THE NORTHERN HOSPITAL

RIVAROXABAN TOXICITY

"Heracles at the Feet of Omphale", oil on canvas, 1856, Gustave Moreau. Omphale wears the Lion skin headdress and cloke Heracles gained in his "First Labour".

Zeus was overjoyed when his son was born, he wanted him to be a great hero and protector of the mortals, however his wife Hera always loathed any of the offspring of her husband's - all too frequent - "liaisons". She would do everything in her power to hinder, and hopefully destroy them, and her loathing applied most especially to the great Heracles. When Heracles had grown to manhood, he was given the hand in marriage of Megara, the beautiful daughter of the king of Thebes, Creon. Heracles had many children with Megara, but then Hera in a rage of jealousy cast a powerful spell over him that sent him into a paranoid rage. Thinking he was surrounded by enemies on all sides he slew all of his children. When he realized what he had done he was inconsolable and went to the Oracle of Delphi to seek a means of penance and atonement. The hero was ordered to go into the service of King Eurystheus of Mycenae, as a common slave. The evil and dishonorable King Eurystheus was in fact a protégé of Hera, and so it seems that Hera herself had malignly influenced the sacred Oracle! Hera ordered King Eurystheus, to send Heracles on a suicide mission. Eurystheus, in his extreme eagerness to please Hera, did better than that - he ordered Heracles to ten suicide missions - which he later, extended to twelve, by trickery that showed a sick genius for manipulating contract law, which would have made his fortune in a later era! And so it was that Heracles was condemned to his famous twelve labours.

The very first labour that Heracles had to endure was to kill the great Lion of Nemea. King Eurystheus, not understanding how immensely strong Heracles was, remained snug in the thought that he had sent the hero to certain death with his very first labour. Nemea was region of Greece that lay between Argos and Corinth. No traveler between the two cites was safe, because this was the territory that belonged to the great lion. It was the largest and most ferocious lion of all. Its hide was so tough it resisted not only hurled stones and metal weapons, but even the arrows of Apollo himself. Heracles discovered the lair of the lion and immediately he went to attack it. But to his horror his arrows were completely useless against it. He could not even bring the creature down with his immense club. Heracles was reduced to tackling the lion with his bare hands. A desperate life and death struggle ensued, and eventually Heracles' enormous strength won out, and he managed to strangle the lion and break its neck. To prove his victory he took the lion's body back to King Eurystheus and tossed it at his feet. King Eurystheus was so startled and now so afraid of Heracles that he forbad him to enter the city of Mycenae again. Using the beast's own claws Heracles cut off its hide and fashioned a great headdress and cloak for himself. From now on he would wear it as his near-invulnerable armour. In subsequent ages, heroes such as Alexander the Great would emulate Heracles by having headdresses and cloaks fashioned from lion skins and the Emperor Commodus would go to such lengths as entering the Coliseum dressed in the same and armed with a club to do battle with lions. But Zeus, though he was pleased for his son's success was also distressed that so noble a beast had been slain. He placed the lion amoung the stars in a position of great honour, as one of the twelve Constellations of the Zodiac, in the region where Apollo drove the Sun across the sky during the day, and Selene drove the Moon across it at night, followed in their wake by all the planets.

After many adventures Heracles managed to complete all twelve of his labours successfully. Much to the annoyance of Hera, Zeus declared that his son had fulfilled all his tasks of atonement, and so now was free from the service of King Eurystheus. Understandably Megara wanted a divorce from Heracles and he had to admit that this

was justified. He then went his own way again and had many other adventures, until one day he in a dispute over the his prize for winning an archery contest he killed Iphitus the son of the King of Oeschalia. Again he would seek atonement at the Oracle of Delphi, but his time the Pythia, (priestess of the Oracle) who was terrified of Heracles refused to have anything to do with him, and would not allow him to enter. Heracles, always far too quick to anger, flew into a terrible rage and threatened to tear the Oracle down with his bare hands. This threatened sacrilege against the gods, angered Apollo who immediately challenged Heracles to a fight to the death. The encounter was only stopped at the last minute by a furious Zeus, who sent a thunderbolt to separate his two sons. By this time Zeus had lost all patience with his son, and decided that he must be punished. He sent him into slavery again, but this time under the most humiliating circumstances to teach him a lesson he would not soon forget. He would go into the service of a woman, the arrogant Queen Omphale. She would force Heracles to sit with the women of her court and to do female chores, such as spinning and weaving. She even made Heracles dress in women's clothing and wear flowered garlands in his hair. To humiliate him even further Queen Omphale would dress herself up in Heracles' own lion skin, as if to take the place of a man and stand over him while he weaved, all the while threatening him with his very own club. But amidst all of this intense psycho-sexual cross-dressing, Omphale and Heracles fell passionately in love! Heracles gave Omphale a son and then commenced to get rid of all her enemies by killing them one by one - not exactly the plan Zeus had in mind when he sent his son into the service of Queen Omphale! This situation became so horribly complex that Zeus, finally had had enough, and suddenly decreed that his son had competed quite enough "atonement" - his punishment was now at an end and he should leave Queen Omphale's "service" immediately!

Our new wonder drug, Rivaroxaban, acts like the marvellous hide of the Nemean lion! It forms an impenetrable barrier by specifically fending off the factor Xa arrows of a hostile coagulation cascade - all remains well. However the situation can become horribly complex when things do not go according to the intended plan! A knock on the head leaves us with a perplexing problem. The marvellous protective hide has suddenly been turned against us!

Left: Silver tetradrachm of Alexander the Great, Minted at Babylon. c. 323 B.C. Alexander as Heracles with lion skin headdress, (collection of Alexander Hayes).

RIVAROXABAN TOXICITY

Introduction

Rivaroxaban is a drug from a novel class of non-coumarin anticoagulants, (loosely known as **NOACs** or "**N**ew **O**ral **A**nti**c**oagulants") which is an orally active **direct Factor Xa inhibitor.**

It offers some significant therapeutic advantages over warfarin, but is more problematic with respect to its haemorrhagic complications.

Most NOAC related bleeding occurs in the context of therapeutic administration, often as a result of drug interactions, renal failure or significant underlying pathology predisposing to bleeding complications.

Clinical experience with deliberate self-poisoning with NOACs is limited.

Assessment and management is further complicated by the poor correlation of anticoagulant activity with classic coagulation tests and the lack of reliable strategies to reverse anticoagulation.

Unlike dabigatran, rivaroxaban does not currently have a specific reversal agent, although work continues on the "decoy" agent **Andexanet Alfa.**

See also separate document on:

- **Rivaroxaban (in Drugs folder)**
- **Andexanet Alfa (in Drugs folder)**

Preparations

Rivaroxaban as:

Tablets:

- 10, 15, 20 mg.

Toxicology

Rivaroxaban is an orally active **direct Factor Xa inhibitor.**

This action is in contrast to **warfarin**, which inhibits normal vitamin K metabolism, which is a co-factor that is required for the synthesis of the vitamin K dependent coagulation factors, II, VII, IX and X, (as well as proteins C and S).

It is also in contrast to the heparins which are direct Antithrombin III *activators*, (which inhibit thrombin).

Pharmacology

Advantages compared to warfarin:

- Fast onset of action:

  Onset of action is rapid, (within 2 hours) thereby potentially negating the need for initial treatment with a rapidly acting injectable anticoagulant.

- Fast offset of action:

Anticoagulant effect lasts around 12 hours, which is much shorter than warfarin, (48-72 hours). This means toxic effects, if they occur, will not be as long lasting.

- Predictable response:

  Anticoagulation response is sufficiently predictable that routine coagulation monitoring is not required - therefore avoids the need for repeated blood tests to monitor activity, and adjust dosages that warfarin therapy requires.

Disadvantages compared to warfarin:

- The routine coagulation monitoring tests (APTT / PT / INR) are *not* indicative of the anticoagulant effect of Rivaroxaban

- There is no current specific antidote for drug reversal, (unlike warfarin which has vitamin K and Prothrombin X as its antidotes or heparin which has protamine as its antidote) which makes management of life threatening bleeding problematic.

Rivaroxaban is an orally active **direct Factor Xa inhibitor** and not a clotting factor depleting agent, as is the case with warfarin. As such the administration of blood clotting products will not be wholly effective in reversing its effects.

Pharmacokinetics

Absorption:

- Rivaroxaban is given orally.

- Bioavailability is 80 - 100 %

- Peak concentrations are reached 3-4 hours following ingestion.

Distribution:

- Plasma protein binding is high, at around 95%.

- The volume of distribution is moderate at about 50 liters.

Metabolism and excretion:

- About 1/3 is renally excreted unchanged.
- About 2/3 is metabolised by the liver:
    - ♥ Rivaroxaban is metabolized by the CYP- 3A4 enzyme.
- Half-life is generally around 5 - 9 hours
    - ♥ In the elderly however it is around 11-13 hours.
    - ♥ Note that single daily doses of rivaroxaban prolong clotting parameters up to 24 hours, irrespective of the short half-life

Risk assessment

The NOACs as a group are potent anticoagulant agents and overdose with any amount could result in clinically significant bleeding.

Classic coagulation tests correlate **poorly** with the anticoagulant effect of these agents and have a *limited* role in refining the risk assessment.

There are no published reports of NOAC overdose in children but accidental ingestion of just 1 or 2 tablets will produce significant anticoagulation and an undefined risk of bleeding.

Specific risk factors for adverse events with rivaroxaban include:

- Age older than 75 years
- Low body weight (less than 50kg)
- Moderate or severe renal impairment (Creatinine Clearance < 50mL/min).

Clinical assessment

Overdose of the NOACs does not cause clinical manifestations in themselves, unless complicated by bleeding episodes.

In the absence of co-ingestants, the presence of altered mental status or seizures should be considered to be due to intracranial bleeding until proven otherwise.

Important points of history:

1. Note the dose of the last rivaroxaban tablet

2. Note the time of the last rivaroxaban tablet.

3. Note the indication for treatment with rivaroxaban.

Classification of bleeding severity:

Bleeding complications may be classified (somewhat arbitrarily) as:

Mild:

- Local soft tissue hematomas
- Bleeding from minor wounds to non-life threatening regions.
- Bruising
- Gingival bleeding
- Epistaxis
- Haematuria.

Moderate to severe:

- Reduction in Hb of 20gm/L
- Transfusion of 2 units of RBCs
- Bleeding into critical regions:

  These may include:

  - ♥ Intraocular
  - ♥ Intracranial
  - ♥ Intrapulmonary
  - ♥ Pericardial space
  - ♥ GIT
  - ♥ Retroperitoneum
  - ♥ Peri or Intraspinal
  - ♥ Major muscle group with resulting compartment syndrome.

Life-threatening:

This is really a matter of extent, with uncontrolled *progression* of any of the above scenarios of moderate to severe bleeding, that results in worsening symptoms

Note that the above classification is a generalization only and other factors such as co-morbidities will also come into consideration in any particular individual patient.

Investigations

In the patient with significant bleeding:

1. FBE:
    - Hb / Platelets in particular.
2. Coagulation profile:

Parameter	**Dabigatran effect (Thrombin inhibitor)**	**Factor Xa Inhibitors (Rivaroxaban/ Apixaban)**
INR	Mildly prolonged	Variable
aPTT	Prolonged but with poor correlation with drug concentrations. aPTT > 90 seconds *suggests* a high drug level. Normal aPTT suggests minimal drug is present.	Variable
Thrombin Clotting Time (TT, TCT)	Very sensitive Normal values exclude the presence of drug. Exceeds measurement times of coagulometer at high concentrations.	Not useful

Haemoclot assay (dilute thrombin time)	Useful to derive levels	Not useful
Factor IIa (i.e. thrombin) assay	Best correlation with bleeding risk.	Not useful
Factor Xa assay	Not useful	Good correlation with levels.

Notes:

- For dabigatran:
  - ♥ A combination of INR > 2 and aPTT > 90 seconds *suggests* high plasma levels of dabigatran.
  - ♥ Normal INR and normal aPTT *suggest* low plasma levels of dabigatran.
- For factor Xa inhibitors:
  - ♥ A combination of normal PT and aPTT *suggests* low plasma levels of apixaban and rivaroxaban.

Factor IIa, Xa and Haemoclot assays are only currently available in a few hospitals and can take more **than 24 hours to perform.**

Thromboelastography is effective at measuring anticoagulant activity of NOACs but specific assays have not yet been developed

4. U&Es/ glucose

5. Calcium level

6. Blood group and hold or Cross match as clinically indicated.

Management

Clinical experience in the setting of acute overdose as well as bleeding whilst on normal therapy is limited and so there should be close consultation with a Clinical Toxicologists and/ or Haematologist.

Acute deliberate overdose with dabigatran:

1. Oral charcoal:

    - This may be given in cooperative patients and without airway concerns, within **4 hours** of ingestion.

2. Procoagulant blood products may be considered (see below)

3 Andexanet alfa:

    - **This is an antidote under development, but is not yet currently available for clinical use.**

Note that hemodialysis is *not* useful for rivaroxaban (or Apixaban) overdose or toxicity (in contrast to dabigatran where it may be useful).

Significant bleeding whilst taking therapeutic rivaroxaban:

As a *general* guide:

For Mild Bleeding:

- Stop rivaroxaban therapy:

  Anticoagulant should be ceased at least temporarily in all patients presenting with significant bleeding.

  The timing of recommencement will be influenced by:

  - ♥ The severity of the bleeding event
  - ♥ The presence of ongoing risk factors for bleeding (e.g. anatomical lesions, persisting renal dysfunction).
  - ♥ The initial indication for anticoagulant therapy.

- Hydration:

  - ♥ Adequate hydration should be maintained to enhance renal clearance of rivaroxaban

- Local compression measures where relevant

- Close observation/ monitoring

For Moderate to Severe Bleeding to Life Threatening Bleeding :

Above measures plus:

- Oral charcoal:
    - ♥ May be given, if the last dose of rivaroxaban was < 2 hours and there are no concerns about the airway.
- IV fluid resuscitation:
    - ♥ Apart from volume resuscitation a good urine output is also useful as rivaroxaban is partly renally excreted.
- RBCs as clinically required.
- Consider platelet transfusion:
    - ♥ If levels are less than 50 x 10^9/ L or the patient is on an anti-platelet agent.

Consider the use of one of the following haemostatic agents if bleeding continues and becomes life-threatening:

- **Prothrombinex-VF**: [3]
    - ♥ This is possibly the best current option, till specific antidotes become available.
    - ♥ Give 50 U/kg IV, (or 8 x 500 unit vials for an average 80kg patient).
    - ♥ This may be repeated following consultation with Haematology

Or

- **FEIBA:**

  FEIBA is an Anti-Inhibitor Coagulant Complex usually indicated for use in haemophilia A and B patients with inhibitors.

  It contains Factors II, IX, and X, mainly non-activated, and Factor VII mainly in the activated form. The product contains approximately equal unitages of Factor VIII inhibitor bypassing activity and Prothrombin Complex Factors. In addition, 1- 6 units of Factor VIII coagulant antigen (FVIII C:Ag) per mL are present. [4]

    - ♥ Give 50 IU/kg

Or

- Anti-fibrinolytic agent:

- ♥ IV bolus; Tranexamic acid 15-30mg/kg

Then consider:

- ♥ Continuous infusion Tranexamic acid at 1 mg/kg/hour.

Additionally correct the *underlying* cause of bleeding , where possible.

Note that there is *no* evidence that administration of coagulation factors in the *absence* of bleeding has any beneficial effect. Indeed the administration of coagulation factors in the *absence* of significant bleeding is associated with a risk of *thromboembolic* events.

Disposition:

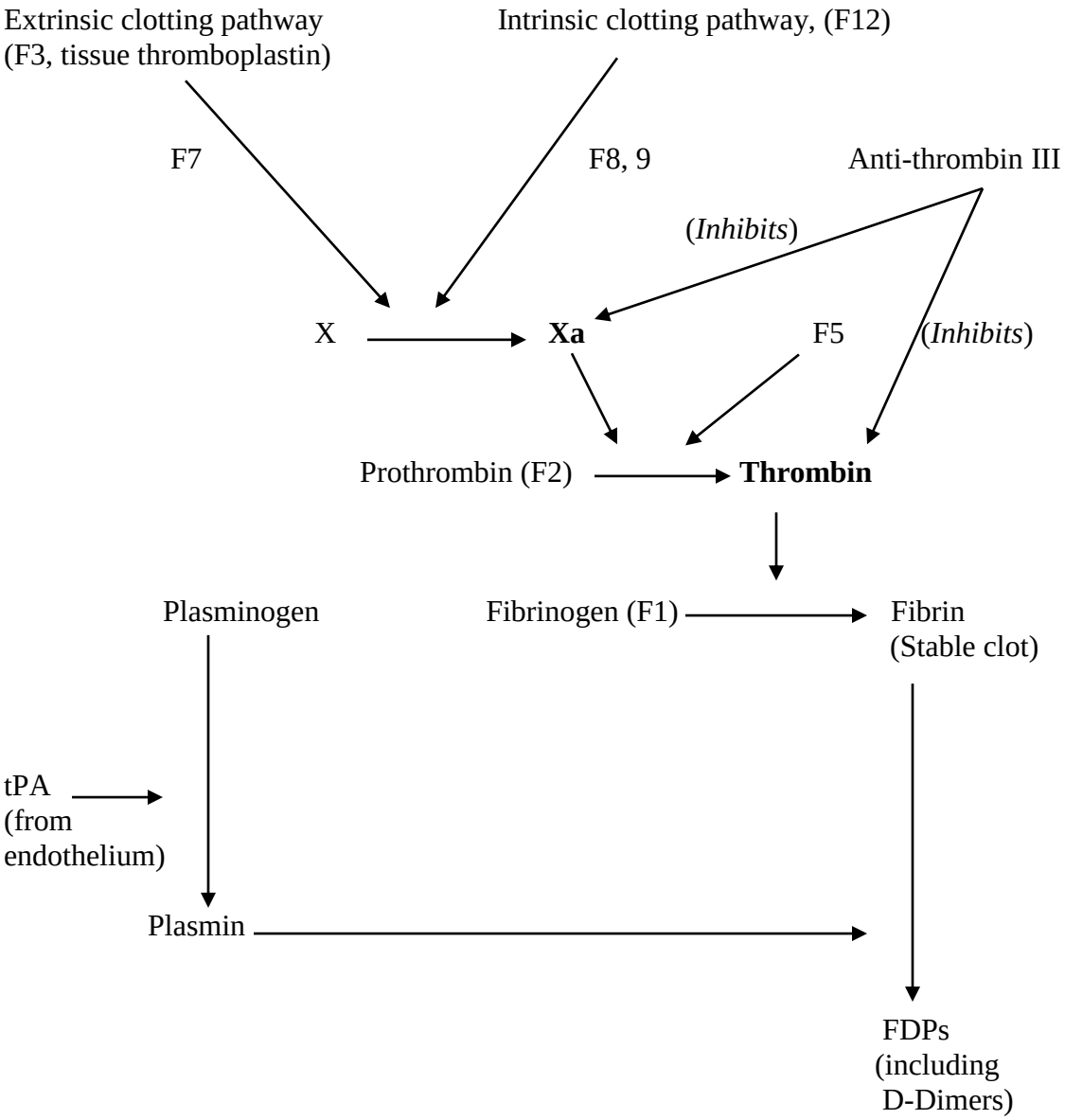
All patients who overdose on NOACs must be admitted to hospital for observation and serial coagulation studies until these are normalised.

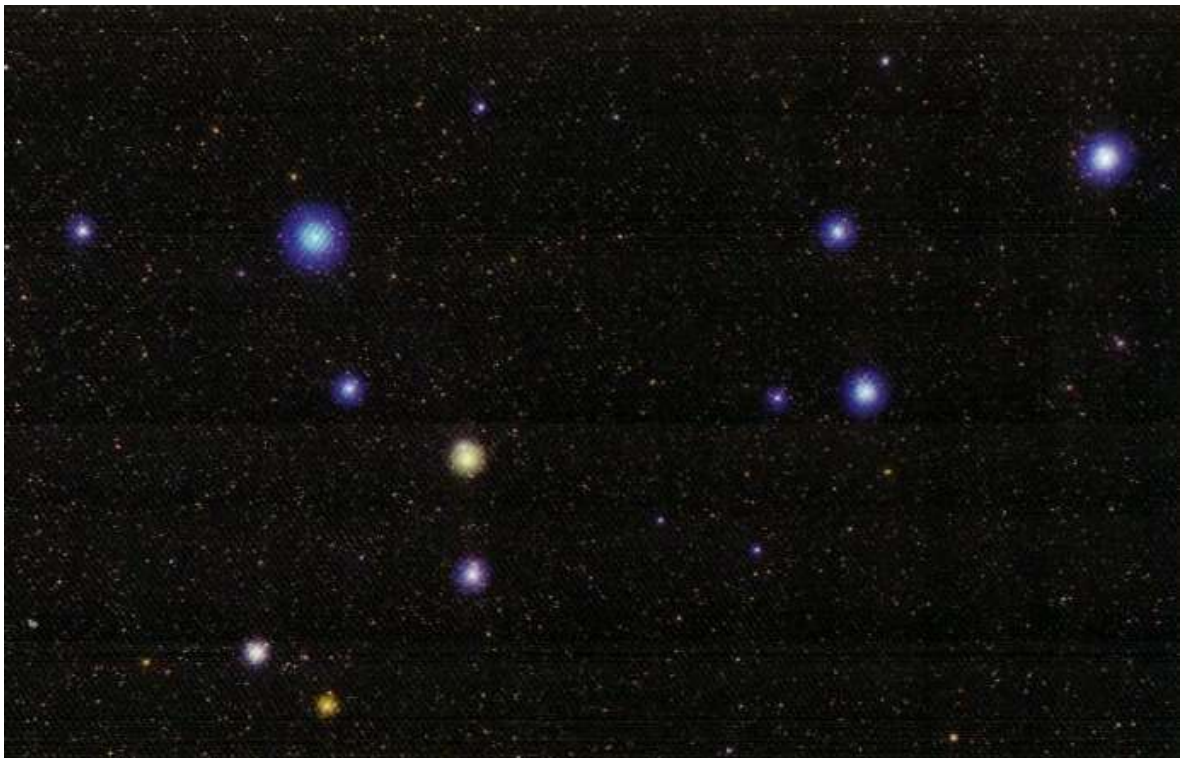
All patients with NOAC related bleeding are admitted to hospital for active treatment as above.

Following factor Xa inhibitor overdose, patients are medically cleared if the PT and aPTT remain normal at 12 hours post ingestion.

Appendix 1

The coagulation cascade and fibrinolytic system:





Constellation of Leo the Lion, (Southern Hemisphere) showing the sickle and the triangle asterisms.

References

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3. Mike Makris, **Prothrombin Complex Concentrate (PCC)** for Non-Vitamin K Oral Anticoagulant (NOAC) reversal: Good enough for now? Journal of Thrombosis and Haemostasis. (Pending: doi: 10.1111/jth.12667)

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