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Stroke: a Bleeding Dilemma

60 Second Summary

The following article contains some thoughts on difficult clinical decisions that I have encountered in the therapeutic management of acute ischaemic stroke. It is intended to be educational but not comprehensive. The important message I feel is to be aware of the evidence as much as possible and use the clinical skills you have learned to help with difficult scenarios and remember that with care treatment is more likely to do good than not.

Introduction:

The treatment of acute ischaemic stroke (AIS) is well established since the introduction of the National Clinical Programme for Stroke (NCPS) in 2010. Moreover, in terms of acute AIS it is moving very much in the direction taken in cardiology with primary percutaneous coronary intervention (PCI) recognising that the definitive treatment of AIS is to remove the clot. However with regard to acute assessment and treatment the focus is still on thrombolysis and the need for a well organised pathway which facilitates decision making.

It is the consequences of getting this decision wrong and causing a fatal brain haemorrhage which attracts a lot of attention to the treatment of acute stroke. There is much to be gained and much at stake and this can result in hesitation and delay regarding decision making. It is important to remember therefore that this treatment is more likely to be beneficial than not.

In relation to both treatment and prevention there are many drugs involved and it will help to have knowledge of their indications, how they work and interact with each other and with other agents. It is well worth having knowledge of haemostasis and the clotting cascade and the mechanisms with which the circulatory system responds to injury. Of course, it is worth remembering that bleeding results for iatrogenic reasons like over or inappropriate use of antithrombotic drugs.

The formation of a clot in the body is a complex process that involves multiple substances called clotting factors that work together in a coagulation cascade. Anticoagulent agents exert effects at various sites in this pathway (Figure 1). Tissue plasminogen activator (tPA), currently licenced to treat ischaemic stroke (IS), injected into artery or vein will bind to fibrin in the thrombus and initiates fibrinolysis therefore dissolving the clot and restoring blood flow. Getting the timing right i.e. within the recommended time window of 4.5 hours means that this 'clot busting' drug will have the best chance of dissolving a clot before it becomes established and before significant damage is done to the brain and where benefits still outweigh the risk of bleeding.

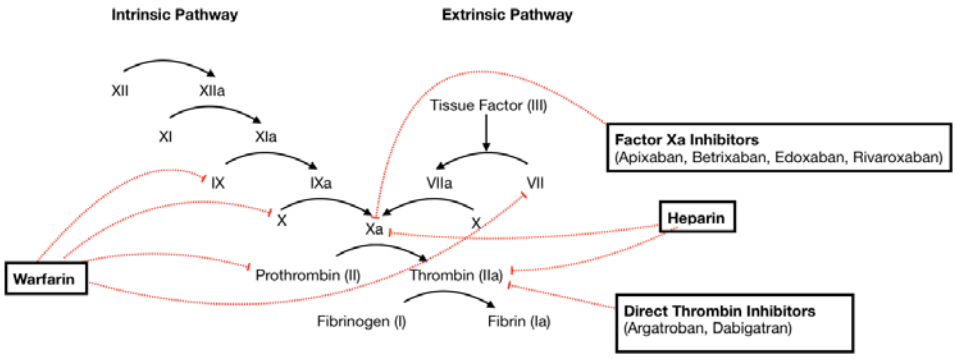

Figure 1: Major classes of anticoagulants include warfarin, heparin, direct thrombin inhibitors, and factors Xa inhibitors. This figure illustrates the sites within the coagulation cascade at which these major classes of anticoagulant exert their effects.

Reflection - Is this area relevant to my practice? What is your existing knowledge of the subject area? Can you identify any knowledge gaps in the topic area?

Planning - Will this article satisfy those knowledge gaps or will more reading be required? What resources are available?

Action - After reading the article complete the summary questions at www.pharmacynewsireland.com/cpdtraining and record your learning for future use and assessment in your personal log.

Evaluation - How will you put your learning into practice?

Have I identified further learning needs?

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Unfractionated heparin (UFH) is a naturally occurring glycosaminoglycan and low molecular weight heparin (LMWH) is UFH, which has undergone fractionation in order to make its pharmacodynamics more predictable. It acts 'indirectly' at various sites in the coagulation cascade preventing the formation of clots and extension of existing clots. Unlike tPA it does not break down clots that have already formed. It allows the body's natural clot lysis mechanisms to work normally to break down clots that have formed. Its indications include prophylaxis and treatment of thromboembolis disease, for example, deep venous thrombosis (DVT) and pulmonary embolus (PE). Warfarin is a vitamin K antagonist (VKA) which is a synthetic anticoagulant that acts by inhibiting vitamin K-dependent coagulation Factors II, VII, IX and X.

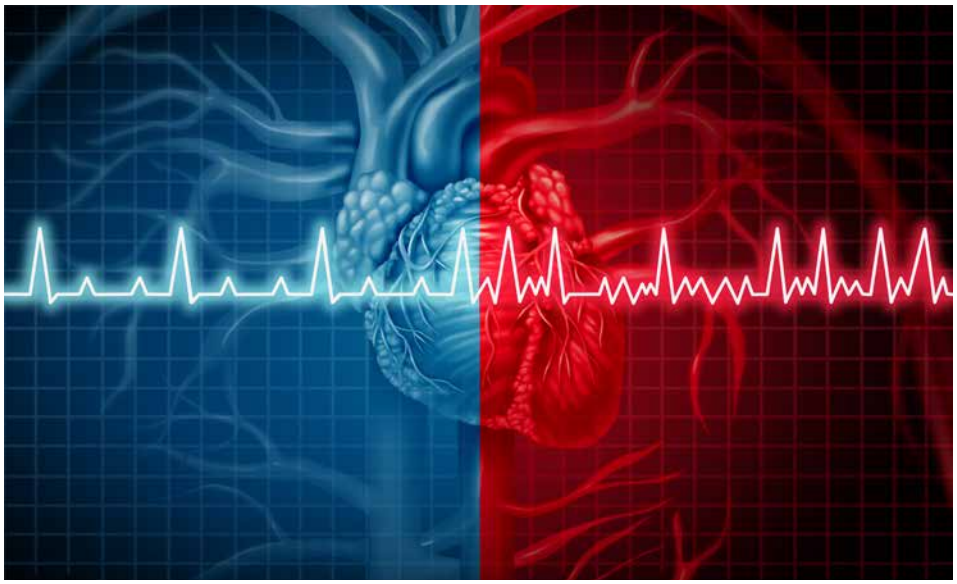
Unlike heparin and warfarin which act at multiple sites of the clotting cascade, direct oral anticoagulant (DOAC) agents are anticoagulant drugs that have only one site of action. Dabigatran is a direct thrombin (IIa) inhibitor and apixaban, edoxaban and rivaroxaban are factor Xa inhibitors. In terms of reversal of effect in ICH idarucizumab is approved as reversal agent for dabigatran and andexanet alfa or 4-complex PCC (prothrombin complex concentrate) for reversal of rivaroxaban, edoxaban and apixaban (Cuker et al, 2019). Remember that reversal agents are prothrombotic and carry a risk of life-threatening thrombosis and should only be used in someone who is at imminent risk of death from bleeding.

Antiplatelet drugs decrease platelet aggregation and inhibit thrombus formation. Aspirin inhibits the enzyme cyclooxygenase reducing the production of thromboxane A2, a stimulator of platelet aggregation. Clopidogrel is a thienopyridine that inhibits adenosine diphosphate-dependent platelet aggregration. They are used in primary and secondary prevention of thrombotic cerebrovascular and cardiovascular disease. Antiplatelet drugs can reversibly or irreversibly inhibit platelet aggregation, one of the initiating steps in clot formation, resulting in a decreased tendency of platelets to adhere to each other and adhere to damaged blood vessel endothelium.

Regarding COVID 19, there are some suggestions in early studies of increased incidence of stroke but these tend to occur in cases associated with co-morbidities like hypertension and diabetes, this clouds the issue and further work is needed to clarify this.

Acute Ischaemic Stroke:

Stroke is common and rehabilitation of victims is a huge national drain on resources both financially but also in terms of health service resources and in terms of the physical and emotional well being of carers in the community. Over 80% of strokes are ischaemic, that is, due to a blocked blood vessel with the remaining to a burst blood vessel or haemorrhage (Adams et al, 1993).



Of the ischaemic strokes only a small percentage (10 to 20%) are suitable for thrombolysis. Key to success in the treatment of AIS is a well organised pathway that includes rapid assessment and access to imaging that prevents delays and allows appropriate selection of patients for treatment. Remember that outside the time window of 4.5 hours the risk of bleeding due to tPA outweighs the benefits of treatment. It is expected that each case will present unique difficulties to be overcome before a decision can be safely made, for example, a history of previous stroke including intracranial (ICH) will raise concern. Patients may present late or wake up with their symptoms or already be using anticoagulant medications. However the only absolute contraindication to thrombolysis is intracranial bleeding on the CT brain. Often the right decision is not to thrombolyse, however there should be a good reason not to offer this life saving treatment. Serious complications of treatment including ICH and allergic reaction may occur following treatment and patients need monitored in a high dependency area or high dependency stroke unit (HASU) for 72 hours following treatment.

TIAs and small strokes:

When does a stroke become a TIA or when is a stroke too small to treat with thrombolysis? An NIHSS < 3 implies a small stroke but when vital functions are like speech or limb weakness are an issue it might still be reasonable to treat with thrombolysis. A TIA is an impending stroke and an opportunity for prevention. The first few weeks after a TIA or a small stroke is the time of greatest risk of recurrence and so dual antiplatelets (DAPT) is becoming the typical of treatment. However, here the risk of IS must again be weighted with the risk of causing bleeding by doubling antiplatelet cover and so DAPT is usually limited to about three months after a TIA or small ischaemic stroke. DAPT is not an option for large strokes due to the risk of causing bleeding into the infarct (Clairborne el al, NEJM, 2018; Wang et al, NEJM, 2013).

For long term stroke prevention a single antiplatlet agent is recommended. The use of proton pump inhibitors is not routine among stroke physicians in preventing upper gastrointestinal bleeding but some would suggest that in the long run this is a cost effective option (Kaiser et al, 2019). More aggressive early anticoagulation for minor (NIHSS<3), non-cardioembolic stroke or TIA, beyond treatment with DAPT, has been reviewed (Seiffge et al, 2020) but larger trials are recommended.

Atrial Fibrillation:

Atrial fibrillation (AF) is relatively common in hospital medicine, its incidence increasing with age. It is associated with an increased risk of cardioembolic stroke which can largely be counteracted by oral anticoagulation (OAC) medication but this carries the risk ICH (Luengo-Fernandez et al, 2012).

In general, OAC medication is tolerated well but following an ICH treatment it must be stopped. Where the indication for OAC still remains the risks of recommencing treatment must be weighed against the continued risk of cardioembolic stroke due to AF. Guidelines (Hawkes et al, 2018) are not explicit here but recommencing OAC should be considered depending on the case circumstances, for example, a spontaneous ICH might have greater chance of recurrence than a traumatic haemorrhage that is due to a fall. It is important to highlight out that antiplatelet agents give no protection against the risk of IS due to AF.

Occasionally IS will occur despite OAC therapy and the question is what to do next? It is important to consider compliance as the cause of treatment failure and this needs to be discussed with the patient. In the case of patients on DOACs the short elimination half-lives mean that even short periods of non-compliance may rapidly result in sub-therapeutic levels. Although compliance with DOAC treatment is better than with VKA,

compliance can be as bad as 1 in 3 adhering <80% of the time and although it is convenient that DOACs do not require monitoring greater effort should be made to follow up to prevent poor compliance (Ozaki et al, 2020).

In patients with AF who have an IS, despite being on OAC they are at a higher risk for recurrent ischaemic strokes. Simply changing the type of anticoagulation was not associated with a reduced risk (Seiffge et al, 2020). The risks and benefits of adding an antiplatelet might be discussed with patients but this treatment is outside current guidelines.

Interestingly, while guidelines recommend anticoagulation for all AF patients over 75 years, the evidence for a net clinical benefit (NCB) is sparse and one study found the NCB of treatment decreases with advancing age due to the competing risk of death from other causes e.g. cancer. In general though, elderly patients have a lot to gain from OAC treatment to prevent IS in AF.

Bridging Therapy:

'Bridging Therapy' is used prior to a procedure or surgery, where short acting heparin replaces anticoagulation to reduce the risk of thromboembolism due to discontinuation of treatment and to reduce the risk of excessive bleeding during the procedure. Long acting VKAs need to be stopped several days before a procedure and will take several days to become therapeutic again afterwards. Some authors have found that periprocedural bridging therapy does not significantly reduce thromboembolic events compared with no bridging, however, it significantly raised the risk of both major bleeding and minor bleeding (Kulkarni et al, 2019; Douketas et al, 2015).

The American College of Cardiology (2017) produced a decision pathway for VKA in non-valvular AF using a patient's estimated stroke and bleeding risk to determine whether bridging was indicated. For example, bridging was not recommended with a CHA2DS2-VASc of four or lower and no history of stroke, TIA or systemic embolism owing to their low day-to-day risk of thromboembolism without anticoagulants. Clinicians need to decide on individual cases; it may be that parentral bridging anticoagulation is not indicated in setting of a CHA2DS2-VASc <4 and no recent history of stroke and it may be reasonable to simply resume warfarin therapy without bridging.

DOACs have shorter half-lives than warfarin and it is likely parentral bridging is less of an issue. Some feel that heparin bridging does not make pharmacological sense given the short, 8-14 hour DOAC elimination half-lives, its association with increased bleeding and its questionable efficacy. The PAUSE study (Douketis et al, 2019), for example, demonstrated that periprocedural discontinuation of DOACs without administering a bridging agent was associated with low thromboembolic and bleeding rates.

The risks and benefits of bridging with a shorter acting agent like heparin are unclear and a plan needs to take account for all factors in each case.

ICH in the elderly and restarting OAC treatment:

ICH accounts for 10 - 15% of all strokes and is associated with a high mortality rate of approximately 50% and a high functional dependency (approximately 2/3) in survivors. It is a recognised side effect of antithrombotic treatment that the incidence of ICH increases with age; probably the result of changes to blood vessels that are part of the aging process. Spontaneous ICH in the elderly can occur on a background of cerebral amyloid angiopathy (CAA) which tends to be lobular and in the general population hypertensive ICH tends to be in the region of the basal ganglia, thalamus or pons. The prevalence of both AF and of ICH due to CAA increases with age, confounding the problem of managing one without causing the other (Shah et al, 2019) and given the demographics of our western population, this is an issue which is likely to increase.

As mentioned above, Maximailano et al (2018) found that most published data show a net benefit in terms of IS prevention and mortality when anticoagulation is restarted.

Sometimes an aneurysm is noticed on CT brain, which raises the risk of causing ICH by treating with OAC (or indeed tPA). Again the individual circumstances need to be recognised but in general bleeding is made worse but not caused by antithrombotic treatment and the presence of an incidental aneurysm should not preclude treatment which is indicated.

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