REVIEW

Duloxetine, an antidepressant with analgesic properties – a preliminary analysis

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Abstract

Serotonin and norepinephrine reuptake inhibitors are second-line antidepressants largely used because of their good tolerance and their reduced side effects. Two of these drugs, duloxetine and venlafaxine, are used also in chronic pain management.

In this review we present recent data regarding duloxetine’s effects on the central nervous system, linked to acute pain management, and their efficiency in reducing postoperative chronic pain. The drug’s efficacy results from its modulating effect on the descending inhibitory pain pathways and the inhibition of the nociceptive input. There are already several studies in favor of the analgesic properties of duloxetine. However, further and larger randomized studies are necessary in order to clarify duloxetine efficiency in acute postoperative settings, and thereafter on persistent chronic postoperative pain.

Keywords: duloxetine, serotonin-norepinephrine reuptake inhibitors, acute postoperative pain, chronic post-surgical pain

Introduction

Chronic post-surgical pain (CPSP) as a concept was introduced in 1998 by Crombie et al. [1]. The International Association for the Study of Pain stated that CPSP represents “a pain that develops after surgical intervention and lasts at least 2 months” while other causes for pain have been explored and excluded [2].

The incidence of the CPSP shows a wide variability between 20 and 50%, probably because it relates to the surgical technique, the extent of tissue damage and to the secondary neural injury. It has been shown that relatively minor surgeries such as caesarian section and groin hernia repair lead to CPSP in about 10% of patients and the incidence of the severe form of CPSP is found in 2-10% of cases [3].

The mechanisms of CPSP are still incompletely understood but it is accepted that this pain syndrome is mainly neuropathic and is the expression of the postsurgical changes in the nervous system. The peripheral nerve injury and the tissue damage promote the discharge of nearby nociceptive receptors and results in sensitization and primary hyperalgesia. In this situation previously non-noxious stimuli applied in the wound surrounding area, results in hyperalgesia and it represents an important contributor to CPSP. During the healing process the new neuroma formation causes ectopic activity, increased nociceptive output and central sensitization. This nociceptive output leads further to modifications in the cerebral cortex and brain stem with alteration of the connection between the
brain and the spinal cord, with an increase in the descending facilitatory influences, and a reduction in the inhibitory stimuli [3].

Spinal cord microglia becomes activated following surgical incision and nerve injury. The mediators released by the microglia, suppress inhibitory synaptic transmission and lead to hyperexcitability of the neurons in the dorsal horn, showing an important contribution to CPSP [4, 5].

Another mechanism of CPSP development is inflammation. It promotes primary nociceptor hyperexcitability, with the implication of the epsilon isoform of protein kinase C (PKC epsilon), as a second messenger, in response to the cytokines release. Epsilon protein kinase C is known also to be linked to opioid-induced hyperalgesia (OIH) [6].

Chronic opioid use has been proved to induce perioperative OIH and to be involved in CPSP development [7-10].

In this regard, regional anaesthesia and antiepileptics play an important role in preventing CPSP by reducing OIH and chronic sensitization [11-13].

The goal of postoperative pain management is to provide adequate analgesia with the minimum of medication and to minimize as much as possible the side effects of the administered drugs. There is a consensus regarding the fact that an optimal/dynamic postoperative pain management is necessary for an early postoperative recovery [14] and the inability to adequately treat acute pain in the first 48 postoperative hours represents a risk factor for the development of CPSP.

There are opinions that both analgesia and anti-hyperalgesic interventions are necessary during the perioperative period [15].

This brief analysis aimed to survey the pertinent literature in order to bring relevant data that support duloxetine’s (DLX) efficacy in the acute postoperative pain management.

Serotonin-norepinephrine reuptake inhibitors

Recently, serotonin-norepinephrine reuptake inhibitors (SNRIs) entered the field of analgesic adjuvants, due to their modulating effect on pain pathways and their antinociceptive effect that could interfere with CPSP occurrence [16].

It has been found that the (+)-enantiomer of LY227942, a molecule which resembled fluoxetine, inhibited serotonin reuptake in rats twice as its (-)-enantiomer. Later on, assigned as LY248686 this molecule was named duloxetine and the first data was published in 1988 [17]. It was developed for the treatment of stress urinary incontinence. After that, venlafaxine was discovered and then found that its metabolite, desvenlafaxine, possesses almost the same pharmacological properties and fewer side effects.

To date, FDA has approved duloxetine, venlafaxine and desvenlafaxine mainly for the treatment of major depressive disturbances, anxiety and stress urinary incontinence.

The Agency also approved DLX for the management of diabetic peripheral neuropathic pain, chronic musculoskeletal pain and fibromyalgia [18].

In addition, there was a moderate recommendation of DLX, given by the American Society of Clinical Oncology in 2014, for patients with chemotherapy induced neuropathies [19].

Chemically, DLX is related to fluoxetine and includes a secondary amine structure. It has a high inhibition constant (K_i) that indicates its potency, as well as the affinity of binding to the monoamine transporter. Duloxetine inhibits the reuptake of serotonin and norepinephrine in Onuf’s nucleus in the sacral spinal cord and increases the urethral striated muscle tone. Studies using synaptosomal preparation isolated from rats have shown that in vivo the potency of DLX in inhibiting the reuptake of serotonin was 3 fold higher than in inhibiting norepinephrine reuptake [20].

It has been shown that DLX lacks affinity for monoamine receptors within the central nervous system and shows few effects on the muscarinic, histaminic H_1, opioid and α_1-adrenergic receptors [20, 21].

Administered in healthy young male subjects at doses between 20-40 mg twice a day, DLX had a mean oral clearance of 114 l/h, a distribution volume of 1943 l and a half-life of 12.5 h [22]. It has a bioavailability of 50% and a protein binding of 90%. From its hepatic biotransformation results glucuronide or sulfate conjugates metabolites, which are eliminated through urine (80%) and feces (20%) [22].

Duloxetine binding capacity to the human serotonin transporter and norepinephrine transporter shows a 100 times greater potency as compared with another SNRI, venlafaxine. Side effects are those common to antidepressants, but less frequent, and represented by: headache, dry mouth, constipation or dizziness. Three main risks are recognized with the use of DLX: hepatic, suicidal and bleeding, though at very low rates. Regarding the bleeding risk there are insufficient data in the perioperative settings but it has been shown that it increases when DLX interacts with anticoagulants (acenocoumarol, dabigatran, dalteparin, danaparoid, desirudin, enoxaparin, fondaparinux, tinzaparin, warfarin).

A recent study on 4136 users of SNRIs (DLX and venlafaxine) scheduled for coronary artery bypass graft surgery, did not report significant bleeding events.
[23]. When compared with non-steroidal anti-inflammatory drugs in spontaneously reported post-marketing data, DLX was not associated with an increased reporting of bleeding-related events [24]. It is not recommended to administer DLX in patients who are known to have chronic liver disease or are heavy drinkers.

The serotonin syndrome is a severe condition caused most often by the concurrent use of two or more agents that enhance synaptic serotonin levels, and might have a fatal evolution.

Duloxetine shows numerous major drug-drug interactions (DDIs) that can promote severe CNS toxicity (isocarboxazid, linezolid, procarbazine, rasagiline, selegiline, tranylcypromine), cardiac arrhythmia and QT prolongation (thioridazine, clozapine), severe extrapiramidal reactions (metoclopramide), increased cardiotoxicity (class 1C antiarrhythmic agents). In a retrospective study, Ellis et al. [25] searched for DDIs in patients with peripheral diabetic neuropathy treated with DLX vs pregabalin. These authors found that the prevalence of potential duloxetine DDIs was substantially greater than that of potential pregabalin DDIs.

**Analgesic mechanisms**

Serotonin and norepinephrine are known as principal mediators of endogenous analgesic mechanisms in the descending pain pathways [26] and this could explain SNRIs pain modulating properties.

It was also demonstrated that cognitive modulation of pain is related to the activation of several prefrontal areas: dorsolateral prefrontal cortex, ventrolateral prefrontal cortex and anterior cingulated cortex and that the net effect of SNRIs results in an increase of serotonin and norepinephrine in these regions, an effect which has been shown to correlate with reuptake of this mediators at the synaptic cleft [27].

It seems that DLX possesses a dual central and peripheral analgesic effect and current experimental studies are in order to elucidate some aspects of these mechanisms.

Leventhal et al. have used separately in animal studies different serotonin reuptake inhibitors (SRIs) and norepinephrine reuptake inhibitors (NRIs) on the spinal nerve ligation model of neuropathic pain and found a differentially reversed tactile allodynia. Further evaluation of a broader spectrum of reuptake inhibitors in the para-phenylquinone (PPQ)-induced abdominal constriction model, a model of acute visceral pain, demonstrated that both the SRIs and the NRIs significantly blocked abdominal constrictions. The effect was proportional with the affinity for NRIs. Authors claimed that effectiveness of NRIs might be enhanced by the presence of serotonin activity and also that serotonin possesses a dual action by promoting and inhibiting pain (by separate mechanisms) as compared with norpinyinephrine which is mostly inhibitory [26].

By microiontophoretic application in rats, Rueter et al. indicated that DLX inhibited neuronal cell firing and their results showed that long-term DLX administration desensitized the α2-adrenergic heteroreceptors [28].

Using the whole cell patch clamp technique, Wang et al. tested whether DLX interacts with the neuronal Nav1.7 Na+ channel as a potential target. Resting and inactivated Nav1.7 Na+ channel blocks by DLX were measured by conventional pulse protocols in transfected human embryonic kidney cells. A similar open-channel block by DLX was found in the muscle Nav1.4 Na+ isoform. The block produced by DLX was done via the conserved local anaesthetic receptor as determined by site-directed mutagenesis [29]. The mechanism involved in antinoceception, similar to that of local anaesthetics, could be due to the secondary aminic structure of DLX.

Wang et al. showed that a preincisional subcutaneous administration of 2 mg DLX, as compared with bupivacaine in rats, reduced both allodynia and hyperalgesia for several days, while bupivacaine did not [30].

It has been found also in an experimental study that an increased level of norpinephrine in the spinal cord is a contributor to the antihyperalgesic effect of SNRIs, after peripheral nerve injury [31].

Summarizing the above data, DLX with a high potency of inhibition in reuptake of serotonin and norpinephrine exerts a combined central and peripheral pain modulating role. By activating several cerebral prefrontal areas and influencing the spinal pain pathways, DLX modulates pain. The antinociceptive effect of DLX is validated through Nav1.7 Na+ channel and realized by interaction with the local anaesthetic receptor. DLX shows antihyperalgesic effects through the inhibition of the spontaneous nerve impulses resulting from peripheral injury.

**Evidence regarding DLX effects in acute postoperative pain management**

There is not enough evidence regarding the effect of SRIs on acute postoperative pain. However, there is a growing interest in searching for potentially beneficial effects of DLX in acute postoperative pain management, as a modality for reducing perioperative opioid consumption and the incidence of postoperative chronic pain. The analgesic effect seems to be linked to the antihyperalgesic effects showed by perioperative...
administration of DLX, mainly in experimental animal studies.

It has been demonstrated that the short term administration of DLX elevates extracellular monoamine levels and in this way exerts the modulating effect on spinal pain circuits [28].

Sun et al. found in a rat pain model that DLX inhibits postoperative pain by increasing spinal norepinephrine and serotonin levels and activating spinal 5-HT2A or α₂-noradrenergic receptors [32]. In a previous rat skin incision pain model study they found that the combined administration of DLX and celecoxib showed significant analgesia attributed to the antinociceptive effects that were almost completely derived from DLX. The concomitant administration of DLX and celecoxib exerted a synergism on somatic pain behavior but not on emotional pain behavior [33].

Few clinical trials involving DLX in acute postoperative management have been published. In spine surgery for low back pain, many patients presenting with chronic pain and on heavy analgesic regimens, often including opioids showed a high incidence of chronic postoperative pain. It is probably not a coincidence that the majority of data on the perioperative use of DLX is in this surgical area, some trials being still in process [34]. Recently, Heyer et al. published the results of their randomized controlled trial (RCT) on 68 patients, scheduled for spine surgery. They were randomized to receive DLX + opioid or placebo + opioid as postoperative pain management. The main endpoints were pain scores, opioid consumption and the level of perioperative depression. Their results indicate that DLX improved pain and improved functional scores [35].

Ho et al. searched the effect of pre- and postoperative (first postoperative day) administration of 60 mg DLX after knee arthroplasty in 50 randomized patients, measuring postoperative pain scores, 48-hour total morphine consumption and side effects. The results showed no differences between the treated group and the placebo group regarding pain scores at rest and with movement, but a significant difference (p = 0.017) regarding 48-hour total morphine consumption. 19.5 (14.5) mg in DLX group vs 30.3 (18.1) mg in the placebo group [36].

Another RCT studied the effect of DLX in 50 patients with radical mastectomy. The treated group received 60 mg DLX daily two days before surgery and up to the 14-th postoperative day, and 30 mg daily up to 6 months. The results showed significant differences between the groups regarding the time to the first rescue analgesic and total opioid consumption (p < 0.001), and in addition, the incidence of chronic pain at 3- and 6-month follow-up was significantly lower [37].

A recently published study on the effect of DLX on females scheduled for abdominal hysterectomy [38] showed that 60 mg of DLX taken twice, the day before surgery and after 24 hours, reduced the 24-hour total opioid consumption (p = 0.004) and improved the postoperative quality of recovery.

Given its antihyperalgesic effect, there is consensus that DLX might represent a valuable analgesic adjuvant in the acute pain management of the opioid-tolerant patient [39-42].

Conclusions

Duloxetine has demonstrated analgesic effects in animal models of acute pain and in clinical studies in humans. Duloxetine, included in the multimodal analgesic regimens, also has lead to a reduced postoperative opioid consumption, a longer time to the first rescue analgesic and a reduced incidence of chronic postoperative pain at 3 and 6 months follow-up. It is unclear if its antihyperalgesic qualities would reduce the incidence of CPSP and future studies are required.

Paucity of data cannot permit stronger interpretation and further larger and well designed randomized trials will establish if this antidepressant should be included in the pain therapy armamentarium.

Conflict of interest

Nothing to declare

References


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Duloxetina, un antidepresiv cu proprietăți analgezice – o analiză preliminară

Rezumat

Inhibitorii recaptării de serotonină și noradrenalină sunt antidepresanți larg utilizați în prezent datorită unei bune toleranțe și a efectelor secundare reduse. Două medicamente din această clasă, duloxetina și venlafaxina, sunt de asemenea utilizate în terapia durerii cronice.

Această analiză prezintă datele recente privind efectele duloxetinei asupra sistemului nervos central, legate de tratamentul durerii acute și eficiența sa în reducerea durerii cronice postoperatorii. Eficacitatea terapeutică a duloxetinei rezultă din efectul său modulator asupra căilor descendente inhibitorii ale durerii și de asemenea prin inhibiția accentuată a aferențelor nociceptive. Efectul analgezic al duloxetinei a fost confirmat de o serie de studii dar sunt necesare studii viitoare randomizate care să clarifice eficiența duloxetinei în tratamentul durerii acute postoperatorii și mai departe asupra durerii cronice postoperatorii.

Cuvinte cheie: duloxetină, inhibitorii recaptării de serotonină și noradrenalină, durere acută postoperatorie, durere cronică postoperatorie