Duloxetine- A novel therapeutic regimen for trigeminal neuralgia

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Abstract

Duloxetine is a potent and selective inhibitor of serotonin and noradrenaline transporters and a weak inhibitor of dopamine transporters. Duloxetine is highly protein bound and is widely distributed throughout tissues. It is rapidly and extensively metabolized in the liver by cytochrome P450 (CYP) 1A2 and 2D6 and its numerous metabolites which are inactive are mainly excreted in the urine. It is more effective for recurrent/refractory type of TN. Duloxetine holds the promise in complete remission of TN in future. So in coming days it may be a drug of choice for medical management of TN. This article is an insight in chemical features, pharmacodynamics, pathophysiology and therapeutics of Duloxetine.

Keywords: Antidepressants, Serotonin uptake inhibitors, Trigeminal Neuralgia, Major depressive disorders

Introduction

Trigeminal neuralgia (TN) is defined by the International Headache Society (IHS) as "unilateral disorder characterized by brief electric shock like pains, abrupt in onset and termination, and limited to the distribution of one or more divisions of the trigeminal nerve".[1]

Trigeminal neuralgia, a neuropathic pain syndrome is considered one of the most painful conditions experienced by people and is characterized by a severe, almost exclusively unilateral, neuropathic pain located within the distribution of the trigeminal nerve. Its relapsing-remitting and excruciating characteristics can severely and negatively affect the quality of life and increase the risk of depression in affected people.[2]

The IHS has classified TN into classical type (CTN) and symptomatic type (STN). The classical TN is also known as essential/idiopathic TN. The pain in STN is indistinguishable from that of classical trigeminal neuralgia (CTN) but caused by a demonstrable structural lesion other than vascular compression. The diagnosis of CTN requires the absence of a clinically evident neurological deficit. CTN starts in the second or third divisions of trigeminal nerve affecting the cheek or the chin.[1] The ophthalmic division alone is involved in less than 5% of cases.[3]The single attack generally lasts from less than a second to a few seconds, but it may present in clusters of variable intensity with up to 2 minutes duration. In many cases it is followed by a brief refractory period during which a new stimulation is not able to evoke another attack. Between paroxysms the patient is usually pain free but a dull background pain may persist in some cases.[1] Growing neurosurgical data advocate the distinction of these two subtypes of TN into type 1 as defined as >50% episodic onset of TN pain and type 2 defined by >50% constant pain.[4,5]

Trigeminal neuralgia (TN) is a facial pain syndrome characterized by paroxysmal, shock-like pain attacks located in the somato-sensory distribution of the trigeminal nerve. The prevalence of TN in the general population is 0.015%.[6] Facial pain has a considerable impact on quality of life. It has been recently shown that TN is the most frequent type of facial pain[7] and that, among facial pain syndromes, the overall incidence of TN has remained constant[8] ranging from 12.6/100,000/year[7] to 27/100,000/year.[8] TN is uncommon in population younger than 40 years (overall incidence of 0.2/100,000/year) and increases in incidence with advancing age, occurring in 25.9/100,000/year in individuals older than 80 years[9] TN appears to be slightly more common among women and has both classical and symptomatic (~15% of cases) subtypes with the former most often associated with a neurovascular conflict of the trigeminal nerve in the prepontine cistern.[10] The right side is more frequently involved.[11] When TN occurs in young age or presents with bilateral symptoms, lack of triggered pain, absence of a refractory period, or an abnormal neurologic examination, secondary causes such as multiple sclerosis (MS) should be suspected[10]Bilaterality may be seen in 5% of classical cases, but even in these cases, synchronous pain is not observed. Patients with bilateral TN often have a positive family history12. In patients affected by MS, prevalence is higher, ranging from 1%[13] to 6.3%.[14]

Duloxetine is a potent and selective inhibitor of serotonin and noradrenaline transporters and a weak inhibitor of dopamine transporters. It has a low affinity for neuronal receptors like α adrenergic, dopamine D, Histamine H, Muscarinic, opioid and serotonin receptors as well as ion channel binding sites and other neurotransmitter transporters such as choline and GABA transporters. It does not inhibit monoamine oxidase types A or B. Duloxetine is highly protein bound and is widely distributed throughout tissues. It is rapidly and extensively metabolized in the live cytochrome P450 (CYP) 1A2 and 2D6 and itsnumerous

metabolites which are inactive are mainly excreted in the urine. The mean elimination half-life of duloxetine is ≈12 hours.

Duloxetine is a substrate for CYP1A2 and CYP2D6 and a moderate inhibitor of CYP2D6. Duloxetine is rapidly hydrolyzed in acidic media.[15]The pellets inside the duloxetine capsule are enteric coated but the capsule is not to avoid hydrolysis in gastric media. This enteric coating of the pellets resists dissolution until pellets reach a segment of the gastrointestinal tract where the pH is favorable. This explains why the maximal plasma concentration (Cmax) of duloxetine usually does not occur until 6 hours post dose.[15]

Duloxetine has a mean plasma half-life of 12 hours but it can be dosed once daily as the central nervous system half-life may be very different from the plasma half-life. In one reported study, duloxetine dosed at 20 to 40 mg twice daily in 12 healthy male volunteers exhibited linear pharmacokinetics with steady state plasma concentrations typically reached within 3 days of stable dosing.[16] Duloxetine is highly protein bound (96%) primarily to albumin and alpha-1-acid glycoprotein.[15]

Duloxetine is metabolized by CYP-2D6 and 1A2 isoenzymes with no active metabolites.[1] Because of CYP-1A2 metabolism, duloxetine use in smokers results in one third reduction in bioavailability compared with non-smokers.[15]However there is no clinical recommendation for a dosage adjustment based on smoking status.[15] Duloxetine should not be used with CYP-1A2 inhibitors such as fluvoxamine.[16]

Chemistry of Duloxetine

LY 227942 was the starting point for the development of duloxetine.It is a chiral compound, ((+/-)-*N*-methyl-3-(1-naphthalenyloxy)-3-(2-thiophene) propanamine formed from the building blocks of (S)-3-chloro-1-(2-thienyl)-1-propanil and the corresponding (R)-butanoate.[17,18] The positive enantiomer of this compound (LY 248686) is slightly more potent than the negative enantiomer (LY 248685) as an inhibitor of serotonin uptake. Neither enantiomer is a substantial inhibitor of the dopamine (DA) uptake pump.[19] LY 248686 is duloxetine. Thus duloxetine is analogus to LY 227942.[20] Based on both in vitro and in vivo preclinical pharmacological evidence, duloxetine has been promoted as being a more balanced inhibitor of serotonin and nor-adrenaline re-uptake pumps.[21,22] Duloxetine has minimal affinity for muscarinic, histamine-1, adrenergic,dopamine, serotonin, opiate, GABA and substance P receptors.[22]

Pharmacodynamics of Duloxetine

The pharmacokinetics of duloxetine in healthy volunteers was dose proportional over the range of 40–120 mg once daily. Steady state was typically reached by day 3 of administration. Duloxetine may be administered without regard to food or time of day. The ratio of duloxetine's affinity is constant for serotonin (5HT) and norepinephrine (NE) reuptake pumps is closer to 1 i.e., it is a balanced and potent inhibitor for these two reuptake pumps[2]. Duloxetine has greater affinity for both 5HT and NE[15] however Duloxetine has minimal affinity for dopamine, histamine (H1), adrenergic, muscurinic, opiate, gamma amino butyric acid (GABA) and substance P receptors[16]. Concomitant use of duloxetine and potent CYP1A2 inhibitors should be avoided and duloxetine should be used with caution in patients receiving drugs that are extensively metabolized by CYP2D6 particularly those with a narrow therapeutic index.

Pathophysiology of Duloxitene

The mechanisms of duloxetine in pain relief have been associated with the descending inhibition with the modulation of the synaptic availability of nor-epinephrine and serotonin.[23,24] Strong evidence derived from path analysis suggests that this analgesic effect comes directly from duloxetine itself rather than its indirect antidepressant effect.[25] However, pain is a complex experience, which consists of the physiological responses of the nociceptive system and the processing of that information in the emotion-related brain network.[25] Thus, the pain relief gained from duloxetine may be partially related to some of the pain caused by the depression itself.

In addition to duloxetine's relatively balanced mode of action on norepinephrine and serotonin,[25] it is suggested that the rapid analgesic effect of duloxetine is related to its ability to antagonize *N*-methyl-d-aspartate (NMDA) receptors and impede the l-arginine-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway, according to preliminary evidence from animal research.[26] Evidence indicates that both NMDA receptors and NO are involved in the development of neuropathic pain.[27-29]

C.C Hsu et al[30] observed a rapid onset of the analgesic effect of duloxetine 60 mg/d for trigeminal neuralgia and this analgesic effect clearly preceded its antidepressant effect. The improvement in both the trigeminal neuralgia and depression is supported by their observations and changes in the Pain Intensity NRS and the CGI Severity Scale. In brief, hereby they emphasized the literature that supports the view that duloxetine 60 mg/d could effectively manage the co-occurrence of trigeminal neuralgia and major depressive disorder.

Conclusion

Duloxetine is drug of choice in treatment of all types of trigeminal neuralgia. It is more effective for recurrent/refractory type of TN and orofacial pain caused by idiopathic etiologies. In coming days Duloxetine will be a novel drug in treatment of TN.

References

1. International Headache Society (2004) The International Classification of Headache Disorders: 2nd Edition. Cephalalgia 24(Suppl 1): 9–160.
2. Macianskyte D, Januzis G, Kubilius R, Adomaitiene V, Sciupokas A. Associations between chronic pain and depressive symptoms in patients with trigeminal neuralgia. Medicina (Kaunas). 2011;47:386-392.
3. De Simone R., Marano E., Brescia Morra V., Ranieri A., Ripa P., Esposito M., et al. (2005) A clinical comparison of trigeminal neuralgic pain in patients with and without underlying multiple sclerosis.Neurol Sci 26(Suppl 2): s150–s151.
4. Tatli M., Satici O., Kanpolat Y., Sindou M. (2008) Various surgical modalities for trigeminal neuralgia:literature study of respective long term outcomes. Acta Neurochir (Wien) 150: 243–255.
5. Limonadi F.M., McCartney S., Burchiel K.J. (2006) Design of an artificial neural network for diagnosis of facial pain syndromes. Stereotact Funct Neurosurg 84: 212–220.
6. Penman J. Trigeminal neuralgia. In: Vinken PJ, Bruyn GW, editors. Handbook of Clinical Neurology. Vol. 5. Amsterdam: North-Holland Publishing Company; 1968. pp. 296–322.
7. Koopman JS, Dieleman JP, Huygen FJ, de Mos M, Martin CG, Sturkenboom MC. Incidence of facial pain in the general population. Pain. 2009;147(1–3):122–127.
8. Hall GC, Carroll D, McQuay HJ. Primary care incidence and treatment of four neuropathic pain conditions: a descriptive study, 2002–2005. BMC Fam Pract. 2008;9:26.
9. Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. Ann Neurol. 1990;27(1):89–95.
10. Gronseth G, Cruccu G, Alksne J, et al. Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. Neurology. 2008;71(15):1183–1190.
11. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia – a prospective systematic study of clinical characteristics in 158 patients. Headache. 2014;54(10):1574–1582.
12. Pollack IF, Jannetta PJ, Bissonette DJ. Bilateral trigeminal neuralgia: a 14-year experience with microvascular decompression. J Neurosurg. 1988;68(4):559–565.
13. Ruge D, Brochner D, Davis L. A study of the treatment of 637 patients with trigeminal neuralgia. J Neurosurg. 1958;15(5):528–536.
14. Putzki N, Pfriem A, Limmroth V, et al. Prevalence of migraine, tension-type headache and trigeminal neuralgia in multiple sclerosis. Eur J Neurol. 2009;16(2):262–267.
15. Gupta S, Nihalani N. Duloxetine: review of its pharmacology, and therapeutic use in depression and other psychiatric disorders. Ann Clin Psychiatry. 2007;19(2):125–132.
16. Preskorn SH. Duloxetine. J Psychiatr Pract. 2004;10(6):375–385.
17. Wong DT, Robertson DW, Bymaster FP, et al. LY227942 an inhibitor of serotonin and norepinephrine uptake: Biochemical pharmacology of a potential antidepressant drug. Life Sci 1988;43:2049–57.
18. Liu H, Hoff BH, Anthonsen T. Chemo-enzymatic synthesis of the antidepressant duloxetine and its enantiomer. Chirality 2000;12:26–9.
19. Wong DT, Bymaster FP, Mayle DA, et al. LY248686 a new inhibitor of serotonin and norepinephrine uptake. Neuropsychopharmacology 1993;8:23–33.
20. Preskorn SH. Basic neuropharmacology of SSRIs. In: Preskorn SH, ed. Clinical pharmacology of selective serotonin reuptake inhibitors. Caddo, OK: Professional Communications; 1996: 33–62.
21. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology 2001;25:871–80
22. Beique JC, Lavoie N, de Montigny C, et al. Affinities of venlafaxine and various reuptake inhibitors for the serotonin and norepinephrine transporters. Eur J Pharmacol 1998;349:129–32.
23. Bymaster FP, Lee TC, Knadler MP, Detke MJ, Iyengar S. The dual transporter inhibitor duloxetine: a review of its preclinical pharmacology, pharmacokinetic profile, and clinical results in depression. Curr Pharm Des. 2005;11:1475-1493.
24. Verdu B, Decosterd I, Buclin T, Stiefel F, Berney A. Antidepressants for the treatment of chronic pain. Drugs. 2008;68:2611-2632.
25. Perahia DG, Pritchett YL, Desaiah D, Raskin J. Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? Int Clin Psychopharmacol. 2006;21:311-317.
26. Zomkowski AD, Engel D, Cunha MP, Gabilan NH, Rodrigues AL. The role of the NMDA receptors and l-arginine-nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant- like effect of duloxetine in the forced swimming test. Pharmacol Biochem Behav. 2012;103:408-417.
27. Calabrese F, Guidotti G, Molteni R, Racagni G, Mancini M, Riva MA. Stress-induced changes of hippocampal NMDA receptors: modulation by duloxetine treatment. PLoS One.2012;7:e37916.
28. Levy D, Zochodne DW. NO pain: potential roles of nitric oxide in neuropathic pain. Pain Pract. 2004;4:11-18.
29. Wu LJ, Zhuo M. Targeting the NMDA receptor subunit NR2B for the treatment of neuropathic pain. Neurotherapeutics.2009;6:693-702.
30. Hsu CC, Chang CW, Peng CH, Liang CS. "Rapid Management of Trigeminal Neuralgia and Comorbid Major Depressive Disorder With Duloxetine A Case Report." Ann Pharmacother. 2014 Aug;48(8):1090-1092.