



Blood Day 2010

When platelets
aren't enough...

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D6 Patient

80 year old female
Bone marrow failure

Date (October)	8	9	10	11	12	13	14	15	16
Platelets (adult units)	1	1	1		1		3		1
Platelet count (x10 ⁹ /L)	6	8	9	9	10	5	34	8	6
Platelet count post platelet infusion	14				13				23



Objectives

1. Identify the intravenous antifibrinolytics currently available in Canada.
2. Review the mechanism of action, dose and side effects of tranexamic acid.
3. Review current literature for use of antifibrinolytics in post partum hemorrhage, trauma and cardiac surgery.



Aprotinin

- Bovine pancreatic trypsin inhibitor
- BART trial
 - (Blood Conservation Using Antifibrinolytics in a Randomized Trial)
 - Compared efficacy & safety of aprotinin and lysine analogues in cardiac patients with respect to bleeding outcomes
- Concerns regarding increase all-cause 30-day mortality
- Suspended October, 2007

N Engl J Med 2008;358:2319-31.



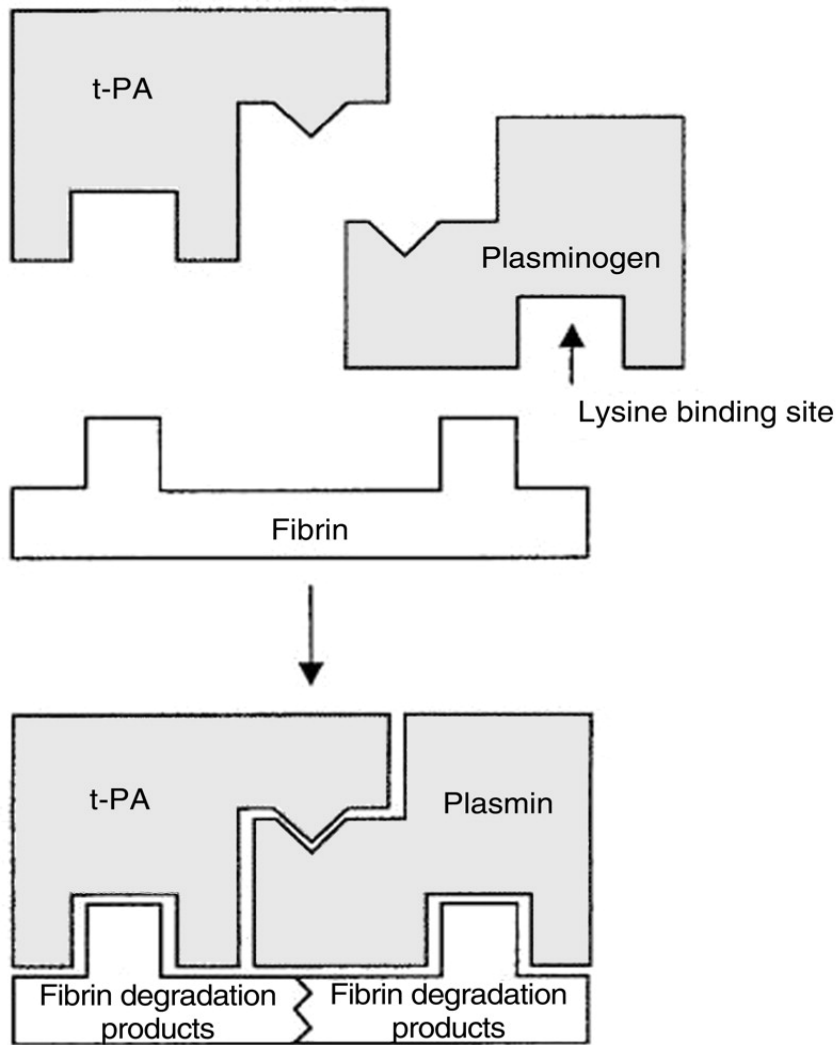
Antifibrinolytic Amino Acids

- 6-aminohexanoic acid
 - **Aminocaproic Acid**
 - Withdrawn 2005
- 4-(aminomethyl)cyclohexanecarboxylic acid
 - **Tranexamic Acid (TXA)**

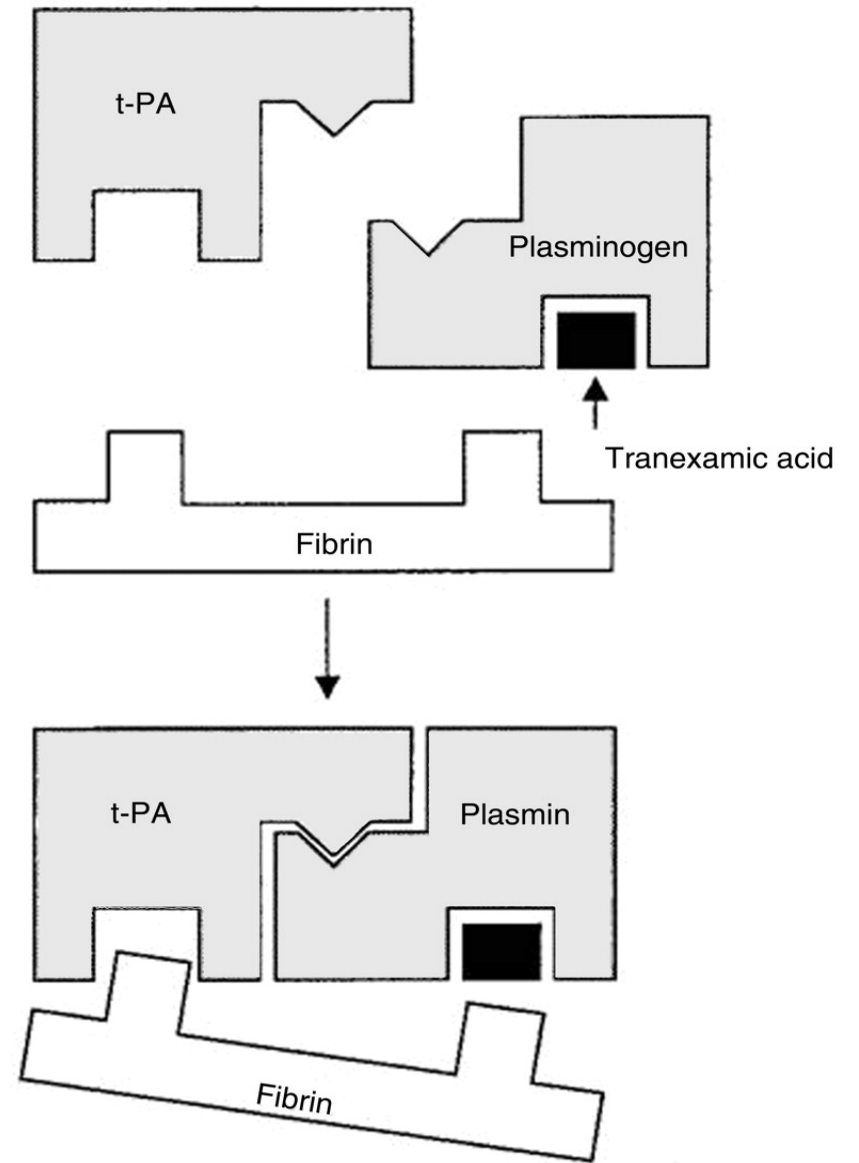


Tranexamic acid

- Antifibrinolytic Agent
- Antihemophilic Agent
- Hemostatic Agent
- Lysine Analog
- 1000 mg/10 mL ~\$15



A
Normal fibrinolysis



B
Tranexamic acid



Dose of tranexamic acid

- *Dental surgery in patients with coagulopathies:
 - 10mg/kg IV or 25 mg/kg orally 2 hours preop, then 25 mg/kg orally tid-qid for 6-8 days
- **Cardiac surgery
 - 100 mg/kg IV pre-op, then 50 mg/kg IV post-op; or
 - 15 mg/kg IV then 1 mg/kg/hr for 5-6 hours prior to initiating coronary bypass
- ***10 mg/kg IV tid-qid
- ****10 mg/kg IV bid

*eCPS 2010

**Micromedex 2010

***Ann Pharmacother 1996:30:868-70

****Package insert



Pharmacokinetics

- Short half life 1-2 hours
- Distribution: V_d : 9-12 L
- Protein binding: ~3%, primarily to plasminogen
- Excreted in urine, ~95% unchanged
- Reduced blood levels of D-dimer



Dosing: Renal Impairment

- Clcr 50-80 mL/minute: Administer 50% of normal maintenance dose
- Clcr 10-50 mL/minute: Administer 25% of normal maintenance dose
- Clcr <10 mL/minute: Administer 10% of normal maintenance dose



Adverse Reactions

- Hypotension (with rapid I.V. injection)
- Diarrhea, nausea, vomiting
- Blurred vision
- Postmarketing and/or case reports: Cerebral thrombosis, deep venous thrombosis, postoperative visual loss, pulmonary embolus, renal cortical necrosis, retinal artery obstruction, retinal vein obstruction, ureteric obstruction, visual disturbances (defective color vision)



Contraindications

- History or risk of venous or arterial thrombosis*
- Acquired colour vision disturbances
- Active thromboembolic disease
- Subarachnoid hemorrhage



Tranexamic acid for preventing postpartum haemorrhage

1. Tranexamic acid (1 g or 0.5 g) IV 2-3 minutes post vaginal delivery versus no treatment (n=273)
2. Tranexamic acid 1 gram IV 10 minutes before caesarean section versus no treatment (n=180)

Mean blood loss lower with TXA

Higher dose caused mild side effects.

BUT, "unclear quality", more research needed.



The WOMAN Trial: tranexamic acid for the treatment of postpartum haemorrhage

- World Maternal Antifibrinolytic Trial
- International, randomised, double blind placebo controlled trial, n=15,000
- Effect of early administration of tranexamic acid on mortality, hysterectomy and other morbidities (surgical interventions, blood transfusion, risk of non-fatal vascular events)
- Eligibility criterion is clinician's uncertainty as to whether or not use an antifibrinolytic agent



Antifibrinolytic use for minimising perioperative allogeneic blood transfusion

- 211 RCTs
- n=20,781
- Aprotinin superior to lysine analogues:
 - in reducing operative blood loss (but small differences)
 - in reducing need for RBC transfusions



Authors' conclusions

- Antifibrinolytic drugs provide worthwhile reductions in blood loss and need for allogeneic RBC transfusion
- Efficacy does not appear to be offset by serious adverse effects
- Lysine analogues probably as effective as aprotinin and cheaper
- Evidence stronger for tranexamic acid over amiocaproic acid.



The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis

- Update of 2007 Cochrane review
- 11 randomized controlled trials
- Comparison of relative benefits and risk of aprotinin and lysine analogues
- All effective in reducing need for red blood cell transfusion
- No evidence of increase risk of myocardial infarction with use of aprotinin compared with lysine analogues



Authors' Conclusions

- Risk of death consistently higher with aprotinin than lysine analogues
- Aprotinin had no clear advantages
- Tranexamic acid or aminocaproic acid should be recommended to prevent bleeding after cardiac surgery



14 JUNE 2010

Drug will save lives of accident victims, says study

EARLY TREATMENT WITH TXA COULD COMBAT THE EFFECTS OF SERIOUS BLEEDING



UP TO 100,000 LIVES COULD BE SAVED EVERY YEAR IF A KNOWN DRUG WERE GIVEN TO SERIOUSLY BLEEDING TRAUMA PATIENTS, SAYS A REPORT FROM A GLOBAL TRIAL.



Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2)

- placebo controlled trial
- early administration of tranexamic acid
- n = 20,211 adult trauma patients with, or at risk of, significant bleeding
- randomly assigned within 8 h of injury to tranexamic acid or placebo
- loading dose 1 g over 10 min then infusion of 1 g over 8 h



Crash 2

- All-cause mortality reduced with tranexamic acid

(14.5% TXA *vs* 16% placebo; RR 0.91, 95% CI 0.85–0.97)

- The risk of death due to bleeding was reduced

(4.9% *vs* 5.7%; RR 0.85; 95% CI 0.76–0.96)



Crash 2

- Vascular occlusive events (fatal or non-fatal) *not* significantly different

(1.7% *vs* 2.0%; RR 0.84, 95% CI 0.68–1.02)

- No reduction in receipt of blood transfusion or amount of blood transfused

(50.4% *vs* 51.3% RR 0.98, 95% CI 0.96–1.01)



Authors Conclusions

- Tranexamic acid
 - Could be given in a wide range of health-care settings
 - Safely reduced the risk of death in bleeding trauma patients
 - Should be available worldwide
 - Should be considered for use in bleeding trauma patients



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*Recent history of ischemic event

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