One hundred years of Heparin

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Discovery of Heparin

- Discovered by Jay McLean (a second-year medical student at Johns Hopkins University) in 1916
- Isolated the fat-soluble anticoagulant in canine liver

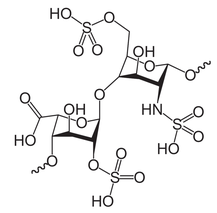
Jay McLean; 1890–1959

Expectations from an Ideal Injectable anticoagulant

1. Wide therapeutic margin
2. No food and drug interaction
3. No adverse effects such as bleeding, alopecia, osteoporosis, or HIT
4. No need for routine blood monitoring
5. Predictable anticoagulant effect
6. Anticoagulant effects can be easily antagonized

Chemical Structure of Heparin

- Chemical Formula: $C_{12}H_{19}NO_{20}S_3$
- Molar Mass: 12,000 – 15,000 grams/mole



Chemical Structure of Heparin: Heterogenous mixture of polysaccharides linked by glycosidic linkages

Mechanism of action of Heparin

- Heparin prevents development of blood clots
- Binds to antithrombin (AT) and augments the anticoagulant potential of antithrombin by thousand fold
- The molecular basis for the anticoagulant action of heparin lies in its ability to bind to and enhance the inhibitory activity of the plasma protein antithrombin against several serine proteases of the coagulation system, most importantly factors IIa (thrombin), Xa and IXa

Uses of Heparin

- Used to treat and prevent blood clots in the veins, arteries, or lung.
- Used before surgery to reduce the risk of blood clots

Formulations of Heparin

Unfractionated Heparin (UFH)

- Used in surgeries, must be delivered through I.V. injection

Low Molecular Weight Heparin (LMWH, Lovenox)

- Works similarly to Heparin, it produces its primary anticoagulant effect by activating Antithrombin
- Less potent compared to unfractionated heparin
- More predictable anticoagulant effect due to less binding to plasma proteins
- Less incidence of HIT
- Can be administered subcutaneously, twice a day dosage
- Longer half-life compared to UFH

Side effects / Toxicity of Heparin

- Bleeding and easy bruising
- Pain, redness, warmth, irritation, or skin changes at the injection site
- Itching
- Bluish-colored skin
- Osteoporosis: bones become brittle and weak: Result of long-term Heparin treatment
- Alopecia: partial or complete

Side effects / Toxicity of Heparin (cont'd)

- Heparin-induced thrombocytopenia (HIT)
  - o Deficiency of platelets in the blood
  - o Heparin binds to platelets, causing activation and release of platelet factor 4
  - o Heparin complexes PF4 and stimulates the formation of antibodies that cause heparin-induced thrombocytopenia

Gangrenous changes as a result of HIT

Antidote of Heparin

- Heparin has a short half-life of about 6 hours
- Simply stopping the administration of heparin may be enough to reverse some adverse effects without needing the antidote for heparin
- Protamine sulfate, a compound derived from purified fish sperm

Summary and Conclusion

1. Heparin, though 100 years old, is still being used widely
2. For the most part, fits the definition of an ideal anticoagulant agent
3. More work is needed to reach the goal of an ideal anticoagulant agent

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