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Deligoparin Sodium

USAN

Anticoagulant
Treatment of IBD
LMW Heparin

OP-2000

Sodium salt of depolymerized heparin. The starting material is obtained from porcine intestinal mucosa. The process results in oligosaccharide fragments of heparin of ranging lengths with an average relative molecular mass of about 3200 Da. The degree of sulfation is approximately 2.5 sulfate residues per disaccharide unit

EN: 271271

Abstract

There is accumulating evidence that low-molecular-weight heparins (LMWHs) are safe and effective alternatives to unfractionated heparin and offer practical and therapeutic advantages. Deligoparin sodium (formerly OP-2000) is an ultra LMWH derived from unfractionated heparin by a process of copper-catalyzed free radical cleavage. Due to its extremely low average molecular weight (about 3200 Da), deligoparin has a unique pharmacological profile characterized by high subcutaneous bioavailability (100%) and a greater volume of distribution. The product is currently being developed for the clinical management of inflammatory bowel disease, particularly in ulcerative colitis.

Introduction

Heparin is a very complex glycosaminoglycan composed of alternate sequences of differently sulphated residues of uronic acid (usually α-L-iduronic acid) and α-D-glucosamine linked by α (1-4) bonds. Heparin is polydisperse in chain length and heterogeneous in degree and type of sulphation, with molecular weights varying from 5,000-30,000. Heparin is synthesized endogenously and stored in the basophilic granules of mast cells, which are found in most tissues of mammalian species. The greatest concentrations are found in the liver, lung and intestines (1).

Heparin has numerous activities, the most important being its anticoagulant properties (Fig. 1). Heparin forms a complex with antithrombin III which undergoes configuration changes to become a more rapid-acting inhibitor of thrombin, kallikrein and several activated blood coagulation factors: XIIa, XIa, Xa, IXa and VIII (2) (Fig. 2). Platelet aggregation and activation of coagulation are key events in the development of acute coronary syndromes (3).

Intravenous unfractionated heparin (UFH) has long been used effectively in reducing the risk of death or myocardial infarction in patients with acute coronary syndromes (4), as well as in patients with unstable angina (5). Similarly, conventional treatment of deep vein thrombosis (DVT) has until recently been based on UFH administered by continuous intravenous infusion in a hospital setting (6). Since UFH binds to various plasma proteins, which competes with its binding to antithrombin III, there is dose-response variability in the development of resistance. Moreover, UFH also binds to platelets and inhibits their function, which contributes to its adverse hemorrhagic effects.

There is accumulating evidence that low-molecular-weight heparins (LMWHs) are safe and effective alternatives to UFH and offer practical and therapeutic advantages. Compared to UFH, the improved pharmacological

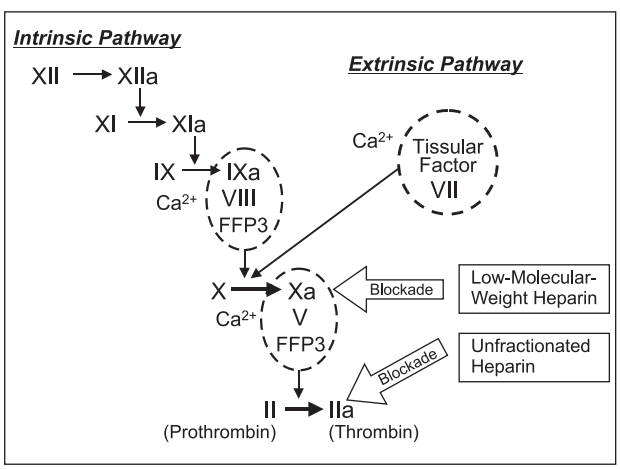

Fig. 1. The coagulation cascade showing the sites of action of unfractionated heparin (preferentially blocks at factor IIa stage) and low-molecular-weight heparin (preferentially blocks at factor Xa stage).

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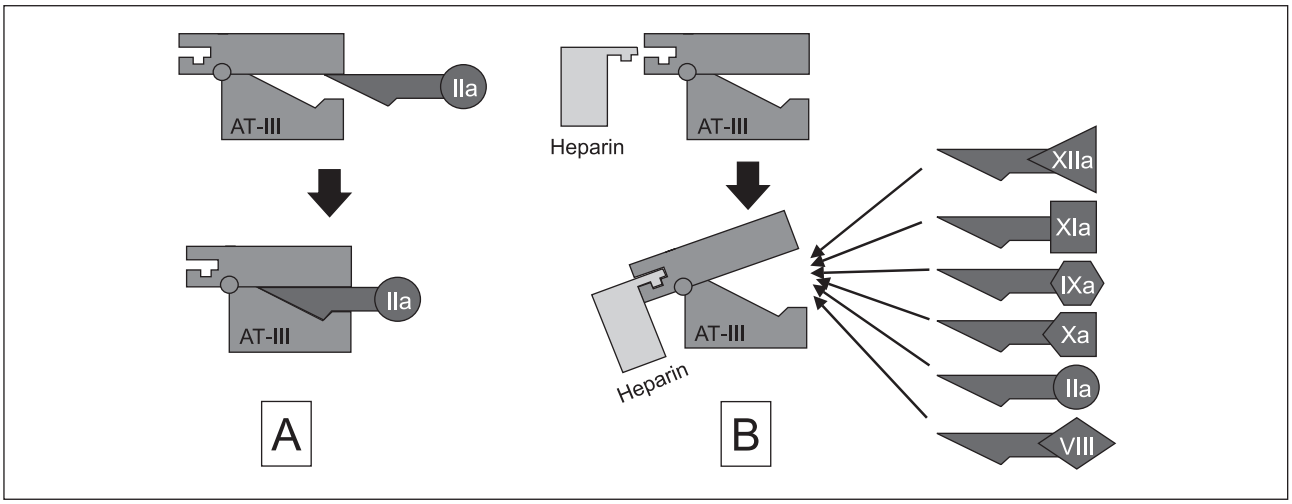

Fig. 2. Schematic representation of the anticoagulant action of heparin. Under normal conditions, antithrombin III binds predominantly to factor IIa (A). Heparin forms a complex with antithrombin III which undergoes configuration changes to become a more rapid-acting inhibitor of factor IIa and several other activated coagulation factors (B).

and pharmacokinetic profile of the LMWHs results in an excellent, predictable dose response together with rapid, effective and stable anticoagulation. The antithrombotic properties are similar to UFH although with fewer adverse effects (7). As a consequence, LMWHs are gaining wider recognition and support not only as an alternative to UFH but also as the standard of care. In addition to their application in acute coronary syndromes, current studies are investigating whether the LMWHs can be used to help control ulcerative colitis by preventing the formation of blood clots and by their antiinflammatory actions.

LMWHs are derived from UFH through either chemical or enzymatic depolymerization. Whereas standard heparin has a molecular weight of 5,000-30,000 Da, the molecular weight of LMWHs ranges from 1,000-10,000 Da, resulting in properties that are distinct from those of traditional heparin. The antithrombotic properties of LMWHs are characterized by a higher ratio of anti-factor Xa to anti-factor IIa activity than UFH. LMWHs also have less affinity for plasma proteins, more predictable dose-response relationships, bind less to platelets and have fewer adverse hemorrhagic effects. LMWHs possess properties which may contribute to a greater antithrombotic effect than UFH. During coagulation, platelets release factor IV which is a potent inhibitor of UFH but not of LMWHs. Furthermore, factor Xa is bound to the platelet membrane and is protected from inhibition by UFH but not by LMWH (2, 8).

In addition to their therapeutic benefits, the economic impact of using LMWHs has been studied in randomized controlled studies, in managed care institutions and in decision models. These studies provide valuable insight into the ways in which LMWHs can be economically attractive despite higher per unit costs compared with UFH. The use of LMWHs has resulted in cost benefits in the treatment of acute DVT, unstable angina and acute coronary syndromes, as well as in prophylaxis against venous thromboembolism (9).

Deligoparin sodium is a novel ultra LMWH that is currently being developed for the clinical management of inflammatory bowel disease, particularly in ulcerative colitis. Due to its extremely low average molecular weight, apparently the lowest of the LMWHs, deligoparin has a unique pharmacological profile.

Pharmacological Actions

Deligoparin has much less anti-factor IIa activity than other LMWHs and UFH, but retains much of their anti-factor Xa activity (about 2/3 and 1/3 of the activity of LMWHs and UFH, respectively). Therefore, deligoparin possesses an extremely high anti-factor Xa/anti-factor IIa ratio compared to other LMWHs and UFH, thus providing a greater degree of antithrombotic activity while significantly reducing anticoagulant effects (10).

A study in experimental and animal models showed that partial neutralization of the anticoagulant and bleeding effect of deligoparin was produced by using heparinase-I. Activated clotting time (ACT) and thromboelastography (TEG) tests were performed to evaluate the anticoagulant effects of deligoparin. A concentration-dependent increase in the ACT and changes in the TEG parameters were noted. The neutralizing effect of heparinase-I was studied at concentrations of 0.05-5.0 U/ml. In experimental models, heparinase-I at a concentration of 2 U/ml completely neutralized the anticoagulant effects of deligoparin (10-100 μg/ml) added to whole blood. In rats, rabbits and primates, 0.25 U/kg of heparinase-I markedly reversed the prolongation of the bleeding time produced by 10 mg/kg of deligoparin. In contrast to heparinase-I, protamine sulfate showed partial neutralization of

deligoparin in these models. These results indicate that neutralization of deligoparin by heparinase-I may be useful during surgical procedures (11).

Clinical Studies

An open-label, randomized study was performed to test the hypothesis that the therapeutic effects of deligoparin in inflammatory bowel disease are attributable to the generation of antiinflammatory mediators such as tissue factor pathway inhibitor (TFPI). A total of 38 healthy subjects aged 18-45 years received deligoparin at doses of 100 or 150 mg/kg s.c. once daily for 8 days. TPFI release and anti-factor Xa activities were measured. Results showed that deligoparin produced a sustained release of TPFI after s.c. administration. The corresponding anti-factor Xa levels were consistent with the TPFI release. These results, therefore, appeared to confirm the hypothesis (12).

The progression of the generation of anti-heparin-platelet factor 4 (AHPF4) antibodies and their functionality were evaluated in plasma samples from 38 healthy subjects administered once-daily deligoparin (100 or 150 mg/kg s.c.) for 8 days. It is known that generation of AHPF4 is associated with both UFH and LMWHs at almost a similar frequency (15-20%) but the prevalence of thrombocytopenia is significantly lower in LMWHs-treated patients. Analysis of plasma samples obtained from the subjects administered deligoparin revealed that AHPF4 antibody titers were present in about 25% of the samples. These antibodies, however, were inert (non-functional/nonpathogenic) and therefore unlikely to elicit thrombocytopenia or pathogenic responses (13, 14).

A further study was performed by the same invetigators to differentiate the prevalence of heparin-induced thrombocytopenia defined by the presence of AHPF4 antibodies utilizing anti-human-Ig specific for various isotypes. Thus, results of the previous study were compared to plasma samples obtained from 111 patients with UFH-treated symptomatic heparin-induced thrombocytopenia and 50 normal subjects. Results indicated that most of the samples, which were of IgG isotypes of AHPF4 in the UFH-treated group, could induce platelet activation response, but this was not observed in the deligoparin-treated or normal plasma group of IgG samples. These observations indicate that patients treated with deligoparin are less likely to be at risk of developing heparin-induced thrombocytopenia (15).

The efficacy, tolerability and safety of deligoparin and standard UFH were compared in 120 hospitalized patients with unstable angina. In this pilot study, patients were randomized to treatment with deligoparin (200 mg i.m. on the first day followed by 150 mg/day) or standard UFH (5000 UI/ml i.v. followed by continuous infusion at an activated partial thromboplastin time-adjusted dosage). In all patients, aspirin (100 mg/day) was administered on the same day as heparin. Nitroglycerin infusions (20-40 cc/h) were administered during the acute phase. Fourteen clinical events (death, acute myocardial infarction, recurrence of angina or urgent revascularization) were reported in the deligoparin group as compared with 25 events in the control group. These findings demonstrated that treatment with deligoparin plus aspirin was more effective than standard UFH plus aspirin during the acute phase of unstable angina. Deligoparin exhibited a better safety and tolerability profile than UFH, and thrombocytopenia and transaminase levels were significantly increased in the UFH-treated group (16).

Deligoparin is being developed for the management of inflammatory bowel disease, particularly in ulcerative colitis. A phase II/III double-blind, placebo-controlled clinical trial to determine the safety and efficacy of deligoparin in patients with active ulcerative colitis is currently under way (17).

Source

Discovered by Opocrin SpA (IT) and licensed to Incara Pharmaceuticals Corp. (US) who is codeveloping the compound with Elan Corporation, plc (IE).

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