Introduction

Historically, anaesthetists have believed that their actions only have immediate or short-term consequences. Morbidity or mortality that occurs after discharge is invariably assumed to be secondary to the patient’s underlying medical condition. Recently, a growing body of evidence has emerged suggesting that anaesthesia may have long term implications in susceptible individuals, particularly in patients anaesthetised at the extremes of age. Research suggests that anaesthetic agents may be neurotoxic under certain circumstances, and has raised the possibility that even a routine anaesthetic might pose a risk in vulnerable brains at the extremes of age: the very young and the elderly.

Scientific data is extremely sparse at present, and there are many limitations to the evidence that currently exists. In particular, most of the research has been carried out either in vitro or in animal models, and there is deserved scepticism concerning the extrapolation of animal data to humans. Nevertheless, enough concern has been generated in the relevant medical circles to warrant the Anesthesia Patient Safety Foundation (APSF) in the US convening an experts’ workshop in September 2004 to discuss long term outcomes after surgery and anaesthesia.1 Considering that mortality rates in the first year after surgery are as high as 5 – 14% in certain patient populations, small improvements in these rates could save many lives each year.

This lecture will review the latest research on the long term effects of anaesthesia in the very young and the elderly, and examine some of the pathophysiological mechanisms that have been implicated.

Long term effects of anaesthesia in the very young

Developmental susceptibility to neurodegeneration

Neuronal apoptosis, or programmed cell death, takes place during normal development of the central nervous system (CNS). Apoptosis is a physiological process initiated by the nuclei of normally functioning cells by which neurons are programmed to commit suicide if their synaptic mission is thwarted to some critical degree, thereby eliminating redundant neurons. Disruption or exacerbation of apoptosis by genetically determined disturbances, environmental factors, drugs and stressors (e.g. pain, hypoglycaemia, hypoxia and ischaemia) is a non-physiological phenomenon and may result in elimination of crucial brain cells, leading to neurodevelopmental disorders in the foetus or infant.

Recently, studies in animal models have shown that transient interference in the action of certain neurotransmitters during a critical stage of development can trigger apoptosis of millions of neurons that otherwise would not have been deleted from the developing brain.2 This stage of development is known as “synaptogenesis” and, in the human brain, correlates with a period of rapid growth (the brain growth spurt) which starts in the sixth month of pregnancy and extends to the third year after birth.

In the immature mammalian brain, neuronal apoptosis can be triggered by the transient blockade of excitatory glutamate N-methyl-d-aspartate (NMDA) receptors, or the excessive activation of inhibitory γ-aminobutyric acid (GABA) receptors. Since the commonly used anaesthetic agents have strong affinity for these receptors, it has been postulated that anaesthetics may induce apoptosis of immature neurons via the same receptor-mediated processes seen in animal models. Ketamine and nitrous oxide are potent NMDA-receptor antagonists, whilst propofol, volatile agents, benzodiazepines and barbiturates are GABA-agonists. The brain develops under the influence of neural input as the foetus interacts with its environment, whereas anaesthesia removes the input and suppresses normal neural traffic, and may consequently decrease synaptogenesis. In other words, NMDA and GABA receptor stimulation are critical for neuronal survival during development, and either excessive stimulation or suppression of this activity results in apoptotic cell death. The effect is specific for NMDA and GABA receptors because it is not reproduced by blockade of other major excitatory or inhibitory systems in the brain, namely muscarinic and dopaminergic.3

Ethanol provides a prime example of an agent that, by interfering with neurotransmitter systems, can delete large numbers of neurons and give rise to neurobehavioural disturbances and physical abnormalities collectively known as foetal alcohol syndrome (FAS). Ethanol is a potent NMDA-antagonist and GABA-agonist, and studies in rodents show that administration of ethanol to infant rats triggers robust neuroapoptosis.4 In addition, superimposing the neurodegeneration pattern that results from treating infant rats with NMDA-antagonists and GABA-agonists results in the same degeneration pattern caused by ethanol. Especially noteworthy is the fact that it only requires a single ethanol intoxication episode for foetal brain damage to occur in the rat model.
Studies in rodents

A number of animal studies have been conducted to evaluate the effects of NMDA-antagonists and GABA-agonists on the developing brain. Much of the work has focused on ketamine, which does not imply that the risk of neurodegeneration is greater with ketamine; rather, it is simply the drug for which the most preclinical data exists.

The first reported study to indicate that NMDA-receptor antagonists could produce neurotoxicity was published in 1999 by Konamidou et al. This study in rat pups demonstrated that MK-801 (an NMDA-antagonist) and ketamine led to widespread apoptotic neurodegeneration in the developing rat brain. The results indicated an age-related sensitivity correlating with the period of synaptogenesis in humans, with no apoptosis occurring in the infant rat brains exposed to these agents after postnatal day 21. In addition, a dose-related and duration effect were clearly demonstrated.

The concerns raised in this study about the safety of ketamine in infants and young children warranted further investigation to confirm and elaborate on the original findings. Scallet et al confirmed histologically that the ketamine dosing regimen used in the original study did result in apoptosis in rat pups, but less aggressive dosing did not, suggesting that the neurotoxicity of ketamine depends on the dose administered and the duration of exposure.

Following these preliminary studies, it became imperative to attempt to extrapolate these findings to humans in order to determine whether or not this is a clinical problem at currently administered doses of anaesthetic agents, and which age groups are most at risk. The period of synaptogenesis during which rodents are most vulnerable corresponds to human development that occurs approximately from the third trimester in utero through the third year of life. In addition, there is a second period of accelerated synaptogenesis that occurs during adolescence, and there is some evidence that there is increased neurological vulnerability to the effects of alcohol and certain drugs used recreationally during this time.

Based on the evidence found in rodents, the scientific community recommended that non-human primate studies should be carried out. Primate studies have been initiated but, for logistical reasons, have been outpaced by ongoing rodent data being generated internationally. Jevtovic-Todorovic et al reported apoptosis in neonatal rats exposed to 6 hours of “mock anaesthesia” using isoflurane, nitrous oxide and midazolam. Neither nitrous oxide nor midazolam alone produced apoptosis, whereas isoflurane did. However, the combination of two or more of any of these agents produced significant neurodegeneration, with the “triple cocktail” producing the greatest increase in the number of apoptotic cells. In addition, the triple combination of drugs resulted in persistent memory and learning impairment later in life. This was the first report of observed behavioural impairment subsequent to anaesthetic exposure and, not surprisingly, generated considerable debate within the scientific community about the correct interpretation of the findings.

Collectively, the rodent studies suggest that these animals are sensitive to NMDA-antagonists and GABA-agonists, and imply that anaesthetic agents other than ketamine are neurotoxic to the developing CNS and may produce neurobehavioural problems later in life. Most worrying is that a combination of drugs commonly used for routine anaesthesia in human infants may produce greater toxicity than individual drugs. The big question is whether or not these findings are clinically relevant to humans.

Studies in non-human primates

Studies conducted with cultured monkey frontal cortical neurons found that prolonged exposure of these cells to high concentrations of NMDA-antagonists resulted in apoptosis, but also suggested that there may be dose-related safety margins for ketamine and other agents commonly used in the clinical setting.

Data from initial primate studies conducted in 2005 confirmed that ketamine administered to pregnant females causes enhanced cell death in the foetal brain, consistent with an apoptotic mechanism. However, the apoptosis occurred in different regions of the primate brain as compared to the rodent brain, and there was some evidence suggestive of neuronal compensation. Whether the observed cell death affects overall brain function, or whether the injured brain tissue can recover with no loss of normal function, remains to be seen.

Where to from here?

The results of primate studies currently underway with ketamine will impact on how other anaesthetics will be evaluated for safety and efficacy in paediatric patients, particularly new NMDA-antagonist and GABA-agonist agents. Regardless of the mechanism, the available data raise the spectre that standard clinical anaesthesia practice could promote brain injury in the human foetus, infant and young child. These reports led the United States Food and Drug Administration (FDA) to convene an Advisory Committee Meeting in April 2007 (meeting transcript available at http://www.fda.gov/ohrms/dockets/ac/07/transcripts/2007/4285t1.pdf). The purpose of the FDA meeting was to evaluate the potential neurodegenerative effects of anaesthetics in infant and juvenile animals. In addition, the FDA and National Institute of Health have formally requested paediatric safety studies for a number of commonly used anaesthetic agents, including isoflurane, sevoflurane, desflurane, morphine, fentanyl, remifentanil, propofol and midazolam. As many of these drugs are used in combination, studies will be conducted to determine whether the neurodegenerative effects are additive or synergistic compared with the individual drugs.

Results from the Victorian Infant Collaborative Study Group of 1996 have already suggested that there is an adverse association between the need for surgery requiring general anaesthesia during the primary hospitalisation, and sensorineural outcome in extremely premature or low birth weight infants.

The GAS (GA vs. Spinal) study, which is currently recruiting participants, is a multicentre, randomised controlled trial comparing regional and general anaesthesia for effects on neurodevelopmental outcomes at 2 years and 5 years post surgery for inguinal hernia repair. Infants aged 26 to 60 weeks post conceptional age will be...
randomised to receive either sevoflurane general anaesthesia (combined with regional analgesia), or spinal/caudal anaesthesia alone. The outcome is eagerly awaited, as it will provide the greatest evidence to date for safety or toxicity of general anaesthesia for human infants.

**Summary of long term effects of anaesthesia in the young**

This brings us to the critical question: how can we know whether or not anaesthetic drugs trigger apoptosis in the vulnerable developing human brain? Rodent data provide an imprecise basis at best, and an irrelevant basis at worst, for evaluating human risk. Primate studies have only recently been initiated but, so far, appear to corroborate the rodent data.

There is another vital issue: what are the alternatives to anaesthesia? Pain and the unchecked stress response are well known to be associated with adverse outcomes. Which anaesthetic is the safest? Should surgery be delayed in infants and young children and, if so, until when? Given the prolonged human development phase, this would mean months to years; usually not a practical option. In the interim, the FDA has advised clinicians to minimise exposure to potentially offending drugs whenever possible and to consider alternative, non-surgical therapies if available.

Anand and Sorianno summarised current knowledge as follows:11

- **Duration of exposure**: It is likely that prolonged exposure to anaesthetic drugs may be essential for apoptosis to manifest clinically.
- **Dose-related effects**: Low dose or single exposures to high concentrations have not consistently resulted in pathophysiological effects in animal studies. In addition, ketamine in very high doses is known to induce seizure activity, which may contribute significantly to neuronal apoptosis.
- **Effects of malnutrition on the immature brain**: Decreased weight gain following prolonged anaesthesia points to the clinical role of nutrition in early brain development. Human neonates routinely receive nutritional support and metabolic monitoring in the peri-operative period, thus minimising the risks of hypoglycaemia and impaired nutrition.12
- **Anaesthesia and cerebral oxygen delivery**: Anaesthetic agents depress circulation and respiration in a dose-dependent manner, leading to reduced cerebral perfusion and hypoxia. In humans, continuous monitoring and optimisation/manipulation of haemodynamic and metabolic parameters is routine, whereas animal studies are characterised by a lack of monitoring and support.
- **Anaesthesia with and without surgery**: Prolonged anaesthesia without surgery reduces sensory input during a critical period of brain development, which can be aggravated by administration of NMDA antagonists or GABA agonists. We also know that painful stimuli during surgery activate NMDA and other excitatory receptors in the immature brain, and anaesthesia and analgesia will reduce these extreme degrees of neuronal excitation. Thus, the effects of anaesthesia without surgery and surgery without anaesthesia may be equally detrimental to the developing brain.
- **Consequences of withholding anaesthesia/analgesia**: Short-term consequences include an increased incidence of intra-operative and postoperative complications leading to poor surgical outcomes. Long term consequences include prolonged changes in pain sensitivity and pain processing, as well as a variety of neurodevelopmental, behavioural and cognitive deficits manifesting in later childhood. These risks need to be weighed up against the recent experimental data showing the neurotoxic effects of anaesthetic agents. Currently, it seems clear that anaesthesia is still better than no anaesthesia if surgery is required.

**Long term effects of anaesthesia in the elderly**

**Cognitive function and anaesthesia**

Elderly surgical patients constitute a unique surgical group, and they require special consideration in order to pre-empt possible long term adverse effects of anaesthesia. The crude peri-operative mortality rate in the general population is 1,2% compared with 8,4% in patients over 90 years.13 These numbers are significantly worse when one considers major surgery alone. One of the most common and serious side-effects is postoperative cognitive dysfunction (POCD), as its presence may herald an increase in both morbidity and mortality.

To begin with, it is important to recognise that intellectual decline is a common, although not invariable, finding in the elderly. About 5% of persons older than 65 years will suffer from some degree of dementia, and more subtle cognitive impairment is detectable in over 60% of “normal” elderly people.14 Cognitive decline can be ameliorated to some extent by remaining intellectually engaged and, even more importantly, through ongoing physical activity. Consequently, there is no such thing as the “typical” older person, and chronological age is not a reliable indicator of cognitive ability.

Until recently, it has been assumed that most anaesthetic agents provide some degree of neuroprotection.15 Volatile agents, barbiturates and propofol suppress excitatory neurotransmitters like glutamate and AMPA and potentiate inhibitory ones like GABA, thereby inhibiting ischaemic cascades. They also reduce the cerebral metabolic rate of oxygen consumption (CMRO₂). Unfortunately, no agent has ever been shown to have long term protective effects. Recently, new evidence has come to light casting doubt on the notion of anaesthetic agents as neuroprotective, and suggesting that they may in fact be responsible for aggravating a number of long term adverse sequelae in the elderly surgical patient, including POCD and Alzheimer’s disease (AD).

**Postoperative cognitive dysfunction**

The incidence of POCD is related to the type of surgery, medications...
received peri-operatively, and pre-existing comorbidity. The estimated incidence of POCD in the elderly surgical population is 15 – 25% after non-cardiac surgery and 24 – 80% after cardiac surgery, and constitutes a risk factor for poor functional recovery and increased morbidity. Up to 10% of elderly patients will exhibit signs of POCD three months after surgery, placing a huge emotional and financial burden on family members, as these patients are invariably unable to live independently. The avoidance and treatment of POCD therefore represents one of the greatest challenges of modern medicine and surgery.

The link between postoperative cognitive dysfunction and anaesthesia

General anaesthesia is a profound form of CNS suppression and is often blamed for POCD, although the clinical evidence for this is surprisingly sparse. Most data indicate that the risk of POCD is identical with regional and general anaesthesia; however, intravenous sedation is often used to supplement regional anaesthesia, making it difficult to isolate the influence of the type of anaesthetic itself. Nevertheless, a systematic review of anaesthesia techniques and POCD has failed to show a difference.

Anaesthesia, by affecting the release of neurotransmitters within the CNS, could potentially damage memory processes in elderly surgical patients. It is generally believed that the effects of anaesthetic agents do not outlive their pharmacological actions, yet there is increasing evidence that this concept is not true. It seems that long-term neurological changes can follow administration of anaesthetic drugs, and the elderly brain may be particularly vulnerable.

Animal studies suggest that even short exposure to a volatile agent can irreversibly alter proteins in the brain. Rats exposed to desflurane anaesthesia were found to have persistent changes in brain cytosolic protein expression, challenging the notion that the effects of volatiles disappear within minutes or hours. Other laboratory studies have found that isoflurane-nitrous oxide anaesthesia without surgery impairs spatial learning for weeks in aged rats. Since the agents are long cleared from the brain by the time behavioural testing is undertaken, these results suggest that memory is somehow altered in an enduring way by anaesthesia itself. Further confirming these findings, anaesthetic-induced neuroapoptosis occurs in cell culture after exposure to clinically relevant doses of isoflurane, as well as in the brains of old rats after nitrous oxide and ketamine.

The findings from animal studies indicate that general anaesthesia, either by changing or damaging the old brain, could be one of the factors responsible for the development of POCD. However, they do not provide any insight into the pathophysiology of POCD following regional anaesthesia. POCD remains a problem with a multifactorial aetiology, and there is currently no scientific basis for recommending or avoiding a specific anaesthetic agent or technique.

Alzheimer’s disease

AD is the most common cause of dementia and a prototype of pathological brain ageing. Ten to 15% of persons older than 65 years will develop AD, and by 85 years, about 30 – 50% will be afflicted. Brain changes observed in normal ageing are present in an exaggerated form in AD, with loss of brain mass occurring at a rate 2.5 times normal. Cholinergic deficiency is a hallmark of AD, but the leading hypothesis as to the cause centres on an imbalance between the generation and clearance of b amyloid (ßA) protein, a protein produced by proteolytic cleavage of a larger precursor, amyloid precursor protein (APP). Accumulation (also called oligomerisation) of these proteins into so-called amyloid plaques is an early pathological feature in the brain of asymptomatic carriers of gene mutations that predispose to the development of AD, and plaques are widespread in the late stages of this disease. In addition, ßA itself appears to be toxic and contributes to synapse loss and dysfunction even before plaques are detected. Another pathological hallmark of AD is the neurofibrillary tangle, which is composed of filaments of hyperphosphorylated tau, a microtubule-associated protein.

The link between Alzheimer’s disease and anaesthesia

In addition to the concerns over general anaesthesia and POCD, recent reports suggest that AD is also accelerated by anaesthesia and surgery. In fact, although delirium and dementia have long been considered separate conditions, recent evidence has increasingly highlighted their inter-relationship. Long-term follow-up of patients following coronary artery bypass surgery (CABG) revealed that PODC is present in 53%, 36%, 24% and 42% of patients at discharge, 6 weeks, 6 months and 5 years, respectively. Three separate studies produced odds ratios of between 1.2 and 1.6 for the association between previous surgery and AD, although none were sufficiently powered to demonstrate statistical significance. In addition, the age of onset of AD was inversely related to the cumulative exposure to anaesthesia before age 50. A recent study also reported that patients having CABG under general anaesthesia were 70% more likely to develop AD, compared to those having percutaneous transluminal angioplasty under local anaesthesia. If larger studies confirm these findings, it would imply a 20 to 60% increase in AD as a result of surgery and general anaesthesia.

Eckenhoff et al showed that halothane and isoflurane enhance ßA oligomerisation, potentiate the cytotoxicity of ßA, and increase activity of the APP cleavage enzyme b-secretase of cell cultures, resulting in apoptosis. This effect occurs even at clinical concentrations of these drugs, but the severity appears to be dose-dependent. Interestingly, in this study, ethanol appeared to inhibit ßA aggregation at low concentrations, suggesting that light to moderate ethanol consumption may reduce the risk of dementia in humans. The same study also showed that very high concentrations of propofol can enhance Ab oligomerisation. The authors emphasise that the above mechanism is not expected to cause AD, but rather to accelerate the underlying pathogenesis and symptomatology.

Further studies by Xie et al confirmed that clinically relevant concentrations of isoflurane cause neuroapoptosis, alter APP processing and increase ßA production in vitro. The authors
concluded that isoflurane may indeed contribute to the well-described mechanism of Alzheimer’s neuropathogenesis. The mechanism by which isoflurane causes apoptosis appears to involve activation of inositol trisphosphate (IP3) receptors on the endoplasmic reticulum, resulting in excessive calcium release. Indeed, dantrolene, by inhibiting cytosolic calcium release, has been shown to attenuate isoflurane-induced apoptosis. In another study, memantine, an NMDA receptor antagonist that inhibits isoflurane-induced calcium release was able to prevent apoptosis, further reinforcing the calcium dependent mechanism of anaesthetic induced apoptosis. It is not yet clear whether all anaesthetics activate IP3 receptors. In one study, sevoflurane did not induce similar neuronal apoptosis as isoflurane at equipotent concentrations, at least during in vitro studies.

Anaesthesia has also been shown to induce massive and rapid hyperphosphorylation of tau. This is independent of the anaesthetic used (intravenous vs. volatile) and is not a direct result of the agent per se, but from the hypothermia consequent to anaesthesia. Re-establishing normothermia during anaesthesia completely rescues tau phosphorylation to normal levels. Further studies are required to examine the effects of anaesthesia-induced hypothermia on the risk and progression of AD.

These studies provide a pathophysiological basis linking the more acute process of delirium and POCD following volatile-based general anaesthesia, with the longer term consequences of dementia.

**Summary of long term effects of anaesthesia in the elderly**

Whilst the aetiology of postoperative delirium, cognitive dysfunction and dementia is undoubtedly multifactorial, it is possible that general anaesthesia itself can cause prolonged cognitive alterations in aged patients. The aged brain differs from the younger brain in several important aspects, including size, distribution and type of neurotransmitters, metabolic function and capacity for plasticity, suggesting that it might be more susceptible to anaesthetic-mediated changes. Once again, the clinician should exercise caution in extrapolating data obtained from animal and in vitro studies to the clinical setting, but these concerns should be borne in mind when scheduling elderly patients for purely elective surgery.

**Conclusion**

The long term effects of general anaesthesia on brain function represent a burgeoning area of interest in clinical research. Long term outcome is a new safety concern, since a number of recent studies suggest that perioperative events and care decisions may affect the patient adversely months or even years after surgery. This is particularly true of patients at the extremes of age who appear to be more vulnerable to the subtle adverse effects of general anaesthesia.

A number of mechanisms have been proposed for these unanticipated outcomes, including anaesthetic-induced apoptosis. So far, the available information is extremely sparse, complicated and has many limitations, but should be pursued until its conclusion.

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