Abstract

Gabapentin (Neurontin) and pregabalin (lyrica) are first and second-generation α2δ ligands, respectively, and are both approved for use as adjunctive therapy in pain control.1,2 Although they do not bind to gamma-aminobutyric acid receptors they have been successfully used to treat neuropathic pain which can be multifactorial. Their mechanism of action is not yet fully understood, but research has demonstrated promising results. Despite their similarities, they have been effectively used in combination both in clinical and research settings. This combined approach can be made use of to reduce the dose of individual agent, associated side effects, and enhance the therapeutic response compared to a single agent. Pharmacokinetics, drug interactions, and adverse reaction to the combined use of both drugs have to be taken into consideration before combination therapy with gabapentin (GBP) and pregabalin (PRG). This purported as first line treatment in refractory pain situations and in patients with renal impairment or low levels of tolerance for higher doses of individual agent.

Methods

• Simultaneous use of GBP and PRG in pain management was evaluated by searching MEDLINE and PubMed articles.
• We searched for “GBP and PRG” OR “pain management” AND “combined use” with limits on the years from 1995 onwards.
• Only six articles were deemed to be useful and relevant to the objective at hand. They were reviewed, and the relevant points were summarized.
• Additional sources were added to the literature search by way of being referenced.
• We excluded articles in languages other than English, as well as, studies for which no outcomes were reported.

Proposed Mechanism of Action

Antagonism of calcium channels in the central nervous system, and antagonism of N-methyl-D-aspartate receptors (NMDA), have most supporting evidence for the synergism between GBP and PRG in pain management.3,4

![Diagram showing model of the synergistic action of both agents.][6]

Figure 3. Effect of a 1:1 fixed dose 1.1 of gabapentin and pregabalin on the maintenance of Carrageenan-Induced Hyperalgesia. The theoretical additive line was calculated from the dose response data.6

Figure 4. Effect of a 1:1 fixed dose 1.1 of gabapentin and pregabalin on the maintenance of Carrageenan-Induced Hyperalgesia, in comparison to gabapentin and pregabalin. The theoretical additive line was calculated from the dose response data.9

Results

Combined use of GBP and PRG:
• Increased analgesic effect
• Achieving a sense of wellbeing
• Reduction of anxiety
• Improvement of sleep
• Can be used in patients who are intolerant to other classes of analgesics, have no response to either of those drugs attempted alone, unable to tolerate the higher doses of either PRG or GBP, and/or have renal impairment
• Have co-morbidities which preclude the use of other options
• Results from two clinical pharmacological studies conducted to assess the effects of concomitant administration of GBP and PGB, indicate that these compounds can be co-administered without any concern for clinically significant pharmacokinetic interactions.3,4
• But, currently there is only one available study highlighting synergy based on conversion rates.9
• In addition to a 1:1 fixed dose ratio of GBP and PGB, a 10:1 ratio was also found to demonstrate synergy, but the optimum ratio has to be individualized based on the intensity of pain, body mass, renal function and other co-morbidities of the individual being treated.9

Objectives

This review aims to explore the use of combination therapy with GBP and PRG, and suggests future directions in this important aspect of pain research.

Background

Neuropathic pain presents a large unmet need for improved therapies. The analgesic actions of GBP and PRG have been well-characterized in a large number of studies. GBP and PRG are structurally similar but have variations in their side chains (Fig 1). This small but important structural difference causes profound effects in their pharmacokinetic and pharmacodynamic properties.1,2

References


For Inquiry: please contact Dr H. Senderovich at hsenderovich@baycrest.org

Figure 1 [5]