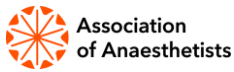


# TIVA for Tots



Dr Kay Davies  
Consultant Anaesthetist  
Royal Aberdeen Children's Hospital



# Objectives

- Benefits
- Mandatory indications
- Barriers + Pitfalls



# Objectives

- Paediatric TCI models
- Remifentanyl as an adjunct



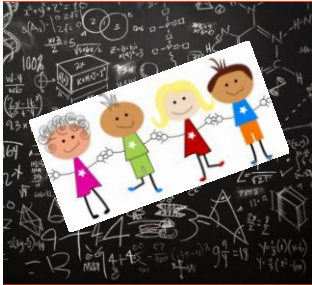
# Disclosures

None



## TIVA in children

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## TIVA in children

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## Choose your TCI model

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## Choose your TCI model

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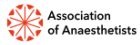


Paedfusor



Set your target  $C_p$ 

	<b>PROPOFOL</b>
<b>Induction</b>	<b>5 - 6 mcg/ml</b>



## Press "Go"

Maintenance target  $C_p$ 

	<b>PROPOFOL</b>
<b>Maintenance</b>	<b>4 - 6 mcg/ml</b>

Maintenance target  $C_p$ 

	<b>PROPOFOL</b>
<b>Maintenance</b>	<b>4 - 6 mcg/ml</b>
<b>+ Regional block</b>	<b>4 mcg/ml</b>



## Maintenance target $C_p$

	PROPOFOL
Maintenance	4 - 6 mcg/ml
+ Regional block	4 mcg/ml
+ REMIFENTANIL	2.5 - 4 mcg/ml



## Inter-individual variation

Titrate infusion rates to:

- clinical signs of depth of anaesthesia
- vital signs
- BIS if longer case / neuromuscular blockade



## UK survey - 2008

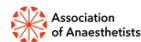
- 242 consultant paediatric anaesthetists
- 26% used propofol infusions on a monthly basis



Hill, Peat, Courtman  
*Paediatric Anaesthesia 2008 18: 488-493*

## Repeat survey - 2019

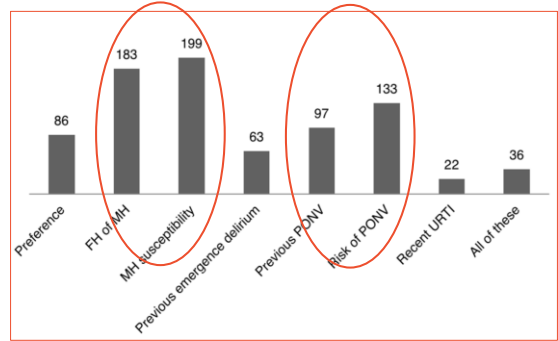
- 291 anaesthetists who anaesthetise children
- 46% used TIVA on a monthly basis



Goh, Bagshaw, Courtman  
*Paediatric Anaesthesia 2019 29 (2): 180-185*

## Repeat survey - 2019

- **8%** used TIVA as their default anaesthetic in children



Goh, Bagshaw, Courtman  
Paediatric Anaesthesia 2019 29 (2): 180-185



Goh, Bagshaw, Courtman  
Paediatric Anaesthesia 2019 29 (2): 180-185

## TIVA - Mandatory Indications

### Volatiles

- Unavailable
- Contraindicated



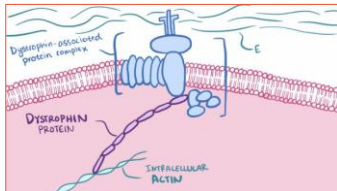
## Children at risk of MH

- MH / Family history
- Congenital myopathy
  - Central Core Disease
  - King-Denborough Syndrome



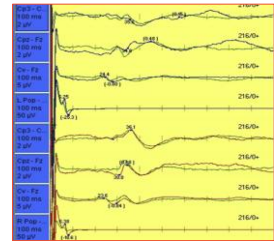
## Children at risk of rhabdomyolysis / hyperkalaemia

- Muscular dystrophies

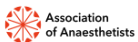
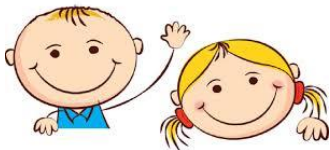


## Children requiring neurophysiological monitoring

- SSEP / MEP in spinal surgery

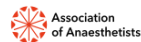


## Benefits of TIVA in children



## Benefits of TIVA in children

- ↓ Postoperative vomiting
- ↓ Emergence delirium
- ↓ Laryngospasm



## Postoperative vomiting



Incidence is **13 - 42%** of children

**Twice** as frequent in children compared to adults.




Association of Anaesthetists

*Rose, Watcha  
BJA 1999 83; 104-117*

## Postoperative vomiting



Association of Anaesthetists

<b>PATIENT RISKS</b>	Age > 3 years Previous history of POV History of motion sickness Post-pubertal female	 The Association of Paediatric Anaesthetists of Great Britain & Ireland Published in the Proceedings of the Association Meeting in London 2016
<b>SURGICAL RISKS</b>	Strabismus surgery Adenotonsillectomy Surgical procedure duration > 30 mins	
<b>ANAESTHETIC RISKS</b>	Volatile Long-acting opioid Anticholinesterase	

## How effective is TIVA at reducing POV?

Accepted: 30 September 2017  
DOI: 10.1111/joa.12268

**SYSTEMATIC REVIEW**

WILEY Paediatric Anaesthesia

**Total intravenous anesthesia vs single pharmacological prophylaxis to prevent postoperative vomiting in children: A systematic review and meta-analysis**

Maximilian S. Schaefer<sup>1</sup> | Peter Kranke<sup>2</sup> | Stephanie Weibel<sup>2</sup> | Robert Kreysing<sup>1</sup> | Janika Ochel<sup>1</sup> | Peter Kienbaum<sup>1</sup>

<sup>1</sup>Department of Anesthesiology, University Hospital Düsseldorf, Düsseldorf, Germany

<sup>2</sup>Department of Anesthesiology, University Hospital Würzburg, Würzburg, Germany

**Correspondence**  
Dr. Maximilian S. Schaefer, Department of Anesthesiology, University Hospital Düsseldorf, Düsseldorf, Germany.  
Email: Maximilian.Schaefer@med.uni-duesseldorf.de

**Summary**

**Background:** Postoperative nausea and postoperative vomiting are frequent but often missed complications after general anesthesia in pediatric patients. Because inhaled anesthetics are known to trigger postoperative vomiting, total intravenous anesthesia is often administered in high-risk children to avoid the use of inhalational anesthesia. Since inhalational anesthesia might be advantageous in some situations, the question is raised whether administration of pharmacological prophylaxis offers equal protec-

How effective is TIVA at reducing POV?

- **JUST AS EFFECTIVE** as single agent antiemetic
- Patients **EAT AND DRINK EARLIER**
- **1.4 hours**



Schafer, Kranke, Weibel, Kreysing et al  
Paediatric Anaesthesia 217 27: 1202-1209

Emergence delirium

- **10 - 50%** incidence
- Increased risk 2 - 5 years



Vlajkovic, Sindjelic  
Anaesthesia + Analgesia 2007 104: 84-91

Does TIVA reduce emergence delirium?

Pediatric Anesthesia

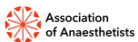
Pediatric Anesthesia ISSN 1155-5845

ORIGINAL ARTICLE

**Emergence delirium in children: a randomized trial to compare total intravenous anesthesia with propofol and remifentanyl to inhalational sevoflurane anesthesia**

John R. Chandler<sup>1,2</sup>, Dorothy Myers<sup>1,2</sup>, Disha Mehta<sup>1,2</sup>, Emma Whyte<sup>1,2</sup>, Michelle K. Groberman<sup>3</sup>, Carolyne J. Montgomery<sup>1,2</sup> & J. Mark Ansermino<sup>1,2</sup>

1. Department of Pediatric Anesthesia, BC Children's Hospital, Vancouver, BC, Canada  
2. Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Vancouver, BC, Canada  
3. Post-Anesthesia Care Unit, BC Children's Hospital, Vancouver, BC, Canada



Does TIVA reduce emergence delirium?

	TIVA	SEVO
Emergence delirium	<b>14.9%</b>	38.3%

94 children, 2 to 6 years old

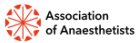


Chandler, Meyers, Mehta, Whyte, Groberman, Montgomery, Ansermino  
Paediatric Anaesthesia 2013 23: 309-315



Does TIVA reduce emergence delirium?

NNT to avoid ED is 4.3



Chandler, Meyers, Mehta, Whyte, Groberman, Montgomery, Ansermino  
Paediatric Anaesthesia 2013 23: 309-315

Reduced airway reactivity

	TIVA (n=1289)	SEVO (n=6221)
Bronchospasm	19 (1%)	123 (2%)
Laryngospasm	20 (2%)	251 (4%)

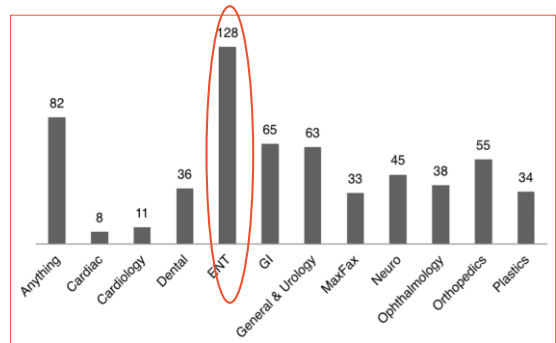
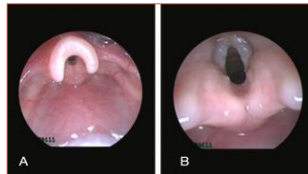


Von Ungern-Stenberg, Boda, Chambers, Rebman, Johnson, Sly, Habre  
Lancet 2010 367: 773-783

Reduced airway reactivity

TIVA is ideal if there is increased risk of coughing / bronchospasm / laryngospasm

- Bronchoscopy
- Adenotonsillectomy
- Recent URTI



Goh, Bagshaw, Courtman  
Paediatric Anaesthesia 2019 29 (2): 180-185



## Avoid atmospheric pollution

International Society for Anaesthetic Pharmacology

Anesthetic Pharmacology Section Editor: Marcel E. Durieux  
Clinical Pharmacology Section Editor: Tony Gin

### Global Warming Potential of Inhaled Anesthetics: Application to Clinical Use

Susan M. Ryan, MD, PhD,\* and Claus J. Nielsen, CSc†



**Table 1. Tropospheric Lifetime and 20-Year Global Warming Potential of Inhaled Anesthetics**

Compound	Lifetime (y)	GWP <sub>20</sub>
Carbon dioxide <sup>15</sup>		1
Sevoflurane	1.2	349
Isoflurane	3.6	1401
Desflurane	10	3714
Nitrous oxide <sup>15</sup>	114	289

GWP<sub>20</sub> = 20-year global warming potential.



Ryan, Nielson  
*Anesthesia+Analgesia* 2010 11: (1) 92-98

## Propofol + the environment



## Barriers to TIVA



## Propofol infusion syndrome

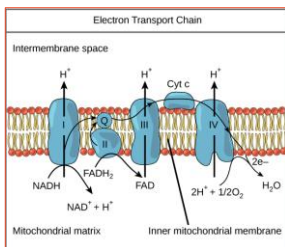
### Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports

T J Parke, J E Stevens, A S C Rice, C L Greenaway, R J Bray, P J Smith, C S Waldmann, C Verghese

*BMJ 1992 305: 613-6*



## Lipid load inhibits complexes in electron transport chain



## Propofol infusion syndrome



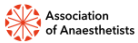
**Propofol infusion contraindicated:**  
 > 4 mg/kg/hour  
 > 48 hours



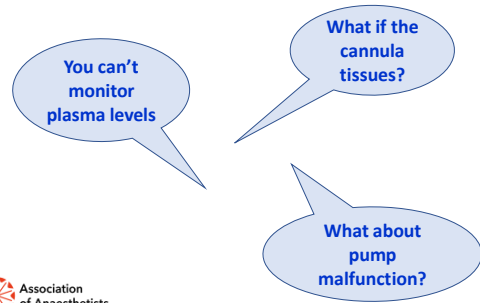
## Children with mitochondrial diseases are more prone to PrIS

- Progressive external ophthalmoplegia
- Sporadic
- Familial
- Kearns-Sayre syndrome
- Ophthalmoplegia
- Pigmentary retinopathy
- Cardiac conduction defects
- Cerebellar ataxia
- Sensorineural deafness
- Limb-girdle myopathy
- Infantile myopathy
- Benign reversible
- Severe fatal
- MERFF syndrome
- Myoclonus
- Epilepsy
- Myopathy
- MELAS syndrome
- Myopathy
- Lactic acidosis
- Stroke-like episodes

➔ **Avoid TIVA**



## Risk of awareness



## NAP 5



Out of 2.8 million general anaesthetics  
**141 cases of AAGA** (8 children)



NAP 5 BJA 2014 113: 549-59

## NAP 5



**141 cases of AAGA** (8 children)  
**18% involved TIVA** (1 child)  
**% preventable**



NAP 5 BJA 2014 113: 549-59

## NAP 5



**Fixed rate infusions** for transfer of patients from theatre, after volatile anaesthesia, to ICU / scan

**No bolus doses**

**Infusion rates too low**

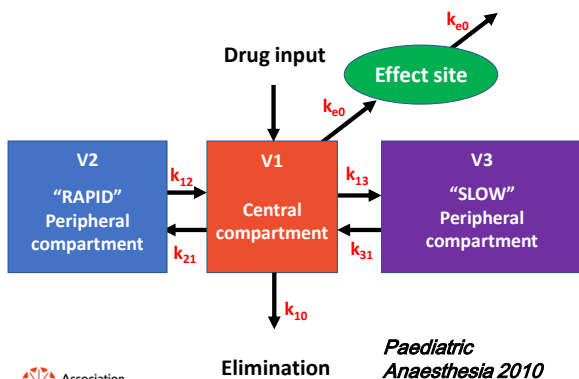
**± neuromuscular blockade**



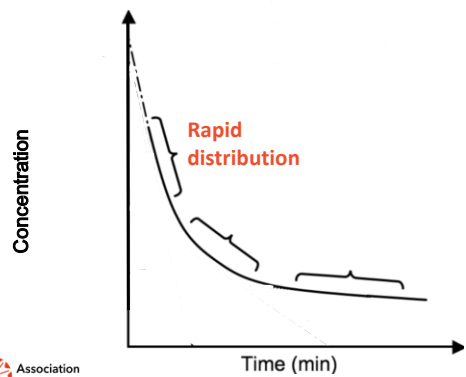
*NAP 5 BJA 2014 113: 549-59*

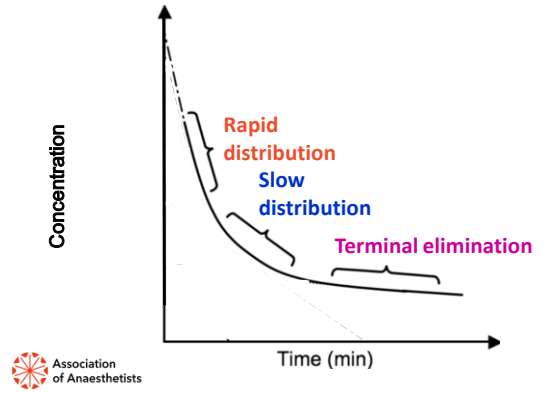
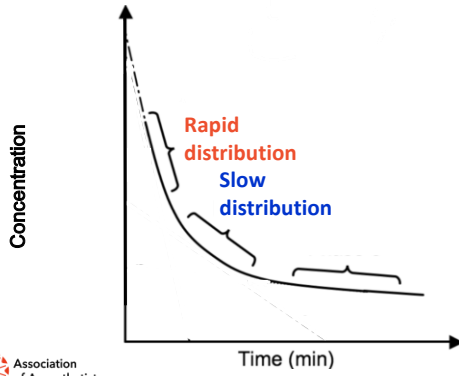
## To avoid awareness

Use TCI where possible



*Paediatric Anaesthesia 2010 20: 211-222*





## PK in children

- **Larger compartments**
  - Twice the size of adult compartments

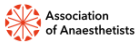
## Children require.....

50% greater initial bolus

25% higher initial infusion rate

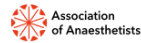
## PK in children

- Larger compartments
- Higher clearance



## Children require.....

Higher maintenance rates



## Paedfusor

1 - 16 years  
5kg - 61kg

*Absalom, Kenny  
BJA 2005 95: 110-113*



## Kataria

3 - 16 years  
15kg - 61kg

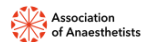
*Kataria, Ved, Nicodemus et al  
Anesthesiology 1994 80; 104-22*

## Paedfusor accuracy

Median Performance Error

Paedfusor	4.1 %
Marsh (Diprifusor)	16 %
ET isoflurane monitoring	20 %

*Absalom, Amutike, Lal, White, Kenny  
BJA 2003 91: 507-513*



## TCI - Marsh

- Teenage children weighing > 61kg

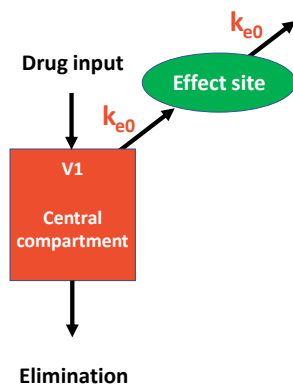
> 16 years  
> 61kg



## No $K_{e0}$ described for children



$K_{e0}$



## No $K_{e0}$ described for children

- Paediatric TCI models use **PLASMA** targets not effect site





## NAP 5

- Training
- Visible cannula
- DoA monitor
- Set of standards

**RECOMMENDATIONS**

**RECOMMENDATION 18.1**  
All anaesthetists should be trained in the maintenance of anaesthesia with intravenous infusions.

**RECOMMENDATION 18.2**  
When using total intravenous anaesthesia, wherever practical, anaesthetists should ensure that the cannula used for drug delivery is visible and patient at all times.

**RECOMMENDATION 18.3**  
Depth of anaesthesia monitoring should be considered in circumstances where patients undergoing TIVA may be at higher risk of AAGA. These include use of neuromuscular blockade, at conversion of volatile anaesthesia to TIVA and during use of TIVA for transfer of patients.

**RECOMMENDATION 18.4**  
The relevant anaesthetic organisations should establish a set of standards and recommendations for best practice in the use of TIVA.



NAP 5 BJA 2014 113: 549-59

## NAP 5

- Training
- Visible cannula
- DoA monitor
- Set of standards



NAP 5 BJA 2014 113: 549-59

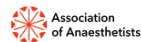
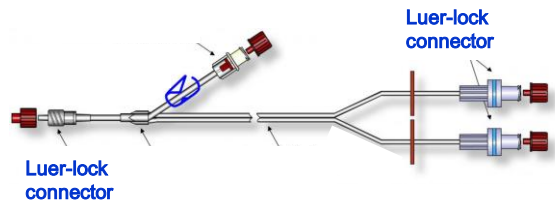
## NAP 5

- Training
- Visible cannula
- DoA monitor
- Set of standards



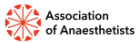
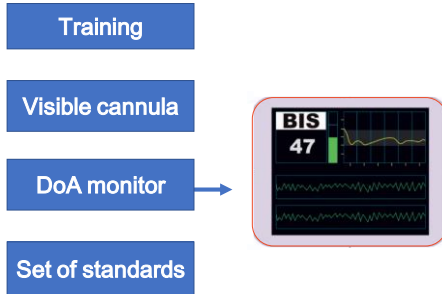
NAP 5 BJA 2014 113: 549-59

## Specific TIVA infusion set



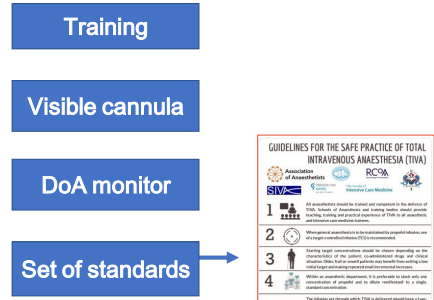
Guidelines for the safe practice of total intravenous anaesthesia - Nimmo et al Anaesthesia 2019 74: 211-224

## NAP 5



NAP 5 BJA 2014 113: 549-59

## NAP 5



NAP 5 BJA 2014 113: 549-59

**GUIDELINES FOR THE SAFE PRACTICE OF TOTAL INTRAVENOUS ANAESTHESIA (TIVA)**

Association of Anaesthetists | SIVA | Intensive Care Society | RCOA | The Faculty of Intensive Care Medicine

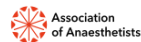
- 1 All anaesthetists should be trained and competent in the delivery of TIVA. Schools of Anaesthesia and training bodies should provide teaching, training and practical experience of TIVA to all anaesthetic and intensive care medicine trainees.
- 2 When general anaesthesia is to be maintained by propofol infusion, use of a target-controlled infusion (TCI) is recommended.
- 3 Starting target concentrations should be chosen depending on the characteristics of the patient, co-administered drugs and clinical situation. Older, frail or unwell patients may benefit from setting a low initial target and making repeated small incremental increases.
- 4 Within an anaesthetic department, it is preferable to stock only one concentration of propofol and to dilute remifentanyl to a single, standard concentration.

The infusion set through which TIVA is delivered should have a Luer-



Guidelines for the safe practice of total intravenous anaesthesia - Nimmo et al Anaesthesia 2019 74: 211-224

## Paediatric Pitfalls



## IV access in children

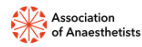
- Topical local anaesthetic



Association  
of Anaesthetists

## IV access in children

- Distraction techniques
- Play specialist



Association  
of Anaesthetists

## I can't get the IV!



- Obtain IV access after inhalational induction



Association  
of Anaesthetists

## Propofol injection pain



- Tape IV tubing
- Hold hand
- Warn the child / parent



Association  
of Anaesthetists

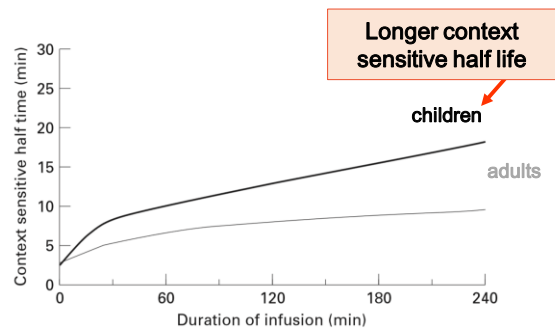
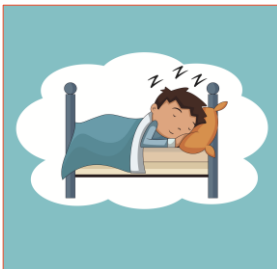
Intervention	Relative risk (95% CI)
Antecubital vein	0.14 (0.07 - 0.3)
Lidocaine pre-treatment with venous occlusion	0.29 (0.22 - 0.38)
Lidocaine/propofol admixture	0.4 (0.33 - 0.48)
Lidocaine pre-treatment	0.47 (0.4 - 0.56)
Opioid pre-treatment	0.49 (0.41 - 0.59)
Ketamine pre-treatment	0.52 (0.47 - 0.57)
Propofol emulsion with medium + long chain triglycerides	0.75 (0.67 - 0.84)



*Jalota, Kalra, George et al  
BMJ 2011 342: d1110*



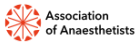
## Longer recovery times



*Mcfarlan, Anderson, Short  
Paediatric Anaesthesia 1999 9: 209-216*

## To avoid prolonged recovery....

- **Reduce propofol infusion rates early**
  - $C_p$  5 - 6 mcg/ml quickly leads to accumulation of propofol



*Mcfarlan, Anderson, Short*  
*Paediatric Anaesthesia 1999 9: 209-216*

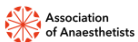
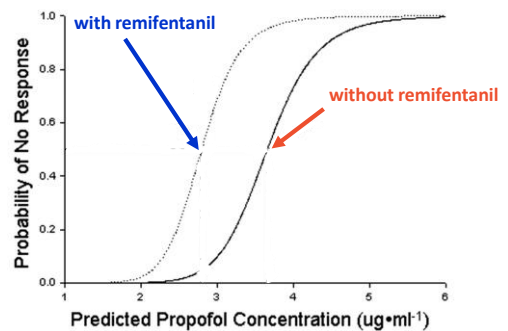
## To avoid prolonged recovery....

- **BIS**
  - Useful in longer procedures to avoid excess propofol



## To avoid prolonged recovery....

- **Remifentanil infusion**
  - Synergy with propofol



*Mcfarlan, Anderson, Short*  
*Paediatric Anaesthesia 1999 9: 209-216*



*Drover, Italian, Wellis, Shafer, Hammer*  
*Anesthesiology 2004 100: 382-6*

## Propofol TCI

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- Propofol alone does not provide adequate surgical conditions



Association  
of Anaesthetists

## Propofol TCI

---

Hyponotic



Association  
of Anaesthetists

## Propofol TCI

---

Hyponotic



~~Analgesic~~



Association  
of Anaesthetists

## Adjuncts to propofol TCI

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- Regional blockade
- Local anaesthetic
- N<sub>2</sub>O
- Opiate
- Ketamine
- $\alpha_2$  agonist



Association  
of Anaesthetists

## Remifentanil - advantages

- Synergism + titratability

- Rapid onset of action

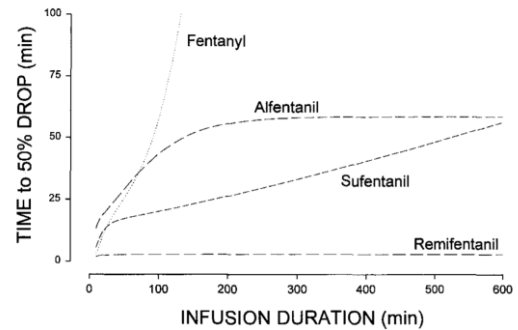
$C_e$  reached in 1 - 2 mins

- Ultrashort acting

$t_{1/2}$  is always 3 - 4 mins



*Egan - Journal of Anaesthesia*  
1998 12: 195-204



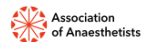
*Egan - Journal of Anaesthesia*  
1998 12: 195-204

## Remifentanil - delivery

- TCI - Minto model

≥ 12 years

≥ 30kg



*Guidelines for the safe practice of total intravenous anaesthesia - Nimmo et al Anaesthesia 2019 74: 211-224*

## Remifentanil - mcg/kg/min

Maintenance  
0.08 - 0.2 mcg/kg/min

**“ Mixing of propofol and remifentanil in a single syringe is not recommended ”**

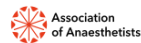
GUIDELINES FOR THE SAFE PRACTICE OF TOTAL INTRAVENOUS ANAESTHESIA (TIVA)	
1	All anaesthetists should be trained and competent in the delivery of TIVA. Schools of Anaesthesia and training bodies should provide teaching, training and practical experience of TIVA to all anaesthetic and intensive care medicine trainees.
2	When general anaesthesia is to be maintained by propofol infusion, use of a target-controlled infusion (TCI) is recommended.
3	Starting target concentrations should be chosen depending on the characteristics of the patient, co-administered drugs and clinical situation. Older, frail or unwell patients may benefit from setting a low initial target and making repeated small incremental increases.
4	Within an anaesthetic department, it is preferable to stock only one concentration of propofol and to dilute remifentanyl to a single standard concentration.
The infusion set through which TIVA is delivered should have a Luer-	



Association of Anaesthetists

**to mix...?**

- Effective
- Easy titration for spontaneous ventilation
- Practical delivery - single pump + syringe
- Less programming
- Less plastic waste



Association of Anaesthetists

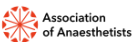
**to mix...?**

- Propofol + remifentanil mixtures decrease bacterial growth
- Glycine preservative



Association of Anaesthetists

*Apan, Apan, Sahin, Cacirca - Journal of Clinical Anaesthesia 2007 19: 346-350*



Association of Anaesthetists

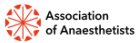
**or not to mix...?**

- Individual titration of hypnotic and analgesic components is possible



## or not to mix...?

- 5 mcg/ml remifentanil mixed with 1% propofol in a plastic syringe **breaks down after 1 hour** at 22 - 24°C
- Hydrolysis of ester group at pH 7 - 7.5



*Stewart, Warren, Maddox et al*  
*Anesthesia Analgesia 2000 90: 1450-1451*

## or not to mix...?

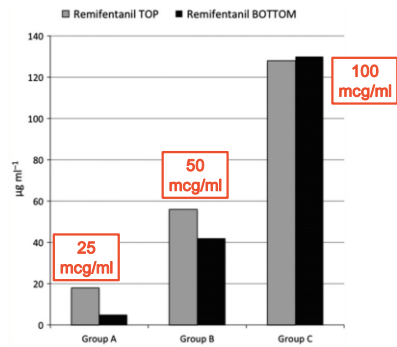
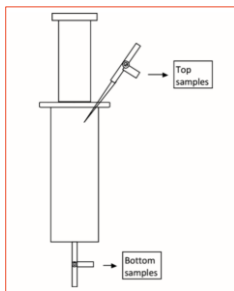
### Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

RESEARCH REPORT

#### Remifentanil and propofol undergo separation and layering when mixed in the same syringe for total intravenous anesthesia

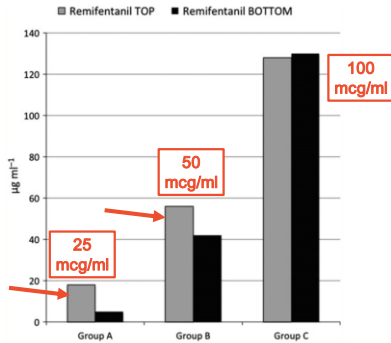
Sean O'Connor, Yan Ling Zhang, Uwe Christians, John E. Morrison Jr & Robert H. Friesen  
Department of Anesthesiology, Children's Hospital Colorado and University of Colorado School of Medicine, Aurora, CO, USA



*O'Connor, Ling Zhang, Christians*  
*Paediatric Anaesthesia 2016 26: 703-709*



*O'Connor, Ling Zhang, Christians*  
*Paediatric Anaesthesia 2016 26: 703-709*



O'Connor, Ling Zhang, Christians  
Paediatric Anaesthesia 2016 26: 703-709

## to mix or not to mix...?

- 24% of paediatric anaesthetists frequently mix remifentanyl with propofol



Goh, Bagshaw, Courtman  
Paediatric Anaesthesia - Nov 2018

Too fiddly +  
Lack of confidence



Goh, Bagshaw, Courtman  
Paediatric Anaesthesia 2019 29 (2): 180-185

TIVA time  
is  
time well  
spent



## Summary

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Do use TIVA in children



## Think TIVA

- ↓ Vomiting
- ↓ Emergence delirium
- ↓ Laryngospasm



## Think TIVA



## Summary

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Do use TIVA in children



Do use TCI models



## Summary

- 
Do use TIVA in children

- 
Do use TCI models

- 
Do use remifentanil

REMIFENTANIL



## The future

### Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

REVIEW ARTICLE

**Total intravenous anesthesia will supercede inhalational anesthesia in pediatric anesthetic practice**

Gillian R. Lauder

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## Thank-you

