Efficacy of Sodium Channel Inhibitors as Anticonvulsants in the Rat MES Assay is Predictive of the Therapeutic Plasma Concentration in Humans

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INTRODUCTION

- Sodium channel inhibitors are widely used as antiepileptic drugs (AEDs) but seizure control is often inadequate at maximally tolerated doses.
- Currently available Na_AEDs are nearly equipotent inhibitors of isoforms widely expressed in the CNS (Na_1.1, Na_1.2, Na_1.6).
- Loss of function mutations in Na_1.1 cause Dravet Syndrome, indicating that Na_1.1 is the dominant Na channel in inhibitory GABAergic neurons (Catterall et al., 2010). Thus, inhibition of Na_1.1 is likely counter-productive for treatment of epilepsy.
- Reduced expression of Na_1.6 reduces seizures in epilepsy mode (Blumenfeld et al., 2009; Makinson et al., 2014; Wong et al., 2018).
- XEN901 is highly selective for inhibition of Na_1.6.

We explored whether plasma levels in the Maximal Electroshock Stimulus assay correlate with therapeutic plasma concentration for nonselective sodium channel inhibitors, thereby enabling an estimate of the necessary concentration of XEN901.

Maximal Electroshock Seizure (MES) Model

- Highly predictive of clinical efficacy of Na_AEDs against human seizures.
- Clinically effective concentration of nonselective Na_AEDs at 1-3 times EC50 in rat MES assay.
- XEN901 is well tolerated at a plasma concentration 32-times higher than the EC50 in the rat MES assay.

Selecting Inhibition of Na_1.6

- Efficacy in the rat MES assay is plotted vs measured plasma concentrations for XEN901, Carbamazepine, Phenytoin, and Lacosamide. The vertical dotted line in the plot for XEN901 corresponds to the highest plasma concentration achieved in a phase I study with healthy humans, achieved at a well tolerated dose.
- The shaded areas on the graphs for Carbamazepine, Phenytoin, and Lacosamide correspond to reported effective plasma concentrations for human patients.
- Binary seizure readout – animals are monitored for presence/absence of tonic-clonic seizure.
- Seizures were induced by a constant current stimulus applied to cornea of 150 mA, consisting of 0.5 ms pulses delivered at 60 Hz for 200 ms.

Potency in MES Assay Correlates with Inhibition of Na_1.6

- Upper panel: Efficacy in the MES assay increased with brain concentration of compounds.
- Lower panel: Dividing the brain concentration by the in vitro potency on Na_1.6 results in close overlay of all curves.
- IC50 concentration in vivo corresponds to a brain concentration approximately 0.3-5 fold the IC50 for Na_1.6 in vitro. The greater potency of XEN901 in the MES assay can be accounted for by the greater potency for inhibition of Na_1.6 in the brain.
- After the MES assay, animals were euthanized and plasma and brain concentrations were measured by mass spectrometry. All points represent results of 5-8 animals in a single study group. Error bars on the x-axis are standard errors of the mean but in many cases are smaller than the symbols.

CONCLUSIONS

- Clinical efficacy of nonselective sodium channel inhibitors is achieved at 1-3 times the EC50 in the rat MES assay.
- Nonselective sodium channel inhibitors are effective at approximately the same multiple of IC50 for Na_1.6 as the selective inhibitor, XEN901.
- Na_1.6 inhibition is likely the primary driver of the efficacy of non-selective Na_AEDs in the rat MES assay.
- The rat MES assay suggests that therapeutically effective plasma concentrations of XEN901 may be attained in humans without toxicity.