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Review Article

Duloxetine- Pharmacological aspects

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ABSTRACT

Duloxetine was developed for the management of depression. This drug was later found to be effective in the treatment of Stress Urinary Incontinence. It exerts its action by blocking the reuptake of serotonin and nor epinephrine in an area of the sacral spinal cord that contains a high density of these neurotransmitter receptors, thus stimulating specific motor neurons that regulate the urethral striated muscle sphincter.

1. Introduction

Duloxetine is a balanced dual serotonin and norepinephrine reuptake inhibitor recently approved for the treatment of stress urinary incontinence in women. It may be of benefit in women who are unable to perform pelvic floor muscle training, who are poor candidates for surgery or who wish to delay or avoid surgery. Duloxetine is thought to exert its action by blocking the reuptake of these neurotransmitters in an area of the sacral spinal cord that contains a high density of serotonin and nor epinephrine receptors, thus stimulating specific motor neurons that regulate the urethral striated muscle sphincter.

2. History of Duloxetine

Duloxetine was created by Lilly researchers. David Robertson, David Wong, a co-discoverer of fluoxetine, and Joseph Krushinski are listed as inventors on the patent application filed in 1986 and granted in 1990. The first publication on the discovery of the racemic form of duloxetine known as LY227942 was made in 1988. The (+)-enantiomer of LY227942, assigned LY248686, was chosen for further studies, because it inhibited serotonin reuptake in rat synaptosomes two times more potently than (–)-enantiomer. This molecule was subsequently named Duloxetine[1].

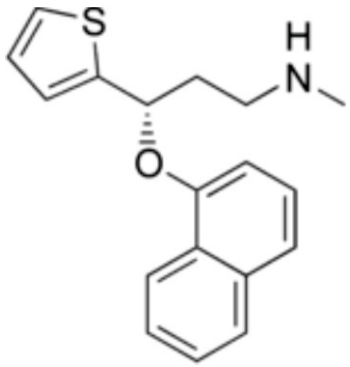
In 2001 Lilly filed a New Drug Application (NDA) for duloxetine with the US Food and Drug Administration (FDA). Duloxetine was approved by the FDA for depression and diabetic neuropathy in 2004. In 2007 Health Canada approved duloxetine for the treatment of depression and diabetic peripheral neuropathic pain. Duloxetine was approved for use of stress urinary incontinence (SUI) in the Europe in 2004[2].

3.Physicochemical characteristics:

Duloxetine (Duloxetine Hydrochloride: LY 248686, N-methyl-g-1-napthalenyloxy-2-thiophene propanamine hydrochloride) is a new orally administered, balanced dual serotonin and norepinephrine (noradrenaline) reuptake inhibitor that has been developed for the treatment of stress urinary incontinence[3]. The chemical structure of Duloxetine is represented in fig 1.

Figure 1. represents chemical structure of Duloxetine.

Duloxetine



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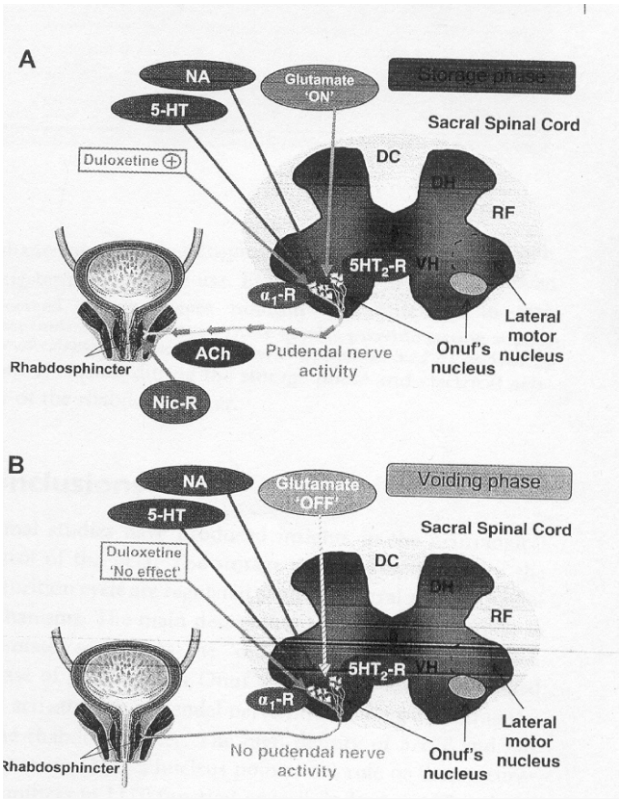
4. Pharmacodynamic properties:

Figure 2 shows mechanism of action of Duloxetine

Duloxetine is thought to block the reuptake of serotonin and norepinephrine in Onuf's nucleus in the sacral spinal cord, there by activating pudendal motor neurons that increase the urethral striated muscle tone and the force of sphincter contraction. This increased sphincter activation prevents involuntary urine loss[4]. In vitro binding studies using synaptosomal preparations isolated from rat cerebral cortex indicated that duloxetine was approximately 3 fold more potent at inhibiting serotonin uptake than norepinephrine uptake[5].

However, in vivo studies indicated equivalent inhibition by duloxetine of the uptake of serotonin and norepinephrine[5].

Figure 2 shows the mechanism of action of Duloxetine



While duloxetine had only weak effects on bladder function in female cats with non-irritated bladders under conditions of bladder irritation induced by the infusion of acetic acid, the drug increased bladder capacity 5-fold and increased periurethral striated muscle activity 8-fold[6].

The effect of duloxetine on bladder capacity was reversed by a non selective serotonin 5-HT receptor antagonist, while its effect on sphincter activity was reversed by 5-HT 2 receptor and α1-adrenoceptor antagonists. Moreover, the effects of duloxetine appeared to be central effects, since duloxetine had no effect on bladder contractions evoked by direct stimulation of efferent fibres in the pelvic nerve[6].

The effects of the dual reuptake inhibitor venlafaxine on bladder function and sphincter activity were an order of magnitude lower than those of Duloxetine[7].

In contrast to the effects observed with the dual reuptake inhibitors duloxetine or venlafaxine, combined use of the selective serotonin reuptake inhibitor seproxetine (norfluoxetine) and the norepinephrine reuptake inhibitor thionisoxetine had no effect on the bladder capacity or sphincter activity[7].

Glutamate is believed to be the main descending neurotransmitter for the storage reflex, with glutamate release to Onuf's nucleus during the storage phase, which is located in the ventral horn of the sacral spinal cord. In Onuf's nucleus, axons projecting from the CNS synapse with the pudendal nerve. The release of glutamate activates the pudendal nerve which in turn induces a release of acetyl choline from its nerve endings and elicits contraction of the rhabdosphincter[8].

Onuf's nucleus is also densely populated with 5-HT and NA terminals and contains a high density of 5-HT and NA receptors, suggesting a role for 5-HT and NA in the control of lower urinary tract. Indeed, in the presence of 5-HT and NA, the somatic nerves are activated even more, leading to an enhanced rhabdosphincter contraction. It should be pointed out that 5-HT and NA have only a modulatory effect, as they are not able to induce a contraction of the rhabdosphincter in the absence of glutamate[8].

During the voiding phase, glutamate is no longer released and hence pudendal nerve activity ceases. As stated before, this is irrespective of the presence of 5-HT and NA. Consequently, in analogue with e.g. a radio, glutamate might be depicted as 'on/off' switch for micturition while 5-HT and NA represent the 'volume control'[8].

5. Pharmacokinetic properties

Duloxetine is well absorbed by oral route. It is given once daily[9]. Following single oral doses of duloxetine 20 mg, the time to reach Cmax was typically in the range of 4 to 6 hours in healthy adult volunteers[10].

Bioavailability is 50%. Volume of distribution is 10-14L/kg[9]. Studies using 14C- labeled duloxetine indicate that the drug was highly bound to plasma proteins (>95%) [11]. It has a plasma half life of about 12 hrs[9].

In vitro studies suggest that duloxetine may inhibit CYP2D6 and can be metabolized by both CYP1A2 and CYP2D6 into multiple inactive metabolites[11].

5.1.Uses:

1.Major depression[12]
2.Diabetic neuropathy[13]
3.Stress urinary incontinence[14]

6. Dosage and administration[15]

Duloxetine is available as 20-160 mg tablets.

Duloxetine is taken orally, can be taken with or without food. Treatment duration should be individualized.

Dose in renal impairment: Duloxetine is not recommended for patients with end stage renal disease. Dose adjustments are not necessary for patients with lesser degrees of renal impairment.

Dose in hepatic impairment: Duloxetine is not recommended for patients with any hepatic insufficiency.

Dose for the elderly: A dose adjustment is not necessary.

7. Adverse reactions

1. Nausea
2. Central nervous system adverse effects: sleep disturbances[16].
3. Suicide and suicidal behavior
4. Urogenital adverse effects: obstructive voiding symptoms, acute urinary retention[17].
5. Cardiovascular effects: Minor and inconsistent elevations of blood pressure and heart rate
6. Increase in hepatic enzymes such as alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase
7. Allergic reactions
8. Other adverse effects are dry mouth, constipation, decreased appetite, weight loss, fatigue, dizziness, somnolence, tremor, sweating, hot flushes, blurred vision, insomnia, anxiety[15]

8. Drug interactions:

8.1. Pharmacodynamic drug-drug interaction: A classic pharmacodynamic drug-drug interaction of all serotonin uptake inhibitors is the induction of a serotonin syndrome upon concomitant use of an irreversible, nonselective monoamine oxidase inhibitor such as tranylcypromine. Since serotonin uptake and metabolism by monoamine oxidase are the two main physiological mechanisms for its clearance from the synaptic cleft, concomitant inhibition of both mechanisms can yield excessive local serotonin concentrations, which can potentially be lethal. Fortunately, such monoamine oxidase inhibitors are used only rarely such interactions are not likely to occur[17].

8.2. Pharmacokinetic drug interactions

Duloxetine is metabolized by CYP1A2 and CYP2D6 isozymes, as such interactions with other medications or substances that inhibit, induce or compete for these isozymes can affect duloxetine concentrations. Duloxetine is a moderate inhibitor of CYP2D6 potentially affects the elimination of other medications metabolized by this isozyme[15]. Table 1 shows drug interactions with Duloxetine

Table 1 represents drug interactions of Duloxetine

CYP1A2 Inhibitors
Fluvoxamine – increases duloxetine's bioavailability Quinolones – increase duloxetine's bioavailability
CYP2D6 Inhibitors
Paroxetine – increases duloxetine's concentration by 60%. Similar results would be expected with other CYP2D6 Inhibitors
Drugs metabolized by CYP2D6
Desipramine – Duloxetine increases desipramine levels in the blood, suggesting that duloxetine may inhibit the metabolism of other medications metabolized by CYP2D6.

8.3. Precautions/Contraindications

1. Duloxetine had been associated with mean increases of systolic and diastolic blood pressure. It is recommended that blood pressure be measured prior to starting duloxetine and periodically throughout treatment[15].
2. Duloxetine should be prescribed with caution to patients with a history of a seizure disorder[15].
3. Activation of mania or hypomania can occur in patients taking Duloxetine[18].
4. Duloxetine was associated with mydriasis and should be used with caution in patients with narrow angle glaucoma.
5. Abruptly stopping duloxetine may result in a discontinuation syndrome. Symptoms of these syndrome consisted of dizziness, nausea, headache, paresthesia, vomiting, irritability and night mares. Patients taking duloxetine should have their dose tapered, rather than abruptly discontinuing the medication[15].
6. Pregnancy (Category C):- No adequate studies in pregnant women and animal studies are lacking or have shown and adverse effect on foetus, but potential benefit may warrant use of the drug in pregnant women despite potential risk[19].
7. Duloxetine is contraindicated in patients with a known hypersensitivity to duloxetine Capsules[15].
8. Duloxetine is contraindicated in patients who are concurrently taking or have taken a monoamine oxidase inhibitor in the past 14 days[15].

9. Conclusion

Duloxetine is a potent and relatively balanced inhibitor of serotonin and nor epinephrine reuptake. Duloxetine is useful in the acute treatment of symptoms of depression[20]. Serotonin and nor epinephrine have been implicated in the modulation of endogenous analgesic mechanisms via the descending inhibitory pain pathways in the brain and spinal cord[13]. Duloxetine is efficacious in the treatment of persistent pain conditions in humans[13]. Studies have implicated serotonin and norepinephrine in the neural control of lower urinary tract function. Duloxetine has been developed for the treatment of stress urinary incontinence[14].

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