical trials without causing mechanism based toxicity in humans.