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The effect of gabapentin and pregabalin on symptoms other than pain and seizures. A review of the evidence

Abstract

Gabapentin and pregabalin are drugs that act through reduction of the central sensitization. They are useful in conditions such as partial seizures and neuropathic pain. However, in the last decade these drugs appear to have been effective against a variety of other symptoms, such as pruritus, hot flushes in post-menopausal women and intractable hiccups. The drugs are probably also effective for many other symptoms related to central sensitization but the paucity of data does not allow for support of these claims. Both gabapentin and pregabalin have a good safety record.

Key words: gabapentin, pregabalin, nausea, vomiting, pruritus, restless legs syndrome, hot flushes, sweating, hiccup, tinnitus

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Introduction

Gabapentin (GBP) and pregabalin (PGB) are two drugs which have been recently developed to treat partial seizures [1]. Both drugs also appear to have been effective against neuropathic pain [2]. Although the drugs resemble gamma-aminobutyric acid (GABA), they do not have affinity to both GABAA and GABAB receptors or interact with GABA transporters. (For a review see Taylor 2007) [3].

The drugs show a high affinity to the α-2-δ units of voltage-gated calcium channels [3]. Binding to the α-2-δ units reduces the release of glutamate from the hyper-excited neurones [4]. GBP and PGB also decrease the release of substance P in the spinal cord and, in this way, reduce the sensitization of the spinal cord [5]. Reduction of central sensitization has been evidenced in healthy volunteers [6].

Apart from this effect, GBP and PGB increase the concentrations of extracellular GABA. This happens either by the stimulation of GABA release[7] or changes in GABA metabolism by interaction with glutaminic acid decarboxylase and GABA-transaminase [8].

Neither mechanism, the influence on voltage-gated calcium channels or the increase of extracellular concentrations of GABA, is specific to seizures or pain and hence GBP and PGB may also have other pharmacological effects. The most important is that both drugs have proven safety records at the pharmacologically effective doses.

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The scope of the article

GBP and PGB are licensed for the treatment not only of partial seizures but also postherpetic neuralgia and PGB in Europe for the treatment of anxiety disorders [3]. However, since the drugs were introduced they have become very popular for the treatment of many conditions unrelated to partial seizures and neuropathic pain. In this article we examine the evidence for these claims. Symptoms encountered in psychiatry are excluded from this review, as they deserve separate examination.

The hiccup

The hiccup-evoking centre is localized in the medullary reticular formation lateral to the nucleus ambiguus. These centres receive impulses from the sensory vagal neurones and communicate with the vagal motor neurones to, among others, the larynx and diaphragm. This was investigated most thoroughly in cats [9, 10]. Hiccups are not specific to any disease and more than 100 conditions are known to be associated with this recalcitrant symptom [11]. Any increase of impulses from the periphery (irritation, inflammation) or decrease in the threshold of the firing of the central neurones not counteracted by the central inhibitory mechanisms, may result in hiccups. It seems that hiccups may result from sensitization of central neurones which may be attenuated by GBP and PGB. Many remedies have been invented through the centuries. Most of these remedies increased the central inhibition of hiccups. However, many of these remedies were only effective for acute hiccups. They are usually ineffective in chronic and persistent hiccups, where there is a permanent irritation of the afferent nerve endings. These impulses can be diminished by the increase of the gastric and oesophageal pH with omeprazole [12]. Yet another approach, especially when the cause of the hiccup is "central" and the firing threshold is too low, is the use of anti-convulsive treatments. In this area, baclofen was found to be effective in small double-blind controlled trials [13, 14]. However, the use of baclofen in palliative care is sometimes difficult because of adverse effects such as somnolence. More recently GBP [15–21] and, to a lesser extent, PGB [22] were described as being effective in several series of patients with persistent hiccups. This effect, although used widely, has not been confirmed in formal controlled trials. The drugs have a rapid onset of action, few adverse effects and above all fewer interactions with other drugs [18]. GBP can thus be used alone or in combination with other drugs such as omeprazole[21]. After discontinuation of treatment the hiccups may reoccur [17].

Tinnitus

Tinnitus is the annoying perception of sounds in the absence of acoustic stimulation. Tinnitus commonly accompanies hearing loss and is more common in the elderly [23].Occasionally, an underlying structural lesion (*e.g.* acoustic neuroma) or an otological disease (*e.g*. Meniere's disease) is identified as the cause of the tinnitus. More often, tinnitus and hearing loss occur together without associated conditions or structural lesions: as we consider it, idiopathic subjective tinnitus. It is not known whether terminal disease and weakness are associated with the increased frequency of tinnitus but occasionally this symptom is encountered in the terminally ill and is particularly difficult to treat. The pathogenesis of tinnitus is unknown so when the treatment is offered it is not usually based on the mechanism of tinnitus. Various mechanisms have been proposed, including loss of central inhibition in which many peripheral impulses, not necessarily acoustic, are experienced as an annoying sound. It is unclear whether this hypothesis originated before or after the first reports on the efficacy of anticonvulsant drugs in tinnitus. Zapp was the first to report the serendipitous effect of GBP on tinnitus in one single patient [24]. In the study performed at Washington University, GBP was claimed to decrease the Tinnitus Handicap Inventory in a group of 19 patients treated for a week with GBP 900 mg a day (http://www.auditio.com/tinnitus/aaa2000). However, this study was never reported in a peer reviewed journal. An uncontrolled study by Bauer et al suggested that GBP given up to 2400 mg a day may be effective in the treatment of tinnitus, especially when it was associated with a history of acoustic trauma [25]. In a double-blind controlled study of GBP (900–3600 mg) in 59 patients treated through the GBP arm, no effect of GBP was observed [26]. Similarly, a prospective double-blind, placebo-controlled trial with GBP by Bakhshaee et al included 30 patients [27]. The dose of GBP was gradually increased to 900 mg a day. In this study there was no significant difference between the effect of the placebo and GBP. In another study on 52 patients with tinnitus randomized to the GBP arm, no effect of GBP 1800 mg a day was observed [28].

It can thus be concluded that despite several case reports suggesting a positive effect of GBP on tinnitus, this effect can not be replicated and confirmed in controlled studies. There are no reports or

even suggestions that PGB would be effective in this context.

Hot flushes and sweating

Hot flushes and sweating are the most annoying symptoms of advancing menopause but are also experienced by patients with breast and prostate cancer [29, 30]. Sweating as a separate symptom occurs in many forms of cancer, especially when liver metastases are present and when the patient is treated with opioids for pain [31, 32]. As treatment with hormones has the potential to improve a patient's prognosis it is difficult to advise on discontinuing them. There is a lot of interest in finding an "add-on" to hormonal treatment that would be able to control these annoying symptoms. One of the treatments that has recently emerged is one with clonidine, GBP and SSRIs [33]. In a case series, Guttuso reported that GBP appeared to be effective in treating hot flushes in post-menopausal women [34]. He later performed a placebo-controlled study confirming these observations [35].In this study performed on 59 post-menopausal women suffering severe hot flushes, GBP reduced the flush composite score from 54% to 31% ($p = 0.01$). The doses needed to achieve these results were up to 2700 mg of GBP daily. In a much larger study comprising 420 women with a history of breast cancer and hot flushes during a course of treatment with tamoxifen, Pandya et al found a 31% decrease in hot flushes with a low dose of GBP (300 mg per day) and a 46% reduction when the dose was increased to 900 mg per day. In this study the placebo produced a reduction by 18%. The p was significant only for 900 mg GBP per day [29]. In a small controlled study with 60 post-menopausal women who suffered hot flushes, GBP appeared to be as effective as oestrogens in relieving this annoying symptom [36]. In conclusion, the data suggest that GBP may be effective in the treatment of hot flushes in post-menopausal women. Data concerning excessive sweating in cancer [patients] are limited to a series of 9 patients who all responded to GBP up to 1800 mg a day [37].

Pruritus

There are different mechanisms for pruritus and one of them is pruritus due to neuropathy [38]. It is thus logical that GBP was first applied in such conditions as *brachioradial pruritus* [39–41] and *notalgia paraesthetica* [42]. Mendham et al reported a positive effect in a series of 35 children with itchy scars following burns [43]. However, the anti-pruritic effects were also observed in conditions only remotely connected to neuropathy. Twenty-five patients with *uraemic pruritus* were treated in a cross over, placebo-controlled design [44]. Several patients in this study responded to the treatment with GBP, although the overall effect was not significant. In a comment on this study it was concluded that to avoid the nephrotoxicity of GBP, this drug should be given in a low dose (100 mg) after every haemodialysis session [45]. Overall, GBP is found to be interesting and potentially effective in uraemic pruritus [46–48]. GBP was also claimed to be effective in pruritus of unknown origin [49].

GBP may be effective in the reduction of pruritus caused by opioids [50–52]. However, GBP was found to be ineffective in the treatment of the pruritus of cholestasis, a condition known to be caused by endogenous opioids [53]. Interestingly, there was a suggestion that GBP was effective in several cases of patients with cutaneous T-cell lymphoma and Sézary Syndrome [54]. However, although still unconfirmed this is of particular importance because few other drugs appear to be effective for this syndrome and the pruritus is overwhelming.

There are few reports of the anti-pruritic effects of PGB [55–57] and Stander et al, basing this on her own and unconfirmed observations, has suggested that PGB's effect on pruritus is weaker than those of GBP [58].

In conclusion GBP, but not PGB, seems to be effective in different pruritic conditions, not only those related to neuropathy and nerve damage. Most important is the activity of GBP in uraemic pruritus. Further studies should be undertaken to confirm or refute this significant effect.

Restless legs syndrome

Restless legs syndrome (RLS) is a sensorimotor disorder, characterized by an irresistible urge to move the legs and is usually accompanied or caused by uncomfortable and unpleasant sensations. It begins or worsens during periods of rest or inactivity, is partially or totally relieved by movement and is exacerbated or occurs at night and in the evening. Typically, the condition responds to dopaminergic treatment. Theoretically, the anti-dopaminergic drugs frequently used in palliative care, such as haloperidol or metoclopramide, should increase the frequency and intensity of RLS. However, this effect has not been reported so far. Dopamine-resistant RLS has been suggested to be responsive to GBP, although without provision of any details or controlled data. In one study GBP was compared with ropinirole, a dopamine agonist, in its effectiveness

in RLS. The study was randomized but not placebo controlled. The authors concluded that both drugs were equally effective in the treatment of RLS and were equally well tolerated [59]. In two patient series GBP was found to be effective for RLS and tremors [60, 61]. In a formal randomized, placebo-controlled study GBP appeared to be effective in the treatment of the symptoms of RLS. Meta-analysis which included all trials with anti-epileptic drugs — including GBP [62] — for RLS was inconclusive, mainly because of the scarcity of data [63].

PGB was reported to be effective in 16 patients with RLS [64]. However, 3 other patients in this study needed to discontinue therapy because of intolerable adverse effects and loss of benefit.

Miscellanea

GBP appears to have been effective for a number of other symptoms, including nausea and vomiting [65–68], alcohol dependency [69–72], smoking cessation [73], erythromelalgia [74], stiff-limb syndrome [75], benign fasciculations [76] and symptoms of hepatic encephalopathy [77]. The majority of these claims are not supported by controlled trials.

Conclusion

GBP and PGB act through a diminishing of the release of the neurotransmitters responsible for central sensitization. These drugs are, therefore, potentially effective for multiple symptoms that are related to the increased excitation of the central nervous system. Although most of the clinical data concerns GBP, it is expected that PGB does not have an effect on these symptoms that would be very much different. The most important actions of GBP and PGB are their effects on various forms of pruritus, including uraemic pruritus, intractable hiccups and hot flushes in post-menopausal women. Further studies are needed to support other claims. From not one study does it appear that PGB is more effective than GBP, which means that, for the time being, GBP should be the preferred drug because of economical reasons.

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