Tranexamic Acid Summary

1. Introduction

1.1 Trauma is the leading cause of death in all groups under 45 years of age and a significant cause of short and long-term morbidity.[1] The National Audit Office (NAO) estimate that there are at least 20,000 cases of major trauma each year in England, resulting in 5,400 deaths and many others resulting in permanent disabilities requiring long-term care.[2] Trauma costs the NHS between £0.3 and £0.4 billion a year in immediate treatment alone, as well as resulting in an annual lost economic output of between £3.3 - £3.7 billion.[2]

2. Background

2.1 Haemorrhage is responsible for about a third of in-hospital trauma deaths and contributes to deaths from multi-organ failure.[3] The haemostatic system helps to maintain circulation after severe vascular injury, which can be an extreme challenge for the coagulation system. Fibrinolysis (breakdown of clots) is part of the response to surgery and trauma, and may progress to become pathological (hyper-fibrinolysis).

2.2 Ambulance Paramedics have not previously administered medicines specifically aimed at supporting survival and recovery from trauma related haemorrhage. Interventions were confined to the delivery of physical haemorrhage control (direct/indirect pressure, dressings, pressure dressings, celox gauze, arterial tourniquets) and supportive interventions (oxygen and IV sodium chloride).

2.3 Anti-fibrinolytic agents reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to trauma, and do so without apparently increasing the risk of complications.[4] Tranexamic acid is a synthetic derivative of the amino acid lysine, that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen.[5]

2.4 Early coagulation abnormalities are frequent in severely injured trauma patients and are associated with substantially increased mortality. Recent research showing that hyper-fibrinolysis is a common feature of these abnormalities, raises the possibility that anti-fibrinolytic agents such as tranexamic acid might operate via this mechanism.[6]

3. Clinical Effectiveness

3.1 The use of tranexamic acid has historically been confined to administration during surgery. A systematic review of the randomised trials of tranexamic acid in patients undergoing elective surgery (53 studies including 3,836 participants) identified that tranexamic acid reduced the need for blood transfusion by a third (relative risk [RR] 0·61, 95% CI 0·54–0·70), with no significant reduction in mortality (0·61, 0·32–1·12).[4] Because the haemostatic responses to surgery and trauma are similar, it was proposed that tranexamic acid might reduce mortality due to bleeding in trauma patients.

3.2 The CRASH-2 (Clinical Randomisation of an Anti-fibrinolytic in Significant Haemorrhage 2) study was a large placebo controlled trial of the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion. The trial was undertaken in 274 hospitals in 40 countries. Patients were randomly allocated to receive a loading dose of 1g of tranexamic acid infused over 10 minutes, followed by an intravenous infusion of 1g over 8 hour, or matching placebo (0·9% saline).[7]

3.3 The results demonstrated that the early administration of tranexamic acid to trauma patients with, or at risk of, significant bleeding reduced the risk of death from haemorrhage (489 [4·9%] vs 574 [5·7%]; relative risk 0·85, 95% CI 0·76–0·96; p=0·0077), with no apparent increase in fatal or non-fatal vascular occlusive events. All-cause mortality was also significantly reduced (1463 [14·5%] tranexamic acid group vs 1613 [16·0%] placebo group; relative risk 0·91, 95% CI 0·85–0·97; p=0·0035).[7] The study concluded that tranexamic acid safely reduced the risk of death in bleeding trauma patients, and should be considered for use in practice.[7]

3.4 A further 2011 systematic review of randomised controlled trials in trauma concluded that tranexamic acid safely reduces mortality in bleeding trauma patients.[9]

4. Medicines Safety and Legislation

4.1 Pharmacokinetics

4.1.1 Peak plasma ATX concentration is obtained immediately after IV administration (500mg). Then concentration decreases until the 6th hour. Elimination half-life is about 3 hours. Tranexamic acid is delivered in the cell compartment and the cerebrospinal fluid with delay; distribution volume is about 33% of the body mass. Tranexamic acid is excreted in urine as unchanged compound. 90% of the administered dose is excreted by the kidney in the twelve first hours after administration (glomerular excretion without tubular re-absorption).[12]

4.2 Pharmacodynamics

4.2.1 Tranexamic acid is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen,[5] competitively inhibiting the activation of plasminogen to plasmin.[12]

4.3 Safety

4.3.1 No interactions have been reported with other IV medications. Rapid administration may lead to hypotension. Although there is no evidence from animal studies of a teratogenic effect, tranexamic acid passes into breast milk to a concentration of approximately one hundredth of the concentration in the maternal blood; an anti-fibrinolytic effect in the infant is unlikely.

4.3.2 Very rare adverse events have been reported including:[12]

- Gastro-intestinal disorders: digestive effects such as nausea, vomiting and diarrhoea.
- Cardio-vascular disorders: malaise with hypotension, with or without loss of consciousness (generally following a too fast intravenous injection, exceptionally after oral administration), arterial or venous thrombosis at any sites.
- Nervous system disorders: dizziness and convulsions, particularly in case of misuse.
- General disorders: hypersensitivity reactions including anaphylaxis

4.3.3 No cases of overdosage have been reported. Symptoms may theoretically include nausea, vomiting, orthostatic symptoms and/or hypotension. Maintain a high fluid intake to promote renal excretion.

4.4 Medicines Legislation

4.4.1 Tranexamic acid is a prescription only medicine, which can be administered by register Paramedics and Nurse under a patient group direction (PGD).

4.5 Presentation and Storage

4.5.1 Tranexamic acid is supplied in a glass ampoule containing 100mg/ml tranexamic acid diluted in 5ml of water for injection (e.g. 500mg tranexamic acid). There are no special requirements for storage and the medicine has a three year shelf life.[12]

4.6 Cost Effectiveness

4.6.1 On the basis of the CRASH-2 trial results, it has been estimated that the widespread use of tranexamic acid could save between 70,000 and 100,000 lives per year around the world.[10] A complex evaluation of the cost effectiveness of tranexamic acid in trauma concluded that the intervention is highly cost if administered routinely to bleeding trauma patients in high, middle and low income countries.[10] Evidence on the cost effectiveness of the medicine was an important factor in the World Health Organisation's decision to include tranexamic acid on their list of essential medicines.[11]

5. Local Implementation

5.1 Evidence indicates that the intervention may be more effective if administered as soon as possible after the onset of the injury. CRASH2 indicated that when administered within one hour of the time of injury, tranexamic acid significantly reduced the risk of death due to bleeding (198/3747 [5·3%] in tranexamic acid group vs 286/3704 [7·7%] in placebo group; RR 0·68, 95% CI 0·57–0·82; p<0·0001). Treatment given between 1 and 3 hours also reduced the risk of death due to bleeding (147/3037 [4·8%] vs 184/2996 [6·1%]; RR 0·79, 0·64–0·97; p=0·03).[7]

5.2 A subsequent review of the study concluded that there was strong evidence that the effect of tranexamic acid on death due to bleeding varied according to time from injury to treatment (p<0·0001).[8] Tranexamic acid has been included as a core medicine within the 2011 Joint Royal Colleges Ambulance Liaison Committee (JRCALC) clinical guidelines, which are set to be released during late 2011. The Ambulance Service Directors of Clinical Care Group have committed to introduce tranexamic acid within ambulance services during 2012.

5.3 The Trust will introduce tranexamic acid for the treatment of haemorrhage due to trauma from the 30th November 2011, to facilitate earlier administration of the agent. Two 500mg ampoules of tranexamic acid would be carried within every front-line emergency ambulance medicines bag, with Paramedics administering through the agreed PGD. Stocks will not be carried on rapid response vehicles to reduce out-of-date drugs wastage, as all suitable patients will require admission.

6. Conclusion

6.1 The introduction of tranexamic acid as a proven evidence based intervention in cases of trauma, has the potential to save lives across the South West. The intervention is both clinically and cost effective, and appears to be suitable for inclusion into the skills set of Trust Paramedics.

7. References

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