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REVIEW

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Headache and neck pain: Gabapentin as a possible treatment

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Abstract Pain is a common situation and it is one of the most frequent presenting symptoms of different pathologies. Treating pain could be a precise request to the doctor, from the patient and his caregiver. Management of neuropathic pain is particularly challenging and many patients presenting with chronic or subacute head and neck pain need a multidisciplinary approach. The principal targets of effective pain control are to ameliorate nociception, to reduce threshold of pain sensation and to improve quality of life. We offer a panoramic view of nociception, from a central perspective, and discuss various pharmacological options available to treat headache and neck pain. We also debate the role of a new antiepileptic drug, gabapentin, in the management of headache and neck pain. It is now considered to be an emergent treatment for pain syndrome. We delineate its pharmacological, laboratory and clinical profiles, with a review of the world literature.

Key words Gabapentin • Headache • Neck • Neuralgia • Pain treatment

Introduction

Pain is a multidimensional experience including sensory-discriminative and affective-motivational components: from electrical brain stimulation, there is a possibility to attribute its control to different cortical areas [1, 2]. More recent studies, based on positron emission tomography (PET) and functional magnetic resonance imaging (f-MRI) [3–7] demonstrate a multiplicity of activated brain sites during acute and chronic pain states. Simultaneously, it has become evident that there may not be a common structure or neuronal master switch [8, 9] for the generation of pain. The most interesting aspect is that the overall picture of activation may depend not only on the nature, duration and intensity of the noxious stimulus, but also on the psychological disposition of the patient, with his subjective and personal perception of pain. A statistical analysis of the pain-induced cerebral blood flow increases confirms the agreement on the activation of the cingulate cortex, in particular the more rostrally localized sites (concerning attention and motor control/intention zone) [8–11]. The adverse and affective aspects of pain are tightly related to the posterior sector of the cingulate cortex (Broadmann area 24) confirmed by an f-MRI study using electrical pain, which allocates the coding of pain intensity to this area [9]. Pain intensity is positively correlated also with an increase of the cerebral blood flow in the posterior cingulate cortex and the high-level opiate binding in this region, associated with a reduced binding in chronic patients, enforces the conviction

of its role in pain processing [12]. In acute situations, the pain generally resolves quickly enough, so that there is a little time for substantial changes in the internal state; chronic pain is, by definition, of longer or indefinite duration and much more time occurs for the variations in pain awareness. Conventionally defined as "pain that persists beyond the normal time of healing" [13–15], chronic pain involves a neuropathic component, usually harder to treat than acute somatic pain.

Common pharmacological treatment

Managing acute pain is frequent and not particularly difficult: on the contrary, managing patients with chronic pain is intellectually and emotionally challenging, especially since several factors can cause, perpetuate and exacerbate chronic pain. The patient may simply have a characteristically painful disease (e.g. arthritis, cancer, migraine), but there may coexist perpetuating conditions, such as damaged sensory nerves, sympathetic efferent activity and painful reflex muscle contraction, and psychological conditions can exacerbate painful sensation too [16]. The longer pain lasts, the more evident is the patient's perception of pain. A singular and definite evidence [17] demonstrated that the pressure pain threshold is significantly lower in tension-type headache patients than in control subjects. Even more illuminating is the evidence of significantly lower levels of beta-endorphins in peripheral blood mononuclear cells and of substance P in platelets, as well as significantly higher levels of serotonin in platelets in tension-type headache patients, with a concomitant significant positive correlation between pressure pain threshold values and beta-endorphin levels in both control and patient groups [17].

"Few things a doctor does are more important than relieving pain….pain is soul destroying" [18]. Once the causative and exacerbating factors have been identified, a multidisciplinary approach may be used to improve quality of life, but the first demand of the patient is to interrupt pain feeling. The majority of the adjuvant medications are neuroactive substances that are used most often to treat neuropathic pain syndromes: there is growing evidence that some forms of neuropathic symptoms do respond to opioids [19–21]. On the contrary, there is little evidence that neuropathic pain does not respond as well to the primary non-steroid analgesic treatment [19]. Of the neuroactive drugs, the most commonly used and best studied are the anticonvulsants [22] and the antidepressants [23]. It is highly likely that almost all the adjuvant pain medications have both peripheral and central affects and it is often difficult to know which of the two is more efficacious. In particular, the best studied effects of the anti-convulsivants and antidepressants are central and maybe their influence on the pain process is mediated through a central inhibition [24] as far as a most certain effect on the affection and on the mood of the patient.

Writing and discussing about pain and even of migraine treatment are not anachronistic in our period, called the one of "triptan wars".

Migraine headache, cluster headache, tension-type headache and other causes of facial pain (which can be enrolled in the "atypical facial pain", Sluder's syndrome, post-herpetic neuralgia and so on) do need analgesic treatment. Both prescription and non-prescription analgesics are widely used by headache sufferers for the treatment of acute headache and chronic daily headache. Unexpectedly, recent studies [25–28] presented at the International Meeting of the American Association for the Study of Headache proposed even opioids for pain treatment, and suggested that long-acting opioids in a select subgroup of patients with refractory chronic daily headache have improved quality of life and reduced pain intensity. Apart from this specific subgroup, the majority of patients in the US with primary headache have never consulted physicians, have never received a prescription medication, and use (and more often abuse) different self-prescribed drugs [29–31]. Another study [32] found that paracetamol with codeine was the most frequently prescribed medication for headache. Other reports [33, 34] described that different combinations of codeine were the most frequently prescribed agents for chronic mild pain in the US.

To find the most ideal analgesic drug, the attention of research shifts on selective therapeutic classes. Many authors focus their attention on NMDA receptor antagonists, the best studied of which is dextromethorphan [35]. These drugs are suspected to enhance the efficacy of opioid agents and block the development of tolerance. As a consequence, ketamine has been studied and found to have spectacular results in head pain [36, 37]. However, the broader clinical experience concluded that the drug is only occasionally effective, producing, on the contrary, significant side effects in the central nervous system (CNS), including occasional prolonged hallucinations [38, 39].

Considering the side effects of antidepressants, most authors polarize their attention on anticonvulsant medications, which are used primarily to treat abnormal neuronal firing of the CNS leading to epilepsy. Therefore, they are presumed to suppress spontaneous neuronal firing rates through their action on ion channels or neurotransmitters, also on abnormally firing pain fibers. In particular, gabapentin has been widely used for the treatment of pain in laboratory tests. Then, the drug extended its role in clinical tests on pain, with slow but incessant progression [40].

To review the use of gabapentin as an adjuvant agent to treat neuropathic pain, we decided to review MEDLINE and EMBASE, in order to search from 1980 to December 1999 for reports on gabapentin and pain. Search terms included gabapentin, pain, head and neck, diagnosis, controlled trials, and analgesic treatment. There were approximately 90 citations. Additional articles covered the pharmacokinetics of the drug, laboratory analyses and molecular experiments on gabapentin.

Gabapentin: from molecule to experimental practice

Gabapentin (1-(aminomethyl)-cyclohexane acetic acid) is a novel amino acid derived by addition of a cyclohexyl group to the chemical backbone of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in mammalian brain. Gabapentin possesses low inherent toxicity. It is not metabolized and does not affect hematological or biochemical variables to any significant degree [41]. Gabapentin crosses several membrane barriers in the body via a specific amino acid transporter (the so-called system L) and competes with different amino acids, such as leucine, isoleucine, valine and phenylalanine, for transport. Radiotracer studies with [14-C]gabapentin suggest that it is rapidly accessible to brain cell cytosol. Even more evident (confirmed by recent studies with [3-H]gabapentin), is the existence of a specific site of binding in the superficial layer of neocortex and dendritic layers of hippocampus, in the brain stem and white matter (and not in other organs).

Although gabapentin's mechanisms of action remain undetermined, experimental evidence demonstrates that it enhances GABA synthesis and inhibits its degradation in the brain. Designed as a GABA-mimetic, gabapentin does not interact with any of the known pharmacological sites on either the GABA-A or GABA-B receptor, nor does it block GABA uptake or inhibit the GABA-metabolizing enzyme or GABA-transaminase [42]. This way, gabapentin may act by an enhancement of GABA-mediated inhibition or a modulation of voltage-dependent ion channels involved in action potential propagation or burst generation [43].

Recent findings [42] suggest that gabapentin preincubation increases the non-synaptic release of GABA from glial structure. This way, gabapentin causes an increase in brain GABA synthesis, not limited to the substantia nigra and to the corpus striatum but extended throughout the brain.

Some electrophysiological studies suggest that gabapentin may act as a partial agonist at the glycine modulatory site of the NMDA receptor [42]. Gabapentin has an anti-hyperalgesic effect which has been tested in different experimental studies. This drug seems not to possess an antiphlogistic action. On the contrary, gabapentin induces an elevation of serotonin (5HT) in the CNS, which has been demonstrated in humans [44]. 5HT plays an important role in the inhibition of pain via the raphe-spinal descending control system. This system carries signals from the raphe magnus to inhibit nociception at the substantia gelatinosa of the spinal cord, which contains a high density of projections from the raphe magnus and substance P terminals, opiate receptors and serotonin terminals. Therefore, 5HT has a prominent role in analgesia [45]. Moreover it is interesting to note that thermal hyperalgesia is mediated predominantly by C-fibers which produce their effect mainly via NMDA receptors. The first in vitro experiments focused on the possibility that gabapentin acts as a modulator of NMDA receptor [46]. It remains to be seen whether gabapentin indirectly modulates glutaminergic transmission at the level of the NMDA receptor [46]. Effectively, the in vivo effect of gabapentin as an NMDA/glycine modulator has been confirmed [47], defining therefore its analgesic profile.

Different studies reinforce the analgesic properties of gabapentin. Its efficacy on formalin-evoked behavior in diabetic rats has been tested. In this case, gabapentin displays efficacy against abnormal sensory processing [48, 49]. Moreover, gabapentin (and the related compound, regabalin) but not morphine or amitriptyline block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat [50, 51]. Above all, the analgesic properties of gabapentin in in vivo experiments are demonstrated by its action on allodynia in neuropathic rats [52]. This study effectively demonstrated that gabapentin suppresses the ectopic discharge activity from injured peripheral nerves, which may contribute at least to suppress the allodynic effect. Last, but not least, gabapentin analgesic effect is not due to a systemic effect, nor to local anesthetic effect. On the contrary, it is blocked by D-serine and not by L-serine. Therefore, it can be concluded that it possesses a peripheral site of action, extremely important for the treatment of neuropathic pain [53].

Gabapentin in head and neck pain

Starting from this perspective, gabapentin has been used in different trials in head and neck pain. The clinical presentation and pharmacological management of three patients with acute herpetic neuralgia and of two patients with postherpetic neuralgia confined to the head and neck region (two in the ophthalmic division of the trigeminal nerve, two in the C2-C4 dermatomes and one patient with pain radiating from the C2 region with referred pain to the second and third divisions of the trigeminal nerve) demonstrate that all

the patients reported a complete pain relief, following gabapentin up to 1800 mg per day. All the patients noted a dose-dependent decrease in pain almost immediately after starting gabapentin. The more interesting aspect of the study was that pain was treated in a more systematic way: the McGill pain questionnaire was used to assess cognitive-evaluative aspects of pain. Initially, patients reported high scores on the questionnaire and described their pain as annoying, disturbing and weary. At the final visit, all the patients were pain free and none experienced side effects from the drug [54].

In view of the encouraging results in these patients, blinded controlled studies are needed to determine the efficacy of gabapentin. Therefore, this study was followed by extensive work on post-herpetic neuralgia, with a randomized controlled trial [55]. The study was a multicenter, randomized, double-blind, placebo-controlled, parallel design, 8-week trial, conducted from August 1996 through July 1997, on a total of 229 randomized subjects. The primary efficacy measure was the change in the average daily pain score, from baseline week to the final week of therapy. Secondary measures included average daily sleep scores, quality of life and modification of mood states. The study concluded that gabapentin is effective in the treatment of pain and sleep interference associated with post-herpetic neuralgia; by intent-to-treat analysis, subjects receiving gabapentin had a statistically significant reduction in average daily pain score, compared to controls. Mood and quality of life also improved with gabapentin therapy. That study also considered the adverse aspects of gabapentin therapy, but the conclusions seem hurried. Somnolence, dizziness, ataxia, peripheral edema and infections were reported to be more frequent in the gabapentin group, but withdrawals were comparable in the two groups (13.3% in the gabapentin group vs. 9.5% in the placebo group). No more was said about the side effects: some of them are clearly drug-related (such as ataxia and dizziness); others may be simply idiopathic. However, it may be relevant to know if some of them, such as peripheral edema, are somehow related to alterations in laboratory values (eventual and transient renal sufferance, for instance).

Another confirmation of a good response to gabapentin therapy comes from the treatment of intolerable pain in patients suffering from post-herpetic neuralgia in the area of the first branch of the trigeminal nerve and from thalamic infarct which gave rise to a contralateral Dejerine-Roussy syndrome [56–58]. In all cases, administration of gabapentin was followed by such a striking improvement in pain, that co-adjuvant treatment could be reduced or stopped, with excellent tolerance and a minimal incidence of side effects. In particular, one study [58] of a large case series found that 65% of patients had moderate-to-excellent improvement in symptoms. The criticism of this study is the absolute absence of parametric measures to quantify pain, whose relief was evidenced only by clinical practice.

Even more interesting are the results obtained with migraine. Despite the variety of medications used for migraine prophylaxis, over 11 million Americans continue to experience chronic migraine attacks and almost one-half experience more than one attack each month. Commonly used medications such as ergotamine, non-steroid anti-inflammatory substances (NSAIS), beta-blockers, tricyclic antidepressants, monoamine oxidase inhibitors and various anticonvulsants such as phenytoin and carbamazepine are at best partially effective and moreover cause a number of unpleasant side effects that may limit their utility. Progress in general pain relief has recently been achieved with the introduction of new opioid analgesics such as tramadol, administered per os, or percutaneously for transdermal fentanyl. Obvious limit of their use and potential side effects restrict their diffusion to a narrow-spectrum population [59, 60].

To identify a more tolerable drug, a double-blind, placebo-controlled, multicenter study was conducted to determine whether gabapentin is effective in reducing the migraine headache rate, during a 4-week period, measured by daily headache diaries in 145 subjects (81 women) who experienced 3-8 migraine episodes per month and had failed no more than two prophylactic antimigraine regimes. They were randomized 2:1 to gabapentin (n=99) or placebo (n=46). During the titration phase, a dose-escalation of gabapentin up to 2400 mg daily or matching placebo was administered. The primary efficacy measurement was the migraine headache rate during the final stabilization phase. Additional efficacy parameters included the 50% responder rate and the average duration of migraine headache. The responder rate was 36% for gabapentin and 14% for placebo. The two treatment groups were comparable with respect to treatment limiting adverse events. The study was well-designed for the eligibility criteria and for the study assessments. Well delineated were also the adverse events profile, where there was no statistically significant difference between the two groups.

Gabapentin has been demonstrated to be an effective and safe prophylactic treatment for migraine headaches [61]. That study was sustained by different open trials [62–65] which gave encouraging results also in refractory to treatment migraine without unbearable side effects, sleepiness apart. In particular, the first open trial [62] proposed gabapentin for prophylactic treatment of migraine on 63 patients with intractable headache. Gabapentin was administered from 600 to 1800 mg daily for 12 weeks. The most important end point was the average frequency of migraine episodes, starting from baseline week until the end of the study. 59% of patients registered a reduction of migraine attack of more than 50%,

with a concomitant decrease of duration attack and, of peak intensity, with a melioration of life quality and with a reduction of the intake of other drugs by the subjects enrolled in the trial. That is, from our point of view, the real limitation of the study: the possibility of the subjects to use other symptomatic drugs was not clearly stated. Therefore, it is difficult to delineate the real possibility of gabapentin treatment in a prophylactic therapy. Another study [66] reported a consistent and significant decrease in the number, intensity and duration of migraine attacks by more than 50%. The improvement was even more evident in the successive months of treatment, with modest and transitory side effects. The biological demonstration of gabapentin effect may be tightly bound to the neuropeptidergic 5HT system, main neuromodulator of nociception, considering gabapentin induction of an elevation of CNS 5HT [44].

The most surprising evidence is that arising from intractable neuropathic pain, such as trigeminal neuralgia, both idiopathic and symptomatic [67, 68], with a prompt action and above all without side effects, considering the most frequently referred symptoms of therapeutical drugs, commonly used in such cases: ataxia, nystagmus, lymphopenia, dizziness and so on. In the study by Sist et al. [68], the most interesting aspect was the particularity of the presented cases: an 88-year-old woman and an 84-year-old woman, suffering from therapy-resistant trigeminal neuralgia, were studied with a complete follow-up at 6 months. The obvious limit is that only two cases do not permit an exhaustive delineation of general principles, but the age of the two subjects enrolled extended gabapentin also to the geriatric population.

Even more encouraging are the results of another study [69] which referred to various painful syndromes not responding to common therapeutic choices, such as Parsonage-Turner neuralgia, not responsive to steroid treatment, atypical facial neuralgia and reflex sympathetic dystrophy. These different pathologies share only the acute and constant painful sensation: that is the reason for the wide range of gabapentin dosage (from 200 to 1800 mg daily). Starting from this point, it cannot be denied that 86% of patients responded with a complete pain relief, without side effects.

Another therapeutic success [70] is the treatment of a rare painful condition, glossopharyngeal neuralgia, which responded promptly to gabapentin after various attempts with different drugs, not well tolerated and above all not efficacious.

The other aspect which must be considered and which emerges from the literature is the long-term safety, as has been established by dosages up to 2400 mg per day for periods of up to 2 years as add-on-therapy in patients with medically refractory partial seizures [71]. Gabapentin was studied on 1800 subjects (volunteers and patients) in order to identify side effects. It has been established it is quite well tolerated. From the technical schedule of the drug, two overdoses of the drug were reported: the first patient's intake was 8 grams, associated with a concomitant intake of other anticonvulsivant drugs. The second patient took an unknown dosage of gabapentin. In both cases, side effects were dysarthria and dyplopia. Moreover, a 16-year-old patient intentionally assumed 30 grams of gabapentin in a single day, without particularly worrying side effects, apart from sleepiness, moderate diarrhea and dizziness. Above all, it has been widely tested on children (both considering cognitive and visceral aspects of treatment) and in subjects with acute intermittent porphyria (particularly sensitive to drug catabolism), without exacerbating problems. Moreover, considering that gabapentin does not bind plasma proteins, it gives no interference with other drugs [72–75].

Conclusions

Pain is a major public health problem. The management of orofacial pain may be a difficult challenge to the medical profession. Ideally, severe cases of this type of pain should be treated by a team drawn from several disciplines. Although acute pain serves a protective function, alerting us to real or potential tissue damage, chronic pain serves no useful function. It may be imperative, useful, convenient and ethical to treat pain with the most complete and tolerable drugs. Moreover, early recognition of a case of chronic pain improves the chances of successful management and avoids frustration and disillusion both to patient and doctor. From the profile which emerges from the literature, gabapentin can be considered an emergent solution for the "pain riddle", even if some aspects of the drug must be clarified. Starting from this point, more randomized, double-blind studies, comparing traditional analgesic drugs with gabapentin, may be relevant to identifying the first choice therapy for acute and chronic pain relief.

From these studies, an eventual flow chart may be drawn to assure the better and progressive treatment for pain. Even more necessary are further studies to evaluate the side effects of the treatment, with eventual modifications of laboratory parameters.

This review gives us the opportunity to propose that all specialists who treat pain should evaluate and optimize the therapeutic treatment with parametric measures (pain scales), which can easily be compared and can give an objective and universal perception of the clinical situation faced.

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