Anaesthetics safe in neonates

Proposal for update of Section 1-ANAESTHETICS included in the 3rd WHO Model List of Essential Medicines for Children (2011)

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For WHO Secretariat

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Anaesthesia in neonates

Introduction

Safe anaesthesia for neonates (children of age 0-28 postnatal days) is based on understanding their unique physiology and response to medications so as best to provide analgesia and amnesia, depress stress responses, maintain cardiovascular stability, and return them to baseline status. Medications administered by any route have a similarly rapid uptake (alpha phase) followed by the slower elimination phase (beta phase) as in adults. However, the duration of these phases is altered by changes in body composition, protein binding, and maturation of organ function.\(^1\)

Since the 1980s, a large number of studies and scientific data have shown that both neonates and premature babies do possess the neuro-anatomical and synaptic prerequisites to perceive nociceptive stimulation. Not only may insufficient pain relief be associated with negative short-term effects but insufficient neonatal analgesia also has long-term effects. Taddio et al.\(^2\) and Brady-Fryer\(^3\) have clearly shown that neonatal boys who were circumcised without analgesia have a more pronounced pain experience to later immunisation injections, compared with boys who had received active analgesia by means of EMLA cream (EMLA, eutectic mixture of lidocaine and prilocaine). Thus, there is no doubt that both neonates and premature babies should receive adequate pain relief for both surgical interventions as well as painful procedures outside the operating theatre, for example, in the neonatal intensive care unit (NICU). One of the best, and may be also the safest, ways to provide high-quality analgesia is with the use of local anaesthesia, either alone or in combination with other drugs. The small size of neonatal patients does not in any manner preclude the use of local or regional anaesthetic techniques.\(^4\)

Over the last decade there have been great advances in techniques, drugs and monitoring in anaesthesia. Recently concern has arisen over potential anaesthetic neurotoxicity to the developing brain. The issue stems from the recent publication of several studies in the animal model which demonstrated accelerated neuronal apoptosis and long term behavioural changes

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4 Per Arne Lönnqvist. Regional anaesthesia and analgesia in the neonate. Best Practice & Research Clinical Anaesthesiology 24 (2010-) 309e321
in rodents exposed to anaesthesia in the neonatal period. The injury is likely to involve both NMDA (N-methyl-D-aspartate) and GABA (gamma-aminobutyric acid) receptors though the exact mechanism of injury remains unknown. Recent data in primates have also found that prolonged exposure to ketamine is associated with neuronal apoptosis. The relevance of these findings to human clinical practice is very unclear. When translating animal data, significant questions arise in terms of dose, duration, timing and the human potential for recovery.

A growing number of studies in immature animal models demonstrate degenerative effects of several anesthetics on neuronal structure. A few studies reveal cognitive impairment in adult animals after neonatal anesthesia. There are no prospective studies evaluating neurocognitive function in children after neonatal exposure to anesthetics. However, several retrospective reviews demonstrate temporary neurological sequelae after prolonged anesthetic exposure in young children and larger studies identify long-term neurodevelopmental impairment after neonatal surgery and anesthesia. The evidence for anesthesia-induced neurodegeneration in animal models is compelling. Although this phenomenon has not been prospectively studied in young children, anecdotal data point toward the possibility for neurological impairment after surgery and anesthesia early in life. Given the serious implications for public health, further investigations of this phenomenon are imperative, both in laboratory animals and in young children. In neonatal mice, equipotent doses of the three commonly used inhaled anesthetics demonstrated similar neurotoxic profiles, suggesting that developmental neurotoxicity is a common feature of all three drugs and cannot be avoided by switching to newer agents.

Taken as a whole, the available data appear to indicate that anaesthetic drugs such as barbiturates, propofol, xenon and most volatile anaesthetics (halothane, isoflurane, desflurane, sevoflurane) show neuroprotective effects that protect cerebral tissue from adverse events—such as apoptosis, degeneration, inflammation and energy failure—caused by chronic neurodegenerative diseases, ischaemia, stroke or nervous system trauma. Nevertheless, in several studies, the administration of gaseous, volatile and intravenous anaesthetics (especially isoflurane and ketamine) was also associated with dose-dependent and exposure time-

dependent neurodegenerative effects in the developing animal brain. At present, available experimental data do not support the selection of any one anaesthetic agent over the others. Furthermore, the relative benefit of one anaesthetic versus another, with regard to neuroprotective potential, is unlikely to form a rational basis for choice. Each drug has some undesirable adverse effects that, together with the patient's medical and surgical history, appear to be decisive in choosing the most suitable anaesthetic agent for a specific situation. Moreover, it is important to highlight that many of the studies in the literature have been conducted in animals or in vitro; hence, results and conclusions of most of them may not be directly applied to the clinical setting. For these reasons, and given the serious implications for public health, further investigation--geared mainly to clarifying the complex interactions between anaesthetic drug actions and specific mechanisms involved in brain injury, within a setting as close as possible to the clinical situation is imperative.7

Many anaesthetic agents are not licensed for children. The reasons for this are complex, but in part must relate to lack of safety or toxicity data for children, especially neonates. When considering the potential neurotoxicity of anaesthesia it is also important to recognize the well described risks associated with inadequate anaesthesia in this age group. There is increasingly good evidence that unrelieved pain causes prolonged physiological and behavioural change in human neonates. No randomized control trials examining different strategies exist. Standard evidenced-based approaches for guidelines used by many organizations attempting to link the "strength of the evidence" to the "strength of the recommendations" therefore cannot be used in this instance. There is, however, considerable experimental consensus within observational studies in the pediatric population.

While it remains prudent to avoid elective surgery in infants the current evidence suggests a very high degree of safety for anaesthesia in this age group, and that inadequate anaesthesia and analgesia, or delay in non-elective surgery are all associated with more tangible risks (2012).8

Several different types of drug are given together during general anaesthesia. Anaesthesia is induced with either a volatile drug given by inhalation or with an intravenously administered drug; anaesthesia is maintained with an intravenous or inhalational anaesthetic. Analgesics, usually short-acting opioids, are also used. The use of neuromuscular blocking drugs necessitates intermittent positive-pressure ventilation. Following surgery, anticholinesterases can be given to reverse the effects of neuromuscular blocking drugs; specific antagonists can be

used to reverse central and respiratory depression caused by some drugs used in surgery. A topical local anaesthetic can be used to reduce pain at the injection site.

Individual requirements vary considerably and the recommended doses are only a guide.

**Pharmacologic considerations**

The neonate is different than older children and the adult from physiological point of view. The differences are in following areas:

- Total body water accounts for ~ 85% body weight in a premature infant, ~ 75% in a term infant and, in infants 6 months and older, the total body water only accounts for 60% of body weight. These differences have important implications for drug effect, loading dose, interval of dosing and drug metabolism. A premature infant has only ~ 18% of weight as muscle, a term infant ~ 30%, a 6-month-old ~ 40%, and most children >one year ~ 50%. If giving a medication that has its primary effect at the myoneural junction, one could postulate that a lower dose or a lower plasma level would be required to have a clinical effect compared to the other child; this has been demonstrated for most muscle relaxants;

- Total body fat content in premature infant accounts for only ~ 4% body weight as fat; the term infant ~ 15%; the 6-month-old ~ 25%; and older children nearly 30%. If a drug redistributes into fat, then the volume of tissue into which that drug can be distributed varies by age. For example, the effect of thiopental is diminished through redistribution rather than metabolism. Prolonged sedation might result in neonates simply on the basis of them not having much fat tissue to redistribute into. In preterm infants, the only place where there is any fat is in the brain.

Another factor is maturity of hepatic function. Newborns are capable of conjugating and glucuronidating most medications, but the rate of metabolism is generally delayed compared to the older child or adult. The half-life of thiopental is ~18 hours in a term newborn, ~7 hours in a child 4 - 10 years of age, and 10 hours in the adult.

- Maturity of renal function also markedly alters a drug’s half-life. There is a very rapid maturation of renal function in the first months of life. In preterm infants, the glomerular filtration rate (ml/minute/1.73 m2 surface area) is only ~ 25, in the term infant ~ 35, by two weeks of age it has doubled to ~ 60, by 6 months it is ~ 80, and at 1 year it is equivalent to an adult. Thus, drugs that are excreted by the kidneys, are given at less frequent intervals in the premature compared to the term newborn, and at less frequent intervals in the term newborn compared to older children.

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The neonate’s response to inhalation anesthetic agents differ. There is still unknown why the minimum alveolar concentration (MAC) is higher compared with older children. The rate of rise of inhalation agent depends upon the combination of delivery of drug to and removal from the lungs. A steady state exists once the alveolar and the inspired concentrations (FA/Fi) equilibrate; this equilibrium is more rapid in children. In neonates, the greater cardiac output increases the equilibration of FA/Fi because of the high distribution to vessel rich groups (~ 18% neonate vs. ~ 8% adult). The rate of increase of FA/Fi of inhalation anaesthetics varies inversely with the solubility in blood: nitrous oxide > desflurane > sevoflurane > isoflurane > enflurane > halothane > methoxyflurane. Another factor is the tissue/gas solubilities of the inhalation anaesthetics, which is about half that of adults. This reduced tissue solubility decreases the time for partial pressure equilibration. Thus FA/Fi equilibrates more rapidly in neonates and infants compared with adults.

A gaseous induction is not generally recommended, since all inhalation agents depress the heart long before they adequately depress airway reflexes, and because of the effects of inhalation agents on the airway: increased respiratory rate, decreased tidal volume, loss of intercostal muscle function (decreased functional residual capacity), and collapse of upper airway structures leading to upper airway obstruction (often relieved with 5 - 10 cm PEEP). If the infant has apparent normal airway anatomy, then a standard intravenous induction with muscle relaxant to facilitate intubation is indicated.

Special precautions and close monitoring of the patient are required. These drugs may be fatal if used inappropriately and should be used by non-specialized personnel only as a last resort. Irrespective of whether a general or conduction (regional or local) anaesthetic technique is used, it is essential that facilities for intubation and mechanically assisted ventilation are available. A full preoperative assessment is required including, if necessary, appropriate fluid replacement.

With the above considerations in mind, the choice for maintenance of anaesthesia is often a combination of short acting opioid, muscle relaxant, and low dose inhalation agent.

The goals of Anesthesia for the Neonate essentially are the same as those for adult or for a child:\(^{11}\):

- Minimization of physiological, humoral and behavioral signs of distress
- Reduction of pain
- Ablation of consciousness
- Maximization of perioperative outcomes\(^{12}\)

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\(^{11}\) Davidson A. Pediatric Anesthesia 2007; 17:102

The actions of the anesthetics should alleviate the programmed neuronal death (apoptosis). These agents are expected to act as:\textsuperscript{13}

- NMDA receptor antagonists (ketamine, nitrous oxide)
- GABA\textsubscript{A} receptor antagonists (barbiturates, benzodiazepines, propofol, etomidate)
- Volatile agents (Halothan, Isoflurane, Servoflurane, Desflurane)

Current Essential medicine list for children (WHO EML children) 3\textsuperscript{rd} list, March 2011\textsuperscript{14}

1. ANAESTHETICS

1.1 General anaesthetics and oxygen
1.1.1 Inhalational medicines

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>halothane</td>
<td>Inhalation</td>
</tr>
<tr>
<td>isoflurane</td>
<td>Inhalation</td>
</tr>
<tr>
<td>nitrous oxide</td>
<td>Inhalation</td>
</tr>
<tr>
<td>oxygen</td>
<td>Inhalation (medicinal gas)</td>
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</tbody>
</table>

1.1.2 Injectable medicines

<table>
<thead>
<tr>
<th>Anaesthetic</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>ketamine</td>
<td>Injection: 50 mg (as hydrochloride)/ml in 10-ml vial.</td>
</tr>
<tr>
<td>propofol*</td>
<td>Injection: 10 mg/ml; 20 mg/ml.  * Thiopental may be used as an alternative depending on local availability and cost.</td>
</tr>
</tbody>
</table>

1.2 Local anaesthetics

- bupivacaine
  
  | Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 7.5% glucose solution. |

- lidocaine
  
  | Injection: 1%; 2% (hydrochloride) in vial.  
  | Injection for spinal anaesthesia: 5% (hydrochloride) in 2-ml ampoule to be mixed with 7.5% glucose solution.  
  | Topical forms: 2% to 4% (hydrochloride). |

- lidocaine + epinephrine (adrenaline)
  
  | Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000.  
  | Injection: 1%; 2% (hydrochloride or sulfate) + epinephrine 1:200 000 in vial. |

The objectives of this review were:

\textsuperscript{13} Blaylock M. Pediatric Anesthesia 2010;20:383

\textsuperscript{14} http://whqlibdoc.who.int/hq/2011/a95054_eng.pdf
1. To review the literature regarding anesthesia in neonates as special group of children in terms of their immaturity of the organs and systems
2. To review the evidence about the effectiveness and safety of the medicines used for anesthesia in neonates, especially those included in identified Clinical guidelines
3. To find the evidence of license status of the medicines used in neonates, including premature neonates born before 37-th gestational week
4. To propose changes in the WHO EML for children regarding age, or to propose application of other medicines more appropriate for the neonates. These medicines should be used in a variety of settings to allow the provider of anaesthesia to:
   a. Provide preoperative medication as indicated
   b. Induce anaesthesia for a variety of procedures via IV and inhalational routes in neonates
   c. Provide maintenance of general anaesthesia via inhalational and alternative routes

Methods for the review performance
Literature review in a systematic manner, regarding the context, setting, mode of conducting, purpose and other information related to anaesthesia in newborns and infants. For such purpose, bellow mentioned databases were extensively explored.

1. Available WHO web sites were searched looking for treatment guidelines, or other publications related to the medicines in neonates/infants/children. Several documents were identified:
   - WHO Guidelines for safe surgery 2009: Safe surgery saves lives, 2009\(^{15}\) and the extended Project review \(^{16}\)
   - Pocket book of hospital care for children: Guidelines for the management of common illnesses with limited resources, 2005\(^{17}\)
   - Surgical care at the district hospital, 2003 WHO "Guide to anaesthetic infrastructure and supplies at various levels of health care facilities" was compiled from this document \(^{18}\)


\(^{16}\) Merry, A. F., Eichhorn, J. H. and Wilson, I. H. (2009), Extending the WHO ‘Safe Surgery Saves Lives’ project through Global Oximetry. Anaesthesia, 64: 1045–1048


• Managing complications in pregnancy and childbirth: A guide for midwives and doctors, 2003\textsuperscript{19} ISBN 92 4 154587 9 NLM Classification WQ 240

• Essential medicines Training Resources accessed at
  http://www.who.int/medicines/training/en/
  Extrapolated Quality and Safety: Medicines teaching resources

Eight Guidelines were identified, some of them relevant to the topic, but the recommendation were not directly linked to the anaesthetics in neonates

3. National Institute for Clinical Excellence and National Institute for Health Research was searched, looking for treatment Guidelines and the evidence based on. The Clinical Guidelines was available at:
The recommendations and summary tables were based on evidence provided in the Full Guideline

4. Information about the treatment was obtained from different Guidelines recognized as evidence based websites were explored too. Those are listed below:
New Zealand District Hospital, continuously updated, accessed at
http://www.adhb.govt.nz/newborn/
Royal prince Alfred Hospital in Sydney continuously updated, accessed at
WHO Pharmacopeia accessed at
5. Geneva Foundation for Medical Education and research, accessed at
http://www.gfmer.ch/000_Homepage_En.htm http://www.gfmer.ch/000_Homepage_En.htm

6. MEDLINE database was searched with the relevant terms, including “anaesthesia”, “anesthesia”, “neonate”, “newborn”, “premature neonate”, “premature newborn”, “pediatric anaesthesia”, “analgesia”. Over 150 Abstracts/Full texts were retrieved which had some relevance to the explored topic.

The databases MEDLINE and EMBASE were searched for primary literature review regarding drug analysis, adverse events, cost benefit analysis, efficacy and effectiveness of different medicines included in the treatment Guidelines. The name of each of the medicines used for analgesia and anaesthesia was searched separately in the database, regarding all of its properties. The available website for this purpose was:

7. Detailed review of the WHO EML for children, 3rd list of March 2011, related to the generic names of the medicines, dosage forms, formulations was performed. The EML for children was extracted from the WHO publication available at:

8. The Cochrane database of systematic reviews was searched using all the above mentioned terms. The website of Cochrane Anaesthesia group was also examined and CENTRAL Cochrane Register of Controlled trials was searched. There were identified few not so relevant systematic reviews, which will be discussed in details bellow. The explored website was:
www.cochrane.org/reviews/index.htm

9. Database of Abstract of Reviews of Effects (DARE)-Centre for Reviews and Dissemination was searched and several papers, publications and Guidelines were identified. There were found several meta-analysis regarding benefits and adverse effects of anesthetic and analgesic agents, but the participants were not separated according to the age. The website of this database is http://www.crd.york.ac.uk/crdweb/
The Systematic reviews and the meta-analysis retrieved from this database were mostly related to adults, few of them mixed population, or children, but the age was over one month in all of them.


13. Websites of the Food and Drug Agency and European Agency for Medicines was explored looking for licensing status of medicines. Web site: http://www.fda.gov/default.htm

14. Scanned Journal websites using above mentioned terms
   - British Medical Journal, accessed at http://www.bmj.com/content
   - British Journal of Anaesthesia, accessed at http://www.bja.ac.uk/british-journal-of-anaesthesia/
   - Pediatrics accessed at www.pediatrics.aappublications.org/
   - The Journal of Toxicological Sciences accessed at www.jtoxsci.org/

All information were matched with the WHO EML for children (3-rd from March 2011) and available data extrapolated form the obtained evidence and information. The Tables in the WHO EML for children were enriched with new information, suggestions and appropriate recommendations presented.

### ANAESTHETICS

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Volatile liquid anaesthetics

Volatile liquid anaesthetics can be used for induction and maintenance of anaesthesia, and following induction with an intravenous anaesthetic.

Isoflurane is a volatile liquid anaesthetic. Heart rhythm is generally stable during isoflurane anaesthesia, but heart-rate can rise. There are many severe adverse effects to the child, especially to the neonate. Desflurane is a rapid-acting volatile liquid anaesthetic; it is reported to have about one-fifth the potency of isoflurane. Emergence and recovery from anaesthesia are particularly rapid because of its low solubility. Desflurane is not recommended for induction of anaesthesia as it is irritant to the upper respiratory tract; cough, breath-holding, apnoea, laryngospasm, and increased secretions can occur. In a study was shown that neonates wake faster from general anaesthesia when maintained with desflurane as compared with sevoflurane, but no difference in postoperative respiratory events was demonstrated between the groups.\(^{21}\)

Sevoflurane is a rapid-acting volatile liquid anaesthetic and is more potent than desflurane. Emergence and recovery are particularly rapid but slower than desflurane. Sevoflurane is non-irritant and is therefore used for inhalational induction of anaesthesia. There are some comparisons between few of them in terms of the time and success after extubation in NICUs.\(^{22}\)

Halothane is a volatile liquid anaesthetic that has largely been superseded by newer agents, but is used occasionally by very specialised paediatric anaesthetists to manage difficult airways (with careful monitoring for cardiopulmonary depression and arrhythmias). Its advantages are that it is potent, induction is smooth, and the vapour is non-irritant and seldom induces coughing or breath-holding.

### Halothane

**ATC code:** N01AB01

A clinically important issue for neonates (with a minimal alveolar concentration- MAC for halothane of 0,87%, and a MAC of sevoflurane of ~3%) is that the currently available vapourisers deliver more MAC multiples of halothane than sevoflurane. Excessive

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concentrations of sevoflurane cannot be administered, because the large MAC values more than offset reduced solubilities. Thus the cardiovascular safety profile of sevoflurane appears to be far better than halothane.\textsuperscript{23} However, cardiac arrest may occur with both agents with the onset of controlled respirations which forces more drug into the lungs. Once respirations are controlled, the inspired concentration must be dramatically reduced to avoid cardiac depression. Neonates are more likely to display cardiovascular instability during induction of inhalation anesthesia than any other age group\textsuperscript{24} Halothane, traditionally used in infants and children, is associated with potent negative inotropic and chronotropic cardiac effects and is rarely used anymore for neonatal anesthesia. Sevoflurane, a methyl isopropyl ether anesthetic, is a recent alternative to halothane for neonates who are at greatest risk of halothane-induced hypotension and bradycardia.\textsuperscript{25} The MAC of sevoflurane is twice that of isoflurane and 3 times that of halothane, indicating that sevoflurane is far less potent.\textsuperscript{26} However, sevoflurane has other advantages, such as low tissue and blood solubility, which speed its elimination in infants and children. Sevoflurane also causes less bradycardia and less airway irritation than some other anesthetic agents, making induction a smoother event. In summary, sevoflurane provides for a rapid and smooth induction of, and recovery from, anaesthesia. These features combined with its favourable cardiovascular profile should make sevoflurane the agent of choice for inhalation induction in adult and paediatric anaesthesia.\textsuperscript{27}

The adverse impact from halothane exposure on the developing brain was reported two decades ago, when it was demonstrated that long-term exposure to halothane, beginning \textit{in utero} and continuing for several days in the postnatal period, led to impaired synaptogenesis, reduced dendritic branching, suppressed axonal growth, and reduced myelination in rodents. Yet, these studies did not achieve notoriety because the manifestation of central nervous system toxicity required prolonged exposure to halothane, a situation not encountered in clinical practice.\textsuperscript{28}

\textbf{Quoting from WHO Model Formulary for Children}\textsuperscript{29}

\textit{‘Special Notes:} This medicine is listed as a representative of its pharmacological class. Other
medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

**Indications:** Induction and maintenance of anaesthesia.

**Contraindications:** History of unexplained jaundice or fever following previous exposure to halothane; family history of malignant hyperthermia; raised cerebrospinal fluid pressure; porphyria.

**Precautions:** Anaesthetic history should be carefully taken to determine previous exposure and previous reactions to halothane (fulminant hepatic failure is a rare complication of re-exposure to halothane); avoid use if adequate resuscitation facilities are not available.

**Indications and Dose are presented for infant or children over 1 month**

**Summary for Halothane:**
- Halothane is not a preferred agent in neonates
- Adverse effects likely to be severe in neonates compared to infants and older patients;
- Contraindication in jaundice is a condition very frequently met in newborns in the first week of life;
- Halothane is a representative of the class, so it could be replaced by other similar inhalational medicines.

**Isoflurane**

ATC code N01AB06

The use in pediatrics is presented in the Report of the Center for Drug Evaluation and Research within FDA.  

Isoflurane is always administered in conjunction with air and/or pure oxygen. Although its physical properties imply that anaesthesia can be induced more rapidly than with halothane, its pungency can irritate the respiratory system, negating this theoretical advantage conferred by its physical properties. It is usually used to maintain a state of general anesthesia that has been induced with another drug, such as thiopentone or propofol. It vaporizes readily, but is a liquid at room temperature. It is completely nonflammable. Safety issues in neonates are found in the New Zealand Governmental datasheet of safety of medicines. **FDA access data shows its properties in the summary of the pharmacokinetics and pharmacodynamics of the medicine.**

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31 Department of Health and Human Services, Public Health Service, Food and Drug Administration; Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology Department of Health and Human Services. April 21, 2010


33 [http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/017624s036lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/017624s036lbl.pdf)
Concerns have been raised as to the safety of certain general anesthetics, in particular ketamine and isoflurane in infants and young children due to significant neurodegeneration. The risk of neurodegeneration is increased in combination of these agents with nitrous oxide and benzodiazepines such as midazolam. This has led the FDA and other bodies to take steps to investigate these concerns.

ADVERSE REACTIONS

Isoflurane, liquid for inhalation. Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – February 2010

Isoflurane has also been associated with perioperative hyperkalemia.

Indications and dose are presented in Clinical Guidelines, and neonates are included as patients.

Induction of anaesthesia
- By inhalation through specifically calibrated vaporiser. 
  *Neonate* increased gradually according to response from 0.5–3% in oxygen or nitrous oxide-oxygen

Maintenance of anaesthesia
- By inhalation through specifically calibrated vaporiser
  *Neonate* 1–2.5% in nitrous oxide-oxygen; additional 0.5–1% may be required if given with oxygen alone

**Summary for Isoflurane:**
- There are data suggesting its safety and adverse reactions are dose dependent
- In all clinical Guidelines It is recommended for use in neonates, either for induction or in maintenance of anesthesia
- Main disadvantage are concerns about its potential neurodegeneration.

**Sevoflurane**

**ATC code** N01AB08

Precaution: The concentration of sevoflurane required for maintenance of general anesthesia is age dependent. When used in combination with nitrous oxide, the MAC equivalent dose of sevoflurane should be reduced in pediatric patients. MAC in premature

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35 Forane (isoflurane) liquid for inhalation. Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – February 2010
http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm204140.htm

infants has not been determined (see PRECAUTIONS - Drug Interactions and DOSAGE AND ADMINISTRATION for recommendations in pediatric patients 1 day of age and older).  

**Indications and dose**

**Induction of anaesthesia**
- By inhalation through specifically calibrated vaporiser
  
  *Neonate* up to 4% in oxygen or nitrous oxide-oxygen, according to response

**Maintenance of anaesthesia**
- By inhalation through specifically calibrated vaporiser
  
  *Neonate* 0.5–2% in oxygen or nitrous oxide-oxygen, according to response

Animal studies:
Sevoflurane has been implicated in neuronal degeneration in infant mice. This activity is thought to occur via blockade of NMDA receptors or hyperactivity of GABA neurotransmission. In one study, the researchers showed exposure of infant mice to inhaled sevoflurane resulted in learning deficits and abnormal social behaviour. Sevoflurane raises intracranial pressure and can cause respiratory depression.

**Summary for Sevoflurane:**
- There are data suggesting its safety and dose dependent adverse reactions;
- In all clinical Guidelines It is recommended for use in neonates, either for induction or in maintenance of anesthesia;
- Main disadvantage are concerns about its potential neurodegeneration, although there are no such data in human models;
- It is worth considering to be included in the WHO EML

**Desflurane**

**ATC code** N01AB07

**Indications and dose are presented for neonates only for maintenance of anaesthesia**
- By inhalation through specifically calibrated vaporiser
  
  *Neonate* 2–6% in nitrous oxide-oxygen; 2.5–8.5% in oxygen or oxygen-enriched air

Desflurane is a general inhalation anesthetic that is administered via vaporizer and is used

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for the induction and maintenance of general anesthesia for inpatient and outpatient surgery in adults and maintenance anesthesia in children. Desflurane is available as a 240 ml bottle and was approved on September 18, 1992. Pediatric Exclusivity was granted on September 13, 2006. The supplemental new drug application, NDA 20-118/S-012 dated December 15, 2006, provided for the inclusion of data for the pediatric population (ages 2-16 years) as outlined in the FDA issued Pediatric Written request dated March 6, 2006. The elimination and half-life are strongly dependent on the minute ventilation, thus the indicators are not sure.

**Summary for Desflurane:**
- The medicine could be used in neonates only for maintenance of the anesthesia, but not for induction;
- There are no safety data for neonates because the neonatal pharmacokinetics is unknown, the elimination depends on the minute ventilation (a physiological process that is very variable in neonate regarding gestational age, birth weight, associated morbidity)
- Not included in Guidelines for Anesthesia in newborns

<table>
<thead>
<tr>
<th>Nitrous oxide</th>
<th>ATC code N01AX13</th>
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**BNFc**

**Indications and dose**

**Maintenance** of anaesthesia in conjunction with other anaesthetic agents
- **By inhalation using suitable anaesthetic apparatus**
  - *Neonate* 50–66% in oxygen

**Analgesia**
- **By inhalation using suitable anaesthetic apparatus**
  - (see also notes above)
  - *Neonate* up to 50% in oxygen, according to the child's needs

**WHO Model formulary**

Dose:

**Maintenance** of light anaesthesia.

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41 Department of Health and Human Services, Public Health Service, Food and Drug Administration; Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology Department of Health and Human Services. April 21, 2010
43 WHO Model Formulary for Children, 2010
Inhalation using suitable anaesthetic apparatus: Neonate, Infant or Child up to 66% in oxygen.

**Analgesia.**

Inhalation using suitable anaesthetic apparatus: Neonate, Infant or Child up to 50% in oxygen, according to the child’s needs.

**NICE**: 50% nitrous oxide licensed for use in sedation for all ages; Nitrous oxide in concentrations greater than 50% is not licensed for analgesia without loss of consciousness

**Summary for Nitrous oxide**
- This gaseous agent should remain in the EML

**Oxygen**

**ATC code:** V03AN01

**Special Notes:** Inhalation gas.

**Indications:** Oxygen should be regarded as a drug, to maintain adequate tissue oxygenation in inhalational anaesthesia and other indications for use in neonates and children. Used during resuscitation and in the treatment of respiratory problems requiring supplemental oxygen.

**Dose:**
Concentration of oxygen in inspired anaesthetic gases should never be less than 21%, and preferably 30% or above.
The concentration required depends on the condition being treated.

**Renal impairment:** No dosage adjustment necessary.

**Hepatic impairment:** No dosage adjustment necessary.

**Adverse effects:** Long-term use of concentrations greater than 80% have a toxic effect on the lungs leading to pulmonary congestion, exudation and atelectasis. Short-term use of 100% is not associated with these toxic effects.
The concentration required depends on the condition being treated; if available, monitoring of the oxygen delivered is strongly recommended, as inappropriate concentration may have serious or even lethal effects. Risks include morbidity, brain damage, and especially in pre-term neonates can cause retinopathy with blindness and chronic lung disease.
Use of 100% oxygen should not be withheld in an emergency situation.

**Interactions with other medicines (** indicates severe):**

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* **Bleomycin:** serious pulmonary toxicity in patients exposed to conventional oxygen concentrations during anaesthesia. Oxygen should be added routinely during anaesthesia with inhalational agents, even when air is used as the carrier gas, to protect against hypoxia.

**Oxygen**

Oxygen should not be given to neonates except under expert supervision. Particular care is required in preterm neonates because of the risk of hyperoxia (see above).

*Low concentration oxygen therapy* (controlled oxygen therapy) is reserved for children at risk of hypercapnic respiratory failure, which is more likely in children with several diseases, including an overdose of opioids, benzodiazepines, or other drugs causing respiratory depression.

**A systematic review has shown the following:**

Neonatal exposure to 100% oxygen is almost never necessary. Much lower concentrations of inspired supplemental oxygen during the neonatal period can also lead to oxygen toxicity if oxygen is used when it is not necessary. Excess oxygen is associated with serious morbidities such as retinopathy of prematurity, bronchopulmonary dysplasia, injury to the developing brain, and childhood cancer. When providing supplemental oxygen, monitoring with modern SpO2 technology and avoidance of SpO2 values of 95-100% are less frequently associated with hyperoxemia.

**SUMMARY:**

Even brief neonatal exposures to pure oxygen must be avoided during neonatal anesthesia. When any dose of supplemental oxygen is given, a reliable pulse oximeter aiming to avoid hyperoxemia is necessary. Even though further research is essential, administration of oxygen by healthcare providers to neonates when it is not necessary, is a foe and a neonatal health hazard.

**Summary for Oxygen**

- It should remain without any changes, only with precautions that monitoring of blood saturation with oxygen should be mandatory, but also and desirable measurement of inspired fraction of Oxygen.

**1.1.2 Injectable medicines**

Intravenous anaesthetics may be used either to induce anaesthesia or for maintenance of anaesthesia throughout surgery. Intravenous anaesthetics nearly all produce their effect in

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one arm-brain circulation time and can cause apnoea and hypotension, and so adequate resuscitative facilities must be available. They are contra-indicated if the anesthetist is not confident of being able to maintain the airway. Extreme care is required in surgery of the mouth, pharynx, or larynx and in children with acute circulatory failure (shock) or fixed cardiac output.

**Drugs used for intravenous anaesthesia**

**Propofol**, the most widely used intravenous anaesthetic, can be used for induction or maintenance of anaesthesia in children, but it is not commonly used in neonates. Propofol is associated with rapid recovery and less hangover effect than other intravenous anaesthetics. It causes pain on intravenous injection which can be reduced by intravenous lidocaine. Significant extraneous muscle movements can occur. Rarely, convulsions, anaphylaxis, and delayed recovery from anaesthesia can occur after propofol administration; the onset of convulsions may not be immediate and can be delayed. Propofol is associated with bradycardia, occasionally profound; intravenous administration of an antimuscarinic drug is used to treat this.

Propofol can be used for sedation during diagnostic procedures but is contra-indicated in children under 16 years receiving intensive care because of the risk of propofol infusion syndrome (potentially fatal effects, including metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidaemia, and hepatomegaly).

**Thiopental sodium** is a barbiturate that is used for induction of anaesthesia, but it has no analgesic properties. Induction is generally smooth and rapid, but dose-related cardiorespiratory depression can occur. Awakening from a moderate dose of thiopental is rapid because the drug redistributes into other tissues, particularly fat. However, metabolism is slow and sedative effects can persist for 24 hours. Repeated doses have a cumulative effect particularly in neonates, and recovery is much slower.

**Ketamine** causes less hypotension than thiopental and propofol during induction. It is sometimes used in children requiring repeat anaesthesia (such as for serial burns dressings), however recovery is relatively slow and there is a high incidence of extraneous muscle movements. Ketamine can cause hallucinations, nightmares, and other transient psychotic effects; these can be reduced by a benzodiazepine, such as diazepam or midazolam

**Ketamine**

ATC code: N01AX03

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Licensed for use in anaesthesia for all ages; intravenous and intramuscular. If deep sedation is needed, ketamine may be used. It should be used only under the supervision of a specialist experienced in its use.

**Indication:** Anaesthesia (lower doses are used for sedation than for anaesthesia for surgery)

**Indications and doses**

**Induction and maintenance of anaesthesia (short procedures)**

- **By intravenous injection over at least 60 seconds**
  
  *Neonate:* 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response

- **By intramuscular injection**
  
  *Neonate:* 4 mg/kg usually produces 15 minutes of surgical anaesthesia, adjusted according to response

- **By intravenous administration**
  
  *Neonate:* initially 0.5–2 mg/kg by intravenous injection, followed by a continuous intravenous infusion of 8 micrograms/kg/minute adjusted according to response; up to 30 micrograms/kg/minute may be used to produce deep anaesthesia

**Summary for Ketamine**

- The medicine should remain in the EML for all types of anaesthesia,
- Paediatric formulations will be useful

**Propofol**

**ATC code** N01AX10

**Indication:** Anaesthesia

Licensed for use in all children older than 1 month in doses of 0.5% or 1%; intravenous

**Indication: sedation**

Licensed for use in people older than 17 years. The Guideline Development Group decided to recommend off-label use of propofol for sedation in children of all ages. This was because propofol is widely used in the UK for sedation in children of all ages and the doses used for sedation are much lower than those used for anaesthesia.

If deep sedation is needed, propofol may be used. It should be used only under the supervision of a specialist experienced in its use.

**Indications and doses are prescribed in the Clinical Guidelines only for children over one month of age**

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Summary for Propofol
- The medicine should not be used in neonates as it is age restricted for infants older than 1 month.
- No systematic review is performed so far to investigate the safety issues of Propofol in neonates.
- The use of Propofol could be included in Guidelines ONLY if National Regulatory Body permits its use in neonates as off-label medicine.
- Dosage formulation is suitable for infants (and neonates).

Thiopental
ATC code N01AF03

Indications and dose

Induction of anaesthesia
- By slow intravenous injection
  Neonate initially up to 2 mg/kg, then 1 mg/kg repeated as necessary (max. total dose 4 mg/kg).
- Prolonged status epilepticus
  - By slow intravenous injection and intravenous infusion
    Neonate initially up to 2 mg/kg by intravenous injection, then up to 8 mg/kg/hour by continuous intravenous infusion, adjusted according to response.

Quoting from WHO Model Formulary for Children

Powder for injection: 0.5 g; 1 g (sodium salt) in ampoule

Special Notes: Specialist skills required for administration and supportive management.

Indications: Induction of anaesthesia prior to administration of inhalational anaesthetic; anaesthesia of short duration.

Contraindications: Inability to maintain airway; hypersensitivity to barbiturates; severe cardiovascular disease; dyspnoea or obstructive respiratory disease; porphyria.

Titrate dose to effect.
Neonate initially up to 2 mg/kg, then 1 mg/kg repeated as necessary (maximum total dose 4 mg/kg).

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Summary for Thiopental
- As is noted in WHO EML, Thiopental may be used as an alternative depending on local availability and cost;
- Thiopental is licensed for neonates
- Adverse effects are common, rare
- Recommended lower strength of the dosage form because the indicated dose is very low, and current formulation poses risk for medication errors

1.2 Local anaesthetics
Topical application and Local infiltration

Bupivacaine
ATC code  N01BB01

Results from a Clinical trial:\(^5^5\)
The new dosage guidelines for continuous epidural infusions of bupivacaine appear to be safe, since no adverse reactions were encountered and all samples of total bupivacaine concentrations were below the supposed seizure threshold of 4 Fg/mL. Assuming a half-life of seven hours after the infusion of bupivacaine epidurally in the neonate, without a bolus dose, it would take 30-35 hours to reach equilibrium. In the present study, however, after a bolus of bupivacaine in a dose of 1.8 mg/kg, five of nine patients still had rising total plasma concentrations after 48 hours of infusion. This observation causes concern regarding the safety of more prolonged epidural infusions in this patient population.

Bupivacaine for circumcision:\(^5^6\)
Given the rarity of accidental intravenous injection and its longer analgesic effect bupivacaine is superior to lidocaine for Dorsal Penile Nerve Block when performing neonatal circumcision.

Summary for bupivacaine
- There is neither strong evidence for use of bupivacaine in newborns, nor age restriction for its use;

lidocaine
ATC code  N01BB02WHO Model Formulary for Children lists lidocaine as a representative local anaesthetic. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability

\(^5^5\) Larsson BA, Linqvist A, Olsson GL. Plasma concentrations of Bupivacaine in neonates, after continuous epidural infusion. Anesth Analg; (1997); 84:501-505
\(^5^6\) Stolik-Dollberg O.C and Dollberg S. Bupivacaine versus lidocaine analgesia for neonatal circumcision
and price. Indications listed are Local anaesthetic blocks, dental work and spinal anaesthesia.

<table>
<thead>
<tr>
<th>Lidocaine + epinephrine (adrenaline)</th>
<th>ATC code N01BB52</th>
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<tbody>
<tr>
<td>Listed in WHO Model Formulary for Children for indications: Dental anaesthesia; infiltration anaesthesia; peripheral nerve block.</td>
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**Summary for lidocaine + epinephrine (adrenaline)**
- Very limited indications for use of lidocaine + epinephrine (adrenaline) and many contraindications and precautions.
- No age restriction

**EMLA**
Still not licensed for use in neonates. Review needed

**Summary** There are very limited data for the use of anaesthetic agents in neonatal age, due to the difficulties in conducting ethical clinical trials in neonates. The information is extrapolated from the trials conducted in infants and older children, and also trying to find analogy with preclinical results. Therefore, information in the review is limited, data sparse, and recommendation based on weak, low level evidence. This problem is the major reason for using some anaesthetics as off-label medicines.

All inhalational agents should be administered through specifically calibrated vaporizer.

All medicines indicated for anesthesia and analgesia should be administered by, or under direct supervision of skilled medical professional, and for majority of them intensive monitoring is recommended.

There is also lack of evidence for almost all anesthetics in neonates for their safety

**Recommendations for EMLc Update**
1. Halothane: This is not the preferred inhalational anesthetic in neonates.
   - Include age restriction of above one month in the listing.
   - Consider adding square box
2. Isoflurane: This is safe in neonates for induction and maintenance
   - Retain in EMLc as it is now

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57 WHO Model Formulary for Children 2010
3. Nitrous oxide: Retain in EMLc as it is now
4. Oxygen: Retain in EMLc as it is now
5. Ketamine: Retain in EMLc as it is now.

   It will be good to have paediatric formulations of this medicine, to improve safety while administering

6. Propofol: This is not licensed for use in those below 17yrs. However, it is frequently used in children. Age restriction above one month could be added in EMLc
7. Thiopental: This is licensed in neonates. Adverse effects are rare. Consider listing this in EMLc. Paediatric formulations will be useful in improving safety while administration
8. Local Anaesthetics - Retain in EMLc as it is now

A systematic review for efficacy and safety of Sevoflurane as an inhalational anaesthetic agent in neonate will be useful, since (still sparse) information about its potential preference over halothane and isoflurane exists.