



**Association
of Anaesthetists**



RCOA
Royal College of Anaesthetists



CAI
SALUS DUM VIGILAMUS

Joint Professional Guidance on the use of general anaesthesia in young children

UPDATE – September 2019

Association of Paediatric Anaesthetists of Great Britain and Ireland

Royal College of Anaesthetists

Association of Anaesthetists

The College of Anaesthesiologists of Ireland

Executive summary

- **Studies on immature animals have demonstrated that general anaesthetic agents can induce changes in the central nervous system. Some of these studies have also suggested longer-term effects on learning and memory tests.**
- **To date the results from both epidemiological studies and prospective trials in the human infant have failed to show adverse effects on cognitive development from a single anaesthetic episode of short duration (less than an hour). Data from longer exposures and multiple exposures to surgery and anaesthesia are difficult to interpret due to multiple confounding variables.**
- **Continuing to use reliable familiar techniques for paediatric anaesthesia is emphasised. There is no evidence of a particular anaesthetic technique being better than another in terms of influencing any potential long-term neurological effects in humans.**
- **Parents/ carers enquiring about the neurological effects of anaesthesia in their infant should be advised that surgery is carried out in infants only when necessary and that there is no indication of a long-term neurological effect from a single anaesthesia exposure. They should be referred to the current advice to parents on the APAGBI website.**
- **We do not regard a discussion of the potential influence of infant anaesthesia on long term cognitive development as mandatory at every preoperative consultation.**

Introduction

There is still debate on the approach anaesthetists and the wider medical team should take in response to publications about the potential of general anaesthetic agents to cause changes in the developing brain. The debate centres on initial observations in immature animals that a variety of anaesthetic agents including volatile anaesthetic agents, propofol, ketamine and benzodiazepines can induce both cytological, biochemical and behavioral changes after anaesthesia. An increasing number of published studies looking at the potential relevance in the human infant are now available and it is possible that additional ongoing studies will provide information in the near future. These studies have concentrated on the potential harms of anaesthesia on cognitive development in the young after exposure to anaesthetic agents through different approaches: retrospective epidemiological data, prospective cohorts, and randomised controlled trials. The data continues to emerge and therefore any guidance has to remain time sensitive. New opinions, statements and editorials have been published since the previous Joint Professional Guidance document in 2017 and these are referenced below. Several of these documents offer conflicting advice on the 'at risk' population, the interpretation of potential harm and advice for anaesthetists on what to discuss with parents and carers before surgery.

In response to requests from the anaesthesia community in the UK and Ireland, we have updated a brief summary of key points that we hope are clear and provide a safe and sensible response to the current knowledge. This does not take the place of a systematic review on the topic and is not intended to present a prescriptive view on anaesthesia in the very young. The guidance has been prepared to help clarify current knowledge and provide a balanced approach to the data. We have provided suggestions on how to discuss the subject when it has been brought up by parents. There is also a 'Frequently Asked Questions' section with suggested responses, and an up to date reference list. Other data may still emerge that will help to clarify the issue, and we will continue to review this guidance document in the light of new knowledge. Advisory statements from the MHRA may emerge on this topic, which will also need monitoring. This Guidance must, therefore, be seen within the context of a broad approach to this issue and adjusted if and when new information emerges.

Current State of Knowledge

Laboratory studies have shown dose-dependent alterations in brain morphology following exposure of neonatal and infant animals to anaesthesia. [1-3] Dose-dependent acute tissue effects have been reported with many anaesthetic drugs (volatile agents, propofol, thiopental, ketamine, benzodiazepines). Effects vary with the age of the animal, but it is difficult to directly translate ages across mammalian species. Maturation varies in different brain regions, and structural changes may not reflect significant alterations in function. Some studies have shown long-term adverse effects on memory tests in rodents and cognitive tests in primates following prolonged initial exposures. However, monitoring and maintaining physiological stability is difficult in small animals, and the impact of anaesthesia alone, versus anaesthesia and surgical injury, and potential preventive strategies require further evaluation. As a result, it is difficult to directly extrapolate from the laboratory results to current clinical practice.

Human clinical studies evaluating the potential adverse effects of anaesthesia on behavioural and cognitive outcomes in children have been undertaken through prospective randomised trials and epidemiological methods. Importantly, recent prospective studies have shown no difference in outcome after 2 years following hernia repair in infants [4,5] or at 8-15 years of age following a single anaesthetic before 3 years of age. [6] Evidence from epidemiological cohort studies is mixed, as exposures and outcomes vary, but several recent studies have shown no major adverse effects following single anaesthetics. [7-14] The lack of adverse effect following a single anaesthetic exposure of approximately one hour is reassuring.

The FDA Drug Safety Communication for General Anaesthetic and Sedation Drugs has raised concern in 2016 (<https://www.fda.gov/Drugs/DrugSafety/ucm554634.htm>) which led to responses from anaesthesia bodies [14-16]. This communication included recommendations for health care professionals on balancing the benefits and potential risks of prolonged anaesthesia (greater than 3 hours) or repeated anaesthesia in children under 3 years. It also provided recommendations to parents/caregivers on discussing potential risks and benefits with their child's health care professional. The designation of specific risk, ages and durations of anaesthesia are, at this time, however, without substantive data to support these limits. [17] It also needs to be understood that while non-urgent procedures can be delayed until a child is older, the risks of postponing or cancelling life-saving procedures or time-sensitive surgeries in infancy carries clear and documented risks. Furthermore, there is good evidence that inadequate anaesthesia and analgesia may result in significant and serious complications.

Practical issues in Paediatric Management

No child should undergo a procedure that is unnecessary, and in general, infants and young children do not undergo general anaesthesia for diagnostic investigations, elective surgery or emergency surgery for trivial reasons. It is recommended that if there are concerns about undertaking a procedure and/or the rationale for the planned surgery is unclear, the issues should be discussed with the surgical team as early as possible. Direct communication may allow an exchange of relative or perceived risks from each discipline to make a clear balanced decision.

There is currently no evidence to support any particular anaesthetic technique or drug regimen that has benefit over another in terms of reducing the potential effects of anaesthesia on the human infant brain. Established and safe anaesthetic techniques, delivered by trained and experienced staff, in an environment with the necessary monitoring, support and infrastructure underpins good quality care. [18-20]. Minimising known risks, such as cardiovascular or respiratory complications, should take precedence over the theoretical risk of neurotoxicity [7], particularly as there is currently insufficient comparative data to make any recommendations regarding changes of anaesthetic practice. Moreover, changing from a familiar established technique to something unfamiliar can potentially introduce new and quantifiable risks.

It is important to discuss all aspects of perioperative safety with patients, parents and carers before surgery in the usual fashion. However, unlike major known side-effects and complications of anaesthesia, [21] it is more difficult to deal with the current and as yet unknown risks of anaesthesia in infancy on cognitive development. Transparency in patient care is mandatory and there has been some confusion on whether the current state of knowledge requires the anaesthetic team to raise this specific issue with all parents of younger children about to undergo anaesthesia. Some statements suggest routine discussion of anaesthetic toxicity with all parents [16]. It is our view that based on current knowledge, a discussion of potential effects of anaesthesia in infancy on cognitive development is not mandatory and must be balanced against the potential to cause unnecessary fear and stress. However, each consent process should be individualised, considering the clinical need for anaesthesia and parental requests for further information regarding risk. Parents may raise the issue of potential toxicity prior to surgery and this should prompt a careful discussion of the current state of knowledge emphasising the points made above. Parents should also be directed to further resources outlining the issue for parents and carers and a short series of 'Frequently Asked Questions' as below. We continue to liaise with other organisations on this issue. The situation is being monitored and as new information becomes available, we will modify this guidance document as necessary in liaison with partner organisations.

References

1. Creeley CE. From Drug-Induced Developmental Neuroapoptosis to Pediatric Anesthetic Neurotoxicity- Where Are We Now? *Brain Sci* 2016; 6.pii E32.
2. Lin EP, Lee JR, Lee CS, Deng M, Loepke AW. Do anesthetics harm the developing human brain? An integrative analysis of animal and human studies. *Neurotoxicol Teratol* 2016; 60:117-128.
3. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. *Nat Rev Neurosci* 2016;17:705-717.
4. Davidson AJ, Disma N, de Graaff JC, Withington DE, Dorris L, Bell G, Stargatt R, Bellinger DC, Schuster T, Arnup SJ, Hardy P, Hunt RW, Takagi MJ, Giribaldi G, Hartmann PL, Salvo I, Morton NS, von Ungern Sternberg BS, Locatelli BG, Wilton N, Lynn A, Thomas JJ, Polaner D, Bagshaw O, Szmuk P, Absalom AR, Frawley G, Berde C, Ormond GD, Marmor J, McCann ME, consortium GAS. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2016;387(10015):239-250.
5. McCann ME, de Graaff JC, Dorris L, et al. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): an international, multicentre, randomised, controlled equivalence trial. *Lancet* 2019; 393:664.
6. Sun LS, Li G, Miller TL, Salorio C, Byrne MW, Bellinger DC, Ing C, Park R, Radcliffe J, Hays SR, DiMaggio CJ, Cooper TJ, Rauh V, Maxwell LG, Youn A, McGowan FX. Association Between a Single General Anesthesia Exposure Before Age 36 Months and Neurocognitive Outcomes in Later Childhood. *JAMA* 2016;315:2312-2320.
7. Davidson A. The effect of anaesthesia on the infant brain. *Early Hum Dev* 2016;102:37-40.
8. Glatz P, Sandin RH, Pedersen NL, Bonamy AK, Eriksson LI, Granath F. Association of Anesthesia and Surgery During Childhood With Long-term Academic Performance. *JAMA pediatrics* 2017;171:e163470.
9. Graham MR, Brownell M, Chateau DG, Dragan RD, Burchill C, Fransoo RR. Neurodevelopmental Assessment in Kindergarten in Children Exposed to General Anesthesia before the Age of 4 Years: A Retrospective Matched Cohort Study. *Anesthesiology* 2016;125: 667-677.
10. Hansen TG, Pedersen JK, Henneberg SW, Morton NS, Christensen K. Educational outcome in adolescence following pyloric stenosis repair before 3 months of age: a nationwide cohort study. *Paediatr Anaesth* 2013;23: 883-890.
11. O'Leary JD, Janus M, Duku E, et al. Influence of Surgical Procedures and General Anesthesia on Child Development Before Primary School Entry Among Matched Sibling Pairs. *JAMA Pediatr* 2019; 173:29.

12. Warner DO, Zaccariello MJ, Katusic SK, et al. Neuropsychological and Behavioral Outcomes after Exposure of Young Children to Procedures Requiring General Anesthesia: The Mayo Anesthesia Safety in Kids (MASK) Study. *Anesthesiology* 2018; 129:89.
13. O'Leary JD, Janus M, Duku E, Wijeyesundera DN, To T, Li P, Maynes JT, Crawford MW. A Population-based Study Evaluating the Association between Surgery in Early Life and Child Development at Primary School Entry. *Anesthesiology* 2016;125: 272-279.
14. Australian & New Zealand College of Anaesthetists (ANZCA) and Society of Paediatric Anaesthesia in New Zealand and Australia (SPANZA). Warnings: Young children, pregnant women. <http://www.anzca.edu.au/front-page-news/warnings-young-children,-pregnant-women> (accessed June 2019).
15. Hansen TG. Use of anaesthetics in young children: Consensus statement of the European Society of Anaesthesiology, the European Society for Paediatric Anaesthesiology, the European Association of Cardiothoracic Anaesthesiology and the European Safe Tots Anaesthesia Research Initiative. *Eur J Anaesthesiol.* 2017; 34:327-328.
16. Andropoulos DB, Greene MF. Anesthesia and Developing Brains - Implications of the FDA Warning. *N Engl J Med* 2017. ;376(10):905-907.
17. Szmuk P, Andropoulos D, McGowan F, Brambrink A, Lee C, Lee KJ, McCann ME, Liu Y, Saynhalath R, Bong CL, Anderson BJ, Berde C, De Graaff JC, Disma N, Kurth D, Loepke A, Orser B, Sessler DI, Skowno JJ, von Ungern-Sternberg BS, Vutskits L, Davidson A. An open label pilot study of a dexmedetomidine-remifentanyl-caudal anesthetic for infant lower abdominal/lower extremity surgery: The T REX pilot study. *Paediatr Anaesth.* 2019; 29:59-67.
18. Weiss M, Hansen TG, Engelhardt T. Ensuring safe anaesthesia for neonates, infants and young children: what really matters. *Arch Dis Child* 2016;101: 650-652.
19. Weiss M, Vutskits L, Hansen TG, Engelhardt T. Safe Anesthesia For Every Tot - The SAFETOTS initiative. *Curr Opin Anaesthesiol* 2015;28: 302-307.
20. Engelhardt T, Ayansina D, Bell GT, Oshan V, Rutherford JS, Morton NS; APRICOT Group of the European Society of Anaesthesiology Clinical Trial Network. Incidence of severe critical events in paediatric anaesthesia in the United Kingdom: secondary analysis of the anaesthesia practice in children observational trial (APRICOT study). *Anaesthesia.* 2019; 74:300-311.
21. Habre W, Disma N, Virag K, Becke K, Hansen TG, Jöhr M, Leva B, Morton NS, Vermeulen PM, Zielinska M, Boda K, Veyckemans F; APRICOT Group of the European Society of Anaesthesiology Clinical Trial Network. Incidence of severe critical events in paediatric anaesthesia (APRICOT): a prospective multicentre observational study in 261 hospitals in Europe. *Lancet Respir Med.* 2017; 5:412-425.

Further Reading

Davidson AJ, Sun LS. Clinical Evidence for Any Effect of Anesthesia on the Developing Brain. *Anesthesiology*. 2018; 128:840-853.

Jevtovic-Todorovic, V. Exposure of developing brain to general anesthesia: What is the animal evidence? *Anesthesiology* 2018; 128:832–9.

Statements

FDA Drug Safety Communication for General Anaesthetic and Sedation Drugs (<https://www.fda.gov/Drugs/DrugSafety/ucm554634.htm>) (accessed June 2019).

Australian & New Zealand College of Anaesthetists (ANZCA) and Society of Paediatric Anaesthesia in New Zealand and Australia (SPANZA). Warnings: Young children, pregnant women. <http://www.anzca.edu.au/front-page-news/warnings-young-children,-pregnant-women> (accessed June 2019).

Hansen TG. Use of anaesthetics in young children: Consensus statement of the European Society of Anaesthesiology, the European Society for Paediatric Anaesthesiology, the European Association of Cardiothoracic Anaesthesiology and the European Safe Tots Anaesthesia Research Initiative. *Eur J Anaesthesiol*. 2017; 34:327-328.

Editorials and Commentaries

Andropoulos DB, Greene MF. Anesthesia and Developing Brains - Implications of the FDA Warning. *N Engl J Med* 2017. ;376: 905-907.

Davidson A. The effect of anaesthesia on the infant brain. *Early Hum Dev* 2016;102:37-40

Weiss M, Hansen TG, Engelhardt T. Ensuring safe anaesthesia for neonates, infants and young children: what really matters. *Arch Dis Child* 2016;101: 650-652.

Davidson A, Vutskits L. The new FDA drug safety communication on the use of general anesthetics in young children: what should we make of it? *Paediatr Anaesth*. 2017; 27:336-337.

Vutskits L, Davidson A. Update on developmental anesthesia neurotoxicity. *Curr Opin Anaesthesiol*. 2017 30:337-342.

Culley DJ, Avram MJ. Young Brain and Anesthesia: Refusal of Anesthesia Is Not an Option! *Anesthesiology*. 2018, 128: 697-699.

Disma N, O'Leary JD, Loepke AW, Brambrink AM, Becke K, Clausen NG, De Graaff JC, Liu F, Hansen TG, McCann ME, Salorio CF, Soriano S, Sun LS, Szmuk P, Warner DO, Vutskits L, Davidson AJ. Anesthesia and the developing brain: A way forward for laboratory and clinical research. *Paediatr Anaesth*. 2018; 28: 758-763.

Vutskits L, CulleyDJ. Gas, PANDA and MASK. No evidence of Clinical Anesthetic Neurotoxicity. *Anesthesiology*. 2019 (in press).

Weiss M, Engelhardt T, Hansen TGH. Long-term neurocognitive impairment after general anesthesia in childhood. Is obstructive sleep apnoea to blame? *Eur J Anaesthesiol*. 2019; 36:1-3.

Resources and Information for Parents

Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI)

Information for Parents. [\(separate page below\)](#)

Safe Anesthesia For Every Tot (Safetots) Initiative

What to tell parents. <https://www.safetots.org/parents-faq/>

SmartTots

Collaborative group including International Anesthesia Research Society (IARS) and the U.S. FDA.

Consensus Statement On The Use Of Anesthetic And Sedative Drugs In Infants And Toddlers

<http://smarttots.org/about/consensus-statement/>

Nemergut ME, Aganga D, Flick RP. Anesthetic neurotoxicity: what to tell the parents? *Pediatr Anaesth* 2014;24:120-126.

Frequently Asked Questions

1. What should I say to the parents/ carers of a young infant who express concern about anaesthesia and the potential for long-term effects on the brain?

This should prompt an open discussion using the advice to parents/ carers and also the advice to professionals from the APA website. It may be helpful to have these to hand and give them a chance to read these documents before further discussion. The central points to explain are:

- a) That the surgery or procedure is only being scheduled because it is necessary.
- b) The experimental data and measures used in animals cannot be directly translated into serious long-term effects in human infants.
- c) A single anaesthetic of short duration has not been shown to cause long-term changes in cognitive development.
- d) The importance of careful management of paediatric anaesthesia by trained personnel within a safe environment need to be emphasised.
- e) That all babies and children are closely monitored during anaesthesia and surgery to maximise safety and minimise side-effects.
- f) That surgery cannot be safely performed without adequate anaesthesia and analgesia.

2. If parents still remain unsure or are concerned about providing consent for anaesthesia and surgery, what should you do?

In the rare case when parents or carers remain sufficiently concerned to withhold consent for elective procedures, it may be necessary to organise a further discussion with all the relevant disciplines, to discuss the benefits of the procedure/surgery and risks of delay. This may result in postponement for cases that are not urgent.

Emergency or urgent surgery may still need to take place, and risks associated with delay clearly outweigh the theoretical issues about anaesthesia on long-term cognitive development.

3. If I am called to anaesthetise a young infant should I instigate a discussion about long-term effects of anaesthesia on cognitive development?

It is important to discuss all the known risks of anaesthesia in the pre-surgical discussion. Based on the current data, we do not believe that discussion of effects of anaesthesia on cognitive development is mandatory or should be instigated.

4. Should I alter my current anaesthesia practice in response to the current evidence base information or other published statements?

No. There is currently no evidence to support one particular anaesthetic technique or drug regimen that has benefit over another in terms of reducing the potential effects of anaesthesia on the infant brain. In addition, changing anaesthesia practice from a familiar to an unfamiliar technique can itself introduce risk.

5. Is repeated exposure or long duration exposure to anaesthetic agents more harmful than short-duration single exposure?

There is not enough evidence to answer this question at this time. Evidence from both epidemiological and prospective studies indicate that a single exposure to anaesthesia of an hour appears to be safe in terms of cognitive development. The epidemiological studies carried out so far have not shown major adverse effects on the infant brain that can be specifically related to anaesthesia. Infants who need multiple anaesthetics or those who require complex surgery and anaesthesia of long duration usually have additional comorbidities that can affect development. This has made data analysis on multiple exposures or longer-term exposures unable to definitively resolve the issue and is unlikely to do so in the future.