When Should I Use Tranexamic Acid for Children?

Dr Andrea Kelleher
Consultant Adult and Paediatric Cardiac Anaesthetist
When a drug is licenced for (the proposed) use
When its use is supported by expert opinion
When I understand which of my patients will benefit
When I understand the side effects and contraindications
When I know what dose to give
When I understand the timing of administration
Licenced Uses:

- Excessive fibrinolysis
- Hereditary angioedema
- Prevention of excessive bleeding following dental extraction (e.g. in haemophilia)
- Menorrhagia, traumatic hyphema and epistaxis
- Thrombolytic overdose
- Cardiac surgery
Not licenced for:
* reduction of blood loss during cardiac surgery
* Injection not licenced use in children under 1 year
* Injection not licenced for administration by intravenous infusion
Consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (greater than 10% blood volume).

NICE guideline [NG24] Blood Transfusion November 2015
The core list presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost–effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

### 10.2 Medicines affecting coagulation

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>20mg/0.2ml; 40mg/0.4ml; 60mg/0.6ml; 80mg/0.8ml/100mg/1ml; 120ml/0.8ml; 150mg/1ml</td>
</tr>
<tr>
<td>Heparin sodium</td>
<td>Injection: 1000IU/ml; 5000IU/ml; 20,000IU/ml in 1 ml ampoule</td>
</tr>
<tr>
<td>Phytomenadione</td>
<td>Injection: 1mg/ml; 10mg/ml in 5ml ampoule</td>
</tr>
<tr>
<td>Protamine sulphate</td>
<td>Injection: 10mg/ml in 5ml ampoule</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>Injection: 100mg/ml in 10ml ampoule</td>
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<tr>
<td>Warfarin</td>
<td>Tablet: 1mg; 2mg; 5mg</td>
</tr>
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19th WHO Model List of Essential Medicines (April 2015)
Recommendations for Tranexamic Acid:

* Tranexamic acid should be considered in all children undergoing (non-cardiac) surgery where there is risk of significant bleeding (1B).

* Consider using antifibrinolytic therapy in neonates and children undergoing cardiac surgery at high risk of significant bleeding (1B).
Tranexamic Acid

- A lysine analogue
- Inhibits plasmin mediated fibrinolysis at low doses by forming a reversible complex with plasminogen
At higher concentrations tranexamic acid also:

* Non-competitively blocks plasmin

* Inhibits thrombin activation of platelets by plasmin-TXA binding to platelet receptors

* Blocks plasmin dependent complement pathway interactions

* Promotes thrombin generation via activation of factor XII
Tranexamic Acid and Paediatric Cardiac Surgery

* Blood Loss mls/kg

* Red cell transfusion

## Tranexamic Acid and Non-Cardiac Surgery

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<td>9-18</td>
<td>100mg/kg 10mg/kg/hr</td>
<td>Significant reduction in blood loss -855mls (-1408 to -301mls) NS reduction in blood transfusion 0.85 (0.56-1.30</td>
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<td>Ng 2016</td>
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<td>2 months – 6 years</td>
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**Target Plasma Levels**

**In adults:**
- *in vitro*, tranexamic acid inhibits fibrinolysis at a serum concentration of 17.5 µg/ml
- Clinically efficacious levels in adults seem to range from 52.5 - 150 µg/ml  
  Wesley MC et al. *Anesthesiol*; 122 (4): 746-758

**In children:**
- *in vitro* the plasma level required to inhibit fibrinolysis has been defined as 10 µg/ml with suppression of plasmin induced platelet activation at 16 µg/ml
- Full inhibition may require concentrations of around 100 µl/ml  

**In neonates**
- *in vitro*, the plasma level required to inhibit fibrinolysis may be as low as 6.54 µg/ml  
Possible Dosing Regimen for Children undergoing Cardiac Surgery

A Practical Tranexamic Acid Dosing Scheme Based on Population Pharmacokinetics in Children Undergoing Cardiac Surgery

Stanislas Grassin-Delyle, Pharm.D., Ph.D.,* Roland Couturier, M.D.,† Emuri Abe, Pharm.D.,‡ Jean Claude Avarez, Pharm.D., Ph.D.,§ Philippe Devillier, M.D., Ph.D.,¶ Salik Urten, M.D., Ph.D.#

- 21 children mean age 5.35 years randomised to different tranexamic acid regimes
- Serum concentrations measured at 8 time points
- Bolus dose of 6.4mg/kg followed by a weight adjusted infusion of 2.0-3.1mg/kg/hour maintained the concentration between 20 and 30 µg/ml with a low amplitude

*Fig. 5. Dosing simulation to readily obtain a 20-µg/ml tranexamic acid concentration plateau after a 5-min loading dose followed by a 4-h infusion in children with body weights between 5 and 40kg. The dotted horizontal line represents the threshold target concentration of 20 µg/ml. TA = tranexamic acid.*
Possible Dosing in Neonates and Infants undergoing Cardiac Surgery

- 55 children 2 days – 58 months, 21 sample time points
- Dosing requirements necessary to achieve 20µg/ml in the first year of life change rapidly

**Pharmacokinetics of Tranexamic Acid in Neonates, Infants, and Children Undergoing Cardiac Surgery with Cardiopulmonary Bypass**

Mark K. Wesley, M.D., Luis M. Pereira, Ph.D., Laurie A. Scharf, B.S., Staram M. Emari, M.D., Francis X. McGowan, Jr., M.D., James A. D’Nerio, M.D.

<table>
<thead>
<tr>
<th>Age</th>
<th>Loading dose (mg/kg)</th>
<th>Infusion (mg · kg⁻¹ · h⁻¹)</th>
<th>CPB prime dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2 months</td>
<td>15</td>
<td>2.5</td>
<td>20 µg per ml of prime volume</td>
</tr>
<tr>
<td>2-12 months</td>
<td>9 (6-12)</td>
<td>2</td>
<td>20 µg per ml of prime volume</td>
</tr>
<tr>
<td>&gt;12 months and ≤20 kg</td>
<td>4</td>
<td>2</td>
<td>20 µg per ml of prime volume</td>
</tr>
</tbody>
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Possible Dosing in Neonates and Infants undergoing Cardiac Surgery

- 55 children 2 days – 58 months, 21 sample time points
- Dosing requirements necessary to achieve 20µg/ml in the first year of life change rapidly
Possible Dosing Regimen for Children undergoing Non-Cardiac Surgery

Population Pharmacokinetics of Tranexamic Acid in Paediatric Patients Undergoing Craniosynostosis Surgery

Susan M. Goobie · Petra M. Meier · Navil F. Sethna · Sulpicio G. Soriano · David Zurakowski · Snehal Samant · Luis M. Pereira

* 10mg/kg loading dose followed by 5mg/kg/hour to produce a plasma concentration of 16µg/ml
CRASH-2

- randomized placebo-controlled trial
- 20,211 adults in 40 countries
- unstable vitals (systolic blood pressure <90 mmHg and/or heart rate >110 beats per minute, or both) or a high clinical suspicion for significant hemorrhage
- randomized to TXA vs placebo

- significant reduction in risk of death due to bleeding for the TXA group (risk of death 0.85; 95% confidence interval 0.76 to 0.96; \( P \leq 0.004 \), NNT 121
- significant reduction in all-cause mortality (risk of death 0.91; 95% confidence interval 0.85 to 0.97; \( P \leq 0.0035 \), NNT 67
### Are children just small adults?

<table>
<thead>
<tr>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma tends to be penetrating</td>
<td>Trauma tends to be blunt</td>
</tr>
<tr>
<td>Coagulation systems are mature</td>
<td>Coagulation systems may be immature</td>
</tr>
<tr>
<td>Vascular structures may be diseased</td>
<td>Vascular structures unlikely to be diseased</td>
</tr>
<tr>
<td>the leading cause of mortality is traumatic brain injury, known to be</td>
<td>the leading cause of mortality is traumatic brain injury, known to be</td>
</tr>
<tr>
<td>associated with coagulopathy</td>
<td>associated with coagulopathy</td>
</tr>
<tr>
<td>hemorrhage is the second overall cause of death, the first preventable</td>
<td>The incidence of death specifically from hemorrhage with traumatic</td>
</tr>
<tr>
<td>cause of death and first cause of mortality after arrival in hospital.</td>
<td>injuries has not been described in children</td>
</tr>
<tr>
<td>25% of adult trauma victims are coagulopathic upon arrival to hospital,</td>
<td>27%-77% of the patients may be coagulopathic on arrival to the emergency</td>
</tr>
<tr>
<td>≤ 6% of these have massive hyperfibrinolysis, ≤ 60% have less intense</td>
<td>department, hypofibrinogenenemia has been reported in ≤ 52% of children</td>
</tr>
<tr>
<td>hyperfibrinolysis</td>
<td>requiring transfusion support</td>
</tr>
</tbody>
</table>
Rationale for the use of tranexamic acid in paediatric trauma

* Trauma is the leading cause of death in children aged 1-18
* Immediate need for transfusion if:
  * Systolic blood pressure low (<80 mmHg <5 years and <90 mmHg ≥5 years)
  * Poor blood pressure response to crystalloid 20–40 ml/kg
  * Obvious significant bleeding

The Hospital for Sick Children Massive Hemorrhage Protocol for the use of tranexamic acid in pediatric trauma. April 2014.
Tranexamic acid reduces mortality in adult trauma
Early administration is vital for efficacy
Due to the lack of published data on the use of tranexamic acid in paediatric patients who have undergone major trauma there is no evidence for a specific dose
The RCPCH and NPPG Medicines Committee recommend a pragmatic dosage schedule
### Suggesting dosing regimen in Paediatric Trauma

<table>
<thead>
<tr>
<th>Age</th>
<th>Loading Dose</th>
<th>Subsequent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥12 years: adult protocol</td>
<td>1 g intravenously over 10 minutes and within 3 hours of injury</td>
<td>1 g intravenous infusion over 8 hours</td>
</tr>
<tr>
<td>&lt;12 years</td>
<td>15 mg/kg intravenously over 10 minutes (maximum dose 1 g) and within 3 hours of injury</td>
<td>2 mg/kg/hr intravenous infusion over 8 hours or until bleeding stops</td>
</tr>
</tbody>
</table>


RCPCH Evidence Statement 2011
The Hospital for Sick Children Massive Hemorrhage Protocol for the use of tranexamic acid in pediatric trauma 2014.
CRASH-2 effect of 1 hour delay in the start of treatment

Roberts I et al Lancet 2011; 377: 1071-1072
Side Effects and Cautions

- Seizures - the structural similarity of tranexamic acid to γ-aminobutyric acid (GABA) and glycine; inhibition of these inhibitory receptors by TA results in lowering of the depolarization threshold and enhanced excitability.

- Thrombosis – there is no current evidence that TXA increases the risk of thromboembolic events in children.

- DIC

- Massive haematuria

- Significant renal impairment
Tranexamic Acid and Seizures

- Seizures are dose related
- Approximately 95% of tranexamic acid is excreted unchanged in the urine
- Excretion decreases with increasing creatinine

Sharma V et al Anaesthesia 2014; 69: 124-130

Risk of early postoperative seizure according to TXA dose with 95% confidence intervals

Conclusions

* Tranexamic acid has been repeatedly shown in multiple small studies to reduce bleeding and transfusion in children, but without an impact on mortality
* Tranexamic acid is shown by cumulative evidence to be a well tolerated drug in children regardless of route of delivery
* Recent pharmacokinetic studies may guide treatment towards ever more appropriate dosing
* Thromboembolism appears no more common than in placebo groups but no studies so far have been adequately powered to look at this
* More research is required to define seizure risk in children
When Should I Use Tranexamic Acid for Children?

* All licenced uses listed in the BNF
* All ages of children undergoing any surgery in which blood loss is likely to be significant i.e. greater than 10% of their circulating volume
* When I am comfortable with the appropriate dose specific to the age/weight of the child and considered the contraindications
* In all ages of children who have suffered significant trauma (and give early!)