Weaning from High Dose Opioids and Sedatives in the ICU

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Learning Objectives:

Upon completion of this lecture, the attendee will be able to

- Appreciate the mechanisms of opioid and sedative tolerance and withdrawal
- Identify groups at increased risk for tolerance and withdrawal
- Choose strategies for prevention and management
- Discuss potential novel therapies and future research opportunities

In the early 1990’s, shortly after publications urging more consistent administration of opioids in children to decrease perioperative morbidity and mortality, the first reports describing opioid tolerance and withdrawal symptoms emerged. As we enter the third decade of prescribing opioids and sedatives to critically ill pediatric patients we have to realize that only limited progress has been made in the prevention and management of these adverse effects. While development of tolerance may be obvious when medication infusion rates reach astronomical heights withdrawal is more difficult to diagnose as signs and symptoms are nonspecific. Most researchers agree that gradual weaning of medications is indicated after prolonged administration of opioids and sedatives but the specifics of the weaning process itself remain sketchy. More research will be required.

Opioids and sedatives exalt their effect at the appropriate cellular receptors leading to a chain of intracellular signal transduction mechanisms. Continued or repeated interaction of opioid or sedative with the receptor will result in alterations affecting multiple steps of the cellular changes. Down regulation and internalization of opioid receptors, up-regulation of cyclic AMP, interaction with NMDA and other receptors are considered to be the most important mechanisms of development of opioid tolerance. As similar mechanisms of intracellular signal transduction including cyclic AMP activation have been described after interaction of benzodiazepine with GABA receptors comparable adaptation may occur in the event of prolonged or repeated exposure to sedatives.

These cellular mechanisms are thought to be associated with the development of tolerance, a condition requiring higher administration of a particular drug to achieve the same
pharmacological effect. Increased delivery of the drug will result in higher serum levels, as metabolism does not appear to be substantially augmented. Development of tolerance is affected by a multitude of factors including the particular analgesic or sedative chosen, the mode and duration of drug administration, metabolism of the drug, interaction with other drugs, and finally patient-specific factors such as age and gender. Tolerance to short-acting synthetic opioids seems to develop quickly; continuous infusions are more problematic than intermittent administration.

Prevention of tolerance has focused on pharmacological interventions to ameliorate the described intracellular processes such as limiting NMDA receptor activation by administration of ketamine, ultra-low dose naloxone or opioid rotations to decrease the chance of receptor changes, or multi-modal analgesia. In addition, systems-based improvements such as the introduction of sedation protocols, providing “cluster care” to limit patient disturbances, or constructional measures decreasing noise levels in intensive care units have been put in place.

Withdrawal, a clinical presentation of autonomic, cardiovascular, gastrointestinal, and neuropsychological disturbances after a decrease in administration of an opioid or sedative can be associated with the development of tolerance but may also be observed in patients who consistently received a stable dose for a prolonged period of time. Exposures to particular total doses and duration of administration of opioids and sedatives may result in rates of occurrence of withdrawal as high as 100%.

Diagnosis of withdrawal in pediatric intensive care patients has been complicated by the difficulties of distinguishing its signs from very similar ones due to pre-existing conditions such as borderline congestive heart failure. Several authors have therefore focused on finding the most efficient and reliable method for assessment of withdrawal. These methods include:

- Neonatal Abstinence Scale (NAS) – Finnegan et al. 1975
- Opioid and benzodiazepine withdrawal Scale (OBWS) – Frank et al. 2004
- Sophia Observation withdrawal Symptoms-scale (SOS) – Ista et al. 2009
- Withdrawal Assessment Tool-1 (Wat-1) – Frank et al. 2008

Level of evidence for weaning protocols to treat or prevent withdrawal is limited. There are few randomized controlled trials; most recommendations are based on expert advice. Common approaches to weaning opioids and sedatives include reducing rates of administration by fixed daily percentages, either based on the original dose or the preceding day’s dose. No agreement exists concerning the duration of weaning beyond the understanding that brief exposures to opioid and sedatives can be followed by rapid reductions in dose whereas patients with high-dose and prolonged medication administrations will best be managed with weaning schedules.
extending for weeks or even months. While authors generally report the number of weaning failures in their studies they usually do not offer recommendation on how to approach these patients beyond the suggestion to try again at a slower rate of weaning.

Further research of the development of tolerance, withdrawal and weaning procedures in children is needed. The realization that current analgesics and sedatives may have detrimental long-term effects on the health and cognitive development of the child should accelerate explorations. Prospective observational studies assessing prevalence and risk factors on a larger scale, or evaluations examining validity of current assessment tools in a variety of populations may provide the basis for interventional randomized controlled trials exploring more effective measures to prevent the development of tolerance itself or at least a safer, and more predictable and efficient way to wean analgesics and sedatives.

References: