(380) Z160: A potent and state-dependent, small molecule blocker of N-type calcium channels effective in nonclinical models of neuropathic pain

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N-type voltage-gated calcium channels are validated targets for chronic and neuropathic pain, yet the only approved pharmacological agent that directly modulates this target demonstrates significant limitations. Ziconotide potently blocks the channel, but lack of selectivity for nociceptive N-type channels, including effects on peripheral N-type channels that regulate the cardiovascular system, results in severe side effects when administered systemically. Gabapentin and pregabalin, through interaction with the channel alpha-2-delta subunit, are thought to reduce the number and function of calcium channels at synaptic terminals. While this mechanism is better tolerated in humans, it has a slow onset of action, limited responder rates and side effects such as somnolence and sedation, possibly associated with nonspecific effects on calcium channel subtypes or lack of state-dependent effects. These limitations have driven the discovery and development of Z160, a potent, selective, state-dependent, small molecule N-type calcium channel blocker. Z160 blocked native and recombinant N-type channel currents in an irreversible, dose-dependent manner with sub-micromolar potency and 25- to 100-fold selectivity over P/Q- and L-type calcium channels. Z160 mediated a hyperpolarizing shift in steady-state inactivation, consistent with a mechanism involving inactivated state blockade. Z160 also demonstrated use-dependent block of N-type channels, with significantly greater potency at stimulation frequencies similar to the action potential firing rate typical of neurons processing pain signals. After oral administration in the Chung and CCI rodent models of neuropathic pain, Z160 demonstrated dose-dependent reduction of thermal hyperalgesia and tactile allodynia at levels comparable to morphine, ω-conotoxin MVIIA and gabapentin with no motor effects as measured by rotarod. These data demonstrate that Z160 is a novel, potent, selective and state-dependent N-type channel blocker with efficacy in animal models of neuropathic pain. The attractive nonclinical profile of Z160 supports further investigation in human clinical trials of neuropathic pain. Supported by Zalicus Pharmaceuticals LTD.

(381) Baclofen IV in the clinic: effective treatment for muscle spasm pain and migraines

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IV baclofen was used to treat refractory cervical muscle spasm/pain associated with migraines/daily headaches in an outpatient headache clinic. IV baclofen is not commercially available in the USA. A sterile preparation of baclofen (2.5mg/ml, pH 6.6) was made with a compounding pharmacist, and studied to reduce neck pain/spasm accompanied by refractory migraine headaches. 63 patients were treated in the clinic with pulse oximetry monitoring. 5-10 mg of IV baclofen given at intervals of 10-15 minutes with rating of muscle pain/spasm and headache/migraine every 15 minutes. A 0-10 VAS was used to monitor severity. Average initial muscle spasm/pain was rated 9.1/10. Migraines/headaches were rated 7.9/10. Muscle spasm/pain was diminished to 1.6/10 ($p < .001$, 2-tailed t test). Some patients (n=19) were treated up to 6 times ; 21 were treated once. Headache severity diminished to 3.2/10 ($p < .001$) at end of treatment; migraine was absent (n = 24 pts). Muscle spasm 0/10 in 30 of 63 patients treated. Duration of response was 22.9 hrs (+/- 6.5 hrs) for muscle spasm and migraine headache. 11 patients had failed prior oral baclofen treatment. Transient drowsiness was seen in 14 patients, no other side effects were reported, and nausea was treated with ondansetron. IV baclofen is a very efficacious and safe treatment for refractory muscle spasm/pain, associated with migraines/headaches in an outpatient setting with monitoring. Both symptoms were reduced to a highly statistically significant degree. IV baclofen offers a unique approach to treatment in the clinic. Side effects were minimal and the medication was well tolerated. Double-blind studies for this medication are definitely warranted, given the impressive open-label results. Type B GABA receptor activity may be altered or reduced in muscle spasm pain and in associated migraines. Baclofen is postulated to play a promotive or modulatory role in this painful disorder.

(382) IV tramadol: very efficacious treatment for pain and headache in the outpatient clinic

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Tramadol is used orally for chronic pain in the world and USA, but no IV form is available,except in Europe. We created and used an IV sterile preparation, to treat refractory pain and headaches in the outpatient clinic. Tramadol, 50mg per ml, was given IV in the clinic to patients with intractable pain and headaches. 79 patients were treated with IV tramadol, after placement of an IV line and pulse oximetry monitoring. A 50 mg test dose was given and 50-100mg was given every 7-10 minutes with monitoring of headache severity by the patient on a 0-10 VAS scale. All patients treated had response to IV tramadol. Average dose of tramadol was 423mg (range 250-1100mg), given over 95 minutes in the clinic. Average reduction in pain severity was 7.46/10 to 2.81/10 after treatment [$p < .001$, 2-taild t test]. No side effects other than transient drowsiness or nausea were noted in 6 patients. 21 patients were subsequently placed on oral tramadol.14 had failed prior oral tramadol for pain. Headaches returned within 24 hours in 2 patients not treated with oral tramadol. IV tramadol is quite effective in treating intractable pain, even where oral product failed. It also reduced migraines and headaches acutely in the clinic. It has virtually no toxicity IV and can be the starting point for oral treatment without titration. Typical dosage IV compares to daily oral dosing. Tramadol IV offers a new possibility in treating intractable pain and migraines effectively and safely in the clinic and should be studied in a double-blind manner. The mechanism(s)for its effects are discussed in the poster.

(383) Z944: A first in-class T-type calcium channel blocker effective in nonclinical models of acute and inflammatory pain

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Low voltage-gated T-type calcium channels contribute to neuronal hyperexcitability by impacting the threshold for action potential generation as well as firing frequency. The expression of T-type channels has been shown to be upregulated in several models of neuropathic and inflammatory pain and is thought to contribute towards pain hyperexcited states. Using a high-throughput fluorescence based assay for T-type calcium channel inactivation and a rational structure-based design approach, we developed Z944, a first-in-class T-type calcium channel blocker with enhanced affinity for the inactivated state. Z944 was observed to inhibit currents from the CaV3.1, CaV3.2 and CaV3.3 T-type isoforms with sub-micromolar potencies while maintaining selectivity for the inactivated state over the closed state, and between 260- to 2000-fold selectivity versus other voltage-gated calcium and sodium channels. Using manual patch clamp in primary rat dorsal root ganglion neurons, Z944 demonstrated sub-micromolar affinity for native T-type channels and at least 200-fold selectivity over endogenous N-type calcium channels. Following oral administration in the Complete Freund's Adjuvant (CFA) model of inflammatory pain, Z944 caused a significant, dose-responsive reversal of mechanical hyperalgesia after drug treatment and showed a 2-fold greater reversal than naproxen. Likewise in formalin models of acute and inflammatory pain, pretreatment of Z944 in rats resulted in a significant decrease in the rate of flinch responses during the inflammatory pain phase and in mice during both the acute and inflammatory pain phases. Collectively, these data demonstrate the utility of Z944-mediated T-type calcium channel blockade in limiting nociceptive signaling during acute and inflammatory pain states. Based upon the pharmacological profile and non-clinical efficacy of Z944, investigation in human subjects is warranted.