DALTEPARIN **AHFS 20.12.04**

Class: Low molecular weight heparin (LMWH).

Indications: Prevention of deep vein thrombosis and pulmonary embolism, †treatment of deep vein thrombosis and pulmonary embolism, †thrombophlebitis migrans, †disseminated intravascular coagulation (DIC).

Contra-indications: Active major bleeding, history of heparin-induced thrombocytopenia with unfractionated heparin, thrombocytopenia with positive anti-platelet antibody test.

Pharmacology

Dalteparin acts by potentiating the inhibitory effect of antithrombin III on Factor Xa and thrombin. It has a relatively higher ability to potentiate factor Xa inhibition than to prolong plasma clotting time (APTT) which cannot be used to guide dosage. Anti-factor Xa levels can be measured if necessary, e.g. if a patient is at increased risk of bleeding, but routine monitoring is not generally required because the dose is determined by the patient's weight. LMWH is as effective as unfractionated heparin for the treatment of deep vein thrombosis and pulmonary embolism and is now the initial treatment of choice.[1,2] Other advantages include a longer duration of action which allows administration q.d. and possibly a better safety profile, e.g. fewer major hemorrhages.[1-5] **LMWH** is the treatment of choice for *chronic* DIC; this commonly presents as recurrent thromboses in both superficial and deep veins which do not respond to **warfarin**. **Tranexamic acid** and **aminocaproic acid** (antifibrinolytic drugs) should not be used in DIC because they increase the risk of end-organ damage from microvascular thromboses. All LMWH is derived from porcine heparin and some patients may need to avoid it because of hypersensitivity, or for religious or cultural reasons. The most appropriate non-porcine alternative is **fondaparinux**.

Bio-availability 87% SC (based on plasma anti-factor Xa activity).
Onset of action 3min IV; 2–4h SC.
Time to peak plasma anti-factor Xa activity 4h SC.
Plasma anti-factor Xa activity halflife 2h IV; 6h IV in hemodialysis patients; 3–5h SC.
Duration of action 10–24h SC.

Cautions

Serious drug interactions: enhanced anticoagulant effect with anticoagulant/antiplatelet drugs, e.g. NSAIDs; reduced anticoagulant effect with antihistamines, cardiac glycosides, **tetracycline** and **ascorbic acid.**

Risk of spinal (intrathecal or epidural) hematoma in patients undergoing spinal puncture or with indwelling spinal catheter, particularly if concurrently receiving a drug which affects hemostasis; monitor for neurological impairment. Increased risk of hemorrhage if underlying bleeding diathesis (e.g. thrombocytopenia), recent cerebral hemorrhage, recent neurological or ophthalmic surgery, uncontrolled hypertension, diabetic or hypertensive retinopathy, subacute bacterial endocarditis, current or past peptic ulcer, severe liver disease. Severe renal impairment: the anti-Factor X activity halflife of dalteparin is prolonged in patients requiring hemodialysis and the manufacturers recommend caution in its use. Specialist guidelines suggest using IV

unfractionated heparin instead of LMWH but the evidence is not strong (grade 2C, i.e. not based on RCT).[6]

Undesirable effects

For full list, see manufacturer's PI.

Common (<10%, >1%) pain at the injection site, minor bleeding (generally hematoma or ecchymosis at the injection site), major bleeding in surgical patients (e.g. from the surgical wound, intra-operative vessel damage, gastro-intestinal), reversible increases in transaminases (occasionally associated with increased bilirubin levels), hematuria.

Uncommon (<1%, >0.1%) major bleeding in medical patients (e.g. gastro-intestinal, subdural hematoma), thrombocytopenia (platelet count $<50 \times 10^9$/L).

Both standard heparin and LMWH can cause thrombocytopenia (platelet count $<100 \times 10^9$/L). An early (<4 days) mild fall in platelet count is often seen after starting heparin therapy, particularly after surgery. This corrects spontaneously despite the continued use of heparin and is asymptomatic.[7] However, occasionally, an immune heparin-induced thrombocytopenia (HIT) develops associated with heparin-dependent IgG antibodies (*see* LMWH p.000).[4,7] Dalteparin should be stopped immediately if there is a fall in the platelet count of >50% and the advice of a hematologist obtained. Anticoagulation should be continued with a hirudin derivative, e.g. **lepirudin**, or a direct thrombin inhibitor, e.g. **argatroban**, even if there is no clinically evident thrombosis (*see* LMWH, p. 000).[8]

Dose and use

All patients should have a baseline platelet count before starting dalteparin. Subsequent routine monitoring depends on the relative risk of HIT (see LMWH, p.000).[8]

May cause transient stinging and local bruising. Inject SC, rotate sites daily between instead the lower anterior abdomen, outer upper thigh or outer upper quadrant of the buttock; introduce the total length of the needle vertically into the thickest part of a skin fold produced by squeezing the skin between the thumb and forefinger. Do not rub the injection site.

The anti-Factor X activity halflife of dalteparin is prolonged in patients with severe renal impairment requiring hemodialysis. The manufacturers recommend caution in its use but give no specific dose reduction.

Thromboprophylaxis

Patients with cancer undergoing surgery

- give 5000units SC q.d., starting the evening before surgery
- continue for 2–4 weeks;[9] four weeks is more effective than one week.[10,11]
- consider additional mechanical measures such as graduated compression stockings or intermittent pneumatic compression.[9]

Patients with cancer who are immobile or confined to bed because of a concurrent acute medical illness

- give 5000 units SC q.d. (see LMWH, p.000)
- duration of therapy is generally ≤2 weeks.[12,13]
- if anticoagulation is contra-indicated, use graduated compression stockings instead.[9]

Patients with cancer undertaking long-distance air travel (>6h)

- if a LMWH is deemed necessary (see LMWH, p.000), prescribe three injections (one each for the outward and return journeys, and one spare)
- provide training in the correct administration of the injection (see the information on self-administration included in the patient information leaflet)
- self-administer 5000 units SC 2–4h before departure.[9]
- if there is a stop over, followed by another long flight, another injection is not necessary unless the second flight is more than 24h after the first.

Treatment

Deep vein thrombosis and pulmonary embolism in patients with cancer: initial treatment

- confirm diagnosis radiologically (ultrasound, venogram, V/Q scan, CT pulmonary angiography).
- give 200units/kg SC q.d. for 4 weeks, then
- 150units/kg SC q.d. for at least the first 3–6 months of indefinite anticoagulation.[6]

Deep vein thrombosis and pulmonary embolism in patients with cancer: ongoing treatment

Indefinite anticoagulation should be considered for patients who have a deep vein thrombosis, a sudden and severe pulmonary embolism or a persistent major risk factor for thrombo-embolism such as cancer[6] (see LMWH, p.000). In patients with cancer, long-term LMWH appears as effective as (possibly more effective than) **warfarin**, with a similar (or reduced) risk of bleeding.[14,15] **Warfarin** should be reserved for those patients whose cancer is relatively stable. When switching to **warfarin**, LMWH should be continued for 2 days after achieving a therapeutic INR. Patients undergoing anticancer treatments should receive LMWH.

In palliative care, because hemorrhagic complications with **warfarin** occur in nearly 50% (possibly related to drug interactions and hepatic dysfunction), LMWH (e.g. dalteparin 150units/kg SC q.d.) is preferable. It has been used indefinitely and is acceptable to patients.[16-18] Generally, indefinite anticoagulation is discontinued only if contra-indications develop, or when the patient reaches the stage when symptom relief alone is appropriate, e.g. in the last few weeks of life.

Some centers use a fixed low-dose regimen, independent of body weight (Box 2.A) With this regimen, 15% of patients did not complete the first week (6% experienced a major bleed, 5% required a smaller dose of dalteparin due to abnormal coagulation and 2% had massive recurrent pulmonary emboli). Subsequently, almost 80% of patients received chemotherapy, 27% experienced transient thrombocytopenia (generally related to the chemotherapy) and 23% required surgery or an invasive procedure. Major bleeding occurred in 5% (fatal in 3%) and minor bleeding in 8%. Recurrent thrombo-embolism occurred in 9%. Complications were no higher in patients with liver or brain metastases, thrombocytopenia, or those undergoing surgical or invasive procedures.[19]

Box 2.A Modified dalteparin regimen in patients with metastatic cancer and venous thrombo-embolism[19]

First week
Give dalteparin in a dose according to body weight (see Deep vein thrombosis and pulmonary embolism, p.000).

Subsequent weeks (continue indefinitely)
Dalteparin in a fixed-dose of 10 000 units SC q.d.
If deep vein thrombosis recurs
Increase the fixed-dose of dalteparin to 12 500 units SC q.d.
If pulmonary embolism occurs/recurs
Treat with an inferior vena caval filter.

Dose modifications
Thrombocytopenia
If the platelet count falls below 50 × 10^9/L reduce the dose of dalteparin to 5000 units SC q.d.
If the platelet count falls below 10 × 10^9/L reduce the dose of dalteparin to 2500 units SC q.d.
Surgical procedures
Give dalteparin 5000 units SC q.d. for the first 4 days postoperatively and then return to the patient's usual dose.
Other invasive procedures (e.g. biopsy)
Give dalteparin 5000 units SC on the day of the procedure and then return to the patient's usual dose.

Disseminated intravascular coagulation (DIC)
- confirm the diagnosis (see LMWH, p.000)
- do not use **warfarin** because it is ineffective
- for chronic DIC presenting with recurrent thromboses, give dalteparin as for treatment of deep vein thrombosis
- for chronic or acute DIC presenting with hemorrhagic manifestations (e.g. ecchymoses and hematomas), seek specialist advice.

Thrombophlebitis migrans
- do not use **warfarin** because it is ineffective
- generally responds rapidly to small doses, e.g. 2500–5000units SC q.d.
- continue treatment indefinitely[20,21]
- if necessary, titrate dose to maximum allowed according to weight, i.e. 200units/kg.

Overdose
In emergencies, **protamine sulfate** can be used to reverse the effects of dalteparin:
- for each 100units of dalteparin, give 1mg of **protamine sulfate**
- give a maximum of 50mg by IV injection over 10min
- give a further 0.5mg of **protamine sulfate** per 100units of dalteparin after 2–4h if APTT still prolonged.

Note: even with high doses of **protamine sulfate**, the anti-Xa activity of dalteparin is not completely neutralized (maximum reversal ~60–75%).

Supply
Fragmin® (Pharmacia [Pfizer])
Injection (prefilled single dose graduated syringe for subcutaneous injection)
10 000units/ml, 1ml (10 000units) = $ 53.61.
Injection (single dose syringe for subcutaneous injection)
12 500 units/ml, 0.2ml (2500units) = $16.52.
25 000units/ml, 0.2ml (5000units) = $26.81, 0.3ml (7500units) = $40.21.
Injection (multiple dose vial; for subcutaneous injection)
10 000units/ml, 9.5ml (95 000units) = $???.
25 000units/ml, 3.8ml (95 000units) = $ 460.79.

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