VANCOUVER HOSPITAL & Health Sciences Centre

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CHANGES TO FORMULARY

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Additions

1. Tinzaparin 10,000IU/mL - 2mL vial (Innohep®)
   - low molecular weight heparin
   - restricted to treatment of deep vein thrombosis
   - Cost: refer to tinzaparin article, page 2

2. Nefazodone 100mg,150mg, 200mg tablets (Serzone®)
   - antidepressant for management of refractory depression
   - Cost: refer to nefazodone article, page 5

3. Venlafaxine 37.5mg, 75mg tablets (Effexor®)
   - antidepressant for management of refractory depression
   - Cost: refer to venlafaxine article,

UPDATED POLICY AND PROCEDURES

1. Prescription Interpretation Policy (PIP)

The following PIPs have been added:

T if **docusate** is ordered with **no strength** indicated, the **100mg** strength will be **dispensed**

T if **urea cream** is ordered with **no strength** indicated, the **10%** strength will be **dispensed**

2. Therapeutic Interchange Program (TIP)

The following TIPs have been approved and are effective September 16, 1996.

* All orders for **lorazepam oral** will be

dispensed with the **sublingual dosage form** and labelled **"for oral or sublingual administration"**

* All current and new orders for **Centrum® Forte will be interchanged to Centrum® Junior Complete** (Banfield Extended Care and Discharge Planning Units only). Centrum® Junior Complete is similar to Centrum® Forte (Table 1) but is chewable and more palatable hence administration to residents/patients with swallowing difficulties will be facilitated.

Table 1. Comparison of Centrum® Forte to Centrum® Junior (Jr) Complete

	Centrum® Forte	Centrum® Jr Complete
Betacarotene	1000 IU	
Vitamin A	4000 IU	5000 IU
Vitamin E	30 IU	10 IU
Vitamin C	90 mg	50 mg
Folic acid	0.4 mg	0.1 mg
Vitamin B_1	2.25 mg	1.5 mg
Vitamin B_2	2.6 mg	1.7 mg
Niacinamide	20 mg	20 mg
Vitamin B_6	3 mg	2 mg
Vitamin B_{12}	9 Fg	4 Fg
Vitamin D	400 IU	400 IU
Biotin	45 Fg	30 Fg
Pantothenic acid	10 mg	10 mg
Calcium	175 mg	162 mg
Phosphorus	125 mg	125 mg
Iodine	0.15 mg	0.15 mg
Iron	10 mg	4 mg
Copper	2 mg	1 mg
Magnesium	100 mg	
Manganese	5 mg	
Potassium	30 mg	
Chlorine	27.2 mg	
Chromium	25 Fg	
Molybdenum	25 Fg	
Selenium	25 Fg	
Zinc	15 mg	
Nickel	5 Fg	
Tin	10 Fg	
Vanadium	10 Fg	
Silicon	10 Fg	

Tinzaparin for Treatment of Deep Vein Thrombosis

Introduction

Tinzaparin is one of three low molecular weight heparins (LMWH) available in Canada (Table 2). It has recently been added to the VHHSC formulary for the treatment of deep vein thrombosis (DVT). LMWH's are obtained by depolymerization of unfractionated porcine heparin. Compared to unfractionated (traditional) heparin, LMWH's are better absorbed subcutaneously (SC), have a longer duration of action, have a higher affinity for factor Xa, and require less laboratory monitoring.

Table 2. Comparison of Low Molecular Weight Heparins to Unfractionated Heparin

Drug	**Heparin**	**Tinzaparin (Innohep®)**	**Dalteparin (Fragmin®)**	**Enoxaparin (Lovenox®)**
Average Molecular Weight (range)	15,000 d (5000-30,000)	4500 d (3000-6000)	5000 d (2000-9000)	4500 d (3000-6000)
Anti-Xa: Anti-IIa ratio	1:1	1.9:1	2:1	4:1
Bioavailablility (SC)	30%	90%	90%	90%
Peak Onset (SC)	20-30 minutes	4-6 hours	4 hours	3 hours
Plasma t1/2 (minutes)	60-150 (IV)	111	119-139	129-180
Elimination	RES + Renal	Renal	Renal	Renal
Dose for DVT treatment	Dosed to achieve 1.5-2.3X aPTT	175 IU/kg SC daily	100 IU/kg SC BID	1mg/kg SC BID

Availability	1000U/mL 10,000U/ mL	10,000IU/ mL (2mL multidose)	5,000IU/ 0.2mL	30mg/0.3 mL
Cost/5 day course	$26.02[a,b]	$68.64[a]	$132.30[a]	$228.08[a]

RES = reticuloendothelial system
[a] VHHSC acquisition cost based on 70kg patient
[b] based on 6000 U bolus, 1100U/hr

Comparative Studies: DVT Treatment

Several studies have compared dalteparin with heparin for DVT treatment.[3-8] Despite differences in dalteparin administration (IV continuous infusion, SC), all studies demonstrated similar efficacy and incidence of bleeding complications compared to heparin.

There are two studies evaluating tinzaparin for DVT treatment.[9,10] In a multicentre double-blind trial of 432 patients, Hull *et al* compared the effectiveness and safety of tinzaparin (175 units/kg SC daily to IV heparin (adjusted to maintain an aPTT 1.5-2.5 times the mean control value).[9] Warfarin therapy was initiated on day 2 and continued for 3 months. Treatment with heparin or tinzaparin was discontinued on the sixth day of therapy provided the INR was greater than 2.0. Tinzaparin was found to be as effective as heparin (incidence of new episodes of venous thrombosis 2.8% and 6.9%, respectively). There were, however, significantly fewer episodes of early major bleeding in the tinzaparin group (0.5%) compared to heparin (5%). There was no significant difference in the incidence of thrombocytopenia defined as platelet count less than 150,000 (tinzaparin 2.8%, heparin 1.4%). In a smaller randomized trial, tinzaparin 150U /kg SC once daily was found to be equivalent to 75U/kg SC twice daily in preventing thrombosis progression in patients with venographically proven DVT.[10]

Adverse Effects

Similar to unfractionated heparin, bleeding is the major adverse effect associated with LMWH.[11] Protamine sulphate is the antidote for tinzaparin overdosage given at the same dosage as per heparin overdosage. Thrombocytopenia may also occur with LMWH (incidence < 3%). Heparin-induced thrombocytopenia (HIT) may be immune-mediated associated with antiplatelet antibodies. Kikta *et al* demonstrated that LMWHs had a high likelihood of causing platelet aggregation in patients who had heparin associated antiplatelet antibodies.[12] Thus, LMWH's cannot be recommended as a heparin substitute in patients with HIT.

LMWH may also cause transient elevations in hepatic aminotransferases and alkaline phosphatase, usually reaching a maximum within the first seven days of therapy.[13] Other potential adverse effects of LMWH include rash (rare) and hematoma, bruising or pain at the subcutaneous injection site. LMWH has been reported to be successful in the treatment of a patient who developed osteoporosis while on unfractionated heparin, however inadequate data

precludes a useful comparison. [11]

Monitoring of Therapy

Initial studies recommended that plasma anti-Xa levels be monitored to assess efficacy of LMWHs. [3,4] However, anti-Xa assays have not been shown to correspond well with the response of LMWHs[5,7] and subsequent trials indicated that monitoring anti-Xa activity did not result in improved efficacy or safety[7-9]. Baseline and twice weekly CBC (with platelets) is necessary for the duration of LMWH therapy; treatment should be discontinued if thrombocytopenia occurs.

Summary

Subcutaneous tinzaparin is a safe and effective alternative to IV heparin for the initial treatment of DVT. The once daily SC dosing and decreased laboratory monitoring could potentially lead to outpatient management of DVT. Despite higher acquisition costs of tinzaparin compared to heparin, the lack of laboratory monitoring of anticoagulant activity (e.g. aPTT) and costs associated with maintain ing an IV infusion offset the additional costs of the drug. Due to the potential risk of bleeding and HIT, laboratory monitoring of CBC is still required during LMWH therapy.

There is limited data on LMWH for the treatment of pulmonary embolism. Until further studies are available, IV heparin infusions are still preferable in this patient population.

References

1. Green D et al. Low molecular weight heparin: a critical analysis of clinical trials. Pharmocol Rev 1994;46:89-109.
2. Krogh CME, ed. Compendium of Pharmaceutical Sciences (CPS), 1996.
3. Bratt G et al. A comparison between low molecular weight heparin and standard heparin in the intravenous treatment of deep vein thrombosis. Thrombosis Hemostas 1985;54:813-7.
4. Holm HA et al. Subcutaneous heparin treatment of deep vein thrombosis: a comparison of unfractionated and low molecular weight heparin. Hemostasis 1986;16 (Suppl 2):30-7.
5. Albada J et al. Treatment of acute venous thromboembolism with low molecular weight heparin (Fragmin): results of a double blind randomized study. Circ 1989;80:935-40.
6. Bratt G et al. Two daily subcutaneous injections of Fragmin as compared with intravenous standard heparin in the treatment of DVT. Thrombosis Hemostas 1990;64:506-10.
7. Lindmarker P et al. Comparison of once daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in treatment of deep vein thrombosis. Thrombosis Hemostas 1994;72:186-90.
8. Alhenc-Gelas M et al. Adjusted versus fixed doses of the low-molecular-weight heparin Fragmin in the treatment of deep vein thrombosis. Thrombosis Hemostas 1994;71:698-702.
9. Hull RD et al. Subcutaneous low molecular weight heparin compared with continuous intravenous heparin in the treatment of proximal vein thrombosis. NEJM 1992;326:975-82.
10. Siegbahn A et al. Subcutaneous treatment of deep venous thrombosis with low molecular weight heparin. A dose finding study with LMWH-NOVO. Thrombosis Res 1989;55:767-78.
11. Tapson VF et al. Management of venous thromboembolic disease. Clin Chest Med 1995;16:281-94.
12. Kikta MJ et al. Can low molecular weight heparin and heparinoids be safely given to

patients with heparin induced thrombocytopenia syndrome? Surg 1993;14:705-10.
13. Cziraky MJ et al. Low-molecular-weight heparins for the treatment of deep vein thrombosis. Clin Pharm 1993;12:892-99.

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Two New Formulary Antidepressants: Venlafaxine (Effexor®) and **Nefazodone (Serzone®)** are two new antidepressants recently added to VHHSC formulary for the treatment of depression resistant to traditional antidepressant therapy.

Venlafaxine (Effexor®)

Venlafaxine is an atypical antidepressant which is structurally unrelated to other antidepressants currently in use. Similar to tricyclic antidepressants (TCA), it inhibits the reuptake of both serotonin and norepinephrine.[1] However, it does not have affinity for histamine, cholinergic, or alpha$_1$-adrenergic receptors[1,2], and thus has a reduced propensity to cause anticholinergic (dry mouth, constipation, urinary retention), CNS (sedation, anxiety), and cardiac (orthostatic hypotension, tachycardia) side effects.

Four randomized, double-blind comparative trials indicate that venlafaxine is at least as effective as imipramine, trazodone, and fluoxetine.[3-6] One uncontrolled trial suggests that venlafaxine may be of benefit in a minority of patients with depression refractory to traditional antidepressants and electroconvulsive therapy (ECT).[7]

Venlafaxine is well absorbed orally. It is extensively metabolized to an active metabolite which is renally excreted. The half-life of venlafaxine is 3-5 hours and its metabolite is 10-11 hours. Although it has been suggested that the onset of effect with venlafaxine may be more rapid (within 1-2 weeks)compared to other antidepressants, clinical data to support this assertion is sparse.[1,8] Venlafaxine does not significantly affect the metabolism of other drugs.[9]

Venlafaxine's adverse effect profile is similar to that of selective serotonin reuptake inhibitors (SSRI) but with a higher incidence of nausea. Nausea is dose related and may be lessened with food. Common side effects include nausea (37%), somnolence (23%), headache (25%), dry mouth (22%), constipation (15%), and sweating (12%). Sustained mild hypertension is more common among patients receiving higher doses (> 225 mg/day).

The initial dose of venlafaxine is 75mg/day given in 2 doses which can be increased at 4 day intervals to the usual dosage range of 150-225mg/day.[9] Dosage adjustments are necessasry for both renal and hepatic impairment. Table 3 compares the cost of venlafaxine to other agents.

Table 3. Cost comparison of antidepressants

Drug	Usual Dose (mg/day)	[a]Cost/month
Fluoxetine	20	$46.80
Paroxetine	30	$50.70
Sertraline	100	$61.20
Fluvoxamine	100	$49.20

Amitriptyline	100-150	$0.60-0.90
Imipramine	150-200	$3.60-4.32
Trazodone	200-300	$35.40-53.10
Venlafaxine	**150-225**	**$58.80-88.20**
Nefazodone	**300-400**	**$81.00-108.00**

[a] based on VHHSC acquisition costs

Nefazodone (Serzone®)

Nefazodone is a phenylpiperazine type antidepressant that is structurally related to trazodone. It inhibits serotonin reuptake post-synaptically and is also an antagonist at the 5-HT_2 receptor. Nefazodone possesses no anticholinergic or antihistaminic activity, suggesting it may be better tolerated than TCAs.

Blinded clinical studies have shown nefazodone to possess similar antidepressant activity to imipramine[11-13], sertraline[14] and paroxetine[15]. Compared to amitriptyline, nefazodone's antidepressant efficacy was found to be inferior[16]. This may be due to the relatively small mean nefazodone dose used in this trial (242 mg/day). There are no trials comparing nefazodone to its closest relative, trazodone. As well, there are no published trials evaluating nefazodone's efficacy in patients with depression refractory to other antidepressant agents.

Nefazodone is extensively metabolized resulting in an oral bioavailability of only 20%. The half-life of the parent drug is 2-4 hours and the half-lives of its three active metabolites range from 2-33 hours. As with other antidepressants, the onset of significant antidepressant effects does not usually occur before 3-5 weeks of therapy.[17] Improvement in depression-related anxiety symptoms and agitation may occur as early as one week into therapy.[18]

The most common adverse effects of nefazodone include somnolence (25%), nausea (22%), dizziness (17%), constipation (14%), and lightheadedness (10%). Compared to SSRIs, nefazodone causes less sexual dysfunction, nervousness, insomnia, and tremors; however, it causes a higher rate of confusion, dizziness, and visual disturbances.[9,19] Nefazodone has not been reported to cause priapism, a serious side-effect of trazodone.

Dosage of nefazodone is initiated at 50-100mg BID which can be increased weekly to the usual dose of 300-500mg/day. Lower doses are suggested in the elderly and those with liver dysfunction. Nefazodone inhibits hepatic microsomal p450 3A4 enzymes, and has been shown *in vivo* to increase plasma levels of triazolam and alprazolam.[19] In both cases, the increased serum levels resulted in untoward effects. Through this same mechanism, there is a possibility for interaction with cyclosporine, midazolam, quinidine and nifedipine.

Conclusions

Both venlafaxine and nefazodone are atypical antidepressants which are generally well tolerated, are administered at least twice daily and are expensive. In the absence of data demonstrating the superiority of these agents over more established antidepressants, their use should be reserved for patients with depression who are intolerant to or have failed

more traditional antidepressants.

References

1. Morton WA et al. Ann Pharmcother 1995;29:387-95.
2. Muth EA et al. Biochem Pharmcol 1986;35:4493-7.
3. Schweizer E et al. J Clin Psych 1994;55:104-8.
4. Cunningham LA et al. J Clin Psychopharmacol 1994;14:99-106.
5. Clerc GE etal.Int Clin Psychopharmacol1994;9:139-40.
6. Shrivastava R e tal. J Clin Psychopharmacol 1994;14:322-9.
7. Nierenberg AA et al. J Clin Psychopharmacol 1994;14:419-23.
8. Montgomery SA. Int Clin Psychopharmacol 1995;10(Suppl 2):21-7.
9. Krogh CME ed. CPS 1996.
10. Shrivastava RK et al. J Clin Psychopharmacol 1994;14:322-9.
11. Rickels K et al. Br J Psych 1994;164:802-5.
12. Cohn CK et al. J Clin Psych 1996;57(Suppl 2):15-8.
13. Fontaine R et al. J Clin Psych1994;55:234-41.
14. Feiger A et al. J Clin Psych 1996;57(Suppl 2):53-62.
15. Baldwin DS et al.JClin Psych 1996;57(Suppl 2):46-52.
16. Ansseau M et al. Psychopharmacol 1994;115:254-60.
17. Nefazodone. In Drugdex. Micromedex, Inc., 1996.
18. Fawcett J et al. J Clin Psych 1995;56(Suppl 6):37-42.
19. Preskorn SH. J Clin Psych 1996;56(Suppl 2):12-21.

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