DRUG THERAPY FOR TRIGEMINAL NEURALGIA

Melvin George[1] Senior Resident, **Sandhiya Selvarajan**[2] Senior Resident, **Indumathi C**[3] Phd Scholar,

[1&2]Division of Clinical Pharmacology, JIPMER, Pondicherry, Puducherry (UT), India.

[3]Department of Pharmacology, JIPMER, Pondicherry, Puducherry (UT), India.

Correspondence: Melvin George, Senior Resident, Division of Clinical Pharmacology, Jipmer, Pondicherry, Puducherry (UT), India.
E-mail: melvingeorge2003@gmail.com

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ABSTRACT

Trigeminal neuralgia(TN) is a rare disorder presenting with lancinating pain in the face in the area distributed by the trigeminal nerve. Both medical and surgical modalities exist in the treatment of patients with TN. Carbamazepine still remains as the gold standard drug in terms of efficacy in TN. Several other drugs can be used as alternatives for TN such as oxcarbazepine, baclofen, lamotrigine, levetiracetam, gabapentin, valproate, botulinum toxin A injection. This paper reviews the clinical evidence and the safety profile of these drugs for the treatment of TN.

Keywords: Trigeminal neuralgia, drugs, pharmacotherapy, first line therapy, second line therapy.

Introduction

Trigeminal neuralgia is an uncommon disorder seen in dental and neurologic practice, that presents with brief lancinating pain in the face, in the area distributed by the trigeminal nerve. The disease is also known by less familiar names such as 'Fotergill's disease' or 'tic douloureux'. The prevalence of this condition is about 1 in 25000 people. The International Headache Society classifies trigeminal neuragia (TN) as classic TN or symptomatic TN.[1] If a clinically evident neurologic deficit cannot be detected, a diagnosis of classic TN can be made; while a diagnosis of symptomatic TN would require a demonstration of structural lesion other than vascular compression. A single attack may last for a few seconds but may also present in clusters of variable intensity for 2 minutes in a paroxysmal fashion. The pain is excruciating and can affect the patient's quality of life. The patient is usually free from pain between attacks but a dull background pain may persist in some cases, who have poorer treatment outcomes.[2]

Although the exact cause of the disease is not known, there is some evidence that demyelination at the trigeminal root entry zone with subsequent ephatic cross talk between axons could be involved in triggering a cascade of events resulting in trigeminal neuralgia.[3] In the demyelinated regions of the trigeminal nerve, there may be an altered expression of voltage gated sodium channels which might contribute to increased pain sensitivity.[4] Another popular hypotheses for trigeminal neuralgia is the vascular compression of the trigeminal nerve.[3]

There are indeed a gamut of medical and surgical treatment modalities available for trigeminal neuralgia. As per AAN-EFNS(American Academy of Neurology- European Federation of Neurological Societies) guidelines[5], medical therapy is started and surgical options are considered only if there is failure to respond to medical therapy.

First line therapy

Carbamazepine has still retained its position as the initial drug of choice for trigeminal neuragia despite the entry of several new drugs for this condition over the last few decades. This is because of the robust evidence of its efficacy in RCTs (randomized controlled trials) among patients with trigeminal neuralgia.[6;7] The mechanism may relate to its ability to block voltage sensitive sodium channels which result in stabilization of the hyperexcitable trigeminal neural membranes.[8] A much lower dose(300-800 mg/day) than the conventional antiepileptic dosage is sufficient in alleviating the pain of trigeminal neuralgia. The efficacy at the start of therapy may be even as high as 80% but only 70% obtain complete relief.

Common side effects include drowsiness, diplopia, ataxia and hyponatremia. The uncommon but serious adverse effects include allergic rash, myelosuppression, hepatotoxicity, lymphadenopathy, systemic lupus erythematosus, Steven-Johnson syndrome and aplastic anemia. The prevalence of aplastic anemia is 1 in 200,000 patients although mild leukopenia may be seen during early stages of therapy(10%). Skin rashes are more common in the Asian population. Adverse effects require discontinuation in 5-20% of patients. After commencing therapy it is prudent to monitor the complete blood count, serum sodium and liver function test within a few weeks of therapy to detect any adverse reactions. Drug interactions with carbamazepine are a potential problem as the drug has the capacity to induce hepatic drug metabolizing enzymes. Oxcarbazepine is a keto analogue of carbamazepine which has a better toxicity profile. It may be a useful alternative in patients who do not tolerate carbamazepine.[9;10] In double blind RCTs there was a reduction in the number of attacks (88% of patients showed atleast 50% reduction or more) and the global pain assessment scores were equally good for both oxcarbazepine and carbamazepine. [11,12]

Second line therapy

Uniform consensus does not exist as to which should be the second line drug in a patient who does not respond to carbamazepine since there are no large scale trials which have examined this issue. Baclofen, a central spasmolytic which is used in many spastic disorders has been found to be effective in relieving the symptoms of trigeminal neuralgia . It is a GABA-B agonist given at doses of 10 -60 mg/day. In a randomized double blind placebo controlled trial involving 30 patients comparing carbamazepine, baclofen and a combination of both, baclofen showed more efficacy(71% vs 30%, ;RR2.38, 95% CI 0.83 to 6.85).[13;14] However as the study did not use an intention to treat analyses and had a high drop out rate, the results should be judged with caution. One of the limitations of baclofen is the high rate of recurrence after one year of therapy(22%). Neverthless, baclofen has the strongest evidence for efficacy of trigeminal neuralgia after carbamazepine.[15] Decrease in muscle tone and transient sedation are expected side effects Patients with multiple sclerosis and trigeminal neuralgia derive special benefit with baclofen as the drug can target the symptoms of both the disease conditions.[16]

Tizanidine

Tizanidine is another central muscle relaxant which was evaluated in a small double blind cross over study with placebo in 10 patients. The study found that the drug caused pain relief in 8 out of 10 patients(RR 8.00, 95% CI 1.21 to 52.69, p = 0.03). However symptoms recurred after 3 months in all participants.[17] An RCT done in 12 patients comparing tizanidine with carbamazepine did not show any difference in efficacy between the two drugs. However the trial had significant limitations due to its small sample size and per protocol analysis.[18] Overall the evidence for use of tizanidine for trigeminal neuralgia is far from satisfactory.

Lamotrigine

Lamotrigine is a phenyltriazine derivative developed for the treatment of partial and generalized tonic clonic seizures. It acts as a voltage sensitive sodium channel and stabilizes neural membranes.[19] In an RCT done in 14 patients with refractory trigeminal neuralgia it was found that more patients showed improvement with the addition of lamotrigine to current medication compared with adding placebo.[20] The adverse effects which are common are ataxia, constipation, vomiting and rash. Rash can vary from a mild reaction to severe life threatening Steven Johnson syndrome. This reaction, which is more common at the advent of therapy can be prevented to a certain extent by taking care not to escalate the dose too rapidly.[21] The usual starting dose is 25 mg twice daily and it can be increased gradually to a maintenance dose of 200-400mg/day in two divided doses.

Levetiracetam

Levetiracetam, a popular antiepileptic in the paediatric as well as adult population has also been tried in trigeminal neuralgia. Its mechanism of action is thought to involve binding to the high voltage N type calcium channels as well as the synaptic vesicle protein 2A (SV2A).[19] In an observational trial that included 23 patients, the number of daily attacks decreased by 62.4% in patients receiving levetiracetam as add-on therapy.[22] However as the study was open labeled in design using subjective outcome measures one cannot rule out the possibility of bias in the results. Randomized placebo controlled studies are definitely warranted before making any definitive claim of the efficacy of levetiracetam in trigeminal neuralgia. Nasopharyngitis, influenza and somnolence are adverse reactions that one should watch for while starting treatment with levetiracetam. The effective dose range is 1000 - 4000 mg/day.

Gabapentin

Gabapentin, an antiepileptic drug has shown promise in relieving some forms of neuropathic pain. In a retrospective study, involving 194 cases of trigeminal neuralgia, with paroxysmal facial pain resistant to previous surgical interventions or treatment with multiple medications, 92 patients received a trial of gabapentin, and of this 43 patients reported decline in facial pain. The benefit obtained was complete in 16, nearly complete in 9, moderate in 12 and partial in 6 patients. Onset of pain relief was found to occur during the first 1 to 3 weeks of therapy. In these patients, gabapentin was found to be effective at a daily dose range of 100 to 2400 mg per day in three divided doses with a mean dose 930 mg/day. During a mean follow-up time of 8 months, pain relief was found to continue in two third of patients.[23] From the studies done so far, it appears that treatment should be started at a dose of 900 mg/day (300 mg/d on day 1, 600 mg/d on day 2, and 900 mg/d on day 3). The dose can also be increased to a maximum of 1800 mg/d for greater efficacy. Some patients may be requiring up to 3600 mg/d.[24] However the effective dose should be individualized based on response and tolerability. Hyperlipidemia is one of the important side effects known to occur while other side effects such as dizziness, coordination problems, infections, nausea, vomiting are usually self limiting within ten days of initiation of therapy.

Pregabalin

Pregabalin is a GABA analogue structurally related to gabapentin which modifies the synaptic or non synaptic release of GABA. The drug binds to the a_2d subunit of the voltage gated calcium channels causing decreased presynaptic calcium entry leading to decreased synpatic release of glutamate. In an open label study carried out in 53 patients, pregabalin at a dose of 150-600 mg/day showed reduction of pain by over 50% in 74% of patients. Ataxia and tremor may occur. Since this drug does not bind to plasma proteins, it is almost free of drug interactions.

Topira-mate

Topira-mate, a newer antiepileptic drug acts by sodium channel blockade, enhancing GABA activity by binding to a non-benzodiazepine site on $GABA_A$ receptors, and selectively blocking AMPA/kainite glutamate receptors. In a study, topiramate given to eight patients with classical trigeminal neuralgia at a dose of 50 to 100 mg a day, showed complete symptom remission in three patients, with moderate improvement in three patients and failure in two patients.[25] Similarly in another study done in eight patients with classical trigeminal neuralgia, complete remission was reported in 3 patients who received topiramate at a dose of 50 mg/day. This study suggests that in patients with trigeminal neuralgia topiramate can be tried initially at lower doses. Moreover in the same study, a moderate improvement was obtained in 3 patients at a dose of 50, 75 and 100 mg / day of topiramate respectively. The side effects reported with topiramate include dizziness, sedation, cognitive impairment, fatigue, nausea, blurred vision and weight loss. However tolerance develops to these adverse effects after two months of treatment.

Other Drugs

Sodium valproate, an antiepileptic drug was tried in a study with 20 patients having trigeminal neuralgia. It was found that six out of 20 patients had no attacks for six to 18 months. Moreover in three patients, the frequency and severity of attacks were found to be reduced by at least 50%. However, four patients responded well only when sodium valproate was used along with other drugs. In this study six patients showed little or no response while one patient showed poor tolerance.[26] In patients with trigeminal neuralgia which is resistant to carbamazepine, sodium valproate at a dose of 800 to 1600 mg/day, has reported 50 to 75% improvement in reducing the frequency of attacks in eight out of ten patients who received valproic acid alone.[27] Valproate has also been shown to provide significant pain relief in post-herpetic neuralgia patients, with very little incidence of adverse reactions like weight gain, hepatic and renal impairments. These studies provide a basis for trials with valproate in larger group of patients with trigeminal neuralgia.

Botulinum toxin has been found to effective in the treatment of several pain syndromes such as migraine and occipital neuralgia. A study evaluating the role of botulinum toxin A in 15 patients with refractory trigeminal neuralgia showed a significant reduction in the number and severity of attacks, six months after the injection ($p<0.001$).[28] These findings are similar to earlier reports demonstrating a beneficial effect with botulinum toxin-A in trigeminal neuralgia.[29,30] The mechanism of action is not known but it is believed that injection of botulinum toxin causes inhibition of acetylcholine release in nerve endings causing relaxation of muscles and pain relief. Another hypothesis is that botulinum stops secretion of some nociceptive neuropeptides which prevent pain sensation.[29,31] Transient paresis of the buccal branch of the facial nerve may occur. This injection may be tried before resorting to invasive methods of treatment.

A number of drugs have been attempted in trigeminal neuralgia showing limited benefit such as phenytoin, topical capsaicin cream, intranasal lidocaine, clonazepam, sumatriptan and amitriptyline. Besides medical treatment, there are a number of surgical procedures for the treatment of trigeminal neuralgia such as microvascular decompression, Gasserian ganglion percutaneous technique, radiofrequency thermocoagulation, balloon compression and percutaneous glycerol rhizolysis.[5] These are reserved for patients with incapacitating symptoms despite a trial of atleast three drugs in sufficient dosage. Side effects of medication and relapse of symptoms might also be another strong factor in opting for surgical treatment.

Conclusion

Although trigeminal neuralgia is a rare disorder with a high degree of morbidity a myriad of medical and surgical options do exist to alleviate the patient's symptoms. Carbamazepine and oxcarbazepine have clearly surpassed other drugs in terms of strength of evidence and experience in this condition. Surgical options may be considered for patients who do not respond to medical management. Considerable debate exists as to which should be the alternative drug in patients who fail to respond to carbamazepine/oxcarbazepine. Baclofen, antiepileptic drugs such as lamotrigine, gabapentin, topiramate, levetiracetam and botulinum toxin appear to be promising second line options though well designed double blinded RCTs are still lacking. The need of the hour is to generate more evidence using well designed double blind controlled trials to substantiate their efficacy and safety in these patients. This may be feasible, only if the trial is done as a

multicentric study owing to the uncommon occurrence of trigeminal neuralgia in dental and neurologic practice.

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