VENLAFAXINE - A REVIEW OF ITS PHARMACOLOGY AND THERAPEUTIC POTENTIAL IN VARIOUS PSYCHIATRIC CONDITIONS

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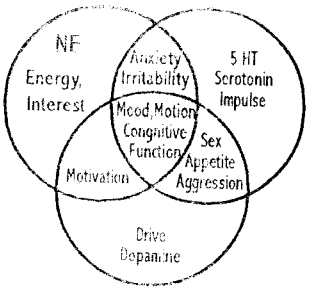
Major depression, either alone or combined with other psychiatric disorders is one of the most functionally disabling disorder in the community. Despite tremendous strides towards gaining a better understanding of the disease and its diagnosis as well as improvements in pharmacotherapy, major depression and its treatment continues to raise concerns among patients and family. The first class of antidepressants, including the tricyclic antidepressants and monoamine oxidase inhibitors were discovered by chance. However, over the 20 years, in parallel with the understanding of the neurobiology of depression, more and more newer antidepressants have been developed which act at selective sites in brain. Of late, the potential advantages of antidepressant therapy involving more than one putative site of action were recognized. For example, combination of disimipramine a NE reuptake inhibitor with, SSRI fluoxetin has shown more rapid onset of neuronal activity and robust response than did either agent alone. Like combination therapy, an antidepressant that has multiple mechanism of action may offer more robust response that do single action agents. For Example, a study comparing Clomipramine with SSRI paroxetine showed higher remission rate as well as early and sustained antidepressant effect with clomipramine (Danish study, 1990)

Venlafaxine differs from all existing antidepressants in that it exhibits a combined action effect on neuronal reuptake of serotonin and nonepinephrine, thereby prolonging the neurotransmitter action. However, the physician's acceptance of venlafaxine was initially limited by a number of factors unrelated to its pharmacologic profile. The are :

- Late entry into market place
- Misperception that its use was limited to refractory cases of depression only
- Poor understanding of its pharmacologic profile and the clinical implications, posed by its multiple mechanism of action.
- Early poor tolerability including nausea and increase in blood pressure
- Need for twice - daily dosing
- Wide dose-titration range.

However, extensive clinical studies including double-blind, placebo conrolled and cross over studies have proved its efficacy and tolerability in various clinical conditions.

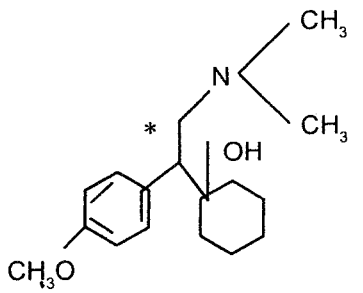
VENLAFAXINE'S UNIQUE CHARACTER PROFILE :



Dysregulation of serotonin, norepinephrine and dopamine are implicated in various symptomatology of depression.

Because of venlafaxines, dual reuptake blockade of NE, 5HT and to some extent dopamine, it is effective for all the above neurotransmitter mediated dysfunctions while showing no significant affinity for adrenergic, muscarinic or histamine receptors.

Venlafaxine is a bicyclic phenylethylamine derivative that is chemically distinct from both TCAs and SSRIs.



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PHARMACOKINETICS

Following absorption of venlafaxine from the gastrointestinal tract, the drug undergoes extensive first pass metabolism in liver. Food delay the absorption of venlafaxine. The large volume of distribution and its low plasma protein binding of approximately 30 % indicate extensive tissue binding. Venlafaxine is metabolised in the liver to a major active metabolite, 0-demethyl venlafaxine, and 2 minor marginally active metabolites, N-demethyl venlafaxine and N, 0-demethyl venlafaxine. Importantly, none of the metabolites demonstrated appreciable affinity for muscarinic cholinergic, α 1-adrenergic or histamine H1 receptors (Muth etal, 1991)

Excretion of venlafaxine and its metabolites is primarily by the renal route with only 4.7% of administered dose appearing in urine as unchanged drug. The elimination half life of O-dimethyl venlafaxine (≈ 10 hours) is longer than that of parent drug. (≈ 4hours) There were no apparent differences in steady-state pharmacokinetics when 2 and 3 times daily regimen were compared. Therefore, although the majority of published clinical trials used a 3 times daily administration schedule, use of a twice-daily regimen is justified.

DRUG INTERACTIONS.

Although venlafaxine is metabolished by the CYP2D6 isoenzyme it also inhibits this enzyme. However, venlafaxine is a less potent inhibitor of the CYP2D6 isoenzyme than paroxetine, fluoxetine, sertraline and fluvoxamine (Sellers & Ball, 1993). Hece clinically significant inhibition of CYP2D6 isoenzyme is less likely with venlafaxine than with SSRIs. Venlafaxine does not have interaction with lithium, diazepam or ethyl alcohol when co-administered. Cimetidine can slightly increase the blood level of venlafaxine's active metabolites but this is not clinically significant. Fluoxetin can significantly increase the concentration of venlafaxine and its active metabolites as well as potentiate side effects. As venlafaxine inhibits the reuptake of serotonin and norepinephrine, it should not be administered with MAOI (Manley & Wozniak, 1983). When switching from a MAOI to venlafaxine there should be a 14 day interval between the discontinuation of the MAOI and the initiation of venlafaxine therapy. When switching from venlafaxine to a MAOI, a 7- day interval is adequate because of venlafaxines short half life. This time frame is not applicable to reversible MAOI like moclobemide or brofaromine.

TOLERABILITY :

Short term treatment (6 weeks) with venlafaxine upto 450mg/day was generally well tolerated in clinical trials. Most adverse effects are of mild to moderate in severity, tending to occur early in the course of treatment, and many resolved with continued therapy. Most commonly reported adverse effects are nausea, headache, sweating, sleeping, dry mouth, decreased appetite, anxiety, dizziness and insomnia [5]. The incidence of classical anticholinergic symptoms such as dry mouth and constipation was significantly lower with venlafaxine than TCAs. There are reports of modest increase in systolic blood pressure, particularly at high doses (Fabre & Putamon, 1987). Lethality with suicidal overdose is not

reported with venlafaxine. In comparison with other antidepressant drugs, venlafaxine was better tolerated than imipramine and clomipramine, at least as well tolerated as trazodone, and fluoxetine. The long term tolerability of venlafaxine has also been reported to be good (Magni & Hackett, 1992; Tiller etal, 1992). Nausea, sweating, headache and anxiety were the common adverse effects reported in 10% of patients in long term trials. Because of its shorter half life, venlafaxine should be discontinued gradually over atleast 2 weeks. If venlafaxine is suddenly discontinued, a withdrawal syndrome involving fatigue, nausea, dizziness, headache, insomnia and nervousness may develop.

Safety and effectiveness of venlafaxine has not been established in individuals below 18 years. Because of excretion of its active metabolite O - demethyl venlafaxine in breast milk, mothers on this drug are advised not to breast feed their infants. Safety of venlafaxine in pregnancy also has not been established.

DOSAGE AND ADMINISTRATION

The recommended starting dose of plain venlafaxine is 75mg daily administered as 2 or 3 times daily regimen, taken with food. The starting dose of XR preparation is once daily. Depending on the tolerability and the need for further clinical effect the dosage may be gradually increased to a maximum of 375 mg daily. When increasing the dose, increments of upto 75mg/day should be made at intervals of not less than 4 days. Regular blood pressure monitoring is recommended when increasing the dose. No dosage adjustment is required in elderly patients who are otherwise healthy. The dosage of venlafaxine should be reduced by approximately 50% in patients with moderate hepatic impairment and by 20% in patients with mild to moderate renal impairment.

FREQUENCY OF ADMINISTRATION AND ONSET OF THERAPEUTIC EFFECT

Pharmacokinetic and clinical data suggest that a twice daily plain venlafaxine regimen is as effective as once daily dosing without compromising the therapeutic efficacy. Limited data suggest that venlafaxine may have an onset action of about 2 weeks. Khan et al (1998) demonstrated significant improvements in mean depression rating scale scores versus baseline from weeks 2 or 3 onwards in a non-comparative study[10]. Comparison with fluoxetine (Clerc et al, 1999) also shows rapid onset of action with venlafaxine. However, this is yet to be confirmed by further clinical trials.

INDICATIONS

DEPRESSION :

Venlafaxine Versus Placebo controlled trials

Rudolph (1998) in a randomised, double-blind, placebo-controlled, dose response trial reported that venlafaxine is effective and well tolerated at dose range of 75-375 mg per day. Khan (1998) in double blind, placebo controlled trial reported significant improvement with venlafaxine in doses of 75-200 mg / day with early onset of antidepressant effect within 1-2 weeks.

Venlafaxine compared with TCAs & SSRIs

Einarson (1999) in a meta-analysis of randomised controlled trial of venlafaxine XR demonstrated statistically significant greater success rate (73.7%) as compared to SSRIs (61.1%) and TCAs (57.9%). The drugs included in the comparison were the SSRIs such as (citalopram, fluoxetine, fluvoxamine and sertreline); and the TCAs such as (amitriptyline, imipramine, desimipramine and nortriptyline). Venlafaxine is reported to be well tolerated and effective in the tretment of dysthymia (Ballus, 2000). Venlafaxine has shown beneficial effects in treatment - resistant depression (Poirier, 1999) Zonardi (2000) have reported that venlafaxine is effective in delusional depression. A metanalysis of extension studies (Entsuah, 1986) showed a 80%

prevention of recurrence in the venlafaxine group indicating that it is effective in maintaining the intial response and thereby preventing relapse in major depression.

ANXIETY DISORDERS

There are many studies showing that venlafaxine is effective and well tolerated in the short term and long treatment of anxiety disorders (Feighner, 2000; Lydiard, 2000). The efficacy of venlafaxine in GAD may be related to the dual inhibition of serotonin and norepinephrine reuptake as there is evidence that both these neurotransmitters are dysregulated in GAD. For e.g., norepinephrine may mediate non rewarded behaviours, where as serotonin may mediate fear induced inhibition of movement and also punishment. There are sporadic reports about the efficacy of venlafaxine in panic disorder, social phobia, obsessive compulsive disorder and trichotillomania (Sheehan, 2000). Venlafaxine's anti-anxiety effect is independent of antidepressant effect.

OTHER INDICATIONS

Venlafaxine is effective in the treatment of anorexia nervosa, borderline personality disorder, adult ADHD, fibromyalgia, choronic fatigue syndrome and hot flashes in men and women receiving androgen deprivation therapy for prostate cancer and breast cancer respectively.

COMBINATION TREATMENT

Bernardo et al (2000) in a small trial of 9 patients reported that combined use of venlafaxine and ECT is safe and well tolerated in depression. Combination of venlafaxine with clomipramine or imipramine who are partial responders to the later is also reported to be safe and effective in depression (Gomez 2000). Walter (1998) reported that addition of lithium to venlafaxine was rapidly followed by improvement in mood and fucntion in adolescent major depression.

In conclusion, this review suggest that both sustained release and plain venlafaxine in a dose range of 75-225 mg/day is an effective, safe and well tolerated antidepressant for all types of depression and to some extent various types of anxiety disorders. The once daily dose also facilitates administration and enhances compliance. However, this newer agents role in psychopharmacologic armamentorium requires further exploration including long term evaluation in Indian setup.

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