The history of anticoagulation

Mike Greaves [1949-]
University of Aberdeen
Disclosure

• I have avoided financial support from the pharmaceutical industry for around 7 years
The history of heparin

• 1916  Heparin isolated from dog liver
TWO NEW FACTORS IN BLOOD COAGULATION—HEPARIN AND PRO-ANTITHROMBIN

W. H. HOWELL AND EMMETT HOLT
From the Physiological Laboratory of the Johns Hopkins University
Received for publication October 17, 1918

A survey of the results of recent work indicates that at least six different substances are concerned in one way or another in the process of blood coagulation; namely, fibrinogen, thrombin, prothrombin, calcium, antithrombin and the so-called zymoplastic or thromboplastic substances furnished by the body cells in general, including the blood corpuscles. With regard to the last mentioned factor satisfactory

THE PURIFICATION OF HEPARIN AND ITS PRESENCE IN BLOOD

W. H. HOWELL
From the School of Hygiene and Public Health, Johns Hopkins University
Received for publication November 28, 1924

In 1918 in a paper by Howell and Holt (1) a substance was described under the name of heparin which has a marked effect in preventing the coagulation of blood. The nature of its effect upon the processes of coagulation was investigated in some detail. Subsequently in a brief com-
The history of heparin

- 1916  Heparin isolated from dog liver
- 1927-30’s Used in physiological experiments
- 1934 Purified as a crystalline barium salt
A note on the use of heparin in blood transfusion

Mason EC

*J Lab Clin Med* 1924-5

• ‘Heparin might be effective against certain kinds of thrombosis, considering the thrombosis as a kind of intravascular clotting of the blood’
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- 1938 Administered for CRVO
- 1940 Administered in vascular surgery
- 1941 Administered to treat arterial/venous thromboembolism
The use of heparin in thrombosis

Murray GDW, Best CH
Annals of Surgery August 1938

• ‘Neither in experimental animals nor in human beings, when the heparin has worn off, has there been any demonstrable change in the blood. The clotting time does not become shorter’
The use of heparin in thrombosis

Murray GDW, Best CH
Annals of Surgery August 1938

• ‘In patients whose clotting time has been raised to 20 minutes the effect has completely disappeared in an hour. This knowledge was comforting in one patient who had been heparinised for 4 weeks for phlebitis and who developed symptoms of re-activation of an old duodenal ulcer and a haemorrhage. With the discontinuance of heparin the bleeding ceased and the patient recovered.’
Heparin and Thrombosis

C H Best, Professor of Physiology, Toronto

*Harvey Lecture, November 28th, 1940*

- ‘The effect of a given dose of heparin on the clotting time varies from individual to individual, Crafoord has observed clinically that the curve changes in the same individual after operation’
The use of heparin in thrombosis

Murray GDW, Best CH
Annals of Surgery August 1938

• ‘Heparin in its purified form is nontoxic, both experimentally and in human beings
• In lesions where intravascular clotting is a problem, heparin may be useful
• Experimentally, heparin will prevent thrombosis in blood vessels; clinical results thus far obtained do not contradict this conclusion
• As all this work is in the experimental stage, final conclusions cannot as yet be drawn’
The use of heparin in thrombosis

Murray GDW, Best CH
Annals of Surgery August 1938

Dr Frederic W Bancroft [New York] responded:
• ‘I am impressed with the marvellous work that has been done in the use of heparin. There is no doubt that anticoagulants are an adjuvant in the treatment of thrombosis and embolism’
The use of heparin in thrombosis

Murray GDW, Best CH
Annals of Surgery August 1938

And:

‘The disadvantage, it seems to me, is that heparin has a very short duration of action and continuous infusion has to be kept up for 72-120 hours. This amounts to about $80 per patient which does not entirely include the discomfort to the patient and increased nursing cost’
The use of heparin in thrombosis

*Murray GDW, Best CH*

*Annals of Surgery August 1938*

Dr Howard Lilienthal [New York] responded:

- ‘I have used leeches for a long time, and I have achieved absolutely amazing results’
- ‘Of course heparin is not yet generally available. In the meantime, I certainly would recommend in any case of angina where the disease is supposed to be due to thrombosis, that leeches should be applied. You can use as many as 10 or 15. They do not need to be put on or near the heart’
Indications:

- Postoperative embolism which was not immediately fatal $n=24$
- Arterial embolectomy $n=3$
- Luetic thrombosis of posterior tibial artery $n=1$
- Hemiplegia from common carotid artery occlusion $n=1$
Methods:

- Liquaemin [Roche-Organon] or Solution of Heparin [Connaught Laboratories, University of Toronto]

- Clotting time 3x normal [15 mins. by capillary method and 15-30 mins. by test tube method]
HEPARIN ADMINISTRATION
Methods and Results in Thirty Cases
*Annals of Surgery June 1941*

Results:

• ‘Satisfactory in a general way’
• 2 deaths from recurrent pulmonary embolism/cardiac failure
• Circulation restored in 2 of 3 embolectomies
• Hemiplegia was not favourably affected
• 4 instances of haemorrhage from the operative wound
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- 1960 First randomised trial published in VTE
Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial

Barritt DW, Jordan SC Lancet 1960, 1:1309-12

- Pulmonary embolism diagnosed by clinical features, ECG and CXR
- Randomised by envelope
- Heparin IV 10,000U 6 hourly for 6 doses + nicoumalone for 14 days
- Bed rest for 10 days
Anticoagulant drugs in the treatment of pulmonary embolism: a controlled trial
Barritt DW, Jordan SC Lancet 1960, 1:1309-12

• Of 19 untreated 5 died of PE and 5 had non-fatal recurrence
• Of 16 treated none died of PE and there was no recurrence. 1 died of pneumonia and b bleeding ulcer
• p<0.05
• Of a further 38 treated there was no fatal PE and 1 non-fatal recurrence
• The existing evidence ‘seemed decisive enough to make reasonable the view that in this condition neglect of anticoagulant treatment was neglect of the patient’

• The cause of the controlled clinical trial is a good one, in season, but we fear it may be damaged by such intemperate enthusiasm for it as has been shown in this instance by Dr Barritt and Dr Jordan’
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- 1980’s LMWH introduced
Low Molecular Weight Heparins versus Unfractionated Heparin

- 100% bioavailability
- Predictable dose response
- Longer t/2
- Once daily dosing
- No need for monitoring
- Lower incidence of thrombocytopenia and osteoporosis

- Accumulate in renal failure (GFR<15)
- Partial response to protamine
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- 1980’s LMWH introduced
- 1992 Randomised trials demonstrated efficacy of weight-adjusted LMWH in treatment of VTE
LMWH versus UFH

- Treatment of DVT/PE: Equivalent
- VTE prophylaxis in major orthopaedic surgery: Equivalent
- ACS: Both reduce risk of MI or death additional to aspirin. LMWH less MI, bleeding and HIT. LMWH superior
Fondaparinux

- Chemical synthesis-no animal source.
- No batch-to-batch variation
- Plasma peak 2hrs
- t/2 17hrs
- Renal excretion
Fondaparinux: current status

- Licensed for prevention of VTE in medical patients, general surgery and high risk orthopaedic surgery
- Licensed for treatment of DVT and PE
- Licensed for treatment of ACS, NSTEMI and STEMI
Idraparinux & idrabiotaiparinux

- T1/2 80 hours
- Idrabiotaiparinux has a biotin moiety which allows reversal by avidin
The history of warfarin

• Early C20th Sweet clover introduced as cattle feed in USA

• 1920’s Bleeding and abortions noted in cattle
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- 1997-Optimal duration of anticoagulation investigated
Duration of oral anticoagulation after VTE

- 6 months better than 6 weeks
  *Schulman S Wien Med Wochenshr 1999, 149:66-9*

- 3 months equivalent to 6 months
  *Campbell IA et al BMJ 2007, 334:674;
  Pinede L et al Circulation 2001, 103:2453-60*
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- 1998- Near-patient testing, self-testing and self-dosing introduced
- 2007 FDA supports pharmacogenomic information for more precise initial dosing
Warfarin: Less than ideal

- Delayed onset of action
- Steep dose-response curve
- Variable sensitivity
  - Dietary vitamin K

- CYP 2C9 and VKORC-1 polymorphisms

- Dosing unpredictable
- Interactions
- Need to monitor

- Embryopathy/foetopathy
Warfarin: Advantages

• Long experience
• Non-haemorrhagic toxicity minimal
• Reversibility
The ideal anticoagulant

- Active by the oral route
- Once daily dosing
- Rapid anticoagulant effect
- Predictable dose-response relationship
- No interactions
- No requirement for laboratory monitoring
- No increased bleeding
- Rapidly-acting antidote available
- Low cost
<table>
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<th>Fondaparinux</th>
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Modern history

• 2003- Trials of an oral direct thrombin inhibitor reported

• 2007-2011 Trials of next generation oral direct thrombin inhibitor and direct factor Xa inhibitors reported
New Antithrombotics

Intrinsic → TF pathway

Xa

Rivaroxaban
Apixaban
Edoxaban, Betrixoban, YM150, TAK-442

IIa

[Lepirudin]
[Bivalirudin]
[Argatroban]

[Dabigatran etexilate]
Ximelagatran

- Rapid oral absorption and bioconversion to melagatran - $C_{\text{max}}$ at \(~2\) to \(3\) h
- Bioavailability \(~20\%\)
- Renal excretion \(~80\%\)
- Not bound to plasma proteins
- Half-life of melagatran
  - \(3\) h in young healthy subjects
  - \(4\) to \(5\) h in patients
The Pharmacokinetics and Pharmacodynamics of Ximelagatran – Conclusions

- Stable and reproducible pharmacokinetic characteristics
- No food or alcohol interaction
- No drug interactions mediated by P450 metabolism
- Predictable profile supported fixed dosing with no coagulation monitoring
Ximelagatran in 2006

• Approved in 12 countries

• Withdrawn, and further development abandoned by AstraZeneca due to serious hepatic toxicity and possible cardiovascular events
Principal studies

Dabigaran etexilate

RE-NOVATE  THR
RE-MODEL  TKR
RE-MOBILIZE  TKR [USA]
RE-COVER  ACUTE VTE
RE-LY  ATRIAL FIBRILLATION

Rivaroxaban

RECORD 1-4  THR/TKR
EINSTEIN  ACUTE VTE
ROCKET-AF  ATRIAL FIBRILLATION
[MAGELLAN  MEDICAL IN-PATIENTS]

Apixaban

ADVANCE  THR
APPRAISE  ACS*
AVERROES  ATRIAL FIBRILLATION*
[ARISTOTLE  ATRIAL FIBRILLATION]
• Dabigatran etexilate and Rivaroxaban licensed in the UK and over 70 other countries for thromboprophylaxis in orthopaedic surgery
• Dabigatran etexilate approved for atrial fibrillation in the USA
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Concerns

• Cost in long term use
• Use in high risk patients eg. Renal impairment, co-medications
• Management of interventions
• Management of acute bleeding
• Compliance