



18 April, 2017

Joint professional guidance on the use of general anaesthesia in young children

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.
- 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 currently 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.
- At this time, 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 currently much 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 behavioural changes after anaesthesia. There are a number of published studies looking at the potential relevance in the human infant and additional ongoing studies will provide information in the near future. The 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 needs to be time sensitive. However there have already been many statements published on this topic with wide spectra of opinion and advice. These include (to date) SmartTots, Safetots, an FDA advisory statement, a European working party statement and editorials in *Pediatric Anesthesia* and *The New England Journal of Medicine* (1). These are referenced in the text below. Several of the 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 UK and Ireland, we have provided 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 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 potential (but as yet unproven) problem and adjusted as 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.[2; 8; 11] 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 2 years following hernia repair in infants [4] or at 8-15 years of age following a single anaesthetic before 3 years of age.[10] 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.[3; 5-7; 9] The lack of adverse effect following a single anaesthetic exposure of approximately one hour is reassuring.

The recent FDA Drug Safety Communication for General Anaesthetic and Sedation Drugs (www.fda.gov/Drugs/DrugSafety/ucm532356.htm) has raised concern and led to responses from anaesthesia bodies. This communication includes 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 provides recommendations to parents/caregivers on discussing potential risks and benefits with their child's health care professional. The FDA Safety Communication specifically refers to prolonged or repeated exposure, which is a clinical group where there is limited evidence and it is difficult to attribute effects specifically to anaesthetic drugs. There are many confounders in this clinical cohort: underlying illness, repeated procedures, and/or the effect of altered physiological parameters, inflammation and trauma associated with prolonged surgery. These factors all have effects that may influence outcome. The designation of specific risk, ages and durations of anaesthesia are, at this time, without substantive data to support these limits. 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 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.[12; 13] Minimising known risks, such as cardiovascular or respiratory complications, should take precedence over the theoretical risk of neurotoxicity [3], 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, 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 [1]. 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 the webpage on the APAGBI

website and other literature outlining the issue for parents and carers (www.apagbi.org.uk/parents-and-carers).

The APAGBI continues to liaise with other organisations, both nationally and internationally, 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 in the UK and Ireland. We have prepared a short series of Frequently Asked Questions that may also be of some help and provided a reference list of recent manuscripts and review articles for further reading.

Association of Paediatric Anaesthetists of Great Britain and Ireland

Royal College of Anaesthetists

Association of Anaesthetists of Great Britain and Ireland

The College of Anaesthetists of Ireland

ENDS

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Recent Statements

- [1] FDA Drug Safety Communication for General Anaesthetic and Sedation Drugs www.fda.gov/Drugs/DrugSafety/ucm532356.htm
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Resources and Information for Parents/Carers

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Recent Editorials and Commentaries

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