19th Expert Committee on the Selection and Use of Essential Medicines  
April 8-12 2013

Expert peer review on Anaesthesia for the Newborn- Review

1. Assessment of efficacy
   a. Have all relevant studies on efficacy been included
      Yes

   b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
      Anesthesia in Neonates has same basic aims as in older children and adults—to provide analgesia, hypnosis or amnesia, depress reflexes while maintaining cardiovascular stability and reversal to baseline status after surgery. Practically the same medicines are used, except that neonatal anatomy, physiology and organ maturity are different warranting special considerations of safety, so there are no doubts about efficacy. Many medicines licensed for older children and adults are not done so for neonates, not because of efficacy but more for the reason of safety in view of peculiarity of neonates and lack of studies as to their safety in human

   c. Please provide any additional relevant information with reference
      None

2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes

   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
      Over dosing is likely to produce exaggeration of normal anesthetic effects e.g. severe CVS and RS depression, not just because of size, but also because of other considerations of anatomy, physiology and immaturity, hence affecting medicine redistribution and elimination. Developmental neurotoxicity after neonatal anesthesia is a concern as animal studies (rodents and nonhuman primates) provide compelling evidence that neurodegeraton is a serious possibility. Local anesthesia combined or not with other medicines shows a high safety margin.

   c. Please provide any additional relevant information with reference
      Animal studies do not show that one anesthetic agent is particularly better than another in regards to neurotoxicity. Of note is the fact that combining several medicines produced worse apoptosis than a single agent. This effect is probably mitigated in clinical practice in humans. Many anesthetic agents are not licensed for children because lack of safety and toxicity data. 1. Halothane produces cardiac arrhythmias and depression, but is non irritant to respiratory tract; sevoflurane has less cardiac effects, even less irritant to the respiratory tract but produces greater emergence agitation (Kurani et al), isofurane has a better cardiac profile than halothane with faster recovery, but is irritant to the respiratory system and potentiates action of muscle relaxants. Nitrous Oxide has a potent analgesic property at 50% concentration with oxygen and low toxicity if used with more than 33% O2.
2. Pentothal- Reduce its dose in neonates than in older children (Westrin et al), as can produce severe and prolonged depression and hypotension. Propofol is not commonly used in neonates, but it may cross the placenta barrier in caesarian section to depress the baby’s brain more than thiopentone (Djordjevic et al., D Cello no et al BJA). Ketamine is widely used for anesthesia in the neonate providing potent sedation, amnesia and analgesia while maintaining cardiovascular and respiratory stability. Its action as a NMDA receptor antagonist has been widely studied in animal models for neuroapoptosis.

3. Benzodiazepines—Diazepam and Midazolam both produce hypnosis, amnesia and anxiolysis, but Midazolam is much shorter acting than diazepam.

4. Opiates—Morphine has potential to produce prolonged depression. Fentanyl is shorter acting but has cholinergic effects that can produce bradycardia. All opiates are vasodilators that can produce hypotension. But opiates should not be avoided for intra-operative and post surgery analgesia in NICU (Barash P. G. clinical Anesthesia).

5. Neuromuscular blockers ---Succinylcholine has a very high volume distribution so its dose has to be increased. Vecuronium is metabolized in liver so action is prolonged as liver is immature. Atracurium is a safe neuromuscular blocker particularly in liver and renal impairment.

6. Reversals-- Neostigmine should be used with atropine.

7. Local anesthesia and Regional blocks—there is no hypotension with spinal anesthesia, but may rather produce respiratory depression and apnea (Fallman et al). In premature babies who are prone to post-operative apnea spinal or regional block reduces the incidence drastically. 0.25% bupivacaine is licensed for neonates. Lidocaine is the representative of the group. It is useful as local infiltration in minor painful procedures like deep penile block for circumcision, placement of I.V catheters, insertion and removal of chest tubes etc.

8 Oxygen—It should be used routinely during inhalational anaesthesia in neonates. It is a medicined and is toxic and should not be given to neonates except under supervision. Retinopathy Prematurity or hyperoxic vasoconstriction of retinal vessels imposes a need for a Fio2 that is acceptable. 50-80mm Hg Po2 corresponding to Spo2 of 90-95%(Phelps DL NEJM) is good

3. Assessment of cost and availability
   a. Have all relevant data on cost and cost –effectiveness been provided?
   Yes

   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)
   The older agents such as Halothane, ketamine, thiopentone and diazepam may be less desirable but they widely available and more cost effective than the newer ones, particularly for the low and middle income countries. Moreover Neonatal anaesthesia is relatively limited in the majority of developing countries because neonatal surgery is also quite rudimentary. The newer agents such as isoflurane and sevofluranne, midazolam are quite appropriate in the big and developed centres.

   c. Please provide any additional relevant information with reference

   d. Is the product available in several low and middle income countries?
   Yes- Several of the products are.

4. Assessment of public health need?
   a. Please provide the public health need for this product (1-2 sentences)
   Neonatal anaesthesia is usually performed for emergencies specifically for congenital defects and these occur worldwide. What would be considered as compatible with life and hence subject to surgery depends on level of development of the society
b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

5. Are there special requirements for use or training needed for safe/effective use?
If yes, please provide details in 1-2 sentences
   YES. Highly trained personnel and close monitoring are required.
   Equipment for intubation and mechanical ventilation is required even when using local anaesthetic techniques.

6. Is the proposed product registered by a stringent regulatory authority?
Yes All

7. Any other comments
Neonates and preterm babies have particular physiological differences from the older child and adult. Their proportion of body water is high; body fat and muscle mass reduced, and their liver and kidney (key organs in drug elimination) are immature. The brain and nervous system are still developing and may be subject to neurotoxicity by anaesthetic agents (as in animal studies). Their respiratory and cardiovascular functions are also subject to alterations by the pharmacokinetics of inhalational anaesthetics. The understanding of these physiological differences is important when using anaesthetic agents. Thus, for example, the doses of medicines like muscle relaxants and thioptone have to be reduced accordingly.
Both neonates and preterm babies need adequate analgesia and anaesthesia as studies show that insufficient pain relief at this age does have prolonged physiological and behavioral effects in later life.

8. What is your recommendation to the committee (please provide the rationale)
The inhalational agents, nitrous oxide, halothane and isoflurane should be used in the Neonate. In addition sevoflurane should be added to the EMLc to be used for induction and maintenance in the newborn because of its reduced cardiovascular and respiratory side effects. Inhalational induction may be preferable because of the difficulties that are encountered in placement of I.V. line in neonates (pain, bradycardia and paravenous infiltration).
Preferably midazolam should be used but if not available, then Diazepam to provide hypnosis.
Ketamine and thiopental are useful for induction and maintenance.
Suxamethonium, atracurium and vecuronium should be used as muscle relaxants.

Analgesia and anaesthesia are mandatory in the Newborn in the peri-operative period and in the NICU Anaesthesia in neonates like in adults should provide analgesia, amnesia, depress reflexes, and maintain cardiovascular stability and reversal to baseline status after surgery. While there is concern about the safety of Neonatal anesthesia, there is neither proof nor studies to show that this is particularly deleterious in human. There is ample proof on the other hand that failure to provide adequate analgesia, and amnesia to painful and noxious stimuli has untoward short and long term effects on the Newborn.