Effects of Tranexamic Acid

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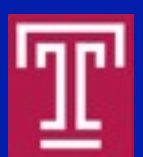


“Medicine is a science of uncertainty and an art of probability”

Sir William Osler

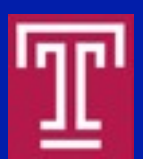
Response to Surgery and Injury

- Surgery and trauma results in stimulation of clot breakdown (fibrinolysis) which can become pathological (hyper-fibrinolysis)
- Most believe that this is through a Protein C mediated pathway and activation of fibrinolysis

Brohi K, et al. Ann Surg 2007

Response to Surgery and Injury

- Anti-fibrinolytic agents (TXA) can reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery and trauma without increasing the risk of post-operative or post-injury complications



TXA – Mechanism of Action

- **TXA is a synthetic derivative of lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen**

TXA – Pharmacology

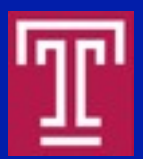
- Anti-fibrinolytic that inhibits both Plasminogen activation and Plasmin activity thus preventing clot breakdown rather than promoting new clot formation
- 10x more potent (in vitro) than Amino-caproic acid

TXA – Pharmacokinetics

- Absorption –
  - Onset of action: 5-15 minutes
  - Duration: 3 hours
- Distribution –
  - Protein binding ~ 3%; primarily to Plasminogen
- Metabolism –
  - T1/2: 2-11 hours
- Excretion –
  - Urine (>95% as unchanged drug)

TXA – Dosing/Storage

- TXA (Cyklokapron) – 1gm in 100cc/NSS given over 10 minutes (loading dose)
  - Followed by 1gm in 100cc/NSS over 8 hrs
- Can be mixed with just about any available solution
- Not to be administered in the same line as blood or blood products or in a line used for rFVIIa or Penicillin
- Should be stored between 15-30C or 56-86F



TXA – Side Effects

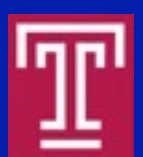
- Ocular – color vision change, vision loss
- Seizure – probably related to neuronal GABA inhibition
- Renal Impairment
- Ureteral Obstruction – upper tract obstruction may lead to bleeding

TXA - Contraindications

- Acquired defective color vision
- SAH
- Active intravascular clotting
- Hypersensitivity to TXA

Data – CRASH 2

- CRASH -2:
  - Randomized, prospective study
  - 247 hospitals, 40 countries, 20211 included
  - Primary outcome was death at 4 weeks with intention to treat
  - All cause mortality decreased by 10% (RR 0.91, 95% CI 0.85-0.97)
  - Risk of death from bleeding decreased by 15% (RR 0.85, 95% CI 0.76-0.96)



Data – MATTERs Study

- Retrospective, observational trial
  - Compared TXA administration with non-TXA administration in combat casualties receiving at least 1u pRBC. A subset of patients receiving a massive transfusion was also analyzed
  - 896 consecutive patients with combat casualties of which 293 received TXA
  - TXA group had lower unadjusted mortality (17.4% vs. 23.9%; P=0.3); benefit greater in patients receiving MT (14.4% vs. 28.1%; P=.04); TXA independently associated with survival (OR=7.7228; CI 3.016-17.322)

Data – Meta Analysis

- BMJ May 2012 (K Ker et al.)
- 129 Trials; 10488 patients, reduced the probability of receiving a blood transfusion by a third (risk ratio 0.62, 95% confidence interval 0.59 to 0.65; P<0.001)
- Fewer deaths in TXA group (0.61, 0.38 to 0.98; P=0.04)
  - Statistical concerns about this group

Final Thoughts

- TXA is a highly valuable adjunct that can improved survival from hemorrhage secondary to trauma
- Still some basic science questions outstanding and in the process of being answered
- BOTTOM LINE – severe trauma - GIVE