Case Report

Pregabalin in post traumatic neuropathic pain: Case studies

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ABSTRACT

Pregabalin is effective in the treatment of peripheral and central neuropathic pain. This study evaluated the effectiveness of pregablin in management of post traumatic peripheral nerve injury facial pain not responding to other medication like analgesics. Pregabalin was well tolerated. The most common adverse effects were dizziness and tiredness.

Key words: Neuropathic pain, pregabalin, traumatic nerve injury

Introduction

Neuropathic pain may be defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" Post traumatic peripheral nerve pain is a difficult condition to treat that occurs after nerve damage due to trauma from accidental injury or surgery. A change in function, chemistry and structures of neurons (neural plasticity) underline the production of the altered sensitivity characteristics of neuropathic pain. Peripheral sensitization acts on the nociceptors and in addition abnormal interactions between the sympathetic and sensory pathways contribute to mechanism mediating neuropathic pain. The management of patients is challenging, despite several attempts for a more rational therapeutic approach. However, recommendations can be proposed for first line, second line and third line pharmacological treatments based on the level of evidence for the different treatment strategies. These injury cause long lasting changes to the peripheral nervous system. The communication network that transmits information to and from the central nervous system (the brain and spinal cord) and every other part of the body is believed to be cause of this persistent pain. The incidence of nerve damage is reported to vary between 0.5% to and 2% depression, anxiety and sleep disorder were significantly more associated with neuropathic pain compared to those without such pain. In oral and Maxillofacial surgery in traumatic peripheral neuropathic pain resulting from trauma/ nerve injury is a standard practice to reassure the patient kept under observation and if patient shows no improvement, then sometime Inj/Tab B12 (methylcobalamin)are prescribed. The use of pregabalin in some cases of peripheral nerve injury responded well. Hence, two cases were selected with different nerves involvement responded well to medication.

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Review of Literature

Trauma/ injury that cause direct nerve damage a pronounced local inflammatory response ensues around the site of injury noicisponsive primary afferent neurons (PAF), damage tissue, infiltration of inflammatory cells, the vasculature and sympathetic terminals result in the release of an inflammatory "soup". This soup includes histamine, bradykinin, serotonin, adenosine triphosphate products from the cyclooxygenease (prostaglandin E2) and lipoxygenease pathways (leukotriene B4) of arachidon acid metabolism, nerve growth factor (NGF) and cytokines. Because of this inflammation, nociceptors which are rather inactive and unresponsive in normal circumstances may show enhanced sensitivity (lower threshold for stimulation and a more prolonged response to stimulation) with development of spontaneous discharges in neuropathic pain there may also be an involvement of

the sympathetic nervous system (sympathetic-induced pain). Following damage of mylinated PAF, spourting of sympathetic axons into the PAF and the dorsal root ganglia. These new connections enhance the ectopic activity of dorsal root ganglia cells. In addition, injured and uninjured PAF begin to express - adrenoreceptors that render them sensitive to sympathetic inputs.[1] Post traumatic and post surgical nerve injuries in a US survey of oral and maxillofacial surgeons reported 76% cases complicated by lingual nerve anesthesia, dysthesia or paresthesia. In 18.6% of cases the sensory symptoms failed to resolve. Presentation of pain may vary from numbness, tingling and prickling sensations, sensitivity to touch or more extreme including burning pain

Tricyclic antidepressants are often the first drugs selected to alleviate neuropathic pain (first-line pharmacological treatment).[2] Although they are very effective in reducing pain in several neuropathic pain disorders, treatment may be compromised (and outweighed) by their side effects. In patients with a history of cardiovascular disorders, glaucoma, and urine retention, pregabalin and gabapantin are emerging as first-line treatment for neuropathic pain.[3] In addition, these antiepileptic drugs have a favorable safety profile with minimal concerns regarding drug interactions and showing no interference with hepatic enzymes. In patients with post herpetic neuralgia and in patients with diverse peripheral neuropathic pain conditions and allodynia, topical administration of lodocaine may be recommended as first-line treatment. Opioid agonists have demonstrated efficacy in patients with neuropathic pain, comparable with TCA and gabapantin/ pregabalin. Issues such as long-term safety, possible association with the development of immunologic changes, opioid induced hyperalgsia, and the risk of addiction have to be taken into account before commencing opioid treatment.[4] Thus, opioid treatment is considered for second-line use in patients who fail to response adequately to first-line treatment, analgesics with less established efficacy are recommended. Second-line treatments include duloxetine, venlafaxine and lamotrigine. Finally there are a number of medications that are generally be used as third-line treatments because of weak efficacy, discrepant results or safety concerns. These analgesics include carbamazepine (except trigeminal neuralgia), oxcarbazepine, SSRIs, mexilitine, NMDA receptor antagonist and topical capsaicin despite numerous treatment options available for relieving neuropathic pain, the most appropriate treatment strategy is only able to reduce pain in 70% of these patients (these patients may still experience residual pain). In the remaining patients, combination therapies using two or more analgesics with different mechanisms of action may also offer adequate pain relief. In addition, beside the effectiveness of treatment, the adverse-event profiles of these analgesics have to be considered before starting therapy or combining different agents. 10% of patients still experience intractable pain and are truly refractory to all forms of pharmacotherapy. If medical treatments have failed, invasive therapies such as intrathecal drug administration and neurosurgical stimulation techniques (spinal cord stimulation, deep brain stimulation, and motor cortex stimulation) may be considered.

Pregabalin

In July 2004 pregabalin was granted approval in all European member states for the treatment of peripheral neuropathic pain. Martinez *et al* used intranasal, intrathecal, and near-nerve chamber forms of delivery of varying concentrations of pregabalin or saline delivered over 14 days in rat models of experimental diabetic peripheral neuropathy and spinal nerve ligation. As well, radio labeled pregabalin was administered to determine localization with different deliveries. We evaluated tactile allodynia and thermal hyperalgesia at multiple time points, and then analyzed harvested nervous system tissues for molecular and immune histochemical changes in CaV$\alpha_2\delta$-1 protein expression. Both intrathecal and intranasal pregabalin administration at high concentrations relieved Ne P behaviors, while near-nerve pregabalin delivery had no effect. Ne P was associated with up regulation of CACNA2D1 mRNA and CaV$\alpha\delta$-1 protein within peripheral nerve, dorsal root ganglia (DRG) and dorsal spinal cord, but not brain. Pregabalin's effect was limited to suppression of $Ca_2\delta$-1 protein (but not CACNA2D1 mRNA) expression at the spinal dorsal horn in neuropathic pain states. Dorsal root ligation prevented $CaV_2\delta$-1 protein trafficking anterograde from the dorsal root ganglia to the dorsal horn after neuropathic pain initiation.

The efficacy of gabapantin (GBP) and pregabalin is established in diabetic neuropathy and post herpetic neuralgia. Its main site of action appears to be on the α2-§ subunit of presynaptic, voltage dependent calcium channels, resulting in a reduction in the release of several neurotransmitters including glutamate, noradrenaline, serotonin, dopamine and P substance that are widely distributed throughout the peripheral and central nervous system. Pregabalin appears to produce an inhibitory modulation of neuronal excitability, particularly in areas of the central nervous system. The most common side effects included dizziness, and somnolence, peripheral edema, weight gain, and asthenia. Outside US, pregabalin is indicated in adults for the management of peripheral and central neuropathic pain treatment of anxiety disorder and adjunctive therapy for partial seizures with or without secondary generalization.

Pregabalin is primarily eliminated by renal excretion; the dose should be adjusted for patients with reduced renal function. Dosing should begin at 75mg twice daily, 50 mg thrice times a day (150 mg / Day) and may be increased to 300 mg twice a day or 200 mg thrice daily (600 mg/day) on efficacy and tolerability. Treatment with pregabalin may cause side effects as other common adverse reactions include weight gain, euphoric mood, balance disorder, increased appetite and thinking abnormality. Pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency and dose should be tapered over a minimum of 1 week.

Neurophysiology

Nerve injuries can be classified on the following types:

Compression

Peripheral nerve compression may result in a neuropathic pain syndrome or sensory deficit. The acute response to compression is oedema and inflammation. In nerve compression neuropathy, large mylinated fibres are lost and A delta and C fibres spared. There is an increase in circulating substance P and calcitonin gene related peptide and a decrease in dynorphin in dorsal horn. There may also be activation of N-methyl-D-aspartate (NMDA). These changes are responsible for the dysthesia or paresthesia. The response to peripheral or central nerve injury may involve neuroinflammation. The presence of a distinct neroinflammatory even without significant nerve injury is generating persistent neuropathic pain and paresthesia. Nerve compression may occur with tracheal intubation, use of a laryngeal mask airway tongue retraction or jaw injuries.

Compartment syndrome

The nerve injury seen in a compartment syndrome is largely due to ischemia caused by diminished flow in the compartment. Increased venous pressure results from increased local tissue pressure or edema. The recovery is dependent upon how long and amount of pressure applied but early decompression or anti inflammatory therapy may prevent the pain and numbness.

Stretch injury

The injury may begin with axonal rupture followed by rupture of endoneural tubes perineurium and finally endoneurium. Lundborg and Rydevik have studied the deleterious effects stretchingon the physiologic nerve function and 8% stretch produced changes in intraneural blood flow. 15% elongation can cause complete cessation in arterial flow. Lingual nerve injury during jaw retraction has postulated stretching as mechanism.

Chemical injury

Some chemical used in dentistry like eugenol, alcohol, phenol, and paraformaldehyde-containing endodontic filling materials. When nerve is exposed to the chemical, an inflammatory response ensues. Neuropathic pain may develop depending upon the duration and severity of damage.

Nerve injection injury

Injury may be caused by intraneural injection, scarring and fibrosis that prevent axonal regeneration disrupt the fascicular architecture. This may lead to conduction block and dysthesia may develop. Local anesthesia with vasoconstrictor injected into nerve and preservative may injure the nerve permanently. If lodocaine molecule is hydrolysed while still bound to the receptor and the alcohol by-product persists, the metabolite may disrupt nerve conduction causing paresthesia.

Trans section, Laceration, Rupture, or Avulsion

This type of injury requires approximation of the two ends and suture. Scar tissue prevents the natural regrowth. Surgical repair should be delayed unless sensory testing overtime shows no improvement.

Clinical Features of Neuropathic Pain

- Abnormal pain quality: burning, stabbing, raw, gnawing, sickening, poorly localized, sometimes diffuse
- Paroxysmal pain is common immediate or delayed onset after injury
- Pain intensity altered by emotion and fatigue
- Sensory impairment usually in an anatomical distribution
- Associated allodynia, hyperalgesia
- Vasomotor and psudomotor changes
- Associated dystrophic change in a minority of patients

Report of Cases

Case 1

A 32 years old female with history of mandibular first molarextraction followed by pain left side of face since past 03 months was presented to the department of oral and maxillofacial surgery for consultation. Work up revealed that pain occurred several time in a day. Detailed history was taken. There was no significant medical history. She denied symptoms / history of psychiatry illness. Physical examination revealed no underlying cause. Her vital parameter was within normal limit. Submandibular lymph nodes were non tender.

Intra oral examination revealed no abnormal finding in the floor of the mouth and other area of oral cavity. Oral mucosal lining of the floor of mouth, tongue were healthy and intact. Socket of the extracted molar tooth was healed and covered with over lyingmucosa. On palpation there was no tenderness present in first molar region bucally as well lingually. Patient was partially edentulous and remaining teeth were in healthy condition without anyradiographic evidence of disease OPG showed partial obliteration of first molar socket with ill defined radiolucency extending up to inferior alveolar canal (history of traumatic transalveolar extraction healed by secondary intention as by socket dressing).

Pain was recorded on visual analogue scale (VAS) and a score of 6was obtained.

The diagnosis of peripheral neuropathic pain was based on the physical examination of the patient, which revealed no other pronounced abnormalities, coupled with her description of burning pain and dysthesia on face.

Initially tablet Pregabalin was started with 75 mg daily for one week followed by 75 mg twice daily. After 07 days patient reported reduction in pain intensity, but not completely relief in pain and her sleep was also improved.[5] Gradually dosage of tab. Pregmate was increased up to 150mg twice daily without any difficulty. After 03 months follow up of drug therapy patient reported complete relieve in pain.

Discussion

This case illustrates the importance of history which clearly suggested of traumatic transalveolar extraction with extensive curettages resulted into traumatic neuropathy of Inferior alveolar nerve. Clinical examination revealed two point discrimination, pointed/ dull discrimination and pin prick, diminished sensation in lower lip area. The nature of pain was burning, intermittent and not radiating to adjacent region. Initial Antibiotic therapy showed marginal improvement may be due to subsidence of inflammatory process. Radiological examination (OPG) demonstrated the interruption of superior outline of inferior alveolar canal. Patient was depressed as previous therapies could not provide her pain relief as she was unable to perform domestic work for last 03 months. The above mentioned finding suggested the diagnosis of traumatic neuropathy. Treatment with Tablet Pregabalin (medication binding to the calcium channel in the spinal cord and decreasing its excitability),was started with 75 mg daily for one week followed by 75mg twice daily. Gradually dose was increased to 150 mg twice daily without any difficulty Pregabalin is preferred over gabapentin in neuropathic pain as first line drug reported by Gibson *et al*.[6] In addition to significant analgesic efficacy, Pregabalin also improves pain related sleep disturbances and generally well tolerated in neuropathic pain. The anxiolytic activity of pregabalin has been demonstrated in several clinical trials in generalized anxiety disorder (GAD) in which pregabalin was associated with a significant improvement in anxiety rating scales.[5,7] Most of the pain treatment used for neuropathic pain have not been approved by FDA, including all the Tricyclic antidepressants and most of the anticonvulsants. Two medications are approved for Diabetic peripheral neuropathy by the FDA duloxetine and Pregabalin.[8] Dizziness and somnolence were the two most common adverse events reported with Pregagblin therapy. This finding was not reported in this case, may be the patient was unable to notice relatively mild or moderate dizziness.

Case 2

A 42 year old male patient of zygomatic complex fracture attended department of oral and Maxillofacial Surgery OPD. The chief complaint was numbness of the right side face and heaviness of all right sided maxillary teeth past 07 days following accident. Patient had taken antibiotic and supportive therapy as advised at previously attended hospital. Clinically there was step defect at infraorbital margin and tenderness at F-Z suture. On Intra oral examinations onlytenderness was present at zygomatic buttress region. Interincisal mouth opening was 40 mm and eye movements were normal. Radiological examination revealed Zygomatic complex fracture involving infra orbital rim, frontozygomatic suture and zygomatic buttress region. Due to non displaced fracture, patient was reluctant for surgery and consented for medicinal therapy, as previous centre had prescribed medications only and referred to our centre for consultation. For the paresthesia problem (numbness) Tab Pregabalin 75 mg once daily was prescribed for seven days followed by 75 mg twice daily. After one week patient reported OPD without any relief in pain. Pregabalin dose was increased to 150 mg twice daily (300 mg/day). Patients reported two weeks after medication with improvement in paresthesia, as well as heaviness of teeth. Now he was able to occlude his teeth of affected side. On clinical examination there was change (improvement) in perception of all tested stimuli: feather light touch, two point discrimination, location of touch, pin prick and brush stroke direction. After three months of treatment patient was again reviewed and recovery was significant for perception of tested stimuli. Paresthesia was improved. Clinical testing also demonstrated almost complete recovery.

Discussion

The above mentioned case of road traffic accident resulted into traumatic peripheral neuropathy. On Clinical examination revealed the diagnosis of zygomatic complex fracture right side. Infra orbital nerve sustained injury was noticed during examination.[9,10] There was no indication for surgery except infra orbital nerve involvement. Surgery could not be planned due to refusal of patient, De Man *et al* reported that group of patient treated conservatively showed recovery rate similar to that with rigid fixation, reflecting spontaneous recovery as has been observed in other studies.[11] Assuming that the patients left untreated were those with the least fracture displacement, and therefore the least esthetic and functional impairments. Hence, Tab Pregabalin 75 mg daily gradually increased to 75 mg twice daily given. Dosages were increased to 150 mg twice daily due to non improvement in paresthesia. After 03 months of therapy results almost complete recovery.

Conclusions

The above discussed two cases of traumatic peripheral neuropathy involving inferior alveolar nerve and infra orbital nerve respectively resulted from traumatic surgical exploration and accidental trauma. Both patients were treated with Pregabalin 150 mg twice daily with good results and encouraged us to evaluate drug efficacy in mandibular third molar surgery associated with traumatic nerve injury. This study will definitely help to other colleagues to manage similar type nerve injury more efficiently.

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