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Hyperpolarization-activated cyclic nucleotide-gated ion channels a new target for neuropathic pain? A proof-of-concept study with ivabradine

Aim: Mouse data suggest that ivabradine (a nonselective hyperpolarization-activated cyclic nucleotide-gated [HCN] ion channel antagonist) in high concentrations is equianalgesic with gabapentin. The authors sought to translate these findings to patients with chronic peripheral neuropathic pain.
Methods: An open-label design, administering increasing doses of ivabradine to target a heart rate of 50 to 60 beats per minute (bpm), up to a maximum of 7.5 mg twice daily. Participants scored their pain on an 11-point numerical rating scale (NRS).
Results: Seven (7) participants received the drug and completed the study. There was no significant treatment effect on the primary endpoint, the difference between the mean score at baseline and at maximum dosing (mean reduction=0.878, 95% CI=−2.07 to 0.31, P=0.1). Exploratory analysis, however, revealed a highly significant correlation between ivabradine dose and pain scores ($\chi 2(1)=74.6$, $P<0.001$), with a reduction of 0.12±0.01 (SEM) NRS points per milligram. The 2 participants with painful diabetic neuropathy (pDN) responded particularly well.
Conclusions: Ivabradine may be efficacious at higher doses, particularly in patients with pDN. Importantly, participants reported no adverse effects, suggesting that ivabradine, a peripherally restricted drug (devoid of central nervous system side effects), is well tolerated. Ivabradine is now off-patent, and its analgesic potential merits further investigation in clinical trials.

Comments: The drive to discover novel targets and therapies for neuropathic pain is still extremely high. The current study is the first of its kind to explore the use of ivabradine, a nonselective HCN blocker, in neuropathic pain. Ivabradine is currently licensed in most countries as an adjuvant in the management of angina and heart failure. Preclinical work has shown that ivabradine has analgesic properties in neuropathic pain states. In itself, the above study was an open-label, uncontrolled and underpowered in that they were only able to recruit only 7 of their intended 36 participants due to recruitment challenges, of which 2 had pDN. The maximum dose was gradually increased to 7.5mg BD or a heart rate between 50-60 bpm, as one would for cardiac indications. There was no significant difference in the primary endpoint noted in this short-duration study (6-9 weeks of treatment). What the investigators noted however was that there was indeed a significant correlation between increments in ivabradine dosing and NRS reduction. Analysis of the 7-day moving average suggested that the 2 participants with pDN showed the best response.
While this sets the scene for a putative role in the use of HCN antagonism for neuropathic pain, it is difficult to derive any clinical management conclusions as yet and plenty of scope to view the work with scepticism. Ivabradine is the only HCN antagonist agent currently available. Furthermore, its true analgesic effectiveness may be limited by its impact on heart rate – indeed it only achieves approximately 10% of HCN2 (the isoform expressed in nociceptors) blockade at the doses that give an acceptable reduction (drop) in heart rate. The way forward would be the development of selective HCN2 antagonists, which if proven to be clinically effective, may add another arsenal to our rather currently weak armamentarium of drugs for neuropathic pain.

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Reference: Bernard Healey SA, Scholtes I, Abrahams M, McNaughton PA, Menon DK, Lee MC. Role of hyperpolarization-activated cyclic nucleotide-gated ion channels in neuropathic pain: a proof-of-concept study of ivabradine in patients with chronic peripheral neuropathic pain. Pain Rep. 2021 Oct 18;6(4):e967.doi: 10.1097/PR9.0000000000000967.
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