Editorial

Emergence delirium: The past, the present, and maybe the future

There is nothing more disturbing to parents than to observe their child in the recovery room completely out of control and, although staring at their parents, not actually recognizing them! They are irritable, uncooperative, thrashing around, trying to rip off their monitors or pull out their intravenous access, and may even attempt to remove wound dressings or casts. This situation is upsetting for everyone, but especially the parents. After "abandoning" their child to strangers during the surgery or procedure, they just want to hold their child and provide comfort, but nothing seems to work and they feel utterly helpless. This "strange behaviour" was first described by James Eckenhoff et al. in 1961.[1] His group reviewed the records of 12 294 paediatric and adult patients at the Hospital of the University of Pennsylvania and found an overall incidence of 5.5% (654 patients). The study included 1 397 children under the age of 19 years: 233 children in the age group 3–9 years, and 1 094 children aged 10–19 years.

It is fascinating to go back in history to see that good science holds up over time. Eckenhoff et al. observed a clear age-dependent incidence of emergence excitement or agitation: 13% in the age group 3–9 years (30 out of 233 children), 9% for children aged 10–19 years (98 out of 1 094) and only 2.4% for the elderly defined as older than 70 years (16 out of 676). The younger the patient, the more likely the occurrence of emergence agitation.

The authors felt that this observation may have been related to the premedication which at that time consisted of scopolamine and a barbiturate. They found that the lowest incidence (0.4%) occurred with a balanced anaesthetic technique consisting of nitrous oxide, a narcotic and thiopental. On the other hand, inhalation agents (ether or cyclopropane) were associated with the highest incidence, independent of the speed of emergence. Their study also showed that the subgroup of children undergoing tonsillectomy and adenoidectomy experienced a 14% incidence of emergence agitation, by far the highest incidence among the groups. Eckenhoff et al. recommended administering a narcotic, e.g. morphine, 15 minutes prior to emergence or a phenothiazine in the recovery room.

What Eckenhoff and his group described over 50 years ago, is exactly what we are still experiencing today: a greater incidence in children anaesthetized with potent inhalation agents compared to those undergoing a procedure under a total intravenous anesthesia (TIVA) technique, the highest incidence in young children after a tonsillectomy, and the fact that opioids and/or a sedative just prior to emergence or after emergence are helpful.

So, nothing has really changed, despite the introduction of new inhalation agents (halothane, enflurane, isoflurane, sevoflurane, and desflurane) and the replacement of thiopental and methohexital with propofol. We no longer use scopolamine or barbiturate premedication. Instead, many children receive a short acting benzodiazepine such as midazolam or no premedication at all. The old medications are gone, but the problem of emergence agitation still exists, with the same incidence and disturbing features as before. Nowadays, parental expectations, social media and the internet are stimulating the discussion and the need for explanations.

One of the great dilemmas in paediatric anaesthesia is the differentiation of pain from emergence agitation. A variety of scoring systems have been developed, with varying success. They can be based on psychiatric assessments from the Diagnostic and Statistical Manual of Mental Disorders, (DSM-IV), or on simple observations. It appears that the simple observations of non-purposeless movement, avoiding eye contact, staring blankly and non-responsiveness are common features.[2-5] These maladaptive behaviours last on average for 10 to 20 minutes and generally resolve spontaneously. Differences between inhalational agents have been evaluated in many studies, with results that vary from study to study. One study randomized eighty children undergoing adenoidectomy and found an incidence of 55% with desflurane, 10% with sevoflurane and 25% with halothane.[6] In order to eliminate pain as a contributing factor, one study examined 32 children undergoing magnetic resonance imaging with either halothane or sevoflurane anaesthesia. The authors reported an 80% incidence of minor agitation with sevoflurane versus 12% with halothane;[7] the incidence of major agitation was 33% with sevoflurane and 0% with halothane. Thus, without any pain (or analgesics), the incidence of emergence agitation may be as great as 80% with sevoflurane.

Many attempts have been made to determine the contribution of other factors. Several well conducted studies have shown that emergence delirium occurs with or without the presence of parents, is unrelated to the duration, depth of anaesthesia[8,9] or the time to emergence and full wakefulness (similar to Eckenhoff et al. observations with cyclopropane vs. ether).[10] A wide range of medications has been used to prevent emergence agitation including fentanyl, propofol, clonidine, dexmedetomidine, and midazolam, all with varying success.[11-15]

So, it seems that there is clearly a relationship between anaesthetic agents and emergence delirium, especially with sevoflurane, less with propofol. But what is the real underlying cause? Could this be related to the fact that sevoflurane causes central excitation and temporarily "scrambles" the neural connections within the central nervous system, as suggested by a paradoxical rise of the Bispectral Index (BIS) when the inspired concentration of sevoflurane exceeds 3%?[16] Likewise ketamine sedation is not associated with a reduction in the BIS and it is well known that ketamine sedation or anaesthesia is associated with night terrors in children and unpleasant dreams in adults.[17-20] Or, is there something else that makes certain children susceptible to this very disturbing behaviour?

Genetic, genomic and ethnic factors have been shown to influence the response to various medications. For example, African American and Caucasian children can manifest very different reactions to opioid medications. After tonsillectomy, opioids seem to be less effective in African Americans (they require larger doses) whereas Caucasians have an increased incidence of adverse opioid effects despite lower doses.[21] Likewise, Latino children have a four-fold greater incidence of pruritus and seven-fold greater incidence of vomiting than Caucasians with similar doses of morphine.[22] There are huge pharmacogenomic differences in the ability to convert codeine to its active metabolite morphine[23] which places children who are ultra-rapid metabolizers (~29% African/Ethiopian, ~21% Saudi Arabia, ~3.4–6.5% African American and Caucasians) at risk for overdose with standard doses

previously thought to be safe. On the other hand, slow metabolizers may receive little or no morphine analgesia from codeine [https://www.fda.gov/Drugs/DrugSafety/ucm313631.htm]. Another interesting observation is that women with red hair have a greater anaesthetic requirements than those with dark hair, possibly in some way related to a specific genotype.[24]

In this issue of SAJAA, two papers touch on these topics. In the first paper, Pradeep et al. found a greater incidence of emergence agitation in children anaesthetized with sevoflurane compared with isoflurane, similar to the observations of previous investigations.[6,7] Interestingly, in accordance with other reports, they also found greater incidence in children who exhibited pre-induction agitation.[25] They confirmed the old adage *"a child who goes to sleep upset will wake up upset*."

In the second paper, Swart et al. examined the relationship of emergence agitation with ethnicity and found a greater incidence in non-African patients (10.4%) vs. African patients (3.1%) in an otolaryngology population. The sample size of non-African patients was rather small and their ethnic origin was likely mixed and not reported, but the authors have opened a new and fascinating door for future investigations. If genetic and ethnic factors can determine our response to medications, could they also affect the susceptibility to emergence agitation? Are these observations linked, and if so, in what way? The authors of both papers are to be congratulated for stimulating our awareness of this very important issue and for encouraging other paediatric anaesthesiologists to further investigate these questions with more extensive and detailed studies in the future.

Charles J Coté, MD

Professor of Anaesthesia (Emeritus), Harvard Medical School, The MassGeneral Hospital for Children, Boston, MA

References

1. Eckenhoff JE, Kneale DH, Dripps RD. The incidence and etiology of postanesthetic excitment. A clinical survey. *Anesthesiology*. Sep-Oct 1961;22:667-73.
2. Przybylo HJ, Martini DR, Mazurek AJ, Bracey E, Johnsen L, Cote CJ. Assessing behaviour in children emerging from anaesthesia: can we apply psychiatric diagnostic techniques? *Paediatr Anaesth*. Sep 2003;13(7):609-16.
3. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology*. May 2004;100(5):1138-45.
4. Malarbi S, Stargatt R, Howard K, Davidson A. Characterizing the behavior of children emerging with delirium from general anesthesia. *Paediatr Anaesth*. Sep 2011;21(9):942-50.
5. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. *Paediatr Anaesth*. Aug 2010;20(8):704-11.
6. Welborn LG, Hannallah RS, Norden JM, Ruttimann UE, Callan CM. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. *Anesth Analg*. Nov 1996;83(5):917-20.
7. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. *Paediatr Anaesth*. 2000;10(4):419-24.
8. Oh AY, Seo KS, Kim SD, Kim CS, Kim HS. Delayed emergence process does not result in a lower incidence of emergence agitation after sevoflurane anesthesia in children. *Acta Anaesthesiol Scand*. Mar 2005;49(3):297-99.
9. Faulk DJ, Twite MD, Zuk J, Pan Z, Wallen B, Friesen RH. Hypnotic depth and the incidence of emergence agitation and negative postoperative behavioral changes. *Paediatr Anaesth*. Jan 2010;20(1):72-81.
10. Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. Rapid emergence does not explain agitation following sevoflurane anaesthesia in infants and children: a comparison with propofol. *Paediatr Anaesth*. Jan 2003;13(1):63-7.
11. Costi D, Cyna AM, Ahmed S, et al. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. *Cochrane Database Syst Rev*. Sep 12 2014(9):CD007084.
12. Kanaya A. Emergence agitation in children: risk factors, prevention, and treatment. *J Anesth*. Apr 2016;30(2):261-67.
13. Moore AD, Anghelescu DL. Emergence Delirium in Pediatric Anesthesia. *Paediatr Drugs*. Feb 2017;19(1):11-20.
14. Wang X, Deng Q, Liu B, Yu X. Preventing Emergence Agitation Using Ancillary Drugs with Sevoflurane for Pediatric Anesthesia: A Network Meta-Analysis. *Mol Neurobiol*. 04 Nov 2016.
15. Fang XZ, Gao J, Ge YL, Zhou LJ, Zhang Y. Network Meta-Analysis on the Efficacy of Dexmedetomidine, Midazolam, Ketamine, Propofol, and Fentanyl for the Prevention of Sevoflurane-Related Emergence Agitation in Children. *Am J Ther*. Jul-Aug 2016;23(4):e1032-1042.
16. Kim HS, Oh AY, Kim CS, Kim SD, Seo KS, Kim JH. Correlation of bispectral index with end-tidal sevoflurane concentration and age in infants and children. *Br J Anaesth*. Sep 2005;95(3):362-66.
17. Hirota K. Special cases: ketamine, nitrous oxide and xenon. *Best Pract Res Clin Anaesthesiol*. Mar 2006;20(1):69-79.
18. McDermott NB, VanSickle T, Motas D, Friesen RH. Validation of the bispectral index monitor during conscious and deep sedation in children. *Anesth Analg*. Jul 2003;97(1):39-43, table of contents.
19. Ivani G, Vercellino C, Tonetti F. Ketamine: a new look to an old drug. *Minerva Anestesiol*. May 2003;69(5):468-71.
20. Blagrove M, Morgan CJ, Curran HV, Bromley L, Brandner B. The incidence of unpleasant dreams after sub-anaesthetic ketamine. *Psychopharmacology (Berl)*. Mar 2009;203(1):109-20.
21. Sadhasivam S, Chidambaran V, Ngamprasertwong P, et al. Race and unequal burden of perioperative pain and opioid related adverse effects in children. *Pediatrics*. May 2012;129(5):832-38.
22. Jimenez N, Anderson GD, Shen DD, et al. Is ethnicity associated with morphine's side effects in children? Morphine pharmacokinetics, analgesic response, and side effects in children having tonsillectomy. *Paediatr Anaesth*. Jul 2012;22(7):669-75.
23. Tobias JD, Green TP, Cote CJ, Section On A, Pain M, Committee On D. Codeine: Time to Say "No". *Pediatrics*. Oct 2016;138(4).
24. Liem EB, Lin CM, Suleman MI, et al. Anesthetic requirement is increased in redheads. *Anesthesiology*. Aug 2004;101(2):279-83.
25. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. *Anesth Analg*. Dec 2004;99(6):1648-54, table of contents.